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Printable Program

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### MARS Lecture 1

**Chair(s):** Suzanne Dickson  
**5:00**  
**The Sweet Hormone?**  
Gareth Leng  
University of Edinburgh, Edinburgh, United Kingdom

In this talk, I will reflect on how studies of the oxytocin system of the hypothalamus have transformed our understanding of the brain, and are continuing to challenge our preconceptions. Here, I will focus on trying to understand the functional roles of oxytocin in the regulation of appetite and food choice, and how these roles relate to its better known roles in reproduction.

Salivary Protein Profile Predicts Bitter Acceptance But Chemical Similarity Does Not

Verenice Ascencio Gutierrez¹, Samantha L. Brooker¹, Kimberly F. James¹, Ann-Marie Torregrossa¹,²
¹Department of Psychology, University at Buffalo, Buffalo, NY, United States, ²Center for Ingestive Behavior Research, University at Buffalo, Buffalo, NY, United States

Food choice is critical for survival. We have shown animals can increase intake of tannic acid and quinine after repeated exposure, in part due to changes in salivary proteins (SPs) decreasing the bitterness of the stimulus. We do not know the specificity of the increased acceptance. Here we asked if diet-induced changes in SP expression, which increase the animal’s acceptance of safe bitter substances, will increase acceptance of similar but potentially toxic stimuli. To do this, we used a brief-access taste test to measure taste-driven responses to the bitter compounds quinine, caffeine, and denatonium (DB) before and after salivary proteins were manipulated. All animals were tested on a control diet, then half of the animals were switched to a 0.375% quinine diet and retested. The other half was tested again on control diet. We found that rats on the quinine diet demonstrated a trend to lick more to quinine (p = 0.06).Â They did not differ in their licking to caffeine, a chemically similar but potentially toxic bitter stimulus, suggesting diet-induced SP changes do not generalize to all bitter stimuli. However, they did show a significant shift in licking to DB (p = 0.05). DB was meant to be a control stimulus, as it is chemically distinct from quinine.Â To explore the mechanism of the curve shift we examined the DB induced SP profile and compared it to that of quinine. We fed animals a DB-containing diet (or control) and collected saliva samples throughout diet exposure. We found that the SP profile induced by DB largely overlapped that of quinine in the 35, 25, 18.5, and 14 kDa bands. These data suggest that while similar SP profiles may predict decreased bitterness perception, chemical similarities of the stimuli do not.

The Influence Of Exercise On Neural Activity In The Ventral Medial Hypothalamus.

Jamie Carty, Ryan Post, Rachael Villari, Nitsan Goldstein, J. Nicholas Betley
University of Pennsylvania, Philadelphia, PA, United States

Exercise provides a range of health improvements which can reverse the effects of obesity. Hypothalamic circuits influence glucose metabolism and body composition. Expression of the transcription factor steroidogenic factor-1 (SF1) in the ventromedial hypothalamus is required for energy homeostasis and muscular adaption to the metabolic challenge of exercise. Therefore, we hypothesized that neurons expressing SF1 may be important mediators of the benefits of exercise. To determine how SF1 neural activity is influenced by exercise training, we monitored the neural activity of SF1 neurons during and following exercise. We found a consistent increase of SF1 neuronal activity in the VMH at the end of exercise which intensifies over the course of additional training. In addition, exogenous activation of SF1 neural activity was found to increase exercise capacity and influence fat metabolism. Taken together, these results suggest SF1 neurons in the VMH play an important role in health benefits that occur following exercise.

Reward And Stress-Related Eating Behaviour After Vertical Sleeve Gastrectomy In Mice

Eva Guerrero-Hreins¹,², Renee Papalaca¹, Claire J Foldi³,⁴, Brian J Oldfield¹,⁴, Aneta Stefanidis³,⁴, Andrew J Lawrence², Priya Sumithran⁵,⁶, Robyn M Brown¹,²
¹Department of Biochemistry and Pharmacology, University of Melbourne, Parkville, Victoria, Australia, Melbourne, Australia, ²Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia, Melbourne, Australia, ³Department of Physiology, Monash University, Clayton, Melbourne, Australia, Melbourne, Australia, ⁴Biomedicine Discovery Institute, Monash University, Clayton, Melbourne, Australia, Australia, ⁵Department of Medicine (St. Vincent’sf Â£â€Â©, Â£â€Â¬â€Â»s), University of Melbourne, Victoria, Australia, Melbourne, Australia, ⁶Department of Endocrinology, Austin Health, Melbourne, Australia, Melbourne, Australia

Bariatric surgery is currently the most effective, long-term weight loss treatment for obesity, which results in reduced appetite and improved glyceemic regulation due to pronounced changes in the gut-brain axis. People seeking bariatric surgery often display high levels of disordered eating including compulsive eating triggered by stress, which can hinder weight-loss outcomes. Accumulating evidence suggests neuroendocrine alterations after bariatric surgery have favourable implications on reward-related food intake and taste preference changes. However, there is a paucity of research investigating the mechanistic underpinnings of reward and stress-related eating after bariatric surgery, particularly vertical sleeve gastrectomy (VSG). The aim of this study is to investigate the effect of bariatric surgery on reward and stress-related eating in a mouse model of VSG. Male and female C57BL/6 (n=54) mice were fed a high-fat diet before undergoing VSG or sham surgery.Â Prior to and after surgery, mice were tested for taste preferences and motivated behaviour towards palatable high-fat, high-sugar food in an operant conditioning chamber. All mice were perfused for Fos protein immunohistochemistry. Outcomes from this study will provide valuable insight into the neurobiological underpinnings of motivated eating behaviour in the context of bariatric surgery.

Access Schedule To High Fat Diet Alters Trial Numbers But Not Unconditioned Licking In A Brief Access Paradigm

Kimberly F. James¹, Verenice Ascencio Gutierrez¹, Ann-Marie Torregrossa¹,²
¹Department of Psychology, University at Buffalo, Buffalo, NY, United States, ²Center for Ingestive Behavior Research,
The data on food preference and taste responding after diet induced obesity are equivocal. We previously demonstrated that diet and body weight differentially affected unconditioned licking patterns to artificial sweeteners in mice, but we found no difference in the number of trials initiated suggesting taste responding was altered but not motivation to drink. A In the current study, we used a rat model to further explore these effects. Rats were divided into four groups: Ad-lib Chow, Ad-lib HFD. Pair-fed HFD (limited HFD) and Ad-lib Chow group), and to control for the fact that pair-fed groups usually eat all of their food early in the dark cycle we included a 3-hr Time Restricted Chow group. Both HFD groups regardless of caloric intake, had significantly more body fat (g) per body weight (g) than the rats consuming chow (p’s < .05). A However, only the Ad-lib HFD group gained significantly more body weight than all other groups (p’s < .05). A Pair-fed HFD rats were not heavier than the Ad-lib Chow group (p = .64). Rats were tested in brief access taste tests with AceK and saccharin solutions (as in our previous mouse work). There were no significant differences in licking response between the diet groups for either solution (p’s > .05), however there were significant differences in trial number. Ad-lib HFD took significantly more trials than pair-fed HFD rats (p’s < .05) suggesting that the feeding schedule may have altered motivation to perform the task. These data also suggest there may be species differences in response to HFD in the brief-access taste testing task.

DREADD-Mediated Activity Of Ghsh-Expressing Cells In Ventral Hippocampus Differentially Impacts Feeding Behavior Of Obese Induced And Obese Resistant Male And Female Mice

Athanasios Kondilis, Khalil H. Stockling, Alexander W. Johnson
Michigan State University, East Lansing, MI, United States

The gastric hunger signal, ghrelin, influences feeding behavior via activation of the growth hormone secretagogue receptor (GHSR). GHSR’s are expressed in multiple brain regions including the ventral hippocampus (VHPC)—a region that plays a critical role in ghrelin-evoked feeding behaviors. We used a GHSR-IRES-Cre mouse line to examine whether differences in the vulnerability to dietary obesity disrupts feeding behaviors controlled by VHPC GHSR-expressing cells. Male and female adult mice were exposed to 8 weeks of high fat diet exposure (HFD) to discern phenotypes of diet resistant (DR) or diet-induced obesity (DIO) based off a sex-specific quartile split. Mice then received either a Cre-dependent excitatory DREADD, inhibitory DREADD, or control mCherry virus into the VHPC. On test days, mice were injected with clozapine-N-oxide (CNO) or vehicle prior to the onset of the dark cycle and given portioned access to either lab chow or HFD. In all mice, HFD feeding tests failed to reveal any effects of VHPC GHSR-expressing cell manipulations. However, when tested with Chow, DREADD stimulation of VHPC GHSR-expressing cells significantly enhanced consumption in DR but not DIO mice. This indicates that vulnerability to dietary obesity more readily disrupts the capacity for stimulation of VHPC GHSR-expressing cells to evoke feeding. By contrast, chemogenetic inhibition of VHPC GHSR-expressing cells revealed interactions between dietary state and sex, whereby chemogenetic inhibition suppressed chow intake in DIO females and DR males only. These findings suggest VHPC GHSR function is impacted by vulnerability to dietary obesity in a manner that is dependent on the nature of chemogenetic stimulation, biological sex, and the nutrient composition of food.

Single And Multi Session Tdcs Fmri Studies Distinguished Distinct Neural Mechanisms Between Acute And Cumulative Anti-Obesity Treatment Effects

Miwoo Lee1,2,3, Myungeun Kim1, Kyung Hwa Lee4, Jae-Chang Kim1,2, Hyeon-Man Baek4, Hyung Jin Choi Choi1,2
1Functional Neuroanatomy of Metabolism Regulation laboratory, Seoul, South Korea, 2Department of Anatomy, Seoul National University College of Medicine, Seoul, South Korea, 3BK21Plus Biomedical Science Project Team, Seoul National University College of Medicine, Seoul, South Korea, 4Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University Hospital, Seoul, South Korea, 5Center for MR Research, Korea Basic Science Institute, Ochang, South Korea

Background: Transcranial direct current stimulation (tDCS) is a neuromodulation technique that shown to be effective to reduce food craving and consumption. The present study aimed to examine the acute and cumulative effects of single session tDCS and multi-session tDCS, respectively, on appetite and neural response to food images in adults with obesity.

Method: Single session study: Single-blind sham-controlled crossover study was performed for 14 obese adults (4 female, BMI=29.6±1.2, age=29.5±12.7). Appetite related scores and food image task fMRI were performed after single real or sham tDCS. Multi-session study: Single-blind randomized control study (real tDCS: n=14 and sham tDCS; n=13) was performed for 10 multi-sessions during 2 weeks among obese adults (6 female, BMI=30.1±3.8, age=22.3±3.6). The same assessment protocol was performed before first session and after last session. Results: Single session study: Compared to sham session, real tDCS session showed significantly higher fullness score and significantly lower left nucleus accumbens area activity to high-calorie food cue(t(10)=2.246, p<.05, t(12)=2.555, p<.05, respectively). Multi-session study: Compared to sham group, real tDCS group showed significantly higher composite appetite score decrease (repeated measures ANOVA with time and group interaction p<.05). There was no significant change in sham group, but there was significant decrease in composite appetite score in real tDCS groups (paired t-test, t(13)=3.324, p<.01). After 10 sessions of tDCS, there was significant increase in bilateral occipital gyrus in real tDCS group (repeated measures ANOVA with time and group interaction p<.05), no change in sham group. Conclusion: This study demonstrated that tDCS successfully decreased appetite in both single and multi-session tDCS and modulated reward and perception related areas in single and multi-session studies, respectively. These results suggest that tDCS may reduce appetite regardless of single or multiple sessions, but have different effects of single and multiple sessions on neural function in obese adults.

Perinatal High-Fat Diet Results In Delayed Attainment Of Developmental Milestones In Neonatal Rat Offspring

Lindsey K Macias1,2, Zachary Cordner1, Shannon O’Brien1, Andrew Aston1,2, Timothy Moran1, Kellie Tamashiro1,2
1Psychiatry & Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, United States, 2Cellular and Molecular Medicine Graduate Program, Johns Hopkins School of Medicine, Baltimore, MD, United States

Delayed attainment of developmental milestones is often indicative of impaired neurodevelopment and intellectual disability seen in conditions such as autism and ADHD in humans. Previous data from our lab and others have shown that maternal high-fat (HF) diet results in cognitive impairment and altered hippocampal gene expression in adult rat offspring. Here we determined whether deficits in early neurodevelopment may be a prelude to cognitive deficits later in adulthood. Timed-pregnant Sprague Dawley rats were fed either standard laboratory chow (CH) diet (13% kcal fat) or a purified HF diet (60% kcal fat) during gestation and lactation (n=6/diet group). On postnatal day (P)1, litters were culled to 10 pups per litter (5
Selective Bred Dio And Dr Rat Strains Perform Similarly In Flavor-Nutrient Learning And Deprivation Discrimination Tasks.
Kevin P Myers
Bucknell University, Lewisburg, PA, United States

Learning and memory abilities are crucial for coordinating motivational and food-seeking behaviors in response to external cues for food availability and internal signals for energy status. Overconsumption of sugar and fat produce learning and memory impairments which disrupt that coordination. Thus individual differences in memory function can be both predisposing factors and consequences of excess energy intake. Given some evidence that selectively bred DIO and DR rat strains exhibit subtle differences in memory task performance prior to any obesogenic diet access, this work investigated whether they differ in two learning tasks that are directly relevant to energy balance. In flavor-nutrient learning, rats learn to prefer a flavor paired with post-ingestive nutrient sensing, and in deprivation discrimination, rats learn to use their current food deprivation state as a predictive cue in an outcome expectancy problem. Flavor-nutrient learning has previously been shown to differ between outbred rats who gain the most vs least weight during extended access to high-energy diets. In the current experiments DIO and DR rats maintained on ordinary chow showed similar appetitive responses to IG glucose infusion and equivalent learned preference for a nutrient-paired flavor, and similar success at learning the deprivation discrimination task. These results suggest the previously documented differences in flavor-nutrient learning between high vs low weight-gainers are more likely a consequence of overeating and/or weight gain, not a predisposing factor for obesity proneness. Further, prior evidence for pre-existing hippocampal learning deficits in DIO rats does not extend to deprivation discrimination performance.

Eating Context Determines The Effectiveness Of Nutritional Warning Labels To Promote Healthier Choices And Reduce Conflict During Food Choice
Claudio E Perez, Sara Caballero, C Moenne, M Delgado, Y Jimenez, Jose Galgani
Universidad Catolica de Chile, Santiago, Chile

Food choice is influenced by eating context and nutritional information. In Chile, mandatory nutritional warning labels (NWLS) aim to promote healthier dietary choices. Whether eating context alters how NWLS influence food selection and conflict during food choice is unknown. In an online study, participants (n=97; BMI=23.1±2.4; 50% female) chose, using a computer mouse, between food pairs of different healthiness within NWLS and then with NWLS in a healthy, typical, or desired eating context (healthy: choose the food you would eat to stay healthy; typical: choose the food you would normally choose in your daily life; desire: choose the food you would eat if nothing was stopping you). When participants made a healthy choice without NWLS, the probability of a healthy choice with NWLS was above 90% in all contexts. However, the probability of a healthy choice with NWLS was reduced in all contexts (healthy: -15.8±1.1%, typical: -56.9±1.9%, desire: -69.4±1.2%; P<0.01) when participants first made an unhealthy choice without NWLS, and was below chance in the typical (36.5±2.4%) and desired context (20.6±1.7%). The presence of NWLS reduced mouse-tracking variables of area under the curve (AUC) and reaction times (RT) during healthy choices and increased AUC and RT during unhealthy choices (ΔAUC: β=0.0034±0.006 arbitrary units; ΔRT: β=0.0071±0.006 ms; P<0.05 for all endpoints) without an effect of context (P>0.05 for ΔAUC and ΔRT). These data indicate that NWLS facilitate healthier choices and make unhealthy food choices more difficult across healthy, typical, and desire eating contexts, but the efficacy of NWLS to revert an unhealthy food choice is above chance only in a healthy eating context.

Regulation Of Motivation For Sucrose By Orexin And Dynorphin A Peptides
Carolina L Sandoval, Nicolas L Luarte, Claudio E Perez
Universidad Catolica de Chile, Santiago, Chile

Orexin-A (OXN-A) and dynorphin-A (DYN-A) are peptides co-released by the hypothalamic Orexin/Dynorphin neurons that regulate feeding and motivated behaviors. OXN-A is neuroexcitatory and acts through Orexin receptors, while DYN-A is neuroinhibitory and acts through the kappa opioid G-protein receptor (KOR). We have shown that in the paraventricular hypothalamic nucleus (PVN), DYN-A increases hedonic intake and OXN-A blocks this effect. However, if increased motivation for food mediates the increase in hedonic intake by DYN-A in PVN is unclear. We hypothesized that, in PVN, DYN-A acting through KOR increases motivation for sucrose and OXN-A inhibits this behavior. To test this, we built a lickometer in which adult male C57BL6 have simultaneous access to sucrose and water under different reinforcement schedules. The lickometer captured the circadian rhythm of water intake (n=4, light phase=83.7±3.1 licks, dark phase=216.54±22.22 licks, P<0.05) and can be used to train mice into a progressive ratio (PR) for sucrose (n=7, licks at end of PR session, water = 10.4±1.9, sucrose = 788.16±160.59, P<0.05). Unilateral PN injection of DYN-A increased licks for sucrose compared to vehicle injection (n=11, 314.18±107 licks, P<0.02), suggesting increased motivation for sucrose. Opposite to our hypothesis, co-injection of OXN and DYN-A increased sucrose licks compared to DYN-A alone (n=10, 169.43±48.3 licks P<0.05). Bilateral injection of the KOR antagonist norBNI in PN reduced sucrose licks 15 min, but not 24 h after injection (n=10, P=0.04 for interaction between norBNI dose and time). Together, these data indicate that DYN-A promotes motivated behaviors in PN through KOR and OXN-A might potentiate this effect.

The Acute Effects Of A Vegetable-Based Meal And L-Methylfolate Drink On Affect And Mood In Healthy Adults.
Nicola-Jayne Tuck, Claire Farrow, Jason M Thomas
Aston University, Birmingham, United Kingdom

Research suggests that folate (a nutrient in vegetables) has a protective effect on psychological health. This study assessed the effects of consuming folate via a meal and/or a drink, on affect and mood. One hundred and eight healthy adults...
Intended Serving Behavior At Social Meals: Does A Dining Companion's Hunger Level Matter?
Emma V Long1, Lenny R Vartanian1, Kate Faasse4, Suzanne Higgs2
1UNSW Sydney, Sydney, Australia, 2University of Birmingham, Birmingham, United Kingdom

In behavioral studies, people tend to serve themselves larger portions before social meals than before eating alone (‘social precitilation’ of eating). In contrast, self-report studies show that people consistently report that they would serve themselves smaller portions when eating with others than when eating alone. The ‘serve less’ pattern observed in self-report studies may be due to people’s presumptions about how much their companions would be eating. To address this possibility, we examined whether providing information about a dining companion’s hunger level would influence participants’ reported serving behavior for the social meal. We hypothesized that, when imagining dining with a hungry companion, participants would select a larger portion than when imagining dining alone. Participants (N=339) first imagined dining alone and selected how much food they would serve themselves by moving a slider that allowed them to select increasingly smaller or larger portions of pasta. For the second scenario, participants read one of three hypothetical text message exchanges with a friend before selecting their portion size. The text message indicated whether their friend was hungry, not hungry, or did not mention hunger (control condition). Consistent with previous research, participants in the control condition chose smaller portions for a meal with their friend vs. a meal alone (Cohen’s d=-2.3; A p=0.026). This same pattern was observed when the friend mentioned not being hungry (d=2.7; p<0.004), and even when the friend mentioned being very hungry (d=3.3; p<0.001). The ‘serve less’ phenomenon, then, does not appear to be due to presumptions about one’s dining companions, and rather suggests that people may be unaware of how social context influences their behavior.

Evaluation Of The Effect Of Glucose Tolerance On Cognition In Youth With Overweight/Obesity
Henry M. Quillian 1, Tuki Attuquayefo 1, Justin Sung 1, Tiffany Ko1, Xue Davis1, Chavonn Duncan1, Xi Fang1, Yulu Pan1, Kathryn Wall1, Kaitlin Maciejewski1, Fangyong Li1, Fuyuze Tokoglu1, Nicola Santoro1, Hubert Preis1, Sonia Caprio1, Dana M. Small1
1Yale University, New Haven, CT, United States, 2University of Tuebingen, Tuebingen, Germany

It is now established that type-2 diabetes (T2D) is associated with cognitive impairment. The mechanisms behind this association are unclear because studies are conducted in older adults with co-morbid conditions that may affect cognition, and because glucose metabolism and adiposity are often confounded. Here we evaluated cognition and the effects of intranasal insulin (INI) on cognition in youth with overweight/obesity (OW/OB) with and without glucose impairment. To evaluate cognition, we performed the WISC/WAIS and trail making tests (TMT) in a behavioral session. To evaluate the effect of central insulin signaling on cognition, reaction time index, spatial working memory, and delayed matching to sample episodic memory tests were conducted after administration of INI or placebo on separate days. Oral glucose tolerance tests diagnosed 23 participants with impaired and 45 with normal glucose tolerance (IGT, NGT respectively). IGT and NGT groups did not differ significantly in age, sex, race, IQ, or BMI. Visceral to subcutaneous fat ratio was higher in IGT. We observed trends for worse performance in IGT vs. NGT in the block design, TMT, and similarities tasks (p=0.053-0.076). INI did not improve working or episodic memory in either group. However, reaction time was increased in IGT vs. NGT in the placebo (p<0.047) but not INI condition. We conclude that there is evidence for reduced processing speed in youth with OW/OB with prediabetes with minimal to no effects on cognitive functions and no evidence for a main effect of central insulin administration on cognitive function. These findings suggest cognitive impairments observed in older adults with T2D are secondary to co-morbid conditions, such as cerebral vascular disease, rather than glucose intolerance per se.

Effects Of Duodeno-Jejunal Bypass Liner Insertion On Food Cue Reactivity, Appeal, Liking And Wanting In Adults With Obesity And Type 2 Diabetes Mellitus.
Ghadah Aldubaikhi1, Navpreet Chhina1, Lililam Flores1, Moaz Al Lababidi1, Madhawi Aldhwayan2, Werd Al-Najim3, Graham Finlayson4, Alex D. Miras5, Aruchuna Ruban5, Michael A. Glaysher6, Christina G. Prechtl7, James Byrne6, Julian P. Teare5, Anthony P. Goldstone1
1PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, United Kingdom, 2Community Health Sciences Department, King Saud University, Riyadh, Saudi Arabia, 3Division of Metabolism, Diabetes and Reproduction, Imperial College London, London, United Kingdom, 4Appetite Control and Energy Balance Research Group, School of Psychology, University of Leeds, Leeds, United Kingdom, 5Department of Surgery and Cancer, Imperial College London, London, United Kingdom, 6Division of Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, 7Clinical Trials Unit, Department of Public Health, Imperial College London, London, United Kingdom

Background: The duodeno-jejunal bypass liner (DJBL) Endobarrier device is a 60 cm polymer sleeve inserted endoscopically being trialled for obesity and type 2 diabetes mellitus. It excludes food from the proximal bowel, one mechanism by which Roux-en-Y gastric bypass surgery achieves its beneficial effects. The impact of the DJBL device on eating behaviour is currently uncertain. A Methods: Mechanistic sub-groups from randomised trial of DJBL vs. standard medical management (SMM) for obesity (BMI 30-50 kg/m2) and T2DM with inadequate glycaemic control (PMID 29146657, 34647708). At baseline and 26 weeks when fasted, participants had functional MRI to measure BOLD signal in reward system ROIs during appeal rating (vs. objects, max 4) of low- (LE) or high-energy (HE) food pictures (n=11-12, and
**Discovery Of A Novel Micropeptide That Stimulates Feeding Behavior**

Angie I. Bookout, Sally Lyons-Abbott, Sakara Perry, Max Hoofnagle, Jon Davis
Novo Nordisk Research Center Seattle, Inc, Seattle, WA, United States

Cardiometabolic disease due to maladaptive systemic energy homeostasis is a formidable unmet medical need, despite many available therapeutics. Understanding the molecular mechanisms that coordinate metabolic homeostasis will lead to refined treatment approaches. Recent sequencing efforts and bioinformatic analyses have revealed the existence of a previously overlooked class of molecules called micropeptides, small proteins composed of ~100 or fewer amino acids. The work herein describes the discovery of several putative micropeptides that potentially represent a novel class of endocrine signaling molecules. Our goal is to understand if these novel proteins regulate energy balance. Using ribosome profiling, we identified an adipocyte-derived mouse IncRNA predicted to encode a 132aa protein with a signal peptide and two O-linked glycosylation sites. Importantly this microprotein is encoded on a mRNA primarily expressed in a subset of orexigenic NPY+/AgRP+ neurons within the hypothalamus. Recombinant expression of the mature 108aa protein results in a glycosylated form that, when injected ICV, reliably stimulates food intake in diet-induced obese mice. Based on these observations we hypothesize that this novel microprotein stimulates hunger via a potentially novel endocrine signaling mechanism that converges on orexigenic NPY+/AgRP+ neurons to promote appetite. The work presented here describes a suite of in vitro and in vivo efforts that support this hypothesis. We contend that this approach could reveal unique drug discovery opportunities to combat cardiometabolic disease.

**Brain Angiotensin II Behavioral Control Of Sodium Taste**

Natalie A.R. Fernandes, Bruna M. Santos, Glacía M.F. de Andrade-Franze, Patricia M. de Paula, Carina A.F. de Andrade, Jose V. Menani, Laurival A. De Luca Jr
FOAR - UNESP, ARARAQUARA, SP, Brazil

Brain angiotensin II (Ang II) controls sodium palatability in response to acute sodium depletion (Zenatti et al., 2021). It is unclear whether similar role applies to sodium intake sensitization, and whether it relates with capsaicin-induced oral nociception. Adult rats were instrumented with an intraoral cannula to receive intraoral infusions (1 ml for 1 min) of 0.5 ÅM capsaicin and, 20 minutes later, a second one of 0.3 M NaCl. The animals received subcutaneous injection of a diuretic/natriuretic, furosemide (Furo), combined with a low dose of the angiotensin converting enzyme inhibitor, captopril (Cap). The Furo/Cap enhances the supply of Ang I to the brain, thus increasing local production of Ang II. Then, the animals had 1-h free access to water to quench their thirst. Immediately after, they received the sequence of intraoral infusions. The number of orofacial motor responses was monitored on video. The sequence, Furo/Cap injection - quench thirst - intraoral infusions, was repeated twice every three days. The repetition of Furo/Cap produced about 3-fold increase in hedonic responses and 2-fold reduction in aversive responses to 0.3 M NaCl. It also produced a transient reduction in neutral responses to capsaicin. The increased palatability of 0.3 M NaCl produced by repeated Furo/Cap suggests that brain Ang II also organizes the sensitization of sodium taste. A possible interaction between sodium appetite and the effects of capsaicin remains under investigation in our laboratory.

**Individual Differences In Consumption Of A Varied, Palatable 'Cafeteria'-Style Diet Do Not Predict Short-Term Memory Or Adiposity In Rats**

Michael D Kendig1,2, Sarah-Jane Leigh1,3, Kyoko Hasebe1, R Fred Westbrook4, Margaret J Morris1
1School of Medical Sciences, UNSW Sydney, Sydney, Australia, 2Current address: School of Life Sciences, University of Technology Sydney, Sydney, Australia, 3Current address: APC Microbiome Ireland, University of Cork, Cork, Ireland, 4School of Psychology, UNSW Sydney, Sydney, Australia

Studies in rodents and humans show that diets high in fat and/or sugar lead to cognitive and metabolic impairments, linked to changes to neuroinflammation and the composition of the gut microbiome. While both fat and sugar can induce these deficits, these nutrients are typically found together in human foods, and their consumption varies over time and according to availability and preferences. Here we tested whether individual differences in food and macronutrient selection of a varied, palatable 'cafeteria' (CAF) diet were associated with the degree of metabolic and cognitive impairment. Thirty adult male Sprague-Dawley rats were housed individually with free access to chow and water (CON, n = 15) or chow, water, 10% sucrose and a range of high-fat, high-sugar foods, which varied daily (CAF, n = 15) for 7 weeks. Food intake was measured daily during weeks 1 and 4, and twice weekly otherwise. Place recognition memory, whole body adiposity and plasma lipids of HE/LE foods after DJBL (0.33, P=0.011) was greater than after SMM (0.04, P=0.76). There were no differences between interventions for food cue reactivity BOLD signal, dependent on or independent of ROI/energy density (P=0.51-0.77), nor explicit liking/wanting or implicit wanting of any foods (P=0.77-0.98). A Conclusion: A greater reduction in appeal rating of foods may have contributed to greater weight loss after DJBL insertion for obesity with T2DM, but there was no evidence for any greater reduction in cue reactivity, or liking/wanting of foods. Interpretation is limited by the small sample sizes and fasted state of participants.

**Neurobiological Mechanisms Underlying Compulsive Eating In Female Rats**

Lital Moshe1,2, Roma Parikh3, Carmit Levy3, Aron Weller1,2
1Department of Psychology, Bar Ilan University, Ramat-Gan, Israel, 2Gonda Multidisciplinary Brain Research Center, Ramat-Gan, Israel, 3Department of Human Genetics and Biochemistry, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

liking/wanting ratings of low/high fat, savoury/sweet food pictures using Leuds Food Preference Questionnaire (n=25-30), analysed by RMANOVA. A Results: At 26 weeks, there was greater mean % weight loss with DJBL than SMM (fMRI: 18.9 vs. 6.9%, P=0.035; LPFQ: 21.2 vs. 8.5%, P=0.008), but similar reductions in fasting glucose. Decrease in appeal rating of HE/LE foods after DJBL (0.33, P=0.011) was greater than after SMM (0.04, P=0.76). There were no differences between interventions for food cue reactivity BOLD signal, dependent on or independent of ROI/energy density (P=0.51-0.77), nor explicit liking/wanting or implicit wanting of any foods (P=0.77-0.98). A Conclusion: A greater reduction in appeal rating of foods may have contributed to greater weight loss after DJBL insertion for obesity with T2DM, but there was no evidence for any greater reduction in cue reactivity, or liking/wanting of foods. Interpretation is limited by the small sample sizes and fasted state of participants.
Binge eating (BE) is the compulsive consumption of larger amounts of food, in a briefer period of time than would normally be consumed. BE is not driven by hunger, is often comorbid with addiction and anxiety disorders and its etiology is not yet understood. Identifying underlying neurobiological mechanisms will have therapeutic and scientific importance. We hypothesized that BE tendency can be more readily identified in individuals predisposed to anxiety. A limited access to preferred food paradigm was employed in adult female Wistar rats, later characterized as BE prone (BEP) or resistant (BER) phenotypes. Biological mechanisms examined by serum proteomic mass-spectrometry (MS) and gene expression in brain and adrenal. MS results showed that BEP rats had lower levels of stress, expressed by proteins representing low inflammatory response, autoimmune proneness and impaired cholesterol homeostasis. Consistent patterns from the brain and adrenal were found. Compared to BER rats, BEP rats had lower expression of glucocorticoid receptors in the PVN, which may impair negative feedback on CRH secretion. BEP rats had lower levels of StAR and CYP11B1 expression in the adrenal compared to BER rats, implying dysregulated steroidogenesis. We also found that BEP rats had increased satiety signals, as showed by higher expression levels of the receptors for leptin, insulin and CCK in the ARC. Furthermore, BEP rats presented lower expression of Pomp and MC4r in the amygdala compared to BER rats. We conclude that dysregulated stress response may underlie BEP rat’s ability to ‘ignore’ satiety signals that promote adaptive food intake, thus underlying susceptibility to compulsive eating of preferred food.

Correlations Between Plasma Ghrelin And Human Appetite And Food Intake: A Systematic Review And Meta-Analisis

Marcela Rodriguez-Flores, Sandra Luur, Raghav Bhargava, Mimoza Emini, Anthony P. Goldstone

PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, United Kingdom

Background: It is widely accepted that the gastric hormone acyl ghrelin (AG), agonist at the hypothalamic/midbrain GHSR receptor promotes hunger, food reward and intake in animals and humans. However, without widely available GHSR antagonists or GOAT inhibitors (enzyme activating AG precursor) for clinical use, human data is derived from exogenous AG administration (usually producing supraphysiological plasma concentrations), or correlations of endogenous plasma total ghrelin (TG)/AG with eating behaviour. Results may be biased by lower plasma TG/AG in obesity, and increase when fasted and after weight loss. Methods: Systematic review of human studies correlating plasma TG/AG with appetite ratings or food intake. Studies were excluded if only post-bariatric surgery, anorexia/bulimia nervosa, cancer, renal failure, liver cirrhosis, genetic obesity or illnesses involving the gastrointestinal tract. Results: From 803 screened studies, 53 met inclusion/exclusion criteria: 60 groups, median n=20 (6-100), 73% male, 95% adults, 23% obese, 74/53% fasted/fed state, A 90/15% TG/AG assay. Number of significant correlations (P<0.05) for ratings of appetite (3/19 +ve, 2/19 -ve), hunger (15/61 +ve, 11/61 -ve), food craving (13/40 +ve, 7/40 -ve). Analysis is comparing results by age, nutritional state and BMI category, with meta-analyses of regression coefficients as appropriate. Conclusion: Results were very heterogenous and did not usually find positive correlations between plasma TG/AG and appetite or food intake. Proof of a physiological role of endogenous ghrelin in human (over)eating behaviour is therefore incomplete. Analysis of correlations with food hedonics/reward are also needed.

Oligofructose Alters The Small Intestinal Microbiota To Improve Intestinal Lipid-Sensing Mechanisms

Savanna N Weninger1, Chloe Herman2, Hallie R Wachsmith1, Rachel K Meyer4, J. Gregory Caporaso2,3. Frank A Ducra,5,6

1Physiological Sciences GIDP, Tucson, AZ, United States, 2Center for Applied Microbiome Science, Pathogen and Microbiome Institute, Flagstaff, AZ, United States, 3Department of Biological Sciences, Flagstaff, AZ, United States, 4Department of Nutritional Sciences, Tucson, AZ, United States, 5School of Animal and Comparative Biomedical Sciences, Tucson, AZ, United States, 6BIO5, Tucson, AZ, United States

Given recent evidence highlighting the importance of the small intestinal (SI) microbiota on regulating metabolic homeostasis via a gut-brain axis, we tested whether the prebiotic oligofructose (OFS) alters the SI microbiota to impact SI lipid-sensing mechanisms controlling food intake and glucose homeostasis in high fat (HF)-fed rats. While OFS is known to alter the distal gut microbiome, no studies have examined the effect of OFS on the SI microbiota and SI gut-brain nutrient sensing mechanisms that regulate food intake and glucose homeostasis. OFS supplementation (5wks) decreased bodyweight gain, food intake and adiposity in HF-fed rats (n=8), and this was associated with a unique SI microbiota profile compared to HF-feeding alone as determined by 16S rRNA gene sequencing. Furthermore, acute (3d) OFS treatment restored SI lipid-induced satiation during HF-feeding along with restoration of SI CD36 expression, portal GLP-1 levels and nucleus tractus solitarius neuronal activation. Additionally, OFS restored SI lipid-sensing mechanisms that decrease glucose production during glucose clamp experiments. SI microbiota transplants between HF- and acute HF-OFS-treated rats recapitulated these results, demonstrating OFS-induced changes to the SI microbiota was necessary to restore nutrient-induced gut-brain signaling. Both long- and short-term OFS altered the SI microbiota, increasing Bifidobacterium pseudolongum abundance. SI administration (3d) of cultured B. pseudolongum restored SI lipid sensing in HF-fed rats. These results highlight the SI microbiota as a regulator of SI nutrient sensing that impacts overall energy and glucose homeostasis and identify a novel probiotic bacterium that may play a role in mediating the beneficial effects of OFS via a gut-brain axis.

Peripheral Oxytocin Is Sufficient To Reduce Food Intake And Motivation, While Cns-Entry Is Required For Locomotion Reduction And Nausea Effect In Rats A

Mohammed Asker1,2, Jean-Philippe Krieger1, Amber Liles3, Tito Borner4,6, Ivana Maric1,2,5, Pauline Van der Velden1,2, Francesco Longo1,2, Stina Borchers1,2, Bart de Jonghe6, Matthew Hayes8, Robert Doyle3,7, Karolina Skibicka1,2,5

1Department of Physiology/Metabolic Physiology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, 2Wallenberg Centre for molecular and translational medicine, University of Gothenburg, Gothenburg, Sweden, 3Department of Chemistry, Syracuse University, Syracuse, NY, United States, 4Translational Neuroscience Program, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, 5Department of Nutritional Sciences, Pennsylvania State University, University Park, PA, United States, 6Department of Biobehavioral Health Sciences, University of Pennsylvania, School of Nursing , Philadelphia, PA, United States, 7Departments of Medicine and Pharmacology, State University of New York, Upstate Medical University, Syracuse, NY, United States
Oxytocin (OT) recently emerged as an important regulator of energy homeostasis. In addition to CNS, OT is found in the plasma and oxytocin receptors (OTR) are found in peripheral tissues relevant to energy balance regulation. Here we aim to determine whether peripheral OTR activation is sufficient to alter energy intake and expenditure. Systemic OT potently reduced food intake and food-motivated behavior in male and female rats. Since it is plausible that peripherally injected OT crosses the BBB to produce some of the metabolic effects within the CNS, we screened, with a novel fluorescently labeled-OT (f-Cy5-OT), for the presence of IP-injected f-Cy5-OT in CNS tissue relevant to feeding control and compared such to BBB-impermeable fluorescent OT-B12 (f-Cy5-OT-B12). While f-Cy5-OT did penetrate into the CNS, f-Cy5-OT-B12 did not. To evaluate the behavioral and thermoregulatory impact of exclusive activation of peripheral OTR, we generated a novel BBB-impermeable OT-B12, with equipotent binding at OTR in vitro. In vivo, IP-injected OT and OT-B12 were equipotent at food intake suppression in rats of both sexes, suggesting that peripheral OT acts on peripheral OTR to reduce feeding behavior. Importantly, OT induced a potent conditioned taste aversion, when applied peripherally, whereas OT-B12 did not. Limiting the CNS entry of OT resulted in a dose-dependent reduction of emesis, measured in shrews. While both OT and OT-B12 proved to have similar effects on body temperature, only OT resulted in home-cage locomotor suppression. A Thus, therapeutic targeting of peripheral OTR, while limiting systemic OT CNS penetrance, may be a viable strategy to achieve appetite suppression without the CNS OTR-mediated undesired side-effects: emesis, taste aversion, and locomotor depression.

Central oxytocin receptors (OTRs) in several brain areas are known to modulate food intake and play a role in stress responses. Here, we focused on the bed nucleus of the stria terminalis (BNST). Recent data implicated OTRs in the anteromedial nucleus of the BNST (amBNST) in stress-induced social vigilance. We first asked whether these OTRs modulate chow intake under normal conditions. Mice with unilateral cannulas targeting the amBNST were single-housed in a BioDAQ continuous food intake monitoring system. Intracranial injections of vehicle or 0.03, 0.1, or 0.3 μg OT were delivered an average of 30 min before dark onset, then intake was measured for 20 hours (n=15; M=7, F=8). None of these doses of OT significantly affected food intake. Next, we delivered vehicle or 1 or 5 μg of the OTR antagonist L-368,899 an average of 30 min before dark onset (n=12; M=8, F=5). Again, there was no effect of the drug on chow intake. Finally, we asked whether amBNST OTRs contribute to stress-induced hypophagia. Mice (n=9; M=6; F=3) were given intra-amBNST vehicle or 5 μg L-368,899 before a 30-min restraint stress, which ended 10 min before dark onset. Under these conditions, blockade of OTRs significantly increased chow intake by 107% relative to vehicle at 1 hour (p<0.05), and significant elevation persisted to 20 hours (12% above vehicle, p<0.05). Histological validation of cannula placements is ongoing. Together, these data suggest that OTRs in the amBNST may not contribute to feeding under non-stressed baseline conditions, but endogenous stimulation of these receptors does play a role in restraint stress-induced hypophagia.

The thalamus receives pre- and postsynaptic external sensory signals that guide food seeking behavior. Based on past work identifying the importance of calcitonin gene-related peptide (CGRP) for negative valence signaling, we hypothesized a role for thalamic CGRP neurons in linking aversive tastants to predictive external cues. To test this, we implemented an assay where water-restricted mice received auditory cues that signaled the availability of either a sweet or bitter tastant in a BioDAQ continuous food intake monitoring system. Intrathalamic injections of vehicle or 0.03, 0.1, or 0.3 μg OT were delivered an average of 30 min before dark onset, then intake was measured for 20 hours (n=15; M=7, F=8). None of these doses of OT significantly affected food intake. Next, we delivered vehicle or 1 or 5 μg of the OTR antagonist L-368,899 an average of 30 min before dark onset (n=12; M=8, F=5). Again, there was no effect of the drug on chow intake. Finally, we asked whether amBNST OTRs contribute to stress-induced hypophagia. Mice (n=9; M=6; F=3) were given intra-amBNST vehicle or 5 μg L-368,899 before a 30-min restraint stress, which ended 10 min before dark onset. Under these conditions, blockade of OTRs significantly increased chow intake by 107% relative to vehicle at 1 hour (p<0.05), and significant elevation persisted to 20 hours (12% above vehicle, p<0.05). Histological validation of cannula placements is ongoing. Together, these data suggest that OTRs in the amBNST may not contribute to feeding under non-stressed baseline conditions, but endogenous stimulation of these receptors does play a role in restraint stress-induced hypophagia.

Sex differences in binge-type eating and expression of pituitary adenylate cyclase-activating polypeptide in the paraventricular nucleus of the thalamus of binge eating mice

Genevieve Curtis, Brody Carpenter, Breanne Pirino, Jessica Barson
Drexel University College of Medicine, Philadelphia, PA, United States

Binge eating disorder, characterized by the overconsumption of food in a discrete period, is the most common eating disorder in the United States and affects women more than men. Although both are associated with feeding behavior, the roles in binge eating of the limbic paraventricular nucleus of the thalamus (PVT) and the neuropeptide, pituitary adenylate cyclase-activating polypeptide (PACAP), remain unknown. To examine sex differences in binge-type eating, we gave 4-day (females: n = 17; males: n = 13) and 7-day binge mice (females: n = 8; males: n = 5) limited access to Milk Chocolate Ensure Plus® for 2 hours/day, 4 or 7 days/week, for 6 weeks. Control mice (females: n = 12; males: n = 8) were given access to chow and water only. Female 4- and 7-day bingers engaged in greater binge-type eating of Ensure than males (0.20 vs. 0.16 kCal/g BW, p < 0.001; 0.25 vs. 0.18 kCal/g BW, p < 0.001) while controls showed no sex difference. Female bingers, as compared to male bingers, also consumed more of their total kCal as sucrose (13% vs. 12%, p < 0.05). We then used quantitative real-time PCR to examine PACAP mRNA in the PVT of control and 4-day mice (n = 6-8/sex/group). Female controls had higher levels of PACAP than control males (+79%, p < 0.05) and female 4-day bingers (+56%, p = 0.059), sacrificed immediately prior to the binge session. In contrast, control males had lower levels of PACAP than males, sacrificed on a day without Ensure access (+83%, p < 0.05). Thus, PACAP appears to decrease immediately prior to a binge in females, whereas it increases on non-binge days in males. Together, our results suggest that females engage in greater binge-type eating than males and that PACAP may contribute to these sex-related differences in binge eating behavior.

Chronic states of thirst decrease reward sensitivity as assayed by intracranial self-stimulation

Rachel M Donka, Ted M Hsu, Mitchell F Roitman, Jamie D Roitman
University of Illinois Chicago, Chicago, IL, United States

Physiological need states such as thirst invigorate goal-directed behaviors to restore homeostatic balance. Neural circuits that command motivated behaviors are engaged by the positively reinforcing properties of needed fluid or by the alleviation of negative affect associated with need (i.e. negative reinforcement). Previous work from our lab demonstrated that thirst elevates locomotor depression and suppresses lever-pressing behavior in the PAG (the primary emetic center). Here, we sought to determine whether activation of peripheral OTRs could provide an alternate strategy to achieve appetite suppression without the CNS OTR-mediated undesired side-effects: emesis, taste aversion, and locomotor depression.
Corticostriatal Dynamics Underlying Loss-Of-Control-Relevant Behaviors In Mice With Binge-Like Eating
Britny A. Hildebrandt1, Hayley Fisher1, Michael E. Young1, Zoe LaPalombara2, Susanne E. Ahmari1
1University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, 2Kansas State University, Manhattan, KS, United States

Binge eating (BE) is a maladaptive feeding behavior present across nearly all eating disorder diagnoses. Loss of control (LOC) over eating (i.e., being unable to control the quantity of food consumed) is a core feature of BE and predictor of weight gain and obesity. However, there have been no investigations of in vivo neural activity underlying LOC-relevant behavior during BE. The aim of this study was to longitudinally examine in vivo neural activity associated with LOC-relevant behavior within the dorsolateral striatum (DLS), a key region involved in behavior cessation, in a robust pre-clinical model for BE. Female C57BL/6 mice (N=32) were randomized to receive: intermittent (daily, 2-hour) binge-like access to palatable food (BE mice), or continuous, non-intermittent (24-hour) access to palatable food (control mice). In vivo calcium imaging was performed via fiber photometry at baseline and after 4 weeks of engagement in the model. LOC-relevant behaviors (feeding bout onset/offset) were captured using contact lickometers that generated TTL outputs for precise alignment of behavior to neural data. Multilevel spine regressions were used to examine neural activity 3 seconds prior to and after feeding onset/offset. While there were no differences between groups at baseline, after 4 weeks, BE animals had reduced activity -2.5 to -1.0 seconds prior to feeding onset ($z=-4.46$ to $-2.72, p<.01$), and a trend toward reduced activity at -0.5 and 0 seconds prior to feeding offset ($z=-1.76$ to 1.80, $p<.09$) versus controls. Results suggest that reduced recruitment of DLS, particularly during feeding onset, is specific to animals with a history of binge-like eating, highlighting a neural mechanism in the DLS as a potential target for future BE treatment intervention.

Conditioned Taste Aversion-Induced Suppression Of Phasic Dopamine Activity And Its Extinction Scales With Conditioning Trials
Samantha J Hurh, Mitch F Roitman
University of Illinois at Chicago, Chicago, IL, United States

Pairing visceral malaise with sweet taste leads to the development of a long-lasting conditioned taste aversion (CTA). Dopamine signaling increases in response to sucrose but, as we've shown previously, is suppressed after a single pairing of sucrose and lithium chloride (LiCl; i.p.). We asked whether this plasticity scales with conditioning and extinction trials. In vivo fiber photometry was used to measure the response of ventral tegmental area (VTA) dopamine neurons to intra-oral (IO) infusions of sucrose (0.3M). In naïve rats, infusions evoked an increase in dopamine activity. Immediately after, rats were randomly assigned to injection conditions: 20ml/kg 0.15M LiCl (Paired) or equal volume 0.15M NaCl (Unpaired). The day after, rats received the opposite injection in the homecage which was then followed by a day of no treatment. One cohort of rats received two additional cycles of treatment (3Cond) before, while the other moved on (1Cond) to the next phase of the experiment. In subsequent daily recording sessions (Extinction), rats received IO infusions followed by a homecage sucrose preference test. Dopamine responses in Unpaired rats were unchanged across all days. On Extinction Day 1, in both 1 and 3Cond Paired rats, the dopamine response was significantly suppressed and to a similar degree relative to the when rats were naïve. However, across extinction sessions, the dopamine response quickly recovered in 1 relative to 3Cond rats which correlated well with home cage preference. Paired with malaise, VTA dopamine coding of sucrose radically changes. The underlying plasticity associated with this change strengthens as a function of conditioning trials. Future studies aim to explore interventions that can modulate the dopamine and behavior extinction rates in CTA.

Does The Rate Hypothesis Of Addiction Hold For Food?
Amber Kelly1,2, Mary Oster1, Mary Elizabeth Baugh1, Monica Ahrens3, Alexandra L. Hanlon3, Alexandra G. DiFeliceantonio1,4
1Center for Health Behaviors Research, Roanoke, VA, United States, 2Translational Biology, Medicine, and Health Graduate Program, Roanoke, VA, United States, 3Center for Biostatistics and Health Data Science, Roanoke, VA, United States, 4Department of Human Nutrition, Foods, and Exercise, Roanoke, VA, United States

The speed at which a drug reaches the brain affects its abuse potential; this is known as the “rate hypothesis.” However, much less is known as to whether the rate hypothesis can be applied to food, especially in humans. Many ultra-processed foods deliver calories rapidly and are highly rewarding. Here, we test the rate hypothesis for food, specifically whether nutrient availability, or the speed at which carbohydrate becomes available for use, contributes to food reward. In this five-week study, metabolically healthy participants, aged 18-45 years, were exposed to 3 beverages, 6 times each. Each beverage contains a novel flavor and either no calories (CS-), calories in the form of slow metabolizing carbohydrate (CS+Slow), or in the form of fast-metabolizing carbohydrate (CS+Fast). Each beverage is consumed 6 times with 2 in-lab conditioning sessions. In one session, blood is drawn in order to measure blood glucose over the course of one hour post-consumption. In another, we perform indirect calorimetry with a metabolic cart to assess post-consumption changes in metabolism and substrate oxidation rates pre and post-consumption. At the post-testing session, changes in self-reported liking, wanting, and ad libitum intake of each beverage are recorded. Brain response to each flavor cue (without calories) is measured using fMRI at the post-test. We hypothesize the flavor paired with the CS+Fast will be the most liked, wanted, and consumed. We expect greater BOLD activation to the CS+Fast relative to the CS+Slow and CS- in the nucleus accumbens and
Widespread Increases In White And Grey Matter Densities 24 Months After Bariatric Surgery

Marianne Legault1,2, MAfÂ®lissa Pelletier1, Sylvain Iceta1, Yashar Zeighami3, Laurent Biertho3, Stephanie Fulton4, AndrAfÂ© Tchernev5, Alain Daghei6, Denis Richard1, Mahsa Dadar3, AndrAfÂ©anne Michaud1,2

1Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de QuAfÂ®bec (IUCPQ), QuAfÂ®bec, QC, Canada, 2Centre NUTRISS, UniversitÃ© Laval, QuAfÂ®bec, QC, Canada, 3Douglas Research Center, UniversitÃ© McGill, MontrÃ©al, QC, Canada, 4DÃ©partement de chirurgie, IUCPQ, QuAfÂ®bec, QC, Canada, 5CRCHUM and Montreal Diabetes Research Center, UniversitÃ© de MontrÃ©al, MontrÃ©al, QC, Canada, 6Montreal Neurological Institute, UniversitÃ© McGill, MontrÃ©al, QC, Canada

Our recent study reported that bariatric surgery-induced weight loss is associated with widespread increases in white (WM) and grey matter (GM) densities. These post-operative changes overlapped with brain alterations observed in participants with obesity, possibly suggesting a recovery of WM and GM alterations post-surgery. It remains unclear if these changes persist over time. **Aim:** To characterize WM and GM changes occurring 24 months post-bariatric surgery and their associations with metabolic variables. **Methods:** 84 participants (age: 49.8±5.5 years; BMI: 44.0±4.1 kg/m²) scheduled to undergo bariatric surgery were recruited. MRI T1-weighted images were acquired before and 4-, 12- and 24-months post-surgery. GM and WM densities were quantified using voxel-based morphometry. A linear mixed-effect model was used to compare whole-brain structural changes before and after surgery, controlling for age, sex, initial BMI, diabetic status, and surgery type. **Results:** A widespread increase in WM density was observed 24 months after surgery compared to baseline mainly in the cerebellum, brain stem, and corpus callosum and significant increases were found in GM density mainly in the occipital and temporal cortex (p<0.05 after FDR correction). The increase in WM density in some regions was significantly associated with weight loss and improvement of metabolic variables (HOMA-IR, blood pressure as well as circulating levels of insulin and triglycerides, p<0.05). **Conclusion:** Our results show widespread increases in WM and GM densities up to 24 months after surgery. These increases are related to weight loss and improved metabolic profile. Our next step is to examine pre-operative abdominal adipocyte size as a potential predictor of GM and WM density changes after bariatric surgery.

Astrocytes Bidirectionally Regulate Pvn Neuronal Activity And Systemic Glucose Metabolism Via Modulation Of Glutamate Transporter Activity

Daniela H. Moro Chao2, Matthew K. Kirchner1, Cuong Pham3, Ewout Poppen2, Raphael G.P. Denis2, Juan Castel2, Chloe Morel2, Enrica Montalban5, Cristina Garcia-Caceres5, Matthias H Tschop2, Dongdong Li2, Claire Martin5, Javier E. Stern1, Serge H. Luquet2

1Georgia State University, Atlanta, GA, United States, 2Universite de Paris, Paris, France, 3Department of Neurology, Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig, Germany, 4Helmholtz Diabetes Center (HDC), Munich, Germany

Astrocytes play a key role in information processing within the hypothalamus. Still, their roles in systemic metabolic control and the precise underlying mechanisms remain largely unexplored. Using astrocyte-targeted chemogenetic manipulations in the hypothalamic paraventricular nucleus (PVN), we show that chemogenetic activation of PVN astrocytes in lean mice decreased glucose clearance and increased plasma insulin (p<0.05), supporting an impaired peripheral glucose metabolism. These effects were exacerbated in diet-induced obese (DIO) mice. Conversely, chemogenetic inhibition of PVN astrocytes promoted a beneficial effect in DIO mice by reducing glucose clearance (p<0.05) and insulin levels. To address the mechanisms by which PVN astrocytes influence systemic glucose metabolism, we obtained simultaneous ex-vivo patch-clamp recordings from presympathetic PVN neurons and confocal imaging of astrocyte Ca²⁺ signals. Chemogenetic stimulation of PVN astrocytes increased their Ca²⁺ activity (p<0.0001) and evoked a delayed (~100 s) increase in PVN neuronal firing (p<0.01). Opposite effects were evoked by chemogenetic inhibition of PVN astrocytes. Importantly, blockade of glutamate receptors (1 mM KYN) or excitatory aminoacid transporter (EAAT) activity (1µM TBOA) prevented astrocyte-evoked changes in PVN neuronal activity. In DIO mice, we found an enhanced basal astrocyte Ca²⁺ activity (p<0.05) and a blunted neuronal response to astrocyte chemogenetic stimulation. TBOA per se increased firing of PVN neurons in lean (p<0.05) but not in DIO mice were observed. Together, these results indicate that PVN astrocytes exert a bidirectional control on presympathetic neuronal activity via regulation of EAAT activity and activation of extrasynaptic glutamate receptors. Finally, our results support exacerbated astrocyte Ca²⁺ levels and blunted EAAT activity as potential mechanisms contributing to altered glucose metabolism in DIO mice.

The Association Of Self-Reported Intake Of Fat And Sugar With Mrna Expression Of Dopaminergic Genes In The Blood

Franziska Rausch1,2,3, Hendrik Hartmann2,3,4, Lieneke K Janssen5,5, Dorit John6, Peter Kovacs6, Annette Horstmann1,2,3,4

1IFB AdipositasDiseases, University of Leipzig, Leipzig, Germany, 2Collaborative Research Centre 1052, University of Leipzig, Leipzig, Germany, 3Department of Psychology, Otto-von-Guericke University Magdeburg, Magdeburg, Germany, 4Medical Department III - Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig, Germany

The western food environment is dominated by foods high in saturated fat and added sugar. Animal studies provide evidence that diets high in fat and sugar (HFS) can modulate dopamine signal transmission by regulating mRNA expression of dopaminergic genes and ultimately affect cognition and choice behavior. The possible association between HFS diet and the dopaminergic system has not been studied in humans. We aimed to find evidence that increased self-reported HFS intake is associated with mRNA expression of dopaminergic genes and cognition in humans. We grouped 69 male participants according to their self-reported dietary intake of unsaturated fat and added sugar into low- (LFS) and high-consumers (HFS). As surrogate for central gene expression, we used mRNA expression of dopaminergic genes in blood leukocytes. Using qPCR, we quantified expression levels of 8 genes that are part of the dopaminergic system (COMT, DAT, DRD2, DRD3, DBH, DRD1, DRD3, GAD1). Among the dopaminergic genes, our qPCR revealed a significant association of self-reported intake of fat and sugar with mRNA expression of dopamine transporter (DAT) and dopamine receptor 2 (DRD2) in the LFS group. These findings suggest that diets high in fat and sugar (HFS) can modulate dopamine signal transmission by regulating mRNA expression of dopaminergic genes and ultimately affect cognition and choice behavior.
Psychological Stress In Dam’S And Rodent Offspring Anxiety-Like Behavior.

Heidi Rivera1, Benjamin Chase1, Justyna Cage1, Jacqueline Gerstenberger1, Chris Collins1
1Hartwick College, Oneonta, NY, United States, 2Hartwick College, Oneonta, NY, United States, 3Hartwick College, Oneonta, NY, United States, 4Hartwick College, Oneonta, NY, United States, 5Hartwick College, Oneonta, NY, United States

Clinical research in humans has identified maternal stress as a risk factor for mental-health diseases in offspring. Animal models of this phenomenon exist, but prior studies have focused on behavioral outcomes at single age timepoint in offspring. While data exists on maternal stress in adult offspring, there is a lack of information across. The goal of the present study was to begin to examine the role of maternal stress on anxiety-like behavior across all three developmental stages (e.g. infancy, adolescence, andadulthood). Rat dams were assigned to the maternal stress group (n = 4, dams underwent variable psychological stress during the last 7 days of gestation) or the maternal control group (n = 5, dams underwent no stress). Anxiety-like behavior was determined in offspring with the elevated-plus maze. One female and one male offspring were used to prevent cohort effects. Group differences in offspring elevated-plus maze behavior were calculated with a mixed-design two-way analysis of variance (ANOVA.) One factor was maternal stress, which is a between-subjects design. A second factor was developmental timepoint across life, which is a within-subjects design. When looking at offspring anxiety-like behavior in the elevated-plus maze (as measured via the number of entries made into the open arms), there was a main effect of developmental period as a factor alone on anxiety-like behavior, F(2,46)=19.58, p<0.0001. There was no main effect of maternal stress as a factor alone, F(1,48)=0.75, p=0.39. However, there was a trend for an interaction between these two factors F(2, 48)=2.50, p=0.09. Bonferroni posthoc tests showed that the infant offspring from stressed dams revealed a significantly lower number of entries made into the open arms relative to juvenile (p=0.0007) and adult (p=0.03) offspring. Infant offspring from control dams did not reveal statistically significant changes in the number of entries made into the open arms across all stages of development. That includes during the juvenile and the adult phases (P=0.09 to 0.82). Together, these findings suggest that maternal stress impacts offspring anxiety-like behavior differently across their lifespan. Maternal stress enhanced offspring anxiety-like behavior during infancy but not during adolescence or adulthood.

Differentiating Subgroups In Overweight And Obese Children Using Data-Driven Clustering Approach With Brain Imaging Data

Mari Shishikura1, Filip Morys1, Eric Yu1,2, Alain Dagher1
1Montreal Neurological Institute, McGill University, Montreal, QC, Canada, 2Department of Human Genetics, McGill University, Montreal, QC, Canada

Obesity is the result of both genetic and environmental factors, and studies have shown its association with altered brain structure and cognitive function. Despite such complexity, the state of being overweight or obese is usually determined simply by body mass index (BMI), and this may be insufficient in capturing the details of obesity phenotypes. As variation in genetics and environmental exposures affect the brain heterogeneously, distinct patterns of brain features may be found within individuals with excess weight. In this study, we sought to identify subgroups among higher-BMI children based on anatomical brain features. In addition, we investigated if these subgroups differed in terms of socioeconomic status, genetics, and personality. We used a sample of 8,092 children from the Adolescent Brain Cognitive Development study (mean age=9.93 years, mean BMI=18.66 kg/m²), of which 2,963 were categorized as overweight or obese. By using data-driven clustering algorithms, we found that the overweight and obese cohort could be subdivided into two or three clusters based on anatomical measurements of gray matter, white matter, and subcortical structures. These clusters displayed differences in socioeconomic status, namely parental income and education, but not in genetic risk for obesity or in personality measures of impulsivity. Meanwhile, when the clustering algorithms were applied to the whole cohort, the clusters differed in parental income, BMI, and age, but not in parental education. In sum, our finding highlights the potential of using clustering methods to group overweight or obese individuals into more homogeneous cohorts and underscores socioeconomic status as a key element in distinguishing subgroups.

Central Insulin Action Associates With Age And Peripheral Insulin Sensitivity

Lore Wagner1,2, Christian Kuebler3, Ralf Veit1,2, Andreas Fritzsche1,2,4, Andreas L. Birkenfeld1,2,3, Hubert Preissl1,2,3, Martin Hen1,2,3,5, Stephanie Kullmann1,2,3
1Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tuebingen, Tuebingen, Germany, 2German Center for Diabetes Research (DZD e.V.), Tuebingen, Germany, 3Department of Internal Medicine, Division of Endocrinology, Diabetesology and Nephrology, Eberhard Karls University Tuebingen, Tuebingen, Germany, 4Nutritional and Preventive Medicine, Eberhard Karls University Tuebingen, Tuebingen, Germany, 5Institute for Clinical Chemistry and Pathobiometry, University Hospital Tuebingen, Germany, Tuebingen, Germany

Insulin action in the brain influences cognitive processes, peripheral metabolism and eating behavior. However, the influence of age and peripheral insulin sensitivity on central insulin action remains unclear. Here we used intranasal administration of insulin and functional MRI in a randomized, placebo-controlled within-subject design to assess central insulin action in 110 participants (54 women, BMI 18-49 kg/m², age 21-74 years). Cerebral blood flow (CBF) was measured before and after nasal spray application on both measurement days. A correlational approach was used to investigate associations between age or peripheral insulin sensitivity and central insulin action. Insulin action in the hippocampus correlated negatively with age (r=-0.266, p=0.005). Younger participants revealed higher central insulin action. This correlation was mostly driven by the female participants (women: r=-0.364, p=0.007; men: r=-0.161, p=0.237). Furthermore, insulin action in the insular cortex showed an interaction effect between age and peripheral insulin sensitivity. Only younger participants with high peripheral
Insulin sensitivity showed a pronounced response to central insulin. We could show a region-specific relationship between age, peripheral sensitivity and central insulin action. Especially young participants showed a positive association between peripheral insulin sensitivity and insulin action in the insula, which plays a major role in the integration of physiological and gustatory signals. The hippocampus, essential for cognitive functions, showed a decrease in insulin action with increasing age. These findings potentially link metabolic and neurocognitive functions. Future studies need to elaborate whether hippocampal insulin resistance could act as a trigger for cognitive impairments.

Impact Of Weight Loss On Brain Age: Improved Brain Health Following Bariatric Surgery

Yashar Zeighami1, Mahsa Dadar1, Justine Daoust2, Melissa Pelletier2, Laurent Biertho3, Leonie Bouvet-Bouchard3, Stephanie Fulton4, Andre Tchernof2, Alain Dagher5, Andreanne Michaud2

1The Douglas Research Centre, McGill University, Montreal, QC, Canada, 2Centre de recherche de l’Institut universitaire de cardiologie et de pneumologie de Quebec, Universite Laval, Quebec, QC, Canada, 3Departement de chirurgie generale, Institut universitaire de cardiologie et de pneumologie de Quebec, Universite Laval, Quebec, QC, Canada, 4Centre de Recherche du CHUM, Department of Nutrition, Universite de Montreal, Montreal, QC, Canada, 5Montreal Neurological Institute, Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

Individuals living with obesity tend to have increased brain age, reflecting poorer brain health stemming from grey and white matter alterations. However, it is unclear if the increase in brain age associated with obesity can be reversed following weight loss and cardiometabolic health improvement. The aim of this study was to assess the impact of weight loss and cardiometabolic improvement following bariatric surgery on brain health, as measured by change in brain age estimated by voxel-based morphometry measurements. We used two distinct datasets to perform this study: 1) CamCAN dataset to train the brain age prediction model, and 2) pre-surgery, as well as 4-, 12-, and 24-month post-surgery data from participants (n=87, age: 44.0±9.2 years, BMI: 43.9±4.2 kg/m^2) who underwent a bariatric surgery. We found significant improvement in brain health, indicated by a decrease of 2.9 and 5.6 years in adjusted delta age at 12 and 24 months following bariatric surgery compared to pre-surgery (p-value <0.0005 for both). While the overall effect seemed to be driven by a global change across all brain regions and not from a specific region, our exploratory analysis showed lower delta age in certain brain regions (mainly in somatomotor, visual, and ventral attention networks) at 24 months. This reduced age was also associated with post-surgery improvements in BMI, systolic/diastolic blood pressure, and HOMA-IR (T-value_BMI=3.59, T-value_SBP=4.26, T-value_DBP=3.67, T-value_HOMA-IR=2.81, all p-values <0.05). In conclusion, these results suggest that obesity-related brain health abnormalities (as measured by delta age) could be reversed by bariatric surgery-induced weight loss and widespread improvements in cardiometabolic alterations.
In vertebrates, energy balance is tightly controlled by complex neural circuits that sense peripheral signals and adjust food intake and energy expenditure according to physiological needs. Within neural networks controlling energy balance, tanycytes are peculiar ependymal cells recognized nowadays as multifunctional players in the metabolic hypothalamus. Indeed, their strategic position at the blood-brain interface and their heterogeneous properties give them the role of blood-brain dynamic controllers to monitor energy balance. Our recent results -associating neuroanatomy and transcriptomics-highlighted tanycytes as central nodes in this blood-hypothalamic interface. Indeed, tanycytes contact numerous partners within the parenchyma -including vessels, neurons, and glial cells- establishing diverse cell-to-cell communications. Tanycyte gene expression profiles revealed that neurons are key partners among this tanycyte network. Molecular interactions occur at both the soma and the synapse. Finally, gene expression dynamics according to the energy status revealed that these tanycyte/neuron interactions are crucial for the regulation of energy balance. In conclusion, our recent work highlights the role of tanycytes in the access of peripheral information toward neuronal populations and the necessity to understand the interplay between different neural cell types in the sensing of metabolic cues to regulate energy homeostasis.

**P2**

**Glia-Neuronal Interactions In Health And Salt-Induced Hypertension**

Masha Prager-Khoutorsky

McGill University, Dept of Physiology, Montreal, Canada

Vasopressin-secreting neurons are an integral part of the magnocellular neuroendocrine system, playing a key role in water and salt homeostasis. Circulating vasopressin promotes water retention in the kidney (antidiuresis) and peripheral vasoconstriction. High dietary salt increases the activity of vasopressin neurons, contributing to elevated blood pressure. Magnocellular vasopressin neurons are intrinsically osmosensitive and are activated by cell shrinking in response to increased extracellular sodium levels and osmolality. In addition, local glia cells play an important role in controlling the activity of magnocellular neurons. During the presentation, I will describe recent advances in the understanding of mechanisms by which astrocytes and microglia regulate the activity of vasopressin neurons in healthy organism and high dietary salt-induced hypertension.

**P3**

**The Vagus Nerve As A Gateway To Control Motivation**

Nils B Kroemer

University of Tuebingen, Tuebingen, Germany

By transmitting signals from peripheral organs to the brain, the vagus nerve plays a vital role in the control of food intake according to metabolic state. It has long been assumed that vagal afferent signals primarily provide negative feedback (“satiety”) playing a limited role in goal-directed behavior. In this talk, I will review emerging evidence on the relevance of vagal afferent signals in the prospective regulation of allostatic behavior beyond negative homeostatic feedback. First, in line with recent preclinical findings, I will demonstrate that non-invasive transcutaneous vagus nerve stimulation (tVNS) can boost motivation and mood recovery after exertion. Second, I will outline corresponding changes in reinforcement learning of monetary rewards during tVNS which indicates a broader role of vagal afferents in value-based decision-making. Third, I will review how tVNS modulates bodily signals via vago-vagal signaling and discuss how multimodal studies of stomach-brain coupling with concurrent tVNS may provide a fascinating new perspective on gut-brain communication. Such a perspective on interoception could help us better understand how food-related choices and energy metabolism are regulated in concert. Taken together, the recent progress of research on mechanisms of gut-brain communication has paved the way for innovative treatments of mental and metabolic disorders. To realize this large potential, further advances in multimodal methods are necessary to unravel crucial modes of communication between the brain and the body. Ultimately, an improved understanding of vagal afferent modulation may help resolve long-standing questions about the adaptive control of food intake in humans.

**P4**

**The Low Leptin Incentive: Modulation Of Motivated Behavior By Energy Deficit**

Stephanie Fulton

1University of Montreal, Montreal, QC, Canada, 2Center de Recherche du CHUM, Montreal, QC, Canada, 3Centre for Studies in Behavioral Neurobiology, Concordia University, Montreal, QC, Canada

In a manner corresponding to energy status, leptin exerts diverse effects on many facets of behavior. This presentation will cover evidence amassed illuminating leptin’s influence on brain reward circuits, including midbrain dopamine neurons, and on several goal-oriented behaviors vital to the preservation of energy reserves. Low leptin levels serve as a key driver of appetitive behavioral actions and can reinforce stimulus-response connections that propel anticipation for and engagement in behaviors such as feeding, running and foraging - A effects that can be reversed by leptin administration. Beyond direct observations of motivated behavior, we also show that lack of leptin signaling in these circuits gives rise to negative affective states such as anxiety. As will be discussed, this concomitant effect of low leptin on emotions can be conceived as another biological installation serving to rebuke stagnation to favor behaviors that restore energy and minimize unease. These diverse effects of leptin illustrate the potency of this hormone to serve as a multifarious signal influencing numerous aspects of behavior in a manner responsive to and consistent with an organism’s metabolic state.
Evaluating The Role Of Hindbrain Glp-1R And Npy2R Signaling In Sensory-Specific Satiety

Sarah V. Applebey1, Kyle S. Chichura2, Antonia Caffrey3, Heath D. Schmidt3,4, Robert P. Doyle2, Matthew R. Hayes3,4
1Neuroscience Graduate Group, University of Pennsylvania, Philadelphia, PA, United States, 2Syracuse University, Department of Chemistry, Syracuse, NY, United States, 3Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA, United States, 4Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Sensory-specific satiety (SSS) is the temporary decline in pleasantness and motivation for a specific food following its consumption, which contributes to meal termination. Although meal termination requires post-ingestive negative feedback, it remains controversial whether the "homeostatic" systems underlying this negative feedback are involved in mediating the suppression of food intake occurring in SSS. Here, we investigate the roles of hindbrain neuropeptide Y2-receptor (NPY2R) and glucagon-like peptide-1 receptor (GLP-1R) signaling in mediating the intake inhibitory effects of SSS. We used a rat model of SSS in which within-session exposure to the same food during a second course decreased food intake relative to different food presentation. When administered before the second course, 4th ventricle delivery of NPY2R-specific antagonist BIIE0246 suppressed second course food intake independently of within-session food novelty. However, administering the GLP-1R antagonist exendin-9-39 into the 4th ventricle prevented the intake-suppressing effects of SSS. These data confirm the necessity of hindbrain post-ingestive endogenous GLP-1R negative feedback for SSS expression. Next, to determine the specific hindbrain nuclei active in regulating SSS, we evaluated penetrance of the fluorescently tagged dual agonist of NPY2R and GLP-1R, GEPI44, in the rat nucleus tractus solitarius (NTS). Notably, GEPI44 demonstrated penetration in the rostral NTS (rNTS) and caudal NTS (cNTS). As the rNTS integrates sensory input and the cNTS synthesizes vagally transmitted GI satiation signals, one or both NTS subnuclei may be engaged during SSS, with potential intra-NTS communication. Future studies aim to disentangle the role of GLP-1R signaling in the rNTS and cNTS in mediating SSS.

Gdf15 Induces Anorexia Through Nausea, Emesis, And Aversion.

Tito Borner1,3, Evan D. Shaulson1, Misgana Y. Ghidewon2, Hallie S. Wald2, Charles C. Horn3,4,5, Robert P. Doyle6,7, Harvey J. Grill2,9, Matthew R. Hayes1,8,9, Bart C. De Jonghe1,8,9
1Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA, United States, 2School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA, United States, 3Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, 4UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, United States, 5Center for Neuroscience, University of Pittsburgh, Pittsburgh, PA, United States, 6Department of Chemistry, Syracuse University, Syracuse, NY, United States, 7Department of Medicine, Upstate Medical University, State University of New York, Syracuse, NY, United States, 8Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, 9Institute of Diabetes, Obesity and Metabolism, University of Pennsylvania, Philadelphia, PA, United States

The stress response cytokine growth differentiation factor-15 (GDF15) reduces food intake through activation of hindbrain GFRαL-RET receptors. Elevated endogenous GDF15 is associated with energy balance disturbances, cancer progression, chemotherapy-induced anorexia, and morning sickness. We hypothesized that GDF15 is an emetic stimulus and that the anorectic effects of GDF15 are directly related to its noxious effects. Hence, we examined feeding and emesis and/or emetic-like behaviors in 3 different mammalian laboratory species to help elucidate the role of GDF15 in these behaviors. Mice treated with cisplatin showed elevated levels of GDF15 which correlated with the severity of their anorectic response. Furthermore, increased expression of c-Fos occurred in GFRαL-expressing neurons following cisplatin treatment. In lean and obese rats, GDF15 induced behaviors indicative of nausea/malaise (e.g., anorexia, conditioned flavor avoidance, emesis, and pica [i.e. kaolin consumption, a validated proxy for nausea]). Taking advantage of the musk shrew (Suncus murinus), a small mammal capable of vomiting, we showed that GDF15 causes severe emesis. Importantly, an array of FDA-approved and over-the-counter anti-emetics all failed to counteract GDF15-induced malaise in rats, stressing the need to develop specific pharmacotherapies that will block the GDF15-GFRαL system. Together, these results indicate that GDF15 triggers anorexia through the induction of nausea and/or by engaging emetic neurocircuitry. These data will have significant relevance to any health/disease condition associated with elevated GDF15 levels.
Visceral feedback plays an important role in guiding motivated behaviors. For example, sensory information from the gut during a state of negative energy balance promotes food-seeking behavior and reduces innate avoidance and anxiety-like behaviors. Interoceptive signals are carried by vagal afferents that synapse onto neurons in the caudal nucleus of the solitary tract (cNTS), including pro-protein-releasing peptide (PrP-R)-expressing noradrenergic A2 neurons and glucagon-like peptide 1 (GLP1)-positive neurons that are activated by innate stressors and are implicated in behavioral responses to innate threats. The present study further demonstrates that PrRP+ A2 neurons (but not GLP1+ neurons) are activated in rats exposed to an aversively conditioned context, and that PrRP+ A2 activation and conditioned passive avoidance behavior are suppressed during a state of negative energy balance. To examine the role of these A2 neurons whose axons target the ventrolateral bed nucleus of the stria terminalis (vlBNST) in passive avoidance behavior, we used a norepinephrine-specific toxin conjugate to destroy noradrenergic neurons that project to vlBNST in rats. We discovered that lesioning noradrenergic inputs to the vlBNST increases the expression of passive avoidance, suggesting that these inputs normally are recruited to limit or put a brake on learned passive avoidance behavior. Overall, these data demonstrate that the PrRP+ A2 neurons and their projections to vlBNST play a complex modulatory role in integrating information about metabolic state with information about learned threat to guide behavioral output.

At2R Containing Neurons In The Nucleus Of The Solitary Tract As Mediators Of Energy Balance
Sophia Eikenberry1,2,3, Khalid El Saafien1,2,3, Dominique Johnson1,2,3, Karen A Scott1,2,3, Eric G Krause1,2,3, Annette D de Kloet2,3

1Pharmacodynamics, University of Florida, Gainesville, FL, United States, 2Physiology and Functional Genomics, University of Florida, Gainesville, FL, United States, 3Center for Integrative Cardiovascular and Metabolic Diseases, University of Florida, Gainesville, FL, United States

Angiotensin-II is known for its role in body fluid homeostasis via actions at its receptors (AT1R and AT2R); however, recent evidence has also implicated this peptide in energy balance. The nucleus of the solitary tract (NTS) is a key cardiometabolic regulatory area and we have previously found that AT2R-expressing neurons in the NTS, referred to as NTSAT2R+, function as inhibitory interneurons that increase blood pressure. Here, we hypothesized that NTSAT2R+ are similarly required for the regulation of food intake and energy balance. Initial studies used a Cre-dependent viral tracer and male AT2R-Cre mice to reveal that, in addition to functioning as interneurons, a subset of NTSAT2R+ project to other brain areas that mediate cardiometabolic function, such as the parabrachial nucleus. To determine whether these NTSAT2R+ are indeed necessary for energy balance, AT2R-Cre male mice received a Cre-dependent AAV to direct the expression of caspase to NTSAT2R+ thereby ablating these neurons (controls received AAV-DIO-mCherry). Metabolic measurements were acquired using a TSE PhenoMaster. Because NTSAT2R+ predominantly function as inhibitory interneurons, we anticipated that, under normal conditions, NTSAT2R+ dampen interoceptive signals arising from the gastrointestinal tract. Thus, we predicted that ablation of NTSAT2R+ would enhance sensitivity to such signals, thereby producing an anorexigenic effect. Consistent with this prediction, ablation of NTSAT2R+ dysregulated aspects of compensatory feeding behaviors, which resulted in decreased body weight and adiposity in lean conditions (p=0.011; 2-Way ANOVA). These same animals demonstrated resilience to diet-induced obesity. Collectively, these results are suggestive of a role for NTSAT2R+ in promoting positive energy balance.

Optical Assessment of GcgNTS Neurons In Freely Behaving Mice
Department of Psychiatry, University of Alabama at Birmingham, Birmingham, AL, United States

Obesity and diabetes are one of the leading causes of disease and death in developed nations, with more than a third of US adults classified as obese. The brain integrates peripheral signals and controls eating behavior using a complex symphony of interconnected neural circuits regulated by fast-acting neurotransmitters like glutamate and GABA and neuromodulators like monoamines and neuropeptides. Glucagon-like peptide 1 (GLP1) is a neuropeptide produced by intestinal cells and a small population of neurons in the nucleus of the solitary tract. GLP1 is produced from its precursor gene preproglucagon (Gcg) and GcgNTS cells represent the primary source of GLP1 in the brain. Research studies using Fos mapping have shown that these neurons are activated during food consumption and in particular during large volume binge-like food consumption. However, these studies only reveal a snapshot of the activity state of these neurons. Therefore, we incorporated contemporary optical strategies and engineered custom apparatus to record from GcgNTS in vivo in freely behaving mice during eating. Using fiber photometry and GRIN lens-based imaging with head mounted miniscopes we performed the first ever measurement of GcgNTS activity in freely eating mice. In a binge-like model of high fat diet intake we found GcgNTS neurons show gradual increases in activity over the course of minutes, but that the activity rapidly and transiently decreases during biting and chewing of food. To determine the impact of GcgNTS dynamic activity changes on eating we used in vivo optogenetics to transiently activate these cells. We found that high frequency optogenetic activation of GcgNTS cells is aversive and promotes reversible inhibition of feeding both at low and high frequencies.

From The Stomach To Locus Coeruleus: New Neural Substrate For Ghrelin\&quot;S Effects On Ingestive, Motivated And Anxiety-Like Behaviors.
Ivana Marić1,2,3, Yashaswini Rajendra Bhat3, Suyeun Byun3, Lorena Lopez-Ferreras1, Karolina P. Skibicka1,2,3

1Institute for Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden, 2Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden, 3Department of Nutritional Sciences, Pennsylvania State University, University Park, PA, United States

Ghrelin, a stomach-derived orexigenic hormone, has a well-established role in energy homeostasis, food reward, and...
Nts-Cck Neurons Are Activated By Vagal Inputs, Local Cck And Trpv1 Channels.
Eric T Winzenried, Drew M Neyens, Suzanne M Appleyard
Washington State University, Pullman, WA, United States

Vagal afferents carrying information from the GI terminate in the nucleus of the solitary tract (NTS). Cholecystokinin (CCK) is released following a meal and activates vagal afferents in the periphery. However, CCK is also expressed in NTS neurons and activation of NTS-CCK neurons decreases food intake. What is not well understood is what drives the activity of these neurons. To address this question, we recorded from identified CCK neurons (CCK-IRES-Cre crossed with Rosa-tomato mice) in the NTS in a horizontal brain slice containing vagal afferents in the solitary tract (ST). Stimulation of the ST evoked glutamatergic excitatory post-synaptic currents (EPSCs) in NTS-CCK neurons that were mediated by both AMPA receptors (Rs) and NMDARs. Analysis of EPSCs revealed ~90% of NTS-CCK neurons receive monosynaptic inputs, with many also receiving polysynaptic inputs, suggesting that they can integrate different vagal signals. During high frequency vagal stimulation, as would occur following a meal, AMPAR currents decayed rapidly, while NMDAR currents were sustained; consistent with the key role NMDARs play to decrease food intake following a meal. NTS-CCK neurons were also activated by the TRPV1 agonist capsaicin, indicating they are downstream of C-fibers. Consistent with C-fiber activation they receive asynchronous vagal glutamate inputs that are thought to prolong vagal activation. Lastly, local application of CCK increased both EPSC frequency and firing rate of NTS-CCK neurons. These findings suggest NTS-CCK neurons are strongly driven by CCK-sensitive C-fiber vagal afferents through activation of AMPARs and NMDARs, with NMDARs sustaining activation during high frequency vagal firing. Importantly, local CCK can also increase the firing rate of NTS-CCK neurons.

Hindbrain Control Of Cue-Induced Feeding Behaviors
Jo Ann Yap, Gavan P McNally, Zhi Yi Ong
University of New South Wales, UNSW Sydney, Australia

Nucleus of the solitary tract (NTS) neurons are well-characterized for their role in food intake control. More recent studies show that in addition to the control of food intake driven by internal physiological signals, NTS neurons also regulate environmental cue-driven feeding behaviors. However, the contributing neural phenotypes and underlying mechanisms are unclear. Here, we examined the hypothesis that NTS A2 neurons suppress cue-induced appetitive behaviors by modulating midbrain dopamine neuron activity. TH Cre rats (n=10) were used to target NTS A2 neurons and ventral tegmental area (VTA) dopamine neurons. We used chemogenetics to activate NTS A2 neurons and fibre photometry to record VTA dopamine neuron activity. To measure cue-induced appetitive behaviors, we used the Pavlovian appetitive conditioning paradigm where rats were trained to associate an auditory cue with the delivery of a sucrose pellet (CS+) and another auditory cue without (CS-). Appetitive behaviors were measured by quantifying the number of magazine entries before and during presentation of the CSs. Results showed that activation of NTS A2 neurons significantly increased latency to respond during CS+, suppressed CS+ magazine entries and reduced pellet consumption. When VTA dopamine neuron activity was measured, we showed that activation of NTS A2 neurons attenuated VTA dopamine neuron activity during CS+ presentation, without any effect on CS-, pellet delivery or magazine entries. Together, these findings show that NTS A2 neurons suppress cue-induced feeding behaviors in part by reducing food cue-evoked VTA dopamine neuron activity, thus providing a putative mechanism through which NTS neurons regulate cue-driven feeding behaviors.
Stat3 Degradation A Fast Track To Obesity

Antonio M. Carvalho da Silva¹, Colleen Hadley¹, Pauline Lining Pan¹, Haibin Zhou², Shaomeng Wang², Roger Cone¹, IA...ÅY,Åą Äf>akÄ,Äzr¹
¹Life Sciences Institute, University of Michigan, Ann Arbor, MI, United States, ²Rogel Cancer Center, University of Michigan, Ann Arbor, MI, United States

Regulation of body weight set point is a poorly understood phenomenon. SD-36 is a proteolysis targeting chimera that selectively induces the degradation of STAT3. Due to recognised involvement of JAK/STATs complex in the leptin signalling process we decided to study the effects of SD36 on neuroendocrine regulation of ingestive behaviour and associated metabolic alterations. SD36, induced hyperphagia and led to a 20% weight gain in lean wild-type (wt, males and females, n=6-8) mice administered intraperitoneal (10-50mg/kg) or intracerebroventricular (10 Âµg/mouse) routes. Animals returned to their baseline body weights upon cessation of treatment only if they remained on regular chow such that HFD completely overrode the anorectic effect of SD36 withdrawal. In diet-induced obese wt mice, SD36 also stimulated food intake and weight gain when administered centrally. SD36-induced weight gain was accompanied by a 30t increase in the fat mass and plasma leptin levels of lean wt mice. The metabolicÂ analysis showed that SD36 did not alter the energy expenditure of the animals, however led to a increase (0.7 to 0.9) in RER during the light phase. Notably, SD36 did not alter the blood glucose levels. We next tested whether the effect of SD36-induced hyperphagia was predominately though the ablation of leptin signaling. SD36 treated lean wt mice lost their response to exogenous leptin treatment (n=8, 2% change). Notably, in leptin deficientÂ ob/obÂ mice was not able to induce weight gain or stimulate food intake, but block leptin’s ability to suppress weight gain. Our results collectively suggest that SD36 is a potent orexigenic agent that acts predominantly by abating leptin receptor signaling; SD36 could be a potential tool to address eating disorders, anorexia or cancer cachexia.

Neural Correlates Of Body Weight-Associated Deficits In Performance On The Benton Judgement Of Line Orientation Task (Jlot)

Xue S Davis¹,², H Alex Chen¹,², Dana M Small¹,²
¹The Modern Diet & Physiology Research Center, New Haven, CT, United States, ²Yale University, New Haven, CT, United States

Obesity is associated with impairment in cognitive functions such as learning and memory, executive function and reward processing. Recent evidence also points to the existence of deficits in visuospatial perception, with three independent investigations have reported a negative association between BMI and performance on a line orientation perception task (Hovens et al. 2019, Vainik et al. 2018, Chen et al. submitted). In the current study we used functional magnetic resonance imaging (fMRI) to determine if there is an association between body mass index (BMI) and response in visual cortex during the performance of a line orientation task. Twenty-seven healthy participants with a range of BMIs (15 male; age (M, SD) = 27.5 ±6.2 years; BMI = 25.2 ±5.6 kg/m², range = 18.5-41.4) were scanned while performing a validated fMRI-adapted version of the JLOT. As predicted, we observed a negative behavioral association between BMI and performance on the JLOT. Also as predicted, we identified a whole-brain corrected negative correlation between BMI and response in the primary visual cortex (V1) during JLOT performance. These findings suggest that alterations in neural coding in V1 accounts for the functional deficits in the judgement of line orientation observed in overweight/obesity. The findings also align with recent preclinical data showing altered coding in V1 orientation columns in metabolically compromised rodents that can be reversed by leptin administration (Padamsey et al., 2021). We conclude that obesity in humans is associated with deficits in visuoperceptual functions mediated by V1.

Adults With Healthy Weight Use More Efficient Learning Strategies For Memory Recall Than Adults With Overweight

Dawn M. Eichen¹, Dong-Jin E. Kang-Sim¹, Sara L. Appleton-Knapp², David R. Strong¹, Kerri N. Boutelle¹
¹UC San Diego, La Jolla, CA, United States, ²University of San Diego, San Diego, CA, United States

Although poorer cognitive function characterizes adults with overweight (OW) relative to those with healthy weight (HW), evidence for poorer memory function has been mixed. To understand the salience of food-related items when assessing memory, we adapted an episodic memory task, the California Verbal Learning Test-II, by replacing some non-food words with snack foods. After an initial learning phase with repeated presentations and recall after each of 5 trials, a distractor list is read and followed by short- and long-delayed (20-minute) recall. Participants were 96 weight-loss seeking adults with OW category at long delay (p=0.02) during the learning phase. Adults with HW showed better semantic clustering for both food and non-food words during learning (p=0.02) and short delay recall (p=0.02) but semantic clustering was only better for the non-food category at long delay (p<0.01). These results show that adults with OW utilized less efficient learning strategies throughout the task and food-related content may impact learning. Clinically, these findings may suggest that weight-loss treatments should consider incorporating the teaching of learning strategies to help increase utilization of new skills.

Does Intermittent Fasting Generate A Long-Term Change In Appetite?

Rebecca L. Elsworth¹, Rachel Perry², Angelica Monge¹, Annika N. Flynn¹, Elanor C. Hinton¹, Alex Whitmarsh², Jeffrey M. Brunstrom¹
¹Nutrition and Behaviour Unit, School of Psychological Science, University of Bristol, Bristol, United Kingdom, ²National Institute for Health Research School of Mental Health Biomedical Research Centre, University of Sheffield, Sheffield, United Kingdom
Eating at regular mealtimes (e.g. breakfast, lunch, dinner) is thought to generate a ‘meal pattern’ and an increase in appetite that precedes each meal. Intermittent fasting (IF) provides the opportunity to explore the extent to which appetite can be modified in this way. Previous systematic reviews have narratively considered the effects of IF on appetite. Here, we conduct the first systematic review and meta-analysis (MA) to quantitatively assess the effects of an IF intervention on appetite, when compared to a continuous energy restriction (CER) intervention. Five electronic databases, alongside trial registers, were searched up to February 2021. Abstracts (N=2238) were screened and 14 randomised-controlled trials (RCTs), consisting of a variety of IF regimes, met our inclusion criteria (updated 2022 search ongoing). All RCTs were judged as having either some concerns or high risk of bias (Cochrane RoB 2.0). Only RCTs that measured appetite using a visual-analogue scale were included in the MA. Random effects MA were conducted on post-intervention appetite ratings. There was some evidence that IF increased fullness compared to CER (weighted mean difference [WMD]=1.89; 95% CI [0.00, 3.79]; p=0.05; N=8). There was no clear evidence that IF affected hunger (WMD=1.15; 95% CI [-1.08, 3.38]; p=0.31; N=10), desire to eat (WMD=0.53; 95% CI [-11.23, 12.28]; p=0.93; N=4) or ‘prospective food consumption’ (WMD=2.58; 95% CI [-3.87, 9.03]; p=0.43; N=5), when compared with CER. These preliminary findings indicate that fullness may be modifiable with IF, which may help to explain the success of this diet. Further, our evidence suggests that the effects of IF last beyond the period of fasting, which illustrates a role for learning in the control of appetite and meal patterning.

Chemogenetic Activation Of A2a/Drd2 Medium Spiny Neurons In The Nucleus Accumbens Core Delays Feeding Onset And Decreases Locomotor Activity
Astrid A. S. van Isen, Rick Wenning, Margo Slomp, Tess Kool, Andries Kalsbeek, Anayanci Masis-Vargas, Susanne la Fleur
1Amsterdam University Medical Center, University of Amsterdam, Laboratory of Endocrinology & Dept. Endocrinology and Metabolism, Amsterdam Neuroscience, Amsterdam Gastroenterology, Endocrinology and Metabolism., Amsterdam, Netherlands, 2Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, Netherlands

The nucleus accumbens (NAc) is well known for its involvement in locomotion, motivation, and reinforcement-driven learning. Most accumbal neurons (i.e. 90-95%) are medium spiny neurons (MSNs) that either express dopamine D1 receptors (Drd1) or a combination of dopamine D2 (Drd2) and adenosine Adora2a (A2a) receptors. Previous research has shown that infusing a selective D2 agonist in NAc core (NAcc) or activating NAcc-Drd2 MSNs using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), decreased locomotor activity without having effects on 24-h food intake. In this study, we used a transgenic rat line expressing improved Cre (iCre)-recombinase in A2a-expressing neurons. By using iCre dependent DREADDs, we selectively activated A2a/Drd2 MSNs in the NAcc by injecting Clozapine N-Oxide (CNO; 2 mg/kg; i.p.). Animals were 8h-fasted during the end of the light-phase, received CNO or saline (cross-over design) 1h after onset of the dark period, and regained access to chow-food 30 min after injection (t=0). Food intake and locomotor activity were recorded in 15 min intervals for 24 hours. Activation of NAcc A2a/Drd2 MSNs led to a 30 min delay in feeding onset (between t=45-75m: p<0.002, n=9), and was followed by a decrease in locomotor activity (between t=90-240m: p<0.05, n=9). CNO injection without DREADDD expression did not affect feeding or locomotion. Using anterograde opening viral tracing, we found that these NAcc A2a/Drd2 MSNs mainly project to the dorsolateral ventral pallidum (dVP), Taken together, our detailed analysis points to a role for the NAcc-dVP connection in feeding initiation and locomotor activity. Additional research will need to assess if inhibition of this pathway leads to inverted results and will determine the input of these MSNs.

Neuromolecular Underpinnings Of Human Obesity
Filib Morys, Justine Hansen, Christina Tremblay, Bratislav Mistic, Alain Dagher
Montreal Neurological Institute, Montreal, QC, Canada

Excess weight and increased body mass index (BMI) – an indicator of obesity – are related to changes in brain structure and function. Animal studies implicate several neurochemical systems in obesity, as well as some specific genes and cell populations in the brain. To date, however, those mechanisms have been largely unexplored in humans. Here, we aimed to close this knowledge gap using multiple datasets with information on brain structure, neurochemistry, and brain tissue gene expression. Using the Human Connectome Project dataset and T1-weighted magnetic resonance images we created cortical neurochemical/neurogenetic maps while accounting for spatial autocorrelations (‘spin tests’ with 1000 permutations). We used Pearson correlation to assess spatial correspondence between BMI brain maps and brain measures. Neurochemical maps for 8 different neurotransmitter systems were obtained and curated by Hansen et al. (2022, bioRxiv). Brain tissue gene expression maps for over 15,000 genes were obtained from the Allen Human Brain Atlas. We used Pearson correlation to assess spatial correspondence between BMI brain maps and neurochemical/neurogenetic maps while accounting for spatial autocorrelations (‘spin tests’ with 1000 permutations). We found that BMI-related CT and DBM changes were correlated with availability of the dopamine transporter, serotonin transporter, cannabinoid receptor 1, and expression patterns of 5 genes associated with serotonin transporter and major depression, amongst others. BMI-related brain changes were not related to any cell-type specific gene expression patterns. Our results could support the use of therapeutic interventions for obesity that target dopaminergic, serotonergic and cannabinoid systems.

Energy Intake Compensation: If I Eat Less Now Will I Eat More Later Today Or Tomorrow? Results From Two Systematic Reviews And Meta-Analyses
Eric Robinson, Andrew Jones
University of Liverpool, Liverpool, United Kingdom

Most studies of eating behaviour examine energy intake during a single ‘acute’ meal. Many experimental manipulations like amount of food served (e.g. portion size) affect acute energy intake, but how strongly do these acute changes in energy intake translate to changes in total daily energy intake over several days? We conducted two new systematic reviews and meta-analyses that quantify the impact of experimental manipulations of served food portion size (n=14 studies) and food energy density (n=31 studies) on dietary compensation and daily energy intake. Most studies examined energy intake for between 1-14 days. Using meta-regression we find that reductions to portion size (k=85, d = 0.71) and energy density (k=90, d = 1.0) decrease daily energy intake and that effects on daily energy intake do not change over time (p>0.25), such that the effect portion size/energy density has on day 1 of a study is similar to that at day 7. We also find that when energy intake at an acute meal is reduced, later in the day participants partially ‘compensate’ for this reduction by consuming more...
energy. If acute meal energy intake is reduced by 100 kcal and this is caused by a decrease in volume of food eaten (i.e. manipulation to portion size), later energy intake during that day is increased by ~42 kcal, whereas this figure is much smaller for reductions caused by changes in food energy density (~11 kcal). These findings suggest that extrapolating from reductions in energy observed in ‘acute’ single meal studies will result in overestimation of effects on daily energy intake. However, results also question the proposition that increases or decreases to daily energy intake are in any way compensated for during subsequent days.

Hyperglycemia is a hallmark characteristic of type II diabetes, due in part to increased hepatic glucose production (HGP). The gut microbiota is now recognized as a salient contributor to host metabolism, and our lab has demonstrated that the gut microbiota can impact glucose homeostasis, and that high-fat diet induced obesity is associated with reduced levels of short chain fatty acids (SCFAs). SCFAs are bacterial metabolites, produced primarily in the large intestine from nondigestible dietary fibers, that can bind to free fatty acid receptors (FFARs) 2 and 3 on enteroendocrine cells (EECs) to induce gut peptide release. Exogenous butyrate improves glucose homeostasis, but the mechanisms are not fully understood. We hypothesize that colonic butyrate activates a gut peptide neuronal signaling mechanism to lower HGP. To investigate this, basal insulin euglycemic clamps were conducted in 3 day high-fat diet fed rats (n>5 for all groups). Colonic infusion of butyrate significantly decreased HGP compared to saline, and increased portal GLP-1 levels. Next, a GLP-1 receptor antagonist (exendin-9) was co-infused with butyrate, which abolished the effect HGP-lowering effect of colonic butyrate infusion. Vagotomies of both celiac branches or hepatic vagal branch abolished the HGP-lowering effect of colonic butyrate. Lastly, reduction of FFAR2 signaling through co-infusion of a FFAR2 antagonist with butyrate or by colonic site-directed FFAR2 lentiviral knockdown both abolished the HGP-lowering effect of colonic butyrate. Taken together, these studies establish a FFAR2-dependent signaling mechanism by which colonic butyrate lowers HGP via a GLP-1R vagal gut-brain-liver axis.
Binge eating disorder, characterized by recurrent episodes of overeating with concurrent feelings of being unable to stop eating, may manifest during childhood and adolescence. However, more commonly reported by youth are loss-of-control eating episodes, which involve the experience of a loss of control over eating any amount of food. Loss-of-control eating is cross-sectionally associated with greater consumption of highly palatable foods, several forms of disinhibited eating (e.g., emotional eating, eating in the absence of hunger, hedonic eating, etc.), mood and disordered eating symptoms, high weight and adiposity, and a number of concomitant biomarkers linked to obesity. Prospectively, loss-of-control eating has been shown to predict excess weight and adiposity gain, obesity-related markers of health, and may be a precursor to binge-eating disorder. This presentation will provide data on the salience of loss-of-control eating and its outcomes. Moreover, findings will be presented from interventional research focused on reducing loss-of-control eating to prevent excess weight gain and binge-eating disorder in adulthood. Results from such data suggest that a more robust and precise understanding of the loss-of-control eating construct may be warranted. Moreover, it may be important to consider matching intervention approaches to specific subgroups. A conceptual model is proposed to further elucidate the mechanisms that may play a role in determining which youths who experience loss-of-control eating are at greatest risk for binge-eating disorder and obesity. Future directions for assessment and novel approaches for early intervention will be discussed. 

**Ovarian Hormone Programming Of Neural Systems During Puberty And Their Links To Binge Eating**

Kelly L. Klump, Kristen M. Culbert, Alex Johnson, Cheryl L. Sisk

1Department of Psychology, Michigan State University, East Lansing, MI, United States, 2Neuroscience Program, Michigan State University, East Lansing, MI, United States

Binge eating shows highly stereotypic sex (females > males) and developmental (increases during/after puberty) features across animals and humans that provide important clues to its underlying etiology. Studies probing these features often focus on mechanisms related to affect regulation and their neural processes. Although these processes are clearly important for binge eating phenotypes, emerging data suggest that gonadal hormone regulation of appetitive and neural reward processes may contribute to sex differences and developmental trajectories of binge eating as well. This presentation will focus on the role of ovarian hormones in programming neural pathways during puberty and adolescence and their effects on risk for binge eating in adulthood. Findings from a set of developmental and translational experimental studies in animals will be reviewed and used to highlight potential mechanisms of risk that may translate into novel treatment approaches for binge eating across development.

**Loss-Of-Control Eating In Children And Adolescents**

Marian Tanofsky-Kraff

Uniformed Services University of the Health Sciences, Bethesda, MD, United States

Binge-eating disorder is the most common eating disorder and only one drug, lisdexamfetamine (LDX), is approved for its treatment. BED is associated with Attention Deficit Hyperactivity Disorder (ADHD) and LDX is also approved to treat ADHD. We conducted a systematic review of ADHD and disordered eating and a systematic review and meta-analysis of the efficacy of LDX in treating BED. We also conducted novel online and laboratory studies of the relationship between ADHD and disordered eating and of the mechanisms underlying the efficacy of LDX in treating BED using both behavioural and neuroimaging approaches. We have discovered an important relationship between inattentive symptoms of ADHD and binge eating and identified negative mood and reliance on interoceptive hunger/satiety signals as key mediating mechanisms. This is consistent with deficits in interoception being identified in our systematic review as a core symptom of eating disorders. Our meta-analysis showed that LDX is an effective treatment for BED that reduces symptoms and body weight. The results from our laboratory studies of women with binge eating symptoms have identified potential underlying mechanisms. Thus, LDX reduced intake of a pasta lunch and a cookie snack and enhanced sustained attention and reduced impulsive responding. Increased fMRI signals were observed in the thalamus for food vs non-food pictures and this response was attenuated by LDX. As the thalamus is an important relay centre of the neural interoceptive circuit, altered attention to interoceptive signals may be a common mechanism underlying both BED and the therapeutic action of LDX. Taken together these findings suggest that novel drug therapies for BED should target a broad spectrum of effects on appetite, reward and cognition.

**Drug Therapy For Binge-Eating Disorder: Where Do We Go From Here?**

Colin T Dourish

Plvital, Wallingford, United Kingdom

Binge-eating disorder is the most common eating disorder and only one drug, lisdexamfetamine (LDX), is approved for its treatment. BED is associated with Attention Deficit Hyperactivity Disorder (ADHD) and LDX is also approved to treat ADHD. We conducted a systematic review of ADHD and disordered eating and a systematic review and meta-analysis of the efficacy of LDX in treating BED. We also conducted novel online and laboratory studies of the relationship between ADHD and disordered eating and of the mechanisms underlying the efficacy of LDX in treating BED using both behavioural and neuroimaging approaches. We have discovered an important relationship between inattentive symptoms of ADHD and binge eating and identified negative mood and reliance on interoceptive hunger/satiety signals as key mediating mechanisms. This is consistent with deficits in interoception being identified in our systematic review as a core symptom of eating disorders. Our meta-analysis showed that LDX is an effective treatment for BED that reduces symptoms and body weight. The results from our laboratory studies of women with binge eating symptoms have identified potential underlying mechanisms. Thus, LDX reduced intake of a pasta lunch and a cookie snack and enhanced sustained attention and reduced impulsive responding. Increased fMRI signals were observed in the thalamus for food vs non-food pictures and this response was attenuated by LDX. As the thalamus is an important relay centre of the neural interoceptive circuit, altered attention to interoceptive signals may be a common mechanism underlying both BED and the therapeutic action of LDX. Taken together these findings suggest that novel drug therapies for BED should target a broad spectrum of effects on appetite, reward and cognition.

**Novel Psychological Treatments For Binge-Eating Disorder**

Anja Hilbert

University of Leipzig Medical Center, Leipzig, Germany

Binge-eating disorder (BED), characterized by recurrent binge eating in the absence of regular weight-compensatory behaviors, is the most common eating disorder, associated with increased eating disorder and general psychopathology, mental disorder comorbidity, obesity and related medical sequelae, and impaired quality of life. Current meta-analyses indicate that psychological treatments are suited to efficaciously and sustainably treat BED in adults, leading to long-term remission from binge eating in about 50% of patients, substantial improvement of psychopathology, and stabilization of body weight. Clearly, efficacy needs to be enhanced further through improvement of existing or development of new treatments, based on mechanistic and/or interventional research. This presentation will focus on current developments for the treatment of BED in adults: (1) neuromodulation, including food-specific functional near-infrared spectroscopy- and
electroencephalography-based neurofeedback; (2) neurocognitive training, including cognitive remediation therapy, a comprehensive rehabilitative approach for the restitution of executive dysfunctions; and (3) digital interventions, including smartphone-supported cognitive-behavioral therapy using ecological momentary interventions to foster patients’ therapeutic skills use in daily life. Evidence from randomized-controlled trials will inform about contributions and limitations of these approaches to the treatment of BED.
Astrocytic Melanocortin-4 Receptors In The Hypothalamus Modulate Inflammation And Energy Balance
Nicole L Eliason1,4, Amanda L Sharpe1,3,4, Michael C Rudolph1,2,4
1Department of Pharmaceutical Sciences, College of Pharmacy, Oklahoma City, OK, United States, 2Department of Physiology, College of Medicine, Oklahoma City, OK, United States, 3Harold Hamm Diabetes Center, Oklahoma City, OK, United States, 4University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

World-wide, nearly 40% of the adult population is classified as clinically obese. Central inflammation frequently occurs with obesity and is associated with increased morbidity and deterioration of health. The hypothalamus is a brain region that governs many facets of energy homeostasis, and melanocortins in the hypothalamus both decrease feeding and increase metabolism via melanocortin-4 receptors (MC4Rs). MC4Rs are present on both neurons and astrocytes (aMC4R); however, previous work has focused on the neuronal population. Thus the direct contributions of aMC4R on inflammation and energy balance have not been investigated. Our objective was to determine the effects of deletion of hypothalamic aMC4R on central and peripheral inflammation, as well as body weight homeostasis. Adult MC4R fl/fl mice were microinjected with an astrocyte-specific promoter driving Cre-expression (AAV-GFAP-Cre) or AAV-control (n=4-7/group) to produce a hypothalamic knock-down of aMC4R (KD). Mice were housed in metabolic chambers to monitor body weight, food intake, locomotor activity, and other metrics of indirect calorimetry. Mice were euthanized 4 weeks post AAV injection and brain, blood, fat, and liver tissues were collected. We observed a significant increase in body weight, fat mass, and energy balance in the KD group compared to control as soon as 14 d post AAV injection. Liver red-oil staining revealed an increase in fat deposition, and fat pad weight was increased. Inflammation was increased in KD mice in both the hypothalamus (immunofluorescence for Iba-1 and GFAP) and in the serum (IL-6 and TNF-alpha). These data are the first to demonstrate that hypothalamic aMC4R independent of neuronal MC4R is important in modulating inflammation as well as contributing to energy balance.

Parabrachial Npy Y1 Receptor-Expressing Neurons Allow For The Gating Of Inflammatory Pain By Hypothalamic Agrp Neurons
Nitsan Goldstein, Jamie RE Carty, J Nicholas Betley
University of Pennsylvania, Philadelphia, PA, United States

During food deprivation, competing needs are devalued to promote feeding. Hunger suppresses inflammatory pain through a hypothalamic-to-parabrachial circuit that is activated during caloric deficit. Agouti-related protein (AgRP)-expressing neurons in the arcuate nucleus projecting to the lateral parabrachial nucleus (IPBN) suppress behavioral pain responses in the formalin model of inflammatory pain, an effect that can be blocked by antagonizing the Y1 Neuropeptide Y (NPY) receptor. Conversely, hunger has no effect on acute responses to formalin or noxious heat. To further uncover the mechanism by which hunger specifically attenuates inflammatory pain, we characterized the role of IPBN Y1R neurons in pain processing using calcium imaging, anatomical tracing, and cell-type specific manipulations. We found that IPBN Y1R neurons receive monosynaptic input from the arcuate nucleus as well as the dorsal horn of the spinal cord. Y1R neurons condition a strong place avoidance and are required for proper expression of pain behavior. Y1R neurons exhibited increased activity in response to a variety of noxious stimuli. However, single-cell neural activity recordings revealed that distinct populations of IPBN Y1R neurons responded to either acute nociceptive stimuli or noxious inflammatory input. Hunger or AgRP neuron stimulation selectively blocked stimulus-evoked Y1R neuron activity during the inflammatory phase of the formalin assay but not during the acute phase nor during acute thermal pain. Together, our work suggests that a subpopulation of IPBN Y1R neurons may be targeted for treatment of inflammatory pain without disruption of protective pain.

Impairment Of Hypothalamic Astrocyte Fatty Acid Uptake Alters Energy And Glucose Homeostasis In Mice
Patricia Kulka, Christelle Le Foll
Institute of Veterinary Physiology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

Growing evidences support the essential role of astrocyte-neuron communication in regulating physiological processes.Â ÂNeurons in the ventromedial hypothalamus (VMH=ARC+VMN) are able to sense extracellular fatty acids (FA) to alter their activity in order toÂ control multiple physiological processes.Â Acute high fat diet feeding induces VMH astrocyte-derived ketone bodies production which overrides FA sensing neurons activity and inhibits caloric intake. We here postulate that astrocyte FA uptake plays an important role in the control of energy homeostasis. Thus, we tested our hypothesis byÂ depleting theÂ FA acid transport protein 4 (FATP4), the most abundant FATP in mouse astrocytes, inÂ aÂ primary hypothalamic astrocytes. FATP4 depleted astrocytes treated with 20mM oleic acid or palmitic acid (PA) for 72h showed decreased ketone bodies but higher lactate production compared to controls. Fluorescently labelled PA (C16-BODIPY) was less present (-50%, P<0.05) in lipid droplets of FATP4-depleted astrocytes than in controls, indicating impaired uptake. In vivo, FATP4 floxed male and female mice were injected bilaterally in the VMH with an AAV-GFAP-cre to specifically deplete FATP4 in astrocytes. No sex specific effects were observed. Chow diet-fed GFAP-FATP4Â depleted mice presented a significant increase in body weight gain (+228%, P<0.001) and food intake (+15%, P<0.01) compared to control AAV injected mice. This was accompanied by a significant decrease in glucose tolerance, increase in body fat mass (+90%, P<0.01) and liver triglycerides (+33%, P<0.05). GFAP-FATP4Â depleted mice showed a 10% decrease in energy expenditure compared to control mice (P<0.05). During the light phase, respiratory quotient of GFAP-FATP4Â mice was increased indicating a preference for carbohydrates as their main energy source (P<0.05). VMH GFAP, Iba1, IL-1Î² and TNF-Î± mRNA expression were increased compared to controls but GFAP-FATP4Â depletion did not alter the expression of genes involved in FA metabolism. Together, these results highlight the important role of VMH fatty acid uptake on neuronal function and on the control of energy homeostasis.Â 

Oxytocin Neurons In The Paraventricular Hypothalamus And Supraoptic Nucleus Differentially Influence Food
Temporal Dynamics Of Hypothalamic Agrp Neurone Mediate Context-Conditioned Overeating In Mice.

Felicia Reed, Harry Dempsey, Catherine Makdsi, Claire J Foldi, Sarah Haas Lockie, Zane B Andrews
Monash University, Clayton, Australia

Non-homeostatic feeding is typically a product of conditioned behaviour. Context specific cues are known to drive this response, but little is known about the neural mechanisms involved in acquiring this behaviour to begin with. We sought to understand the contribution of hunger-sensitive Agouti-related peptide-expressing neurons (AgRP neurons) in acquiring context-induced feeding (CIF) behaviour in mice, using a model that requires mice to be hungry (fasted) during the training phase. Given that AgRP neurons underpin a hunger-driven feeding response, we hypothesised their involvement in hunger-mediated acquisition of CIF which results in fed mice over-eating to a specific context. We first addressed whether AgRP neurons are required for fasting-driven CIF independent of an acute feeding response by chemogenetically inhibiting AgRP neurons in AgRP-Gi mice prior to 30 min training sessions in a discrete context (context A). When we tested all mice under fed conditions in the absence of treatment, we found that AgRP-Gi mice failed to discriminate their food intake in context A versus an alternate context (context B); which was present in the AgRP-WT control group (A vs B; p<0.05). Suggesting AgRP neurons are necessary to acquire CIF in fasted mice independent of a historical feeding response. To assess efficiency in fed mice, we employed two excitatory approaches, 1. chemogenetic activation of AgRP neurons with CNO prior to training (AgRP-Gq: n = 6; AgRP-WT: n = 7), and 2. optogenetic activation of AgRP neurons restricted to the training context (AgRP-ChR; n = 5; AgRP-WT: n = 10). Both approaches drove spontaneous feeding during training (Gq vs WT: p<0.05; ChR vs WT: p<0.05), however, only the optogenetic approach was sufficient for CIF expression at test (ChR p<0.05; Gq p = 0.98), suggesting AgRP neurons facilitate CIF through dynamic changes in neuronal firing. Together we highlight an important functional dissociation between acute and conditioned feeding mediated by AgRP neurons, and show the timing and duration of neuronal silencing is critical to achieve the latter

Amphetamine Regulates Feeding Behaviour, Metabolism And Cardiovascular Function Through The Melanocortin System.

Stephanie E Simonds1, Jack T Pryor1, Brian YH Lam2, Georgina K Dowsett2, Tomris Mustafa3, Astrid Munder2, Kayla Elyse2, Eglantine Balland1, Lachlan O Cowley1, Giles SH Yeoh2, Andrew Lawrence3, David C Spanswick1, Michael A Cowley1

1Department of Physiology, Monash Biomedicine Discovery Institute
Monash University, Clayton, Victoria, Australia
2Department of Physiology, Monash University, Clayton, Victoria, Australia
3MRC Metabolic Diseases Unit, University of Cambridge

Amphetamine (AMPH) induces substantial and sustained weight loss, additionally AMPH increases blood pressure and heart rate. The central melanocortin system is a key regulator of both metabolic and cardiovascular functions. This research demonstrates that hypothalamic proopiomelanocortin (POMC) neurons and the central melanocortin system are required for AMPH-induced anorexia, energy expenditure, tachycardia and hypertension. In diet induced obese (DIO) wild-type mice AMPH excited POMC neurons and significantly increased hypothalamic α-melanocyte stimulating hormone (αMSH) secretion. AMPH reduced the food intake and bodyweight, increased BAT thermogenesis, blood pressure and heart rate. In melanocortin 4 receptor deficient obese (MC4R KO) mice, AMPH significantly increased αMSH secretion although metabolic and cardiovascular effects were significantly attenuated compared to effects in DIO mice. Chronic AMPH treatment in DIO and MC4R KO mice induced significant and sustained weight loss, with cumulative food intake significantly reduced compared to vehicle-treated controls. Despite significant weight loss, blood pressure was elevated in AMPH-treated DIO mice but not in MC4R KO mice. Central serotonergic and noradrenergic systems are responsible for melanocortin-dependent effects of AMPH as antagonism of either or both neurotransmitter systems attenuated AMPH-induced αMSH secretion as well as AMPH-induced metabolic and cardiovascular effects. A We propose that AMPH increases serotonergically excitation of POMC neurons and reduces the noradrenergic inhibition of POMC neurons. These presynaptic mechanisms result in elevated POMC neuron activity, αMSH release and MC4R pathway activation resulting in metabolic and cardiovascular systems outputs.
nin-concentrating hormone (MCH) is an orexigenic neuropeptide produced in the lateral hypothalamic area and zona incerta. Whether MCH’s food intake-promoting effects are based on enhanced appetitive processing, consummatory processing, or both is poorly understood. Here we evaluated the effects of MCH neuron activation via Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) driven by an MCH promoter on various behavioral procedures that isolate appetitive or consummatory processing in rats. Results reveal that MCH neuron activation via injections of deschloroclozapine (DCZ; DREADDs ligand) increased appetitive responses to both discrete and contextual cues independent of consumption, as evidenced by increased operant responses to discrete cues in a Pavlovian Instrumental Transfer extinction test, and increased expression of conditioned place preference based on context-meal associations relative to vehicle treatment. To assess whether MCH neuron activation enhances the reinforcing aspects of specific nutritive cues associated with consumption, rats were trained to associate flavor or location cues with sweet taste, intragastric (IG) glucose, water, or combinations thereof while receiving DCZ or vehicle injections. Results reveal that MCH neuron activation enhances a preference for cues associated with either water consumption or oral low calorie sweetener consumption paired with IG glucose, yet had no effect on flavor preference for low calorie sweetened pellets. Overall these data suggest that the orexigenic effects of MCH neurons are based on enhancement of both appetitive and consummatory processes for caloric and hydrational substances.

6:24

T-Type Calcium Channel Cav3.1 Gates Leucine Sensing In Hypothalamic Pomc Neurons And Regulates Energy Homeostasis
Anthony H. Tsang, Nicholas Heeley, Tamana Darwish, Brian Lam, Amar Sarkar, Danae Nuzzaci, Peter Kirwan, Marcella Ma, Florian Merkle, Clemence Blouet
Wellcome-MRC Institute of Metabolic Science and Medical Research Council Metabolic Diseases Unit, University of Cambridge, Cambridge, United Kingdom

In this study we explore the molecular underpinnings of leucine sensing in the mediobasal hypothalamus (MBH). Using the unbiased PhosphoTRAP technique, we found that the expression of Cacna1g, which encodes for the T-type voltage-gated calcium channel Cav3.1, is enriched in leucine-activated neurons. Cav3.1 is expressed in discrete subsets of hypothalamic populations, including POMC neurons which are known to sense leucine and mediate its anorectic actions. We hypothesised that Cav3.1 in MBH POMC neurons contributes to leucine sensing and mediates the effects of dietary protein on energy balance. In vitro, pharmacological inhibition of Cav3.1 activity blunted the electrophysiological responses to leucine in both murine primary MBH cultured neurons and human induced pluripotent stem cell (hiPSC) derived MBH neurons. In vivo, pharmacological and genetic inhibition of MBH Cav3.1 significantly blunted the appetite-suppressing effects of local leucine injections. Importantly, genetic ablation of MBH Cacna1g abolished the feeding and metabolic responses to high protein feeding. Selective ablation of Cacna1g in MBH POMC neurons largely recapitulated the behavioral and metabolic phenotypes observed following whole-MBH Cacna1g KO. Using a HEK293 cell system we found leucine binds to Cav3.1 and increases the plasma membrane localisation, providing a potential mechanistic basis for modulation of Cav3.1 function by leucine. Together, these results indicate that Cav3.1 mediates MBH leucine sensing and the effects of dietary proteins on appetite and energy balance and identify a novel nutrient-sensing mechanism in POMC neurons, forming the basis for future work investigating the efficacy of this novel target in anti-obesity treatments.

6:36

Q&A
Douro Sky Lounge
Alameda de Basilio Teles 29
4050-015 Porto, Portugal

The new investigator social is an opportunity for graduate students and post-docs to network while enjoying a spectacular view of the Douro River. Food and drinks will be available for purchase.

Chair(s): Molly McDougle
Roux-En-Y Gastric Bypass Surgery Does Not Induce Neophobia To Novel Foods In Female Rats Despite Decreasing Intake Of A Cafeteria-Style Diet.

Ginger D. Blonde¹, Kellie M. Hyde¹, Ruth K. Price², M. Barbara E. Livingstone², Carel W. Le Roux³, Alan C. Spector¹
¹Dept. of Psychology & Program in Neuroscience, Florida State University, Tallahassee, FL, United States, ²Nutrition Innovation Center for Food and Health (NICHE), School of Biomed Sciences, Ulster University, Coleraine, United Kingdom, ³Diabetes Complications Research Centre, Conway Institute, School of Medicine, University College Dublin, Dublin, Ireland

After Roux-en-Y gastric bypass (RYGB), rats reduce intake of calorically dense foods. However, how animals respond to novel multiple (>2) foods varying in macronutrient content provided simultaneously is unclear. Here, female rats were postsurgically tested after RYGB (n=10) or SHAM (n=6) surgery in a specialized 5-Item Food Choice Monitor that allowed continuous measurement of intake and meal patterns of rat chow (4 days) and then a cafeteria-style diet (4 human foods + chow; 8 days). SHAM rats showed the expected hyperphagia of the cafeteria diet compared to rat chow alone, primarily due to larger meal sizes. As shown previously, compared with SHAM rats, when on the cafeteria diet RYGB rats: 1) ate fewer calories each day by consuming smaller meals, 2) ate at a slower rate (kcal/min), 3) had a more distributed nycthemeral intake pattern, and 4) consumed fewer proportional calories from fat and more from complex carbohydrates and protein, which yielded a lower average energy density within meals. Despite not overconsuming (kcal) the cafeteria diet relative to chow, RYGB rats ate a single large first meal upon presentation of the cafeteria diet. While the first meal of RYGB rats was smaller than the first meal eaten by sham rats, it was larger than subsequent RYGB meals which were similar in size to those of rat chow meals. This first meal also included intake from all foods available, resulting in a higher energy density than later meals. Together, these results suggest that the effects of RYGB on ingestive behavior in the context of multiple palatable foods is largely unaffected by prior exposure to the foods. Thus, under these conditions, RYGB rats do not display food neophobia and appear to be able to rapidly respond to postoral feedback after eating new substances.

Omnivores' Explicit And Implicit Attitudes Towards Vegetarians And Vegetarians' Perceptions Of Omnivores' Treatment Of Them.

Catherine A Forestell¹, Harini Krishnamurti¹, Joanna Tomczyk², Marzena Cypryanska², John B. Nezlek¹,²
¹William & Mary, Williamsburg, VA, United States, ²SWPS University of Social Sciences and Humanities, Warsaw, Poland

Vegetarians often report experiencing more negative social experiences, more strain in their relationships with family and peers, and higher levels of depression, anxiety, and neuroticism relative to omnivores. Because vegetarians are considered a social minority, we hypothesize that they are consequently subject to some of the same problems experienced by other social minorities, including ostracism, exclusion, disrespect, and derogation. In this series of studies, we measured omnivores' implicit and explicit attitudes toward vegetarians as well as vegetarians' perceptions of how they are treated by omnivores as a function of their dietary habits. In study 1, 275 omnivore adults (184 women) between the ages of 18-25 years completed the Implicit Association Test that assessed implicit attitudes towards vegetarians. Results showed that while explicit attitudes were positive for both men and women, men’s implicit attitudes were negative, and women’s attitudes were indifferent toward vegetarians. In study 2, we assessed 1744 participants (145 vegetarians), and found that vegetarians thought that others treated them more negatively because of their diet than omnivores did. Interestingly, in this same study, we found that vegetarians also thought that others treated them more positively in some ways due to their diets than omnivores did. These findings suggest that people may feel ambivalent toward vegetarians. They may admire vegetarians for the moral principles they hold and for their commitment, while they may simultaneously view them as arrogant and overcommitted.

Lingual Gustatory Denervation Blunts Concentration-Dependent Licking Of Maltodextrin And Sucrose In Wild Type And T1R3 Knock-Out Mice In A Brief-Access Test.

Elizabeth A Hamel, Ginger D Blonde, Alan C Spector
Florida State University, Tallahassee, FL, United States

Maltodextrins (MD) appear to elicit a taste sensation that: a) is distinct from sugars, b) not dependent on the T1R2+R3 taste receptor that binds with sweeteners, and c) drives responsiveness in taste-related behavioral tasks, at least in rodents. To test the contribution of lingual taste signals to MD responsiveness using a task that focuses on orosensory stimulus properties, we bilaterally transected (NX) the chorda tympani (CT) and glossopharyngeal (GL) nerves or performed sham surgery in male and female C57BL/6J mice, with (WT) or without (KO) a functional T1R3 receptor subunit (n=8-12/surgery/genotype) and tested them in a brief-access paradigm (10-s trials, 30-min sessions) in a Davis rig lickometer. NaÂ¬ve mice were first presurgically trained while water-deprived to lick water and eventually Intralipid (8%). After recovery from surgery, 23-h food-deprived mice were tested with a concentration array of Maltrin (3 sessions, week 1; 0-32%, and then of sucrose (3 sessions, week 2, 0-32%). Both WT and KO mice with NX displayed severely blunted concentration-dependent licking to Maltrin and initiated fewer trials, as compared to their sham counterparts. T1R3 KO mice did exhibit concentration-dependent licking to sucrose, though attenuated, possibly due to prior exposure to MD and learning associated with postigestive cues. However, NX blunted this responsiveness in both WT and KO mice; in the latter severely so. These results, pending histological confirmation, suggest that, in mice with or without T1R3, an intact CT and/or GL are required for typical concentration-dependent responding to Maltrin in a brief-access test. The fact that some degree of Maltrin responsiveness remained after NX implicates the additional contribution of a CT&GL-independent sensory pathway.
Factors Associated With Caregivers’ Offering Of Complementary Foods To Infants And Toddlers: The Approaching Eating Through Language (Appeal) Study
Susan Johnson, Allison Shapiro, Megan Lawless
CU Anschutz Medical Campus, Aurora, CO, United States

The APPEAL (Approaching Eating through Language) Study investigated household, caregiver, and child factors associated with number of foods offered to children during the complementary feeding period. We conducted an online survey that recruited caregivers of infants and toddlers (4 – 26 months; n=408) through Qualtrics panels and queried them about: 1) sociodemographic descriptors (caregiver education, race/ethnicity, household income, food security [FS] and other children in the household); 2) caregiver characteristics (sex [F,M,I] and age [y]); 3) child characteristics (age, birthweight, and temperament [surgency, negative affect, effortful control]); and feeding (milk feeding [human, formula, mixed], total foods offered to date (Yes/No; ∑TF) summed). A multivariable linear regression model was run with backwards stepwise selection of variables applied (P<0.10 criterion for removal) to develop the most parsimonious, final model. In the final model (R²=24.1%), child sex (female, -3.2 [-6.3, -0.2]; β [95% CI]), milk feeding (mixed feeding, 5.6 [1.6, 9.7], other children (>3, 8.4 [3.2, 13.6]), child age (<12 months, -9.0 [-12.9, -5.1]) and FS (moderate/high, -8.1 [-11.8, -4.3]) were significantly associated with ∑TF. Thus, younger infants, female sex, and moderate/high FS were associated with offering less ∑TF while having more children in the home, human milk/formula, and children’s negative affect were associated with introduction of greater ∑TF. In conclusion, characteristics specific to the child (age, sex, temperament), caregivers’ previous experience with other children and milk feeding decisions, and current sociodemographic factors contribute to the variety of foods offered during the complementary feeding period.

Protein Restriction Alters Cue-Evoked Licking Behavior In Head-Fixed Mice
Mette Kongsor, James Edgar McCutcheon
Department of Psychology, UiT The Arctic University of Norway, Tromso, Norway

Ensuring appropriate intake of dietary protein is a compelling problem faced by many animals, including humans. Our lab and others have shown that rodents on a protein-restricted (PR) diet develop a preference for protein-rich foods. However, much is still unknown about the neuronal mechanisms orchestrating this behavior. Our goal is to examine the role of specific neuronal populations in the lateral hypothalamus (LH), a brain area crucial for feeding, in response to different nutrients. To study the role of individual neurons we are using two-photon microscopy which requires the development of procedures for assessing protein preference in head-fixed mice. Here, we used a Pavlovian conditioning task, in which 2 ÂµL of either a high-protein or low-protein solution was delivered to mice following an auditory cue. Adult male C57BL/6 mice (n=8) were habituated to head-fixation and placed on PR or non-restricted (NR) diet for 1 week before testing. In high-protein solution sessions, PR mice licked more and had shorter latency to lick from cue onset, compared to NR mice. These differences were not observed in low-protein solution sessions. When PR mice were switched to NR diet, the number of licks remained similar to that on PR diet, while the latency to first lick increased. Furthermore, when NR mice were placed on PR diet, number of licks increased. In addition, despite variability in cue-evoked licking, there was an indication that PR mice learned to associate the cue with the high-protein solution more readily than NR mice. In summary, cue-evoked licking behavior in head-fixed mice was sensitive to the physiological state, i.e., PR. Thus, this protocol can be integrated with in vivo calcium imaging to record neuronal activity associated with protein appetite.

Exploratory Analysis Of The Effects Of A Two-Week High-Fiber Diet On Food Memory In Overweight Adults
Evelyn Medawar¹, Ronja Thieleking¹, Arno Villringer¹,², A. Veronica Witte¹,²
¹Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, ²Clinic for Cognitive Neurology, University Hospital Leipzig, Leipzig, Germany

Fiber-rich diets have been suggested to modulate gut-brain-behavior-communication by altering homeostatic and hedonic control of food decision-making. However, causal evidence and underlying mechanisms of how fiber affects the human brain with regard to feeding and food memory remain to be shown. We aimed to test the effects of a dietary fiber intervention (27g/day over 14 days) compared to equiloricus placebo, on food memory and its neuronal correlates in overweight adults in a double-blinded cross-over within-subject randomized clinical trial (NCT03829189, osf.io/ynkxw). 60 diet-naive participants (20F, 28 years ± 6.2 SD, BMI 27.3 kg/m² ± 1.4 SD) underwent a food memory task during functional 3T magnetic resonance imaging at four time points; i.e. pre- and post-intervention for both conditions, respectively. Also, 16S rRNA microbiota profiling, blood and stool short chain fatty acid and glucose/lipid metabolites as well as extensive questionnaire data were assessed. We used Bayesian mixed model comparisons for the analysis. Behaviorally, we did not observe intervention effects neither on recognition performance (d’) nor on lure discrimination (LDI) nor considering the single image responses (correctly recognizing old images or correctly rejecting similar/new images vs. false image categorization) (n=57). Ongoing analyses include BOLD response during encoding and recognition in response to intervention. We did not find evidence that a high fiber diet impacts food memory performance on a behavioral level. We further investigate whether neural activity of food wanting or memory processes will change in response to high fiber intake and ifÂ these potential effects might be predicted by intervention-related changes in gut microbiota or metabolism.

Alyssa Palumbo, Devon Stewart, Jacob Mansell, Clare M Mathes
Baldwin Wallace University, Berea, OH, United States

Most patients receiving bariatric surgery are female, but most studies feature only male organisms. Here we characterized how Roux-en-Y gastric bypass (RYGB) surgery impacts the metabolic and reproductive profiles of female rats and assessed if RYGB would increase ethanol preference. At weaning, female rats were provided either with chow only (CHOW; n=12) or with chow + high-fat / -sugar supplements (“cafeteria diet”, CAF; n=24). By 20 weeks, CAF induced weight gain and blood glucose imbalances but did not alter insulin responsivity or estrous cycling. RYGB surgery (n=8) decreased body weight and fasting glucose levels of CAF rats and blunted their glucose responsivity compared to their sham-operated sisters (SHAM, n=11). RYGB did not independently alter cyclicity, although estrus profiles unexpectedly changed pre- to post-surgery in all CAF rats. The CAF-RYGB & CAF-SHAM rats as well as unoperated CHOW rats (n=8) were given ad libitum access to ethanol alongside water and intakes were measured daily; 2% EtOH was given for 8 days, then 10 days each of 4% and 6% EtOH. In the cafeteria diet, both sexes preferred the ethanol solution more than water (EtOH > water) and CAF preferred more than CHOW. RYGB surgery did not affect ethanol preference in either sex. When PR mice were switched to NR diet, the number of licks remained similar to that on PR diet, while the latency to first lick increased. Furthermore, when NR mice were placed on PR diet, number of licks increased. In addition, despite variability in cue-evoked licking, there was an indication that PR mice learned to associate the cue with the high-protein solution more readily than NR mice. In summary, cue-evoked licking behavior in head-fixed mice was sensitive to the physiological state, i.e., PR. Thus, this protocol can be integrated with in vivo calcium imaging to record neuronal activity associated with protein appetite.

Behaviorally, we did not observe intervention effects neither on recognition performance (d’) nor on lure discrimination (LDI) nor considering the single image responses (correctly recognizing old images or correctly rejecting similar/new images vs. false image categorization) (n=57). Ongoing analyses include BOLD response during encoding and recognition in response to intervention. We did not find evidence that a high fiber diet impacts food memory performance on a behavioral level. We further investigate whether neural activity of food wanting orÂ memory processes will change in response to high fiber intake and ifÂ these potential effects might be predicted by intervention-related changes in gut microbiota or metabolism.
Food insecurity and palatable food putatively promote food and ethanol (EtOH) bingeing. Models can pose the tested relations to find mechanisms. We tested the hypothesis that chronic variable energy restriction, Western diet, or their interaction increase binge-like feeding and EtOH intake in mice. Adult C57BL/6J mice (n=42) were randomly assigned to one of 4 diet conditions in a 2×2 factorial design: restriction weekly was 4 days of 25-75% energy ration at varying times, then 3 days of ad lib feeding. Refeeding on ad lib access was studied for 8 weeks. Mice then received 3 weeks of 2 hr/day access to 20% ad lib EtOH vs. water on weekdays per a Drinking in the Dark model (DID). To test the aversion-resistant compulsivity of EtOH intake, Week 4 of DID used quinine-adulterated (100 μM) EtOH. Restricted W mice refed 5.2±0.4 kcal/hr more than restricted C mice (Diet X Schedule). W diet and chronic restriction in C mice reduced EtOH intake, yielding EtOH rank-ordered intake (M±SEM g/kg) of ad lib C (3.0±0.1) > restricted C (1.7±0.1) > restricted W (0.9±0.1) = ad lib W (0.7±0.1). Restricted C and W mice increased EtOH intake on days with >24 hr of food restriction vs. days closer to refueling. Quinine reduced EtOH intake of restricted C and W mice by 0.5±0.1 and 0.3±0.1 g/kg, but not ad lib W or C mice (increased 0.6±0.1 g/kg). Thus, chronic variable restriction with W diet most promoted binge-like feeding; but, contrary to hypotheses, W diet and chronic C restriction reduced EtOH intake, while ad lib C chow-fed mice showed the most aversion-resistant EtOH intake. Mechanisms remain to be determined.

**Review: Notable Sex Differences In Sodium Appetite**

Jessica Santollo1, Derek Daniels2, Jay Schulkin3, Micah Leshem4

1University of Kentucky, Lexington, KY, United States, 2University at Buffalo, Buffalo, NY, United States, 3University of Washington, Seattle, WA, United States, 4University of Haifa, Haifa, Israel

There are notable sex differences in salt ingestion in humans and the laboratory rat, the species most studied. Numerous inconsistencies exist in design, including a variety of stimuli used to generate intake, make synthesis of the literature difficult. We nevertheless attempted to thoroughly review the literature and found consensus that ad libitum salt intake is greater in female rats than in males, but the opposite is true for humans. Moreover, males and other animals ingest salt in accordance with bodily requirement which humans do not. For instance, the female rat’s critical need for sodium during pregnancy and lactation may enhance salt intake and indicates an evolutionary adaptation that supplies salt to the litter. Again, this is not found in pregnant and lactating women. In addition to ad libitum intake in rats, sex differences in stimulated salt intake have been reported, but there is inconsistency in the findings. Our synthesis suggests that this inconsistency relates to the nature of the stimulus. Specifically, greater salt appetite is found in females when the stimulus is acute, but when deficit is more chronic, intake is greater in males. Extending this to human subjects is difficult because humans do not ingest salt in response to bodily deficits, even in life-threatening hyponatremia, although there are dramatic sex differences too: *inter alia*, women ingest 20% less salt than men, sweat 20% less, and may suffer depression in low sodium intake. Accordingly, we propose future research to test hypotheses arising from our synthesis of the literature, hoping for a better understanding of the sex differences, as well as the notable differences between laboratory rats and humans.

**Oral, Peri-Taste Digestion Contributes To The Hedonic Appeal Of Sugar In Mice**

Aracely Simental-Ramos1, Ahyun Jung1, Sandrine Chometton2, Caroline Metyas2, Tricia Saputra2, Lindsey Schier1,2

1Neuroscience Graduate Program, University of Southern California, Los Angeles, CA, United States, 2Department of Biological Sciences, University of Southern California, Los Angeles, CA, United States

Cephalic carbohydrate digestion affects glucoregulation, but whether these enzymatic processes affect taste-guided behavior is unknown. α-glucosidases, which cleave sugars to monosaccharides, are expressed in taste cells. Here, we confirmed that taste cells are capable of digesting two common dietary disaccharides, maltose and sucrose. In a published study, we showed that sugar-experienced (Sug-Exp) mice lacking the TRPM5 channel (KO), required for normal “sweet” taste transduction, and their wild type (WT) counterparts respond more positively to maltose than naïve mice. Here, we tested if this was due to a diet-induced increase maltase glucoamylase (MGAM), which digests maltose, in the taste buds to effectively liberate more ligands for local “sweet” receptors and/or glucosensors. We found that Sug-Exp TRPM5 WT and KO mice had higher MGAM expression in the circumvallate (CV) taste buds than Sug-Exp B6 mice, and this was inversely related to sweet receptor, *Tas1r3*, expression. Next, we tested if MGAM shRNA knockdown (KD) impaired taste-driven maltose appetite in WT mice in a short lick test (300 licks/10 min). MGAM KD in the major taste receptor fields, indeed rendered mice less motivated to consume maltose, as evidenced by a decrease in lick burst size. Finally, we found that naïve mice with the sweet sensitive receptor haplotype (129) lacked significantly more for maltose than B6 mice with the sweet sensitive receptor haplotype, and 129 mice had more taste bud-bound MGAM than B6 mice. Collectively, these data provide the first evidence that MGAM is required for normal for taste-based attraction to maltose and suggest that genetic and dietary factors modulate peri-taste MGAM activity to promote sugar detection and consumption.
MK-801 blocks sodium appetite sensitization, a type of non-associative learning (Hurley & Johnson, 2013). We do not know whether this type of blockade also alters the number of orofacial motor responses to salty taste tested with an intraoral infusion (1 ml for 1 min) of 0.3 M NaCl in an acute sodium depletion model. Adult rats (n = 11) instrumented with an intraoral cannula received a subcutaneous injection of the diuretic/natriuretic furosemide combined with 24 h removal of ambient sodium. Intraperitoneal MK-801 (0.15 mg/kg) versus vehicle15 min prior to 0.3 M NaCl infusion had no effect on hedonics (103 ± 32 vs. 127 ± 27) or aversive (6 ± 3 vs. 6 ± 4) responses to 0.3 M NaCl. However, MK-801 inhibited for 45 min the subsequent 0.3 M NaCl intake (7 ± 2 vs. 13 ± 1 ml; p <0.05). There was no effect for the remaining 95-min intake test (10 ± 3 vs. 14 ± 1 ml), at the end of which we found, again, no effect on orofacial responses to 0.3 M NaCl (hedonic:24 ± 11 vs. 45 ± 17; aversive: 8 ± 3 vs. 20 ± 7). In another group of animals (n = 10), MK-801 produced only a transient 36% inhibition of food chow intake at 30 min of a 120 min-feeding test subsequent to a 24-h food deprivation schedule. All animals ingested an average of 8.0 ± 1.0 g/120 min, with asymptote at 60 min. The results suggest that MK-801 produced a selective inhibition of 0.3 M NaCl intake independent from alterations in salt palatability.

### Differential Neurobehavioral Signatures Of Reward Learning In Obesity And Binge Eating Disorder

Anne Kuehn1,2, Juliane Lucas1, Monja P Neuser1, Vanessa Teckentrup1, Franziska Kraeutlein1, Franziska K Mueller1, Peter Dayan3, Jennifer Svaldi4, Nils B Kroemer1

1 Department of Psychiatry and Psychotherapy, Tuebingen Center of Mental Health, University of Tuebingen, Tuebingen, Germany; 2 Max Planck Institute of Psychiatry and International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany; 3 Max Planck Institute for Biological Cybernetics, Tuebingen, Germany; 4 Department of Psychology, Tuebingen Center of Mental Health, University of Tuebingen, Tuebingen, Germany

Deciding what and how much to eat as well as learning from our choices is an integral part of life. Obesity and binge eating (BE) are characterized by altered food-related decision-making. However, changes in reinforcement learning (RL) in obesity have been inconsistent across studies and not dissociated from BE. Here, we provide an extensive assessment of obesity-related differences in RL using a large sample of 400 participants encompassing a high BMI range and enriched for BE. To dissociate trait and state components of RL, participants completed up to 31 runs of a novel RL game across weeks (1,486,950 choices). We modeled parameters using hierarchical Bayesian sampling and estimated individuals’ trait (averages) and state (variability) components across runs. Moreover, a subset of 61 BMI-matched participants with and without BE completed fMRI tasks assessing reward responsivity. Across RL runs, higher BMI was associated with fewer earned reward points (r = -0.13, 95% CI [-0.22, -0.04]), higher learning rates for rewards (r = 0.15, 95% CI [0.04, 0.24]), and more variable learning rates for punishments (r = 0.18, 95% CI [0.09, 0.29]). In contrast, reward sensitivity was not associated with BMI (r = -0.01, 95% CI [-0.12, -0.11]), but negatively with BE (r = -0.11, 95% CI [-0.20, -0.00]). Conclusively, in an effort for greater findings, patients with BE disorder (BED) showed attenuated anticipatory responses to larger rewards in the nucleus accumbens. We conclude that obesity is primarily associated with differences in reward learning while BE is associated with reduced reward sensitivity, even in a motivational task. Our findings highlight the necessity to complement neurobiological research with behavioral precision mapping to derive mechanistic insight into multidimensional disorders such as obesity and BED.

### Effectivity Of A Non-Viable Probiotic In Irritable Bowel Syndrome - A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study

Isabelle Mack1, Juliane Schwille-Kiuntke2, Nazar Mazurak1, Beate Niesler3, Kurt Zimmermann4, Hubert Moennikes5, Paul Enck6

1 Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tuebingen, Tuebingen, Germany; 2 Institute of Occupational and Social Medicine and Health Services Research, University Hospital Tuebingen, Tuebingen, Germany; 3 Department of Human Molecular Genetics, University Hospital Heidelberg, Heidelberg, Germany; 4 SymbioPharm GmbH, Herborn, Germany; 5 Department of Internal Medicine, Martin Luther Hospital, Berlin, Germany

**Background:** Extensive probiotic research in irritable bowel syndrome (IBS) and other gastrointestinal related fields show that the results are still conflicting. Reasons are that most probiotics are marketed as nutritional supplements and not as drugs impacting the quality of most patients, not all probiotics may be of similar efficacy and that they may not be effective across different patient collectives and even patient sub-groups. Here, we investigated the effectiveness of oral treatment with a non-viable bacterial lysate (BL) of *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) in patients with IBS. **Methods:** A phase IV, randomized, double-blind, placebo-controlled, multi-center, parallel group study in 389 patients with IBS with 26 weeks treatment period was conducted. Outpatients aged ≥18 years of both sexes with IBS diagnosis according to Rome III criteria were eligible. The primary outcome was based on the European Medical Agency guideline on the evaluation of medical products for the treatment of IBS: Improvement in global assessment (GAI) and improvement in abdominal pain. **Results:** Effects of patients (BL n=191; placebo n=198) were similar between BL and placebo for IBS-GAI (17.4% and 14.4%) and abdominal pain (42.0% and 35.4%). Post-hoc analysis for abdominal pain response showed that BL was effective in diarrhea-predominant IBS (IBS-D; p<0.01). Additionally, in IBS-D, improvement of abdominal pain was associated with improvement in stool consistency in the second half of the treatment period and at study termination (p<0.001). **Conclusions:** This non-viable BL offers a promising treatment option for IBS-D. However, verification is needed by an adequately powered drug-trial.

### Depression Scores Predict The Satiating Effects Of The 5-HT2C Receptor Agonist Meta-Chlorophenylpiperazine (M-Cpp)Â

Elizabeth Schneider1, Maartje Spetter1, Elizabeth Sapey1, Kay Por Yip1, Konstantinos N Manolopoulos1, Jason Thomas2, Michelle Lee3, Manfred Hallischmidt4, Samuel R. Chamberlain5, Colin Dourish6, Suzanne Higgs1

1 University of Birmingham, Birmingham, United Kingdom; 2 Aston University, Birmingham, United Kingdom; 3 Swansea University, Swansea, United Kingdom; 4 University of Tubingen, Tubingen, Germany; 5 University of Southampton, Southampton, United Kingdom; 6 Pliva Ltd/IP1 Vital products, Wallingford, United Kingdom

Stimulation of 5-HT2CÂ receptors decreases food intake but there is variability in response. We have previously found using...
Investigating The Temporal Dynamics Of Metabolic Responses To Consumption Of Mono- And Disaccharide-Containing Beverages

Mary Elizabeth Baugh1, Zach Hutelin1, 2, Monica Ahrens3, Mary Oster1, Amber Kelly1, 2, Alexandra Hanlon3, Alexandra DiFeliceantonio1, 4

1Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, VA, United States. 2Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA, United States. 3Institute for Research in Biomedicine (IRB Barcelona), Barcelona Institute of Science and Technology, Barcelona, Spain. 4Behavioral Sciences Institute, University of Basel, 4001 Basel, Switzerland.

There is strong evidence that glucose and sucrose (a disaccharide of glucose and fructose) should support flavor nutrient learning; however, in most animal models, fructose elicits a weaker change in learning and preference. Recent evidence has implicated glucose absorption and metabolism, measured as SGLT1-mediated signaling, elevated plasma glucose, or increased energy expenditure, as the important post-ingestive driver of this food preference learning. The purpose of this study is to investigate the temporal dynamics of metabolic responses to drinks with 75 kcal of mono- or disaccharides and a sucralose-sweetened drink containing 0 kcal. In a crossover design, metabolically healthy participants undergo indirect calorimetry measurements inside a 4.6 m³ metabolic chamber in the fasted state, consume a test drink, and then undergo post-consumption measurements for 70 minutes. Test drinks contain 75 kcal of sucrose, dextrose, or fructose; or 0 kcal of a nonnutritive sweetener, sucralose. Fasting and post-consumption metabolic and substrate oxidation rates are calculated from measurements of VO₂ and VCO₂ for comparisons of responses to test drinks. Data collection is ongoing. Preliminary results suggest the temporal dynamics of the metabolic rate response differ across sugars, with sucrose eliciting a more sustained elevation. Data suggest a faster and greater increase in carbohydrate oxidation following consumption of fructose-containing drinks (sucrose and fructose) compared to sucralose and dextrose drinks. Together, these findings highlight the absorption and metabolism of fructose as a potential modulator of glucose availability and utilization. Studies are needed to elucidate the potentiating effects of fructose paired with glucose in flavor nutrient learning.

Absorption And Metabolization Of The Natural Sweetener Erythritol In Humans: A Dose-Ranging Study

Valentine Bordier1, 2, Fabienne Teyssseire1, 2, Frank Senner3, Goetz Schlatterbeck3, Juergen Drew4, Christoph Beglinger1, 2, Bettina K. Woelnerhanssen1, 2, Anne Christin Meyer-Gerspach1, 2

1St. Clara Research Ltd at St. Claraspital, 4002 Basel, Switzerland, 2Faculty of Medicine, University of Basel, 4001 Basel, Switzerland, 3Institute for Chemistry and Bioanalytics, School of Life Science, FHNW University of Applied Sciences and Arts Northwestern Switzerland, 4132 Muttenz, Switzerland. 4Department of Clinical Pharmacology and Toxicology, University Hospital Basel, 4001 Basel, Switzerland

Introduction: Erythritol, a natural bulk sweetener, is absorbed at high rates in the intestine and excreted unchanged in the urine. However, recently, a conversion of erythritol into erythronate in human cells has been proposed (Hootman et al., PNAS 2017). The aim of this study was to determine the absorption and metabolization of different concentrations of erythritol. Methods: Twelve healthy subjects (7 men; BMI: 21.7±0.4, range: 19.4-24.0 kg/m²; age: 26.3±2.0, range: 18-41 years) received intragastric (ig) solutions of 10, 25 or 50g erythritol on three study days in this randomized, double-blind, crossover trial. Plasma samples were collected at fixed time intervals to assess the concentrations of erythritol and erythronate with gas chromatography-mass spectrometry. Data were analyzed using linear mixed model. Results: We found a dose-ranging absorption of erythritol and of its metabolization into erythronate. The erythritol plasma concentrations increased in response to erythritol (AUC = 10g vs. 25g, p<0.001; 10g vs. 50g, p=0.006; 25g vs. 50g, p=0.034). The absorption of erythritol was slower with the 50g dose compared to the lower doses (1/2 50g vs. 25g: 14.23±2.66min vs. 4.88±0.86min, p=0.015 and 50g vs. 10g: 14.23±2.66min vs. 5.40±1.16min, p=0.024). The erythronate plasma concentrations increased in response to erythritol (AUC = 10g vs. 25g, p<0.001; 10g vs. 50g, p=0.001; 25g vs. 50g, p=0.024). The metabolic ratio AUC erythritol/AUC erythronate was highest with 10g erythritol and decreased with higher doses. Conclusions: i) The absorption of erythritol and its metabolization into erythronate happen in a dose-ranging manner. ii) Erythritol is rapidly absorbed from the gut, however, the slower absorption after the highest load suggests a saturable process. iii) Erythritol is metabolized to a small extent into erythronate, confirming the previous report. iv) The decreasing metabolic ratio with higher doses of erythritol indicates that an increasing fraction of erythritol is metabolized into erythronate.

Glycogen-Mediated POMC Neuron Sensory Activation: Implications For Glucose Homeostasis And Digestive Behaviour

Alicia G Gomez-Valades1, Jordi Duran2, Elena Eyre1, Joan Guinovart2, 3, 4, Marc Clare1, 3, 5

1Neuronal Control of Metabolism (NeuCoMe) Laboratory, Institut d’Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. 2Institute for Research in Biomedicine (IRB Barcelona), Barcelona Institute of Science and Technology, Barcelona, Spain. 3Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA, United States. 4Department of Clinical Pharmacology and Toxicology, University Hospital Basel, 4001 Basel, Switzerland. 5Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA, United States.
Oligofructose Restores High Fat Diet-Induced Alterations To The Small Intestinal Metabolome And Enterohepatic Bile Acids, And Glycodeoxycholic Acid Prevents Diet-Induced Obesity And Glucose Intolerance.

Rachel K. Meyer1, Savanna N. Weninger2, Hallie R. Wachsmuth2, Megan Bime3, Frank A. Duca3,4
1School of Nutritional Sciences and Wellness, Tucson, AZ, United States, 2Physiological Sciences Graduate Interdisciplinary Program, Tucson, AZ, United States, 3BIO5 Institute, Tucson, AZ, United States, 4School of Animal and Comparative Biomedical Sciences, Tucson, AZ, United States

Obesity and diabetes are associated with unique gut microbiome signatures, while strategies that beneficially shift the gut microbiome, like prebiotic treatment, show promise in ameliorating metabolic disease; however, the mechanisms are not understood. A potential role of the gut microbiota in host metabolism is via modification of host and diet-derived intestinal metabolites. Most studies focus on the colonic metabolome, whereas few have investigated the small intestinal metabolome, despite most nutrients being absorbed in the small intestine. We have recently shown that the small intestinal microbiome is altered with high fat diet (HFD)-feeding, which mediates small intestinal nutrient sensing that regulates food intake and hepatic glucose production. Therefore, we evaluated the small intestinal metabolome of healthy Chow, HFD-induced obese, and HFD-fed rats supplemented with the prebiotic oligofructose (OFS; n=12/group) by HPLC-MS, identifying bile acids decreased during obesity but restored with OFS, including amino acids and bile acids. We then quantified bile acids in these same rats by GC-MS, identifying bile acids decreased during obesity but restored with OFS, including glycodeoxycholic acid (GDCA). As some secondary bile acids prevent obesity and improve glucose tolerance, we treated HFD-fed mice with vehicle or 50 mg/kg GDCA (n=10/group) for 8 weeks and measured body weight, adiposity, glucose tolerance, food intake, and indirect calorimetry. GDCA improved glucose tolerance and decreased body weight and adiposity by increasing energy expenditure via locomotor activity. The results of this study implicate GDCA as a possible treatment for obesity and diabetes and future studies will determine the mechanism of the metabolic improvements seen with GDCA treatment.

The Effects Of Colonic Scfa Infusions On Energy Homeostasis

William H. Powell, Frank A. Duca
University of Arizona, Tucson, AZ, United States

Fiber consumption is negatively associated with body weight in humans and fiber supplementation improves energy homeostasis, due in part to the gut microbiome. Bacteria in the distal intestine ferment fiber into short chain fatty acids (SCFAs). We recently demonstrated that obesity is associated with decreased postprandial levels of distal intestine SCFAs; however, the impact of endogenous SCFAs on energy homeostasis is still unknown. Exogenous SCFAs improve energy homeostasis, an effect partly mediated by free fatty acid receptors (FFAR2 and FFAR3) located on enteroendocrine cells and neurons. However, studies outlining the suppressive effects of exogenous SCFAs on food intake often target the small intestine or circulation rather than replicating an increase in endogenous production in the distal intestine. To address this, we equipped male Sprague Dawley rats with proximal colon catheters and, following recovery, infused 200mM acetate, butyrate, propionate or saline at a rate of 0.15mL/min for 15min after a 12hr overnight fast. Rats were then returned to metabolic cages for 24hrs to assess food intake, energy expenditure, RER, and activity. SCFA infusions were bracketed by saline infusions and given every other day. All three SCFAs significantly suppressed food intake 1 and 12hrs post-infusion compared to saline, with no effect on energy expenditure (n=8). None of the acute CFA administrations significantly impacted food intake, energy expenditure, or RER 24hrs post-infusion. Taken together, these data show that exogenous SCFA administration to the distal intestine suppresses food intake up to 12hrs post-infusion. Future studies will evaluate the effects of long-term daily SCFA infusions on energy homeostasis to replicate a chronic, therapeutic role of SCFAs.

Obesity-Correlated Hypothalamic Gene Network In Rodents Moderates The Association Between Maternal Body Mass Index And Postpartum Mental Health In Mavan Women

Danusa M. Arcego1, Yossef Goffer2, Charles A. LeDuc2, Rudolph L. Leibel2, Patricia P. Silveria1,3, Christina N. Boyle4
1Department of Psychiatry, Faculty of Medicine, Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada, 2Naomi Berrie Diabetes Center, Columbia University Irving Medical Center, New York, NY, United States, 3Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada, 4Institute of Veterinary Physiology, University of Zurich, Zurich, Switzerland

Clinical associations between obesity and psychiatric disorders might reflect genetic pleiotropies. Selectively-bred diet-induced obese (DIO) “Levin” rats, for which recent hypothalamic RNAseq analyses were conducted, provide a relevant
Representation Of Naturalistic Food Categories In The Human Brain
Jason A Avery, Madeline Carrington, Alexander G Liu, Alex Martin
Laboratory of Brain and Cognition, National Institute of Mental Health, Bethesda, MD, United States

Studies of the neural response to food pictures have identified responses in food-associated regions, such as the insula, amygdala, and orbitofrontal cortex. However, beyond this domain-specific response, little is known about how finer-grained food categories are represented in the brain. Specifically, are brain responses to food pictures driven by objective measures of food qualities or by subjective estimates of those qualities? To address this question, we asked 487 online participants to perform a behavioral task measuring the similarity of 36 foods with varying levels of fat and sugar. We used the data from this task to identify subjective food categories, via a Principal Components Analysis and K-means clustering approach. PCA indicated 80% of the variance was related to participants’ estimates of food healthiness and sweetness, rather than objective nutritional measures. K-means clustering of this data revealed five emergent categories: sweets, fats, starches, fruits, and vegetables. Using a Represenational Similarity Analysis (RSA) approach, we analyzed the neuroimaging data of 61 healthy subjects who viewed pictures of these foods during fMRI. Multivariate hemodynamic responses to food pictures reflected this food category structure — and not objective nutritional content — in food-responsive brain regions, as pattern similarity was significantly greater within vs. between categories in the mid-insula, OFC, amygdala, and ventral striatum. A searchlight RSA also reflected this category structure in bilateral regions of the ventral occipito-temporal cortex. These results reveal a fine-grained representation of food categories in the brain that corresponds more to subjective assessments of food qualities, than to objective food properties.

Dopamine Responses To Sodium Chloride Integrate Post-Ingestive Feedback During Sodium Appetite
Paula Bazzino, Kayva Nair, Vaibhav Konanur, Ted Hsu, Max Loh, Mitchell Roitman
University of Illinois at Chicago, Chicago, IL, United States

Sodium depletion recruits multiple brain structures to signal sodium deficit and to promote sodium seeking, and consumption. Some of these signals rapidly quiesce with exposure to sodium (e.g. pro-dynorphin neurons of the pre-locus coeruleus as per Lee et al. 2019). We have previously shown that sodium depletion recruits phasic dopamine release in the nucleus accumbens to intra-oral infusions of a hypertonic sodium solution. As sodium consumption continues, the appetite is sated. However, it remains unknown whether dopamine responses quiesce with consummatory behavior during sodium appetite. Here, we made brief intra-oral infusions of either hypertonic (0.45M) or hypotonic (0.1M) sodium chloride (NaCl) in sodium deplete rats. Prior to the experiment, a viral vector to express the genetically encoded dopamine sensor GRAB-DA was injected into the nucleus accumbens shell and during the experiment, dopamine transients were measured during each of 50 trials. On each trial, rats received a 200 microliter infusion over 5s. Relative to a pre-infusion baseline period, intra-oral infusions evoked a significant increase in dopamine that was similar in magnitude across the two concentrations of NaCl. However, when performing regression analysis, the magnitude of the dopamine response, while initially similar, decreased in magnitude across trials only when rats received 0.45M (interaction term p<0.05). The results demonstrate that dopamine responses during sodium appetite integrate post-ingestive signals relating sodium homeostasis. These signals can provide negative feedback to dynamically tune dopamine signaling once need has been met.

A Role For Glucokinase In The Mediobasal Hypothalamus In Glucose Appetition
Sandrine Chometton, Elizabeth Winnicki, Lindsey A. Schier
University of Southern California, Los Angeles, CA, United States

Obesity is related to excess intake of simple sugar. This is widely distributed to their sweet taste, but abundant data show that glucose also rapidly stimulates ingestion from other oral and postoral sites. How this is channeled into brain circuits governing motivation and metabolism remain unclear. Here, we assessed if consumption of small volumes of sugars (~3.5ml/kg over 3 min) or volume/kg-matched intragastric (IG) sugars infusion, meant to mimic the early phase of a meal, governs expectancies and brain responses to IG infusions of glucose, fructose, or α-Methyl-D-glucopyranoside (non-metabolizable glucose analog, αMDG), nor IG infusions of glucose, fructose, or αMDG had the same effect. 4,5 We measured the subjective expectancies by a rating scale and found that IG infusions of glucose did not differ in their expectancies from IG infusions of fructose or αMDG. IG infusions of αMDG induced shorter satiation compared with IG infusions of glucose or fructose. 3,4 Glucokinase (GCK) mRNA, but neither intake of isoconcentrated fructose, α-methyl-D-glucopyranoside, nor IG infusions of glucose, fructose, or αMDG had the same effect. Moreover, oral consumption of a low-calorie sweetener (0.1% saccharin) combined with IG glucose, fructose, or saline was not sufficient to boost MBH GCK under similar conditions. Systemic injection (IP) of low (0.5g/kg) and high (1g/kg) glucose also had no effect on MBH GCK expression compared to IP saline, in fasted male rats. Thus, glucose ingestion appears to be a key determinant. Next, we assessed if streptozotocin (STZ)-induced diabetes (65mg/kg, IP), which destroys insulin-secreting β cells and reduces arcuate nucleus GCK expression, disrupts within meal glucose appetite. Whereas control rats licked significantly more for glucose than fructose, especially in the early phase of the meal, STZ-treated rats failed to express this rapid stimulation of licking in response to glucose. Ongoing experiments are focused on understanding the link between the cephialic phase insulin release, GCK-linked glucosensors of the MBH, and glucose appetite.

Preoperative Inhibitory Control And Weight Loss After Bariatric Surgery
Justine Daoust1,2, Yashar Zeighami2,3, Mathilde Yergeau2,3, Melissa Pelletier1, Vicky Leblanc2, Sylvain Iceta4, Laurent Biertho1, André Thernhof1, Richard Denis1, Catherine Begin1,6, Andrewne Michaud1,2,3

1Institut universitaire de cardiologie et de pneumologie de Quebec, Universite Laval, Quebec, QC, Canada, 2School of
Bariatric surgery (BS) is an effective treatment leading to substantial weight loss. However, there is variability in long-term total weight loss (TWL) after BS. We tested the hypothesis that poor preoperative inhibitory control and lower mean neural brain activity in networks related to executive control are associated with lower TWL at 12 and 24 months after BS. We recruited 96 participants with severe obesity (BMI=43.8±4.1 kg/m²) who underwent BS and we measured TWL at 12 (n=62) and 24 (n=50) months after surgery. The stop signal task was performed at baseline to assess the ability to inhibit an already initiated response (SSRT, stop signal reaction time). A resting state functional MRI was also performed at baseline to assess mean fractional amplitude of low frequency fluctuations (fALFF) signal in 7 functional networks. Participants were subdivided in 3 groups based on SSRT: unsuccessful (n=10, the ones who failed the task), poor inhibitory control (n=43, lower than the median SSRT), and good inhibitory control (n=43). We used linear mixed effect models to examine the TWL by groups, and multiple linear models to test if preoperative mean fALFF signal in networks related to executive control are associated with TWL. Mean TWL was 34.7±7.7% at 12 months and 33.9±8.3% at 24 months. Participants in the unsuccessful group lost significantly less weight at 24 months compared to other groups (p=0.045). We found that preoperative mean fALFF signal in dorsal attention, control, and default mode networks are positively associated with the TWL at 12 months (p=0.019, p=0.041, p=0.029). These preliminary results suggest that inadequate inhibitory control and lower fALFF signal in networks related to executive control before BS seem to negatively influence TWL after BS. A.
Eating behavior results from the integration of environmental cues and interoceptive cues related to energy status, a process that relies on the hippocampus. Primary cilia, which are sensory organelle appendages on brain cells, are critical for the CNS regulation of feeding. Short cilial length or loss of cilia-related genes promotes obesity and hyperphagia. The orexigenic hormone melanin concentrating hormone shortens primary cilia in neurons, but whether primary cilia in the hippocampus per se respond similarly is unknown. We determined the distribution of primary cilia in the hippocampus, identifying whether neurons and/or astrocytes express the ciliary markers Arl13B and AC3. Adult rat hippocampal neurons and astrocytes were grown in co-culture and immunocytochemistry was performed to identify ciliary presence by cell type. We found that Arl13B are present in astrocytes in the adult rat brain, whereas AC3 is primarily localized to neurons of the hippocampus. Immunohistochemical staining in brain tissue sections revealed the presence of neuropeptidergic receptors melanin-concentrating hormone (MCH1R) in excitatory pyramidal neurons. We next determined whether long term consumption of an obesogenic diet impacts levels of ciliary signaling molecules and MCH1R in hippocampal tissue. Female rats were placed on a high fat diet for 6 months and brain tissues dissected out for protein quantification of AC3, and MCH1R, however no differences were observed. We conclude that MCH1R in the hippocampus is largely localized to the primary cillum, and that MCH1R protein levels are not impacted by long term consumption of an obesogenic diet in females.

**AgRP Neuron Activity Potentiates the Expression and Retention of Flavor-Nutrient Associations**

Nathaniel T. Nyma, Aaron D. McKnight, Alexandra Vargas, Kevin P. Myers, Amber L. Alhadeff

1Monell Chemical Senses Center, Philadelphia, PA, United States, 2University of Pennsylvania, Philadelphia, PA, United States, 3Bucknell University, Lewisburg, PA, United States

Mice prefer flavors that are associated with nutrients, but the circuits that coordinate these preferences are not fully understood. Flavor-nutrient learning is commonly used to study how post-ingestive nutrient signaling drives the development of flavor preferences in rodents. Because energy status can influence flavor-nutrient learning, we examined whether hypothalamic Agouti Related Protein (AgRP)-expressing “hunger” neurons modulate flavor-nutrient associations. We engineered mice to optogenetically stimulate AgRP neurons while they separately licked one of two flavors to trigger an intragastric infusion of water or nutrients (glucose or fat). AgRP neuron activation during training potentiated the development of flavor-nutrient learning for both nutrients. To determine whether AgRP neuron activity potentiates flavor-nutrient learning by increasing consumption during training or by improving associative learning, we next controlled the number of licks during training. Limiting flavor consumption of AgRP-stimulated mice to the intake of controls blocked the enhancement of flavor-nutrient learning, suggesting that AgRP stimulation enhances flavor-nutrient associations by increasing motivation to consume during training. Further, AgRP-stimulated mice exhibited a sustained preference for the nutrient-paired flavor after the initial test day. Ongoing experiments are using in vivo fiber photometry to reveal the real-time dynamics through which nutrient-paired cues influence AgRP neuron activity. Overall, our results demonstrate that AgRP neuron activity improves the learnability of flavor-nutrient associations by both stimulating sampling of potentially rewarding flavor cues and reducing the sensitivity of a formed preference to future unrewarded exposures.

**Gdf15-Dependent and -Independent Effects of Cisplatin On Cell Type-Specific Transcriptomes In The Rat Area Postrema And Nucleus Tractus Solitarius**

Benjamin C. Reiner, Richard C. Crist, Tito Borner, Robert P. Doyle, Bart C. De Jonghe, Matthew R. Hayes, Kevin P. Myers

1Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, United States, 2Department of Biobehavioral Health Sciences, University of Pennsylvania, Philadelphia, PA, United States, 3Department of Chemistry, Syracuse University, Syracuse, NY, United States

Cisplatin-induced nausea and emesis is associated with anorexia, weight loss and increased mortality. Cisplatin treatment increases endogenous growth differentiation factor 15 (GDF15) production, a cytokine expressed and secreted as part of stress and disease processes. Exogenous GDF15 administration and increased endogenous GDF15 production suppress feeding and body weight by inducing nausea and emesis via excitatory neurons expressing the GFRAL-RET heterodimeric receptor complex in the area postrema (AP) and nucleus tractus solitarius (NTS). Exogenous GDF15 alters cell type-specific transcriptomes in AP and NTS through direct interaction with GFRAL-RET expressing excitatory neurons and indirect interaction with other neuronal and glia cell types (Reiner et al, 2022). However, the effects of cisplatin on cell type-specific transcriptomes in the AP and NTS is not understood. Furthermore, what portion of cisplatin’s effects is attributable to GDF15-dependent and -independent mechanisms is unknown. To address these knowledge gaps, we performed single nucleus RNAseq on rat AP and NTS following exogenous cisplatin, GDF15 or vehicle treatment. Transcriptomically distinct neural and glial cell types, including GFRAL-RET expressing excitatory neurons were identified, and cisplatin- and GDF15-induced transcriptome alterations were determined. Pathway analyses identified GDF15-dependent and independent molecular signaling pathways altered by cisplatin. Additionally, GDF15-dependent and independent microRNA and transcription factors regulating the observed alterations in gene expression were identified. These data expand our understanding of molecular mechanisms underlying adverse effects of cisplatin and identify cell type-specific targets for future anti-emetic interventions.

**Characterization And Localization Of Adult Hippocampal Primary Cilia**

Grace C Madu, Jessica R Hoffman, Mai O Spaulding, Emily E Noble

Department of Nutritional Sciences, University of Georgia, Athens, GA, United States

Habenula neurons have been implicated in the negative regulation of reward-related feeding, and could play a role in obesity and metabolic disorders. Interestingly, a relationship between habenula volume and Hemoglobin A1c (HbA1c), a diabetes risk marker, has been observed in nicotine smokers. No reports to date, however, have investigated habenula function in human obesity or diabetes. We used 3T functional Magnetic Resonance Imaging data from the S1200 Release of the Human Connectome Project and selected 49 subjects with relatively low (c<7) and 44 subjects with high (c<5.7; i.e. prediabetic) HbA1c values, matched on age, gender, ethnicity, handedness, socioeconomic status and depression scores. Prediabetic and control subjects had an equal body mass index (BMI) distribution, meaning there were an equal number of lean (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI>30) subjects in both groups. Using partial correlation analysis (controlling for thalamic connectivity), we assessed the functional connectivity of habenula with ventral tegmental area (VTA), insula, hypothalamus, amygdala, frontal medial cortex and nucleus accumbens. Using a linear model with age and gender as covariates, we observed a significant BMI x HbA1c interaction effect for the habenula-VTA connection (p=0.02, corrected for multiple testing). The habenula-VTA connection shows a positive correlation with HbA1c, but only in lean subjects (r=0.51). Our findings suggest that the habenula-VTA connection plays a role in glucose regulation in normal-weight individuals, which might be disturbed in overweight and obese individuals. Additional research will assess causality and explore implications of these exploratory observations.
The introduction of ultra-processed food (UPF) has changed the modern food environment and now accounts for over half of all calories consumed in the US. Despite this large increase in consumption, it is still unknown if UPF is disproportionately reinforcing compared to their minimally processed food (MPF) counterparts. To investigate this potential phenomenon our lab has established a novel picture set termed “ProcessedFood.Pics” (PF.Pics). An initial 58 foods (31 UPFs and 27 MPFs) were selected based on NOVA (not an acronym) scores, a standardized method to classify the degree of food processing. These foods were selected to have similar nutritional compositions (energy density, macronutrients, etc.) as quantified with values from Nutrition Data System for Research. Image characteristics such as red, green, blue, intensity, complexity, and contrast were assessed using established methods. This preliminary picture set was assessed on a variety of ratings (liking, estimated store cost, etc.) by 400 MTurk workers. The final photos were selected based on propensity score (PS) weighting which represents the estimated probabilities of a picture being in the UPF group vs. the MPF group, conditioned upon the set of nutritional value, rating, and image characteristics. The use of PS weighting algorithms provides an unbiased and robust methodology for matching UPFs and MPFs on the maximal number of factors, allowing the isolation of processing in interpretation. In future studies, our lab will use PF.Pics to experimentally test the relationship between reinforcing value and metabolic response to UPF and MPF. The final goal of these experiments is to rigorously test degree of processing independently of other factors as a key element driving food reinforcement and food reward.
Chair(s): Guillaume de Lartigue

**P1**

**Thermoregulatory Poa Leptin Receptor Neurons Interact Dynamically With Energy Sensing Circuits**

11:00

Heike Muenzberg

Pennington Biomedical Research Center, Baton Rouge, LA, United States

Obesity is an ongoing epidemic and short-term success of lifestyle intervention (dieting and exercise achieve) have proven largely unsustainable to prevent long-term weight regain. Thus, a better understanding how the brain regulates energy homeostasis during diverse physiological challenges is an important goal to develop improved treatment strategies. We identified leptin receptor (Lepr) expressing neurons within the dorsomedial hypothalamus (DMH^{Lepr} neurons) and the preoptic area (POA^{Lepr} neurons) as part of thermoregulatory circuits. However, these thermoregulatory neurons also robustly modulate body weight. Indeed, we show that POA^{Lepr} neurons are physiologically activated by warm-temperature and as such drive temperature-dependent effects on energy expenditure and food intake, powerful enough modulate body weight. Furthermore, POA^{Lepr} neurons impact metabolic adaptations to energy availability that are classically mediated by neuronal populations in the arcuate nucleus. We will discuss emerging evidence that physiological changes in ambient temperature and energy availability are integrated via overlapping neuronal populations that dynamically impact physiological adaptations of energy expenditure and food intake.Â

**11:25**

**Brainstem Regulation Of Energy Homeostasis**

Alexander R Nectow

Columbia University, New York, NY, United States

Energy balance is maintained by an extended circuitry in the central nervous system that carefully balances food intake with energy expenditure. We have recently shown that the brainstem’s dorsal raphe nucleus (DRN) is an important component of this extended circuit. In particular, we have identified GABAergic and glutamatergic DRN subtypes that are capable of regulating key aspects of energy intake and expenditure. Thus, we studied the role of the DRN in temperature regulation. Experiments were performed in a series of animal models with various genetic manipulations. Using these models, we are able to develop new strategies to treat obesity and other metabolic disorders. This work has important implications for understanding the role of the brain in energy homeostasis and for developing new treatments for obesity and related metabolic disorders.

**P3**

**Enabling New Technologies And Models To Understand The Brain-Body Interface**

11:50

Li Ye, Yu Wang, Neeraj Lal, Victoria Naudell, Ardem Patapoutian, Anton Maximov

Scripps Research, La Jolla, CA, United States

Historically, tools suitable for studying the crosstalk between neural circuits and their somatic targets in an intact biological context have been very limited. We aim to design and develop techniques specifically for studying brain-body crosstalk in its native configuration. Although the recent development of tissue clearing techniques has advanced our ability to visualize the mammalian brain in 3D, it remains challenging to image the peripheral organ systems together with the CNS in the intact body. Here, we developed HYBRID (HYdrogel-Based Reinforcement of DISCO), by recombining components of organic- and polymer-based clearing pipelines and achieved high transparency and protein retention, as well as compatibility with direct fluorescent imaging and immunostaining in cleared mammalian bodies. HYBRID offers a simple and universal solution to visualize large heterogeneous body parts or entire animals for studying brain-body crosstalk. Using HYBRID together with a set of original viral and circuit tools, we begin to study the integrated central and peripheral circuits underlying the neural control of cold adaptations.Â

**P4**

**The Role Of Brs3 (Bombesin Receptor Subtype-3) In Energy Homeostasis**

12:15

Marc Reitman

NIDDK, NIH, Bethesda, MD, United States

Brs3 is an orphan G protein-coupled receptor that is expressed in a limited number of neurons. Brs3 null mice are obese while Brs3 agonists reduce food intake, and increase resting metabolic rate, body temperature, heart rate, and blood pressure. We have characterized the distribution of the receptor itself to physiologic functions and also explored the roles of Brs3-expressing neurons. Stimulation of Brs3 neurons in the paraventricular hypothalamus suppresses food intake. In contrast, stimulation of Brs3 neurons in the dorsomedial hypothalamus increases body temperature, heart rate, and energy expenditure and activates brown adipose tissue, with no effect on food intake or physical activity. These DMH neurons act via the raphe pallidus. In the preoptic area (POA) there are at least five types of Brs3 neurons, some of which have collateral projections. Cold exposure activates POA Brs3 neurons and activation of POA Brs3 neuronal projections to the paraventricular hypothalamus, dorsomedial hypothalamus, or periarcuate grey each increases body temperature, identifying a role in cold defense. These contrasts with the previously identified POA neuron classes, which all reduce body temperature when activated. POA Brs3 neurons also regulate body temperature variability, with selective inactivation of these neurons causing overshoot/undershoot of target body temperatures. Thus, Brs3 neurons regulate aspects of energy homeostasis via multiple sites in the brain and serve as important entry points for defining the neural circuitry controlling body temperature, energy expenditure, and food intake.Â

**P5**

**Q&A**
Legislation aimed at reducing sugar intake assumes that sweet-liking drives overconsumption. However, evidence that greater liking for sweet taste is associated with a more unhealthy body size has been mixed and complicated by relatively small samples, an overreliance on BMI and a lack of phenotyping. Research strongly suggests three phenotypic responses to sweet taste: extreme sweet-likers (ESL), moderate sweet-likers (MSL) and sweet dislikers (SD). We aimed to address these issues by conducting an individual participant data meta-analysis (IPD-MA) to better answer the question is sweet liking a key driver of obesity? Systematic searches across four databases identified 5736 potential articles. Of these, 53 papers published in English between 1st January 1972 to 19th July 2021 met our search criteria. Studies had to include a taste assessment that measured liking using sucrose (>13.7% w/v), which allowed phenotyping and included BMI, body fat percentage (BF%), or fat-free mass (FFM). A one-stage IPD-MA of 15 studies controlling for sex revealed no statistically significant differences in BF% (n = 1836) between the three phenotypes. For BMI (n = 2368), MSL had slightly lower BMI than ESL (b = -0.69, 95% CI (-1.17, -0.20), d = -0.11, p = .006), who had the highest overall BMI. Most interestingly for FFM (n = 768) both MSL and SD showed significantly lower FFM than ESL (b = -1.75, 95% CI (-2.75, -0.75), d = -0.25, p <.001; b = -1.96, 95% CI (-3.21, -0.71), d = -0.22, p = .002) respectively. This pattern of results was consistent with models using robust estimation and excluding participants with a BMI >40. This suggests that the higher BMI often seen in sweet-likers may be due to a larger FFM and questions the simple model where sweet liking alone is a risk factor for obesity.

### From An Empty Stomach To Anxiolysis: Molecular And Behavioral Assessment Of Sex Differences In The Ghrelin Axis Of Rats

Stina Borchers, Jean-Philippe Krieger, Ivana Marie, Jil Carl, Maral Abraham, Francesco Longo, Mohammed Asker, Jennifer Richard, Karolina P Skibicka

1University of Gothenburg, Gothenburg, Sweden, 2Wallenberg Centre for Molecular and Translational Medicine, Gothenburg, Sweden, 3Pennsylvania State University, University Park, PA, United States

Ghrelin is well-recognized for its role in promoting feeding, but also a role in stress and anxiety has been suggested. To date, most studies of ghrelin’s effects on anxiety focused on male rodents. Here, we hypothesize that female rats are wired for higher ghrelin sensitivity. To test this, we compared components of the ghrelin axis between SD rats of both sexes. Second, we assessed the effect of endogenous or exogenous ghrelin on their feeding and anxiety-like behavior. We show that female rats have higher serum ghrelin levels and lower levels of the endogenous antagonist LEAP-2. Further, in females, ghrelin levels are partly dependent on estradiol. Females also express higher levels of the ghrelin receptor GHSR1A in brain areas involved in feeding and anxiety, such as the lateral hypothalamus, hippocampus, and amygdala. Overnight fasting increased GHSR1A expression in the amygdala of females, but not males. To test the behavioral consequences of these molecular differences, both sexes were tested in the elevated plus maze (EPM), open field (OF), and acoustic startle response (ASR) test after three ghrelin manipulations: increased endogenous ghrelin levels by overnight fasting, systemic administration of ghrelin, or blockade of fasting-induced ghrelin signaling with a GHSR1A antagonist. We show that females exhibit a stronger anxiolytic response to fasting and ghrelin in the ASR, supporting our findings in the ghrelin axis. Most importantly, after GHSR1A antagonist treatment, females have a more pronounced anxiogenic response. In summary, females show stronger behavioral responses to ghrelin manipulations in the realm of anxiety-like behaviors, but not feeding behaviors.

### Best Student Presentation Award Finalist

#### Humans Show Sensitivity To Energy Density In Higher Energy-Dense Meals: Further Evidence From A Large 24-Hour Diet-Recall Study In Argentina

Annika N. Flynn, Peter J. Rogers, Jeffrey M. Brunstrom

Nutrition and Behaviour Unit, School of Psychological Science, University of Bristol, Bristol, United Kingdom

It has been argued that meal energy (kcal) intake is largely governed by the weight (g) of food consumed and, in the case of energy-dense meals, this can cause ‘passive overconsumption’ (increased energy intake in higher energy-dense meals). Previously, using a large dataset of meals from the UK National Diet and Nutrition Survey, we reported a surprising sensitivity to meal energy density (ED, kcal/g): meal energy intake decreased with increasing meal ED in high energy-dense meals (people ate smaller meals than necessary). Importantly, it remains to be established whether this overcompensation generalises to other populations, outside the UK. To that end, using segmented regression to analyse 24-hour diet-recall data from Argentina (FAO/WHO GIFT, N = 2,738 meals), we found the same overcompensation pattern observed in the UK. Specifically, for meals with an ED above 2.04 kcal/g, mean centred (within participant) meal energy intakes decreased (β = -149.03, SE = 11.60) with increasing meal ED. This replication lends further support for our two-component model of meal size (g) relating satiation signals from ‘volume’ and ‘energy content’ to meal ED (under review) and suggests that overcompensation for energy in higher energy-dense meals is a widespread behavioural trait.

#### Effects Of Obesity And Sex On Brain Responses To Caloric Sugars And Non-Nutritive Sweeteners

Stephanie Kullmann, Ralf Veit, Kay Jann, Shan Luo, Brendan Angelo, Alexandra G. Yunker, Jasmin Alves, John Monterosso, Kathleen A. Page

1Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tuebingen, Tuebingen, Germany, 2German Center for Diabetes Research (DZD e.V.), 3Department of Internal Medicine, Division of Endocrinology, Diabetology and Nephrology, Eberhard Karls University Tuebingen, Tuebingen,
Evidence suggests that neural responses to post-ingestive signals, including nutrients and taste, affect feeding behavior. We examined the response of the hypothalamus and insula to the ingestion of sugars and the non-nutritive sweetener (NNS), sucralose. Seventy-four participants (23.4±4 years; 42% male; BMI 27.2±5 kg/m2) completed 4 MRI visits with ingestion of drinks containing 75g sucrose, 75g glucose, sucralose, or water in a randomized cross-over design. Cerebral blood flow (CBF) was measured before, 15min and 30min after drink ingestion. Primary outcomes were CBF responses to the drink contrasts: glucose vs. sucrose, sucralose vs. water, and sucrose vs. sucralose. Separate mixed effects models for each drink contrast were computed with sex and weight status as fixed factor and participants as random factor. Bonferroni-Holm was used to adjust for multiple comparisons (p<0.05). In the hypothalamus, weight status was associated with greater CBF increase to both sucrose and sucralose. There was no significant difference between sugars (glucose vs. sucrose). In the insula, there was a drink by sex interaction in response to glucose vs. sucrose: females showed higher CBF response to glucose and males to sucrose. A main effect of weight status and a weight status by sex interaction in the insular response to sucralose vs sucrose and sucralose vs water comparisons. Females with overweight showed the greatest increase in the insula to sucralose and sucrose, and weight status was associated with a greater CBF response to sucralose and water. These findings suggest that weight status and sex are associated with differential activation of brain regions involved in gustation and energy homeostasis to ingestion of sugar and NNS, which may influence eating behavior.

Sexually Dimorphic Effects Of A Western Diet On Brain Mitochondrial Bioenergetics And Neurocognitive Function

Magen N. Lord1, Jun-Won Heo2, Albino G. Schifino2, Jessica R. Hoffman1, Kristen N. Donohue3, Jarrod A. Call2,4, Emily E. Noble1

1Department of Nutritional Sciences, University of Georgia, Athens, GA, United States, 2Department of Kinesiology, University of Georgia, Athens, GA, United States, 3Department of Human and Evolutionary Biology, University of Southern California, Los Angeles, CA, United States, 4Regenerative Biosciences Center, University of Georgia, Athens, GA, United States

Western Diets (WD), high in added sugars and saturated fats, impair learning and memory and contribute to weight gain. Brain mitochondria are vital contributors to weight regulation and neurocognitive function. We hypothesized that consumption of a WD negatively impacts brain mitochondrial bioenergetics, contributing to impaired neurocognitive function and obesity. Rats were randomized to receive a WD consisting of high-fat pellets, an 11% high fructose corn syrup beverage, and water (WD; n=10 males, n=12 females) or standard chow and two bottles of water as the control diet (CD; n=10 males, n=12 females). Cognitive ability was measured using a hippocampal-dependent learning and memory task. Whole hypothalamus (HYP) and hippocampi (HPC) were collected for analyses of mitochondrial O2 consumption, membrane potential, and redox status of NAD(P)H. Results revealed a sexually dimorphic macronutrient preference where females on WD consumed a greater percentage of calories from sugar compared to males, who consumed a greater percentage of calories from fat and protein. WD impaired HPC-dependent learning and memory in males, whereas females in either diet group did not learn the task. Bioenergetics analyses revealed a tissue-specific adaption to WD in the HYP, where males on WD oxidized more fat, and females oxidized more fat and sugar at peak energy demand compared to same-sex controls. In the HPC of males, analyses showed an elevated tendency toward high membrane potential, which has been linked with oxidative stress. Together these findings suggest that a WD alters brain mitochondrial bioenergetics in a brain region and sex dependent manner, possibly due to differences in macronutrient intakes, though further investigation is warranted.

Effects Of Psilocybin On Activity-Based Anorexia And Cognitive Flexibility In Female Rats

Laura K Milton, Gabriella A Farrell, Brian J Oldfield, Claire J Foldi

Monash University, Department of Physiology and Biomedicine Discovery Institute, Clayton, Australia

Anorexia nervosa (AN) has one of the highest mortality rates of any psychiatric disorder and despite this, there are currently no effective medicinal treatments. The therapeutic potential of psilocybin for AN is currently being explored in clinical trials, and is proposed to act by breaking down the cognitive inflexibility that characterises AN. However, the mechanisms through which psilocybin may alleviate anorectic symptoms remain unknown. We used the activity-based anorexia (ABA) rat model and operant reinforcement paradigms to examine the effects of psilocybin on pathological weight loss and cognitive-behavioural flexibility. Female Sprague-Dawley rats (n=23; 7 weeks old) were trained to run in wheels and administered psilocybin (1.5mg/kg) or saline 24h prior to the commencement of ABA, consisting of unlimited access to running wheels paired with time-limited access to food. A separate cohort of rats (n=31) were trained to nose-poke into one of two operant ports in order to obtain a reward and administered psilocybin or saline 24h prior to reversal of the reward-paired port. Extinction and reinstatement of responding for sucrose rewards were also examined the day after treatment in a separate cohort of rats (n=22). Psilocybin attenuated the rapid weight loss elicited by ABA conditions, which was driven by both increased food intake (F_{2,20}=15.45, p<0.0001) and reduced compulsive wheel running (F_{2,20}=12.26, p=0.0003). Psilocybin also improved reversal learning (F_{1,20}=5.128, p=0.031) without effects on extinction (F_{1,20}=0.097, p=0.758) or reinstatement (F_{1,20}=0.081, p=0.779), suggesting a specific improvement in flexible behaviour. Taken together, these findings provide initial support for the therapeutic potential of psilocybin for treating cognitive inflexibility in AN.

Is Emotional Eating Emotional?

Larisa Olteanu1, Geraldine Coppin1

1UniDistance, Brig, Switzerland, 2UniDistance, Brig, Switzerland

In modern societies humans do not consume food only to reduce hunger, but also for hedonic or emotional regulation reasons. Although frequently used in the literature, emotional eating remains a poorly understood concept. Specifically,
numerous studies failed to provide evidence that self-described emotional eaters consume more food than non-emotional eaters. In the current study, we explored emotional eating on a sample of 91 Swiss French-speakers adults using various tools (questionnaires, facial expressions, implicit and explicit tasks) in a well-controlled online experimental setting. Participants were divided in two groups according to their reports on the Emotional Eating Scale. Raven matrix task was used to induce emotions, followed by food images on which participants had to complete explicit and implicit wanting tasks, report on their emotions, while facial expressions, and reaction times were measured. Results showed no significant differences between self-reported emotional and non-emotional eaters in implicit and explicit wanting tasks. The only measure where significant differences between the two eater groups were obtained was reaction time in front of food images. Specifically, emotional eaters ($M = 1479.00 \text{ ms}, SD = 1202.43$) were faster in selecting a food image than non-emotional eaters ($M = 1891.81 \text{ ms}, SD = 2233.17$), $t(693) = 3.23, p = .001, d = .23$. Our findings suggest that self-reported emotional eating represents a construct that could reflect eating concerns more than actual eating behaviors.

The Edinger-Westphal Nucleus: Sex Differences In Midbrain Neuropeptide Control Of Binge Drinking

Leigh C Walker$^{1,2}$, Sarah S Ch’ng$^1$, Felicia M Reed$^3$, William J Giardino$^{4,5}$, Andrew J Lawrence$^{1,2}$

$^1$Florey Institute of Neuroscience and Mental Health, Melbourne, Australia, $^2$Florey Department of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia, $^3$Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, Australia, $^4$Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, $^5$Wu Tsai Neurosciences Institute, Stanford University School of Medicine, Stanford, CA, United States

The circuitry mediating excessive alcohol consumption includes the understudied central projecting Edinger-Westphal (EWcp); a structure dense in neuropeptide expression, including cocaine and amphetamine regulated transcript (CART). While studies have shown a critical role for this nucleus in alcohol consumption, few studies have interrogated the contributions of distinct EW populations. To examine a functional role of these cells in binge drinking we used chemogenetics to inhibit EWcp$^{\text{CART}}$ cells in male or female CART-Cre mice. Chemogenetic inhibition of EWcp$^{\text{CART}}$ cells had no effect on binge drinking, anxiety behaviour or other consummatory behaviours in male mice; however, a specific reduction in alcohol binge drinking was observed in female mice. Using RNAscope we examined the neurochemistry of EW$^{\text{CART}}$ cells observing strong overlap with the ghrelin receptor (GHSR). Given the dense expression of GHSR on EW$^{\text{CART}}$ cells we examined whether CART-GHSR interactions within the EWcp mediate binge drinking in female mice. Ghrelin administration (0.5mg/kg-i.p.) increased binge drinking in female mice, which was reduced by chemogenetic inhibition of EWcp$^{\text{CART}}$ cells. Finally, we knocked down GHSR expression in the EW of male and female mice using a shRNA. Ghsr-shRNA knockdown reduced binge drinking specifically in female, but not male mice compared to scram-shRNA controls. Together, our results suggest the EWcp is a region mediating excessive alcohol bingeing through GHSR and CART interactions in female mice. Given the recent clinical success of GHSR1a inverse agonists to treat AUD, understanding the neural mechanism(s) underpinning how the ghrelin system mediates alcohol consumption are critical.
Lunch

1:15 - 2:15 PM

Meet The Scientist Professional Development Panel

L. Maria Hall

Lunch will be provided to the first 50 attendees.

Please register here: https://docs.google.com/forms/d/e/1FAIpQLSdi0rE_Em3T-qJISqywZb74KgTb-2DfnI6lAdEvTbjNoX8uQ/viewform

During this career development panel and lunch, our panel of scientists will share their advice for pursuing careers within and outside of academia. Panelists will answer questions from the audience and share their expertise across topics such as: transferrable skills for alt-academia careers, navigating the academic job market, early-career grant writing, and finding work-life balance.

2:30 - 3:30 PM

MARS Lecture 2

Chair(s): Alan Spector

2:30

The Reticular Formation, Interoception, And Motivated Behavior

Linda Rinaman
Florida State University, Tallahassee, FL, United States

The reticular formation comprises a diffuse, interconnected network of neurons within the brainstem tegmentum that mediate sensory feedback control over somatic and autonomic motor outflow. In addition, highly collateralized axonal projections from reticular neurons to the thalamus, hypothalamus, and limbic forebrain modulate behavioral state transitions, cognitive processes, and emotionally motivated behavior. Past research has largely focused on pathways through which the reticular formation receives and integrates exteroceptive sensory signals (e.g., visual, auditory, somatosensory) to impact behavioral state and motor functions. In this lecture I will develop the theory that two neurochemically-distinct populations of reticular formation neurons [i.e., noradrenergic neurons of the A2 cell group, and glucagon-like peptide 1 (GLP1) neurons] are uniquely positioned to detect visceral and humoral sensory signals, are highly sensitive to metabolic state, and play a special role in the interoceptive modulation of feeding and other motivated behaviors.

3:30 - 4:00 PM

Coffee Break

4:00 - 6:00 PM

NITA Symposium

Chair(s): Dana Small

Best Student Presentation Award Finalist

4:00

At1Ar⁺ Sensory Afferents In The Caudal Nucleus Of The Solitary Tract Modulate Na⁺ Intake In Dehydrated Mice

Caitlin M. Baumer-Harrison¹,²,³,⁴, Karen A. Scott²,³, Hipatia V. Donoso²,³, Guillaume de Lartigue²,³, Eric G. Krause²,³, Annette D. de Kloet¹,²,³

¹Physiology and Functional Genomics, University of Florida, Gainesville, FL, United States, ²Pharmacodynamics, University of Florida, Gainesville, FL, United States, ³Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, Gainesville, FL, United States, ⁴Center for Smell and Taste, University of Florida, Gainesville, FL, United States

Extracellular dehydration leads to the synthesis of angiotensin-II which acts on angiotensin type 1a receptors (AT1aR) to regulate blood pressure (BP), water (H₂O) and sodium (Na⁺) homeostasis. AT1aR are expressed on afferents that transmit cardiovascular or gustatory sensory information to the nucleus of the solitary tract (NTS). We found the optical excitation of these afferents in the caudal NTS mimics perception of increased vascular stretch. This induced frequency-dependent alterations in BP and Fos immunoreactivity in brain regions involved in fluid balance and cardiovascular function. Thus, we hypothesized that stimulation of these AT1aR⁺ afferents is sufficient and necessary to modulate H₂O and Na⁺ intake during alterations in vascular stretch. Male mice expressing enhanced yellow fluorescent protein (eYFP) and excitatory channelrhodospin2 (ChR2) or inhibitory halorhodopsin (Halo) in AT1aR⁺ cells were implanted with a fiber optic targeting the NTS. H₂O and 0.3M NaCl intake were measured in the home-cage using two-bottle preference tests in the presence and
Trapping A Meal Engram In The Ventral Hippocampus

Thirst Sensitive Neurons Within The Anterior Cingulate Cortex Modulate Water Intake To Maintain Body Fluid Homeostasis

Best Student Presentation Award Finalist

4:12

Trapping A Meal Engram In The Ventral Hippocampus

Lea DeCarie-Spain, Logan Tierno Lauer, Alicia Kao, Ashyah Galbokke Hewage, Alexander Bashaw, Alyssa Cortella, Richard Crist, Benjamin Reiner, Matthew Hayes, Scott Kanoski

Department of Biological Sciences, University of Southern California, Los Angeles, CA, United States; Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

The ventral subregion of the hippocampus (vHPC) has recently been identified as a key brain that integrates memory function and food intake control, yet the neural mechanisms mediating this integration have not been systematically evaluated. We set to illustrate the activity dynamics of vHPC neurons during appetitive and consummatory behaviors and characterize the profile and function of vHPC neurons engaged by eating. Fiber photometry-based recording of dynamic bulk vHPC calcium activity revealed increased activity during a spatial memory-based foraging task, whereas vHPC activity was reduced during actual food consumption. To evaluate a possible functional connection between vHPC neurons engaged by eating and foraging-related memory, rats received vHPC injections of a tamoxifen-inducible virus expressing Cre-recombinase driven by a Fos promoter, paired with a Cre-dependent virus expressing a diphtheria toxin to ablate activated neurons. Recombination was induced by tamoxifen injection in 24h fasted rats given 30-minute access to food (‘Fed’) or not (‘Fasted’). Results show that ablation of food-responsive neurons in the Fed group increased spontaneous meal size and impaired performance in the spatial memory foraging task. To characterize the genetic profile of vHPC food-responsive neurons, the vHPC was harvested in the Fed or Fasted state for single-nucleus RNA sequencing. Results identify that neurons active in the Fed state are enriched in the serotonin receptor type 2a, while those active in the Fasted state express the orexin type 2 and cannabinoid type 1 receptors. Together, these results identify and characterize a population of vHPC neurons that are engaged by eating and contribute functionally to both meal size control and foraging-related spatial memory.

Best Student Presentation Award Finalist

4:24

Thirst Sensitive Neurons Within The Anterior Cingulate Cortex Modulate Water Intake To Maintain Body Fluid Homeostasis

Khalid Elsaafien, Jesus D. Penaloza-Aponte, Scott W. Harden, Karen A. Scott, Charles J. Frazier, Annette D. de Kloet, Eric G. Krause

Department of Pharmacodynamics, Gainesville, FL, United States; Department of Physiology and Genomics, Gainesville, FL, United States; Department of Neuroscience, Gainesville, FL, United States; Center for Integrative Cardiovascular and Metabolic Diseases, Gainesville, FL, United States

The anterior cingulate cortex (ACC) has recently emerged as a cortical structure involved in fluid homeostasis. Extracellular dehydration leads to the synthesis of angiotensin II, which acts on its receptors to regulate fluid ingestion. This study investigates the role of neurons containing angiotensin receptors in the ACC in the regulation of fluid homeostasis. We found an abundance of neurons expressing angiotensin type-2 receptors (AT2R) in the ACC (ACC^AT2R), where ACC^AT2R neurons were either glutamatergic or GABAergic. These ACC^AT2R neurons received input from cortical regions involved in executive function that include the prefrontal cortex, and projected to regions implicated in fluid homeostasis such as the lamina terminalis. To examine whether ACC^AT2R play a role in thirst responses, we directed the expression of the calcium indicator, GCaMP6f, within ACC^AT2R of male AT2-R-Cre mice. Following a GRIN lens implantation in the ACC, we recorded calcium events in conscious freely moving mice during euhydration and dehydration. Interestingly, a subset of ACC^AT2R neurons either increased or reduced their activity in response to dehydration. To evaluate the function of these neurons, excitatory channelrhodopsin-2 (ChR2) or step-wave inhibitory channel rhodopsin (SwiChRca) were expressed in ACC^AT2R. Intriguingly, both optogenetic excitation and inhibition of ACC^AT2R reduced water intake in dehydrated mice. This suggests potential crosstalk between inhibitory and excitatory ACC^AT2R, where the balance between inhibition and excitation predicts ACC^AT2R response to fluid homeostasis. Collectively, these results suggest that AT2R containing neurons within the ACC respond to thirst and mediate water intake, possibly by altering the perception of hydration state.

Best Student Presentation Award Finalist

4:36

Network Targeted Brain Stimulation To Affect Eating Behavior In Obesity

Theresa Ester, Ralf Veil, Marie L. Beermann, Louise Fritzsch, Hubert Preis, Andreas L. Birkenfeld, Martin Heni, Stephanie Kullmann

Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich, TÄfÅ¼ibingen, Germany; German Center for Diabetes Research (DZD e.V.), DÄfÅ¼sseldorf, Germany; Department of Internal Medicine, Division of Endocrinology, Diabetology and Nephrology, Eberhard Karls University TÄfÅ¼ibingen, TÄfÅ¼sseldorf, Germany

Targeted stimulation of the prefrontal cortex, using transcranial direct current (tDCS), can affect eating behavior. However, no study to date evaluated the effects of tDCS on brain areas important for the control of metabolism (i.e., hypothalamus). In a randomized and double-blind study, 43 participants (36.6 ± 13.6 years; BMI 30.6 ± 3.2 kg/m^2; 21 males) received 25 minutes active multichannel tDCS stimulation, or sham (control), on three consecutive days. Active stimulation (either...
Physiological need in general and hunger specifically motivates eating behavior. Decades of research support a role for midbrain dopamine neurons in the generation of motivated behaviors but how they integrate hunger signals is only beginning to be elucidated. We and others have shown that phasic dopamine responses to food and food-related cues are regulated by hunger as well as central action of hormones and neuropeptides that drive food intake in sated rodents. The brain also monitors glucose – its main metabolic substrate. Cytogluconeogenesis enhances hunger ratings and the rewarding value of sucrose in humans. However, it is unknown whether glucoprivic signals modulate dopamine signaling evoked by sucrose. We monitored the activity of dopamine neurons in the ventral tegmental area (VTA) by combining cre-dependent expression of a genetically encoded calcium indicator with in vivo fiber photometry. In ad libitum fed rats, intraoral sucrose delivery evoked a modest, phasic rise in dopamine activity. Administration (intraperitoneal, lateral, or fourth ventricular) of the antiglycolytic agent 5-thio-D-glucose (5TG; either 15 or 45 min prior to testing) – which has been shown by others to induce eating — significantly augmented the phasic dopamine response to sucrose and sucrose cues. Moreover, 5TG failed to alter dopamine responses to water, suggesting the response is selective for caloric stimuli. Interestingly, 5TG enhancement of sucrose-evoked dopamine is more rapid and stronger after fourth ventricular administration, suggesting a critical node of action within the hindbrain. Ongoing work seeks to identify the critical circuit in communicating cytogluconeogenesis to the VTA dopamine neurons in the service of motivated behavior.

Best Student Presentation Award Finalist

4:48

**Cytogluconeogenesis Potentiates Sucrose- And Sucrose Cue-Evoked Dopamine Signaling In The Ventral Tegmental Area.**

Vaibhav R Konanur, Mitchell F Roitman

University of Illinois at Chicago, Chicago, IL, United States

Midbrain dopamine neurons provide motivational reward for eating. Cytogluconeogenesis, the ability of glucose to generate ATP without complete oxidation, potentiates dopamine signaling in the ventral tegmental area (VTA) of the midbrain.

**Hypothesis:** Cytogluconeogenesis potentiates dopamine signaling in the VTA.

**Methods:**

1. Injection of 5thio-D-glucose (5TG) 15 and 45 minutes prior to testing reduced food intake by ~40% in chow-fed conditions, but in the same rats, failed to inhibit food intake at 4 weeks HFD, and only transiently inhibited food intake after 8 weeks HF diet (n=7-8/group).

**Conclusion:** 5TG failed to alter dopamine responses to water, suggesting the response is selective for caloric stimuli. Interestingly, 5TG enhancement of sucrose-evoked dopamine is more rapid and stronger after fourth ventricular administration, suggesting a critical node of action within the hindbrain. Ongoing work seeks to identify the critical circuit in communicating cytogluconeogenesis to the VTA dopamine neurons in the service of motivated behavior.

Best Student Presentation Award Finalist

5:00

**Diet-Driven Vagal Reorganization Promotes Obesity**

Molly McDougle, Arashdeep Singh, Neil MacLang, Claire de La Serre, Guillame de Lartigue

1Monell Chemical Senses Center, Philadelphia, PA, United States, 2University of Pennsylvania, Philadelphia, PA, United States, 3University of Georgia, Athens, GA, United States

Vagal sensory neurons are a key part of the nutrient sensing machinery that cause satiation. In obesity, vagal gut-brain signaling is impaired, however the extent to which this promotes hyperphagia and obesity remains unclear. **Methods:**

Central vagal circuits were mapped using IB4 labeling and human simplex virus (HSV) in lean and diet-induced obese (DIO) rats. To test sufficiency, we stimulated gut-innervating NG neurons (NG<sup>Cre</sup>) by injecting retrograde Cre virus into the stomach and duodenum and Cre-dependent Gq DREADD virus in the NG, then measured CNO-induced satiety in same rats at multiple timepoints (0, 4, and 8 weeks of high fat diet (HFD)). To test necessity, we ablated NG<sup>Cre</sup> by injecting CCK-Saporin into the NG of DIO rats and measured changes in body weight and food intake compared to control rats. **Results:** 4-weeks HFD reduced vagal fibers in the NTS by 2-fold (p<0.05), coinciding with hyperphagia. Reinnervation after 8-weeks HFD did not normalize eating compared to age-matched lean controls. Polysynaptic central projections of vagal sensory neurons with HSV were markedly reduced in DIO rats fed HFD >8 weeks (n=3/group), suggestive of altered synaptic wiring. Acute chemogenetic stimulation of NG<sup>Cre</sup>-reduced food intake by ~40% in chow fed conditions, but in the same rats, failed to inhibit food intake at 4 weeks HFD, and only transiently inhibited food intake after 8 weeks HF diet (n=7-8/timepoint). Gut deafferentation of DIO rats with CCK-SAP resulted in sustained 5-6% weight loss for 2 weeks driven by 20-30% voluntary reduction in food intake (p<0.01), confirmed with pair-feeding experiments (n=7-8/group).

**Conclusion:** HFD causes vagal remodeling that switches vagal gut-brain signaling from a **protective** function in lean animals that prevents overeating and weight gain, towards **promoting** overeating and defending a higher BW in obesity.

Best Student Presentation Award Finalist

5:12

**Switching Between Foods During An Eating In The Absence Of Hunger Paradigm Is Associated With Greater Intake And Weight Status In Children**

Nicholas V. Neuwald, Shana Adisc, Alaina Z. Pearce, Barbara J. Rolls, Kathleen L. Keller

1The Pennsylvania State University, University Park, PA, United States, 2Division of Research on Children, Youth, and Families, Children’s Hospital of Los Angeles, Los Angeles, CA, United States

Hedonic eating is one proposed mechanism for obesity in children. Increased sensorial variety at a meal and switching between foods may continue to stimulate hedonic eating and delay sensory-specific satiation. We tested the hypothesis that frequent food switching would be related to greater intake and weight status in children. To test this, we analyzed data from a study assessing decision-making in children (n=66 children; 8.9±1.3 years, 75±23 BMI%). After consuming a meal ad lib, we administered the eating in the absence of hunger (EAH) protocol (a measure of hedonic eating), in which children had 15 min access to 10 snack foods (>3.9 kcal/g) and toys. Grams and kcal consumed were calculated. Videos of behavior were coded for eating time, number of foods eaten, and food switches. Regressions tested the following effects: 1) switching on intake 2) BMI% on switching. Models were covaried for BMI% (model 1 only), fullness, number of foods eaten, and eating time. To aid in interpretation, switching and BMI% were tested as both continuous and median split variables.

Switching was positively associated with EAH for both grams (p<0.05) and kcal (p<0.03) such that children who switched more frequently consumed 21.8±10.1 g or 105±47.5 kcal more than those who did not switch less (p<0.04). BMI% was positively associated with switching (p<0.03) such that children with overweight/obesity (≥85th BMI%: n=33) switched 28%
more ($p<0.05$) than those with healthy weight (<85th BMI%; $n=33$). Intake did not differ by weight status. These results show that switching between foods can promote EAH intake and may be more common in children at higher weight status. Studies across multiple meals and contexts will help determine if switching is a modifiable target to moderate overconsumption in children.
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<td>A Forward Model For Food Intake: Cerebellar Satiation Circuits Reduce The Reward Value Of Food</td>
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<td>High And Low Alcohol Consuming Rodent Genotypes Exhibit Divergent Responses To Low [Alcohol] (10Mm) On Cerebellar Processing, Cerebellar Output To Vta, And Cerebellar Dependent Behavior</td>
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Nucleus Of The Solitary Tract (Nts)-Projecting Corticotropin-Releasing Hormone (Crh) Neurons In The Hypothalamic Paraventricular Nucleus (Pvn) Are Activated Following Acute Stress And Suppress Feeding

Marie K Holt, Imogen K Hayter, Stefan Trapp
University College London, London, United Kingdom

Within the brain, corticotropin-releasing hormone (CRH) mediates responses to acute stress, including food intake suppression. CRH-rich axons densely innervate the nucleus of the solitary tract (NTS), a region that drives stress-induced hypophagia. While CRH-expressing neurons have been identified in many brain areas, the origin of CRH-rich fibers in the NTS, the sensitivity of NTS-projecting CRH neurons to stress, and their ability to affect food intake are largely unknown. Using retrograde viral tracing, we identify brain-wide populations of NTS-projecting CRH neurons. AAVrg-FLEX-tdTomato was injected into the NTS of adult CRH-Cre mice (n=8; 5 males, 3 females). Three weeks later, mice were exposed to 30mins restraint stress and transcendially perfused with fixative. tdTomato-positive neurons were identified in Barrington's nucleus, the central nucleus of the amygdala, the periaqueductual gray, the parahippocampal nucleus, and the paraventricular nucleus of the hypothalamus (PVN). The PVN comprised the largest population of NTS-projecting CRH neurons and stress increased the number of activated (cFOS-positive) NTS-projecting PVN CRH neurons by 38% (95% Confidence Interval [95%CI]: -0.828, -0.276; p=0.004, Student's T-test). Next, we used an intersectional approach to selectively activate NTS-projecting CRH neurons in the PVN. CRH-Cre mice (n=5; 2 males, 3 females) were injected with AAV2-DIO-FLPo into the NTS followed by AAV2-DIO-hM3Dq-mCherry into the PVN. Mice were injected with saline or CNO (2mg/kg, i.p.) 30mins before dark onset and food intake was monitored using feeding experimentation devices (FED3s). Compared to saline, CNO suppressed feeding by 0.57g (95%CI: -0.828, -0.276; p<0.001, Sidak) over 21 hours. These data suggest a stress-activated PVN CRH input to the NTS that suppresses food intake.

Vagal Modulation Of Gabaergic Signalling In The Amygdala Mediates The Anxiogenic Effects Of Feeding

Jean-Philippe Krieger1,2, Mohammed Asker1,2, Pauline Van der Velden1, Stina Boerchers1,2, Jennifer E Richard1,2, Ivana Maric1,2,5, Francesco Longo1,2, Arashdeep Singh1,4, Guillaume de Laritigue3,4, Karolina P Skibicka1,2,5

1Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden, 2Wallenberg Centre for Molecular and Translational Medicine, Gothenburg, Sweden, 3Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, FL, United States, 4Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, Gainesville, FL, United States, 5Nutritional Sciences, College of Health and Human Development, Pennsylvania State University, State College, PA, United States

Gut-brain communication controls ingestive behavior, but also allows for the interoceptive modulation of anxiety. We recently demonstrated that feeding increases anxiety-like behavior via gut-projecting vagal afferents in rats. The central circuits that underlie this vagal effect on anxiety, however, remain uncharacterized. We hypothesized that the amygdala integrates vagally-mediated feeding signals to modulate anxiety-like behavior. First, we tested whether vagal afferents and the amygdala are synthetically linked. Five days after injection into the nodose ganglia, the anterograde polysynaptic viral tracer HSV129 labels the central amygdala (CeA), indicating the presence of a multisynaptic circuit between the vagus and the CeA. Second, we used RNA sequencing to probe the amygdala response to gut-brain vagal signals. Activating gut-projecting vagal signalling with ad libitum refeeding modulated the expression of immediate early genes (Arc,Fosb,Egr1,...) in the CeA compared to fasting. Conversely, blocking gut-projecting vagal signalling with a saporin-based lesion increased the expression of genes that maintain GABAergic synapses (Erbb4, Adcyap1, Mdga1, ...). We next determined whether pharmacological modulation of CeA GABAergic signalling affects feeding-induced anxiogenesis in male and female rats. Bilateral injections of the GABAAa receptor agonist, muscimol, into the CeA reduced anxiety-like behavior in the acoustic startle reflex test in the refed but not fasted rats. Conversely, the GABAAa receptor antagonist bicuculline increased the acoustic startle response of CCK-SAP rats to the level of controls. Altogether, our results indicate that the anxiety-like effects of feeding are mediated by a vagal brain circuit that requires CeA GABAergic signalling.

Role Of Brain Insulin In The Modulation Of The Serotonergic System And The Regulation Of Mood

Hugo Martin1, Sebastien Bullich2, Maud Martinat1, Mathilde Chataigner1, Mathieu Di Miceli1, Vincent Simon3, Samantha James3, Francis Chaouloff3, Philippe De Deurwaerdere4, Daniela Cota3, Andre Kleinridders5, Sophie Laye1, Bruno Guiraud2, Xavier Fioramonti1

1NutriNeuro institute, INRAE, Bordeaux, France, 2CRCA, Toulouse, France, 3Neurocentre Magendie, Bordeaux, France, 4INCIA, Bordeaux, France, 5Potsdam University, Potsdam, Germany

Type-2 Diabetes mellitus (T2D) is mainly characterized by insulin-resistance and accompanied by comorbidities including major depressive disorders. Our group showed that high-fat diet (HFD)-fed animals characterized by both insulin resistance and anxiety-like behaviors, display impairments in the intrinsic electrical properties of Dorsal Raphe (DR) serotonergic (5-HT) neurons. Improving insulin sensitivity using the antidiabetic drug metformin reversed HFD-induced metabolic, emotional as well as 5-HT neurotransmission alterations, suggesting that 1/ insulin modulates the 5-HT system to control mood; and 2/ insulin resistance at the level of 5-HT neurons contributes to the development of T2D-associated mood disorders. Using in situ hybridization, we show that the insulin receptor (IR) is expressed in 5-HT neurons of the DR. Patch-clamp electrophysiological recordings in brain slices from Pet1-cre-mCherry mice show that insulin increases firing rate frequency of DR 5-HT neurons. Interestingly, the latter effect is abolished in transgenic mice lacking the IR selectively in brain 5-HT neurons (SeIRKO mice: IR<sub>lox/lox</sub> x Pet1-cre-mCherry mice). Our data also show that intranasal and intra-DRN insulin delivery promotes anxious-like effects in the elevated plus maze or the open field. The anxious-like effect of insulin is blunted in SeIRKO mice, suggesting that the action of insulin requires 5-HT neurons to control mood. Finally, patch-clamp recordings show that the response of 5-HT neurons to insulin is impaired after 16 weeks of HFD. These data strongly suggest that insulin directly modulates the activity of DR 5-HT neurons to control emotional behaviors and that impaired insulin-sensitivity in these neurons is critical for the development of T2D-associated mood disorders.
Nucleus Accumbens D1R Expressing Spiny Projection Neurons Control Food Motivation And Obesity.
Bridget A Matikainen-Ankney, Alex Legaria, Yvan Vachez, Caitlin Murphy, Yiyin Pan, Robert Schaefer, Quinlan McGrath, Justin Wang, Maya Bluitt, Aaron Norris, Meaghan Creed, Alexxai Kravitz
Washington University in St Louis, St. Louis, MO, United States

Despite widespread knowledge of the prevalence and health disparities linked to chronic obesity, effective treatments remain elusive – most people who lose weight will re-gain it. Though prior research has often explored metabolic or energy adaptations to explain obesity, this does not address the proven contribution of hedonic feeding mechanisms to chronic weight gain. Human and rodent studies show that obesity causes increased motivation to consume palatable foods, and that activity in brain areas involved in food motivation – namely the nucleus accumbens (NAc) – is altered with obesity. Yet the neural mechanisms underlying obesity-driven enhanced food motivation are unknown. Using a novel behavioral assay that quantifies physical work during food seeking, we show that obese mice work much harder than lean mice to obtain food. We recorded neural activity in the NAc core with both in vivo electrophysiology and cell-type specific calcium fiber photometry, and observed greater activation of D1-receptor expressing NAc spiny projection neurons (NAc D1<sup>SPNs</sup>) during food seeking in obese mice relative to lean mice. With ex vivo slice physiology we identified pre- and post-synaptic mechanisms that contribute to this enhancement in NAc D1<sup>SPN</sup> activity in obese mice. Blocking synaptic transmission from D1<sup>SPNs</sup> decreased physical work during food seeking and attenuated high-fat diet-induced weight gain. These experiments demonstrate obesity is associated with a selective increase in the activity of D1<sup>SPNs</sup> during food seeking, which enhances the vigor of food seeking. This work also establishes the necessity of D1<sup>SPNs</sup> in the development of diet-induced obesity, establishing these neurons as a potential therapeutic target for preventing obesity.

Glucose And Fructose Differentially Impact Hypothalamic And Dopamine Signaling
Aaron D. McKnight<sup>1,2</sup>, Alexandra. Vargas<sup>1</sup>, Misgana. Ghidewon<sup>1</sup>, Amber L. Alhadeff<sup>1,2</sup>

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, United States, <sup>2</sup>Monell Chemical Senses Center, Philadelphia, PA, United States

In our modern diet, we primarily consume sugars in the form of sucrose (a disaccharide of glucose and fructose) or high-fructose corn syrup. In particular, fructose overconsumption is associated with poor metabolic health and increased weight gain. While differences in peripheral glucose and fructose sensing and metabolism have been identified, these sugars impact the brain is not fully understood. Previous work showed that rodents given the choice between glucose and fructose consistently prefer glucose, despite the fact that fructose is sweeter. We recapitulated these findings by measuring licking during a two-bottle choice assay and demonstrated that sugar-naive mice consume glucose over fructose after about 30 minutes (food-deprived) or one hour (sated) of exposure to the sugars. What are the neural circuits that mediate this preference? To begin to address this question, we examined how glucose and fructose impact <em>in vivo</em> homeostatic and reward signaling in the brain. We engineered mice for <em>in vivo</em> fiber photometry to measure neural activity in hypothalamic agouti-related protein (AgRP)-expressing neurons or accumbal dopamine activity in mice outfitted with intestinal catheters. Equicaloric infusions of fructose were much less effective than glucose at both inhibiting AgRP neuron activity and stimulating dopamine signaling. Strikingly, oral consumption of fructose was also less effective at inhibiting AgRP neuron activity, even though food-deprived mice initially consume more fructose due to its sweet taste. Ongoing studies are using optogenetic and chemogenetic neural activity manipulations to determine whether these signaling differences are causally related to the development of sugar preferences.

Eating In The Absence Of Hunger Or Emotional Eating?: Psychometric Properties Of The Eating In The Absence Of Hunger Questionnaire In Adults With Overweight/Obesity
Ellen K Pasquale, BS<sup>1,2</sup>, Michael A Manzano, MS<sup>1,2</sup>, David R Strong, PhD<sup>3</sup>, Dawn M Eichen, PhD<sup>2</sup>, Kerri N Boutelle, PhD<sup>2,3,4</sup>

<sup>1</sup>San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, United States, <sup>2</sup>UC San Diego School of Medicine Department of Pediatrics, San Diego, CA, United States, <sup>3</sup>UC San Diego School of Medicine Department of Family Medicine and Public Health, San Diego, CA, United States, <sup>4</sup>UC San Diego School of Medicine Department of Psychiatry, San Diego, CA, United States

Understanding eating behaviors that contribute to overweight and obesity (OW/OB) is an important public health objective. One eating behavior known to contribute to overeating and OW/OB is eating when not physically hungry. The Eating in the Absence of Hunger Questionnaire (EAH-Q) was developed to assess external events and internal experiences that lead children to overeat. Although the EAH-Q has been used with adults, its psychometric properties have not been investigated in this population. This study aimed to assess the psychometric properties of the EAH-Q in treatment-seeking adults with OW/OB. In total, 311 adults (m BMI=34.5(5.1); m age=46.3(12.1); 81.9% female; 20.6% Hispanic, 59.4% white) completed the EAH-Q, which assesses three eating domains: negative affect, external, and fatigue/boredom. Exploratory Factor Analysis was performed with promax rotation and maximum likelihood factor extraction. Parallel analysis and optimal coordinates suggested three domains be retained but acceleration factor suggested one domain. Due to these discrepancies, the indices of communality, factor reliability, item scalability, and convergent validity were considered and suggested a unitary factor structure best fit the data. Item imbalance across domains favoring affect-related items in the scale resulted in limited contribution from external and fatigue/boredom eating items. Scale responses were driven by a single factor capturing EAH due to emotions. If researchers are interested in the domains of external and fatigue/boredom eating, limited contribution from external and fatigue/boredom eating items. Scale responses were driven by a single factor.
Fewer than 20% of individuals succeed at weight loss maintenance suggesting physiological mechanisms drive weight regain. Lateral hypothalamus (LH) orexin neurons, which are glucose-inhibited (GI), enhance “reward-based” feeding via ventral tegmental area (VTA) dopamine (DA) neurons. We showed previously that overnight fasting reduces glucose inhibition of LH orexin-GI neurons and increases glutamate transmission on VTA DA neurons. We hypothesize that preventing changes in the glucose sensitivity of LH orexin-GI neurons following dieting reduces the enhanced VTA DA glutamate transmission and blunts reward-based feeding. Thus, we determined if enhanced glutamate transmission on VTA DA neurons is sustained during longer term diet restriction (DR). DR significantly increased AMPA current amplitude and the AMPAR/NMDAR (an in vivo measure of glutamate plasticity) on VTA DA neurons. We then inhibited LH orexin neurons in DR mice using designer receptors exclusively activated by designer drugs (DREADDs) and measured conditioned place preference (CPP) for rewarding food. Oral administration of the DREADD agonist C21 (10mg/kg) caused a significant reduction in CPP (p<0.001; two-way ANOVA; N=7-8/group). The glucose receptor has not yet been identified. We found that pertussis toxin (PTX; 100 ng/ml; n = 5), a Gsα-protein coupled receptor (GCPR) inhibitor, and the PKA inhibitor, Rp-cAMP (10μM; n = 5) blocked the effect of low glucose on orexin-GI neurons (p<0.05). These data suggest that DR leads to orexin-dependent increases in glutamate transmission on VTA DA neurons which is associated with increased motivation for rewarding foods. Furthermore, that targeting Gsα-PKA signaling may prevent DR-induced changes in the glucose sensitivity of LH orexin-GI neurons.
The Response Of Rats To Cafeteria Diets Is Influenced By Specific Food Choices And Varies Over Time
Carolina R. Cawthon, Alan C. Spector
1Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, FL, United States

Wide variation of ingredients and sensory properties creates interpretive ambiguity when human food-based cafeteria-style choice diets (HUM) are used with animal models. To begin to address this, we procured custom rodent diets (ROD) with nutritional variance like HUM but with more uniform ingredients, texture, protein, micronutrients, and fiber. We compared the behavior of rats (n=8/sex) given 8 days of HUM, ROD, and powdered chow (PC; 4 d before each choice diet) using our 5-item Food Choice Monitor in a crossover design. Diet arrays included PC plus 4 foods with low (L) or high (H) fat (F) and/or sugar (S). When switched from PC to a choice diet, an overall increase in meal size and a contributing day 1 bent toward more meals led to elevated kcal intake; along with greater ingestion rates, this suggests rats found each choice diet more palatable vs. PC. While kcal intake did not differ on HUM v. ROD in females, it was greater on HUM in males.Â For both HUM and ROD diets vs. PC alone, %kcal from fat and sugar was higher, and from carb and protein was lower. Between choice diets (%kcal) – sugar: HUM=ROD; protein: ROD>HUM (by design); fat: HUM>ROD; and carb: ROD>HUM, with the last two differences driven by relative intake of the HFLS and LFLS choices. Our results suggest that rats will show hyperphagia when multiple palatable foods are available regardless of food characteristics, due mostly to larger meals, though elevated responses on the choice diets had sometimes waned by day 8. The nature of the food choices can affect macronutrient intake. Although responses to HUM and ROD were not identical, they were similarly different from PC. The greater uniformity of ROD choices make it well-suited for preclinical queries better tested with more human-like feeding conditions.

The Amount Of Training In Flavor Preference Learning Determines The Underlying Associative Structure: Implications For Eating Behavior.
Ana Gonzalez, Isabel de Brugada
University of Granada, Granada, Spain

Pairing a palatable taste (US) with an initial neutral flavor cue (CS) results in an acquired conditioned preference for the latter. This type of learning is believed to be involved in eating behaviour, for example by encouraging the selection of foods or the amount eaten in a meal. Acquisition of flavor preferences has been mostly explained by two main associations; flavor-flavor and flavor-nutrient learning (Stimulus-Stimulus learning; S-S). However, the hedonic reaction originated by consuming the US (Stimulus-Response learning; S-R), which has been suggested to be an additional possible component that could underlie the acquired flavor preference, has been majority left aside. In the present research, we studied whether the amount of exposure to the CS-US compound during the training procedure could alter the learned content favoring a Stimulus-Hedonic response association by using rats as experimental subjects and sucrose as US. We expected that the more exposure to the CS-US compound, the greater the chance of a rigid and automatic S-R type association. Furthermore, as S-R associations are featured by not being sensitive to devaluation procedures, we measured the rats’ preference for the CS when the US had been devalued or not by using a Sensory-Specific Satiety procedure. Results showed how the type and amount of exposure to the CS-US compound affected the US devaluation effect. These results suggest that massive exposure to palatable tastes can lead to a rigid learning that may encourage food consumption even when it is not desirable. The implications of these results are discussed in terms of the characteristics of current obesogenic environments.

Using Video Appeals To Reduce Wanting Of And Intentions To Consume Meat
Luke Herchenroeder1, Catherine A. Forestell2, Adrian Bravo2
1George Washington University, Washington, DC, United States, 2William & Mary, Williamsburg, VA, United States

Raising animals to produce meat has negative consequences for the environment, animal welfare, and personal health. The present study investigated whether video appeals that address these topics affect participants’ wanting of meat and their intentions to reduce meat. To this end, 405 participants (61.5% female) between the ages of 18 and 25 years completed an online questionnaire that included a 10 minute video that addressed either the environmental, animal welfare, or health condition. After viewing the video, participants rated their implicit and explicit wanting of meat and the extent to which they would change future meat intake. Using video appeals to reduce wanting of meat has negative consequences for the environment, animal welfare, and personal health. The present study investigated whether video appeals that address these topics affect participants’ wanting of meat and their intentions to reduce meat. To this end, 405 participants (61.5% female) between the ages of 18 and 25 years completed an online questionnaire that included a 10 minute video that addressed either the environmental, animal welfare, or health condition. After viewing the video, participants rated their implicit and explicit wanting of meat and the extent to which they would change future meat intake. Results indicated that environmental video appeals increased intentions to reduce meat. Nevertheless, implicit wanting of meat was lower in all three experimental conditions compared to the control condition. Additionally, for the animal welfare and environment conditions, moral emotions and agreement with the video’s message mediated implicit wanting and intentions to reduce meat. For the health condition, only agreement with the message served as a mediator. These results suggest that although animal welfare-, environmental-, and health-focused video appeals may be effective at shifting immediate desire to consume meat, environmental video appeals may be the most effective for increasing intentions to change future meat intake.

Greater Self-Reported Emotional Eating Predicts Greater Snack Intake Following Stress When Expectations That Eating Will Provide Stress-Relief Are High
Rebecca Klatzkin1, Tzvi Nadel1, Helen Files1, Katie Gaffney1, Olivia Streeter1, Laurence Nolan2, Harry Kissileff3
1Department of Psychology, Rhodes College, Memphis, TN, United States, 2Department of Psychology, Wagner College, Staten Island, NY, United States, 3Diabetes, Obesity, and Metabolism Institute, Icahn School of Medicine, Mount Sinai Morningside Hospital, New York, NY, United States

Increasing emotional eating is associated with increased snacking following stress, and emotional eating predicts increased weight gain. The current study examined whether individual differences in emotional eating and expectations that eating will provide stress-relief predict increased snack intake following stress. Participants (N=157) completed an online survey that included a 10 minute video that addressed either the environmental, animal welfare, or health condition. After viewing the video, participants rated their implicit and explicit wanting of meat and the extent to which they would change future meat intake. Results indicated that environmental video appeals increased intentions to reduce meat. Nevertheless, implicit wanting of meat was lower in all three experimental conditions compared to the control condition. Additionally, for the animal welfare and environment conditions, moral emotions and agreement with the video’s message mediated implicit wanting and intentions to reduce meat. For the health condition, only agreement with the message served as a mediator. These results suggest that although animal welfare-, environmental-, and health-focused video appeals may be effective at shifting immediate desire to consume meat, environmental video appeals may be the most effective for increasing intentions to change future meat intake.
Self-assessed emotional eaters do not reliably eat more in response to stress or negative emotions. This inconsistency in predictive validity of self-reported emotional eating (EE) may be due to individual differences that moderate the relationship between self-reported EE and behavioral measures of EE (more food intake post-stress). We recently reported that self-assessed emotional eaters eat more snack food as stress reactivity and emotional relief upon eating increase. Temporal order of measurement limited our conclusions because emotional relief (moderator) was measured after food intake (dependent variable). Greater emotional relief from stress by eating should lead to greater expectations of stress-relief upon eating and thus we predicted that greater pre-stress expectations of stress relief upon eating would moderate the relationship between self-reported EE and food intake post-stress. Our new sample consisted of 31 undergraduate women (Mean BMI=26) who completed a battery of assessments that included eating expectancies prior to undergoing a mental stress task. Participants were then asked to taste and give ratings for three snacks: M&Ms, golden Oreos, and chips. The moderation model (PROCESS model 1) was significant only for M&M intake, F(5, 25)=2.99, p=.03; R²=37. There was a significant interaction; self-reported EE predicted increased M&M intake post-stress only when expectation of stress-relief upon eating was high (b=-4.2, SE=1.4, R²=22), F(1, 25)=8.7, p=.007. Self-reported EE (b=-5.2, SE=23.79, p=.029) and expectation of stress-relief upon eating (b=-33.3, SE=11.04, p=.006) were significant predictors of M&M intake. Greater self-reported EE predicts greater snack intake post-stress when expectations that eating will provide stress-relief are high.

**The Role Of Infant-Feeding Method In Young Children’S Exposure To Foods: Findings From The Approaching Eating Through Language (Applause) Study**

Megan C. Lawless, Allison L.B. Shapiro, Susan L. Johnson
University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Recent trends in infant feeding have shifted from the traditional caregiver-led (CL) method of offering soft, puréed foods towards an infant-led (IL) approach in which children are encouraged to self-feed table foods at the start of weaning. While this alternative approach is suggested to relate to positive outcomes in children’s eating due to earlier exposure to a variety of table foods, the relationship between caregivers’ self-reported feeding methods and the variety of foods they offer their children is not well characterized. We explored relationships between caregiver-reported feeding method (CL vs. IL) and solid type (puréed vs. table foods) with patterns of exposure to solid foods in 4-26-month-old children. Caregivers of young children (n=408) in the APPEAL study in the US (70.3% female; 73% white) completed an online survey (Qualtrics) about foods offered to their child in the past 30 days and their approaches to introducing solid foods. Latent class analysis (LCA) was used to group foods frequently offered (≥ 1x/week) into 3 patterns (low, moderate, and high exposure). Most infants (59.6%) were introduced to solid foods by 6 months. No relationship was found between age at introduction to solid food and LCA-derived patterns of food exposure, X²(6, 344)=7.7, P=0.26. Almost 50% of caregivers (44%) reported ever trying IL weaning, but associations among feeding method, types of solids offered, and patterns of food exposure were non-significant (P=0.08; P=0.20, respectively, Fisher’s exact test). Caregivers’ perception of an IL approach to introducing complementary foods was not related to type and pattern of food exposure in young children. We don’t know enough about how caregivers define infant-led weaning to make recommendations for feeding methods.

**The Complementary Gabaergic And Glutamatergic Neuron Activity In The Lateral Hypothalamic Orchestrate Palatability-Guided Consumption.**

Monica Luna¹, Alam Coss², Oscar Xavier Guerrero-Gutierrez³, Jorge Luis-Islas⁴, Aketazli Garcia⁵, Ranier Gutierrez¹
¹Department of Pharmacology, Cinvestav, CDMX, Mexico, ²Department of Electrical Engineering, Cinvestav, CDMX, Mexico, ³Department of Computer Science, Cinvestav, CDMX, Mexico, ⁴Department of Physiology, Biophysics and Neuroscience, Cinvestav, CDMX, Mexico, ⁵Neuroscience, IFC, UNAM, CDMX, Mexico

We hypothesized that the opposing activation of GABAergic neurons and silencing of Glutamatergic neurons on the lateral hypothalamic area allows palatability-guided consumption. We used Vgat-ires-Cre and Vglut2-ires-Cre mice to express GCaMP6m on GABAergic and Glutamatergic neurons and fiber photometry in a 4s brief access taste test; water, quinine, or sucrose. We find that GABAergic and Glutamatergic neurons exhibited an opposing activity during the intake of palatable stimuli. Specifically, GABAergic neurons increase activity in response to sucrose, whereas Glutamatergic neurons are inhibited. Then, we used optogenetic tools to test the causal effect of activating (ChR2) or silencing (GtACR2) these neurons in a real-time place preference. Activating GABAergic (or silencing Glutamatergic) neurons is rewarding, whereas the opposite optogenetic manipulations elicit aversion. Likewise, using a sucrose-sucrese two-bottle conditioning test, we observe that activating GABAergic (or silencing Glutamatergic) neurons increases the preference towards the sucrose bottle paired with laser over the non-stimulated bottle. In contrast, silencing GABAergic (or activating Glutamatergic) neurons increases the preference toward the non-photostimulated bottle. Thus, these neurons can shift food preferences. Finally, in well-fed mice with access to Chow, High-Fat Diet (HFD), and sucrose pellet confirmed that activating GABAergic (or silencing Glutamatergic) neurons increased consumption of the most palatable food available (i.e. HFD). In fasted mice, silencing GABAergic (and activation of Glutamatergic) neurons refrain food intake. Collectively, our findings establish how the opposing activities of GABAergic and Glutamatergic neurons might complement each other to guide hedonic feeding.

**Taste Palatability Profile In Spontaneously Hypertensive Rats Submitted To The Water Deprivation - Partial Rehydration Protocol**

Emilson Donizete Pereira Jr, Laurival A De Luca Jr, Jose Vanderlei Menani, Carina Aparecida Fabricio Andrade
Universidade Estadual Paulista, Araraquara, Brazil

The 24 h of water deprivation + 2 h of partial rehydration (WD-PR) protocol allows the rat to quench its thirst ingesting only water during the PR, thereby separating thirst from sodium appetite. The spontaneously hypertensive rat (SHR) has enhanced palatability for NaCl taste as measured by the increased number of hedonic versus aversive responses to intraoral stimuli. Specifically, stomach and taste reflexes to intraoral infusion (1 ml/min) of 0.3 M NaCl, in a taste reactivity test in normovolemic or fluid depleted condition. Here, we investigated whether the same applies to other tastes infused intraorally, in a random sequence, to SHR (n=10) in euhydration condition or with appetite or motivated to ingest substantial amounts of 0.3 M NaCl, at the end of a cycle of WD-PR. SHR had similar number of hedonic responses to 2% sucrose, whether in WD-PR (142 Å± 25) or euhydration condition(95 Å± 19). However, these responses were increased when compared to normotensive rats (n=9) that entered a WD-PR (21 Å± 6) or euhydration condition (13 Å± 3). SHR also showed increased number of aversive responses to 1.4 mM quinine sulphate compared to normotensive rats, whether euhydration (86 Å± 6, vs. normotensive: 54 Å± 7) or at the end of a cycle of WD-PR (89 Å± 9, vs. normotensive: 40 Å± 9). The results suggest that similar to NaCl taste, sweet taste of SHR resisted challenges
Elucidating The Role Of Cart Signaling On The Gpr-160 Receptor In The Dvc In The Control Of Food Intake.
Marcos J. Sanchez-Navarro1, Tito Borner1, Michael Hagan1, Jane Gaisinski1, Benjamin C. Reiner1, Richard C. Crist1, Willis K. Samson2, Gina LC Yosten3, Matthew R. Hayes1, Lauren M. Stein1

1University of Pennsylvania, Philadelphia, PA, United States, 2Saint Louis University School of Medicine, Saint Louis, MO, United States

Cocaine and Amphetamine-Regulated Transcript (CART) neuropeptide exerts anorectic effects when delivered into nuclei involved in energy balance control, such as the dorsal vagal complex (DVC). Recently the orphan G protein-coupled receptor (GPCR) GPR-160 was identified as a receptor for CART. Given the wealth of prior research examining CART-mediated effects on energy balance, and abundant GPR-160 expression in the DVC, we examined the physiological role of this receptor in control of food intake. We performed an AAV-mediated, targeted knockdown (KD) of DVC GPR-160 to evaluate the endogenous role of this receptor on different aspects of normal food intake regulation. Our results indicate that DVC GPR-160KD leads to changes in meal microstructure without affecting fasting-induced refeeding. More specifically, DVC GPR-160KD animals had more frequent, but smaller meals during the dark phase and decreased food intake, as well as number and duration of meals during the light phase. This, however, resulted in no net difference in body weight gain. We next tested the role of DVC GPR160 in mediating the food intake suppressive effects of 4th ventricle CART. Our results show that DVC GPR-160KD has no effect on CART’s ability to decrease food intake in a 24hr period, suggesting that exogenous CART may be mediating an anorectic effect through either a non-brainstem mediated site of action, and/or an alternative GPCR. Finally, we performed DVC single-nucleus RNA sequencing, which uncovered abundant GPR160 expression in DVC microglia and only minimal expression in neurons. Altogether, our results suggest that DVC GPR-160 signaling might not be sufficient to mediate CART’s role in the control of food intake, opening the possibility to other unidentified targets for this peptide.

First Foods And Children’s Early Language Acquisition: The Approaching Eating Through Language (Appeal) Study
Allison Shapiro, Megan Lawless, Susan Johnson
Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Language skills, such as the ability to understand words (receptive language), develop during infancy and may be built through interactions with the environment, including eating. Exposure to complementary foods also begins in infancy and may play a significant role in language development, especially in understanding of food-related words. However, the relationship between the complementary foods to which a child is exposed and early language acquisition has not been previously studied. We hypothesized that young children’s food-related receptive language (FRL) would reflect the complementary foods to which they were frequently offered by caregivers. Caregivers of young children (4-26 months; n=408) in the APPEAL (Approaching Eating through Language) Study in the US were surveyed via Qualtrics. FRL was assessed by caregiver-report via the MacArthur-Bates Communicative Development Inventory. Complementary foods were assessed using a modified Food Frequency Questionnaire. Latent Class Analysis (LCA) was implemented to identify groupings of foods frequently offered (≥1x/week) and groupings of food-related words understood by the young children. A 5-class best fit LCA model was identified for foods (−log likelihood [lik]=−8727) and for FRL (lik=−5476). LCA-derived food groupings were classified by frequency of offering (low [L], moderate [M], moderate-high [MH], high [H]) and by age “appropriate” (A; e.g., apple) vs “inappropriate” (I; e.g., soda). LCA-derived FRL groupings were similarly classified. Consistent with our hypothesis, children having HA-MHI complementary food offerings were most likely to have MHA-MHI FRL (Probability=0.48). These findings support the potential role of introduction to complementary foods in development of food-related language.

Altered Feeding Patterns In Mice Consuming Protein-Restricted Diet Versus Non-Restricted Diet Using Home-Cage Monitoring Units
Hamid Taghipourbibalan, James Edgar McCutcheon
The Arctic University of Norway, UiT, Tromso, Norway

Intake of dietary protein is tightly regulated yet the physiological and behavioural mechanisms that control protein intake are not well understood. In the current study, we have used Feeding Experimentation Devices (FEDs) to monitor feeding patterns in mice given access to foods that vary in protein content. Adult male C57BL/6 mice (n=6) were contact-housed in pairs in custom-made cages with perforated Plexiglas dividers, each having access to a separate individual FED unit. FEDs were either filled with protein-restricted diet (5% casein, PR) or an isocaloric non-restricted control diet (20% casein, NR). All mice experienced each diet for 7 days and order of presentation was counterbalanced. Mice had free access to 20 mg pellets throughout the experiment and the time at which each pellet was collected and a new one released was logged 24 h/d. Analysis of average pellets consumed per day revealed that type of pellet (PR vs. NR) had a main effect and there was a significant interaction between type of pellet and the order in which pellets were presented (P<.001). As such, mice increased intake when transitioning from NR to PR food (174.6 ± 18.5 to 216.6 ± 19.6 pellets) but did not significantly decrease intake when moving from PR to NR food (183.3 ± 6.1 to 174.6 ± 6.6 pellets). Further analysis clustered data into meals suggested that changes in pellet intake may be caused by altered meal size. In summary, home-cage monitoring of feeding in mice showed an asymmetric pattern with respect to available protein sources where altered intake was only observed when the diet was switched from NR to PR pellet. This may reflect persistent changes in feeding or the necessity of replenishing protein stores after a period of scarcity.

Capacity Meal Intake Predicts Weight Loss 1-Year After Bariatric Surgery Without Evidence Of Satiation Deficiency
Jessica Bonheur1, Jeon D. Ham1, Jany Dotel1, Blandine Laferrere2, Jeanine Albu3, Danielle Greenberg4, Claudio Esteban Perez Leighton5, Jeff Brunstrom6, Subhash Kin7, Harry R. Kissileff2

1Diabetes, Obesity, & Metabolism Institute, Icahn School of Medicine, at Mount Sinai, New York, NY, United States, 2Columbia University College of Physicians and Surgeons, New York, NY, United States, 3Division of Endocrinology,
A meal eaten to capacity negatively predicted weight loss 1-year after bariatric surgery [BS] (OBES Surg (2014) 24:2138–2144). To test whether this prediction was attributable to a satiation deficiency, a meal consumed to capacity with appetite ratings was compared between 75 BS candidates (BMI=45.0 kg/m² ± 0.7, mean ± SE) and 34 healthy volunteers [C] (BMI = 21.8 kg/m² ± 0.3). 59 patients [P] reported their weight at 1 year (BMI = 30.3 kg/m² ± 0.8), and 40 P were restated at 2 years (BMI = 32.5 kg/m² ± 1.2). During the capacity meal, participants rated appetite feelings on a GVAS 150 mm line after sipping 150 g aliquots of Ensure®, delivered by a pump, through a straw from a cup, hidden by a box until they could not go on. On average, a 100 g increased capacity meal pre-op predicted a 0.97% ± 0.33 (R = 0.1308, p=0.0053) decrease in weight loss at 1 year, confirming the original prediction. The capacity meal at 2 years was significantly reduced by 37% ± 12 and significantly correlated (R=0.20, p=0.004) with pre-op capacity intake. There were no significant differences between P, before surgery, and C, in three intake-related measures of satiation [mean g ± SE for P, C, difference (C-P)]; 1) amount eaten to reach “just the right amount” [405 ± 34, 350 ± 51, -54.0 ± 61.0], 2) amount of capacity meal eaten [679 ± 68 ± 53, 9 ± 64.0]. 3) increase to capacity from amount eaten to feel comfortably satisfied [318 ± 27, 306 ± 40 -12.0 ± 48.0]. A Prediction of weight loss from the capacity meal in P was not attributable to a deficiency in satiation, since satiation measures P did not differ from those of C. We propose that patients with smaller intakes presurgery lose the most weight because they continue to have reduced intakes after surgery. Grant (R01 DK108643).

The Association Between Meat Consumption And Body Mass Index Varies According To The Socioeconomic Status

Self-Stigma Mediates The Associations Between Experiences Of Devaluation And Elevated Emotional Eating And BMI

A meal eaten to capacity negatively predicted weight loss 1-year after bariatric surgery [BS] (OBES Surg (2014) 24:2138–2144). To test whether this prediction was attributable to a satiation deficiency, a meal consumed to capacity with appetite ratings was compared between 75 BS candidates (BMI=45.0 kg/m² ± 0.7, mean ± SE) and 34 healthy volunteers [C] (BMI = 21.8 kg/m² ± 0.3). 59 patients [P] reported their weight at 1 year (BMI = 30.3 kg/m² ± 0.8), and 40 P were restated at 2 years (BMI = 32.5 kg/m² ± 1.2). During the capacity meal, participants rated appetite feelings on a GVAS 150 mm line after sipping 150 g aliquots of Ensure®, delivered by a pump, through a straw from a cup, hidden by a box until they could not go on. On average, a 100 g increased capacity meal pre-op predicted a 0.97% ± 0.33 (R = 0.1308, p=0.0053) decrease in weight loss at 1 year, confirming the original prediction. The capacity meal at 2 years was significantly reduced by 37% ± 12 and significantly correlated (R=0.20, p=0.004) with pre-op capacity intake. There were no significant differences between P, before surgery, and C, in three intake-related measures of satiation [mean g ± SE for P, C, difference (C-P)]; 1) amount eaten to reach “just the right amount” [405 ± 34, 350 ± 51, -54.0 ± 61.0], 2) amount of capacity meal eaten [679 ± 68 ± 53, 9 ± 64.0]. 3) increase to capacity from amount eaten to feel comfortably satisfied [318 ± 27, 306 ± 40 -12.0 ± 48.0]. A Prediction of weight loss from the capacity meal in P was not attributable to a deficiency in satiation, since satiation measures P did not differ from those of C. We propose that patients with smaller intakes presurgery lose the most weight because they continue to have reduced intakes after surgery. Grant (R01 DK108643).

The Association Between Meat Consumption And Body Mass Index Varies According To The Socioeconomic Status

In A Representative Sample Of French Adults

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Pierre Levassuer1, Francois Mariotti2, Isabelle Denis2, Olga Davidenko2

1Universite Paris-Saclay, AgroParisTech, INRAE, UMR SADAPT, Paris, France, 2Universite Paris-Saclay, AgroParisTech, INRAE, UMR PNCA, Paris, France

There is a growing advocacy for reducing meat consumption in Western countries. However, healthy alternatives to meat may be expensive, and populations with a low socioeconomic status (SES) may be more likely to consume less healthy alternatives instead, losing in dietary quality and risking more negative health outcomes such as weight gain. The objective of this study was to examine the link between the body mass index (BMI), meat consumption and SES. We performed multivariate linear regressions on dietary frequencies data of a representative sample of the French adult population (n=1,300). We found a significant interaction between household income level and frequency of meat consumption: namely, in low-income households, one day less of meat consumption per month was associated with a higher individual BMI (0.074±0.039 kg/m², p <0.05) compared to richer households. This income-based difference in the meat-BMI relationship was particularly strong in male, younger (aged 18-44) and rural adults. This relationship was robust to alternative measurements of SES (level of education, profession). Low-income and higher-income households also had different eating habits associated with higher meat consumption: among low-income households, lower meat consumption was associated with higher consumption of ice cream and sorbet, while among higher income groups, it was associated with lower consumption of high-fat and high-sugar food and beverage items, as well as cheese. Our study is the first to show that SES could moderate the relationship between meat consumption and BMI in a nationally representative sample. The way meat reduction is promoted today has to be adapted to avoid increasing social health inequalities.

Self-Stigma Mediates The Associations Between Experiences Of Devaluation And Elevated Emotional Eating And BMI

Laurence J. Nolan, Gabriela Diorio, Veronica Gallo, Ruth Sysma, Amy Eshleman

Department of Psychology, Wagner College, Staten Island, NY, United States

Some have proposed that stigmatization of persons with high BMI might encourage weight reduction. However, studies suggest that this approach is often associated with weight gain, less exercise, and less healthy eating. In the current study, we examined whether experiences with multiple forms of stigma, both weight-related and nonweight-related, were associated with emotional eating (EE) and BMI. 152 students (120 women) completed questionnaires online including measures of EE, self-stigma, irrational beliefs (IB), impulsivity, and feeling fat. They also reported height and weight for BMI and perception of their own BMI. Correlations among the variables were examined and serial mediation analysis was performed (PROCESS). The model for predicting EE was significant, F(6, 138)=3.0, p<0.008, R²=.12. Serial mediation analysis revealed that experiences with devaluation predicted significantly elevated EE only via an indirect pathway through IB, self-devaluation, and weight perception (b=.001; 95%CI[.000, .004]). The model for predicting BMI was significant, F(4, 145)=24.6, p=.000, R²=.40. Serial mediation analysis revealed partial mediation of the relationship between experiences with devaluation and BMI via a positive indirect path through fear of enacted stigma and weight perception (b=.074; 95%CI[.031, .132]) and a negative direct path between devaluation experiences and BMI (b=-.142; 95%CI[-.264, -.019]). The results suggest that multiple devaluing experiences are linked with elevated BMI via self-stigma countering its direct negative influence on BMI. While the path did not include EE, it was a significant predictor of BMI. Thus, devaluating experiences predict elevated EE, but this was not the mechanism for elevated BMI in this study.

Anxiety/Depression And Glycemia Interaction Related To Altered Cerebellar Functional Correlation

Grace S Heather

University of Wyoming, Laramie, WY, United States

Depression, type 2 diabetes, and obesity are comorbid, and prevention and treatment of all three diseases are needed. We hypothesized an inverse relationship between connectivity between the cingulo-opercular task control network and the somatosensory mouth network and the interaction of HbA1c and depression. Three-hundred and twenty-five participants (BMI: 26.11 ± 29, ASR DSM Depressive Problems T-score [depression]: 54.60 ± 6.77, Age: 28.25 ± 3.90 y, adult self-report anxiety and depression scale [anxiety and depression]: 54.69 ± 7.27, HbA1c: 5.26 ± 0.29, 68% white) were sampled from the Human Connectome Project 1200 subjects PTN release. Inclusion criteria were: 4 (15 minute) resting state fMRI scans, current measured BMI, hemoglobin A1c (HbA1c, a measure of glycemic control), and complete adult self-report data. The following models were run to assess the connectivity between 15 independent fMRI components: interaction of depression...
**Generation And Characterization Of A Gfral-Ret Receptor Peptide-Based Antagonist For The Treatment Of Gdf15-Induced Malaise.**

Tito Borner,1,2,4 Ian C. Tinsley,3,4 Brandon T. Milliken,1 Bart C. De Jonghe,1,2,4 Robert P. Doyle,3,4 Matthew R. Hayes1,2,4

1Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, United States, 2Department of Biobehavioral Health Sciences, University of Pennsylvania, Philadelphia, PA, United States, 3Syracuse University, Department of Chemistry, Syracuse, NY, United States, 4Cantisus Therapeutics, LLC, Lansdale, PA, United States

Growth differentiation factor 15 (GDF15) induces strong anorectic effects driven mainly through the induction of malaise. Elevated endogenous GDF15 levels are associated with energy balance disturbances, cancer progression, morning sickness and chemotherapy. The GDF15 receptor, a GDNF family receptor α-like (GFRAL) and its co-receptor RET, is exclusively expressed in a small subpopulation of hindbrain neurons, within the area postrema (AP) and the nucleus of the solitary tract (NTS). Therefore, inhibition of GDF15-mediated GFRAL–RET signaling in the hindbrain holds promising therapeutic potential against nausea, emesis and anorexia in patients undergoing chemotherapy, or suffering from other health/disease states with elevated GDF15 levels. Following in silico-library generation and deductive design, we generated and characterized a peptide GFRAL-RET antagonist, GRASP, that putatively inhibits GDF15-induced RET recruitment to GFRAL and blocks intracellular signaling in HEK cells co-expressing RET and GFRAL. In vivo testing further showed that central and peripheral GRASP administration attenuated GDF15-induced anorexia and nausea (measured by pica of kaolin) in rats, and attenuated malaise behaviors induced by the emetogenic chemotherapeutic cisplatin. Importantly, GRASP co-administration with ondansetron, the first-line anti-emetic, led to a greater attenuation of cisplatin-induced anorexia. Collectively, these data provide a considerable advance in our understanding of GDF15 signaling. Our results highlight the beneficial effects of GRASP treatment and its potential use for the treatment of chemotherapy-induced malaise, as well as for the treatment of other diseases and/or medical conditions that drive uncontrolled nausea/emesis characterized by elevated GDF-15 levels.

**Short Chain Fatty Acids Direct Intestinal Stem Cell Differentiation To Absorptive Enterocytes In 3D Enteroids From Lean And Obese Patients.**

Mona Farhadipour1, Mathias Clarysse2, Kaline Arnouts1, Kathrin Liszt1, Theo Thijs1, Laurens J Ceulemans2, Ellen Deleu3, Bart Van der Schueren4, Matthias Lannoo3, Marc Ferrante1, Inge Depoortere1

1Translational Research Center for Gastrointestinal Disorders, University of Leuven, Leuven, Belgium, 2Leuven Intestinal Failure and Transplantation (LIFT) Center, University Hospitals Leuven, Leuven, Belgium, 3Department of Abdominal Surgery, University Hospitals Leuven, Leuven, Belgium, 4Clinical and Experimental Endocrinology, University Hospitals Leuven, Leuven, Belgium

Background and aim. Short chain fatty acids (SCFAs) are the main metabolites from dietary fibers, and improve gut health by affecting gut hormone release and the integrity of the intestinal barrier. We hypothesized that SCFAs in the microenvironment of intestinal stem cells (ISCs) in obese patients might affect ISC differentiation by activating free fatty acid receptor 2 (FFAR2) on stem cells or by acting as histone deacetylase (HDAC) inhibitors. This might affect the number of enteroendocrine cells (EECs) that increase satiety or the number of enterocytes that modify epithelial integrity. Methods. 3D enteroids were generated from ISC s from the jejunal mucosa of lean and obese donors and SCFAs (0.3-1mM), FFAR-2 agonist (371725, 1μM), HDAC-inhibitor SAHA (1μM) or vehicle. Changes in epithelial cell markers were assessed via real-time PCR. Results. SCFAs significantly inhibited ISC differentiation in enteroids from lean and obese individuals towards the secretory lineage. This was reflected by a concentration-dependent decrease in the mRNA expression of mucin 2 (MUC2, goblet cells) and of the orexigenic (ghrelin, motilin) and anorexigenic (GLP-1, CCK, chromogranin A) gut peptide containing EECs. In contrast, differentiation towards absorptive enterocytes (ALPI) was favored. The switch in ISC lineage commitment was not mediated via FFAR2 activation, since the FFAR2 agonist was without effect. In contrast, the effect was mimicked with SAHA indicating a role for HDAC inhibition. In conclusion, SCFAs have the potential to increase gut integrity at the expense of gut peptide secreting EECs by altering stem cell fate towards the absorptive enterocytes.

**Impact Of Various Plant-Derived Dietary Fibers On Energy And Glucose Homeostasis.**

Elizabeth J. Howard1, Rachel K. Meyer2, Savanna N. Weninger3, Archana Kangath4, Frank A. Duca5

1Microbiology Graduate Program, Tucson, AZ, United States, 2School of Nutritional Science and Wellness, Tucson, AZ, United States, 3Department of Physiology, Tucson, AZ, United States, 4School of Animal and Comparative Biomedical Sciences, Tucson, AZ, United States, 5School of Animal and Comparative Biomedical Sciences and BIO5 Institute, Tucson, AZ, United States

The gut microbiota contributes to the development of metabolic disease, and it is well known that diet shapes the gut microbiota, emphasizing the need to better understand how diet impacts metabolic disease via alterations in the gut microbiota. Dietary fiber intake is linked with improvements in metabolic homeostasis in humans, and specific prebiotics beneficially alters the gut microbiota, promote weight loss, and improve glucose homeostasis. In a previous study, we found that specific plant-based flours, including wheat and barley, supplemented with a high-fat diet (HFD) reduced body weight and adiposity and improved glucose tolerance in rats. However, whether this was due to specific fibers within the flour remains unknown. To test the impact of various dietary fibers on energy and glucose homeostasis, we supplemented HFD-fed mice with 6 different fibers (beta-pectin, beta-glucan, wheat dextrin, oligofructose, resistant starch, or cellulose as a control) at 10% (w/w) for 18 weeks (n=12/group), measuring body weight, adiposity, indirect calorimetry, and glucose metabolism.
Glucagon-like peptide 1 receptor (GLP-1R) stimulation in the lateral septum (LS) and the bed nucleus of the stria terminalis (BNST) suppresses feeding, and cell-type-specific anterograde tracing suggested that GLP-1R neurons in these locations project to other nuclei where GLP-1Rs are expressed, suggesting coordination of GLP-1 response across the brain. To better understand the organization of this system, we did anatomical tracing studies in GLP-1R-Cre mice (n = 4-5/group, males and females). Mice were injected with retrograde AAV for cre-inducible eGFP into either the dorsal LS (dLS) or the anterior BNST (aBNST), to identify GLP-1R neurons that project to one of these sites. Two weeks later, GLP-1R neurons projecting to the dLS were seen in areas including the basal sub lateralamygdal (BLA), the amygdala-hippocampus transition zone, and ventral hippocampus (vHipp). GLP-1R projections to aBNST were less dense than observed for dLS, with eGFP neurons seen in areas including the posterior BNST, medial preoptic area, BLA and medial amygdala, and vHipp. To identify synaptic inputs to GLP-1R-expressing neurons in the LS and BNST, we took a monosynaptic rabies tracing approach with injections targeting dLS or aBNST. This method identified small groups of “starter” GLP-1R-Cre neurons at our injection sites, and synaptic inputs to these neurons from elsewhere included dorsal and vHipp for the dLS, and posterior BNST for the aBNST. Additional histological analysis is ongoing. Together, these results suggest that GLP-1R-expressing neurons in multiple brain sites project to other nuclei where GLP-1Rs are also expressed, suggest new pathways that may play a role in the response to GLP-1 agonist treatments.

Trpv1 Enhances Cck Signaling In Vagal Afferent Neurons
Rachel A. Arnold, James H. Peters
Washington State University, Pullman, WA, United States

The gut peptide cholecystokinin (CCK) is released during feeding and promotes satiation by increasing excitation of vagal afferent neurons innervating the upper gastrointestinal tract. While the effects of CCK have been studied for decades, specific receptor signaling and coupling to membrane ion channels are not entirely understood. Vagal afferent neurons express CCK1 receptors (CCK1Rs) in the periphery and at central terminals in the nucleus of the solitary tract (NTS). The nonselective ion channel transient receptor potential vanilloid subtype 1 (TRPV1) is expressed throughout vagal afferent neurons and controls many forms of signaling, including quantal forms of glutamate release onto NTS neurons. Previous findings show that CCK preferentially activates TRPV1-containing afferents through a ruthenium-red sensitive pathway. Studies also show that the ability of CCK to acutely reduce food intake is partially dependent on TRPV1-expressing vagal afferent neurons. Together, these findings suggest that CCK1Rs may couple with TRPV1 ion channels to control neural activation and food intake. We tested this hypothesis using selective pharmacology and functional measurements in dissociated vagal afferent neurons, slice electrophysiology in the NTS, and in vivo measurements of food intake. We found that TRPV1 activity was predictive of CCK responses and that inhibition or augmentation of TRPV1 respectively reduced or enhanced the response to CCK. Pharmacological inhibition of TRPV1 targeted to the fourth ventricle suggested that TRPV1 contributes to the control of CCK induced satiety in vivo. Together, these results implicate TRPV1 as an important cellular point of control for mediating the effects of CCK on vagal afferent activation and satiety.

Early Life Stress Reduces Adult Behavioral Sensitivity To Exogenous Cholecystokinin-8 (Cck) In Mice
MICHELLE BALES, NATALIA VALDERRAMA, LINDA RINAMAN
Florida State University, Tallahassee, FL, United States

Early life stress (ELS) in human and rodent models can persistently reduce vagal tone, perhaps by modifying vago-vagal circuits. Exogenous cholecystokinin-8 (CCK) activates a gastrointestinal (GI) vago-vagal circuit to reduce gastric emptying and promote satiety. Thus, we hypothesized that adult mice exposed to a “limited resources” model of ELS from postnatal days 2-9 would display delayed CCK-induced satiety compared to control mice reared under conditions of care as usual (CAU). Using a within-subjects crossover design, adult mice (CAU, N=3/sex; ELS, N=6/sex) received an i.p. injection of saline vehicle containing 0, 1, 5, 10, or 50 ug/kg CCK five minutes before dark onset. Food intake data were collected using a BioDAQ monitoring system for 12 hr after each injection, and then normalized by bodyweight (since males weighed more than females). Three-way ANOVA revealed main effects of CCK dose (p=0.0002), early life rearing (p=0.0005), and sex (p=0.04) on food intake, but no interactions. When data from both sexes were combined, two-way ANOVA revealed main effects of CCK dose (p<0.0001) and rearing (p=0.0003), but no interaction. A Post-hoc tests confirmed that compared to CAU mice, ELS mice were less sensitive to the hypogastic effect of i.p. injection stress, and also were less sensitive to the hypogastic effect of CCK. These results support the view that ELS alters vago-vagal circuits to reduce behavioral sensitivity to vagal sensory stimulation, which may itself reduce vagal tone.

Brain-Wide Neural Activity During Ingestion Is Dominated By Motor Representations
Anna J. Bowen, David J. Ottenheimer, Julia Hopkins, Nicholas A. Steinmetz
University of Washington, Seattle, WA, United States

Animals must eat to live, and to achieve this they must have neural systems to detect food and learn about its value. Both food reward and stimulus salience are modulated by internal state, as food-related stimuli are most important during deprivation. To probe the neural coding of reward, salience, consummatory behaviors, and salience, we designed a Pavlovian task that incorporated a temporally varying reward rate for an auditory conditioning stimulus (CS) to systematically vary CS-evoked anticipatory licking; we also titrated the received reward to ensure that satiety was reached during each session. We used state-of-the-art high-density electrode arrays to record from thousands of individual neurons across >50 brain regions in 11 subjects during this reward seeking task to examine neural encoding of stimulus and behavioral variables. Recorded regions included orbitofrontal and prefrontal cortex, lateral hypothalamus, amygdala, striatum, and parabrachial nucleus. We used kernel regression techniques to decode the unique contributions of sensory, motor, and internal variables to neural activity across each session. Surprisingly, we found overrepresentation of licking behavior and satiety in neural activity across the brain: most ‘stimulus evoked’ neural activity was better explained by the anticipatory or consummatory behaviors of the animal, rather than by the CS or reward. This suggests that motor signals may act as secondary variables that are integrated elsewhere with sensory encoding. Future work will examine the overlap between behavioral and satiety encoding as we expect to observe state-dependent shifts in task engagement.
A Bed Nucleus Of The Stria Terminalis Glp-1R Neuron Projection To Lateral Hypothalamus Affects High-Fat Food Intake

Isabel I. Coiduras1, Lisa R. Anderson1, Stefan Trapp2, Frank Reimann3, Fiona M. Gribble3, Diana L. Williams1
1Department of Psychology & Program in Neuroscience, Tallahassee, FL, United States, 2Centre for Cardiovascular and Metabolic Neuroscience, Department of Neuroscience, Physiology & Pharmacology, London, United Kingdom, 3Institute of Metabolic Science & MRC Metabolic Diseases Unit, Cambridge, United Kingdom

Activation of glucagon-like peptide 1 receptors (GLP-1R) in the bed nucleus of the stria terminalis (BNST) suppresses food intake. We previously showed that BNST GLP-1R neurons project to LH, and GLP-1R stimulation inhibits 60% of GLP-1R-expressing BNST neurons. We therefore hypothesized that activation of the GLP-1R BNST-to-LH pathway increases food intake. Male and female GLP-1R-Cre mice received intra-BNST injection of AAV to induce hM3Dq-mCherry or control mCherry in GLP-1R neurons, and were implanted with LH-targeted bilateral cannulas. Mice were housed in the BioDAQ continuous food intake monitoring system and we examined intake and meal pattern variables. Intra-LH vehicle (VEH) or CNO injections were made 30 min before dark onset in counterbalanced order. CNO had no effect on chow intake in hM3Dq mice (n=7M, 7F) or controls (n=4M, 4F). We then asked if CNO could attenuate the effect of 15-min restraint stress prior to dark onset. Stress suppressed intake similarly in both groups regardless of CNO treatment. Next, we examined effects on high-fat diet (HFD, 60% fat) intake. Mice were maintained on HFD for 4 weeks and then received intra-LH VEH or CNO. hM3Dq mice (n=7M, 9F) significantly increased cumulative HFD intake after CNO by 25-45% at multiple timepoints (p’s<0.05), with no effect in controls (n=6M, 8F). ANOVA revealed significant group X CNO interactions from 4-20 h after dark onset (p’s<0.05), and no sex differences were observed. Meal size tended to be increased by CNO in hM3Dq mice, but we saw no significant effect on any meal pattern variable. We conclude that the GLP-1R BNST-to-LH neuron projection influences food intake under some circumstances, and may mediate some but not all feeding effects of BNST GLP-1R stimulation.

High Fat Diet Feeding Disrupts Thermal Responsiveness Of Agrp Neurons

Jennifer Deen, Tammy Doan, Bao Anh Phan, Kayoko Ogimoto, Michael Schwartz, Gregory Morton
University of Washington, Seattle, WA, United States

Energy homeostasis in the cold requires energy expenditure and energy intake increase, enabling both core temperature and body fat mass to be defended. We recently found that cold exposure activates a subpopulation (~20%) of AgRP neurons, and their thermal responsiveness underlies the hypothermic response to cold. Because thermal input regulates AgRP neuron activity and high-fat diet (HFD)-feeding blunts their responsiveness to gastric hormones and food-related sensory cues, we postulated HFD might also alter their responsiveness to cold and the resulting hyperphagia. Indeed, we find that although 12-wk HFD-fed mice exhibit intact thermogenic responses to cold, they fail to increase energy intake when chronically housed in mild cold and consequently lose weight. This uncoupling is present even after 2 wk of HFD, implying a role for diet separate from obesity. We also find cold rapidly induces Fos in Chow-fed, but not HFD-fed mice and this correlates with a failure to increase Agrp mRNA. To test for changes in AgRP neuron activity across the development of diet-induced obesity, we used photometry in conjunction with a Pellet cooler platform, which allows for rapid control over sensed temperature, and subjected ad lib fed mice to rapid shifts in sensed temperature. We find AgRP neuron activity remains consistently responsive to sensitive in chow-fed mice, but these clear shifts in activity are absent after two weeks of HFD. Surprisingly, the damaged activity seen at 2 wk of HFD is restored at 5 and 10 wk, implying thermal input to AgRP neurons is present but insufficient to drive food intake. Future work will map the circuitry involved in cold-induced hyperphagia and determine how HFD uncouples AgRP neurons from their ability to drive food intake.

The Macronutrient Content Of Food Differentially Modulates Striatal Dopamine Release And Food Reward In Male And Female Mice

Alec Hartle1, Kelly Runyon1, Asia Dofat1, Katie Marshalko1, Josh Sisco1, Alexandra DiFeliceantonio1,2,3, Matt Howe1,3
1Virginia Tech School of Neuroscience, Blacksburg, VA, United States, 2Virginia Tech Dept. of Human Nutrition, Food, and Exercise, Blacksburg, VA, United States, 3Fralin Biomedical Research Institute at Virginia Tech, Roanoke, VA, United States

Midbrain dopamine (DA) cells receive signals from the gut about food content that affect their excitability and thereby contribute to food learning and motivation. Interestingly, fats and carbohydrates recruit separate ascending pathways from the gut to the midbrain to modulate eating. Recent research in humans has also demonstrated that foods made of combinations of fats and carbohydrates are overvalued. We hypothesized that this overvaluation may be due to the ability of such combination foods to augment DA release. To gain insight into such post-ingestive modulation of brain reward circuits, here we examined the impact of single macronutrient and macronutrient combinations on DA release, food intake, and food reinforcememt in mice. We found that when given free access, mice consume nearly 4 times as much of a food made of a combination of fat and carbohydrate compared to either macronutrient alone (n=40). Measurements of DA release using DLight and fiber photometry revealed a doubling of phasic DA release events in the nucleus accumbens (NAc) during consumption of the combination stimulus compared to isocaloric amounts of fat or carbohydrate (n=7). Interestingly, we found that DA release in the dorsal striatum corresponded with the caloric density of food items, with the greatest release during fat consumption (n=8). A this increase in DS DA release was greater in female than male mice, and correlated with an increase in the capacity of fats to create a conditioned place preference in females (n=10 male, female). Our ongoing studies suggest a model whereby caloric density and reward value are differentially encoded by DS and NAc DA.

Impact Of A Western Diet On Brain Mitochondrial Network Dynamics And Behavior

Jessica Hoffman, Magen Lord, Caroline Akemi Soares Izuka, Claire de La Serre, Emily Noble
Department of Nutritional Sciences, University of Georgia, Athens, GA, United States

We found that a Western Diet (WD) impacts hippocampal and hypothalamic mitochondrial bioenergetics, associated with impaired neurocognitive function and metabolic disease. Mitochondria dynamically merge and divide in response to physiological stressors, and alterations in brain mitochondrial function affect memory, whereas mitochondrial network dysfunction in the hypothalamus promotes diet induced obesity. We hypothesize that chronic consumption of a WD negatively impacts mitochondrial network dynamics in the hippocampus and hypothalamus. Female Wistar rats (n=6/group) were maintained on rodent chow or WD for 12 weeks. Mitochondrial network dynamics were assessed by measuring the size and shape of mitochondrial components in hippocampal and hypothalamic tissue using electron microscopy and Western blotting for OPA1 and Tom20. WD consumption increased mitochondrial size in the hippocampus but not the hypothalamus. In addition, WD consumption reduced Tom20 expression in the hypothalamus but not the hippocampus. These findings suggest that WD consumption differentially affects mitochondrial network dynamics in the hippocampus and hypothalamus and may contribute to the development of obesity and related metabolic disorders.
Hypothalamic and mesolimbic glucose sensing in humans. Heterogeneous expression of vagal afferent dopamine receptors. The role of amygdalar GLP-1 signaling in cocaine withdrawal behaviors and reinstatement.

P328 Hypothalamic And Mesolimbic Glucose Sensing In Humans
Bojana Kuzmanovic¹, Eva Schneider¹, Ruth Hansen¹,², Jens C. Bruening¹,²,³, Marc Tittgemeyer¹,³
¹Max Planck Institute for Metabolism Research, Cologne, Germany, ²Policlinic for Endocrinology, Diabetes and Preventive Medicine (PEPD), University Hospital of Cologne, Cologne, Germany, ³Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases (CECAD), Cologne, Germany

Hypothalamic and mesolimbic neurons respond to nutrients such as glucose, thereby adapting metabolism, motivation, and feeding behavior to changing energy states of the organism. Recent advances in rodent research revealed a cascade of signaling following glucose intake, including a rapid deactivation of hypothalamic agouti-related protein neurons, and a down-regulation of mesolimbic circuits via hypothalamic inputs and insulinergic action. However, translating these insights to humans remains challenging. To meet this challenge, we implemented a randomized crossover design, in which healthy overnight-fastened participants consumed 300 ml water or glucose solution (75 g) via peroral tube while undergoing fMRI on two separate days. In contrast to previous fMRI studies on oral glucose intake in humans, we analyzed whole-brain data using general linear models to increase precision and extent of the measured brain activity. Particularly, we compared the time-courses of voxel-wise responses to glucose and water by contrasting each of 20 post-ingestion 1-min-time-bins against a pre-ingestion baseline, separately for the two days. State ratings and blood samples before and after oral intake allowed for monitoring satiety, glucose and insulin. Combining glucose intake and fMRI, we demonstrate glucose sensing in humans that fully resembles the sustained deactivation of rodent hypothalamic and mesolimbic neurons. Furthermore, we investigate how this neural response depends on peripheral insulin sensitivity and dynamics of plasma glucose and insulin. This translational approach provides a critical building block for assessing metabolic sensing in humans, its relation to reward-related sensitivity and motivation, and its impairments by metabolic disorders.

P329 The Role Of Amygdalar Glp-1 Signaling In Cocaine Withdrawal Behaviors And Reinstatement
Riley Merkel¹,², Rae Herman¹,², Yafang Zhang¹,², Heath Schmidt¹,²
¹Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA, United States, ²Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Preventing relapse and promoting abstinence remain the greatest challenges for treating cocaine use disorder (CUD). Activation of central glucagon-like peptide-1 receptors (GLP-1Rs) reduces the rewarding effects of cocaine and attenuates cocaine-seeking behavior during abstinence. However, the neural circuits mediating these effects are not fully described. GLP-1Rs are abundantly expressed in the central amygdala (CeA), a nucleus necessary for drug-related learning and the reinstatement of cocaine seeking. We hypothesized that activation of GLP-1 Rs in the CeA would attenuate the reinstatement of cocaine-seeking behavior. Here, we show that intra-CeA administration of the GLP-1 R agonist Ex-4 dose-dependently attenuated the ability of an acute priming injection of cocaine and drug-paired cues to reinstate cocaine seeking without affecting normal feeding behaviors. Neural tracing and fluorescent in situ hybridization techniques were used to determine the targets of GLP-1R-expressing neurons due to its role in withdrawal-mediated phenotypes. Our data suggest that GLP-1Rs are expressed on a subset of GABA neurons that project from the CeA to the BNST. Given the role of the CeA in both drug and anxiety circuits, CeA GLP-1 signaling may regulate drug reinforcement indirectly by attenuating stressful phenotypes that promote drug seeking during cocaine withdrawal. Preliminary data suggest that systemic administration of Ex-4 reverses the anxiogenic properties of cocaine withdrawal following 14 days of abstinence. These findings establish a functional role for CeA GLP-1Rs in cocaine reinstatement and further support re-purposing GLP-1R agonists for treating CUD, while highlighting a novel avenue of exploration at the intersection of anxiety and drug-mediated behaviors.

P331 Heterogeneous Expression Of Vagal Afferent Dopamine Receptors
Caitlin R Ritchey, BreeAnne Peterson, David J Rossi, James H Peters
Washington State University, Pullman, WA, United States

The catecholamine dopamine (DA) and its receptors (DRD1-5) have been strongly implicated in the control of autonomic reflexes. However, focus has remained on cardiovascular and respiratory functions at the level of the nucleus of the solitary tract (NTS) with limited studies done to understand DA's role in feeding. The presence of functional DRD2 receptors has been confirmed in cell bodies and terminals of rat vagal afferents, but the understanding of the mechanistic effects of this receptor in the feeding pathway is incomplete. In this project, we investigated the responses to DA by vagal afferents using fluorescent calcium imaging and patch clamp electrophysiology on cultured nodose ganglion (NG) isolated from adult male Sprague Dawley rats. We found that DA increases intracellular calcium concentrations in a dose-dependent manner in 21% of responding neurons and caused overall inhibition in 13% of responding neurons. To determine the potential effects of DA signaling in mediating meal-related signals, the response to the satiety hormone cholecystokinin (CCK) was measured in the presence of DA. We found that the response to CCK in the presence of DA was potentiated in 50% of responding neurons and inhibited in 50% of responding neurons. Future experiments will determine the nature of afferents exhibiting inhibited signaling...
Investigation Of Parabrachial Neural Populations Mediating Lipoprivic Feeding
Forrest J. Shaffer, Carlos A. Campos
University of Washington, Seattle, WA, United States

Inhibition of fat metabolism following mercaptoacetate (MA) administration stimulates food intake. This lipoprivic feeding requires intact vagal afferent connections to the nucleus of the solitary tract (NTS) and is occluded following parabrachial nucleus (PBN) lesions. While the underlying neural pathway in mediating this effect is known, the involvement of distinct cell types and their connections remains unexplored. To gain access to PBN neurons activated by MA, Fox-CreER mice received PBN virus injections containing Cre-dependent hM3Dq:mCherry. In these mice, 4-OHT administration permits Targeted Recombination in Active Populations (TRAP), which enables expression of hM3Dq and chemogenetic activation of neurons previously activated by MA. We hypothesized that activating these trapped neurons would replicate the effects of MA. However, we found that MA injection fails to stimulate food intake, suggesting MA activated PBN neuron subpopulations may have divergent behavioral effects. Indeed, immunohistochemistry revealed MA-induced Fox expression in the central lateral and external lateral PBN, including within a subpopulation of CGRP+ neurons, which are known to suppress appetite. To assess the role of CGRP neurons in MA-related behaviors, we injected virus to express tetanus toxin (TeTx) in Calca-Cre mice. Silencing CGRP neurons with TeTx did not inhibit or augment the effects of MA, indicating that non-CGRP neurons mediate the appetitive effects of MA. However, we found that MA injection following access to a novel diet can induce a conditioned taste aversion, an effect that requires activation of PBN CGRP neurons. From these studies, we propose that different populations of neurons in the PBN mediate the appetitive and aversive effects of MA.

Do Wanting, Hunger And Brain Microstructure Predict Recognition Performance And Lure Discrimination Of Food Items? &Ndash; A Pre-Registered Analysis
Ronja Thieleking, Evelyn Medawar, Amo Villringer, Frauke Beyer, Veronica Witte
1Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, 2Day Clinic for Cognitive Neurology, University of Leipzig Medical Center, Leipzig University, Leipzig, Germany

Rising obesity prevalence urges the need to understand unhealthy food decisions and potential modifiers. We aim to identify how psychological factors such as wanting and hunger modify food memory, and how prefrontal-temporal fiber connections contribute to food memory processing. The study was designed as a randomized controlled cross-over intervention in 60 healthy, naive-eating, overweight adults (20f). Data for this pre-registered cross-sectional analysis (osF.io/2z4dn) was drawn from all time points of the larger study (intervention as confounder of no interest). Each testing day included 3T brain MRI with two tasks and diffusion-weighted imaging (DWI). Firstly, food vs. non-food wanting was assessed followed by a recognition memory task incl. lure discrimination. After quality assessment, 57 participants (181 data sets) entered behavioral analyses and 55 (176 data sets) were suitable for DWI analyses. We conducted advanced fiber tracking to assess the microstructure of the uncinate fasciculus (UF). Normalized quantitative anisotropy (nQA) served as outcome measure. We performed the statistical analysis with Bayesian mixed modeling. At the behavioral level, recognition (d') and lure discrimination (LDI) was better for food than non-food. Stronger single item wanting predicted higher response correctness. However, better food memory was not explained by individual hunger or categorized wanting. Neither nQA of the UF nor age nor body composition determined memory performance. Individual food wanting predicted food memory in this sample of young, overweight adults. This might help to improve weight-loss interventions. To better understand reward-related determinants of food memory, we currently investigate reward-related brain activity during encoding and recognition.

Nucleus Accumbens Dopamine Release Evoked By Mixed Nutrient Solutions In Protein-Restricted And Non-Restricted Mice
K. Linnea Volcko, James E. McCutcheon
Institute for Psychology, UiT The Arctic University of Norway, Tromso, Norway

Neural activity in ventral tegmental area (VTA) is higher when protein-restricted rats drink a protein solution than when they drink a carbohydrate solution. The VTA is a major source of dopamine in the brain, and slice preparations show greater stimulated dopamine release in nucleus accumbens (NAc) of protein-restricted rats than in non-restricted controls. Thus, the involvement of the mesolimbic dopamine system in protein restriction is clear. Nonetheless, in vivo measurement of dopamine itself in response to protein consumption has been missing. Here, we used fiber photometry to measure dopamine in NAc of protein-restricted (PR) and non-restricted (NR) mice drinking “Resource Complete”, a high-protein (23%) mixed nutrient solution, and “Scandishake”, a low-protein (4.9%) mixed nutrient solution. We found that PR mice drank significantly more Resource Complete than NR mice, but that intakes were equivalent when Scandishake was offered. Next, we injected mice with the fluorescent dopamine sensor GRABDA and implanted a fiber optic aimed at NAc lateral shell. We observed dopamine-driven changes in fluorescence in response to licking, however, neither the signal peak nor AUC differed between NR and PR mice drinking Resource Complete or Scandishake in different sessions. Ongoing experiments are investigating whether familiarization with each solution, i.e. allowing mice to associate the taste with its post-ingestive feedback, will alter dopamine release. Furthermore, we will test mice when given access to both solutions in the same session and have a choice of which solution to consume. Together, these experiments will provide information about how dopamine release in NAc is (or is not) affected by the state of protein restriction.

Parasympathetic Signaling Controls Biosynthesis Of Small-Intestinal Endocannabinoids And Overeating In Western Diet-Induced Obesity
Courtney P. Wood, Nicholas V. DiPatrizio
University of California, Riverside, Riverside, CA, United States

The endocannabinoid (eCB) system becomes dysregulated in diet-induced obesity (DIO) and contributes to overeating. In DIO mice, overactivation of local cannabinoid receptor subtype-1 (CB1R) inhibits nutrient-induced release of satiation peptides and promotes hyperphagia. We tested the hypothesis that parasympathetic signaling at muscarinic acetylcholine receptors (mAChRs) leads to increased biosynthesis of the eCB 2-arachidonoyl-sn-glycerol (2-AG) in the small-intestinal...
(SI) epithelium, which may drive overeating in DIO. Male mice were maintained on a high-fat/high-sugar western-style diet for 60 days to induce DIO. Mice received IP injections of methylhomatropine bromide (ATR, a peripheralized mAChR antagonist), DAU5884 (DAU, a selective m3AChR antagonist), or pirenzepine (PIR, a selective m1AChR antagonist) 30 minutes prior to tissue harvest. Levels of 2-AG and its precursor, 1-stearoyl-2-arachidonoyl-sn-glycerol (SAG), in the SI epithelium were quantitated by UPLC-MS/MS. In addition, ex-vivo activity of the synthetic enzyme for 2-AG, diacylglycerol lipase (DGL), was analyzed in the SI. Food intake, water intake, and ambulation were recorded with automated feeding chambers. DIO mice exhibited elevated levels of SAG, 2-AG, and DGL activity in the SI epithelium, when compared to lean mice maintained on a low-fat/no-sucrose chow. These effects were blocked by ATR, DAU, or PIR. Furthermore, ATR or DAU reduced caloric intake in DIO mice during a 24-h test and had no effect on ambulation. These results suggest that in DIO, hyperactivity at Gq-coupled mAChRs in the periphery drives increases in the PLC-dependent generation of SAG, which is then converted to 2-AG by DGL in the SI epithelium and contributes to overeating.
**Background**

Roux-en-Y gastric bypass (RYGB) decreases energy intake, and is an effective treatment of obesity. We aimed to identify how RYGB affects changes in macronutrient intake in rats and how humans adapt their ingestive behavior. A Methods: Wistar rats underwent either RYGB (n=15) or sham operations (n=16). Preoperatively a standardized 4-choice cafeteria diet [low-fat/low-sugar, low-fat/high-sugar, high-fat/low-sugar, high-fat/high-sugar] was offered pre- and postoperatively. The intake of all available food items was monitored for 8 weeks. The human ingestive microstructure of a standardized liquid meal was recorded in a cohort of 11 RYGB patients, in 10 patients with obesity, and in 10 healthy-weight adults prospectively for 1 year with a custom-designed drinkometer. Data-driven (3 s) and additional burst pause criteria were used. Results: Rats undergoing RYGB presented a progressive decrease in daily consumption of calories from fat and increased their energy intake mainly from non-sugar carbohydrates. No such differences were detected in sham-operated controls. Patients with obesity differed at baseline from healthy-weight controls in mean meal size (909.2 vs 557.6 kcal), burst size (28.8 vs 17.6 mL), and meal duration (433 vs 381 s). At 1 year, the ingestive differences between the RYGB and healthy-weight groups disappeared due to significantly decreased burst size (P = 0.008) and meal duration (P = 0.034) after RYGB. Conclusion: RYGB induced dynamic changes in ingestive behavior. Rodents progressively decreased their daily calorie intake from fat, whereas humans reduced their meal size by decreasing burst size and meal duration. Our findings suggest that increased postgestive sensibility and learning may mediate postbariatric ingestive behavior.

**Results**

RYGB produced better weight loss relative to VSG, with weight regain and greater weight loss variability observed from six months to one-year post-VSG. At one year, the differences were detected in sham-operated controls. Patients with obesity differed at baseline from healthy-weight controls in mean meal size (909.2 vs 557.6 kcal), burst size (28.8 vs 17.6 mL), and meal duration (433 vs 381 s). At 1 year, the ingestive differences between the RYGB and healthy-weight groups disappeared due to significantly decreased burst size (P = 0.008) and meal duration (P = 0.034) after RYGB. Conclusion: RYGB induced dynamic changes in ingestive behavior. Rodents progressively decreased their daily calorie intake from fat, whereas humans reduced their meal size by decreasing burst size and meal duration. Our findings suggest that increased postgestive sensibility and learning may mediate postbariatric ingestive behavior.

**Conclusion**

Six months post-surgery is a critical window for implementing interventions to mitigate weight gain. Initial anatomical and metabolic changes resulting from RYGB that reset neural processing of reward stimuli in the mesolimbic pathway appear to be temporary and likely contingent upon post-operative eating behaviors returning to preoperative obesogenic tendencies.
Progress in unraveling the nutrient-sensing mechanisms in the taste buds of the tongue has prompted studies on the existence and role of chemosensory cells in extra-oral tissues. The gut, which is the key interface between food and the human body, “tastes” what we eat in much the same way as the lingual system. Indeed, taste receptors are expressed on epithelial cells and monitor the presence of nutrients but also of non-nutrients such as toxic chemicals. This chemosensory system transmits this information to effector cells that will elicit appropriate biological processes to either assimilate or expel the (non)-nutrients from the gut. During this talk, I will focus on the role of taste receptors in the sensing of sweet and bitter compounds by the enteroendocrine cells of the human gut and their importance in regulating the release of appetite regulating hormones. The disturbances and adaptations that occur in these chemosensory signalling mechanisms during obesity in humans will be discussed. Results from in vitro studies will be complemented with some findings from in vivo studies on the effect of administration of sweeteners or bitter compounds on food intake in mice and humans. These studies will elucidate whether targeting of extra-oral taste receptors with specific agonists or functional food components may represent relevant strategies to control energy homeostasis.
To investigate a hypothesized effect on whole-body metabolism, we engineered mice with either enhanced or suppressed excitability of mitral and tufted cells (M/TCs) of the olfactory bulb (OB). To increase neuronal excitability, we used Tbx21-Cre x flox-Cas9 progeny to retroorbitally deliver a sgRNA directed to cleave the Kv1.3 channel in M/TCs. Ex vivo patch clamping confirmed that CRISPR MCs had enhanced excitability: having a less negative RMP, a lower rheobase current, and increased evoked AP firing frequency. MCs of CRISPR mice were insensitive to a selective blocker of Kv1.3, and protein expression of the channel was reduced by 70%. Like global Kv1.3−/− mice, the conditional CRISPR knockouts had increased odor discrimination in a habituation/dishabituation paradigm compared to that of control (Cas9−) littermates. When challenged with a 25-week moderately-high fat diet, CRISPR males demonstrated improved metabolic metrics over control littermates. They were resistant to weight gain, had faster glucose clearance, had reduced serum leptin and liver triglycerides, and reduced RER with a shift toward fat metabolism. In a second cohort of Tbx21-Cre x flox-Cas9 male progeny, inhibitory DREADDs were stereotactically delivered to allow restricted expression to M/TCs. Opposite to that of the CRISPR mice, DREADDs mice had reduced odor discrimination. When assessed for metabolic health, DREADDs mice contrastingly had a reduction in thermogenesis, oxygen consumption, and caloric and water intake in the dark cycle. Clozapine N-oxide (CNO) alone did not have any metabolic effects in the absence of the DREADD receptor. We conclude that the projection neurons of the OB represent an intersection of the neuronal circuitry that regulates both olfaction and metabolism.

Fasting Plasma Acyl Ghrerin To Leap2 Ratio Is Positively Correlated With Human Appetite And Food Intake, And Negatively Correlated With High-Energy Food Cue Reactivity In Posterior Cingulate Cortex

Anthony P. Goldstone1, Bharath K. Mani2, Bruce Gaylinn3, Christina G. Prechtl4, Michelle L. Sleeth4, Samantha Scholtz5, Alexander D. Miras4, Norlida M. Daud4, Claire Pettit4, Navpreet Chhina2, Jeffrey M. Zigman2

1PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, United Kingdom. 2Division of Endocrinology and Metabolism, UT South Western Medical Center, Dallas, TX, United States. 3Department of Endocrinology, University of Virginia, Charlottesville, VA, United States. 4Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom. 5Imperial Weight Centre, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

Background: LEAP2 is a gut hormone acting as an antagonist/inverse agonist at the acyl ghrelin (AG) receptor (GHSR). In mice and humans, plasma AG and LEAP2 are reciprocally regulated with AG/LEAP2 ratio increasing with fasting and weight loss. In rodents, LEAP2 attenuates exogenous AG-induced and spontaneous food intake. However, any role for LEAP2 in human eating behaviour is currently unknown. We hypothesised that fasting plasma AG/LEAP2 molar ratio would be positively correlated with appetite, food intake and brain reward system food cue reactivity. Methods: Overnight fasting plasma AG and LEAP2 were assayed in n=90 adults (19-55 years, 60% female, BMI 19.1-53.1 kg/m^2, 67% overweight/obese). Hormones were correlated with appetite visual analogue scale rating (n=89), food intake (kcal as % estimated resting energy expenditure) at an ad libitum savoury meal (n=74), and functional MRI BOLD signal during evaluation of high-energy (HE) or low-energy (LE) food pictures in whole brain analysis (n=84, cluster-wise FWE Z>2.3, P<0.05). Results: Plasma AG/LEAP2 molar ratio (r=0.25, P=0.020) and AG (r=0.21, P=0.044) positively correlated with appetite rating. Plasma LEAP2 negatively (r=-0.35, P=0.002) and AG/LEAP2 ratio positively (r=0.28, P=0.014) correlated with food intake. Plasma LEAP2 positively (r=0.44-0.29, P<0.001-0.007) and AG/LEAP2 negatively (r=-0.38 to -0.22, P=0.004-0.041) correlated with BOLD signal to HE foods, and HE vs. LE foods, in the posterior cingulate cortex, a region deactivated during external attention. Conclusion: These relationships of fasting plasma LEAP2 and AG/LEAP2 ratio with
Encoding Of Taste Information By Monoamine Dynamics In The Amygdala
Beniamino Hadj-Amar,1, Seth Batten,2, Alec Hartle,3, Amber L Kelly,2, Mary E Oster,2, Terry Lohrenz,2, Marina Vannucci,1, W Matthew Howe,3, P Read Montague,2,4,5, Alexandra DiFeliceantonio2,6
1Rice University, Department of Statistics, Houston, TX, United States, 2Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, VA, United States, 3Virginia Tech, School of Neuroscience, Blacksburg, VA, United States, 4Virginia Tech, Department of Physics, Blacksburg, VA, United States, 5University College London, Wellcome Centre for Human Neuroimaging, London, United Kingdom, 6Virginia Tech, Department of Human Nutrition Foods and Exercise, Blacksburg, VA, United States

Taste is called the gatekeeper to our internal environment, providing essential information on qualities of soon to be ingested foods. Both taste identity and taste intensity are critical for guiding ingestion. The ability to perceive variations in taste intensity serves the crucial role of signaling the concentration of nutritive or noxious elements in what we are about to ingest. Alterations in this process have been linked to important health factors such as diet and food choice; which can lead to obesity and metabolic dysfunction, and excess alcohol intake. Although the peripheral mechanisms of taste intensity perception differences have been well studied, they do not explain all variation in human taste intensity perception, indicating there must be important central mechanisms. Here, we capitalize on the unique recording environment of the epilepsy monitoring unit (EMU), where patients have implanted depth electrodes outside of the operating room setting. Specifically, we recorded from depth electrodes implanted in the amygdala, a CNS structure linked to taste perception. Incorporating a novel machine learning enhanced approach to voltammetry (MLEV), coupled with a probabilistic Hidden Markov model (HMM) approach, we have monitored sub-second monoamine dynamics while patients consume stimuli of varying levels of sweetness and fat. We are expanding upon these preliminary findings in humans with in-vivo experiments in murine models to identify the unique contributions of monaminergic systems in modifying amygdala output. These findings represent the first, to our knowledge, invasive recordings in humans during taste perception. Our collection and analysis strategy opens the door for novel hypotheses about monoamine encoding of taste perception in the human brain.

Circulating Uridine Dynamically And Adaptively Regulates Food Intake In Humans
Ruth Hanssen,1,2, Lionel Rigoux,1, Kerstin Albus,3,4, Alina C. Krestschmer,1,2, Sharmili E. Thanarajah,1,5, Yvonne Hinze,6, Patrick Giavalisco,6, Sophie Steculorum,1,9, Olivier A. Cornerly,3,4,7,8, Jens C. Brueening,1,2,3, Marc Tittgemeyer,1,3
1Max Planck Institute for Metabolism Research, Cologne, Germany, 2University of Cologne, Faculty of Medicine and University Hospital Cologne, Policlinic for Endocrinology, Diabetes and Preventive Medicine (PEPD), Cologne, Germany, 3Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany, 4University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany, 5Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Frankfurt am Main, Germany, 6Max Planck Institute for Biology of Ageing, Metabolomics Core Facility, Cologne, Germany, 7German Centre for Infection Research (DZIF), Cologne, Germany, 8University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZK$ Koeln), Cologne, Germany, 9German Center of Diabetes Research (DZD), Neuherberg, Germany

Feeding behavior must be continuously regulated to maintain a stable body weight. While the physiology of feeding is progressively unraveled in animal models, the mechanisms of appetite regulation in humans remain incompletely defined. Recent discoveries in murine models identified uridine as a regulator of energy balance, yet its potential role in the complex control of food intake in humans has not been addressed. Here, we have monitored circulating uridine concentrations, hunger ratings, and food intake in healthy human participants (BMI: 20-25 kg/m2) being served an ad libitum buffet after an oral dose of a uridine precursor, uridine monophosphate (UMP), in two (0.5 g; N = 17 or 1 g; N = 22) randomized, placebo-controlled, cross-over studies. We first establish that endogenous circulating uridine continuously predicts hunger and food intake in humans. Further, we show that uridine dynamically adapts to caloric ingestion, hence implementing a negative feedback loop regulating energy intake. Finally, we demonstrate that oral UMP administration increases circulating uridine levels and therefore can effectively boost, when in the physiological range, both hunger and food intake. Overall, our results establish uridine as a novel mediator of the regulation of food intake in humans, which can be easily altered by UMP supplementation. Uridine, therefore, emerges as a potential target to tackle dysfunctions of feeding behavior in humans.

A Glucokinase-Linked Sensor In The Taste System Contributes To Glucose Appetite
Lilly Mai,1, Sandrine Chometton,1, Ahyun Jung,2, Aracely Simental,2, Lindsey Schier,1,2
1Department of Biological Sciences, Los Angeles, CA, United States, 2Neuroscience Graduate Program, Los Angeles, CA, United States

The canonical sweet receptor (T1R2+T1R3) plays an important role in motivating sugar and sweetener ingestion, but other oral sensors appear to contribute to the intake-promoting effects of glucose. We found that glucokinase (GCK), a key intermediary in other glucosensing cell types, is expressed in murine taste bud cells. We then assessed if GCK expression in the major taste fields is glucose and/or drive ingestion of sugar and/or drive ingestion of low-calorie sweeteners. NaA"ve B6 mice with a lingual virogenetic knockdown (KD) of GCK took significantly fewer licks per burst for glucose in a short (300 lick) test. GCK KD had no effect on licking for isoconcentrated fructose, or the low-calorie sweetener, sucralose. Lingual GCK KD in mice also lacking the sweet receptor genes (T1R KO and B6) mice given extensive exposure to glucose and fructose come to prefer the orosensory properties of glucose in brief access tests. Thus, we assessed whether this type of sugar experience (Sug-Exp) leads to greater GCK expression in the taste bud cells. Indeed, Sug-Exp B6 and T1R KO displayed significantly more GCK in the circumvallate taste field, than naive controls. Next, to determine if gustatory GCK is critical for expressing the acquired glucose preference, Sug-Exp mice underwent lingual GCK KD during or after the sugar exposure phase, and then were given a brief access taste test for glucose versus fructose. In both cases, GCK KD impaired the ability
A Role For Odor Imagery Ability In Food Cue Reactivity

Emily E Perszyk1,2, Jessica Trinh1,2, Xue S Davis1,2, Zach Hutelin1,2, Maria G Veldhuizen3, Jelena Djordjevic4, Marilyn Jones-Gotman4, Hedy Kober2, Dana M Small1,2

1The Modern Diet and Physiology Research Center, New Haven, CT, United States, 2Yale University, New Haven, CT, United States, 3Mersin University, Mersin, Turkey, 4McGill University, Montreal, QC, Canada

Food cues influence ingestive behavior; however, the mechanisms by which this occurs remain unclear. Here we investigated a role for mental imagery in 45 healthy individuals (22 female; BMI M=26.1, SD=6.8) using behavioral, perceptual, and neuroimaging methods. Specifically, we tested the hypothesis that individuals with better ability to imagine the aromas and flavors of foods experience stronger food cravings and cue reactivity. Odor imagery ability was defined using a validated perceptual test (Djordjevic et al. 2004) that assesses the extent to which imagined odors interfere with the detection of real odors. A stronger odor interference effect reflects more vivid mental imagery. Neural responses to real and imagined odors were also captured with fMRI, and a machine learning classifier was trained and tested for its accuracy to decode the real and imagined odor qualities using voxel patterns in the piriform primary olfactory cortex. Finally, craving intensity evoked during presentation of food images and grams of cookies consumed in a bogus taste test (Robinson et al. 2017) provided measures of food craving and cue reactivity, respectively. A positive interaction between the interference effect and food liking on craving was observed, whereby individuals with better odor imagery ability experienced more intense cravings for foods rated high in liking. Both the interference effect and food intake were positively associated with each other and with piriform decoding accuracy for imagined, but not real, odors. This work establishes a role for odor imagery ability in food cue reactivity and points to coding in the piriform primary olfactory cortex as the neural substrate.

Q&A
Human Abilities Underestimated? Exposing Sensitivities To Food Composition In Everyday Dietary Decisions

Jeffrey M. Brunstrom
Nutrition and Behaviour Unit, School of Psychological Science, University of Bristol, Bristol, United Kingdom

The social and cultural significance of food is woven into every aspect of dietary behaviour, and it contributes to our complex interaction with food. To find order within this complexity, scientists often look for dietary ‘universals’ - phenomena or basic principles that guide our food choice and meal size, irrespective of wider context. One such idea is that taste characteristics provide a signal for dietary composition (e.g., sweet taste signals carbohydrate). Others have suggested that behaviour is guided by learning and is based on associations that form between the flavour of a food and its post-ingestive effects. Despite a large body of research, evidence supporting both processes is equivocal, leading some to conclude that humans are largely indifferent to food composition. Here, I argue that human abilities have been underestimated, and that they can be exposed by embracing alternative methods, including cross-cultural comparisons, large nutrition surveys, and the use of virtual portion-selection tools. In particular, my group has focused on assessments of food choice and expected satiety, and how comparisons across everyday foods can reveal non-linear relationships with food energy density, and even the potential for sensitivity to micronutrient composition. Finally, I will suggest that these abilities might reflect a form of social learning, in which flavour-nutrient associations are formed and then communicated and amplified across individuals. Thus, rather than disregarding sociocultural influences as extraneous, we might reimagine their role as central to a process that imbues a ‘collective dietary wisdom.’ In turn, this raises questions about how rapid dietary, technological, and cultural change might promote or disrupt this fundamental process.

How Does Leptin Talk To The Dopamine System?

Roger Adan1,2
1Dept Translational Neuroscience, UMCU, Utrecht University, Utrecht, Netherlands, 2Sahlgrenska Academy, Univ of Gothenburg, Gothenburg, Sweden

Introduction/Aim: Leptin suppresses the motivation to obtain food reward. VTA neurons projecting to the accumbens are involved in food reward processing. How leptin inhibits the dopamine reward circuitry is unresolved. More insight in this neurocircuitry is important to develop novel treatment strategies for eating disorders and obesity. Methods: we used patch-clamp electrophysiology, fiber photometry, opto- and chemogenetics and immunohistochemistry to unravel how leptin impacts on dopamine neural circuitry function. We used leptin receptor cre mice, TdTomato reporter mice, Ptx3-cre mice and Ptx3-GFP mice and a variety of viral vectors to map and manipulate the VTA neuronal circuit. Results: Given the presence of leptin receptors (LepR) on ventral tegmental area (VTA) DA neurons, it is generally assumed that dopamine direct inhibits DA neurons, but we find that leptin also depolarizes LepR-expressing gamma-aminobutyric acid (GABA) neurons in the VTA that inhibit DA neurons. In addition leptin hyperpolarizes LepR-expressing neurons in the lateral hypothalamus (LH) that synapse onto VTA GABA neurons. Activation of VTA LepR neurons reduces the motivation to lever press for a sucrose reward in food-restricted mice. Activation of LH LepR neurons conversely increases this motivational response in sated mice, likely by decreasing VTA GABAergic input onto VTA dopamine neurons which then are disinhibited. Conclusion: leptin targets multiple inputs to the VTA DA system to reduce food reward seeking, with the indirect inputs playing a major role in controlling its activity. Targeting the cell types via which leptin acts, provides a strategy to suppress the temptation to give in to cues that drive overconsumption.

Amygdalar-Hindbrain Circuit Contributions To Homeostatic And Hedonic Feeding

J. Andrew Hardaway
Department of Psychiatry, University of Alabama at Birmingham, Birmingham, AL, United States

Obesity and diabetes are one of the leading causes of disease and death in developed nations, with more than a third of US adults classified as obese – having a body-mass index over 30. In this oral presentation, I will present published and unpublished data using laboratory transgenic mice in combination with neural circuit techniques that demonstrate a role for the amygdala in modulating hedonic, and not homeostatic food consumption. My presentation will feature the use of largely optical strategies to observe and manipulate the function of amygdala-hindbrain circuits in freely behaving animals. At a cellular and molecular level, I will also discuss a role for glucagon-like peptide 1 and insulin receptors in modulating the activity of the amygdala and the impact of these receptors on feeding and motivated behavior using feeding experimental devices.
Researchers have long recognised a key distinction between ingestion driven by energy deficits (“homeostatic hunger”) and eating stimulated by the presence of food and food cues. This talk focusses on two aspects of cue-driven eating. The first relates to sensory cues experienced during ingestion, with evidence that it is their hedonic tone that drives increased intake. The evidence for these palatability effects is strong, but the critical question of what makes a food palatable remains less well understood. The key idea that this liking is a learned response is reviewed, and then extended to incorporate the concept of hedonic contrast, the idea that how palatable one food is perceived is partly driven by the presence of other less-liked foods. This suggests that palatability requires integration of multiple sensed components, and critically relies on memory processes. The second type of cues are those perceived before ingestion. A great deal of this research has focussed on responses to food images. These responses again critically involve memory, and studies rely on the likelihood on sufficient overlap in individual experience to allow us to interpret the causal nature of responses to these cues. An alternative is to use entirely novel cues paired with specific aspects of food reward: recent studies in our lab using this approach demonstrate that even brief associations between cues and rewards can impact ingestion. These different lines of evidence are then integrated into a conceptual framework which places food-based memories at the centre of our understanding of human appetite, supported by studies that show that disruption to those memory systems greatly alters human eating.

Gastrointestinal Regulation Of Energy Intake And Blood Glucose Control

Christine Feinle-Bisset
Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

The upper GI tract plays a key role in the regulation of energy intake and blood glucose in response to eating, sensing the ingested meal content and signalling this information to the brain and to peripheral organs. The presence of nutrients and other dietary components in the intestinal lumen is sensed by specialised receptors, located on enteroendocrine cells, triggering the release of gut hormones and initiating feedback loops that lead to adjustments in the rate of gastric emptying. These effects can be modulated by intraluminal factors, including nutrient digestion and the length and region exposed to nutrients. Thus, nutrient digestion products potently stimulate gut hormones and slow gastric emptying, associated with energy intake suppression and post-meal glucose lowering. While both fat and protein exert these effects, relatively large loads are required. In contrast, their digestion products, fatty acids and amino acids, when administered in a concentrated form, have marked effects to reduce energy intake and blood glucose, in very low doses, thus, not contributing substantially to overall caloric intake. There has recently also been an interest in bitter substances, which also have the capacity to stimulate gut hormones and slow gastric emptying, associated with intake suppression and glucose lowering. Moreover, these effects can be enhanced when nutrients and/or compounds are combined, even in lower doses that are individually not effective. Finally, there is evidence that at least some of the effects observed in healthy people are maintained in people with obesity and type 2 diabetes, suggesting that activation of gut-based mechanisms may represent an effective strategy for the management and treatment, and possibly prevention, of these disorders.

Q&A
Causal Associations Between BMI and Neurobehaviour in Adolescents and Older Adulthood.

Kadri Arumae, Leonard Kulisch, Daniel Briley, Rene Mottus, Uku Vainik

1University of Tartu, Tartu, Estonia, 2University of Leipzig, Leipzig, Germany, 3University of Illinois, Urbana-Champaign, IL, United States, 4University of Edinburgh, Edinburgh, Scotland, 5McGill University, Montreal, QC, Canada

Obesity has robust associations with behaviour, but its causality is unknown. Recent evidence suggests that obesity may influence personality traits among young adults (Arumäe et al., 2021, IJO). Here, we sought to analyse BMI-neurobehaviour association in both younger and older cohorts and across a wider range of measures.

In the younger sample, we focused on the Adolescent Brain Cognitive Development study cohort comprising 11,875 children aged 9-10. We replicated many associations between BMI and neurobehaviour in both younger and older cohorts and across a wider range of measures.

Recent evidence indicates that "ultra-processed" foods constitute ~65% of total energy intake among children in the U.S. Our study aimed to investigate how preschool children adjust the amounts they serve and eat according to snack weight, volume, or energy content. In a crossover design, 55 children aged 4-6 y (44% girls; 20% overweight) ate an afternoon snack on 2 days in their childcare centers. Before each snack time, children served themselves a consistent volume of the 4 snacks (mean±SEM 137±8 ml; p=0.14), but served over twice the weight of low-ED foods (84±2 g; p<0.0001). At snack time, children ate a greater proportion of self-served strawberries (79±5% vs 67±5%; p=0.016), but due to the ED difference they consumed 57±5 kcal more from pretzels than strawberries (p<0.0001). Ratings showed that greater liking increased both the volume children served (p=0.001) and the weight they consumed (p<0.0001). Children served similar volumes of all 4 snacks (mean±SEM 137±8 ml; p=0.14), but served over twice the weight of low-ED foods (84±2 g; p<0.0001). At snack time, children ate a greater proportion of self-served strawberries (79±5%) than pretzels (67±5%; p=0.016), but due to the ED difference they consumed 57±5 kcal more from pretzels than strawberries (p<0.0001). Ratings showed that greater liking increased both the volume children served (p=0.001) and the proportion they ate (p=0.037). In the fullness task, children were more likely to indicate a completely full stomach for the 2 high-ED snacks than the 2 low-ED snacks (p=0.012). Children served themselves a consistent volume of the 4 snacks, suggesting that these portions were determined more by visual cues than by weight or energy content. There was some adjustment of intake during snack time, in that children ate a greater proportion of self-served strawberries (79±5%) than pretzels (67±5%; p=0.016), but due to the ED difference they consumed 57±5 kcal more from pretzels than strawberries (p<0.0001). Ratings showed that greater liking increased both the volume children served (p=0.001) and the proportion they ate (p=0.037). In the fullness task, children were more likely to indicate a completely full stomach for the 2 high-ED snacks than the 2 low-ED snacks (p=0.012). Children served themselves a consistent volume of the 4 snacks, suggesting that these portions were determined more by visual cues than by weight or energy content. There was some adjustment of intake during snack time, in that children ate a greater proportion of the low-ED food that they rated as less pleasant (p=0.012). There was some adjustment of intake during snack time, in that children ate a greater proportion of the low-ED food that they rated as less pleasant (p=0.012).

Early Life Consumption Of A &quot;Processed&quot; Diet Rich In Advanced Glycation End Products Impairs Hippocampal Function And Alters The Gut Microbiome During Adulthood In Rats

Hanim E. Diktas, Liane S. Roe, Kathleen L. Keller, Barbara J. Rolls

1Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, United States, 2Department of Food Science, The Pennsylvania State University, University Park, PA, United States

We investigated whether when preschool children are offered snacks differing in energy density (ED), they adjust the portions they serve and eat according to snack weight, volume, or energy content. In a crossover design, 55 children aged 4-6 y (44% girls; 20% overweight) ate an afternoon snack on 2 days in their childcare centers. Before each snack time, children served the amount they would like to eat of 4 snacks differing in ED (low: strawberries, carrots; high: pretzels, crackers) presented in equal volumes (300 ml). Across the 2 snack sessions, children were given their self-served amount of either strawberries (0.32 kcal/g) or pretzels (3.93 kcal/g) and intake was measured. Later, children tasted all 4 snacks and rated liking, then viewed 1 cup of each snack and rated how much it would fill their stomach. Children served similar volumes of all 4 snacks (mean±SEM 137±8 ml; p=0.14), but served over twice the weight of low-ED foods (84±2 g; p<0.0001). At snack time, children ate a greater proportion of self-served strawberries (79±5%) than pretzels (67±5%; p=0.016), but due to the ED difference they consumed 57±5 kcal more from pretzels than strawberries (p<0.0001). Ratings showed that greater liking increased both the volume children served (p=0.001) and the proportion they ate (p=0.037). In the fullness task, children were more likely to indicate a completely full stomach for the 2 high-ED snacks than the 2 low-ED snacks (p=0.012). Children served themselves a consistent volume of the 4 snacks, suggesting that these portions were determined more by visual cues than by weight or energy content. There was some adjustment of intake during snack time, in that children ate a greater proportion of the low-ED food that they rated as less pleasant (p=0.012). There was some adjustment of intake during snack time, in that children ate a greater proportion of the low-ED food that they rated as less pleasant (p=0.012).
Change And Stability In Free Sugar Intake From Toddlerhood To Middle Childhood In British Children: Findings From The Gemini Cohort

Lisa Heggie1, Rana Conway1, Alison Fildes2, Andrea Smith1, Jason C. G. Halford2, Clare Llewellyn1
1Department of Behavioural Science and Health, University College London, London, United Kingdom, 2School of Psychology, University of Leeds, Leeds, United Kingdom

Introduction: High free sugar (FS) intake may increase excess weight gain, however data from childhood populations are limited. This research investigates change and stability in FS intake between toddlerhood and childhood using the UK’s largest contemporary dietary dataset of toddlers. Methods: Participants were from Gemini, a population-based cohort of 2402 British families with twins born in 2007. Dietary data were collected using parent-reported, three-day diet diaries when children were 21-months (21 m) with repeat measures in a subsample of children at seven years of age (7 y); the analysis sample included n=426 children with complete data at both ages. Mean intakes of energy and FS (g, %E) were derived at 21 m and 7 y, along with food types contributing FS. Change (mean difference) and stability (partial correlation) in FS %E were examined using Complex Samples General Linear Models, adjusting for clustering of twins in families and age difference between dietary assessments. Results: Mean daily FS intake was 24.4 g (SD=13.3) and 8.8%E (SD=4.3) at 21 m, and 57.6 g (SD=23.0) and 14.2%E (SD=4.8) at 7 y. Food types contributing the highest proportion of FS at 21 m were: pure fruit juices, biscuits, and yoghurts; at 7 y, these were pure fruit juices, cakes and pastries, and chocolate confectionery. Mean FS %E increased over time by 5.4%, with a large effect size (d=1.237, p<0.001), and showed moderate-to-strong longitudinal stability (r=0.5, p<0.001). Conclusion: FS intake is likely to increase between toddlerhood and middle-childhood, and those consuming higher amounts of FS in early life are likely to continue to consume higher amounts in childhood. Research investigating the risk factors for FS intake in childhood is essential for public health policy development.

The Effects Of Added Simple Sugar In Maternal Pre-Pregnancy Diet On Gestational Glucoregulation In Dams And The Progenial Body Weight And Taste-Guided Behavior

A-Hyun Jung1, Chaithra Subbarao2, Krishna Parekh3, Deniz Oncel4, Lindsey A. Schierf1,3
1Neuroscience Graduate Program, University of Southern California, Los Angeles, CA, United States, 2Health Promotion and Disease Prevention Program, University of Southern California, Los Angeles, CA, United States, 3Department of Biological Sciences, University of Southern California, Los Angeles, CA, United States, 4Diversity, Inclusion, and Access Summer Research Program, University of Southern California, Los Angeles, CA, United States

High fat, high sugar diets during gestation and lactation render the dam and her progeny more susceptible to metabolic health issues. Since some people opt to discontinue unhealthy diets during pregnancy, we assessed if a history of added sugar or fat prior to pregnancy disturbs glucoregulation in mouse dams, and postnatal growth and taste-guided motivation for sweeteners in their offspring. Partially food restricted female C57BL6/J mice had daily 20-minute access to water (Con), glucose and fructose (Sug) or corn oil (Fat) for 24 days and then ad libitum chow for a week before mating. Fasting blood glucose level (FBGL) and intraperitoneal glucose tolerance (IPGT) were measured before and during pregnancy in separate cohorts. While pregnancy increased FBGL in all groups, Sug dams had lower FBGL compared to Con dams in gestational week 2. Con and Fat dams became less glucose tolerant during pregnancy. Sug dams remained glucose tolerant and failed to show this normal pregnancy-induced shift. Male offspring from all diet groups were of comparable weights at birth and through the post-weaning period. Sug female offspring had higher birth weights than Fat female offspring and stayed heavier than Con and Fat female offspring in the early post-weaning phase. Pre-pregnancy sugar intake (%) was inversely correlated with maternal FBGL and postnatal weight gain in female offspring. Sug offspring licked more avidly for glucose (vs fructose) than their Con and Fat counterparts in brief access taste tests, though the responses for each sugar alone or non-nutritive sweeteners were unaffected. Collectively, these data suggest that added sugar before pregnancy has pervasive consequences on gestational glucoregulation, progenial growth (sex-specific) and motivated behavior towards sugar.

Children With Lower Executive Functioning Have A Greater Response To The Portion Size Effect

Kathleen L. Keller1, Alaina L. Pearce1, Bari Fuchs1, Barbara J. Rolls2, Steve J. Wilson1, Emma Rose1, Charles F. Geier1, Hugh Garavan2
1The Pennsylvania State University, University Park, PA, United States, 2University of Vermont, Burlington, VT, United States

Deficits in executive functioning (EF), a set of higher order processes related to self-regulation, are associated with the development of pediatric obesity. Prior studies from our group showed that lower food-cue related activation in brain regions implicated in self-regulation was related to larger portion size effects (PSE). In this study, we tested the hypothesis that lower EF in children is positively related to the PSE. Healthy weight children aged 7-8 y who varied by maternal obesity status (n=72) participated in a longitudinal study. At baseline, the parent in charge of feeding decisions completed the Behavior Rating Inventory of Executive Function (BRIEF) to assess child EF, including Cognitive and Behavioral scales. At 4 baseline sessions, children consumed meals in which the portion sizes of all items (pasta, chicken nuggets, broccoli, and grapes) were varied by visit (total meal weight of 769, 1011, 1254, or 1499g). Child intake increased with increasing portions in a curvilinear trajectory. EF moderated the PSE such that poorer Cognitive (p<0.003) and Behavioral (p<0.001) Regulation were associated with steeper increases in intake with increasing portions. Children in the highest quartiles (lowest performance) for both Cognitive and Behavioral regulation increased intake such that by the third portion, they were consuming over 120g (256 kcal) more than children in the lower three quartiles. Thus, in a sample of healthy weight children who varied in risk of obesity, lower parentally reported EF was associated with a larger PSE, and these results were independent of child and parent weight status. Therefore, EF may offer a target that could be strengthened to help children moderate excess intake in an obesogenic environment.

Perinatal Microbiota Composition Modulates Gut-Brain Axis Development

Jillian M Allen1, Rebecca A Kirkland1, Jessica B Lam1, Kellie L Tamashiro2, Claire B de La Serre1
1University of Georgia, Athens, GA, United States, 2Johns Hopkins University, Baltimore, MD, United States
Maternal obesity during the perinatal period significantly increases risk for metabolic disorders in offspring. In rats, pups born to high fat diet (HF)-fed dams have increased susceptibility to diet-induced obesity. The vagus nerve conveys post-ingestive information from the gut to the nucleus of solitary tract (NTS) to regulate meal size, and impairment in vagal signaling leads to weight gain. HF pups display alteration in meal patterns, however, the mechanisms by which the perinatal environment affects gut-brain axis development is not well known. We have previously shown in adults that microbiota composition modulates vagal structure and function. We therefore hypothesize that maternal microbiota transferred to offspring could affect gut-brain axis development. To test this, pregnant germ-free (GF) Fisher rats were kept in GF isolators and inoculated on post natal day (P) 1 with chow (ConvLF) or HF (ConvHF) fecal pellets (15mg, every 48 hours until weaning, n=4). We found that offspring microbiota profiles (16S Illumina) at weaning and in adulthood share similarities with their respective mothers and donors. We used isolectin B4 to visualize vagal terminals in the NTS, male and female ConvHF pups showed a 30% reduction in innervation at weaning compared to ConvLF pups (p<0.05). Though these alterations were not present in adulthood, male and female adult ConvHF rats showed a significant reduction in exogenous cholecystokinin-induced satiety (1.5ug/ml/kg) when compared to ConvLF rats, and a significant increase in average meal size (p<0.05). From these data, we concluded that perinatal microbiota modulates gut-brain axis development independently of diet, and that a HF-type microbiota leads to early vagal structure alterations and sustained vagal function defects.

Best Student Presentation Award Finalist

5:24

Early Life Low-Calorie Sweetener Consumption Disrupts Glucose Regulation, Sugar-Motivated Behavior, And Memory Function In Rats

Linda Tsan¹, Sandrine Chometton², Yanning Zuo³, Shan Sun⁴, Anna M. R. Hayes², Lana Bridi², Rae Lan², Anthony A. Fodor⁴, Emily E. Noble⁵, Xia Yang³, Scott E. Kanoski², Lindsey A. Schier²

¹Neuroscience Graduate Program, University of Southern California, Los Angeles, CA, United States, ²Department of Biological Sciences, Human and Evolutionary Biology Section, University of Southern California, Los Angeles, CA, United States, ³Department of Integrative Biology and Physiology, University of California at Los Angeles, Los Angeles, CA, United States, ⁴Department of Bioinformatics and Genomics at the University of North Carolina at Charlotte, Charlotte, NC, United States, ⁵Department of Nutritional Sciences, University of Georgia, Athens, GA, United States

Low-calorie sweetener (LCS) consumption in children has increased dramatically due to widespread presence in the food environment and efforts to mitigate obesity through sugar replacement. However, mechanistic studies on the long-term impact of early-life LCS consumption on cognitive, sensory-reward, and physiological function are lacking. Here, we developed a rodent model to evaluate the effects of daily LCS consumption (acesulfame potassium, saccharin, or stevia within the recommended acceptable daily intake levels) during adolescence on adult metabolic, behavioral, gut microbiome, and neural outcomes. Results reveal that habitual early-life LCS consumption disrupts post-oral glucose tolerance and impairs hippocampal-dependent memory in the absence of weight gain. Furthermore, adolescent LCS consumption yielded long-term reductions in lingual sweet taste receptor expression and alterations in sugar-motivated appetitive and consummatory responses. While early life LCS consumption did not produce robust changes in the gut microbiome, brain region-specific RNA sequencing analyses reveal LCS-induced changes in collagen- and synaptic signaling-related gene pathways in the hippocampus and nucleus accumbens, respectively, in a sex-dependent manner. Collectively, these results reveal that habitual early-life LCS consumption yields long-lasting impairments in glucose regulation, sugar-motivated behavior, and hippocampal-dependent memory in rats, which may be based in part on changes in sweet taste receptor expression and neuronal gene pathways.

5:36

Q&A
### Symposium 6: Too Much Too Soon? Influence of Early Life Feeding

**Chair(s):** Scott Kanoski

#### P1
**8:30**

<table>
<thead>
<tr>
<th>Effects Of Altered Maternal Metabolic Environment And Resulting Changes In Offspring From The Level Of The Neuron To The Whole Animal</th>
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<td>Rachel N Lippert&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
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<sup>1</sup>German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany, <sup>2</sup>NeuroCure Cluster of Excellence, Universitaetsmedizin Berlin-Charite, Berlin, Germany, <sup>3</sup>German Center for Diabetes Research (DZD), Neurherberg, Germany

The early developmental metabolic environment can have significant impacts on fetal development, specifically within neural circuits of the brain. In humans, a majority of women in Western cultures now show excessive gestational weight gain which is specifically associated with an increase in fat mass predominantly during the third trimester of pregnancy. Through the use of a specific overnutrition model in mice, which closely models gestational weight gain in humans, we can begin to decipher the structural and physiological changes in the brain as a result of acute exposure to overnutrition during this critical period of brain development. Through these studies we have shown specific effects at the level of the hypothalamus and the dopaminergic neurocircuitry. Recent studies in our group using a model of gestational diabetes uncover interesting metabolic links dependent on pre-pregnancy of during pregnancy metabolic conditions with differential effects in offspring. Assessment of the enduring RNA signature, imaging of key neuropeptide markers, electrophysiological parameters and resulting changes to locomotor and reward behavior as well as metabolic markers support the findings from the level of the neuron to the whole animal. In conclusion, altered maternal metabolic environment, both overnutrition and anti-diabetic treatments, result in dynamic changes to neuronal circuits and overarching behavior. This underscores the necessity to understand these changes and their potential changes to the treatment of physiological and neurological disease in the adult offspring based on the early developmental environment.

#### P2
**8:55**

<table>
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<tr>
<th>Sensory Cues In Early Life Program Long-Term Metabolism And A Central Response To Food</th>
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<td>Sophie M. Steculorum&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
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<sup>1</sup>Max Planck Institute for Metabolism Research, Max Planck Research Group Neurocircuit Wiring and Function, Cologne, Germany, <sup>2</sup>Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany, <sup>3</sup>German Center of Diabetes Research (DZD), Cologne, Germany

Maternal obesity predisposes offspring to metabolic diseases. The adverse maternal health effects secondary to high-fat-diet (HFD) consumption, such as adiposity and insulin resistance, are considered pivotal contributors to such developmental programming. We demonstrate that the non-nutritional sensory component of HFD, beyond its hypercaloric, obesogenic component, is sufficient to alter life-long metabolic health in mice. To dissociate the nutritive caloric components from non-nutritive sensory components of HFD, we designed a bacon-flavored diet isonutritional to low-fat normal chow diet but enriched with fat-related odors similar to the commonly used pork-lard-based HFD. Adult offspring exposed to fat-related odors during development display increased weight gain, adiposity and insulin resistance in response to HFD-feeding independently of maternal adiposity, weight gain, insulin resistance, or changes in the milk and blood lipids.

Mechanistically, developmental exposure to fat-related odors primes the mesolimbic dopaminergic circuits and the AgRP hunger neurons towards responses that phenocopy those of obese mice. Using in vivo fiber photometry recordings, we show that developmental exposure to fat-related odors primes a desensitization of AgRP neurons to ghrelin and dietary-fat selectively that precede HFD feeding and its metabolic consequences. Collectively, we report a novel pivotal mechanism by which maternal diet programs obesity by revealing that fat-related sensory cues during development act as instructive signals to prime central responses to food cues, whole-body metabolism, and obesity.

#### P3
**9:20**

<table>
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<tr>
<th>The Chicken And The Egg: Investigating The Dynamic Interplay Between Maternal Eating Behaviors, Infant Feeding Behaviors, And Infant Appetitive Traits</th>
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<td>Leah M. Lipsky&lt;sup&gt;1&lt;/sup&gt;, Kyle S. Burger&lt;sup&gt;2&lt;/sup&gt;, Jenna R. Cummings&lt;sup&gt;1&lt;/sup&gt;, Tonja R. Nansel&lt;sup&gt;1&lt;/sup&gt;</td>
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<sup>1</sup>Social and Behavioral Sciences Branch, Division of Population Health Research, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, United States, <sup>2</sup>Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Infant appetitive traits may influence child obesity risk. While infant appetitive traits are partly heritable, little is known about early life environmental factors. This study describes the dynamic relations among maternal eating behaviors, infant feeding behaviors, and infant appetitive traits in 4 years of follow-up of a pregnancy cohort (n=458 women enrolled; mean age=30.5 years; 52.2% with BMI≥25). Multiple maternal eating behaviors, infant feeding behaviors, and infant appetitive traits were assessed. Relations were examined using regression analysis and structural equation modeling. Findings did not support a strong phenotypic heritability of obesogenic appetitive traits: other than a positive relation of maternal preoccupation with food with infant satiety responsiveness, maternal eating behaviors were not directly related to infant appetitive traits. However, maternal eating competence, restrained eating, and external eating were related to differences in infant feeding practices including exclusive breastfeeding duration, introduction to solids, infant food intake frequency, and feeding to soothe, which in turn were related to infant and early childhood appetitive traits. Maternal ultra-processed food intake during pregnancy was related to infant appetitive traits independent of feeding practices. Additionally, bidirectional
relations were observed of infant appetitive traits with maternal feeding to soothe, exclusive breastfeeding duration, and
introduction to solids. Taken together, relations of infant appetitive traits with maternal feeding behaviors are stronger and
more consistent than relations with maternal eating behaviors, implicating the relative importance of environmental
influences on infant eating behaviors.

Behavioural Susceptibility To Rapid Infant Weight Gain: Genetic Influence On Appetite And Over-Feeding

Clare Llewellyn
University College London, London, United Kingdom

Rapid infant weight gain (RWG) during the first 2 years of life is a well-established risk factor for later obesity, yet its
causes are poorly understood. Behavioural Susceptibility Theory (BST) hypothesises that infants who inherit a set of genes
that confer greater responsiveness to food cues and lower sensitivity to satiety, are more susceptible to overfeeding and
RWG. In 2007, Gemini was established to test BST; it is the largest population-based birth cohort of twins (n=4808) set up
to study genetic and environmental influence on early growth, with a focus on appetite. Appetite was measured at 3 and 16
mths using the Baby/Child Eating Behavior Questionnaires (widely used, validated, parent-report instruments). Food intake
at 21 mths was measured using 3-day diet diaries to derive patterns of overconsumption, and is the largest contemporary
dietary dataset for British toddlers. Gemini has demonstrated that RWG has a strong genetic basis, and variation in
infant/toddler appetite: (i) is highly heritable; (ii) is associated with patterns of overconsumption; (iii) predicts prospective
infant weight gain; and (iv) shares common genetic factors with weight. An independent cohort of older twin children also
reported high heritability estimates for appetite, and other cohorts of children/adults have shown that BMI-related genetic
variants identified through GWAS are associated with various aspects of appetite. Together these studies provide strong
support for BST. Parents are often blamed when their children develop health problems that are poorly understood, such as
RWG. However, infants are not born on a ‘level playing field’; some have an avid appetite and are highly demanding with
regard to milk feeds. These infants present considerable feeding challenges for parents.
Investigating Metabolic And Hormonal Influences On Post-Prandial Increase Of Plasma Satiety Liver/Intestinal Hormone LEAP2 In Adults Without Obesity

Raghav Bhargava¹, Marcela Rodriguez-Flores¹, Mimoza Emini¹, Sandra Luur¹, Christina G. Prechtl², Anthony P. Goldstone¹

¹PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, United Kingdom, ²Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom

Background: LEAP2, a novel satiety liver/intestinal hormone, is an inverse agonist at the acyl ghrelin (AG) receptor (GHSR). Plasma AG and LEAP2 are reciprocally regulated in mice and humans with AG decreasing and LEAP2 increasing after food intake (Mani JCI 2019). The influences on post-prandial increases in LEAP2 are incompletely understood in humans. Methods: Secondary analysis of study comparing endogenous and exogenous hyperghrelinaemia on eating behaviour (Goldstone AJCN 2014). Assay of serial fasting +/- post-prandial plasma/serum AG, LEAP2, glucose, insulin, in n=22 adults (19-44y, 77% male, BMI<30 kg/m²) at fasted (no meal) and fed (730 kcal meal at 0min) visits. At another fed visit, given subcutaneous AG injection (3.6nmol/kg) 55min after meal. Post-prandial changes in plasma LEAP2 and AG (incremental AUC 0-150min for fed-fasted visits) were correlated with BMI, and fasting/post-prandial changes in glucose, insulin, insulin resistance (HOMA-IR). Results: Plasma LEAP2 increased by 18.1% at 70min and 43.5% at 150min after food intake (P=0.014-0.006 fed-saline vs. fasted-saline visit), but was not decreased by exogenous AG administration (P=0.99-0.97 fed-ghrelin vs. fed-saline visit). Post-prandial increase in LEAP2 was negatively correlated with BMI (r=-0.54, P=0.009), but not fasting glucose, insulin or HOMA-IR (r=0.18 to -0.05, P=0.42-0.81), nor correlated with post-prandial increases in glucose or insulin (r=-0.03 to 0.03, P=0.89-0.91). Conclusion: Higher BMI in absence of obesity was associated with lower post-prandial LEAP2 increase (opposite finding to that seen in obesity), unexplained by metabolic status. No evidence found that post-prandial increases in plasma LEAP2 were driven by post-prandial increases in glucose or insulin, nor decrease in plasma AG.

The Effects Of Semaglutide Treatment On Energy Intake, Sucrose Preference, And Body Weight Loss In Rats

Carolina R. Cawthon¹, Ginger D. Blonde¹, Carel W. le Roux², Alan C. Spector¹

¹Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, FL, United States, ²Diabetes Complications Research Centre, Conway Institute, School of Medicine, University College Dublin, Dublin, Ireland

Semaglutide (SEMA), a glucagon-like peptide-1 analog, was approved to treat obesity in 2021. Preclinical research investigating SEMA changes in ingestive behavior is lacking. To begin filling this gap, we monitored body weight (BW) and food and water intake (FI & WD) in chow-maintained rats during baseline (BASE, 2 d), vehicle (VEH, 4/sex) injections or SEMA dose escalation (ESC, 4/sex, 10 d, 0.7 - 70 Âµg/kg, s.c.), designed to emulate what happens in humans, and dose maintenance (MAINT, 10 d, 70 Âµg/kg). SEMA or VEH dosing continued for 14 d after MAINT while rats underwent 2-d 2-bottle preference tests (2BT) for sucrose (0 – 1.0 M). Rats in this study had prior palatable diet exposure (20 d, ending ~2 mo before BASE). During ESC, BW steadily decreased across days in SEMA rats. FI and WD dropped on ESC day 1 and stayed below BASE in the SEMA, but not VEH, rats (p<0.02). During MAINT, FI and WD rose almost to BASE levels in the SEMA rats (p=0.02, p=0.45), but the ~12% BW-loss persisted (p<0.01). By the end of 2BT, BW had partially rebounded but remained 7.5% below BASE and significantly different from VEH by ~18% (p<0.01). Unexpectedly, at lower concentrations, the SEMA rats consumed more sucrose than VEH rats, peaking at 2-3X greater intake at 0.1 M (p<0.01). SEMA and VEH rats uniformly and highly preferred all sucrose concentrations, with intake nearly equal at higher concentrations. All rats decreased chow intake and increased the %kcal taken from sugar as sucrose concentration was raised, but %kcal from sucrose of the SEMA rats exceeded VEH rats at all but the 1.0 M concentration. It appears time attenuates the effects of SEMA on energy intake, and the addition of palatable sugar solutions fosters further increases in kcal intake, challenging weight loss maintenance.

Does Liraglutide Lead To Weight Loss By Altering Food-Related Sensory Pleasure?: A Â Randomized Controlled TrialÂ In Patients With Obesity On Glp-1 Receptor Agonist

Geraldine Coppin¹,², David Munoz Tord¹,², Eva Pool¹,², Loic Locatelli³, Amal Achaibou¹,³, Asli Erdemli¹,², Laura Leon Perez¹,², Lavinia Wuenisch¹,², Donato Cereghetti³, Alain Golay³, David Sander¹,², Zoltan Pataky³

¹Swiss Center for Affective Sciences, University of Geneva, Geneva, Switzerland, ²Department of Psychology, University of Geneva, Geneva, Switzerland, ³Department of Psychology, UniDistance Suisse, Brig, Switzerland, ⁴Department of Medicine, University of Geneva, Geneva, Switzerland, ⁵Firmenich, SA, Geneva, Switzerland

GLP-1 receptor agonist (liraglutide) has been demonstrated to successfully promote weight loss in patients suffering from obesity (OB). Yet, it is unclear whether the observed weight loss is driven by an alteration of food reward processing. Here we investigated the effects of liraglutide on cerebral correlates of food-related sensory pleasure in OB. We conducted a randomized, single-centre, double-blind, placebo-controlled, parallel group, prospective clinical trial. 73 patients with OB and without diabetes were randomly assigned to receive liraglutide 3.0 mg (37.40±11.18 years old, BMI = 35.89±3.01) or placebo (40.04±14.10 years old, BMI = 34.88±5.87) subcutaneously once daily, for 16 weeks. We investigated sensory pleasure during food consumption (liking). Participants reported their trial-by-trial hedonic experience while consuming a high-calorie food (milkshake) and a tasteless solution. The solutions were administered inside the scanner with a Magnetic Resonance Imaging-compatible gustometer to assess neural responses during consumption. The same procedure was repeated for pre- and post-intervention sessions. The liraglutide group lost more weight (8.50 kg Â±0.70) compared to the placebo group (2.12 kg Â±0.63). The sensory pleasure during food reward consumption was associated with the activation of the ventromedial prefrontal cortex and the amygdala. We did not find any statistically significant difference in the MRI data.
Amylin Modulates A Vta To Mpfc Circuit To Suppress Feeding And Impulsive Food-Directed Behavior
Caroline E Geisler1, Wolf Trumbauer1, Lea Decarie-Spain2, Jane Gaisinsky1, Mitchell F Roitman3, Heath D Schmidt1,4, Scott Kanoski2, Matthew R Hayes1
1Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States,
2Department of Biological Sciences, Human and Evolutionary Biology Section, University of Southern California, Los Angeles, CA, United States, 3Department of Psychology, University of Illinois at Chicago, Chicago, IL, United States,
4Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA, United States

A better understanding of the neural mechanisms regulating impared satiety to palatable foods is essential to treat hyperphagia linked with obesity. The β-cell hormone amylin induces postprandial satiation through central actions at multiple nuclei including the ventral tegmental area (VTA). The medial prefrontal cortex (mPFC) receives input from the VTA about food reward to influence behaviors such as impulsivity. We hypothesized that modulation of VTA-to-PFC neurons underlies amylin-mediated decreases in motivated feeding behaviors. To first establish that VTA amylin receptor (CTR) activation can modulate mPFC activity, we showed that intra-VTA amylin decreased intralipid consumption and mPFC fCf in rats. As palatable foods activate VTA dopamine and mPFC neurons, we hypothesized that increased VTA CTR activation decreases dopamine release in the PFC. Pre-treatment with dopamine 1 and 2 receptor agonists in the mPFC blocked the hypophagic effect of intra-VTA amylin on high fat diet, but not chow. To implicate VTA amylin signaling as a regulator of impulsive food-directed behaviors, we performed a differential reinforcement of low rate of responding (DRL) task. Rats were trained to withhold a lever-press for sucrose pellet to assess impulsivity. Impressively, intra-VTA amylin nearly eliminated impulsive action in a food deprived state. Surprisingly, injection of the retrograde tracer, fluorogold, into the mPFC showed no expression with CTR on VTA-to-PFC projecting neurons, however CTR expression is observed on adjacent VTA GABA neurons. These result support that VTA amylin signaling indirectly regulates mPFC neuron activity, putatively through VTA interneuron mediated decreases in VTA-to-PFC dopamine signaling, to mitigate impulsive consumption of palatable foods.

Correlations Of Post-Prandial Increase In Plasma Satiety Gut Hormones Leap2 With Post-Prandial Decreases In Appetite, Food Cue Reactivity And Food Intake In Adults Without Obesity
Sandra Luur1, Raghav Bhargava1, Marcela Rodriguez-Flores1, Mimoza Emin1, Christina G. Prechtl2, Anthony P. Goldstone1
1PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, United Kingdom, 2Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom

Background: The satiety gut hormone LEAP2 is an inverse agonist at the acyl ghrelin (AG) receptor. Plasma AG and LEAP2 are reciprocally regulated in mice/humans with AG decreasing and LEAP2 increasing after food intake (Mani JCI 2019). In rodents, LEAP2 attenuates exogenous AG-induced and spontaneous food intake. However, any role for plasma LEAP2 in human eating behaviour is uncertain. Methods: Secondary analysis of previous food intake study (Goldstone AJCN 2014). n=22 adults (19-44y, 77% male, BMI<30 kg/m^2) had fasted (no meal) and fed (730 kcal meal at 0min) visits. Post-prandial changes (fed-fasted visit) in plasma LEAP2 at 70-150min were correlated with changes in appetite ratings (0-10cm at 70-150min, functional MRI BOLD signal during evaluation (peal vs. objects, max 4) of high-energy (HE) or low-energy (LE) food pictures at 95-115min , and food intake (kcal as % estimated resting energy expenditure) in ad libitum meal at 150min. Results: Food intake increased plasma LEAP2 by 18.1-43.5% at 70-150min (P=0.014-0.006), and decreased appetite (-3.2, P<0.001). HE food intake (r=0.33, P=0.003) and food intake (r=12.3% SEE, P<0.001). Post-prandial increase in LEAP2 correlated with post-prandial decrease in appetite (r=0.47, P=0.026) and food intake (r=0.37, P=0.088), BOLD signal to HE/LE and HE foods in anterior/posterior cingulate, paracingular cortex, frontal pole, middle frontal gyrus (whole brain analysis cluster-wise FWE Z>2.3, P<0.05), but not HE food appeal (r=0.13, P=0.57). Conclusion: In adults without obesity, post-prandial increases in plasma LEAP2 were correlated with post-prandial decreases in appetite, food intake and food cue reactivity. This supports a role for the satiety hormone LEAP2 in regulating changes in human eating behaviour after food intake.

Best Student Presentation Award Finalist
Ghrelin Facilitates Hedonic Drive And Food Reward Signals In Binge Eating Disorder
Corinna Schulz1, Jacob Schwab1, Dana J. Wentz1, Monja P. Neuser1, Manfred Hallschmid2,3, Jennifer Svaldi4, Nils B. Kroemer1
1Department of Psychiatry and Psychotherapy, Tuebingen Center for Mental Health, University of Tuebingen, Tuebingen, Germany, 2Department of Medical Psychology and Behavioral Neurobiology, Tuebingen Center for Mental Health, University of Tuebingen, Tuebingen, Germany, 3Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the Eberhard Karls University Tuebingen, Tuebingen, Germany, 4Department of Psychology, Tuebingen Center for Mental Health, University of Tuebingen, Tuebingen, Germany

Ghrelin is the only circulating orexigenic hormone and modulates reward via direct and indirect effects, including vagus afferent projections. Yet, it remains unclear how ghrelin is involved in binge eating (BE) and mechanisms related to loss of control over eating. Here, we investigated 65 BMI-matched (M_BMI = 31.5 ± 6.98 kg/m²) women with varying symptoms of BE (no BE, subsyndromal BE disorder (sub-BED), BE disorder (BED)). We measured levels of acyl (AG) and des-acyl ghrelin (DG) before (fasting) and after a standardized breakfast. Participants performed a food bidding fMRI task ~60 min after the meal. First, we observed group differences in ghrelin in the meal after the meal, where patients with BED showed attenuated meal-induced decreases in DG (P = 0.047) as well as disturbances in the recovery of DG after larger AG decreases (P = 0.030).
Repeated Chemogenetic Excitation Of Vagal Afferents Expressing Oxytocin Receptors Promotes Negative Energy Balance

Karen A Scutt1,2, Justin A Smith1,3, Dominique N Johnson2,3, Khalid Elsaafien1,3, Nagheme J Thomas2,3, Caitlin Baumer-Harrison1,2, Veronica Donosi1,2, Guillaume de Lartigue1,3, Annette D de Kloe2,3, Eric G Krause1,3

1Pharmacodynamics, University of Florida, Gainesville, FL, United States, 2Physiology and Functional Genomics, University of Florida, Gainesville, FL, United States, 3Center for Integrative Cardiovascular and Metabolic Diseases, University of Florida, Gainesville, FL, United States

Bidirectional communication between brain and periphery is critical for cardiometabolic homeostasis. The vagus is a key pathway and neurons of the nodose ganglia (NDG) transmit sensory information from viscera to brain. Although oxytocin is best known for its role in reproductive and social behaviors, it is also implicated in cardiometabolic control. A population of neurons in the NDG express oxytocin receptors (NDG Oxtr) and innervate the heart and gastrointestinal tract, suggesting a means to modulate cardiometabolic function. Acute excitation of NDG Oxtr significantly reduces blood pressure, energy expenditure, body temperature, food and water intake, but elevates plasma corticosterone and causes conditioned taste aversion. More recently, we have investigated the effects of chronic activation of these neurons. A Cre-inducible adenoassociated virus (AAV) expressing designer receptors exclusively activated by designer drugs (DREADDs) was injected bilaterally into the NDG of Oxtr-Cre mice, allowing selective activation of NDG Oxtr by clozapine n-oxide (CNO). Mice were housed within the TSE Phenomaster system and dosed every other day for 12 days. As before, food and water intake and energy expenditure were significantly reduced for 6h following CNO. Interestingly, lower body weight was maintained for the 12d period; food and water intake and energy expenditure mirrored that of controls on days when CNO was not administered, and did not result in overconsumption to compensate for the prior day’s reduction in intake. Chronic CNO administration did not alter social or anxiety-like behaviors. These results suggest that NDG Oxtr mediate cardiometabolic function and may serve as a putative target for development of novel therapeutics.

Oral Erythritol Affects Subsequent Energy Intake In Healthy Humans: A Randomized, Controlled, Crossover Trial

Fabienne Teysseire1,2, Emilie Flad1, Valentine Bordier1,2, Jens F. Rehfeld1, Lukas Van Oudenhove2, Carel le Roux3, Christoph Beglinger1,2, Bettina K. Woelnerhanssen1,2, Anne Christin Meyer-Gerspach1,2

1St. Clara Research Ltd at St. Claraspital, Basel, Switzerland, 2Faculty of Medicine, University of Basel, Basel, Switzerland, 3Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, 4Laboratory for Brain-Gut Axis Studies, Translational Research Center for Gastrointestinal Disorders, Department of Chronic Diseases, Metabolism & Ageing, KU Leuven, Leuven, Belgium, 5Diabetes Complications Research Centre, Conway Institute University College Dublin, Dublin, Ireland

Introduction: The natural bulk sweetener erythritol might be a potential sugar substitute. The impact of pure oral erythritol on energy intake is currently not known. The aim was to assess the effect of oral erythritol compared to sucrose, sucralose, and water on energy intake during a subsequent ad libitum test meal. Additionally, we investigated the release of cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), glucose and insulin in response to these substances. Methods: We performed a randomized, controlled, double-blind, crossover study with 20 healthy subjects (mean Â±SD: age 29 Â± 2 years, BMI 22.3 Â± 0.4 kg/m²). Subjects received an oral preload with either 50g erythritol, 33.5g sucrose, 0.0558g sucralose dissolved in 300mL water or water (placebo), on four separate test days. Fifteen minutes after the preload intake, a test meal was served and ad libitum energy intake was measured. To assess the energy intake, food and drinks were weighted before and after the test meal. At fixed time points, we collected blood samples to measure CCK, GLP-1, glucose and insulin. CCK was measured by a radioimmunoassay, GLP-1 (currently being analyzed) by a sensitive ELISA, glucose by a glucose oxidase method, and insulin by an electrochemiluminescence immunoassay. Data were analyzed with mixed model analysis using SAS. Results: Energy intake was significantly lower after oral erythritol (mean Â±SEM: 483 Â± 62 kcal) compared to sucrose (573 Â± 52 kcal), sucralose (669 Â± 52 kcal), and water (655 Â± 67 kcal) (all P<0.05). Adding the calories of the sucrose preload, total energy intake was significantly lower after oral erythritol compared to sucrose (707 Â± 52 kcal), sucralose, and water (all P<0.01). Before the start of the ad libitum test meal, oral erythritol led to a significant release of CCK compared to sucrose, sucralose, and water (all P<0.01). Glucose and insulin concentrations were significantly lower after oral erythritol compared to sucrose (both P<0.01) with no significant difference between erythritol and sucralose or water. Conclusion: We show that oral erythritol – a natural bulk sweetener with no calories - leads to an increased release of CCK, which results in a reduced energy intake. Erythritol has no effect on glucose and insulin concentrations, which makes it a potential sugar substitute for people with obesity and diabetes type 2.
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<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>10:30 - 11:00 AM</td>
<td>Foyer</td>
<td>Coffee Break</td>
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<tr>
<td>11:00 - 12:00 PM</td>
<td>Infante Hall</td>
<td>Awards Session</td>
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<tr>
<td>11:00</td>
<td>Infante Hall</td>
<td>Introduction</td>
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<tr>
<td>11:15</td>
<td>Infante Hall</td>
<td>Distinguished Career Award Presentation - Reflections On My Career: Appreciations, Key Themes And Findings</td>
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<tr>
<td>11:00 - 12:00 PM</td>
<td>On Own</td>
<td>Lunch</td>
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<td>2:30 - 3:30 PM</td>
<td>Infante Hall</td>
<td>MARS Lecture 4</td>
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<td>2:30</td>
<td>Infante Hall</td>
<td>Shaping Future Health: Early-Life Determinants Of Obesity And Metabolic Disease Risk</td>
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<td>3:30 - 4:30 PM</td>
<td>Infante Hall</td>
<td>Business Meeting</td>
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<tr>
<td>7:00 - 11:45 PM</td>
<td>World of Wine</td>
<td>Closing Banquet (Ticket Required)</td>
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Chair(s): Rick Samson

**Introduction**

11:15

**Distinguished Career Award Presentation - Reflections On My Career: Appreciations, Key Themes And Findings**
Harvey Grill

Chair(s): Kyle Burger

**Shaping Future Health: Early-Life Determinants Of Obesity And Metabolic Disease Risk**
Katie Page
University of Southern California, Los Angeles, CA, United States

Rates of obesity and type 2 diabetes have continued to rise among all segments of the population, which an alarming 95% relative increase in the prevalence of type 2 diabetes among children and adolescents over the last 16 years. The current obesogenic environment—beginning as early as in utero—â­¬â­¬has undoubtedly contributed to these upward trends. Our work integrates nutrition, metabolic, and neuroimaging data to understand environmental and behavioral factors that influence the neuroendocrine regulation of appetite and risk for the development of obesity and diabetes. This talk will highlight findings from our studies in two interrelated areas: (1) brain and endocrine responses to different types of sugars and non-nutritive sweeteners and the impact on appetite regulation; (2) developmental programming of neuroendocrine systems underlying risk for obesity and diabetes in children. In a series of randomized cross-over trials, we have shown differential effects of dietary sugars and non-nutritive sweeteners on brain and endocrine regulation of appetite, which may influence eating behavior and risk for weight gain and obesity. In prospective cohort studies of children born to mothers with or without gestational diabetes mellitus (GDM), we have shown that in utero exposure to GDM may program appetite systems in the brain to favor greater food intake and a higher risk for obesity and diabetes in children. Overall, our findings suggest that risks for obesity may be programmed very early in life, even before birth, and worsened by consumption of unhealthy sugars. Efforts to slow the co-epidemics of obesity and type 2 diabetes need to start early in life when brain development and eating behavior are malleable and can be shaped in ways that affect long-term health. Å

**Business Meeting**

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<tr>
<th>Time</th>
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<tr>
<td>7:00 PM</td>
<td>Taylor's Port Centro de Visitas - Caves</td>
<td>Tour of Taylor's Port Centro de Visitas - Caves</td>
</tr>
<tr>
<td>7:00 PM</td>
<td>Taylor's Port Centro de Visitas - Caves</td>
<td>Tour of Taylor's Port Centro de Visitas - Caves</td>
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<tr>
<td>Taylor's Port Centro de Visitas - Caves</td>
<td>Rua do Choupelo n 250</td>
<td>Taylor's Port Centro de Visitas - Caves</td>
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<tr>
<td>4400-088 Vila Nova de Gaia Portugal</td>
<td>GPS: 41.13394, -8.61435</td>
<td>Taylor's Port Centro de Visitas - Caves</td>
</tr>
</tbody>
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At Taylor's Port Centro de Visitas - Caves you will enjoy a private guided tour, that will offer an informative visit taking you through hundreds of oak casks and vats, a range of films, historic documents, exhibitions, photographs and paintings, culminating in a very good understanding of the history and production of port wine.

The tour includes port wines to taste.

7:45 PM - 11:45 PM - Awards Ceremony, Dinner and Dancing at World of Wine (WOW)