Operant licking for intragastric sugar: differential reinforcing actions of glucose, sucrose and fructose

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Intragastric (IG) flavor conditioning studies indicate that isocaloric sugar infusions differ in their reinforcing actions, with glucose and sucrose more potent than fructose. Here we determined if the sugars also differ in their ability to maintain operant self-administration via dry licking. Food-restricted C57BL/6 mice were trained 1 h/day to lick a food-baited spout, which triggered IG infusions of 16% sucrose. In testing, the mice licked an empty spout, which triggered IG infusions of different sugars. Mice shifted from sucrose to 16% glucose increased dry licking, whereas mice shifted to 16% fructose rapidly reduced licking to low levels. Other mice shifted from sucrose to IG water reduced licking more slowly but reached the same low levels. Thus IG fructose, like water, is not reinforcing to hungry mice. The rapid decline in licking induced by fructose may be due to the sugar’s satiating effects. Further tests revealed that the Glucose mice increased their dry licking when shifted from 16% to 8% glucose, and reduced their dry licking when shifted to 32% glucose. This may reflect caloric regulation and/or differences in satiation. The Glucose mice did not maintain caloric intake when tested with different sugars. They self-infused less sugar when shifted from 16% glucose to 16% sucrose, and even more so when shifted to 16% fructose. Reduced sucrose self-administration may occur because the fructose component of the disaccharide reduces its reinforcing potency. These data show that sugars differ substantially in their ability to support IG self-administration as well as flavor learning.

Unraveling the role of dopamine neurons in sensing energy balance and in feeding

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Increased activity of mesDA neurons drives motivated behavior and promotes operant responding for food. Ventral tegmental area (VTA) dopamine (DA) neurons are sensitive to leptin. We here further address mesDA’s role in feeding. To investigate how negative energy balance affects reward-signaling by mesDA neurons, in vivo ephys recordings were made of DA neurons in VTA during the execution of a behavioural task. Neuronal activity was subsequently related to cue-presentation and the delivery of food rewards. To manipulate energy balance, animals were mildly food-deprived preceding the recording session. In addition, the effect of peripheral injections of leptin on reward-encoding was measured. Leptin suppressed mesDA neuronal firing during cue presentation. Interestingly, local inhibition of leptin signaling in LH suppressed motivation to press a lever to obtain a sucrose reward, suggesting that leptin acts on VTA DA activity, through projections from the LH. In order to determine the requirement of specific midbrain dopamine neurons for motivation for food, the activity of dopamine neurons was manipulated using DREADD and optogenetics. These studies showed that increasing activity of dopamine neurons projecting to the accumbens reduced food intake but increased the motivation to work for a food reward. Reduction of VTA dopamine neuronal firing reduced licking rates to obtain a sucrose reward. Collectively these data show a dissociation of the role of dopamine neurons in food motivation and consumption.

Variation at a common polymorphism in the CD36 gene is associated with liking of low-fat dairy and parental perception of child weight.
Overconsumption of dietary fat is a risk factor for obesity. CD36, a fatty acid translocase and putative oral fat sensor, is associated with dietary fat acceptance and body mass index (BMI) in adults. However, the role of CD36 in liking of fats and BMI in children is not fully understood. In the current study, children (n=63; 7-9 years old), self-reported liking of dairy foods varying in fat content, while parents answered questions about parental feeding practices. Saliva samples of ~4ml total volume were collected from children and DNA was extracted to genotype CD36 at rs1761667, a polymorphism associated with fat perception and acceptance in adults. We hypothesized that children with the A/A genotype at rs1761667 would have lower acceptance of low-fat dairy foods and greater BMI compared to A/G and G/G children. Results showed that in comparison to A/G or G/G genotypes, children with the A/A genotype reported lower liking of low-fat dairy products (p=0.01). Results of the Child Feeding Questionnaire showed the parents of A/A children perceived their child’s weight to be greater than parents of children with A/G or G/G genotypes (p=0.02), despite no differences in measured BMI between groups (p=0.82). Preliminary results suggest that CD36 variation may be associated with reported liking for some fat containing foods and with parental perceptions of child weight status, independent of actual child BMI. A larger sample is needed to confirm these results and identify the mechanisms underlying these associations.

Seasonal variation in salt appetite

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We have previously shown that salt appetite is high in a desert population, possibly to assist hydration. Therefore, salt intake and preference might increase in summer as a consequence of increased ambient temperature increasing perspiration, thirst increasing water turnover, and their attendant sodium losses. If sodium intake in summer benefits hydration, one possible consequence is conditioning of sodium preference, thereby contributing to global sodium intake. We are testing this hypothesis using our Salt Appetite test battery in the same group of people in different seasons, and by database analyses. Confirmation would add validity to the hydration hypothesis of enhanced salt appetite, would suggest studies comparing different climatic regions, and contribute to awareness of this source of increased salt intake. Tentative results, with 22 women and 5 men indicate that our hypothesis is incorrect (salt appetite score in winter: 110.9±5.8, in summer: 87.1±5.6, p< 0.001, with respective temperature and humidity greater in summer by 4.0±1.4°C and 17.7±4.8%, p’s< 0.02), which if confirmed with a larger, sex-balanced participant pool, and appropriate adjustments as we continue the study, would suggest different implications for the regulation of sodium intake.

Birth weight predicts feeding behavior in siblings

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Background/ Aim: Low Birth Weight (LBW) is implicated in the risk for adulthood diseases such as
overweight, preceded by altered feeding behavior during childhood. Our objective was to investigate if a lower birth weight predicts different feeding behavior and food consumption between siblings. Methods: 30 sibling pairs from the cities of Montreal, Canada, were recruited from an established prospective birth cohort (the Maternal Adversity, Vulnerability and Neurodevelopment – MAVAN - project). At 48-months of age, mothers completed the Children Eating Behavior Questionnaire (CEBQ) and a Food Frequency Questionnaire. Analyses were performed considering each child of a sibling’s pair in one group, so that environmental influences could be controlled. Generalized Estimating Equations were used to evaluate the effect of birth weight (smaller X higher) on the CEBQ scores described at 4 years of age, adjusted by birth order, gender and BMI. Results: Lower birth weight was related to increased satiety (p=0.006), slowness (p=0.030) and desire to drink (p=0.033). This group also presented less responsiveness (p=0.001), enjoyment (p=0.029) and undereating emotion (p=0.048). Conclusions: Those effects were observed within the same family which reinforces that the effect of lower birth weight in feeding behavior is more biological driven than due to environmental variation.

Endogenous GLP-1 receptor signaling in the nucleus tractus solitarius is required for energy balance control

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Nucleus tractus solitarius (NTS) glucagon-like peptide-1 receptor (GLP-1R) signaling reduces food intake and body weight. Here, we examine the role of endogenous NTS GLP-1R in the control of energy balance and glycemia. We developed an AAV-shRNA to chronically knock down (KD) GLP-1R. After microinjecting the KD or a control virus into the caudal NTS of rats, chow intake, meal patterns, body weight gain, and blood glucose levels were analyzed for up to four weeks post-injection. qPCR on mNTS tissue verified that the GLP-1R KD virus significantly (~65%) reduced NTS GLP-1R mRNA expression. As hypothesized, NTS GLP-1R KD rats had elevated dark cycle, daily, and cumulative chow intakes compared to controls. These increases in food intake were mediated by increases in average meal size (no effect on average meal number). Though differences in body weight did not reach statistical significance, there was a non-significant trend for an increase (p=.09) in cumulative body weight gain in NTS GLP-1R KD rats. Finally, NTS GLP-1R KD rats had significantly elevated blood glucose levels two hours after a glucose challenge compared to controls, suggesting that NTS GLP-1R are required for normal glucose clearance. These data complement pharmacological results showing that 4th ICV exendin-4 (a GLP-1R agonist) reduces, and exendin-(9-39) (a GLP-1R antagonist) increases, glucose tolerance in an oral glucose tolerance test. Taken together, these data show for the first time that NTS GLP-1R are physiologically required for the control of energy balance and glycemia.

Central nucleus of the amygdala glutamate receptors mediate cisplatin-induced malaise and energy balance dysregulation through direct hindbrain projections

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Cisplatin chemotherapy is commonly used to treat cancer despite severe side effects such as nausea, vomiting, and anorexia. The neural mechanisms mediating these side effects remain elusive. Recent data highlight the dorsal vagal complex (DVC), lateral parabrachial nucleus (lPBN), and central nucleus of the amygdala (CeA) as potential sites of action in mediating cisplatin’s side effects. Here, we used complementary immunohistochemical (IHC), qPCR, and behavioral approaches to examine the phenotypes of neurons in brain regions activated by cisplatin and their connectivity. Results from IHC studies identified a population of cisplatin-activated DVC neurons that project to the IPBN, and a population of cisplatin-activated IPBN CGRP [marker for glutamatergic neurons in the IPBN] neurons that project to the
CeA. CeA gene expressions of AMPA and NMDA receptor subunits were markedly increased following cisplatin treatment, suggesting that CeA glutamate receptor signaling plays a role in mediating cisplatin’s side effects. Behavioral data showed that CeA AMPA/kainate receptor blockade attenuates cisplatin-induced pica (proxy for malaise in rodents), and that CeA NMDA receptor blockade attenuates cisplatin-induced pica, anorexia and body weight loss, demonstrating that CeA glutamate receptor signaling is critical for cisplatin-induced energy balance dysregulation. These data highlight a novel circuit and CGRP/glutamatergic mechanism mediating cisplatin-induced malaise and energy balance dysregulation.

New insights on food choice: from neurocognitive mechanisms to real-life meals

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Selecting food from a range of available options is a fundamental characteristic of the way humans eat, particularly in affluent societies of the developed world. The study of individual determinants of food choice has been the focus of disciplines as diverse as appetite, health psychology, consumer research, economics, or anthropology. More recently, cognitive neuroscience methods, which facilitate research and hypothesis testing through the generation of objective, sensitive and quantitative information, particularly neuroimaging, have provided a new angle to study food choice mechanisms. Translating data from these laboratory studies to the case of real-life food choice scenarios, however, remains notoriously difficult. In this presentation, I will first review recent concepts that are emerging from functional neuroimaging and cognitive neuroscience studies in the field of food choice for the case of adult humans. This will also include recent applications of noninvasive neuromodulation to manipulate brain circuits related to food choice. Finally, I will present ongoing work in my laboratory aimed at developing new methodologies that can capture naturalistic scenarios of food choice, and could help close this gap between laboratory and real life. By presenting these methods, I will try to make the case that aside from strategies that are based on bringing or presenting food in the scanner, the alternative approach of bringing neurocognition to the meal can also offer relevant information to understand food choice.

Olanzapine reduces the excitability of DMV neurons, including a subset of stomach- and liver-related neurons

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Olanzapine, a second-generation antipsychotic, is widely used in clinical settings due to its positive impact on mental health. However, long-term treatment is associated with undesirable metabolic side effects. Various mechanisms and brain areas have been proposed as contributors to these side effects; however, the role of the dorsal motor nucleus of the vagus nerve (DMV), which plays a crucial part in the regulation of subdiaphragmatic organs and thus governs energy and glucose homeostasis is largely unknown. Likewise, identifying the effect of olanzapine on the excitability of DMV neurons in both sexes is crucial to understanding possible underlying mechanisms. Whole-cell patch-clamp electrophysiological recordings were conducted from stomach- and liver-related DMV neurons identified with retrograde viral tracers and from random DMV neurons. The effect of olanzapine on the neuronal excitability of DMV neurons both in male and female mice was established. Our data demonstrate that olanzapine hyperpolarizes the majority of DMV neurons in both sexes and this effect is reversible. The hyperpolarization is associated with decreased firing rate and decreased input resistance. Olanzapine also decreased the excitability of a subset of stomach- and liver-related DMV neurons. Our study demonstrates that olanzapine has a powerful effect on DMV neurons in both sexes indicating its ability to alter vagal output to the subdiaphragmatic organs,
which likely contributes to the metabolic side effects associated with olanzapine treatment in humans and experimental models.

TRPV1 expressing hypothalamic neurons control glucose metabolism

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Transient receptor potential vanilloid type 1 (TRPV1)-dependent mechanisms participate in the regulation of whole body glucose homeostasis by both peripheral and central mechanisms. Regarding central effects, our previous studies demonstrated that TRPV1 increases excitatory neurotransmitter release, and thus controls preautonomic neurons in the paraventricular nucleus (PVN) of the hypothalamus. Preautonomic neurons play an important role in the regulation of autonomic output, and thus are able to control homeostatic functions including glucose homeostasis. Nevertheless, the location of TRPV1-expressing neurons, their projection sites and target neurons are largely unknown. TRPV1-TdTomato mice were generated to determine the location of TRPV1 expressing neurons in the hypothalamus. TRPV1 expression was detected in the PVN, the dorsomedial hypothalamic nucleus, and the lateral hypothalamus. Application of capsaicin, an exogenous TRPV1 agonist, depolarized TRPV1-expressing neurons, indicating functional expression of TRPV1 at the time of recordings. Furthermore, activation of hypothalamic TRPV1-expressing neurons using DREADD-approach resulted in blunted ip glucose tolerance in vivo. Our study demonstrates that TRPV1-expressing neurons are present in preautonomic neurons and play a role in controlling blood glucose metabolism.Supported by NIH R01DK099598 (Zsombok), and Hypertension COBRE (P30GM103337).

Steep temporal discounting is associated with poor diet quality in humans

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The most rewarding foods are generally high in fat, salt, and sugar, and poor in nutrients. Thus, the immediate gratification from palatable food is at odds with healthy eating. We hypothesized that greater relative preference for immediate versus delayed rewards (temporal discounting) is associated with poorer overall diet quality in humans. Healthy adults (N=92; mean age = 43.1 years; 80% female) completed a temporal discounting task featuring hypothetical monetary rewards. Overall diet quality was quantified by applying the Healthy Eating Index-2010 scoring system to dietary intake data collected in three 24-hour diet recalls. Subjects also complete an operant response task assessing the reinforcement value of energy dense snacks. In covariate-adjusted regression models, steeper discounting of delayed rewards was associated with poorer overall diet quality (p=.003). This association remained significant when adjusting for food reinforcement, which was not itself predictive of diet quality (p=.26). When examining individual diet components, steeper temporal discounting was associated with poorer adherence to recommended intakes for green vegetables and beans (p=.005), seafood and plant proteins (p=.02), refined grains (p< .05), and empty calories (p< .05). Temporal discounting was not associated with adiposity or energy intake (p’s>.20), suggesting that it may influence food choice rather than overall level of consumption.

Physical properties of lipid emulsions affect short-term food intake and gastrointestinal function in rats
The consumption of processed foods with great amounts of emulsified lipids is a leading cause of the increasing prevalence of overweight/obesity. Therefore, it is important to understand how the physical properties of lipid emulsions (LE) affect fat digestion and satiation. Recent studies in humans showed that particle size, acid stability, and re-dispersibility of LE affect hunger/fullness sensations and gastrointestinal function including gastric emptying. To critically examine the physiological mechanisms of these effects, we here aimed at establishing an animal model that mimics the LE effects in humans. In a within subjects crossover design, three isocaloric (1.9 kcal/ml) lipid emulsions differing in particle size, fat source, acid stability and re-dispersibility were intragastrically infused as a preload in male Sprague Dawley rats and subsequent food intake as well as gastric emptying was assessed. Small particle size, acid stability, and re-dispersibility of the LE appeared to have additive effects on the reduction of short-term food intake and gastric emptying. These data are consistent with the findings in humans. Our rat model may therefore provide a valuable and promising tool for further studies addressing the mechanisms of the observed effects.

When a calorie is not a calorie: Decoupling sweet taste from caloric load disrupts metabolic response

Sweet taste perception triggers release of insulin and GLP-1 to optimize carbohydrate metabolism. The intensity of the perceived sweetness provides a signal about the amount of nutrient present so that physiological response can be titrated to caloric load. Here we tested if a mismatch between sweetness and caloric load influences metabolic response to carbohydrate containing beverages. By using tasteless and odorless maltodextrin to deliver calories and sucralose to deliver sweet taste we could independently manipulate sweetness and calories. Beverages contained 0, 37.5, 75, 112.5, or 150 kcals (2 of each) and sweetness was either commensurate with caloric load or held at the equivalent sweetness produced from 70 kcal sucrose. Resting energy expenditure was measured in 18 subjects immediately before and up to 30 minutes after consumption of the 10 beverages (double blind, randomized design). A mixed effects analysis revealed an inverse relationship between metabolic response and magnitude of mismatch (b = -1.05, t = -2.505, p = 0.02). Strikingly this was irrespective of caloric load. That is, metabolic response was similarly attenuated after ingesting a low calorie beverage that was too sweet or a high calorie beverage that was not sweet enough. These results demonstrate that decoupling sweet taste from caloric load disrupts metabolism, suggesting that modern foods and beverages that decouple sweetness from calories may lead to weight gain by disrupting energy expenditure.

Selective reduction of dietary carbohydrate versus fat does not influence subsequent ad libitum intake

Selective reduction of dietary carbohydrate versus fat does not influence subsequent ad libitum intake
Restriction of dietary fat versus carbohydrates may differentially influence food preference. Therefore, the aim of this study was to see if subjects on an ad libitum diet would choose foods with different carbohydrate and fat compositions subsequent to diets selectively reduced in carbohydrate (RC) versus fat (RF). In a randomized, crossover trial, 17 (53% female) adults (mean±SD age: 34±2 years, BMI: 36.3±1.2 kg/m²) consumed eucaloric metabolic diets consisting of 15% protein, 35% fat and 50% carbohydrate for 7 days. They then switched to 6 days of a 30% reduced energy diet achieved solely by restriction of fat or carbohydrate. Participants were then given 3 days of unlimited, 24 hour access to a vending machine containing typical meal and snack items (>10,000 kcal/d). Foods were classified according to the Macronutrient Self-Selection Paradigm (MSSP) which has 6 groups of food categorized as high sugar/high fat, high sugar/low fat, high protein/low carbohydrate/low fat, high protein/low carbohydrate/high fat, high complex carbohydrate/low fat or high complex carbohydrate/high fat. Average ad libitum energy intake did not differ subsequent to the RC vs. RF diets (3225±135 kcal/d vs. 3303±1250 kcal/d, respectively, p=0.862). Intake of foods in the MSSP groups did not differ following consumption of the two diets. Energy intake and the type of food selected from the vending machine did not differ following a diet selectively reduced in carbohydrate vs fat.

Glucose vs saccharin: Tests of the sweet-calories hypothesis

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Two experiments tested the proposal that artificial sweeteners weaken sweet-calorie associations and thus promote greater weight gain (e.g. Davidson et al., 2014). The method used in Experiment 1 was similar to Swithers and Davidson (2008). A Glucose group was given glucose-sweetened yoghurt, a Saccharin group was given saccharin-sweetened yoghurt and a Control group was given unsweetened yoghurt. No difference in body weight or fat pad mass between Saccharin and Control groups was detected at any stage of the 15-week intervention, whereas the Glucose group was the heaviest by the final 5 weeks and at cull had the largest fat pads. Less finickiness towards saccharin measured in Stage 1 was associated with increased weight gain over the whole study. Experiment 2 followed procedures in Swithers et al. (2008). Rats were given 2-hr daily access to solutions in tap water of 10% glucose, 0.3% saccharin, 0.15% saccharin, or water. Intakes and body weights were collected daily for a 21-day period, but no group differences in body weight were observed at any point. In summary, compared to control conditions not exposed to any sweetener, exposure to saccharin had no detectable effect on body weight regulation in either experiment, whereas in Experiment 1 the effects of adding glucose were similar to those previously documented for other sugars. We discuss possible reasons for these discrepancies with previous comparisons between glucose and saccharin.

Rats vulnerable to weight loss during activity-based anorexia lack increased expression of Agrp and Orexin in response to starvation.

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The rodent activity-based anorexia model (ABA) mimics major characteristics of Anorexia Nervosa, like hyperactivity, hypophagia and body weight loss. Our previous studies showed that that passive stress coping behavior in combination with prenatal stress exposure (PNS) was associated with increased weight loss during ABA. Based on their enhanced hypophagia, we hypothesized that these passive PNS rats may have impaired orexigenic signaling in response to starvation. Our data show increased ghrelin and
decreased leptin levels in all proactive rats in the ABA and body weight matched (BWM) groups compared to sedentary (SED) and running wheel (RW) control groups. However, there were no differences among SED, RW, BWM and ABA groups in passive coping rats. All ABA and BWM rats had increased Npy and decreased Pomc expression in the arcuate nucleus (ARC) compared to SED and RW rats. Expression of Agrp in the ARC was increased in all ABA and BWM compared to SED and RW groups, except in the passive coping PNS rats where no differences were observed. Compared to SED and RW groups increased expression of orexin (Hcrt) in the lateral hypothalamus was observed in all BWM rats and in ABA exposed proactive control, proactive PNS and passive PNS rats. However this increase was not observed in the passive PNS rats in the ABA group. Overall, our data suggest that passive coping PNS rats have impaired Agrp and orexin expression which may contribute to their greater weight loss with ABA.

Green Coffee Extract did not affect BW, BMI, Waist Circumference, BP or Basel Plasma Insulin, but appears to Improve Insulin Sensitivity in Obese People

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Green coffee extract has been recently advocated as a weight-loss aid in the respect that it can help boost metabolism. In this double-blind, placebo-controlled study, the effects of green coffee extract on body weight and metabolism in humans were tested in 20 volunteers (7 male, 13 female, mean age 36 years) randomly assigned to either an experimental or control group. The experimental participants took 3 capsules of 350 mg (1050 mg total) green coffee extract per day before meals (morning, noon, evening). Similarly, the control participants took 3 identical capsules without green coffee extract. Antecubital vein blood samples were taken for insulin and plasma metabolite analysis and an oral glucose tolerance test (OGTT, 296mL of 75g glucose solution) was performed at study onset and after one month. Green coffee extract did not change body weight (BW), body mass index (BMI), waist circumference, blood pressure (BP), plasma insulin, and plasma metabolites (glucose, triglycerides, free fatty acids, beta-hydroxybutyrate, and cholesterol). Green coffee extract did, however, appear to improve insulin sensitivity (OGTT) in particular in obese people, which would be very beneficial. Further tests are being conducted on obese participants in a cross-over experiment.

Protective Effects of Subcutaneous Adipose Tissue: Role as the “Metabolic Sink”

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Lower body subcutaneous adipose tissue (LBSAT) accumulation is demonstrated to protect against metabolic comorbidities such as type 2-diabetes and insulin resistance. These effects occur via its ability to sequester surplus lipid and serve as a “metabolic sink”. We have demonstrated that while LBSAT removal in Chow and high fat diet (HFD) mice increased triglyceride deposition in muscle proximal to removal, only HFD mice had a decrease in whole body glucose tolerance. Hence, muscle triglyceride accumulation is not sufficient to explain these differential glucose impairments. We examine the role of LBSAT in glucose homeostasis by a time course study (5 or 13 weeks) that included removal of varying amounts of SAT (unilateral or bilateral removal of inguinal or dorsal adipose tissue) in HFD mice. Glucose tolerance tests and insulin response was performed one week before termination, cytokine concentration was measured in plasma, and lipid species were determined in femoral muscle via lipidomics. Progressive LBSAT removal produces dose-dependent deterioration in glucose tolerance and insulin sensitivity. This effect, however, was less in upper body SAT (UBSAT) removal, but greatest with removal of both LBSAT and UBSAT. Adipose tissue removal causes lipid accumulation in proximal muscle. At 13 weeks lipid signatures of femoral muscle, proximal to LBSAT, are significantly different in Chow and HFD. Overall
these experiments provide a direct test of the metabolic sink concept and identify target tissues and mechanisms involved.

Receptivity to concepts linking genes and eating behaviors

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Evidence is increasing that genes exert an influence on eating behaviors (EB). This pathway of influence on body weight may become a leverage point for future health promotion efforts. Several theories suggest that explanations for health conditions exercise substantial influence on efforts taken to reduce risk. However, the characteristics of this particular explanation are unknown. This report presents data from adult participants (N=261) who took an online survey that assessed genetic and environmental attributions for EB and weight. Participants attributed genetic causes to body weight more so than to EB (p<.0001); and attributed EB to environmental causes more so than to genetic ones (p<.0001). When looking at the genetic attributions for EB, they were negatively associated with confidence to make weight and diet changes (p=.04), unassociated with perceived importance of family members in helping with those changes (p=.34), and positively related to interest in future eating behavior-related genetic testing regarding the participant’s risk for unhealthy eating and weight gain (p=.01). We also found several personal and familial factors that influence individuals’ eating behavior genetic attributions. This exploratory work sheds light on healthy individuals’ beliefs about genomic influences on eating behavior, a critical component of a healthy lifestyle. The relationships identified in this work may inform how genomic concepts can best be integrated into healthy eating and weight management promotion efforts in the future.

Linking mother’s perception of her weight history to psychological attributes and child feeding

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Weight problems run in families and transcend generations. Parent-to-child influences on weight occur through shared genetics, social and physical environments. Insights into these influences could be gained through deeper understanding of mothers’ experiences and beliefs. Overweight mothers (N=221) of 4-5 year-olds recalled their weight at 4 time points since childhood. Three weight history trajectories emerged: recently overweight (72%), always overweight (11.3%), and steady-gain-obese (16.7%). We examined the influence of mothers’ perspectives (cognitive and affective) on child-feeding behavior. Among the cognitive processes, mothers’ concern about the child’s weight increased with more time she spent being overweight (p=.001); her beliefs about factors underlying weight were not related to trajectory. For affective processes, recently overweight mothers felt more shame (p=.0008), while guilt increased with both time spent overweight and increased weight at present (p=.0003). Observed feeding, mothers choice of a meal for the child in a virtual reality-based buffet, was not affected by weight trajectory (p=.06), while perceived feeding was (p=.03); mothers who spent more time being overweight and are still at higher weight are more restrictive. Additional analyses will investigate the relationships between trajectories, affective/cognitive processes and child-feeding. Investigating mothers’ weight trajectory could be used in developing parenting interventions related to healthy feeding.

Differences in Physiological Food Cue Reactivity Between Emotional Eaters and Non-Emotional Eaters
Boredom is an emotion that frequently triggers emotional eating (EE). The current study examined differences in heart rate variability (HRV) between people who eat in response to boredom (EE-B) and people who do not eat in response to boredom (non EE-B), while exposed to highly palatable food. Subjects included a sample of 50 adults (22.3 ± 2.56 years; 74% female; 36% Non-Hispanic Caucasian) who were recruited to participate in a lab experiment. Participants completed the boredom subscale of the Eating in the Absence of Hunger Questionnaire. Participants were guided through an 8-minute baseline, 24-minute food exposure, and 8-minute recovery period while HRV was monitored (J&J Engineering I-330-2 C2+6 Channel Biofeedback System). During the exposure, participants were presented with two foods (pizza, brownie, cinnamon roll) and were asked to look, smell, and imagine how the foods tasted. Mixed between-within subjects ANOVAs were conducted to assess the effects of food exposure and group (i.e., EE-B vs. non EE-B) on HRV components (LF, HF, SDNN). Transformations were performed to control for violations of normality. No significant interaction effects were observed. There was a significant main effect for group on LF (p = .02), Ln HF (p = .01), and Log SDNN (p = .02). As compared to non EE-B, people who endorsed frequent EE when bored exhibited greater increases in sympathetic activity and greater decreases in parasympathetic activity and autonomic flexibility in response to food cues.

Mesotelencephalic and Systemic Ghrelin Signaling in Operant Responding for Food

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Glucagon-like peptide-1 (GLP-1) and serotonergic (5-HT) receptor signaling have previously been implicated in the neural control of appetitive motivation. Specifically, treatment with the GLP1 analogue exendin-4 (EX4) or the 5-HT2c agonist Ro60-0715 suppresses operant responding for food reward. In contrast ghrelin administration increases food reinforcement. In the present study we examined the effects of Ro60-0175 and EX4 on operant responding for banana-flavored pellets, and further investigated the ability of Ro60-0175 and EX4 to attenuate ghrelin’s effects on food reinforcement. Male Sprague Dawley rats with guide cannulae aimed at the ventral tegmental area (VTA) were trained on a progressive ratio schedule (PR3) until intakes had stabilized. Rats were then injected with ghrelin (IP or VTA) or ghrelin paired with Ro60-0175 (IP) or EX4 (IP or VTA). All tests were conducted during the early nocturnal period. While ghrelin reliably increased operant responding for food compared to vehicle, both Ro60-0175 and EX4 pretreatment dose-dependently antagonized ghrelin’s action. Overall, our data provide additional support for an interactive role of ghrelin, serotonin, and GLP-1 in the mediation of food reinforcement.

Energy compensation and dietary learning: A study of Samburu pastoralists from North-Central Kenya.

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Flavour-nutrient learning (F-NL) is thought to influence both choice and intake of food. It occurs when an association forms between the orosensory properties of a food and its postigestive effects. Unfortunately, this process has been difficult to evaluate because F-NL is rarely observed in controlled studies of adult humans. One possibility is that learning is compromised by exposure to a complex Western diet. To test
this idea we explored evidence for F-NL in a sample of semi-nomadic pastoralists who are lean and who eat a very limited diet. Our Samburu participants (N= 68) consumed a sensory-matched portion (400g) of either a novel low (0.72 kcal/g) or higher (1.57 kcal/g) energy-dense semi-solid food on two training days, and an intermediate version on day 3. Before and after each meal we measured appetite and assessed expected satiation and liking for the test food. We found no evidence of F-NL. Nevertheless, self-reported measures were very consistent and, as anticipated, expected satiation increased as the test food became familiar. Surprisingly, we observed insensitivity to the effects of test-meal energy density on measures of appetite. To explore this further we repeated a single training day using participants (N= 52) from the UK. Unlike in the Samburu, the higher energy-dense meal caused greater suppression of appetite. These observations expose differences in sensitivity to the energy content of food and highlight interesting opportunities for cross-cultural work of this kind.

Neural & behavioral consequences of daily high-sugar juice consumption: An fMRI experiment.

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Mapping the neural and behavioral drivers and consequences of food intake are critical in understanding obesity, yet most data are observational. We used an experimental design including random assignment of novel juices paired with original logos that were consumed daily over a 3-week intervention in lean adults (n=19; BMI=22.2±1.6). Pre-/post-intervention we used fMRI to assess brain response to logo-elicited anticipation and juice receipt of both assigned and not assigned juices. We also assessed logo-specific go/no-go behavioral tasks and perceptual hedonic juice ratings. We observed decreases in ventromedial prefrontal cortex response (k=51; Z=4.3) during logo-elicited anticipation of the assigned juice (vs. not assigned) as a function of juice consumption during the intervention. Similarly, dorsolateral prefrontal cortex (k=32; Z=3.1) and caudate (k=28; Z=3.5) response during receipt of the assigned juice decreased (vs. receipt of not assigned juice) as a function of the intervention. Significant interactions between juice assignment and pre-/post-intervention were observed for ratings of desire to drink juice (p< .01) and reaction time responding to logos (p=.04). Namely, as a function of the intervention, there was a relative increase in desire to drink the assigned juice (vs. not assigned) and faster reaction times responding to the assigned logo (vs. not assigned). This study provides initial data indicating that regular intake of high-sugar juice causes specified decreases in neural & behavioral aspects of executive control, while functionally increasing perceived desire to consume that beverage.

PhosphoLean reduces impulsivity in heavy drinkers on a Go/No-Go Task

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Disrupted dopamine (DA) signaling in the dorsal striatum (DS) is associated with reduced inhibitory control over maladaptive behaviors like overeating and drug use. Acute administration of the fatty acid amide oleoelylethanolamine (OEA) in the gut increases DA levels in the DS and normalizes feeding behavior in obese mice (Tellez, 2013). OEA also decreases cocaine sensitization and conditioned place preference in mice (Bilbao, 2013). Thus, OEA may mediate both food and drug reward-related behaviors. We reasoned that in humans, OEA supplementation may increase DA signaling and reduce impulsive behaviors. 22 heavy drinkers were randomized to 3 weeks supplementation with PhosphoLean (PL) or placebo. PL is an approved dietary supplement containing the precursor of OEA, N-oleyl-phosphatidylethanolamine. Pre- and post-tests were performed to assess impulsivity and alcohol use. Though alcohol use did not change as a function of treatment, reduced alcohol intake was associated with improved sensitivity on a go/no-go task. Further, PL treatment significantly reduced false alarms (FA) on
this task. Go/no-go FA rate has been shown to correlate negatively with BOLD response to milkshake in the DS (Babbs, 2012), suggesting that improved performance after PL may reflect enhanced DS activity. In summary, extant data suggest that heavy alcohol use is associated with altered DA signaling in the DS that leads to increased impulsivity, and preliminary data suggest that this may be reversed by rescuing fatty acid derived gut-brain communication.

Membrane-initiated estradiol signaling transiently affects food intake in female rats.

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It is becoming increasingly clear that many of estradiol’s (E2’s) actions are mediated, at least in part, via membrane ERs (mERs). The current study investigated the potential involvement of mERs in mediating E2’s anorexigenic effect. Food intake was measured at 1, 2, 4, and 22 h after administration of a membrane delimited form of E2 (E2-BSA, i.c.v.), an ERa agonist (PPT, s.c.), and a G protein-coupled ER (GPER) agonist and antagonist (G1 and G36, respectively, s.c.) in ovariectomized (OVX) rats (n = 6-9 per group). The non-selective ER agonist E2-BSA produced a reliable but transient decrease in 1h food intake (veh: 3.1±0.2 g vs. E2-BSA: 1.6±0.5 g, p< 0.05). Food intake at the other time points was unaffected by E2-BSA. The selective ERa agonist PPT produced a dose-dependent decrease in 1h FI at low doses (10, 25, 50 mg, p< 0.05), which appear to preferentially activate mERa. Interestingly, higher doses of PPT (>75 mg) decreased food intake through the entire 12h dark phase. All doses of the GPER agonist G1 (0.5, 1, 5 mg) decreased 1h food intake (p< 0.05). G36 appears to be acting as a true GPER antagonist (rather than as a SERM with mixed agonist/antagonist effects) as it failed to alter feeding at all time points across a wide range of doses (1.25-20 mg). These findings provide evidence that membrane-initiated E2 signaling is sufficient to decrease food intake in OVX rats and that mERa and GPER may mediate this effect. (Support: DK073936 and FSU Neuroscience Fellowship). Keywords: ERa, GPER, feeding

Altered response to stress and sucrose licking microstructure in binge eating prone female rats

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Stress appears to be an important factor affecting feeding and women are especially susceptible to emotional and stress induced eating. Our goal was to characterize the licking behavior and stress axis activity in a model of stress-induced binge eating. Thirty adolescent female rats were submitted to a weekly schedule combining food restriction (2days/week), stress (1/week) and 2-h access to sucrose (3/week). After 5 weeks, rats were categorized as binge eating prone (BEP, n=12) and binge eating resistant (BER, n=11) based on the amount and consistency of sucrose intake after stress sessions. BEP displayed stress-induced binge eating since they increased their sucrose intake after stress in comparison to their control intake whereas BER drank similar sucrose quantities across conditions. Sucrose licking microstructure analysis showed that BEP demonstrated higher number of clusters of licks with decreased clusters’ size and duration and inter-cluster intervals when compared with BER. In the elevated-plus-maze, BEP rats showed increased duration and entries in the open arms as well as increased walking in this area. Additionally, the corticosterone response to stress was blunted in BEP compared to BER rats. In summary, BEP rats displayed more frequent, smaller and shorter clusters of licks during sucrose intake suggesting a compulsive-like behavior. According to the decreased anxiety-like behaviors and the blunted stress response of the BEP rats, a dysfunction of the stress axis may contribute to stress-induced binge eating in our model.
Effects of viscosity and nutrient load on gastric emptying as determined by MRI

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Our objective was to compare the relative contributions and interaction effects of viscosity and nutrient content on gastric emptying. 15 healthy males (age 22.6±2.4y, BMI 22.6±1.8kg/m²) participated in a randomized crossover study with four different 500mL shakes: different in viscosity (thick vs. thin) and/or nutrient load (100kcal vs. 500kcal). Subjects arrived in a fasted state. Gastric volume was determined using an MRI scanner. Subjects rated fullness and other appetite related feelings. Subjects consumed one of the shakes, after which they remained in the scanner for 1.5h and were scanned and provided ratings every 10min. The AUC for gastric volume for the four shakes were compared using a linear random effects mixed model. There was a significant interaction effect of viscosity and nutrient load (P< 0.019). Post hoc Bonferroni adjusted tests show that for thick and thin shakes nutrients have a significant effect (both p< 0.0001), but only with the 100kcal shake does viscosity have a significant effect (p< 0.0001, 500kcal p=0.286). For fullness we find only a significant effect of viscosity (p=0.001). We conclude that with increased nutrient load larger gastric volumes are found, indicating delayed gastric emptying time. Viscosity only significantly delays gastric emptying in a low calorie condition. Viscosity does significantly increase fullness ratings. Our results indicate that both viscosity and nutrient load influence gastric emptying, but nutrient load has more of an effect.

The Influence of Experimentally Manipulated Social Status on Eating Behavior: A Pilot Study

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Subjective social status (SSS) – i.e. self-perceived social standing – has been consistently associated with multiple health outcomes, including weight status, but the mechanism for this relationship remains unclear. The study objective is to investigate the effect of experimentally manipulated social status on ad libitum acute dietary intake and stress outcomes as a potential mechanism for the relationship between SSS and weight status. This is a randomized, crossover study design in Hispanic young adults (n=30; age 19-25; Body Mass Index ≥18.5 and ≤30 kg/m²). At visit 1, participants complete anthropometric measurements (weight, height, waist circumference) and questionnaires, consume a standardized breakfast, and are randomized to a high or low social status condition for a game of Monopoly™. Following the game, participants are given an ad libitum buffet lunch. Stress markers (blood pressure & visual analog scales) are measured throughout. Visit 2 is the identical protocol with participants exposed to the opposite social status condition. The primary outcome is dietary intake (total energy, dietary fat, & sugar) at lunch. We will evaluate the within-subject variation in dietary intakes between the two conditions. We hypothesize that participants will consume a greater amount of calories, fat, and sugar and demonstrate higher stress following the low vs. high social status manipulation.

Food choice in children: the past, the present, the future

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Child obesity arguably results from a long series of unfortunate food choices. First a child consistently chooses to consume more milk than is required for his metabolic needs, perhaps by sucking faster, or by crying for food more frequently. During early childhood he might opt for high rather than low energy-density foods, or to seek out food to provide comfort or pleasure. In middle childhood he might choose to consume a favorite food rather than to engage in other amusing activities, and in adolescence he might pick larger rather than smaller portions, or choose to spend time at fast food restaurants with like-minded peers. The terminology, particularly for young children, is moot – we might consider all of this ‘programming’ rather than choice. But the choice perspective highlights a number of classes of ‘event’ which one could target to send someone down a healthier weight trajectory. It also exposes the diversity of relevant internal and external factors, ranging from genetically-influenced appetitive and appetite-related characteristics and epigenetically-mediated food preferences, through neurobehavioral food and food cue responses that might perpetuate the process of weight gain, to externally-imposed behavioral nudges, achievable by subtle engineering of food micro-environments such as schools and homes, and collusion with influential peer models. In this talk I will review studies of child eating behavior and its influences from a choice perspective. I will also highlight knowledge gaps, suggest potentially fruitful directions for future research, and discuss the implications of what we already know for child obesity interventions.

Satiation and elective anorexia compared between ratio and interval schedules in mice

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We have reported an effect we named elective anorexia in which mice with restricted time of access to earn food (via nose pokes) at moderate costs per pellet (FUP) show satiation, thus anorexia and weight loss despite ample time to earn pellets. To further explore this effect, we now examine with finer temporal resolution (10-s) the satiation and responding within each meal opportunity, and compare with a fixed interval (FI) group in which the schedule limits eating rate. Male and female C57BL6 mice were used, but no sex difference was evident so data are presented combined. The FUP group (N=11) was tested for 4 days each at 2, 5, 10, 25, and 50 nose pokes per 20-mg pellet of grain-based food. The FI group (N=12) was tested for 4 days each at 10, 20, 30, 50, and 50-s delays following each pellet delivery, after which two responses acquire the next pellet. Each group had four 40-min opportunities to earn food, every 4-h throughout the night starting at 1800h. Food intake of the FUP group declined precipitously at FUP50; they tended to eat early in each meal opportunity and show satiation. In contrast, the FI group did not show elective anorexia, and spread their intake more evenly throughout the sessions. FI mice emitted more responses than required because they responded during the imposed delay (FI scallop), particularly at higher FI. The ratio of responses to pellets earned decreased monotonically throughout each meal and may be a novel behavioral index of satiation.

Disruption of endocannabinoid signaling decreases ingestive behaviors and curtails accumbal encoding of food related cues

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Endocannabinoids are involved in ingestive behavior and have been targeted therapeutically for disorders such as obesity and metabolic syndrome. Here we show that CB1 receptor signaling is crucial for dopaminergic encoding of food-associated cues. Voltammetric studies show that blocking CB1 receptors with the cannabinoid inverse agonist rimonabant decreases food consumption and this is accompanied by profoundly depressed accumbal dopaminergic encoding of cues. Conversely, raising tissue levels of
endocannabinoids potentiates food seeking. Next, we recorded the neural activity and local field potentials from the nucleus accumbens of rats engaged in food-maintained responding. Rimonabant administration at the beginning of the session greatly reduced food intake and was accompanied by a decrease in accumbal tonic firing rates and by a change in the firing patterns associated with reward delivery and with lever pressing behavior. A leftward shift in gamma power was observed, that might reflect a change in the balance of excitatory and inhibitory neuronal activity. The present results indicate that the endocannabinoid system plays an important role in sculpting patterns of neural activity related to ingestive behaviors.

**Subjective social status modulates evaluation and intake of high calorie foods**

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While animal research has suggested that low social status is associated with increased caloric intake, the influence of subjective social status (perceived access to resources, opportunities and respect relative to others) on human appetite remains unclear. We hypothesize that experiencing subjective feelings of lower status relative to others increases valuation and intake of calories. Three studies that experimentally induced feelings of lower (vs. higher) status supported this hypothesis. Feeling low status was predictive of stronger implicit associations of appetitive qualities with high-calorie foods (e.g., pizza, hamburger) over fruits/vegetables (Study 1, n=167). Lower cognitive restraint was predictive of higher calorie selections from a hypothetical buffet, but only among participants experiencing low status (Study 2, n=101). Furthermore, low subjective status was associated with greater caloric intake from snacks during a fixed time interval (Study 3, n=83). These results were independent of actual socioeconomic status and emotional responses to the status manipulation. We show that the mere perception of lower relative access to economic/social resources than others may stimulate selection and intake of greater calories. These findings suggest a contribution of social comparison processes to socioeconomic gradients in obesity/overweight.

**Enhanced glycolysis mediates the oleic acid (OA)-induced stimulation of glucagon like peptide 1 (GLP-1) secretion from enteroendocrine cells**

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GLP-1 is a potent satiating and incretin hormone released by enteroendocrine L-cells in response to eating. GLP-1 receptor agonists are used to treat obesity and type-II-diabetes. Dietary fat, in particular OA, potently stimulates the release of GLP-1 *in vivo* and *in vitro*. G-protein-coupled receptors and membrane bound fatty acid transporters are implicated in the OA-induced release of GLP-1. It is, however, unclear whether mechanisms related to intracellular fatty acid handling are also involved. To address this question, we metabolically characterized the enteroendocrine GLUTag cell line model using the Seahorse Extracellular Flux Analyzer and assessed GLP-1 release in parallel. OA (250 µM) potently stimulated GLP-1 release from GLUTag cells, enhanced mitochondrial oxidative phosphorylation (OXPHOS) and induced medium acidification, an indicator for glycolysis. To dissociate the different metabolic pathways, we inhibited either long-chain fatty acid oxidation using etomoxir, glycolysis using 2-deoxy-glucose (2DG), the import of pyruvate into the mitochondria using the specific inhibitor of the mitochondrial pyruvate carrier (UK-5099), and/or manipulated OXPHOS. Etomoxir reduced respiration, but did not affect the OA-induced GLP-1 release. In contrast, inhibition of the downstream steps of aerobic glycolysis reduced, and inhibition of the first step of glycolysis by addition of 2DG even abolished, the OA-induced
GLP-1 release. These findings suggest that an indirect stimulation of glycolysis is crucial for the OA-induced release of GLP-1.

The orexin/hypocretin antagonist SB-334867 impairs cue-induced feeding and increases Fos expression in prefrontal cortex and thalamus

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Orexin/hypocretin critically regulates cue-induced feeding. Here we examined the neuroanatomical location/s where orexin mediates this effect. 24 male, food-restricted, Long-Evans rats received training where a tone co-terminated with delivery of food pellets. Following 8 days of training, rats were allowed ad lib access to chow for 3-4 days. On test day all rats received a baseline test, consisting of free access to 14g of the food pellets in the conditioning chamber, followed by an i.p. injection of either the orexin 1 receptor antagonist SB (20mg/kg) or vehicle. 30 minutes following injection half of the animals received a cue test in the conditioning chamber consisting of tone-food presentations (VEH Cue: n=6, SB Cue: n=6). The other animals remained in home cages with no food as controls (VEH Home: n=6, SB Home: n=6). Rats were sacrificed following the cue test and brain tissue was processed for Fos induction as a marker of neuronal activation. During the cue test, SB Cue rats ate significantly less than VEH Cue rats (VEH: 3.3 ± 0.8g, SB: 1.2 ± 0.6g; p< .05). We observed a significant increase in Fos induction, specific to the SB Cue group, in three regions: the prelimbic area, the infralimbic area, and the anterior part of the paraventricular thalamus (ps< .01). Exposure to the cue test independent of drug treatment increased Fos in the anterior cingulate area, and the posterior basolateral amygdala (p< .01, p=.07 resp). These results suggest that orexin is acting through these cortical and thalamic areas to stimulate eating in a sated state.

Diet-induced obesity is associated with a change in the intestinal microbiota, activation of microglia, and reorganization of the nucleus of the solitary tract.

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We evaluated whether high fat diet alters gut microbiota, results in microglia activation, and reorganization of the NTS in Sprague Dawley rats. One group of rats was fed regular rodent diet (RD; 6.4% fat) and a second group received a high fat diet (HFD; 34.9% fat). At the end of the study the hindbrains were collected and stained using immunofluorescence methods. Samples of cecum, duodenum, and jejunum were collected for microbiome analysis. Microglia activation was determined using an Isolectin 4 antibody to label vagal afferents and by quantifying changes in the density of activated microglia stained with Iba1 antibody. We found that HFD-induced obesity triggered a shift in the intestinal microbiota. We observed an increase in Streptococcus mitis in the distal jejunum and an increase in Proteus mirabilis, Lactobacillus animalis, and Enterococcus faecalis in the caecum, as determined by 16S ribosomal sequencing. HFD-induced obesity resulted in withdrawal of vagal afferents and microglia activation in the intermediate NTS. Neural damage was observed when neurons were treated ex vivo with each of the bacteria as determined by fluorescence staining with beta III-tubulin antibody. Our results set the stage to address whether specific bacteria contribute to the disruption of vagal signaling and obesity.

Altered flavor-nutrient conditioning in obesity
Preferences are formed for flavors that predict the arrival of a nutrient into the gut. Whether this learning is altered in obesity is unknown. In the current study 17 healthy weight (HW) and 14 overweight (OW) participants were exposed to novel flavored non-caloric beverages before and after two flavors were repeatedly consumed. One contained 112.5 kcal from maltodextrin (CS+) and the other remained non-caloric (CS-). Flavor liking was rated before and after exposure. Brain response and willingness to work for the flavored beverages was also assessed following conditioning. Replicating prior work, liking ratings increased significantly for the CS+ but not the CS- flavor in the HW group. Liking ratings were unchanged in the OW group for CS+ and CS- flavors. We also observed a negative association between body mass index and willingness to work for the CS+ but not the CS- flavor. A direct comparison of brain response to the CS+ vs. the CS- in OW vs. HW groups revealed greater dorsolateral prefrontal cortex activation. Brain response to the CS+ vs. the CS- in HW vs. OW groups revealed greater fusiform gyrus activation. BMI was also positively correlated with response in the dorsal striatum to the CS+ vs. the CS-. These results show divergent effects of obesity on flavor preference formation, with blunted hedonic conditioning and enhanced neural response to calorie predictive cues.

Novel insights on the role of the endocannabinoid system in the regulation of energy balance

Endocannabinoid signaling through the cannabinoid type-1 (CB1) receptor plays a key role in energy balance regulation. By using conditional mutagenesis, our laboratory has studied the function of CB1 within the hypothalamus or in distinct hypothalamic neuronal populations. Our work has demonstrated that conditional deletion of CB1 in the adult mouse hypothalamus decreases body weight gain by increasing energy expenditure and thermogenesis, likely through increased sympathetic nervous system (SNS) activity. To then assess the role of CB1 in specific hypothalamic neuronal populations, we have generated mice lacking CB1 in steroidogenic factor 1 (SF1) expressing neurons, which are located in the hypothalamic ventromedial nucleus (VMN), or in Single minded 1 (Sim1)-positive neurons, which constitute the hypothalamic paraventricular nucleus (PVN). In chow, lack of CB1 in SF1 neurons decreases adiposity by increasing SNS activity and lipolysis, and facilitates the anorexigenic and metabolic effects of leptin. Conversely, under high-fat diet, it causes leptin resistance, blunts peripheral use of lipid substrates and increases adiposity. Thus, CB1 in SF1 neurons调节 metabolic flexibility and actions of leptin and provide a molecular switch adapting the organism to dietary change. In contrast, CB1 in Sim1-positive neurons do not impact energy balance in chow, but hinder energy expenditure via SNS inhibition in high-fat diet. Overall, these findings imply that the function of the CB1 receptor within the hypothalamus in the context of energy balance regulation is cell type- and diet-dependent.

Dissociation in leptin’s modulation of food intake versus thermogenesis in rats offered a high-fat high-sucrose diet

Leptin regulates distinct aspects of energy homeostasis. We here tested how exposure and subsequent withdrawal from a high-fat high-sucrose (HFHS) diet affected leptin’s regulation of food intake and thermogenesis. Exposure to a HFHS diet impaired leptin’s regulation of food intake, and leptin resistance
was maintained upon withdrawal from the HFHS diet. In contrast, decreased thermogenesis in HFHS withdrawal animals could be reversed by peripheral leptin injections, indicating a dissociation in the effects of leptin on core body temperature versus food intake during withdrawal. We hypothesize that this could be explained by differences in leptin sensitivity of key hypothalamic nuclei regulating food intake and thermogenesis following HFHS diet exposure, and are currently testing this by performing pSTAT3 stainings. In support of this, we discovered that restoring leptin signaling specifically in the dorsomedial hypothalamus (DMH) is sufficient to normalize the reduced thermogenesis caused by HFHS diet withdrawal. In addition, inhibition of leptin signaling in the DMH reduced thermogenesis and promoted adiposity independent of food intake. Leptin’s effect on thermogenesis was regulated by neuronal projections from the DMH to the lateral/dorsolateral periaqueductal grey areas. Together, these data indicate that exposure and subsequent withdrawal from a HFHS diet differently modulates leptin’s regulation of food intake and thermogenesis.

Loss of cocaine- and amphetamine-regulated transcript in vagal afferent neurons drives hyperphagia and weight gain

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Cocaine and amphetamine regulated transcript (CART) is an anorectic neuropeptide transmitter. In vagal afferent neurons (VAN) CART is co-expressed with CCK1-receptors, and its expression changes in response to feeding status; low after fasting and high after a meal. We have recently demonstrated that the release of endogenous CART from VAN into the NTS is required for satiation. We hypothesized that the development of diet-induced obesity occurs as a result of loss in CART mediated gut-brain signaling.

Methods: Immunohistochemistry and Enzyme-linked Immune Assay were used to determine CART abundance in VAN of rats chronically fed chow or 45% high fat (HF) diet. Cannulas implanted into the NTS were used to inject CART antibody to block endogenous CART in the NTS of fed and fasted lean or HF-induced obese rats. Finally, we knocked down CART in VAN by performing bilateral nodose ganglia injection of lentiviral–mediated CART shRNA. Results: CART immuno-positive VAN and CART protein concentration in nodose ganglia were reduced postprandially in HF vs chow-fed rats. CART antibody injected into the NTS failed to increase food intake in ad libitum HF- vs chow-fed rats. CART KD in VAN increased daily chow intake, due to an uncompensated increase in meal size, and increased 4 week postsurgery weight gain compared to control rats. Conclusion: HF feeding blunts postprandially induced CART synthesis. Loss of CART in VAN is sufficient to induce hyperphagia and weight gain.

Obesity-Prone Rats Show Enhanced Cue-triggered Food Seeking

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While the decision to seek out food can be controlled by endogenous hunger signals, it can also be influenced by external Pavlovian cues that predict food availability. Human studies suggest that enhanced sensitivity to food-cues may promote obesity and hamper weight loss is susceptible individuals. Here, we asked whether obesity-prone and obesity-resistant rats differ in cue-driven food-seeking in the absence of overt obesity. We used a Pavlovian-to-instrumental transfer (PIT) procedure to assess the motivational strength of food-associated cues in their ability to invigorate food-seeking behavior. First, rats were trained to lever-press for food (active/inactive levers). Next, they received 8 Pavlovian training sessions where one cue (CS+) was paired with the delivery of food pellets and another cue (CS−) was presented with no consequence. During PIT testing, no food was available, rats had continual access to the levers, and each CS was presented 4 times in a pseudo-random order. PIT was demonstrated by an enhanced elevation in
responding on the active lever in the presence of the CS+ as compared to the CS-. During PIT testing, obesity-prone rats showed enhanced conditioned magazine approach during CS+ presentations and expressed strong and more persistent PIT. In contrast, PIT was nearly absent in obesity-resistant rats. Inactive lever pressing was consistently low throughout testing. These data show that individual susceptibility to obesity is linked with pre-existing differences in the attribution of motivational significance to Pavlovian food-cues and may point to the role of altered mesolimbic reward circuits in the development of obesity.

Dopaminergic dysfunction, food intake, and physical activity in diet-induced obesity

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Nearly two-thirds of adults in the United States are overweight or obese. Physicians generally advise patients to “eat less” and “move more” to combat weight gain and metabolic syndrome. However, it is unclear why individuals consume more calories than they burn. The striatal dopamine system has been linked to compulsive food intake and obesity, as well as the regulation of movement. To better understand the role of diet, physical activity, and dopaminergic function in the etiology of obesity, we placed male C57BL/6 mice on a long-term high-fat diet alongside weight-matched controls that remained on chow. Food intake, body composition, and physical activity were periodically measured in both groups. Striatal dopamine content and dopamine D2 receptor (D2R) binding were measured at multiple time points during the diet. On the high-fat diet, mice increased their caloric intake and decreased their physical activity, compared to the chow controls. The mice on the high-fat diet also had decreased D2R binding, suggesting that striatal D2Rs may play a role in both food intake and physical activity. However, in a multiple regression analysis, we found that caloric intake was a better predictor of weight gain than physical activity. We conclude that obesity is associated with alterations in dopaminergic function that can affect both diet and physical activity. However, changes in diet play a larger role than changes in physical activity on weight gain.

An open source operant conditioning chamber

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The operant conditioning chamber is a cornerstone of animal behavioral research. Operant boxes test learning and motivation in animals, particularly for food reward. However, commercial operant chambers can cost several thousands of dollars. We have constructed an inexpensive and easily assembled open-source operant chamber based on the Arduino microcontroller platform that can be used to train mice to respond for a reward. The apparatus contains two nose pokes, a drinking well, and a solenoid-controlled sucrose delivery system. The chamber can easily run fixed ratio and progressive ratio training schedules, and can be programmed to run more complicated behavioral paradigms. Additional features, such as coordinate and video tracking, can be easily added to the operant chamber through the array of widely available Arduino-compatible sensors. The chamber’s design files and programming code are open source and available online for others to use.

Association among Social Status, Eating Behavior, and Metabolic Efficiency
Low social status animals prefer higher energy density foods, are more metabolically efficient, and have greater fat stores relative to high social status animals. These traits may occur to ensure survival in response to the perception of an inadequate or scarce food supply. Correspondingly, food insecurity is paradoxically associated with obesity in humans, and low social status is associated with obesity. However, it is unknown whether social status is associated with eating behaviors and metabolic traits involved in the development of overweight and obesity in humans. Our objective is to determine the association of social status with eating behaviors and metabolic traits involved in weight gain. We hypothesize that low social status is associated with lesser tendency to compensate for large meals, greater metabolic efficiency, and greater fat storage. We will measure social status and the response to a 14-day feeding protocol of daily large lunches (60% of energy requirements) in 20 Caucasian overweight adult women. Food intake will recorded using the Remote Food Photography Method to measure compensation for the daily meal, and changes in resting energy expenditure and body fat stores over the 14-day period will be measured. Data collection is currently in progress and results are pending. This experiment will serve as a foundation for further study of the relationship between social status and susceptibility to weight gain.

Body weight is related to striatal response to predicted, but not unpredicted milkshake receipt and this relationship is not influenced by baseline cerebral blood flow.

One of the most consistent findings in the neuroimaging of obesity is a negative association between blood oxygenation level dependent (BOLD) response to palatable milkshake (MS) in the dorsal striatum (DS) and body mass index (BMI) (Stice et al., 2008, Green et al., 2011, Babbs et al., 2013). However, the extent to which this association is influenced by relationships between BMI and baseline brain metabolism is unknown. The BOLD signal relies on the magnetic susceptibility of blood deoxyhemoglobin that allows inferences about neuronal activation. However, the signal is relative and not individually quantitative. Therefore, individual differences in cerebral blood flow (CBF) due to high body weight might influence BOLD response. To test this hypothesis we scanned 34 participants using a combined BOLD and pulsed Arterial Spin Labeling protocol. Replicating prior work, we found that DS response to MS correlated with BMI. This association was especially strong in the obese, suggesting brain adaptations in the DS is a consequence of weight gain. Resting CBF did not influence this relationship, indicating that the effect of BMI on CBF cannot account for the association between MS-evoked response and BMI. Interestingly, we observed these associations only when subjects tasted MS that was predicted. No associations were observed between BMI and DS response to the receipt of unpredicted MS.

Children’s attraction to sweetness and its impact on eating behavior

WHO new guideline recommends reducing free-sugar intake to less than 10% of total energy intake (TEI) in children (2015). Is it realistic given children’s attraction toward sweetness? The present study was designed to characterize children’s attraction to sweetness and to assess whether it impacts their eating behavior. French children aged 7 to 10 (n=36) came 3 times to the laboratory. We measured their sweetness
liking optimum (SwLik) for 3 food products varying in sugar content, their level of liking for sweet vs. salty snacks (SwPref) and their motivation to gain sweet vs. salty rewards (SwMot). During a free-choice buffet, food choice (sweet vs. non-sweet foods; SwChoice) and simple sugar intake (SwIntake) were assessed. Results showed that SwIntake during the buffet was high, 29±2.1% of TEI; however, no difference of motivation was observed between sweet or salty rewards (p=.45) and liking was higher for salty compared to sweet snacks (p<.05). SwPref was significantly associated with both SwChoice (R=.61; p=.0001) and SwIntake (R=.54; p=.001) during the buffet. SwMot was associated with SwIntake (R=.35; p<.05) but not with SwChoice (R=.21; p=0.23). SwLik was associated with neither SwChoice (R=.16; p=.37) nor SwIntake (R=-.03; p=.87). The different criteria used to evaluate sweetness attraction do not systematically predict behavior. But when children are provided with a large choice of foods containing sugar, their simple sugar intake is high and well above the WHO recommendation for free sugars. This may imply that food offer have more impact on sugar intake than sweetness liking.

Benefits of a school based nutrition-intervention program in Appalachia: Parent reports and student outcomes.

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A 12-week nutrition intervention program was implemented in 16 second-grade classrooms in SE Ohio. Students and parents completed an assessment of nutrition knowledge and feeding practices (Child Feeding Practices Questionnaire). Children were instructed with an age-appropriate nutrition curriculum (Live Healthy Kids, Athens, OH) and hands-on preparation of themed recipes. Parents and children completed assessments at the completion of the program. Children showed marked improvement in their knowledge of food categories, MyPlate, and willingness to try new things. Parent reports showed no significant changes in feeding practices, but qualitative analysis indicated that parents did purchase “new” foods (i.e., oatmeal, legumes) based on their children’s enthusiasm about the in-class recipes. These data support the efficacy of brief nutritional programming in rural elementary schools.

Blunting of HPA stress responses by sucrose varies between male and female rats

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Many individuals consume highly palatable foods during stress, possibly because they provide stress relief. To study the mechanisms by which such ‘comfort’ food intake reduces stress responses, we previously developed a model of limited sucrose intake (LSI) that reduces HPA activation in adult male rats. However, both men and women use ‘comfort’ foods for stress relief. Thus, the present work asks whether LSI also reduces HPA activation in female rats. Adult female Long-Evans rats (n=25-26/group) with ad libitum chow and water were given twice-daily brief (< 30 min), limited (4 ml, 8 ml/day) access to a 30% sucrose drink vs. water (as a control) for 14d. On d15, rats were given a restraint stress and blood samples were collected to measure plasma ACTH and corticosterone. As seen previously for males, sucrose-fed females drank nearly all the sucrose they were offered, and reduced their chow intake, resulting in no difference in body weight or adiposity relative to water-fed controls. Restraint increased plasma ACTH and corticosterone in females, and this HPA activation did not vary with drink type (water vs. sucrose), nor stage of estrous cycle. Taken together, these results suggest that while female rats have behavioral/metabolic responses to LSI that are comparable to males, they do not exhibit a similar stress relief – implicating an important sex difference in stress relief by ‘comfort’ foods. Future work can address whether females require larger amounts of sucrose for HPA-blunting, or whether another type of palatable food (e.g., high-fat) is more effective in females.
Role of Anxiety in Inhibitory Control Deficits in Eating Disorders

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Eating disorders (ED) are complex psychiatric disorders, associated with alterations in neural and cognitive functioning. Research suggests inhibition deficits in BN, but less is known about the persistence of these deficits after recovery, or their relationship to comorbid psychiatric symptoms. Women aged 19-45 recovered from anorexia nervosa (RAN, N = 28), bulimia nervosa (RBN, N = 14), or both (RANBN, N = 20), and controls (CW, N = 26) completed the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (CWIT). It was hypothesized that RBN, and those with higher State-Trait Anxiety Inventory (STAI) scores would demonstrate worse Inhibition task performance than other groups. CWIT Ratio scores were calculated to control for processing speed. Linear regression analyses show past diagnosis does not predict Inhibition scores ($p = 0.08$), while a history of any ED is predictive ($\beta = 0.25$, $t(86) = 2.37$, $p = 0.02$). Elevated State Anxiety ($\beta = 0.22$, $t(85) = 2.08$, $p = 0.04$) was independently predictive of worse Inhibition scores across all groups; Trait Anxiety was not. Among those with an ED history, a model including State Anxiety and diagnosis revealed a significant independent effect of State Anxiety ($\beta = 0.33$, $t(62) = 2.31$, $p = 0.02$), but not of diagnosis nor their interaction. History of ED may be linked to inhibitory deficits, which may be influenced by anxiety. Consistent with other research, results suggest that anxiety may be a transdiagnostic predictor of impairment among ED individuals. Future research is warranted to elucidate the nature of neuropsychological deficits in ED.

Galanin is upregulated by acute high fat diet intake

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Recent evidence identifies the hippocampus and its connections with other brain regions as key in the regulation of food intake and the development and consequences of obesity. High fat diet (HFD) intake, an important factor in obesity, has been extensively examined in chronic consumption models, but few studies have explored the acute response to HFD intake. In this study, male rats were fed either a control diet (10% fat) or HFD (45% fat) for 72 hours, after which serum and tissues were collected and weighed. Brains were processed for qRT-PCR and immunohistochemistry. Acute intake of HFD resulted in higher serum levels of leptin and cholesterol, with no significant changes in final body weight or adipose tissue mass. qRT-PCR results showed alterations in transcript levels of galanin, galanin receptors, and brain-derived neurotrophic factor, as well as histone deacetylase and histone acetyltransferase enzymes. The most significant finding was an increase in galanin transcripts in both the dorsal hippocampus and prefrontal cortex. Results from immunohistochemistry validate a strong presence of the galanin peptide in the CA1/CA2 region of the dorsal hippocampus. These findings provide evidence for a role for hippocampal and cortical galanin in the acute response to HFD.

Children’s neural response to food images that vary in portion size

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Previous neuroimaging studies have identified brain regions that respond to variations in food energy content, but have not investigated neural response to portion size (PS). We used fMRI to test the neural response to images of foods ranging in energy density at two levels of PS (large and small) using a block design. Children (n=36; age 7-10 y) were scanned during a neutral appetitive state. Repeated measures ANOVA was used to compare differences in BOLD activation in regions-of-interest for the contrast of Large > Small PS. We hypothesized that larger portions of food would be associated with greater activation in regions involved with reward (mesolimbic circuitry), decision-making (prefrontal cortex), and spatial integration (temporal lobe structures) compared to smaller portions. Results of the Large > Small contrast showed increased activation bilaterally in the inferior frontal gyrus (IFG) (p< 0.05). Trends for increased activation in response to Large > Small PS were found in the cingulate, OFC, parahippocampal gyrus, insula and striatum (p< 0.10 for all). The main effect in the IFG, a prefrontal cortex sub-region, suggests children exert greater inhibitory control when faced with large portions. Trends in the insula, striatum, and OFC imply that larger portions of food may be associated with increased reward signaling. Our results link food images of large portions to bilateral activation in brain regions involved in decision-making, which may have implications for moderating energy intake via inhibitory control.

Neural response to images of food varying in energy density is associated with body composition in children

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Previous studies in children have demonstrated that homeostatic and reward regions of the brain are responsive to visual food cues. We examined fMRI BOLD activation to images of foods varying in energy density (ED) and scrambled control images in 36 children (age 7-10 yr). The objective was to determine if activation to High and Low ED foods was correlated with body composition. Repeated measures ANOVA was used to test the effect of ED (High vs Low) for activation in regions of interest (ROIs) previously associated with food reward and energy homeostasis. There was an effect of ED (p< 0.05) for activation in the substantia nigra (Low > High ED), anterior cingulate gyrus (High > Low ED), and thalamus (High > Low ED). Activation in ROIs for specific contrasts (High ED > Low ED, High ED > Control, Low ED > Control) was then correlated with fat-free mass index (FFMI, kg/m²), fat mass index (FMI, kg/m²) and % body fat (%BF). In the substantia nigra, FFMI (r=0.42, p<0.05) was positively associated with activation for the High ED > Low ED contrast, while FMI (r= -0.38, p<0.05) and %BF (r= -0.40, p<0.05) were negatively associated with activation for the Low ED > Control contrast. The positive association between FFMI and neural response to images of food supports literature on FFM as an appetitive driver. In addition, greater adiposity may be related to a reduced reward response to Low ED foods. Our results suggest that the reward response to foods varying in energy content may be influenced by child body composition.

Oleylethanolamide (OEA), an anorectic agent with potent motor side effects

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The endogenous PPAR-α agonist OEA inhibits eating in rats and stimulates fatty acid oxidation (FAO). How activation of PPAR-α is translated into a signal to the brain is still unclear. Because vagal afferents are not crucial for the eating-inhibitory effect of OEA, afferent spinal nerves may be involved. We here
performed a celiac-mesenteric superior ganglionectomy (CGX) in adult, male SD rats to disrupt the GI-brain communication via splanchnic fibers. Animals received intraperitoneal (IP) infusions of OEA (10 mg/kg) or vehicle and food intake was recorded. CGX antagonized the prolongation of the latency to eat (p < 0.01), but not the reduction of cumulative food intake by OEA, suggesting that spinal afferents are only partly involved in OEA’s effect on eating. In further experiments, OEA (10 mg/kg) did not induce a conditioned avoidance reaction, but caused abdominal writhes, immobility, and abdominal stretching. Also, when tested in the Open Field, OEA (1, 5 or 10 mg/kg) dose-dependently impaired locomotor activity. To test whether the OEA effects on motor activity and eating are related, we treated the rats with the dopamine receptor agonist quinpirole (1 mg/kg) 1 h prior to OEA (10 mg/kg) infusion. The latency to eat was reduced in animals injected with quinpirole compared to saline (p < 0.05). Independent of the possible involvement of the dopamine system in the OEA-induced immobility, our findings strongly argue for a cautious approach regarding the mechanistic interpretation of OEA’s anorectic effect.

Dieting history and satiety interact to affect food cue responsivity: an ERP study

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A history of weight loss dieting has been shown to be a robust predictor of future weight gain, although the mechanisms responsible for this relationship are unclear. One potential factor in propensity towards weight gain is the nature of people’s reactions to the abundance of palatable food cues in the environment. Event Related Potentials (ERPs) are unique in their high level of temporal detail, providing information about immediate preconscious, as well as sustained, neural activity. They have been used to measure response to food cues, however ERP differences based on dieting history have not been tested. The present study examined ERP response to moderately and highly palatable food images in 65 young adult, non-obese female historic dieters (HD) and never dieters (ND). ERPs were recorded in both a fasting and a fed state. The effects of hunger and dieting history were tested on the mean amplitude of 7 epochs ranging from 50-800ms following stimulus presentation. A significant dieting history by hunger state interaction was found in early visual (P1, N1, N2), and late (P3, LPP) ERP components. While ERP response to food cues was largely unaffected by hunger among HD, ND had larger early and late mean amplitudes in the fed than fasting state. Results support prior research suggesting that individuals prone to weight gain are more responsive to external than internal cues to eat. Future research should examine whether ERP food cue response is associated with future weight change, with the ultimate objective of better identifying those who would most benefit from obesity prevention programs.

Gastrointestinal (GI) contributions to energy intake and GI symptoms in humans

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Throughout his research career, Harry Kissileff has made major contributions to a wide range of aspects within the field of ingestive behavior. Many of his studies were directional for much further subsequent research, within our field, and, importantly, also beyond. Aspects of his work that have most markedly influenced my own research and thinking relate to the effects of gut hormones, particularly CCK, on energy intake, the interaction of signals arising from the stomach and small intestine, and the “sensitizing” effect of CCK on the stomach. The latter concept has not only provided important, and novel, insights into how GI signals (eg. gastric distension and CCK) interact to modulate subjective appetite perceptions, incl. fullness, but also laid the foundation for an appreciation of the role of altered GI sensitivities, eg. underlying the induction of GI symptoms in functional dyspepsia (a condition characterised by symptoms, incl. bloating, nausea and early fullness, amongst others, after meals, particularly those high in fat, in the
absence of any structural or functional abnormalities in the GI tract), or as a consequence of excess dietary intake in obesity. This presentation will discuss the effects of dietary nutrients, particularly fatty acids, on GI function, and associated effects on appetite perceptions and energy intake, effects of interactions of GI stimuli, as well as the role of altered GI sensitivities (exaggerated, or reduced) in eating-related disorders, particularly functional dyspepsia and obesity.

Pre-existing and diet-induced alterations in nucleus accumbens function in preclinical models of obesity.

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Alterations in mesolimbic circuits particularly within the NAc may contribute to obesity. However, few studies have examined potential pre-existing versus diet-induced alterations in NAc function in preclinical obesity models. Medium spiny neurons (MSN) in NAc receive convergent glutamate and dopamine input. AMPARs provide the main source of excitation to the NAc and repeated activation of dopamine systems can enhance AMPAR-mediated transmission. Here, we used selectively bred obesity-prone and obesity-resistant rats (Levin et al., 1997) to examine pre-existing differences in NAc MSN function (electrophysiology) and mesolimbic circuits (cocaine-induced locomotion), and used outbred rats identified as susceptible or resistant to obesity to examine effects of “junk-food” diet exposure. We found enhanced intrinsic excitability and responsivity to cocaine induced locomotion in obesity-prone vs. obesity-resistant rats without diet manipulation. Intrinsically excitatory is influenced in part by dopamine receptor activation. Likewise, cocaine induced locomotion relies on dopamine transmission from VTA inputs to the NAc. These data suggest that NAc function, and possibly organization, are altered prior to obesity. In addition, after junk-food exposure, transmission via NAc calcium-permeable AMPARs was enhanced only in obese rats. These data suggest that interactions between pre-existing differences and experience may influence subsequent plasticity within the NAc. Data will be discussed in light of the role of the NAc in food-cue-triggered motivation and their contribution to obesity.

Medical Marijuana: A Feeding frenzy

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While marijuana use has been associated with effects ranging from violence to creativity to the “munchies,” the scientific evaluation of such effects has been sparse. We have published over 45 papers on the effects of marijuana and THC. In most studies, research participants lived in a residential laboratory which allowed for careful monitoring of eating behavior. Early studies with individuals who regularly smoked marijuana showed that smoked marijuana significantly increased total caloric intake due to greater snacking behavior. Marijuana specifically increased consumption of sweet solid snack foods. The effects of marijuana on eating behavior were influenced by the time of day, social activity and available foods. Recent studies confirmed that even in daily smokers marijuana or oral THC increased total caloric intake. Oral THC also increased food intake in marijuana smokers who were HIV+, but only in those with a low body mass. In all groups, body weight increased on days when marijuana was smoked, and caloric intake and body weight decreased on placebo smoking days. We also demonstrated that daily marijuana smoking produces physical dependence and marijuana abstinence produces clinically significant withdrawal signs including decreased food intake. Of note, other than the HIV+ participants, data were collected in normal weight marijuana users. Smoked marijuana and oral THC may be used to temporarily increase caloric intake, but its use should be limited to individuals experienced with the subjective effects of those products to limit adverse effects, and long-term use is to be avoided as the products produce physical dependence.
How Does Calorie Information Affect Women’s Food Choices and Intake?

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Research has shown that women choose lower calorie options when provided with menus that include the caloric content of foods (Gerand, 2009). The goal of this study was to assess the healthfulness of college women’s food choices and their intake when provided with menus containing healthful and unhealthful foods that were either high or low in caloric content. Ninety six female undergraduate students were assigned to receive either a calorie menu \((n = 54)\) that contained the caloric content of the foods, or a no calorie menu. Each menu contained eight foods and four beverages that ranged in healthfulness and caloric content. Participants were asked to choose two foods and one beverage from the menu as a snack. Preliminary results revealed that those who received a calorie menu chose less caloric foods \((p < 0.02)\) and as a result, consumed fewer calories \((p < 0.05)\). However their choices were less healthful \((p = 0.05)\) in that they contained fewer nutrients. That women are willing to sacrifice the healthfulness of their food choices to reduce caloric intake suggests that providing the caloric content of foods may have unexpected health consequences.

The Unique Contributions of Episode Size and Loss of Control Eating in Purging Syndromes

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The importance of loss of control (LOC) eating has been examined across both DSM-5 binge episodes and binge episodes that are too small to meet DSM-5 criteria. This approach is useful in understanding what is associated with the experience of LOC, but it ignores pathology that may be uniquely associated with eating episode size. The present study examined the unique correlates of eating episode size and LOC in a sample of 244 women with purging syndromes (bulimia nervosa \(n=141\); purging disorder \(n=101\)) across whom both size and LOC of eating episodes varied dimensionally. Validated interviews and questionnaires were administered as part of four studies. In regression models controlling for parent study and episode size, LOC eating was associated with eating disorder severity \((\beta=.22, p<.01)\), disinhibition around food \((\beta=.51, p<.01)\), hunger \((\beta=.44, p<.01)\), shape concerns \((\beta=.26, p<.01)\), depressive symptoms \((\beta=.35, p<.01)\), trait anxiety \((\beta=.30, p<.01)\), negative urgency \((\beta=.53, p<.01)\), and impairment \((\beta=.39, p<.01)\).

Controlling for parent study and LOC eating, episode size was associated with disinhibition \((\beta=.23, p<.01)\), trait anxiety \((\beta=.15, p=.02)\), and impairment \((\beta=.26, p=.03)\). Results suggest that both episode size and LOC represent informative dimensions in understanding eating pathology across purging syndromes, supporting the DSM-5 definition of binge episodes. Future research should examine predictive validity of episode size and LOC.

Sex Differences in Demand for Highly Palatable Food Rewards: Role of Orexin Neurons

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Demand is a measure of reward consumption as a function of reward price – the effort required to earn a reward. Recent studies (including ours) have found that orexin signaling is involved in responding for highly salient rewards, particularly during high effort (Cason & Aston-Jones 2012). Furthermore, orexin is
sexually dimorphic: female rats have higher pre-pro orexin mRNA, orexin A protein and orexin-1 receptor mRNA in hypothalamus than males (Johren et al 2001; Johren et al 2002; Taheri et al 1999). Here we used a within-session behavioral economics (BE) approach recently developed in our laboratory (Bentzley et al, Psychopharmacology 2013) to evaluate the role of orexin signaling in demand for a highly palatable food reward (HPF). With this method, an entire demand curve (consumption as a function of effort) is generated in each session, allowing for comparisons of demand following different manipulations. In the current study, demand for a low-fat, a high-fat, and a sucrose HPF were evaluated in male and female rats. Female Sprague-Dawley rats revealed increased motivation (lower demand elasticity) for the low-fat, high-fat and sucrose (chocolate-flavored) HPF compared to males. Furthermore, administration of an orexin 1 receptor antagonist SB 334,867 (SB) prior to the BE session resulted in decreased demand for all three rewards in male and female rats. These results indicate sex differences in mechanisms that drive reward motivation for high fat and sucrose rewards that should be evaluated in future studies.

Shades of white: the regulation of fat distribution and function

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Research over the past two decades revealed that adipocytes are highly active endocrine cells that integrate systemic metabolism through the secretion of adipokines and metabolic fuels. In addition, adipocytes from anatomically distinct depots of exhibit depot- and sex-dependent differences in metabolic and endocrine functions. Understanding depot-dependent determinants of adipose tissue growth and function is important because the mass of both the visceral and abdominal subcutaneous (sc) depots is associated with deleterious metabolic consequences, while the mass of lower body (gluteo-femoral) sc adipocytes has protective effects. Our studies of the transcriptome of mouse and human ‘white’ adipose tissues show depot differences, most notably in the expression of developmental genes, and some sex-dependent differences in metabolic and immune genes. These distinct developmental roots appear to confer cell-autonomous functional properties upon both preadipocytes and adipocytes from different sc depots, supporting the old proposition that ‘not all adipocytes are alike’. Studies of cultured human preadipocytes show clear that depot differences in differentiation capacity and fat accumulation are cell-autonomous. In addition, experiments in mice show that transplant of female compared to male subcutaneous adipose tissue to male recipient tends to improve metabolism. It is tempting to speculate that in addition to their capacity to efficiently store lipid, a secretory product of female lower body sc adipocytes directly improves metabolic health.

Inhibition of c-Jun N-terminal Kinase Suppresses Feeding and Reduces Body Weight

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c-Jun N-terminal Kinase (JNK), a stress kinase, is involved in a variety of biological processes. The roles for JNK in the regulation of energy homeostasis are unclear. We explored the roles of JNK in the control of food intake and body weight by use of a potent, selective and brain-penetrant pan-JNK inhibitor, SR3306. In C57BL/6 mice maintained on chow diet, a bolus intraperitoneal (i.p.) injection of the compound, at 30mg/kg, led to reduction of food intake as well as decreases in fat mass and body weight. A pair-feeding study further showed that the weight loss effect was entirely accounted for by the reduced food intake. Importantly, the conditioned taste aversion test showed that the anorectic action following SR3306 treatment was not due to compound toxicity. The potential central actions of JNK were also assessed. Similar to the findings by systemic treatment, a bolus intracerebroventricular (ICV) injection of the compound (15μg) reduced food intake, fat mass and body weight. Thus, the activity of JNK in the CNS appeared to mediate the anorectic actions of JNK inhibition. We also assessed the effects of SR3306 on
mice fed with 60% kcal fat diet (high-fat diet). Daily i.p. injection of the compound (30mg/kg) for 8 days decreased high-fat diet intake, and markedly reduced body weight gain. Collectively, the data demonstrate that inhibition of JNK activity exerts an anorectic effect and reduces body weight. The results suggest that JNK is implicated in the regulation of body weight homeostasis. The compound SR3306 is a potential therapeutic tool in preventing or treating obesity.

Do distracted mothers overfeed their infants?

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Mindless eating, or eating while distracted, leads to overeating. The present study explored whether "mindless feeding," or maternal distraction during bottle-feeding, is associated with higher infant formula/milk intake and lower maternal sensitivity to infant cues. Mothers and their ≥24-week-old infants (N=28) visited our laboratory for a video-recorded feeding observation. Intake was assessed by weighing bottles before and after the feeding. Sensitivity was assessed using the Nursing Child Assessment Feeding Scale. Distraction was defined as looking away from the infant for >75% of the feeding, using a mobile device, interacting with another adult, or sleeping. Mothers completed a measure of infant temperament. Twenty-nine percent of mothers were distracted. While intake differences for infants of distracted vs. not distracted mothers did not reach significance (p=.24), this association was modified by two temperament dimensions: regulation capacity (p=.03) and surgency (p=.04). For infants with low regulation capacity, infants of distracted mothers consumed more (177.1 ± 33.8ml) compared to those of not distracted mothers (92.4 ± 13.8ml). Similar findings were noted for infants with low surgency (distracted: 140.6 ± 22.5ml vs. not distracted: 78.4 ± 14.3ml). No association was seen for infants with high regulation capacity or surgency. A significantly greater proportion of distracted mothers showed low sensitivity compared to not distracted mothers (p=.04). In sum, distracted bottle-feeding may lead to poorer feeding outcomes; further research using experimental designs is needed.

**Regulation of food intake by leptin receptors located in the raphe nuclei**

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Many studies performed to define the circuitry used by leptin to regulate appetite and energy expenditure agree that leptin controls these functions acting through hypothalamic receptors. However, recent reports have examined the participation of extra-hypothalamic leptin receptors, including those located in the midbrain raphe nuclei, upon food intake regulation. While these studies have provided somewhat equivocal results regarding the regulation of feeding behavior by the raphe leptin receptors, we hypothesize that the leptin receptors expressed in the raphe regulate food intake. Our studies show that leptin (5ug/rat) infused directly into the raphe of adult male rats rapidly inhibits food intake in a robust manner that is comparable to i.p. leptin administration. In addition, this inhibition can be blocked by knocking-down the leptin receptor expression in the raphe. Double labeling immunohistochemistry reveals that the majority of the leptin-responsive neurons in the raphe are serotonergic, and serotonin depletion eliminates the ability of intra-raphe leptin infusion to inhibit food intake. Lastly, we expressed the light sensitive channelrhodopsin under control of the leptin receptor promoter in the raphe, and used optogenetics to show that selective activation of these neurons inhibits food intake. Collectively, these data demonstrate that activation of the raphe leptin receptors inhibit food intake, and suggest that this effect is possibly mediated by serotonin.
Neuropeptide Y in the lateral hypothalamus specifically increases carbohydrate intake when rats are fed a free-choice high fat high sugar diet

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Neuropeptide Y (NPY) plays a prominent role in feeding behavior and we previously showed that when injected in the lateral ventricle, rats increase chow and lard when having the choice between chow, lard and liquid sugar. Interestingly others reported that NPY when injected in the 3rd ventricle stimulates carbohydrate but not fat intake. We therefore hypothesized that NPY injected directly in the lateral hypothalamus (LH) increases intake of chow and sugar and not lard when rats are provided the choice. Male rats were fed a CHOW (chow & water) or a free choice high-fat high-sugar (fcHFHS; chow, lard, 30% sugar & water) diet. After 1 week, rats were infused with vehicle, 0.3µg or 0.6 µg NPY in LH in a cross-over design. Food intake was measured after 2 hours. NPY injections into the LH of fcHFHS diet fed rats (N=6) increased intake of chow (3.40±1.13, p< .05) and sugar (1.84±0.81, p< .05) after 0.3µg NPY, and intake of chow (2.61±1.37, p=0.05) after 0.6µg NPY. NPY injections in CHOW fed rats (N=7) did not increase intake after 0.3µg NPY (3.29±2.72, p=.14) but showed a trend towards an increase after 0.6µg NPY (4.99±2.92, p< .07). Taken together, fcHFHS-fed rats were more sensitive to LH-NPY than CHOW-fed rats. Moreover, in line with our hypothesis NPY injections in the LH increased the carbohydrate parts of the diet. Previously we showed that when injected in the nucleus accumbens, NPY only increased lard intake, whereas here we show that in the LH NPY increases carbohydrate intake. Taken together, these data show a region-specific role for NPY in feeding behavior.

Human Bite-Count Variability: Limitations for Measuring Energy Intake

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How variable is the number of bites to eat the same meal on different occasions? What is the impact of bite-count variability on the ability to estimate energy intake? We investigated these questions in twelve obese subjects (6M/6F) with mean (±SE) age of 37.6±7.3 years and a BMI of 35.3± 3.4 kg/m² who were admitted for a pair of 2-week inpatient stays to the metabolic ward at the NIH Clinical Center where they were fed controlled (CON) and ad libitum (ADLIB) diets. All food was prepared and measured by the NIH metabolic kitchen and bites were measured with a bite counter (Bite Technologies) worn on the dominant wrist. Complete data were obtained for 40 ADLIB diet days and for 309 meals over 103 days of CON diets. The within-subject bite count variability was quantified by the Root Mean Square (RMS) deviation from the mean number of bites taken to eat repeated meals. The mean bite count was 173±3.4 bites/day for the CON diets and 197±8 bites/day for the ADLIB diets (p=0.001). The RMS deviation on CON days was 18 bites/day [95% CI=15.7, 21.7], which was significantly lower than the ADLIB days whose RMS deviation = 28 bites/day [95% CI=22.6, 38.6] (p=0.001). Based on ADLIB data, and assuming perfect adherence to wearing the bite counter for all meals, the RMS deviation is ~127 bites over 7 days which corresponds to ~20% error in estimating total energy intake. Shorter durations result in even greater error. Therefore, the substantial within-subject bite number variation limits the use of bite counting for estimating energy intake over short-term periods.

Effects of chronic sucrose intake on cognitive performance of 3xTg-AD and Non transgenic mice.

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High sugar diets are among the most popular within the western societies and their consumption has produced health detriments at the central nervous system level. It is known that high caloric diets and type 2 diabetes are risk factors for the development of dementias, and particularly Alzheimer’s Disease (AD), which is mostly prevalent in women. The molecular and metabolic events that lead to cognitive impairments are not clear; we propose that astroglial activation is an early event that correlates with cognitive dysfunction. Hence, we studied the effect of the administration of a 20% sucrose solution during 5 months (starting at 2 months of age) in two types of female mice: a murine model of AD (3xTg-AD) and a non-transgenic strain (WT). As a consequence of the high sucrose diet administration, we found an early deterioration of object and spatial memories in the 3xTg-AD mice, comparable to the deterioration found in 12 months-old 3xTg-AD mice that had a normal diet. Additionally, the high sucrose diet also induced cognitive impairment in the WT mice’s spatial memories comparable to 12 month-old 3xTg-AD mice. Metabolic and molecular dysfunctions of glucose biochemistry are also related to the cognitive performance of the affected groups, as well as astrocytes activation. This data suggest that an early exposure to high caloric food has a powerful impact on the acceleration or production of cognitive impairments.

Western Diet Exposure Increases Permeability in a Model Blood-Brain Barrier

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We have previously observed that long-term exposure to energy dense Western diets (WD) can alter the integrity of the blood-brain barrier (BBB) by reducing the expression of tight junction proteins, thereby increasing nonselective permeability. However, the relationship between diet and BBB damage is not fully understood, as it is currently impossible to measure BBB leakage longitudinally. We have attempted to circumvent this by creating an in vitro BBB model to screen for BBB deficits in rats fed WD or Chow. At baseline, and at 1, 2 and 4 weeks, serum was collected from all rats via the tail vein. Rat serum or fetal bovine serum were added to growth medium, which was applied to confluent rat brain endothelial (RBE4) cells grown on permeable inserts, which were suspended in reservoirs. A fluorescent probe was then added to the inserts, after which medium was collected from the reservoir to determine the permeability of the RBE4 monolayer. Though there was no difference between treatments at baseline or week 1, serum obtained from rats fed WD induced more permeability than serum obtained form Chow rats at weeks 2 (p < 0.001) and 4 (p < 0.05). Further, a significant correlation between body weight and in vitro permeability was observed for WD (r = 0.4305, p = 0.0007) but not Chow (r = 0.0148, p = 0.94) rats. These data suggest that WD exposure can make RBE4 cells more vulnerable by affecting circulating factors. This procedure may be useful as a bioassay for longitudinal investigation of environmentally-induced neurovascular damage.

Botanical extracts: in vitro calcium imaging

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Botanicals have long been used to treat disease. Understanding mechanisms of action is hampered by impure sources and variable extract protocols. The PBRC/Rutgers Botanical Research Center was established to achieve consistent plant purity and extract protocols that allow for the study of mechanisms
of botanical action relevant to feeding, diabetes and obesity. St John’s Wort (SJW) is used to treat depression but it also produces nausea and anorexia. Since increasing synaptic activity in vagal afferents causes nausea, we evaluated whether SJW modulates vagal neurotransmission within the NST. In vitro imaging and voltage-clamped electrophysiology showed that SJW extract (or its purified hyperforin component) increased calcium levels of stimulated vagal afferent terminals associated with increased neurotransmitter release onto the NST. This in vitro vagal afferent synapse with NST neurons is an ideal model system to examine the mechanism of action of botanical agents on glutamatergic neurotransmission. Artemisia extracts improve metabolic and gastrointestinal control. One potential site of action may be the vagal afferent-NST synapse that regulates these homeostatic functions. Imaging and electrophysiological studies revealed that of the Artemisia extracts examined, only A. santolinifolia significantly stimulated vagal afferents and increased glutamatergic neurotransmission within the NST. Other imaging studies using pancreatic beta cells also show that specific Artemisia extracts may have system-wide effects to enhance resistance to metabolic disease. These results corroborate those seen in insulin secretion assays and analysis of transcriptional activity.

Protein supplementation enhances satiating efficiency in women but not men

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To test whether supplementing a tomato soup preload with whey protein would prevent decline in satiating efficiency (ratio of intake reduction to preload size increase) over repeated exposures, a pilot and main study were conducted. Pilot: Four preloads in two sizes (640 vs. 800 g for men [M], 480 vs. 640 g for women [F]) of 120°F tomato soup were given to 16 normal-weight subjects (8 M), each size supplemented ([S] 25% or 35% protein) or un-supplemented ([U] 9% protein), 30 minutes before a yogurt shake (1 kcal/g). Satiating efficiency was significantly higher by 2.3 cal/cal (± 1.25, p = .045) on S (2.6 ± .97, p = .02), than on U (.3 ± .97) in F and conversely lower in M by 1.1 cal/cal (± 1.25, p = .2), resulting in a significant sex x supplementation interaction (3.4 cal/cal ±1.8, p = .039). Main: 2 groups (n= 17 (9M)) were given both large and small, SUP (n=8) or UNS (n=9) preloads on day 1, 2, 6, and 7, and large on days 3-5 (7 non-consecutive days). Satiating efficiency was low and not different between S and U nor between the first and last two days, but intake on day 5 in M on S was nearly significantly less (246.31g ±143.36, p < .10, [p = 0.049, 1-tailed]) than on U. Protein supplementation increased satiating efficiency in women, but not in men, in the pilot study, but protein supplementation did not influence change in satiating efficiency over repeated exposures. Research on variables such as hunger or fullness may explain why differences in intake did not occur during the main study.

Portion size area affects expected anxiety responses to food cues.

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Portion size area (square cm) is an under-studied, but potentially significant, cue affecting a variety of responses to foods. In a previous analysis of the data to be presented, lower-energy but visually similar portions produced higher expected anxiety (EA) responses per unit energy of portion size. We hypothesized that area might account for the counter-intuitive relationship between EA and energy content. Participants (N = 34; 24 anorexic (AN), 10 controls) rated EA in response to photos of rice, potatoes, pizza, and M&Ms, each served in five portion sizes (20, 40, 80, 160, 320 kcal). After regressing EA from area (measured with a validated computer imaging technique), M&Ms produced the highest EA slope (.64, .25 mm/cm² for AN, and controls, respectively), which was significantly different by .34, ± .05, p = .0001 from
the similarly sized EA slopes of potatoes (.36), pizza (.32), and rice (.25). EA slopes for these foods did not differ from each other significantly in AN patients. In the control group, only the difference between pizza and M&M’s was significant by .16, ± .06 p = .01. These data demonstrate that area may be a visual cue driving portion size effects, as it accounts for a significant percentage of variance (R² = .60, .52) in AN and control subjects’ EA. The relative contributions of area and kcal may be a fruitful avenue of investigation for a range of cognitive, perceptual, and emotional responses to portion size.

A novel hippocampal-hypothalamic neural circuit mediating appetite through ghrelin receptor signaling

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The stomach-derived hormone ghrelin is a robust signal in the reward circuitry that stimulates higher-order aspects of feeding. We have recently shown that ghrelin receptor (GHSR-1A) activation in the ventral hippocampus (vHP) potently increases food intake and food-motivated behavior. However, the relevant downstream neural circuitry is unknown. Our neuroanatomical analyses reveal the presence of vHP GHSR-1A immunoreactive neurons that ipsilaterally project to the lateral hypothalamic area (LHA), suggesting that the LHA is a downstream target for vHP GHSR-1A-mediated feeding effects. To examine this hypothesis we utilized a functional “disconnection” approach in which rats received unilateral NMDA LHA lesions combined with unilateral vHP neuropharmacology. The food intake enhancing effects of vHP GHSR-1A activation were blunted following infusions of 300pmol ghrelin to the vHP ipsilateral to the LHA lesion (vHP>LHA communication eliminated). In contrast, unilateral vHP ghrelin infusions in sham-lesioned animals or in the vHP contralateral to the LHA lesion (vHP>LHA communication intact) resulted in a robust ghrelin induced hyperphagic response. We hypothesize that this vHP-LHA ghrelinergic pathway involves downstream melanin-concentrating hormone (MCH) signaling, as our neuroanatomical and immunohistochemical analyses revealed the presence of vHP-originating axons terminating in close apposition to MCH-producing cells in the LHA. Together, our data highlight the importance of hippocampal-hypothalamic circuitry in regulating higher-order feeding processes.

Central MCH receptor signaling increases food impulsivity and consummatory aspects of feeding independent of palatability

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Melanin-concentrating hormone (MCH) is a neuropeptide produced primarily in the lateral hypothalamic area (LHA). While central activation of MCH receptors increases food intake, its role in higher-order feeding processes requires further investigation. The current study utilizes behavioral neuropharmacology to determine the effects of MCH receptor signaling on various feeding-relevant behaviors. In an operant measure of food-impulsivity involving periodic access to palatable food (differential reinforcement of low rates of responding), lateral cerebral ventricle (ICV) MCH (5μg/μl) administration enhanced impulsive responding for food reward in non-restricted rats. However, central MCH administration had no effects on food seeking behavior independent of consumption in a conditioned place preference test, suggesting that MCH’s food intake-promoting effects require consummatory aspects of feeding. To examine whether central MCH receptor signaling increases the consumption of preferred foods to a greater extent than less-preferred foods, rats were given a choice to consume palatable sucrose pellets or less-preferred bland chow. Interestingly, ICV MCH administration increased the intake of both foods at a comparable magnitude. These data suggest that central MCH receptor signaling stimulates feeding independent of palatability and that MCH increases appetitive responding for food only following recent consumption of the reinforcer.
Overall these findings illuminate behavioral mechanisms through which MCH receptor signaling enhances feeding behavior.

Effects of offering a vegetable pure, diluted or hidden on toddlers' intake

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Only one in five toddlers eats sufficient vegetables. The present study compared three strategies on their effectiveness to increase intake; repeatedly offering a pure or diluted vegetable taste, or 'hiding' the vegetable, and taking food neophobia into account. 103 Toddlers (age 3.0 y (+/- 0.6)) participated and were randomly assigned to one of four groups: pure (plain cooked spinach), diluted (spinach a la creme), hidden (spinach ravioli) and control (green beans). Parents assessed their child's neophobia with the Child Food Neophobia Scale. During an intervention period children consumed their vegetable product (depending on group) once a week during dinner at home for six weeks. Main outcome measure was ad libitum intake of plain cooked spinach, measure pre- and post-intervention. GLM repeated measures analysis with time (pre, post) as within- and group as between-subjects factor, and neophobia score as covariate yielded a significant effect of time (p< 0.001) and a time*neophobia interaction effect (p=0.008). All groups increased spinach intake from pre- (53 g +/- 57) to post-intervention (91 g +/- 75) (p< 0.004). In conclusion, toddlers increased their ad libitum intake of pure spinach after six exposures during an intervention period, irrespective from whether they were exposed to the pure spinach taste, to a diluted taste, or whether the vegetable was 'hidden'. The effect on intake did, however, depend on the child's neophobia, with neophobic children being less responsive to the intervention.

Cannabinoid modulation of sweet taste perception and liking

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Animal studies indicate that the endocannabinoid system plays a major role in the regulation of food reward. Administration of cannabionoid agonists enhances the reward value of food, likely by amplifying palatability of foods, especially for sweet/fatty tastes. Cannabinoid antagonists result in the opposite effect. The sensory and psychophysical processes underlying these alterations in palatability are not characterized in humans, which was the aim of this study. We investigated modulation of sweet taste intensity and liking in a randomized, placebo-controlled, double blind crossover design using a pharmacological challenge. Participants performed 3 test sessions with an interval of 2 weeks, where they received 250 mg of Cannabis sativa (plant material) with different cannabinoid compound composition by use of a MINIVAP vaporizer. The different plant materials contained either 5 mg of delta9-THC (agonist), 35 mg of CBD (antagonist) or placebo. After administration, participants tasted 7 chocolate milk-like drinks with varying sugar content, and rated sweet taste intensity and liking on a general labelled magnitude scale and a labeled affective magnitude scale respectively. Subjective effects were assessed using a 100-mm visual analogue scale. Preliminary results (n=6) showed no effects of THC or CBD on the perception of sweet taste intensity or liking. Participants indicated that they felt slighty 'high', but this was irrespective from treatment, showing that they could not distinguish between the administered compounds in terms of subjective effects. Results of more participants (n=10) will be presented at SIBB 2015.

Disinhibition is associated with the pattern of weight loss and regain in a 1-year trial of portion control strategies
Characterization of psychological factors related to the control of food intake could help to identify individuals most likely to lose weight and keep it off. We administered the Eating Inventory (Stunkard & Messick, 1985) at 5 of the 23 participant contacts in a 1-year randomized weight loss trial. Participants were 186 overweight and obese women (age 50.0±0.8 y; BMI 34.0±0.3 kg/m²) who received one of three interventions, two of which focused on portion control strategies. During the trial, participant scores significantly increased for dietary restraint (from 8.9±0.3 to 14.4±0.3) and decreased for both disinhibition (9.7±0.3 to 7.7±0.3) and tendency toward hunger (6.2±0.2 to 5.1±0.3; all P < 0.0001). However, only disinhibition was significantly associated with the pattern of change in weight and BMI over time (both P < 0.002); these effects did not differ by intervention group. During the first 6 months, individuals with lower disinhibition, or decreased tendency to lose control of eating, had a higher rate of weight loss (P = 0.01). During the second 6 months, individuals with lower disinhibition had lower weight regain (P = 0.002). These findings indicate that improved control over eating as measured by disinhibition could provide an indicator of who is likely to be successful at losing weight and preventing regain.

A cognitive profile of obesity and its translation into new interventions

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Change your lifestyle: eat less, eat better, and exercise. Everybody knows this and if we could do this, obesity would not be a problem. Though the lifestyle advice essentially is correct, unhealthy habits usually are ingrained habits that are extremely difficult to change, especially for people with an “obese cognitive profile”. Knowledge of cognitive mechanisms that maintain the ingrained unhealthy consumption habits is necessary for the development of interventions that can change behavior effectively. This lecture discusses some cognitive processes that might maintain unhealthy consumption habits and make healthier eating and drinking difficult, like learned food cue reactivity and weak executive skills. An effort is done to translate basic scientific findings into new interventions which aim to tackle the sabotaging cognitive processes.

Morphine-induced suppression of saccharin intake: Effects of gender and interstimulus interval

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When the opportunity to self-administer cocaine is preceded by access to a sapid saccharin cue, female rats take more sweet and less cocaine than males. Thus, we hypothesized female rats would consume more sweet cue than male rats when paired with an opiate. Also, because evidence suggests it is aversive having to wait for drug, we hypothesized that a longer interstimulus interval (ISI) would be more aversive, thereby leading to greater avoidance of the opiate-paired cue in female and male rats. To test these hypotheses, 32 male and 32 female Sprague-Dawley rats were given 5 min access to .15% saccharin followed 5 or 15 min later by an i.p. injection of saline or 15 mg/kg morphine (n=8/cell). There was one pairing a day, every other day, for 8 trials. The results found no significant difference in intake between males and females in the 5 or 15 min ISI groups overall. However, when divided into large and small suppressors, large suppressing females consumed significantly more of the morphine-paired saccharin cue than did males in the 5 min ISI group (10.9 +/- .9 ml/kg vs. 2.0 +/- .6 ml/kg, p< .05). This finding is in keeping with the pattern obtained with cocaine. Despite having hypothesized a longer ISI would be aversive, and thus would augment suppression of the drug-paired cue, this proved not to be the case for the male or female rats.
Future studies will test if reduced avoidance of the opiate-paired cue (i.e., greater intake) by large-suppressing female rats is accompanied by reduced opiate self-administration.

Establishing the Mechanisms that Control Neuroendocrine Corticotropin Releasing Hormone Neuronal Activity

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Neuroendocrine corticotropin-releasing-hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVH) are controlled by a variety of afferents, particularly through interactions between catecholamine (CA), GABA, and glutamate mechanisms. In response to glycemic stressors, CA-dependent activation leads to phosphorylation of MAP kinases ERKs 1&2 (pERK1/2), which is necessary for the increase in CRH peptide transcription. pERK1/2 phosphorylates Synapsin I (SynI), a phosphoprotein that anchors vesicles to the cytoskeleton in several regions of the brain. To determine the mechanisms involved in controlling the activity of CRH neurons, we used immunocytochemistry (ICC) to investigate CA input, as well as terminal activation in response to glycemic stressors. A bolus of insulin, 2-deoxy-glucose (2DG), or saline was delivered via jugular catheter, followed 30 minutes later by anesthesia. ICC was run to examine CAs, as well as pERK1/2, pSynI, & VGluT2 in PVH and the external zone of the Median Eminence (MEext). Colocalization of CAs with VGluT2 was found in PVH. Colocalization of pERK1/2 & pSynI occurs in terminals in PVH and MEext, though there are significantly more colocalized objects in MEext. In MEext, 2DG resulted in a significantly greater number of colocalized objects than saline, as well as an increase in colocalization of pSynI & VGluT2. These results suggest that the crucial CA inputs contain glutamate, and that pERK1/2 may act as a link between neuroendocrine synthesis and release programs, helping to elucidate the network controlling neuroendocrine CRH activity.

Integration of Internal and External Cues in the Learned Control of Appetitive Behavior

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The control of energy intake involves the integration of information provided by environmental cues associated with food and physiological signals originating from the internal milieu. To learn more about this integrative control, we trained rats with external stimuli (tone, noise) and cues produced by 0 hr (24 hr with ad libitum food) and 4 hr food deprivation as compound stimuli. For Group Dep+/Ext+ both types of cues were relevant discriminative stimuli for the delivery of sucrose pellets. For Group Dep+/ExtR deprivation cues were relevant but external cues varied randomly with respect to sucrose. For Group DepR/Ext+, the external cues were relevant with deprivation cues random. All groups solved the problem with little difference in terminal performance. We then tested the groups with deprivation cues alone (no external cues). Group Dep+/Ext+ maintained significant discrimination. For Group DepR/Ext+ (trained with deprivation cues irrelevant), discrimination performance was completely abolished. Group Dep+/ExtR showed no significant discrimination based on deprivation cues, even though those cues had been trained a relevant discriminative signals. The results showed that: (a) deprivation cues are not overshadowed by external cues when both are relevant discriminative stimuli; (b) that control is abolished when external cues are not relevant. The results suggest that deprivation cues influence appetitive behavior by signaling when external cues will be reinforced. They are unable to perform this function when external cues do not signal reward.

Nicotine and ethanol co-use in Long-Evans rats: Stimulatory effects of perinatal exposure to a fat-
Clinical studies demonstrate frequent co-existence of nicotine and alcohol abuse, possibly due to their ready access and association with fat-rich diets. With fat intake in adult animals shown to enhance intake of either nicotine or ethanol and maternal consumption of fat during pregnancy increasing operant responding for nicotine in offspring, this study tested in Long-Evans rats whether perinatal exposure to a high-fat diet compared to low-fat chow affects the co-abuse of these two drugs, using a novel paradigm involving their simultaneous intravenous self-administration (SA). Fat- vs chow-exposed offspring were compared in terms of their nicotine and their nicotine/ethanol SA, as well as their SA of ethanol in the absence of nicotine. Perinatal maternal consumption of fat significantly stimulates nicotine SA during fixed-ratio testing. It also increases nicotine/ethanol SA during fixed-ratio and dose-response testing and causes an increase in breakpoint during progressive ratio testing. Furthermore, rats perinatally exposed to fat self-administer significantly more of the nicotine/ethanol mixture as compared to nicotine alone, an effect not evident in the chow control rats. After removal of nicotine from the nicotine/ethanol mixture, this difference between the fat- and chow-exposed rats was lost, with both groups failing to acquire SA of ethanol alone. Together, these findings suggest that perinatal exposure to a fat-rich diet, in addition to stimulating SA of nicotine alone, causes an even greater vulnerability to the excessive co-use of nicotine and ethanol.

Systemic administration of the orexin/hypocretin antagonist SB-334867 attenuates Pavlovian cue-food conditioning

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Food consumption is driven by internal, homeostatic signaling as well as by external, environmental cues, including food-associated cues. Overeating driven by food cues is critically mediated by the neuropeptide orexin/hypocretin (ORX), and we have previously shown that presentation of well-learned cues recruit ORX-containing neurons in the hypothalamus. Here, we examined if ORX mediates the initial acquisition of cue-food associations. Male, Long-Evans rats underwent two sessions of tone-food conditioning on two separate days. Sessions included eight pairings of a 10s tone followed by the delivery of two palatable food pellets, distinct from their chow. Thirty minutes prior to the beginning of each session, rats received an i.p. injection of either vehicle (V) or the ORX 1 receptor antagonist SB-334867 (SB) in a crossover design resulting in four groups: V/V, V/SB, SB/V, and SB/SB (n=8/group). During session 1, SB had no effect on the percentage of food cup behavior expressed during the tone or on latency to approach the food cup after tone onset (ps>0.05), signifying the V and SB groups displayed a similar increase in learning. During session 2, rats that had received SB during either session displayed significantly less food cup behavior compared to the V/V group (V/V: 64.5±3.2, V/SB: 46.7±3.3, SB/V: 49.6±5.5, SB/SB: 46.7±6.2, ps<0.05), and had longer latencies to approach the food cup after tone onset (V/V: 1.9±0.3, V/SB: 3.5±0.5, SB/V: 4.0±0.8, SB/SB: 4.6±0.6, ps≤0.05). These results demonstrate a role for ORX in mediating cue-food Pavlovian appetitive learning.

“But what is the mechanism?” Beyond phenomena in the study of human eating behavior

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Meal energy intake is dictated by an intricate balance between internal, physiological signals and external, food-related cues. These external factors include the food’s palatability, energy density, packaging, and portion size. In this presentation, we posit that sustained reductions in energy intake may be unsuccessful because the understanding of how internal and external cues interact to influence intake is in its infancy. For example, it is well-known that the portion size served is positively related to amount eaten in both children and adults, but the mechanisms underlying this effect are elusive. By using fMRI, we shed light on these mechanisms in a cohort of 38, 7-10 year old children. We tested neural response to food images that varied by energy content and portion size to determine its relation to laboratory measures of intake at multi-item meals that also varied by energy content and portion size. Our preliminary findings suggest that distinct brain regions involved with inhibition, decision making, and reward are engaged specifically in response to food portion size. In addition, we identified substantial variation in laboratory portion size response that was in part related to individual differences in reported child eating behaviors. We are also conducting a related study in children to determine the neural mechanisms underlying the impact of food branding on intake. The results from these studies will be applied toward developing targeted, and hopefully more effective, interventions to teach children how to control energy intake.

The number and type of palatable foods associated with a context affect the selectivity of cue-potentiated feeding.

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Cue-potentiated feeding (CPF) refers to stimulation of food intake by previously neutral environmental cues. Determining the selectivity of this effect is important in light of its relevance to overeating and obesity. Previous evidence for the selectivity of CPF is inconclusive, and few studies have involved palatable “junk foods” (JF). Therefore, we developed a CPF paradigm in which the number of JF paired with contextual cues was manipulated. In 2 experiments, female rats (N = 54) received daily exposures (30-min) to a “Plus” context that contained 1 (Single condition) or 3 (Many condition) JF or regular chow (Control), or to a “Minus” context with no food. In Experiment 1, tests using chow found floor effects in consumption, consistent with past reports. Crucially, however, only the Many group overate in the Plus relative to the Minus context (simple effect: p = .008) when testing on a JF not used in training (Froot Loops). As this effect emerged only on the first day of testing, Experiment 2 replicated this result in a within-subjects design (interaction p = .043; Many condition simple effect p = .007). Despite differences in CPF, acquisition of a lever-press response for reward pellets in the Plus context was equivalent between groups, suggesting that context conditioning modulated feeding behaviour but not instrumental learning. These results indicate that CPF effects are not always selective to the food/s paired with that cue.

Gastric vagal afferents are a food entrainable circadian satiety signal

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Mechanosensitive gastric vagal afferents (GVAs) are part of a coordinated set of mechanisms involved in the regulation of food intake. GVAs exhibit circadian variation in their response to mechanical stimuli allowing time of day specific satiety signaling. This circadian variation is ablated by ad libitum access to a high fat diet (HFD). It is unclear whether the circadian pattern is entrainable by food access. Therefore, we fed 8wk old male C57BL/6 mice either a standard laboratory diet (SLD;12%kJ from fat,N=64) or HFD (60%kJ from fat,N=64) ad libitum for 4wks, and then divided each dietary group so that half had access to food only during the light phase (LP:07:00-19:00) or dark phase (DP:19:00-07:00) for 8wks. Mice were then sacrificed at 3hr intervals from 07:00 and single fiber recordings from GVA tension and mucosal
receptors were taken. Mice from both HFD groups weighed more than the SLD groups at the end of the 12wk period with no difference between LP and DP mice on the same diet. In SLD DP and HFD DP mice, at 01:00 compared to 13:00 the response of tension receptors to 3g tension were both reduced by 72\% and that of mucosal receptors to stroking (50mg) was reduced by 65\% and 55\% respectively. In LP fed mice both SLD and HFD mice showed reversed circadian rhythms with respective 79\% and 72\% reductions in the response to tension and 74\% and 67\% reductions in the response to mucosal stroking at 13:00 compared to 01:00. In conclusion, circadian rhythms in GVA satiety signals can be entrained to a period of food access. This entrainment is unaffected by HFD feeding.

**Partial aberration of oral sensory relay to brain may affect the retrieval of taste-associated memory**

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Some patients in dental clinics appeal altered taste perception and negative emotion after lingual nerve damages. We have reported that partial aberration of oral sensory relay to brain results in the development of psycho-emotional disorders, possibly in relation with a hippocampal dysfunction. In this study, we have examined changes in a taste-associated memory function in rats following bilateral transections of the lingual and chorda tympani nerves (Nx). Male SD rats were trained for drinking with 3-bottles (one sucrose bottle with visual cue and two water bottles without visual cues) and then received Nx or sham surgery. Nx and sham rats were subjected to drinking test with 3 water bottles (one with visual cue and two without visual cues) after a week of post-operative recovery. Another groups of rats were trained with the water maze acquisition test for 9 days before the Nx or sham surgery, and then subjected to the probe test after a week of post-operative recovery. In the 3-bottle drinking test, both Nx and sham rats drank more from the water bottle with visual cue than the others without visual cues; however, water consumption from the cued bottle, but not the non-cued bottles, was significantly reduced in Nx rats compared with sham rats. In the probe test of water maze, dwelling time in the target quadrant was not significantly reduced in Nx rats compared with sham rats. Results suggest that partial aberration of oral sensory relay to brain may affect the retrieval of taste-associated memory.

**In vitro assessment of bitter tastants on gastric acid secretion**

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In gastrointestinal physiology, gastric acid secretion is crucial of all in nutrient digestion and of antibacterial function. If gastric acid secretion is decreased, it could manifest in symptoms such as gastro-esophageal reflux, chronic atrophic gastritis, dyspepsia and/or infections and autoimmune gastritis (Di Mario et al., 2014). Meanwhile, prior to the modern era of medicine, fluid preparation derived from bitter tasting plants were given to promote appetite and thus to aid digestion (Douthwaite, 1963). It is hypothesized that bitter tastants might affect gastric acid secretion, one of digestive processes. The aim of this study was to evaluate the effects of 23 bitter tastants on gastric acid secretion using human gastric cancer cells (HGT-1) by means of a pH-sensitive fluorescent dye which determines the intracellular pH as an indicator of proton secretion. Among the tested tastants, naringin, alopeine and cromolyn revealed their inducing effect in gastric acid secretion. Naringin and alopeine have not been characterized by which the bitter taste receptors belonging to the taste receptor 2 family (TAS2R) are activated. Cromolyn has been known to activate TAS2R7, -R43 and -R49. In conclusion, bitter tastants are involved in gastric acid secretion, and the appetite-stimulatory effect of naringin and the stomach-stimulatory effects of alopeine and cromolyn might be explained through their gastric acid secretion.
Role of hypothalamic microglia in synaptic organization onto proopiomelanocortin neuron for regulation of energy balance

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Hypothalamic neuronal circuit dynamically acts as a command unit for the regulation of energy homeostasis. Microglia has recently been known to play a role in synaptic pruning and remodeling in the fetal and adult brain, which are coupled to neuronal activity. However, impacts of microglia on the hypothalamic control of energy metabolism are largely unknown. Here, we utilized a mouse model in which microglia was specifically activated in the hypothalamus by intracerebroventricular administration of Pam3CSK, a synthetic agonist of Toll-like receptor 2 to interrogate whether microglia activation participates in the regulation of synaptic inputs onto the proopiomelanocortin (POMC) neurons and the initiation of anorexia. In the Pam3CSK-treated mouse hypothalamus, contacts between microglia and POMC cells were elevated, and thereby, resulted in a decrease of GABAergic synaptic ends and an increase of glutamatergic synaptic terminals onto the POMC neurons, which subsequently promoted POMC neuronal activity. The resulting anorexia was effectively mitigated by minocycline, a bacteriostatic antibiotic known to inhibit microglia activation, and SHU9119, a synthetic antagonist of melanocortin receptors 3 and 4. These findings unmask an underappreciated role of microglia in the initiation of hypothalamic synaptic plasticity and short-term regulation of energy metabolism.

Does serving larger portions of all items at a meal affect preschool children’s vegetable intake?

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Serving larger portions of vegetables has been suggested as a strategy to increase children’s vegetable intake, but it is unknown whether this advice is effective when the portions of all items at a meal are increased. In a within-subjects crossover design, we investigated the effect of varying the portion size of all items (100%, 150%, and 200%) in 2 meals differing in energy density (ED; 100% or 142%) that were served to 120 children aged 3-5 y. Across the 6 meals, lunch items were pasta, applesauce, chicken, vegetable, ketchup, and milk in lower- or higher-ED versions. Doubling the portion sizes increased intake of the entire meal by 74 ± 7 grams (26%; P< 0.0001); the effect on intake, however, differed for individual foods. Doubling the portions increased pasta intake by 17 ± 4 g (31%) but did not influence chicken intake. Doubling the portion size of applesauce, which was highly liked, increased intake by 45 ± 4 g (64%); increasing portions had no effect on intake of vegetables, which were less liked. Children did not consume more vegetables in response to larger portions when amounts of all foods were also increased. To promote preschool children’s vegetable intake, amounts of vegetables may need to be increased proportionally to the other components of the meal, and strategies such as increasing palatability and preference may also be required.

Does the energy density or portion size of milk affect preschool children’s intake at a meal?

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Varying the energy density (ED) and portion size of solid foods significantly influences preschool
children’s intake; however, it is unknown whether variations in milk ED and portion size affect intake at a meal. Using a 2-by-2 crossover design, we investigated the influence of differences in ED and portion size of milk served with a meal on preschool children’s intake. Lunch was served once a week for 4 weeks in childcare classrooms and was consumed ad libitum by 79 children (3-5 y). Across the 4 meals milk was varied in ED (3.25% whole fat [0.61 kcal/g] or 1% low-fat [0.42]) and portion size (9 or 6 fl. oz.); the chicken, pasta, broccoli, and bananas served at the meal were not varied. Results showed that serving lower-ED milk decreased milk intake by 30±3 kcal (32%) and increased food intake by 31±8 kcal (12%) compared to serving higher-ED milk (both P< 0.0001). Serving the smaller portion of milk decreased milk intake by 19±3 kcal (21%; P< 0.0001) compared to meals with the larger portion, but had no significant effect on food intake (11±7 kcal; 4%; NS). Differences in milk ED and portion size did not influence total energy intake at the meal, suggesting that children may adjust their food intake in response to changes in milk consumed with a meal. Serving lower-ED milk in smaller portions may not be an effective strategy to reduce energy intake at a meal for all preschool children, but longer-term studies are needed to determine the impact of milk ED and portion size on body weight.

Use of financial incentives for the purchase of healthy groceries: A randomized pilot study

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Providing financial incentives can be a useful strategy for increasing fruit and vegetable intake among consumers. It remains to be determined whether financial incentives can promote intake of other low energy-dense foods and if consumers who are already using promotional tools for their grocery purchases may be especially responsive to receiving incentives. This randomized controlled trial tested the effects of financial incentives for the purchase of healthy groceries on 3-month changes in intake, weight outcomes, and the home food environment among older adults who either frequently or never used coupons for their grocery purchases. Fifty-four men and women were randomly assigned to either an incentive or a control group. Participants in the incentive group received $1 for every healthy food or beverage they purchased. All participants completed a FFQ and home food inventory and had their height, weight, and waist circumference measured at baseline and after 3 months. Participants who received financial incentives for purchasing healthy groceries significantly increased their daily vegetable intake by 144% (P=0.04). Participants in both groups showed significant improvements in their home food environment (P=0.0003). No significant changes were observed in daily energy intake or weight-related outcomes across groups (P< 0.12). Increased consumption of vegetables does not replace intake of more energy-dense foods. Incentivizing participants for making healthy food choices while simultaneously reducing less healthy food choices may be important.

Central GLP-1 signaling limits hedonically- but not homeostatically-driven food intake

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Glucagon-like peptide-1 (GLP-1) neurons within the caudal brainstem have been implicated in the inhibition and/or termination of food intake. In 24h-fasted rats, satiation on Ensure (5% BW consumed in 30 min) activates ~30% of GLP-1 neurons to express cFos; however, this is only marginally higher than “baseline” GLP-1 activation in ad lib-fed rats (i.e., ~20%). Conversely, 5 days of meal entrainment that promotes excessive liquid diet intake (10-15% BW in 60 min) activates up to 90% of GLP-1 neurons. Thus, endogenous GLP-1 may contribute to satiation only when intake is excessive, e.g., due to meal entrainment and/or palatability. To test this hypothesis, the GLP-1 receptor antagonist Ex9 was administered i.c.v. to rats in two different paradigms. In the first, rats were fasted for 24h, infused with Ex9 (100 ug; n=5) or
vehicle (3 ul; n=4), and then allowed to re-feed to satiety on Ensure. Intake was similar at 15, 30, and 60 min, regardless of i.c.v. treatment. In the second paradigm, ad lib-fed rats (n=13) were acclimated for 10 days to Ensure access each afternoon for 2h. Intake stabilized by day 5. On the 7th and 10th day, rats received i.c.v. vehicle and Ex9, respectively, or vice-versa, before 2h Ensure access. Compared to stable baseline intake (no i.c.v. infusion), Ex9 increased Ensure intake by ~19%, significantly more than the ~0.4% increase after vehicle. We propose that central GLP-1 signaling limits excessive intake driven by palatability and/or meal entrainment, but plays little or no role in satiation during normal homeostatic feeding, including re-feeding after an overnight fast.

Molecular inducers of non-homeostatic snack food intake

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Snack food like potato chips (PC) can lead to a non-homeostatic energy intake. To identify molecular inducers of such behavior we established an animal model where PC induced hyperphagia in ad libitum fed rats. A specific fat carbohydrate combination (FCH; F: 35 %; CH: 45%) has already been identified as main trigger of induced food intake. Here we performed 2-choice preference tests with male Wistar rats (n=20; initial BW=136 ± 9 g) to reveal the influence of further components of PC on energy intake. FCH served as control. Tests were performed at 2 consecutive days followed by 1 or 2 days without test. Tests were 3x10 min per day modeling a snacking situation with limited access to palatable food. The snacking of palatable food always induced a significantly higher energy intake compared to days without snacking possibility (95 ± 6 vs. 106 ± 7 kcal/day; p < 0.001). This 13 % higher intake can be considered non-homeostatic, although a partial compensation by reduced standard chow intake could be observed. Remarkably rats consumed during snacking episodes (30 min/24h) up to 50% of total 24h energy intake. Test foods were FCH modified with Salt, Protein, additional free fatty acids, a flavor extract of PC, different fatty acid composition or heating of the oil component. Thus it was shown that the use of heated oil lead to an even higher intake than FCH (FCH vs FCH heated 33 ± 18% vs 67 ± 13 %; p < 0.001). The other components did not influence the intake significantly. This supports our hypothesis that FCH composition is the main trigger of non-homeostatic intake of PC, which is still further increased by heated oil.

Cocaine- and amphetamine-regulated transcript (CART) mediates the satiating effects of glucagon-like peptide-1 (GLP-1) in rat vagal afferent neurons

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GLP-1 is an incretin and satiation hormone produced in the intestine in response to eating. Previously, using a rat model with a specific knockdown (KD) of GLP-1R in vagal afferent neurons (VAN), we demonstrated that vagal GLP-1R is required for endogenous GLP-1-induced satiation. The mechanism by which vagal GLP-1R activation decreases food intake is still unknown. CART, a neuropeptide known for its anorectic property, is expressed in the VAN and has been shown to mediate eating inhibitory effects of other peripheral hormones such as cholecystokinin (CCK). We tested the hypothesis that CART mediates the eating-inhibitory effect of vagal GLP-1R activation. CART is co-localized in GLP-1R expressing cells in rat nodose ganglia. Moreover, GLP-1 (10 nM) application stimulated CART mRNA and protein expression in a primary culture of rat VAN. In vivo, we used two rat models of CART inhibition. First, we reduced vagal CART expression using a lentiviral-mediated CART KD in the VAN. Second, we blocked CART release in the nucleus tractus solitarii (NTS) by administrating a CART antibody into the NTS. CART inhibition abolished intraperitoneal (10 nmol/kg) GLP-1-induced satiation and reduced GLP-1-
induced gastric emptying. We conclude that GLP-1 induces CART synthesis in VAN and that CART released from VAN into the NTS mediates the physiological effects of GLP-1.

Weighing the Evidence: Variance in Brain Responses to Milkshake Receipt is Predictive of Feeding Behavior

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Variation is a prerequisite for adaptation. However, it is unknown if variance in brain responses to the receipt of milkshake contributes to obesity. To test this hypothesis, we used functional magnetic resonance imaging (fMRI) to assess whether brain responses to milkshake in the nucleus accumbens (NAc), thought to reflect approach, under different internal states correlate with body mass index (BMI) and predict weight gain. Healthy non-dieting participants (N = 34) underwent fMRI scanning on separate days where they tasted milkshakes when hungry (4h fast), full (fixed-portion lunch), or satiated as preferred (ad lib lunch). Participants returned after 1 year to assess weight change (ΔBMI). When full, variance in NAc responses to milkshake was correlated with BMI (r = .47 95% CI [.10, .74]) and predicted ΔBMI (r = -.45 95% CI [-.67, -.13]). Moreover, in line with simulations of behavior, high variance in NAc predicted high variance in ad lib food intake after the fMRI session and was correlated with disinhibition (r = .42). Critically, high variance in NAc responses to milkshake was associated with faster increases in insulin blood levels and faster decreases in glucose. Our results demonstrate that variance in brain responses contains information beyond mere measurement noise. Ultimately, understanding brain-signal variability and its physiological correlates might help to explain behavioral variability in feeding behavior, such as loss of control during binges in overweight/obesity.

The brain’s response to the choice to consume saturated fat and liquid sugar

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Excessive food consumption is a major contributor to the obesity problem. To study diet-induced obesity, it is important to mimic human daily consumption, which is characterized by the availability of calorie-dense palatable food items, either in solid or liquid form, that do not always contain minerals and vitamins. Many different high-fat/high-energy diets have been developed to study metabolic diseases in rodents in the past. However, most of these diets consist of pellets that contain all nutrients in one pellet. Because Western-style diets do not exist of a single solid food item (without choice), we started using freechoice diets in which rats are offered two palatable items either in solid or liquid form, in addition to the normal balanced rat chow and water. In a series of studies we showed that when on this free-choice high fat high sugar diet (fHFHS) rats are persistently hyperphagic, become arrhythmic in their palatable intake, and are more motivated to work for a sugar reward. Interestingly, the hyperphagia, arrhythmia and food motivation shown in rats on a fHFHS diet were specific to the fat and sugar combination as a free-choice high fat or a free-choice high sugar diet did not induce these changes. Moreover, when rats were provided with a custom-made non-choice HFHS diet, consisting of the same ingredients as the fHFHS diet, rats did not become hyperphagia or arrhythmia, suggesting an important role for choice and nutrients in excessive food consumption. During the presentation, changes observed in hypothalamus and nucleus accumbens will be presented and their role in choice, feeding patterns and nutrient composition will be discussed.

Adolescent high fat feeding disrupts cognitive flexibility via downregulation of reelin expression in
the prefrontal cortex (PFC)

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High fat diets (HFD) have emerged as one of the most detrimental physiological stressors of Western societies. In particular, HFD elicit disturbances in cognitive functions, but so far pertinent studies have essentially focused on the hippocampal formation (HPC), whereas the PFC has largely been ignored. Here we show that chronic HFD throughout adolescence (but not adulthood) results in PFC-related cognitive abnormalities such as reversal learning and fear extinction in mice. Given the role of cortical GABA circuits in cognition, we examined the histological integrity of GABA neuronal types. We identified early and persistent reductions in the immunoreactivity for reelin, an extracellular matrix (ECM) protein implicated in the maturation of forebrain structures. Such deficits were specific for the PFC (absent from the HPC), did not extend to other GABA neurons, correlated with cognitive deficits, and were associated with changes in the expression of reelin molecular partners. Importantly, reelin overexpression effectively prevented the emergence of cognitive deficits induced by HFD. These effects were specific for the PFC because functions associated with striatal and HPC regions were not reverted. Our findings demonstrate that the ECM protein reelin is functionally involved in the development of PFC cognitive abnormalities after adolescent HFD, and thus provide one of the first putative mechanisms linking nutritional stress to PFC dysfunction.

Intrauterine growth restriction (IUGR) can change the hedonic response to sweet taste - role of the mu opioid receptors in the nucleus accumbens

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IUGR is associated with increased preference for palatable foods. Considering that the hedonic response to sweet taste may be involved and is modulated by the nucleus accumbens’ (nacc) mu opioid receptors, we investigated these outcomes in animals submitted to IUGR. IUGR was induced by maternal food restriction (FR: 50% food restricted diet from pregnancy day 10; Adlib: ad libitum diet). At birth, pups were cross-fostered, generating AdLib/AdLib and FR/AdLib groups (pregnancy/lactation). The hedonic response was evaluated 24 hours after birth and at 90 days of life, by giving sucrose solution or water and analyzing the hedonic facial responses exhibited within 60 sec. As showed previously, pups’ hedonic responses were higher in FR pups exposed to sucrose as compared to water, without differences in Control pups. We also found a decrease in phosphorilation of mu opioid receptor in FR pups compared to Controls. In adult life, hedonic response and mu opioid phosphorilation were not different between groups, suggesting that the alterations in hedonic response and in mu opioid fosforilation observed in early life do not persist. Opioid system alterations in early life can possibly contribute to the increased preference for palatable foods in IUGR animals, however the mechanisms still need to be studied. Supported By: FIPE-HCPA

Brain fatty acid and ketone sensing and the regulation of food intake in DIO and DR rats

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The hypothalamus contains metabolic sensing neurons which play an integral role in the regulation of glucose and energy homeostasis and the development of obesity. Many of these neurons utilize both glucose and fatty acids (FA) to alter their activity as a mean of monitoring the metabolic status of the body. FA can be transformed by astrocytes into ketone bodies (KB) which are sensed by these neurons. This study aimed to determine the potential role of astrocyte-derived KB production in regulating the early changes in caloric intake of diet induced-obese (DIO) vs. diet resistant (DR) rats fed a 31% fat high-energy (HE) diet. When DIO and DR rats are fed HE diet, both overeat for 3 days. While DR rats then reduce their intake to chow-fed levels on day 3, DIO rats continue to overeat, despite their early and persistent increase in leptin levels. Thus, after 3 d on chow or HE diet, DR and DIO rats, were assessed for their VMH serum and KB levels for 6h after dark onset using microdialysis coupled to food intake monitoring. Local VMH astrocyte KB production was similar between DR and DIO rats after dark onset feeding but inhibiting VMH KB production in DR rats on day 3 transiently returned their intake of HE diet to the level of DIO rats. Dissociated VMN neurons from DIO and DR rats were equally sensitive to the excitatory effects of KB. Thus, while DR rats respond to VMH KB levels by decreasing their HE intake after 3 d, this is not the case of DIO rats suggesting that DIO inherent leptin resistance prevents KB inhibitory action on food intake.

Assessing macronutrient diet preference in rats selectively bred to run long vs short distances

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The current study used two novel Wistar rat phenotypes, developed by selectively breeding for either high- or low-levels of voluntary running (HVR and LVR). As of the 10th generation, HVRs ran approximately 10-fold greater distances compared to the LVRs, providing a unique model to examine influence of inactivity on diet preference and feeding behavior. Previous animal studies suggest an interaction between exercise and diet preference. Recent experiments from our lab found that HVRs demonstrate a slight preference for a high-fat diet, while the LVR rats preferred a high-carbohydrate diet. However, six weeks of running or sedentary home cage environment had no effect on this trend. The current study extends these findings by examining home cage diet preference in the HVR, LVR, and outbred rats provided ad lib access to high-fat (60%), high-sucrose (33%), and a high-corn starch (50%) diet for four weeks. Animals were housed with either access to a running wheel or sedentary conditions throughout the study. Animals were analyzed for various biomarkers associated with chronic consumption of the diets. Present data reveal a heterogeneous pattern of diet preference across outbred population, but overall demonstrating a preference for the high-fat diet. Analysis of LVR/HVR diet preference and the influence of exercise condition on these behaviors and biomarkers are ongoing.

GLP-1 receptors in the dorsomedial hypothalamus (DMH) are essential for the regulation of energy balance

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Glucagon-like peptide-1 (GLP-1) produced in the nucleus tractus solitarius (NTS) is required for the control of food intake and body weight by acting on GLP-1 receptors (GLP-1Rs) expressed widely throughout the neuraxis. Here, we focus our attention on the contribution of endogenous GLP-1R signaling
in the DMH, an essential nucleus involved in energy balance regulation. We used viral-mediated RNA interference to knockdown (KD) GLP-1Rs selectively in the DMH in rats maintained on chow. Two weeks after AAV-GLP-1R shRNA injection into the DMH, GLP-1R KD rats developed hyperphagia with a concomitant increase in body weight gain compared to the AAV-control rats. The hyperphagia was due to an increase in meal number without a change in meal size, indicating that DMH GLP-1R KD shortens the inter-meal interval. Moreover, DMH GLP-1R KD rats showed a blunted response to the satiating effect of peripherally administered GLP-1R agonist, exendin-4. Computer tomography (CT) analysis showed a significant increase in adiposity with a concomitant rise in plasma leptin and insulin levels in KD rats. An IP glucose tolerance test revealed that KD rats also developed insulin resistance. In showing that disruption of DMH GLP-1R signaling leads to hyperphagia, obesity and metabolic disturbances, these data indicate that GLP-1R signaling in the DMH is required for the normal regulation of energy balance.

Primary Cilium in the Control of Body Weight.

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Syndromic obesities in humans, and gene inactivating mutations in mice, clearly implicate the primary cilium in the control of food intake and body weight. The molecular mechanisms for these effects remain unknown. Highly prevalent DNA sequence variations in the first intron of FTO are strongly associated with increased food intake and body weight. This effect may be conveyed, in part, by regulation of expression of a nearby gene that is a component of the primary cilium. Studies in transgenic animals and, more recently, neurons derived from human pluripotent cells, have identified aspects of the molecular mechanisms upon which the role of the primary cilium in body weight regulation is based.

Amylin-IL-6 Enhancement of VMH Leptin Signaling

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We recently demonstrated that the mechanism by which amylin enhances ventromedial hypothalamic (VMH) leptin signaling is by inducing VMH microglia to produce IL-6 which acts on the IL-6/gp130 receptor on VMH neurons to increase Lepr-b transcription and apparent transport to the neuronal cell membrane. We now demonstrate that endogenous VMH amylin signaling via its Ctr/RAMP receptor is required for full leptin signaling. Depletion of VMH Ctr1a with an AAV expressing Ctr1a shRNA causes outbred male rats to become obese and insulin resistant without hyperphagia. Furthermore, amylin treatment from P0-16 improves VMH leptin signaling and corrects the defective ARC-PVN aMSH and AgRP pathway development of selectively bred DIO rats. However, these improvements do not produce sustained protection from obesity once amylin treatment is terminated. Finally, incubating ventromedial nucleus (VMN) neurons with IL-6 for 5d improves the excitatory effects of leptin on their activity and increases the expression of both Lepr-b and Bardet-Biedl-6 (BBS6) mRNA in those neurons. Since BBS6 is one of a family of 15 BBS proteins that enhances the transport of Lepr-b to the cell membrane, these results further support our results demonstrating that amylin acts via its Ctr/RAMP receptor on microglia to secret IL-6 which acts on VMH neurons to enhance Lepr-b transcription, transport and downstream signaling.
The tools we use to eat: do they affect the amount we consume?

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The literature on the effect container size on the amount consumed is contradictory. The present set of studies were undertaken to measure the effect of (a) plate size, (b) serving utensil size, and (c) effects of using chop-sticks vs forks on the amount of food consumed at lunch. In the first study, seventeen participants were offered three different size of plates before entering a buffet lunch where they could serve as much or as little as they desired. In the second study, seventeen participants were give the same plate size, but were given three different size utensils in the buffet line to serve themselves. In the third study, twenty-one native chop-stick eaters were given either chops or conventional forks to consume their lunch. Each study used a within subject design. Participants were tested on the same day of the week, one week apart, and all the food served and consumed were weighed. The results indicated that neither plate size, serving utensil size, nor whether one ate with chop sticks or forks affected the amount consumed. However, the test re-test correlation of the total amount of food consumed was highly significant indicating that of the three variables tested the subjects history of what they consumed was the best predictor of how much they would eat.

Selective activation of A1/C1 catecholamine neurons by DREADD enhances food intake in rats

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Hindbrain catecholamine (CA) neurons are required for feeding responses induced by glucose deficit. Retrograde lesion of CA neurons using anti-dopamine beta hydroxylase saporin eliminates feeding induced by systemic 2-deoxy-D-glucose or insulin-induced hypoglycemia or by central administration of 5-thioglucose. Although the particular CA neurons responsible for the glucoprivic feeding response have not been identified, previous work has shown that localized silencing of Dbh and Npy, which are co-expressed in the A1/C1 CA cells, reduces glucoprivic feeding, suggesting a critical role for these particular neurons in control of the feeding response. Here we used DREADD technology to selectively and directly activate A1/C1 neurons to further assess their involvement in control of feeding and blood glucose. Cre-dependent adeno-associated virus (AAV) encoding hM3Dq and a reporter gene (mCherry), AAV2-DIO-hSyn-hMD3Dq-mCherry, was injected into the A1/C1 area in transgenic rats expressing Cre recombinase under the control of tyrosine hydroxylase (TH) promoter (Th-Cre+ rats). Double immunofluorescent staining revealed selective expression of mCherry in TH-positive neurons in A1/C1 6-10 weeks after AAV injections, with nearly half of the TH-positive neurons in the injection site expressing mCherry. Peripheral administration of clozapine-N-oxide in AAV-injected Th-Cre+ rats significantly increased food intake and enhanced c-Fos expression in A1/C1 CA neurons, but had no effect on blood glucose. Results demonstrate the importance of A1/C1 neurons for control of food intake.

Indirect effect of apelin on gastric vagal afferent satiety signaling.

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Apelin is the endogenous ligand for the G-protein coupled receptor, APJ (Biochem Biophys Res Comm 1998;251:471-6) and likely has a role in the central regulation of food intake ( J. Neuroendocrin 2008;20:79-84). However, apelin is expressed in the gastric mucosa (Regul Pept 2005;129:37-41) and has a
modulatory effect on gastric vagal afferents (GVAs). Apelin reduces mechanosensitivity of tension receptors in standard laboratory diet (SLD) fed and fasted but not high-fat diet (HFD) mice. Apelin has no effect on the mechanosensitivity of mucosal GVAs in SLD and HFD fed mice. After an overnight fast, apelin reduced the response of mucosal receptors to mechanical stimulation. Therefore we aimed to further determine: 1) whether the effect of apelin on GVA mechanosensitivity in mice fed a SLD or HFD is mediated directly by APJ receptors expressed on GVA endings, and 2) the anatomical location of apelin in the gastric mucosa in relation to APJ positive cells. APJ mRNA levels in retrogradely traced tension and mucosal GVA neurons were quantified using RT-PCR. Immunohistochemistry was used to determine the relationship between apelin and APJ in the stomach wall. APJ mRNA was detected in the whole nodose ganglia but undetectable in retrogradely traced tension or mucosal GVA neurons. In the gastric mucosa, APJ-expressing cells were found adjacent to apelin-expressing cells. These data suggest apelin may not have a direct effect on GVAs, but instead mediates its effect by an indirect pathway via action on APJ expressing cells in the gastric mucosa.

The effects of CRF receptor antagonists on food intakes and choice in sedentary and wheel running rats

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When access to voluntary running is introduced simultaneously with a novel palatable diet e.g. a high fat, energy dense (HF) diet, rats completely avoid the HF diet and consume only the standard chow diet in an ad libitum, two-diet choice condition during the running period. Brain corticotropin releasing factor (CRF) has been suggested to be involved in the feeding effects of exercise. Accordingly, we hypothesized that blocking CRF signaling with a CRF receptor antagonist would alleviate wheel running induced HF diet avoidance. Sedentary (Sed) and wheel running (WR) rats were given daily intracerebral ventricular injections of the CRF receptor antagonists, alpha-helical CRF (20-40 µg, ahCRF) or asstressin (24 µg), or vehicle (Veh) one day before and three days after the introduction of HF diet and running access. When all rats were sedentary, CRF antagonists resulted in 18% decrease of chow intake. During the two diet-choice condition, diet intakes did not differ between Veh and CRF antagonist treating Sed rats. Although significantly less than Sed rats (83 – 116 kcal/day), ahCRF significantly increased HF diet intakes in WR rats (Veh vs. ahCRF = 5.4 – 0.33 vs. 16.3 – 18.2 kcal/day) without a significant decrease in running activity. These data suggest that the brain CRF system plays a role in wheel running associated HF diet avoidance. Support: the Klarman Family Foundation

Diurnal changes in ingestive behavior: Monitoring food "Micro-Intake" events in mice provides essential information

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Measurement of food intake by small experimental animals like mice or rats is typically performed gravimetrically. However, the low mass resolution of most intake monitoring systems (usually 10-20 mg) dictates the smallest intake event that can be detected. Using a high resolution food intake monitoring system with a detection limit of 2 mg (Sable Systems Promethion) we show that many intake bouts occur below the detection threshold of conventional food intake monitoring and metabolic phenotyping systems. The food uptake of 8 male C57BL/6 mice kept at a diurnal cycle 12h/12h was measured at 6 different temperatures ranging from 19 – 29 °C. “Micro-intake” events (food intake between 2 and 20 mg) typically lasted for < 2.5 min, with some lasting < 1 min. Micro-intake events comprise 20-50% of total intake
events. About 70% of all intake events occurred during the night-phase, but the proportion of micro-intake events to total intake events was higher during the day- then during the night-phase. This uptake pattern was shown by each individual mouse and did not change with temperature or, thus, with metabolic flux rates. Although the contribution of “micro-intake” events to total food intake amounts is relatively minor, each corresponds to a decision to initiate intake followed by rapid satiety and termination of feeding behavior. Micro-intake events cannot be ignored if a complete understanding of model animal feeding behavior is required.

Perceived social norms predict changes in self-reported vegetable intake

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Social norms influence food choice. Evidence from cross sectional questionnaire studies suggests a relationship between a person’s own intake of vegetables and the perception of how many vegetables other people eat (descriptive norm). The aim of the present study was to examine whether perceived social norms predict changes in self-reported vegetable consumption over time. 664 Undergraduate students (113 men and 545 women, mean age = 19.1, mean BMI = 22) completed an online questionnaire asking about demographics, norm perceptions and eating habits at baseline and 3 months later. The loss at follow-up was 41.7%. The change in self-reported vegetable intake was predicted by the mismatch between a participant’s self-reported vegetable consumption at baseline and their perception of the norm. Follow up ANOVA on self-reported vegetable intake over time according to norm mismatch found that participants who perceived that the norm vegetable intake was lower than their own intake significantly reduced their vegetable consumption from baseline to follow-up, whereas those who perceived the norm to be higher than their own intake significantly increased their reported vegetable consumption from baseline to follow up. Where there was no mismatch between self-reported behaviour and the perceived norm there was a significant increase in reported consumption towards the actual intake of the sample. These data suggest that correction of perceptions of low normative consumption levels may be helpful in increasing vegetable consumption.

Brain-Derived Neurotrophic Factor Increased Energy Expenditure of Estradiol-Treated Ovariectomized Rats via Enhancing Sympathetic Activity

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Brain-derived neurotrophic factor (BDNF) decreases energy intake in rats. Ovariectomized (OVX) rats with estradiol (E2) replacement (OVX+E2) at a physiological dose responded to a lower dose of central BDNF administration to suppress feeding than OVX rats with oil injections (OVX+Oil), indicating that E2 modulates the anorectic effect of BDNF. We hypothesized that central BDNF administration differentially regulated energy expenditure in OVX rats with or without E2 replacement. Saline or a low dose (0.1 microgram/microliter) of BDNF was administered in OVX+Oil or OVX+E2 rats, and their energy expenditure was measured during the first 24 hours after the injection. BDNF increased oxygen consumption during light and dark phases in OVX+E2, but not in OVX+Oil, rats, suggesting that E2 promoted BDNF induced increase in energy expenditure. We then hypothesized that the BDNF-induced increase in energy expenditure was due to enhanced sympathetic activity. Norepinephrine turnover (NETO) of each organ was similar among all saline-inject groups. BDNF increased NETO in the heart, liver, skeletal muscle, and brown and white adipose tissues of sham-operated and OVX+E2 rats, whereas BDNF-treated OVX+Oil rats had similar NETO, compared to their saline groups. These findings suggested
that physiologic level of E2 facilitated central BDNF-induced increase in energy expenditure, at least partially via enhancing sympathetic drive to peripheral metabolic organs.

Oral Stimulation with Sucralose Reveals Differential Patterns of FLI in the Rostral NTS of Sucralose-Preferring and –Avoiding Rats

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Psychophysical analyses of the taste quality of sucralose reveal that 25% of rats generalize the taste of concentrated sucralose to that of sucrose (sucralose preferrers; SP), while the remaining 75% of rats detect a quinine (QHCl)-like quality at identical concentrations (sucralose avoiders; SA). ‘Bitter’ and ‘sweet’ tastants evoke starkly different patterns of Fos-like immunoreactivity (FLI) in the rostral nucleus of the solitary tract (rNTS). While ‘bitter’ QHCl elicits FLI clustered in the dorsal medial (DM) area, ‘sweet’ sucrose evokes greater FLI in the dorsal central (DC) area, relative to QHCl. As such, we reasoned that sucralose would elicit differing patterns of FLI in SP and SA. To test this, FLI was quantified in the rNTS after oral infusion of QHCl, sucrose and sucralose in SP and SA. Neuronal representation of the taste of sucralose differed in SP/SA consistent with their phenotype ($F(5,70)=3.46, P<0.01$). In SA, sucralose elicited FLI primarily in the DM rNTS, a pattern indistinguishable from QHCl. Sucralose elicited similar amounts of FLI in the DM rNTS of SP as SA ($P=0.56$), but FLI was increased in the DC area only in SP ($P<0.01$), similar to the effect of sucrose. Analyses of all three stimuli indicate that the pattern of FLI was not associated with taste reactivity measures, suggesting that the FLI pattern was indicative of the salient taste quality. These data provide evidence that the SP/SA phenotype is the result of an increased sweet-like signal generated by sucralose in SP, presumably due to a putative polymorphism in one of the T1R proteins.

Amylin and leptin interact in the control of eating

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In contrast to leptin, obese animals do not seem to develop tolerance towards the eating-inhibitory effect of amylin. Numerous studies indicate that amylin improves leptin sensitivity in various animal models. The aims of this study were to investigate the effect of amylin in animal models of reduced leptin sensitivity and to examine the role of amylin signaling in the area postrema (AP) in these animals. Amylin’s dose-response for the inhibition of eating in animals was assessed in db/db mice (20-1000 µg/kg) and Zucker diabetic fatty (ZDF) rats (5-50 µg/kg). Terminally, amylin’s effect on the activation of hindbrain neurons was assessed by c-Fos staining. Brain sections were also double-labeled for the calcitonin receptor (CTR) protein. Db/db mice and ZDF rats were less sensitive to amylin’s effect. Wt control mice ate significantly less in response to the lowest amylin dose tested whereas the threshold dose in db/db mice was between 100 and 500 µg/kg. Db/db mice also showed reduced activation of neurons and reduced CTR expression. Lean control rats ate significantly less in response to amylin, with a threshold dose between 20 and 50 µg/kg, while no effect on eating was observed in ZDF rats. Surprisingly, amylin induced similarly strong c-Fos responses in ZDF and control rats. In conclusion, amylin action is not fully developed in these two animal models of reduced leptin signaling. In db/db mice, the reduction of the amylin receptor component CTR in the AP suggest that the hindbrain may contribute to the mediation of the interaction of amylin and leptin in the control of eating.

Anxious adolescents reporting poor quality of maternal care have altered food intake according to
Low maternal care increases anxiety and cortisol stress responses. We have demonstrated in rodents that early life trauma leads to anxiety and increased stress responses and modifies food intake in a new environment. We aimed at verifying the interaction between maternal care, anxiety cortisol on food intake in a new environment in humans. A communitarian sample was evaluated using the Parental Bonding Instrument (PBI), caloric consumption in a new environment (meal choice at a snack bar) and baseline salivary cortisol, and a GLM was performed. It was found an interaction between maternal care, anxiety and baseline cortisol levels in the total calories consumption (snack) in a new environment (p=0.022). In anxious adolescents that reported low maternal care at childhood, the calories consumption varies according to cortisol (positive correlation, p< 0.05), without other groups effects. These results in humans reproduced experimental research findings and demonstrate that variations in HPA axis functioning can moderate the maternal care and anxiety effects on feeding behavior in adolescents.

Integrating neurocognitive evaluation during a meal: a feasibility study

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There are presently no methodologies available for the study of neurocognition in the context of naturalistic eating experiments. In this study, we examined the feasibility of integrating portable eye-tracking and electroencephalography (EEG) during a complex meal. 5 volunteers were asked to eat, under 6h fasting, from an experimental buffet meal consisting of 6 randomly distributed plates placed in a 180° arc. During the meal, subjects wore mobile eye tracking glasses and a 32-channel portable EEG system. Resting EEG was recorded at baseline (5'), immediately before eating (2'), every 5' intrameal (2'), and after satiation (5'). The procedure was well tolerated and a full meal experience was possible. All subjects ate to satiation (change in hunger: -6.5/10; change in fullness: 7.2/10) and meal durations and microstructural parameters were within normal values. Complete duration of recordings ranged from 50mins to 1h12mins. EEG activity was severely disrupted during eating-related movements; however, high-quality resting-state EEG was available for analysis in all cases. Large variability was observed in topographic distribution of frequency band power over time. Satiation led to a consistent increase in beta power in frontal locations, an effect that was more prominent in the left hemisphere (7-9% increase in F3, F7 vs 3-4% increase in F4, F8). Eye-tracking activity was collected throughout the meal and the combination of both techniques did not cause any artifact or interference. We conclude that it is possible to integrate portable eye-tracking and EEG during a meal. This methodology can be applied in future studies.

Brain network activity during simulation of dietary restraint is associated with real food choice in a buffet meal

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Individual neurocognitive characteristics, particularly executive functions and underlying brain systems, may support adaptive eating behavior and prevent overeating. In this study, we examined the association between laboratory measures related to eating control and naturalistic food choice. 23 healthy young...
women were evaluated, in a randomized and counterbalanced order, using: (1) brain network analysis during an fMRI task where they had to imagine either restraint or immediate consumption of appetizing foods that were presented as images, (2) a neuropsychology task of inhibitory control over food, and (3) ad libitum eating and eye fixations during a buffet type meal with matched high- and low-calorie dishes. We found that suppression of the default mode network (DMN) by the dorsal attentional network (DAN) was correlated with %high-calorie choices in the buffet ($r=-0.517; p=0.033$). Extreme high-calorie-seeking subjects had a scattered pattern of fixations throughout the meal, particularly at the beginning, and more fixation-behavior mismatches. There was also a negative correlation trend between DAN strength over the orbitofrontal network and inhibitory performance ($p=0.080$). In a multiple regression analysis including all available data, DMN:DAN predicted 26.2% of food choice variance in the buffet ($p=0.042$). These results suggest that excessive engagement of executive attention may represent a sign of inefficient dietary restraint and inability to resist the presence of high-calorie food in the environment. (* equally contributing authors)

Don’t Eat Yourself Sick: Obesity is Associated with Compromised Immunity

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Obesity, specifically dysregulation/accumulation of central/visceral adipose tissue, is associated with many diseases including, but not limited, to CVD, dyslipidemia, cancer, and type-2 DM. The increased propensity for individuals with visceral obesity to experience such comorbidities appears to be linked to the increased capacity of this depot to induce inflammation. The lymphatic system is a conduit for immune cells that plays a fundamental role in health, immune and inflammation regulation of the adipose tissue it resides in. To accurately understand the mechanisms that lead to the prolonged state of inflammation induced by visceral obesity the role of the lymphatics must be elucidated. Here we ask: Do immune cells taken from lymph nodes (LNs) in visceral fat adapt to obesity in a manner that is significantly different from immune cells in subcutaneous fat LN. To assess this, visceral and subcutaneous LNs were collected from mice fed control or western (high sugar/saturated fat) diet for three months. Using transcriptomics, gene profiles revealed LNs in the visceral cavity, were characterized by increased pro-inflammatory genes compared to subcutaneous LNs in both chow and western diet mice. Using cell flow cytometry we demonstrate that diet-induced obesity differentially influences composition and number of immune cells in visceral and subcutaneous LNs. Identifying differential characteristics of regional lymph cell populations is critical to understanding the relationship between central/visceral adiposity and associated susceptibility to inflammatory diseases.

The ‘smart dining table’: a prototype for automatic evaluation of eating behavior during a meal

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There is a need for innovative methods that perform automatic and online evaluation of human eating behavior in naturalistic conditions. Here we examined the feasibility of a new technology for automatic classification of bites during a buffet style meal. We used a SUR40 multitouch tabletop computer, powered by an infrared camera behind the screen. Tags were attached to 3 plates allowing their position to be tracked and the saturation in the surrounding region was measured. A Kinect camera was used to record the meals for manual verification, and provide gesture detection for when the bites were taken. This triggered classification of the source plate using the SUR40 based on saturation flux in the preceding time window. 5 healthy subjects (20-40yo, 1F) were tested, providing a total sample of 320 bites. Sensitivity, defined as the number of correctly detected bites out of the number of actual bites, was 67.5%. Specificity, defined as the number of correctly classified bites out of those detected, was 82.4%. Due to the poor sensitivity, a second
experiment was designed using a single plate and a Myo armband containing a 9-axis accelerometer as an alternative method for bite detection. The same subjects were tested (sample: 195 bites). Using a simple threshold on the pitch reading of the magnetometer, the Myo data achieved 86.1% sensitivity, vs 60.5% with the Kinect. The rate of false positives was also improved. We conclude that the SUR40 + Myo is feasible for automatic detection and classification of bites with adequate accuracy and can be used in future research applications.

**Does dietary variability compromise flavour-nutrient learning?**

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It is widely accepted that changes in the environment are responsible for the current obesity epidemic. One feature of our obesogenic environment is a greater assortment of food products (multiple versions of the same type of food, available in different energy densities and portion sizes). One potential consequence of this increased ‘dietary variability’ is that, for any given type of food, the postingestive effects of eating are more variable and, thus, less predictable. Studies in rodents have shown that being able to reliably predict the energy content of a food is important for food intake control—rats that are exposed to a food that varies in its energy density tend to overeat and gain weight relative to those that are exposed to a more predictable diet. However, it is unclear whether this kind of ‘flavour-nutrient’ (FN) consistency plays as important a role in governing food intake in humans. A likely way in which FN learning could impact human dietary behaviour is by modifying expected satiety (the postingestive effects a person expects will occur after eating a particular food). Here, experiments will be reviewed that have explored the relationship between dietary variability and expected satiety. The results of these studies suggest that dietary variability may promote lower and less confident judgments of expected satiety, potentially at the detriment of food intake control. The mechanisms by which dietary variability undermines flavour-nutrient learning will also be discussed.

**Estradiol modulates the anorexic response to central GLP-1**

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Estradiol is known to suppress food intake by enhancing the response to other anorexic signals. Previous data suggest that estradiol influences female rats’ sensitivity to endogenous glucagon-like peptide 1 (GLP-1) in the periphery. Here, we asked whether estradiol influences the response to GLP-1 delivered to the brain. Naïve female rats were bilaterally ovariectomized and implanted with cannulas targeting the lateral ventricle (LV). Subjects were randomly assigned to groups receiving a weekly injection of either 2 μg β-Estradiol 3-benzoate (EB) (n=9) or sesame oil vehicle (n=9). The following day, they received an intra-LV injection of vehicle or GLP-1 (1 μg or 10 μg) 30 minutes before dark-cycle onset. As expected, after LV vehicle, the EB group showed significantly lower dark-phase chow intake than the oil group (16%). In the EB group, both doses of GLP-1 significantly suppressed cumulative chow intake relative to vehicle starting as early as 1 h (45%) and continuing throughout the 21 h after injection (20%), but the oil group showed no response to GLP-1. Detailed meal pattern analysis showed that EB significantly reduced average meal size and suggested an additional suppressive effect of GLP-1 on meal size and meal number only in the EB group, but this trend failed to reach statistical significance. We conclude that EB enhances the anorexic response to pharmacologic GLP-1 receptor stimulation in the brain. An ongoing study seeks to determine whether estrogen also modulates the response to endogenous central GLP-1.
Roux-en-Y gastric bypass (RYGB) surgery for obesity decreases intake, in part by diminishing sugar and fat enjoyment. Patients report changes in food selection, and operated rats prefer sugary and fatty items less in long-duration tests. It is unclear, however, whether these preference changes represent fundamental decreases in the palatability of such foods. Reports of reward-driven behavior after RYGB are mixed, but in our rat model we have shown that RYGB does not diminish: 1) immediate taste-guided responses to sucrose in a brief-access test; 2) response breakpoints for sucrose, the fat emulsion Intralipid, or the complete-nutrition shake Ensure during a progressive ratio task; or 3) the initial drinking rate or first burst size (considered orosensory motivational measures) of sucrose or Intralipid prior to significant postingestive consequences. These data are inconsistent with the interpretation that RYGB fundamentally lowers the motivational potency of the taste of these stimuli. At times, RYGB rats initially ingest sugary and fatty items similar to controls and then consume progressively less on subsequent presentations. This is suggestive of learning akin to conditioned avoidance in which intake decreases but food maintains its palatability. Collectively, these findings suggest that while RYGB ultimately changes food selection, these changes are not due to immediate alterations of ‘taste’, but rather require some threshold of postoperative postingestive experience.

Self-reported responsivity and psychophysiological responding during a food exposure task

This study examines the relationship between self-reported and psychophysiological indicators of food cue reactivity during an exposure task. Participants were 50 college students (22.30 ± 2.56 years; 74% female; 36% Non-Hispanic Caucasian) who completed a one-session laboratory visit. After consuming a liquid-protein pre-load, participants were connected to the J & J Engineering I-330-C2+ 6 channel biofeedback system to measure psychophysiological responding over a 40-minute period (8-min baseline, 24-min food exposure, and 8-min recovery). During the exposure, participants were presented with two foods (cheese pizza, brownie, cinnamon roll) and instructed to look, smell, and imagine how the foods tasted. The Power of Food Scale (PFS) was administered to measure self-reported responsiveness to the food environment. Variables that violated statistical assumptions underwent transformations. Individuals with high PFS scores had greater levels of parasympathetic responding than individuals with low PFS scores ($p$’s < .05). A mixed effects repeated measures ANOVA revealed a significant time by PFS score interaction on high frequency heart rate variability ($F_{4,43} = 2.82, p = .03$), such that individuals with high PFS scores decreased their parasympathetic cue reactivity more over time than individuals with low PFS scores when presented with highly palatable food stimuli. Additional research is needed to explore whether these psychophysiological differences predict food cravings and consumption in naturalistic settings.

Effect of diet on the number and differentiated type of intestinal epithelial cells

This study examines the relationship between self-reported and psychophysiological indicators of food cue reactivity during an exposure task. Participants were 50 college students (22.30 ± 2.56 years; 74% female; 36% Non-Hispanic Caucasian) who completed a one-session laboratory visit. After consuming a liquid-protein pre-load, participants were connected to the J & J Engineering I-330-C2+ 6 channel biofeedback system to measure psychophysiological responding over a 40-minute period (8-min baseline, 24-min food exposure, and 8-min recovery). During the exposure, participants were presented with two foods (cheese pizza, brownie, cinnamon roll) and instructed to look, smell, and imagine how the foods tasted. The Power of Food Scale (PFS) was administered to measure self-reported responsiveness to the food environment. Variables that violated statistical assumptions underwent transformations. Individuals with high PFS scores had greater levels of parasympathetic responding than individuals with low PFS scores ($p$’s < .05). A mixed effects repeated measures ANOVA revealed a significant time by PFS score interaction on high frequency heart rate variability ($F_{4,43} = 2.82, p = .03$), such that individuals with high PFS scores decreased their parasympathetic cue reactivity more over time than individuals with low PFS scores when presented with highly palatable food stimuli. Additional research is needed to explore whether these psychophysiological differences predict food cravings and consumption in naturalistic settings.

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The intestinal epithelium plays an integral role in ingestive behaviors. Nutrient sensing, absorption and hormone release by epithelial cells contribute to changes in downstream metabolism and feeding behavior. Beyond varied cellular responses, luminal nutrients are able to drive changes in the morphology of intestinal epithelial tissue. The amount of intestinal luminal nutrients dictates the number of intestinal epithelial cells and villus-crypt size. However, it is not known whether the type of diet drives changes in epithelial morphology. Thus, we investigated if there is a differential effect of a low-fat or high-fat diet on the overall number of intestinal epithelial cells or the number of each type of differentiated cells. Male Sprague-Dawley rats were fed 1) ab libitum on a low fat diet 2) ad libitum on high fat diet or 3) pair fed on a high fat diet to the kcal amount of low fat fed animals. After 3 weeks in each feeding condition, animals were sacrificed and intestinal tissue was excised and immunohistochemically processed to visualize and quantify overall epithelial cell number and each of the differentiated epithelial cell types. We found that the amount of nutrients eaten, as measured by the kcal intake of each diet, drives the overall number of epithelial cells. In contrast, the type of diet drives changes in the ratio of the goblet and enteroendocrine cell number to the total number of cells. These nutrient-driven changes in tissue morphology may contribute to many of the functional intestinal differences seen in previous studies.

**Long-term effect of water loading on food intake.**

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There is a close relationship between food and water intakes. The majority of daily fluid intake occurs during mealtimes, and individuals who consume more water tend to consume fewer calories and generally have healthier eating behaviors. Furthermore, several studies have found that drinking a pre-load of water before a meal suppresses food intake during that meal. We have extended these findings by examining water loading several hours before the test meal. All subjects drank 500 ml of water with a standardized breakfast 3 h before their visit to the laboratory. They were then split into three conditions: the “no water” group received no additional water prior to lunch, the “acute water” group received 500 ml of water 30 min before lunch, and the “long-term water” group received 500 ml 2 h and again 30 min before lunch. Subjects were then provided with a buffet lunch and energy intake was measured. Subjects in the long-term water condition consumed fewer calories during lunch than either the no water, or the acute water groups (p=0.01; p=0.03 respectively). This effect is likely due to a general suppression of intake, because drinking three bottles of water throughout the morning suppressed carbohydrate and sodium intake relative to the no water and acute water groups (p=0.009; p=0.02; p=0.01; and p=0.03 respectively). Protein intake was also suppressed, however, only in comparison to the acute water group (p=0.03). This line of inquiry is likely to have important implications in the relationship between food and water intakes, and add to literature on the dietary benefits of water intake before meals.

**Fluid balance challenges influence Glucagon-like peptide-1-associated gene expression both peripherally and centrally**

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Glucagon-like peptide-1 (GLP-1) appears to play a role in fluid intake. We previously demonstrated that administration of GLP-1R agonists decreases both water and saline intakes, and more recently showed that drinking water in a state of water deprivation stimulates production of proglucagon, the GLP-1 precursor, in the nucleus of the solitary tract of rats. In the current set of experiments we extended these findings by measuring gene expression of GLP-1-associated genes in multiple brain areas and ileum after either an
osmotic, or a mixed osmotic/hypovolemic challenge. In the first experiment, mRNA was measured in rats stimulated to drink water by injection of hypertonic saline and the results were compared with control rats given injections of isotonic saline. In a second experiment, rats were stimulated to drink saline by overnight fluid deprivation, and levels of mRNA were compared with those in control rats that were not fluid deprived. Both experiments included rats in four groups: no access to fluid, access to fluid in a bottle, orogastric infusion of fluid, or an orogastric infusion of methylcellulose. Tissue was collected from the ileum, and from the paraventricular nucleus, subfornical organ, and the nucleus of the solitary tract, and mRNA levels for proglucagon and GLP-1R were measured. We found changes in GLP-1-associated gene expression in every region examined in both experiments. These experiments provide additional evidence that the endogenous GLP-1 system is involved in the regulation of fluid balance and suggest a role for both peripheral and central regions.

Control of meal size by direct neuroendocrine signaling in the mesolimbic reward system

EG MIETLICKI-BAASE1, EG MIETLICKI-BAASE

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Behavioral mechanisms that modulate energy balance include changes in meal patterns, which can influence the initiation and/or termination of feeding. For example, increased neuroendocrine satiation signaling may reduce meal size and promote meal termination by reducing the rewarding properties of an ongoing meal; this highlights the need to investigate the role of reward-related CNS nuclei in meal pattern control. Indeed, a variety of peripherally-derived neuroendocrine signals affect energy balance via direct actions in the ventral tegmental area (VTA), a mesolimbic nucleus important for reward and motivated behavior. We have shown that the pancreatic hormone amylin and the intestinal hormone glucagon-like peptide-1 (GLP-1) each activate the VTA in a physiologically relevant manner to reduce food intake. GLP-1 receptor (GLP-1R) or amylin receptor (AmyR) activation in the VTA produces hypophagia primarily by suppressing meal size. However, our understanding of the physiological and neuroanatomical mechanisms by which these peptides act in the mesolimbic system to control food intake and meal patterns is incomplete. Our work shows that VTA AmyR activation suppresses mesolimbic dopamine (DA) signaling to control feeding and food reward. Although GLP-1R signaling in the VTA also may modulate the activity of DA neurons, this occurs predominantly via a presynaptic mechanism involving glutamnergic AMPA/kainate signaling. Ongoing studies continue to evaluate the modulation of mesolimbic signaling by these peptides, including their effects on DA/glutamate signaling in key afferent targets of the VTA. (K01-DK103804)

Mice do not always choose cheap food

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Evolution-based theories propose that animals should forage to maximize their inclusive fitness. Under this prediction, it is assumed that animals should maximize energy yield while minimizing energy expenditure. In these experiments, we examined the extent to which mice would behave as optimal opportunistic foragers. C57BL/6 male mice lived in operant chambers with 23-h per day availability of food pellets via lever press and ad libitum water. The animals were exposed to the following protocol: one (constant) lever was available 23-h per day and delivered one 45 mg pellet of standard growth (AIN-93G) diet upon completion of every 100 responses (the fixed unit price or FUP). A second (cheap opportunity) lever was operational at four fixed times, each 15 min, during the 23-h period and delivered a pellet of AIN-93G for every 5 responses. Animals earned slightly more pellets on the cheap opportunity than on the constant lever, but the difference was surprisingly small. Manipulation of the times at which the opportunity lever was available revealed a large difference depending on whether the cheap food opportunity was available
during the light or dark cycle: mice preferentially earned cheap food if it was available during the dark cycle but not during the light. It is known that rodents consume most of their daily food intake during the dark cycle and the present data suggest that either the exogenous cycle or an endogenous circadian oscillator influences the way in which economic factors affect economic choice or opportunistic feeding.

**Effects of Idealized Media Images on Food Intake and Appearance Anxiety**

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Effects of Idealized Media Images on Food Intake and Appearance Anxiety. A. Mitra, A.C. Thompson, Psychology Department, St. Catherine University, St. Paul, MN 55105 Extensive research has shown that women feel lower body image satisfaction and more pressure to lose weight after exposure to idealized female media images. We examined the effect of the media on the type and amount of food women ate. To prevent our 63 female participants from feeling self-conscious about their food intake, they were told that study’s purpose was to measure memorability of various advertising images. While examining the media images of either thin models, fit models, or living rooms, participants were given a selection of snacks: grapes, carrots, chocolate chip cookies and potato chips. After 10 minutes with the images, the participants were told the true purpose of the study, and asked to complete several questionnaires relating to body image, recent meals and media influence. We found no statistically significant differences in choice of food or quantity of food consumed across the three groups. We did find, however, differences in appearance anxiety across the groups; women who were exposed to the fit and thin images reported significantly lower restrained eating than the control group (p< .05). Also, the group exposed to the thin images reported lower physical appearance anxiety than the control group (p< .05). These results are surprising. The fact that these data were collected at an all-women University, where the women are educated on the adverse influence of the media on women might provide a possible explanation for these results.

**Infants’ Reactions to Novel Foods Predict Food Neophobia during Early Childhood**

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Food neophobia, or wariness to try novel foods, reaches a peak during early childhood. However, there have been no longitudinal studies on the development of neophobia. The purpose of this study was to investigate whether reactions to new foods during infancy predict behavioral and parent-reported food neophobia during early childhood. Data were drawn from a longitudinal study following individuals (n = 82) from infancy through early childhood. When the infants were 6 and 12 months of age, they were recorded tasting a novel food (i.e. green beans, hummus, or cottage cheese). Acceptance of the food (i.e. neutral or positive facial expressions) was coded from the recordings. When the children were 4 years of age, they participated in a laboratory visit where they could taste up to three novel foods: nori, lychee, and haw jelly. Mothers of the children also reported their children’s level of food neophobia using the Food Neophobia Scale for Children (FNS-C). Preliminary results show that reactions to novel foods during infancy predict behavioral and parent-reported food neophobia at age 4. Infants who were more accepting of the novel food at 6 months tasted more novel foods (r = .27, p = .03) and were rated as less neophobic by their mothers (r = -.38, p = .002) at age 4 compared to infants who were less accepting of the novel food. Similarly, infants who were more accepting of the novel food at 12 months were rated as less neophobic (r = - .40, p < .001) at age 4. These results provide preliminary evidence that there may be some stability in responses to novel foods from infancy through early childhood.
Relationships between disordered eating attitudes and executive functioning in an overweight/obese treatment seeking sample

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Research suggests obesity is related to defects in executive functioning; however, there is a lack of research investigating how disordered eating attitudes may be associated with impaired executive functioning among overweight/obese individuals. The purpose of the present study was to examine the relationship between obesity, disordered eating attitudes, and executive functioning in a sample of overweight/obese adults (N=57; 72% female; Mage=42.1, SD=10.3; MBMI=33.3, SD=4.7) seeking treatment for weight loss. The trail making test (D-KEFS version) was administered to measure cognitive flexibility; the digit span task assessed verbal working memory. The Eating Disorder Examination Questionnaire subscales (Restraint, Eating Concern, Shape Concern, Weight Concern) and Global score were used to measure disordered eating attitudes. Height and weight were measured. After controlling for age and education, age-adjusted scaled scores on the digit span were inversely related to Weight Concern ($\beta=-.26, p< .05$) and overall Global scores ($\beta=-.29, p< .05$). Longer time to complete the letter-number switching condition of the trail making task was associated with increased Weight Concern ($\beta=.29, p< .05$). BMI was not associated with performance. Findings provide initial support that there may be underlying relationships between the severity of disordered eating cognitions, working memory, and set-shifting among overweight/obese individuals that have previously been unaddressed.

Maternal obesity regulates taste receptor expression in the heart of rat offspring

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Growing evidence indicates that maternal obesity leads to adverse outcomes for offspring, including cardiac pathologies. Changes in taste preference of offspring from mothers consuming a high fat diet (HFD) have also been reported. Cardiac taste receptors were recently described, and shown to be regulated during development. We hypothesized that maternal obesity would modulate the expression of cardiac taste receptors; effects of maternal exercise were also investigated. Female Sprague-Dawley rats were fed chow (C) or HFD (F) and half of each were provided with a running wheel permitting voluntary exercise (CE or FE) from 10 days prior to mating, whilst the others remained sedentary (CS or FS). Cardiac taste receptors were measured by PCR in pups killed at postnatal day 19. Both lean and obese dams undertook similar amounts of exercise (8.1±2.4 vs 5.1±1.5 km total). Maternal obesity increased offspring body weight, adiposity, heart ventricle mass (all $P<0.05$) and leptin concentration ($P<0.01$), with no effect of exercise. Heart mass remained heavier after correction for body weight. Cardiac ventricle mRNA expression of bitter type 2 taste receptors and beta adrenergic receptor were decreased in response to maternal HFD with no effect of exercise. Maternal obesity and exercise had no impact on umami receptors. In conclusion, maternal obesity selectively affected the expression of bitter taste receptors and other genes in the cardiac ventricle of weanling rats. Further work is required to determine whether these changes have implications for cardiac function.

Short-term Weight Variability Predicts Weight Gain

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Because obesity is so difficult to treat, prevention of unhealthy weight gain is critical. Identifying predictors of accelerated weight gain will aid preventive efforts. A novel candidate for such prediction is weight variability (WV). Body weight in lower animals and humans is typically highly stable despite a tremendous flux in energy intake and expenditure over time. Greater WV may suggest an altered regulatory system that has been compromised by biological and/or environmental influences and, in an obesogenic environment, may be a marker of future weight gain. The current study sought to examine this relationship: longitudinal data were collected from 171 females with BMIs in the normal range on average (M age = 18.27, SD = 0.47; M BMI = 23.55 kg/m², SD = 2.67). Weights were collected at baseline, 6 weeks, 6 months, and 2 years. WV was calculated as the root mean square error around a linear regression curve modeled on both within- and between-subject weight trajectories. Linear regression analysis tested whether individual WV over the first 6 months predicted weight change from 6 to 24 months. Results indicated that WV significantly predicted subsequent weight gain (p < 0.01). Importantly, WV remained a significant predictor of weight gain independent of BMI, BMI change from baseline to 6 months, and when controlling for disinhibition and restrained eating. It will be important to replicate these findings and examine shorter periods of WV. Identification of this objective, readily assessed variable as a reliable predictor of future weight gain could shed light on mechanisms of sustained positive energy balance and benefit preventive programs.

The Myth of the Anti-Obesity Effect of Garcinia Cambogia

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Issues of obesity in America have become an escalating and problematic public health concern. Because of the paucity of approved weight loss drugs, many obese Americans have turned to dietary supplements to improve their health and body image. In addition, some of the supplements have been marketed as having the ability to enhance memory. Although not approved by the FDA, one supplement, Garcinia Cambogia, has been touted as a highly effective substance to induce weight loss. This compound rose to fame after Dr. Mehmet Oz deemed the supplement as “The Holy Grail of Weight Loss” on his popular TV program. Garcinia Cambogia is a small fruit that contains a natural extract, hydroxycitric acid, which is the key ingredient purported to be responsible for rapid weight loss, even in the absence of exercise. The present study was conducted to examine the effects of Garcinia Cambogia on body weight, food intake, water intake, and adiposity in male Long Evans rats. Possible alterations in memory functions, under the influence of the supplement, were also examined utilizing the Morris Water Maze. The experiment consisted of a 7-day habituation period followed by a 25-day experimental period. A dose of 500mg/kg body weight of the drug was administered daily in a condensed milk “treat”. It was hypothesized that Garcinia Cambogia would cause rapid body weight loss and produce significant improvement in memory. It was demonstrated, however, that, with the absence of exercise, Garcinia Cambogia had no significant effect on body weight, food intake, water intake, adiposity, or memory.

Portion size influences meal intake in the pastoralist Samburu people of Kenya

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For people in the modernized food environment, external cues for food availability, variety, and palatability can overcome internal satiation signals to promote excess intake. Portion size is one such external cue; people typically consume more when served more, often without awareness. Though susceptibility to external cues may be attributed to the modernized, cue-saturated environment, there is little research on people living outside that context, or with distinctly different food norms. We studied a
sample of Samburu, a semi-nomadic Kenyan pastoralist group that maintains a traditional lifestyle and eats a limited diet. Participants (12 male, 12 female, aged 20-74, mean BMI = 18.4) attended the study on two days and were provided (in counterbalanced order) an individual serving bowl containing 1.4 or 2.3 kg of a familiar bean and maize stew. Time spent eating and amount consumed were recorded, along with post-meal questions in the local language about appetite and satiety. Data were omitted from two participants who consumed the entire portion in a session. Even though the ‘smaller’ serving was a very large meal, participants consumed 40% more when given the larger serving, despite reporting similar post-meal satiety, and being unable to reliably identify which day they consumed more food. This result in the Samburu demonstrates the portion size effect is not a by-product of the modern food environment and may represent a more fundamental feature of human dietary psychology.

Effects of a modern ‘junk food’ or ‘natural food’ cafeteria diet on flavor-nutrient learning and sweet taste responses in rats

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In the modern diet, food processing manipulates flavor, texture, and sweetness, obscuring the correspondence between sensory properties and postingestive consequences. Long-term exposure to these hyper-palatable ‘junk’ foods may dysregulate appetite, perhaps by impairing ability to adaptively adjust intake based on flavor-nutrient associations. Animal studies of ‘cafeteria diets’ model these effects but typically compare palatable foods to a chow-only diet which is itself unnatural in sensory and nutritional monotony. We attempted to model the extreme variety of the modern diet with long-term exposure to cafeteria diets of unusual breadth (2 or 3 novel foods each day, >80 different foods over 3 months, plus ad lib chow). For one group (PF) these were all processed snack foods. For another group (NF) they were all ‘natural’ foods (minimally-processed, no manipulated flavors, added sugars or fats, e.g., fresh fruits, vegetables, grains). A CON group was fed chow only. In subsequent tests of flavor-nutrient learning PF and NF rats, like CON, consistently acquired strong preferences and dramatically increased acceptance for novel flavors paired with caloric outcome. Thus like prior studies using less variety we find no evidence PF diets impair flavor-nutrient learning. However, in several tests both PF and NF groups had consistently lower ad lib sweet solution intake than CON. This is likely for different reasons, since in lick microstructure analysis PF and NF rats had divergent palatability responses to sucrose, revealing different effects of PF vs NF diet.

Intra-VTA insulin decreases nucleus accumbens dopamine release in vivo

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Mesolimbic dopamine (DA) circuits, implicated in incentive motivation, are an important target for metabolic hormones such as leptin, insulin and ghrelin. We have previously demonstrated that insulin induces long-term depression of excitatory synapses onto ventral tegmental area (VTA) DA neurons and reduces food reward behaviours including food anticipatory behaviour and conditioned place preference for food. Whether insulin acts in the VTA to reduce DA release in key projection areas of VTA DA neurons remains unknown. Using in vivo fast scan cyclic voltammetry to detect rapid fluctuations in extracellular DA concentrations in the nucleus accumbens (NAc) of anesthetized rats, we show that peripheral and intra-VTA administration of insulin reduces stimulated DA release in the NAc, an effect that is blocked by the insulin receptor antagonist, S961. Furthermore, intra-VTA insulin reduces cocaine-evoked increases in NAc DA. These data suggest that insulin's ability to alter feeding behaviour is mediated, in part, by its
ability to modulate DA release. In addition, because insulin decreases cocaine-evoked DA release, CNS delivery of insulin may provide clinical utility by decreasing drug-induced craving.

Decreased dorsal striatal response to a palatable milkshake is associated with impaired negative outcome learning in obese/overweight, but not healthy weight individuals.

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It has been speculated that compulsive overeating is associated with an impaired ability to learn about the negative outcomes of one’s actions. Accordingly, obese individuals are impaired in tasks of negative outcome learning (Coppin et al. 2015). Prior work in humans and animals indicates that impaired negative outcome learning is associated with reduced D2 receptor signaling (Frank et al. 2007; Johnson and Kenny 2011). FMRI studies have documented reduced responses to palatable food in the D2 receptor rich dorsal striatum (DS) in obese individuals (Green et al. 2011; Stice et al. 2008) that appears to be a consequence of obesity (Stice et al. 2010) and is inversely related to impulsivity (Babbs et al. 2012). Here, using a probabilistic learning task, we demonstrate a negative relationship between DS response to milkshake and negative outcome learning in the obese/overweight group (N=16), but not in the normal weight group (N=16). These results add to a growing body of evidence suggesting that adiposity and/or diet leads to adaptations in the DS that are associated with impairments in dopamine-dependent cognitive functions.

Effect of tonicity-responsive binding protein on the hypothalamic regulation of energy balance

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Tonicity-responsive binding protein (TonEBP) is a widely expressed transcription factor whose activity is regulated by extracellular tonicity. Recent studies have reported tonicity-dependent interaction between TonEBP and p65 subunit of NF-κB, which results in an increase of NF-κB activity. Because NF-κB plays an important role in the metabolic inflammation and leptin resistance, we presumed that TonEBP may also be involved in the metabolic diseases. First we found that TonEBP expression was increased in the mouse hypothalamus by feeding high-fat diet (HFD). Mice with heterozygous TonEBP deficiency [TonEBP (+/-)] revealed a higher sensitivity to leptin treatment compared to wild type littermate. When fed HFD, TonEBP (+/-) mice were significantly less obese and showed an alleviated leptin resistance, compared to the wild type. Because suppressor of cytokine signaling 3 (SOCS3) is a negative regulator of leptin signaling, we next determined effect of TonEBP on SOCS3 expression. Leptin-induced SOCS3 expression was significantly decreased in the hypothalamus of TonEBP (+/-) mice. Promoter assays revealed that NF-κB-TonEBP complex further increased SOCS3 transcription than NF-κB alone. These results suggest that TonEBP is involved in leptin signaling pathway via controlling SOCS3 expression in the hypothalamus, and thereby, plays an important role in the development of metabolic disorder.

Variation of caloric intake and dorsovagal complex synapsin phosphorylation in rats fed high fat diet.
Diets high in fat are associated with increased caloric intake, and development of obesity in humans and rodents. On the other hand, dietary fat triggers gastrointestinal (GI) and metabolic signals that reduce meal size. Results from our lab suggest that phosphorylation of synapsin I (pSyn) in vagal afferent terminals contributes to reduced food intake in response to both peripheral (CCK) and central (melanocortin, MC) signaling. Because both GI and central MC signaling may be increased by high-fat feeding, we hypothesized that high-fat diet (HF) would increase pSyn in the dorsal vagal complex (DVC) and that the increase would coincide with alterations in caloric intake. Two groups of rats had ad libitum access to either HF (45% of calories) or chow (LF) (13.5% of calories) between 5PM and 8AM for 7 days. Food intake and bodyweight were monitored, and rats were perfused for IHC quantification of pSyn (serine 9) on days 1, 3, and 7. Nightly intake, in grams, for the two groups did not differ during the first 48h of feeding. However, caloric intake of HF rats was nearly twice that of LF rats. Moreover, HF rats exhibited increased pSyn in the DVC 24h after the start of HF, compared to LF rats. By 7 days the caloric intake of HF rats had decreased, but remained somewhat greater than that of LF rats. Likewise, DVC pSyn decreased by day 7, but remained above the levels observed in LF diet rats. We postulate that increased pSyn in vagal afferent endings is altered in response to HF and may contribute to control of food intake during GI and metabolic adaptation to increased caloric intake.

Stress and personality interact to modulate the neural response to food cues

Psychosocial stress is a contributor to weight gain for some individuals. Here we test the theory that psychosocial stress can lead to over-eating both by increasing the reward value of foods and interfering with self-control mechanisms in individuals with stress vulnerability. 22 non-obese subjects underwent fMRI while viewing food and scenery pictures over two sessions: one during a period of low academic stress and the other during the final exam period. Individual vulnerability to stress was assessed using the Behavioral Inhibition Scale (BIS), and the perception of stress was measured by Perceived Stress Scale (PSS). Higher stress levels (PSS) were observed during exam times (t (21)=2.27, p=0.03). The change in PSS correlated with individual’s BIS scores (R=0.63, p=0.002). Stress vulnerable students (as indexed by BIS) showed increased response to food cues in regions that are thought to reflect stimulus value: the right orbitofrontal and the right ventromedial prefrontal cortex (vmPFC) during the exam period. Functional connectivity of the vmPFC with regions implicated in self-control (e.g., left inferior and right middle frontal gyrus) decreased as a function of the BIS score. These results suggest vulnerable individuals show enhanced reward value and reduced self-regulation in response to food cues during stress, which may account for these individuals' increased vulnerability to stress-related weight gain and obesity.

Functional Brain Changes Associated with Weight Loss

Psychosocial stress is a contributor to weight gain for some individuals. Here we test the theory that psychosocial stress can lead to over-eating both by increasing the reward value of foods and interfering with self-control mechanisms in individuals with stress vulnerability. 22 non-obese subjects underwent fMRI while viewing food and scenery pictures over two sessions: one during a period of low academic stress and the other during the final exam period. Individual vulnerability to stress was assessed using the Behavioral Inhibition Scale (BIS), and the perception of stress was measured by Perceived Stress Scale (PSS). Higher stress levels (PSS) were observed during exam times (t (21)=2.27, p=0.03). The change in PSS correlated with individual’s BIS scores (R=0.63, p=0.002). Stress vulnerable students (as indexed by BIS) showed increased response to food cues in regions that are thought to reflect stimulus value: the right orbitofrontal and the right ventromedial prefrontal cortex (vmPFC) during the exam period. Functional connectivity of the vmPFC with regions implicated in self-control (e.g., left inferior and right middle frontal gyrus) decreased as a function of the BIS score. These results suggest vulnerable individuals show enhanced reward value and reduced self-regulation in response to food cues during stress, which may account for these individuals' increased vulnerability to stress-related weight gain and obesity.
For most adults, dieting does not result in sustainable weight-loss. In order to investigate if functional brain changes can contribute to this phenomenon, we investigated how the neural response to food cues changes as weight-loss progresses over three months. 30 adults enrolled in a three-month weight loss program based on calorie restriction (1 M; mean BMI: 30.9±3.6, range: 25-41). Subjects underwent fMRI while viewing food and scenery images at three time points: at the start, at 1 month, and at 3 months. The average BMI of the weight-loss study participants decreased over the 3 month period from 30.9 to 29.3 ($F(1.3,24.8)=40.34, p<0.001$). Compared to the baseline, at one month, participants showed reduced activation in the ventromedial prefrontal cortex, a brain region that has been implicated in reward valuation. In addition, people who lost more weight showed increased activation in the right inferior frontal gyrus (IFG) – a region involved in self-control. However, at three months the activity of the IFG returned to baseline levels despite continuous weight loss. These results suggest that while the initial weight-loss was associated with greater activity in self-control regions, this response returned to baseline at 3 months post-paradigm initiation. This change may contribute to reduced control over food intake and to subsequent weight regain in long-term.

Engineering a system to monitor home cage feeding behavior in rodents

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Studies have stressed the role of energy imbalance, where food intake exceeds energy expenditure, in the development of obesity. To study mouse models of obesity, researchers need to accurately measure food intake. However, the most common method for monitoring this involves manual periodic weighing of food, which is time consuming, imprecise, labor intensive, and cannot measure feeding patterns. There are commercial systems that automatically capture high-resolution information about food intake, but they can cost thousands of dollars per cage, making it difficult to run high-throughput feeding experiments. Here, we engineered a feeding system that: (1) is low-cost, (2) is home cage compatible, and (3) can measure both food intake and feeding patterns over multiple days. The device combines a custom-designed housing with an Arduino microcontroller and off-the-shelf electronic parts to automatically deliver food pellets and record the frequency of food retrieval. Pellet removal is sensed by a beam break, which initiates the delivery of a replacement pellet into the well. Additionally, the design is easily modified to accommodate food pellets of differing sizes. Collectively, the dispenser offers a reliable and low-cost method to accurately administer and record timestamped food retrieval during high-throughput feeding experiments.

Identifying Diet-congruent Beverages in Dieters and Non-dieters

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The amount of food consumed in a meal by dieters can be influenced by whether they perceive a starter as congruent with dieting to lose weight. Beverages often contribute significantly to daily energy intake and may also affect food consumption of dieters if perceived as diet-congruent. In order to identify which beverages are perceived by dieters and non-dieters as diet-congruent, participants in the UK and USA (N = 320) were presented with images of 14 beverages (both alcoholic and non-alcoholic) and asked to rate frequency of consumption, desirability, and association with dieting to lose weight. They were also asked to complete measures of dietary restraint (TFEQ) and drinking restraint (TRI) as well as report height and weight. Data were collected using an online survey tool. Results suggest that both men and women identified green tea, SlimFast, flavored water, and diet soda as diet-congruent and both reported using these
beverages while on a diet. However, it was common for non-dieters to rate them as more associated with dieting to lose weight than dieters did. While both dieters and non-dieters rated soda, energy drinks, sports drinks, and alcoholic beverages low on diet congruency, dieters rated soda and beer as more diet congruent than non-dieters. Furthermore, dieters often reported consuming more of the beverages including several rated as non-congruent with dieting to lose weight (such as alcoholic beverages and soda, particularly in men). The results suggest several beverages that might be tested in conjunction with food consumption in dieters.

Energetic cost of a running wheel: Implications for exercise-based weight loss interventions

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Obesity affects over 600 million adults worldwide, contributes to four of the top five causes of preventable death, and is the third highest contributor to global socioeconomic burden. Weight loss interventions have stressed the need for increased physical activity to facilitate weight loss due to strong correlative links between obesity and exercise rates; however energy expended during exercise can be compensated for by decreasing other aspects of energy expenditure. Here, we used running wheels, a common translational model of physical activity, to explore energetic compensation and to determine whether exercise results in significant changes in energy expenditure (calculated using an energy balance method from Ravussin et al., 2013). Adult C57BL/6 mice were individually housed with ad libitum access to food and water and given access to a running wheel for 3 weeks. Whereas wheel running significantly increased over the 3 weeks (5000/day in Week 1, 20000/day in Week 3), average daily energy expenditure did not change significantly over the course of the experiment. In a subset of mice, we identified a significant decrease in off-wheel physical activity as one method of energetic compensation. These data highlight the difficulty of exercise alone to cause changes in energy expenditure, due to innate compensatory mechanisms. This point should be strongly considered when utilizing exercise as a facilitator of weight loss.

AM4113 decreases food intake in female rats with greater behavioral specificity than rimonabant.

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Cannabinoid-1 receptor (CB₁) inverse agonists (e.g., rimonabant) suppress feeding, but produce adverse side effects that limit their utility in treating obesity and binge-eating disorders. In comparison, the neutral CB₁R antagonist AM4113 decreases feeding without any apparent increase in anxiety- or depressive-like behaviors in rats. To further evaluate the behavioral specificity by which AM4113 decreases feeding, we conducted the first detailed analysis of its effects on spontaneous meal patterns. Female rats were housed in custom cages equipped with a computerized system for continuous measurement of feeding behavior. Once adapted to the cages, food intake was monitored for 24 h following IP injection of AM4113 or rimonabant (0-8 mg/kg; within-subject randomized design; n=8/group). While both drugs produced dose-dependent decreases in 24 h food intake and average meal size (p< 0.001), AM4113 had a lower effective dose than rimonabant (0.5 vs. 2 mg/kg, respectively). Additionally, rimonabant, but not AM4113, increased the latency to consume the first meal by up to 2 h (p< 0.01, relative to vehicle), suggesting the presence of malaise. These findings provide the first evidence that AM4113 may be more efficacious in decreasing food intake than available CB₁R inverse agonists. Its lower anorexic dose, combined with its immediate anorexic effect, suggests that it could be highly efficacious in treating binge eating and other disorders characterized by chronic hyperphagia.
Glucagon-like peptide-1 receptor signaling in anterior and posterior regions of the paraventricular thalamic nucleus differentially affects feeding behavior

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We reported previously that glucagon-like peptide-1 receptor (GLP-1R) signaling in the paraventricular thalamic nucleus (PVT), an understudied nucleus in feeding control, reduces food intake and reward. Our finding that GLP-1R expression is higher in the posterior PVT (pPVT) than anterior PVT (aPVT), raises the possibility of regional differences in PVT GLP-1R signaling on feeding behavior. This study therefore aimed to examine the feeding effects of GLP-1R signaling in the aPVT vs pPVT. Chow or 15% sucrose (palatable) intake was measured in male rats (n=6-12) that received aPVT or pPVT microinjections of a long acting GLP-1 analogue, Exendin-4 (Ex4; 0, 6.25, 12.5ng/100nL). Results showed that Ex4 delivery to aPVT or pPVT significantly and similarly reduced chow intake 6-24h post-injection. By contrast, aPVT, but not pPVT Ex4 delivery suppressed sucrose intake. Given the well-known role of nucleus accumbens (NAc) in palatable food intake, we examined whether Ex4 differentially activates aPVT vs pPVT projecting neurons to the NAc using immunohistochemistry to colabel Ex4-induced cFos in aPVT or pPVT, with NAc core (NAcc)-injected retrograde tracer fluorogold. Analyses are ongoing but preliminary data suggest greater number of aPVT cells that project to the NAcc, compared to pPVT (189±12 vs 106±8). These findings provide novel evidence for a regional difference in PVT GLP-1R signaling in sucrose but not chow intake and that the difference may be explained by greater aPVT-NAcc neuronal projection. Supported by DK21397.

Study on the Processing of Binary Odor Mixtures in Rat: Implication for the Complex Food Odor Perception

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Food odors are often complex mixture of odor elements (e.g., furan-2-ylmethanethiol, methional etc.), but they are perceived as unitary odor object (e.g., “coffee”). On the other hand, it has been showed learned response to an odor element was generalized to binary odor mixture containing the element, and vice versa. From the findings, it is suggested binary odor mixtures (e.g., odor mixture AB) are processed elementally, and within-mixture association (e.g., odor A and odor B) can be acquired. This study aimed to examine this by combining taste-odor learning and higher-order conditioning paradigms. We used 39 adult male Wistar rats. We used artificial odors of melon (0.05%), lemon (0.1%), vanilla (0.1%) and almond (0.1%) as odor A, B, C and D in balanced manner. In the learning session, rats were exposed to 0.005 M saccharine solution containing odor B and 0.02 M quinine solution containing odor D during the first 5 days (learning between taste US and odor CS in each solution), and exposed to water containing odor mixture AB and water containing odor mixture CD during another 5 days (learning between odor CSs in each solution). Order of these two sessions was counterbalanced. In the subsequent tests, rats preferred odor B to D and preferred odor mixture AB to CD, indicating that generalization from element to mixture occurred. However, rats did not prefer odor A to C. These results indicated that binary odor mixtures might be perceived as having similar quality of their elements, but within-mixture association might not be acquired.

Sucrose-induced plasticity in the basolateral amygdala in a ‘comfort’ food paradigm

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Limited, intermittent sucrose intake (LSI) attenuates the HPA axis response to stress, and the basolateral amygdala (BLA) is necessary for the stress-relieving effects of LSI. LSI increases the expression of synaptic plasticity-associated genes in the BLA however, the nature of this plasticity is unknown. As BLA output normally promotes HPA activation, the present study tests the hypothesis that sucrose decreases excitatory tone in the BLA, thereby blunting HPA responses to stress. Adult male rats with free access to chow and water were given additional brief (< 30 min) access to 4 ml of sucrose (30%) or water twice daily for 14d. Electrophysiological recordings from projection neurons in BLA slices showed LSI increased the paired-pulse ratio for glutamatergic, but not GABAergic inputs, suggesting a reduced probability of evoked glutamate release. In contrast, LSI did not affect glutamatergic or GABAergic miniature and evoked EPSC/IPSC responses. Likewise, LSI did not alter the number of glutamatergic or GABAergic appositions onto BLA projection neurons quantified using multi-channel immunofluorescent labeling with optical sectioning microscopy. Thus, these results suggest that LSI decreased the probability of stimulated glutamate release, without altering spontaneous glutamate release or the number of glutamatergic synapses onto BLA projection neurons. This supports the hypothesis that sucrose acts to reduce BLA stimulation during stress, thereby contributing to the blunted HPA response.

Could peripheral taste-signaling proteins be exploited as targets for anti-obesity pharmacotherapeutic intervention?

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A complex network of neural and hormonal events coordinated by the central nervous system (CNS) is thought to underlie the motivational drive for procurement and consumption of food energy and nutrients. Thus pharmacotherapeutic intervention against unhealthful body weight gain has tended heavily toward a focus on CNS targets. Unfortunately that history is rife with failures due to harmful side effects and limited clinical efficacy. Drug treatment strategies targeting the CNS all are encumbered by the challenge of achieving pharmacologic specificity with receptors that often are broadly expressed and are involved in multiple neural functions. Attaining substantive clinical efficacy against obesity is additionally complicated by the potential for centrally mediated compensatory responses that could counter the actions of drug treatment. An alternative anti-obesity pharmacotherapeutic strategy aimed at regulating the activity of taste signaling proteins expressed in the tongue is proposed. The proposition is based upon the well-supported observation that taste, particularly the aspect of taste referred to as palatability, is a major determinant of consumption. Drugs could be designed to specifically regulate the activity of peripheral taste signaling proteins with the intent of reducing consumption by dampening the initial stages of sensory stimulation by highly palatable, calorie-dense substances. The plausibility and merits of the approach, likely targets and drug design requirements, and chemical entities known to impact peripheral taste signaling, and potentially body weight, will be presented.

Remembering to eat or not: hippocampal regulation of energy intake

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A critical question in neuroscience that is very poorly understood is, “How do top-down cognitive processes such as memory modulate energy intake?” Dorsal hippocampal neurons are critical for autobiographical memory of “what”, “where” and “when” something occurred in an organism’s life and control goal-directed behavior. Interestingly, these neurons are equipped to receive numerous eating-related
signals and are connected to brain regions critical for controlling energy intake. This seminar will present evidence that supports our overarching hypothesis that dorsal hippocampal neurons form a memory of a meal and inhibit intake during the period following a meal. More specifically, evidence will be presented indicating that 1) ingestion engages processes required for synaptic plasticity and memory in dorsal hippocampal neurons and 2) that inhibition of principal dorsal hippocampal neurons or their receptors accelerates meal onset and increases total intake. Evidence implicating impaired hippocampal function and memory deficits in overeating, the development of diet-induced obesity, and the maintenance of the obese state also will be discussed.

Greater Perceived Ability to Form Vivid Mental Images in Individuals with High Compared to Low BMI

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Obese individuals report more frequent food cravings than their lean counterparts. Since mental imagery plays a role in eliciting and maintaining craving we hypothesized that one’s ability to image may be associated with body mass index (BMI) and account, at least in part, for the association between BMI and craving. Twenty-five participants (BMI range: 17.7 kg/m² – 34.2 kg/m²) completed three measures of perceived mental imagery ability (The Vividness of Visual Imagery Questionnaire, The Vividness of Olfactory Imagery Questionnaire, The Vividness of Food Imagery Questionnaire), and one measure of craving (Food-Craving Inventory). As predicted, correlation analyses revealed positive associations between BMI and perceived ability to image odors and foods, but not visual objects. Olfactory imagery was singled out as the best predictor of BMI in a hierarchical regression analysis. A second experiment with 57 participants (BMI range: 19.1 kg/m² – 38.7 kg/m²) then confirmed the significant positive association between BMI and perceived ability to image odors. These results raise the possibility that imagery ability may play a role in the heightened food cue reactvity observed in obese individuals.

Intestinal lipid-derived signals that sense dietary fat

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Dietary fat occupies a central place in the molecular web that controls energy homeostasis in animals. Its fatty acid constituents are not only highly caloric – they pack more than twice the energy than do carbohydrates or proteins – but are also necessary to build cellular membranes and produce essential lipid-derived mediators such as prostaglandins, leukotrienes and endocannabinoids. The intake of this vital macronutrient is closely monitored by an array of molecular sensors distributed throughout the alimentary canal. In the mouth, dietary fat constituents such as mono- and di-unsaturated fatty acids give rise to taste signals that stimulate food intake, in part, by enhancing the production of lipid-derived endocannabinoid messengers in the gut.12 As fat-containing chyme enters the small intestine, it causes the formation of anorexie lipid mediators, such as oleylethanolamide, which promote satiety.3,6. These anatomically and functionally distinct responses may contribute to the homeostatic control and, possibly, the pathological dysregulation of food intake. 1. DiPatrizio, N et al., 2011. Proc Natl Acad Sci USA 108(31):12904-8. 2. DiPatrizio N and Piomelli D, 2015. J Clin Invest 125:891-8. 3. Rodríguez de Fonseca, F et al., 2001. Nature 414, 209-212. 4. Fu, J et al., 2003. Nature 425, 90-93. 5. Schwartz G et al., 2008. Cell Metabolism. 8:281-8. 6. Piomelli D, 2013. Trends Endocrinol Metab. 24:332-41. This work was funded by grants from NIDA (DA012447) and NIDDK (DK073955).
Continuous recording of blood glucose reveals that taste modulates the blood glucose response to a gavaged glucose load

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Bitter taste decreases gastric emptying after an intragastric fat load and decreases blood triglycerides (e.g., Saitou, PlosOne 9: e90717, 2014). To assess whether bitter taste also decreases blood glucose after a glucose load, we took advantage of a new technology that continuously monitors changes in blood glucose – the DSI HD-XG glucose sensor. The HD-XG sensor was inserted into the abdominal aorta of a Sprague Dawley rat and a telemetry transponder was implanted into the peritoneal cavity. After several days to recover from surgery, the rat was gavaged every 1-2 days with 5 mL of 6 g/kg glucose and then it immediately tasted 1 mL of water, 0.125% saccharin (a sweet taste) or 0.15% quinine hydrochloride (a bitter taste). The rat was then returned to its home cage and remained undisturbed while blood glucose levels were monitored every 10 sec for several hours. The rise, peak, and duration of the elevation in blood glucose produced by the glucose load were similar after the rat tasted water or saccharin. However, tasting quinine significantly delayed the return of blood glucose concentrations to their nadir. Thus, stimulation of bitter taste receptors can influence blood glucose levels after a glucose load. This work highlights the advantages of the HD-XG glucose sensor, which allows monitoring of blood glucose with 10-sec temporal resolution without the stress of repeated blood draws.

Distinct relationships of the chemokine CXCL12 to high-fat diet intake, emotional behaviors, and hypothalamic neuropeptide systems

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CXCL12 is an inflammatory mediator that has pro and anti-inflammatory properties and is found in the hypothalamus where neuropeptides are involved in controlling ingestive behavior. With low- and high-grade inflammation to be associated respectively with an increase and decrease in food intake, this study tested in rats whether central injections (icv) of low vs high levels of CXCL12 differentially affect high-fat diet (HFD) intake, emotional behaviors and hypothalamic peptides, and if the CXCL12 system is affected by HFD. At a low dose (50 ng), CXCL12 increased HFD intake, decreased novelty-induced locomotor activity, and reduced defecation, effects suggesting lowered anxiety. In contrast, the high dose of CXCL12 (200 ng) only decreased HFD intake. Expression of enkephalin (ENK) in the paraventricular nucleus (PVN) was increased by both low and high CXCL12, orexin (OX) and melanin-concentrating hormone (MCH) in the perifornical lateral hypothalamus (PFLH) were decreased by the high dose, and neuropeptide Y (NPY) in the arcuate nucleus (ARC), which is related to carbohydrates, was unaffected. Finally, HFD intake increased expression of CXCL12 and its receptors in the PVN and PFLH where ENK, OX and MCH were stimulated, but had no effect in ARC. These results show that CXCL12 has stimulatory and inhibitory effects on ingestive behavior and on peptides, and that endogenous CXCL12 is highly responsive to HFD in the same nuclei where peptides are stimulated by HFD, suggesting that CXCL12 functions in close relation to peptide systems in controlling behavior.

Promoting consideration of long- versus short-term goals reduces impulsivity and snack intake

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The tendency to prefer tasty snacks in the present moment over long-term health and weight loss goals is a contributory factor to overeating. Tasks that enhance access to long-term goals can reduce impulsivity and increase preference for healthy food. Visual cue reminders have been shown to extend these effects and reduce alcohol consumption. The effect of an implicit visual cue, which enhances access to longer-term goals, on impulsivity and snack intake is yet to be examined. Lean and overweight/obese participants (N=176) were randomly assigned to one of two conditions: a condition promoting long-term thought processes or a condition promoting short-term thought processes. A novel cue symbol was embedded in the manipulation to serve as a later reminder of the thought processes that had been primed. After completing the manipulation, participants completed a behavioural impulsivity task and then given an opportunity to consume snack food ad libitum. These tasks were carried out either in the presence or absence of the visual cue reminder. The long-term (versus the short-term) group showed reduced impulsivity and snack intake, an effect that was enhanced by the presence of the visual cue reminder. The effect was present only in the overweight/obese group for impulsivity (p=.002) but held across weight groups for snack intake (p=.037). Using implicit visual cues to enhance consideration of long-term goals during decision making may be an effective practical technique for reducing impulsivity and unhealthy snack intake.

The association of maternal anxiety and depressive symptoms with infant appetitive traits at 3 months and 12 months of age.

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Purpose: Antenatal stress has been linked to fetal programming of appetite and subsequent obesity in offspring. This study examines the association between symptoms of maternal anxiety and depression during and after pregnancy on appetitive traits in offspring in an Asian population. Methods: Maternal anxiety and depressive symptoms were assessed in the GUSTO mother-offspring cohort using the Spielberger State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory II (BDI-II) respectively at 26th week gestation and at 3 months postpartum. Mothers also completed the Baby Eating Behavior Questionnaire (BEBQ) and Child Eating Behavior Questionnaire (CEBQ) when their offspring were aged 3 and 12 months, to ascertain infant appetitive traits. Multivariate linear regressions were used to evaluate associations and potential confounders adjusted for. Results: In 458 mother-dyads, antenatal anxiety was associated with decreased enjoyment of food in infants aged 3 and 12 months (p< 0.05), while antenatal depression was associated with slowness in eating in infants aged at 3 months (p=0.001). Maternal antenatal anxiety and depression were independently associated with slowness in eating and emotional over eating in infants aged 12 months (p< 0.05). Postpartum anxiety and depression was only associated with decreased enjoyment of food in infants at 3 months (p< 0.05). Conclusion: Findings suggest that maternal anxiety and depressive symptoms in particular during the antenatal stage could influence offspring’s appetitive traits, which may modify an infant’s response to food cues later on in life.

Sex-specific memory deficits following sucrose consumption during adolescence in rats

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Excessive consumption of sugar sweetened drinks is a major contributor to the development of obesity and is proposed to evoke enduring neurochemical changes in brain regions involved in reward, learning and memory. Adolescence is a critical period for postnatal brain maturation, thus sucrose consumption may have persistent cognitive effects. In this study we sought to determine the impact of daily sucrose consumption in young male and female rats on spatial and non-spatial recognition memory, and memory
for objects in a particular configuration as adults. Rats were exposed to a 10% sucrose solution for 2 hrs / day for 28 days across adolescence and underwent behavioural testing as adults. Sucrose exposure during adolescence significantly impaired place recognition memory, an assay of spatial memory, in both male and female rats (P<0.001), indicating that sucrose consumption disrupted hippocampal function. This impairment was greater in male than female rats (P<0.05), suggesting an interaction between gender and sensitivity of the hippocampus to disruption. Exposure to sucrose had no detectable effect in either male or female rats on a perirhinal-dependent, object recognition memory task. Object-in-place memory was assessed, which requires the hippocampus, perirhinal cortex and the mPFC. Sucrose exposure significantly disrupted performance of this task in male rats (P<0.01), but not female rats. These experiments indicate that sucrose exposure during adolescence induced different behavioral profiles in male and female rats.

Novel ghrelin receptor inverse agonists as possible therapeutics against overweight and metabolic disease

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Ghrelin positively influences energy balance and has been shown to activate neurons of the medial hypothalamic arcuate nucleus (Arc). The ghrelin receptor exhibits strong constitutive activity and can therefore be targeted to induce inverse ghrelin actions. Using extracellular single unit recordings, we tested if novel ghrelin receptor inverse agonists (IA) inhibit ghrelin-excited ARC neurons. We also assessed whether IA treatment reverses fasting-induced c-Fos expression in the ARC. Effects on food intake were tested in ad libitum fed mice. At a concentration of 10^{-6}M, IA1 (n=8) and IA2 (n=8) decreased the neuronal discharge rate of ghrelin-excited neurons by 60.4 ±7.5 and 62.3 ±7.6%, respectively. This corresponded to an absolute reduction in the discharge rate by 1.7 ±0.4 and 1.5 ±0.6 Hz, respectively. The inhibitory effect of both IAs specifically occurred in ghrelin-sensitive neurons, but not in ghrelin-insensitive cells (100% co-sensitivity). Both IAs significantly attenuated fasting-induced c-Fos expression in the ARC when administered at dark onset in 12h food-deprived mice (IA1 10mg/kg s.c.; IA2 60mg/kg p.o.). Acute IA treatment also reduced food intake in mice (IA1 10mg/kg s.c.; IA2 30mg/kg s.c. and 60mg/kg p.o.). In summary, we provided in vitro and in vivo evidence for the effectiveness of novel synthetic IAs of the ghrelin receptor. Toning down constitutive ghrelin receptor activity might help to counteract obesity-related metabolic perturbations.

GLP-1 receptor signaling in the lateral dorsal tegmental area is physiologically required for the regulation of food intake and body weight

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GLP-1 receptor signaling in the lateral dorsal tegmental area is physiologically required for the regulation of food intake and body weight. Reiner DJ1, Kanoski SE2, Hayes MR1 Univ of Penn, Philadelphia, US 2Univ of Southern Cal, LA, US The central glucagon-like peptide-1 (GLP-1) system regulates energy balance. However, the specific GLP-1 receptor (GLP-1R)-expressing nuclei and circuits that mediate central GLP-1’s anorexigenic effects still require extensive investigation. The lateral dorsal tegmental area (LDTg), a critical but understudied brainstem hub of energy balance control, has reciprocal connections with the nucleus tractus solitarius, lateral hypothalamus, and ventral tegmental area to putatively modulate food intake and reward. Therefore, we tested the hypothesis that GLP-1R signaling in the LDTg regulates food intake in rats. First, qPCR and IHC analyses show that GLP-1R are expressed and GLP-1 fibers innervate the LDTg. Intra-LDTg injection of the GLP-1R agonist Exendin-4 (0.025, 0.05μg) dose
dependently reduces chow intake and body weight over 24h. Acute blockade of LDTg GLP-1R with the GLP-1R antagonist Exendin-9-39 (20μg) increases chow intake over 24h. Together, these data identify the LDTg as a novel nucleus mediating the anorectic effects of GLP-1R signaling. Ongoing studies are examining the role of LDTg GLP-1R signaling in the long-term control of energy balance and the circuits mediating LDTg GLP-1’s anorectic effects. NIH-DK96139; MH014654; DK097147.

Central β3-adrenergic activation is sufficient to induce potent anorexia, weight loss and white fat browning

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Activation of β3-adrenergic receptors (β3AR) leads to increased mitochondrial biogenesis in white adipose tissue (browning), associated with increased thermogenic activity. These effects are associated with improved whole-body metabolic function and weight-loss. It has been assumed that the impact of β3AR agonists (β3ARa) is mediated through activation of β3AR found in adipose tissue. However, β3AR can also be found in the brain, in the brainstem and the hypothalamus, that provide multisynaptic innervation to both brown (BAT) and white adipose depots (WAT). Peripherally injected β3ARa can potentially gain access to these brain areas. Thus, it is possible that, contrary to the adipocentric view, a part of the thermogenic action of β3ARa-treatment is mediated via the CNS. Therefore, the overall aim of this study is to elucidate what role the brain plays in β3ARa-mediated “browning” of WAT, food intake and body weight regulation. Acute ICV injection of β3ARa potently reduced food intake and body weight in fed or overnight fasted rats. These results were mimicked by intra-nucleus tractus solitarius (NTS) β3ARa microinjections, identifying the NTS as a neural substrate for anorexic and weight loss impact of β3ARa. Subchronic ICV β3ARa treatment led to a potent (300-fold) upregulation of UCP-1 in both inguinal and gonadal WAT, reduced fat mass, and two-fold increase in BAT weight. Our results identify the brain as a new site of action for the anorexic and browning impact of β3AR-signaling.

The effect of obesity on hippocampal leptin and spatial memory in the radial arm maze

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Impairment in spatial memory and learning observed in diet induced obese rats may be related to the development of leptin resistance in the hippocampus. Male Long-Evans rats received either a standard chow diet (4% butter fat; n=8) or a high fat diet (45% butter fat; n=7) for 8 weeks prior to behavioral testing. We evaluated the effects of a high fat diet on radial arm maze performance, a hippocampal-dependent memory task. Rats underwent two acquisition trials per day for 8 consecutive days. Extinction trials were conducted 2, 3, 4, 5, and 6 days following the previous acquisition/extinction trial. Latency to enter all four baited arms, correct and incorrect working memory errors, and reference memory errors were recorded and compared between diet conditions. Following behavioral testing, rats were euthanized and hippocampal tissue was collected for protein analysis. Western blots were used to compare leptin, leptin receptor, and pSTAT3 levels in order to assess leptin function in this region between subjects with respect to diet condition and performance in the radial arm maze.

Differential effects of glucose and glucose plus lipid infusions towards the brain on peripheral glucose metabolism and hypothalamic gene expression.
Providing rats a diet with the choice of saturated fat and liquid sugar in addition to chow induces glucose intolerance and decreases hypothalamic proopoiomelanocortin (POMC) mRNA, whereas providing only fat or sugar in addition to chow does not. Although POMC neurons can modulate glucose metabolism, at present it is unknown whether the diet-induced changes in POMC expression are responsible for the observed effect on glucose tolerance. We investigated whether direct infusion of lipids and glucose in the cerebral circulation would decrease POMC expression and increase endogenous glucose production (EGP) and blood glucose concentrations. After an overnight fast, Male rats were infused in the carotid artery with either heparinized Intralipid 20% (IL), glucose (1%), IL plus glucose (IL+G) or control (NaCl) over 2h. We assessed EGP using a stable glucose isotope and hypothalamic gene expression. Blood glucose was significantly decreased after IL infusion and slightly increased after IL+G as compared to IL (P < 0.01). EGP increased upon IL+G infusion only. IL infusion significantly reduced POMC mRNA expression (P < 0.05), whereas IL+G infusion increased acetyl-CoA carboxylase (ACC) mRNA, which reflects energy surplus. This study shows that the composition of the nutrient flow towards the brain has differential effects on hypothalamic expression of genes involved in energy metabolism.

Promoting Metabolic Health and Lifespan by Increasing Oxidative Stress

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We are interested in the biochemical and molecular basis of longevity — in particular the role played by mitochondria in lifespan regulation and prevention of metabolic diseases. Contrary to the widely re-iterated Free Radical Theory of Aging, we have been the first to show that the health-promoting effects associated with low caloric intake, physical exercise and other lifespan-extending interventions like sirtuin signaling are caused by increased formation of Reactive Oxygen Species (ROS) within the mitochondria, causing a vaccination-like adaptive response that culminates in increased stress resistance and extended longevity, a process called mitohormesis. We work with the roundworm C. elegans and mammalian model organisms, as well as occasionally humans.

Astrocytes in the hindbrain trigger counterregulation

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Counterregulation (CRR) is a homeostatic reaction to hypoglycemia. Activation of hindbrain CRR circuits provoke feeding behavior, gastric motility, glycogenolysis, and glucocorticoid release. These actions recover carbohydrate, speed its digestion, release stored glucose, and shift fuel use to non-carbohydrates (1). Astrocytes may be importantant CRR glucosensors (2). Our calcium imaging work shows that NST astrocytes release calcium in response to cytoglucopenia. Further, the CRR digestive acceleration of glucose deficit is due to astrocyte action on gastric reflex circuits (2,3). Preliminary studies indicate that CRR glucose release also involves hindbrain astrocytes. Tail blood glucose measurements were made from rats every 30min. Fourth ventricular (4V) 2-deoxyglucose (2DG) triggers elevation of plasma glucose (~35%). Fluorocitrate (FC; a selective blocker of astrocyte metabotropic signaling) alone in 4V had no effect on glucose levels compared with saline 4V. However, FC blocked the 2DG-mediated increase in glucose. This result provides evidence that hindbrain detection of cytoglucopenia requires astrocytes. 1. Ritter, S. 2011 2. Marty, 2005. 3. Hermann, G. 2014 4. McDougal, D. 2013
What do studies on portion size and energy density tell us about the cognitive control of meal size?

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Controlled studies of the effects of portion size and energy density on food intake provide insights into factors that affect meal size. The influence of both portion size and energy density on intake is significant in 3- to 5-year-old children who are thought to eat primarily in response to physiological cues rather than cognitive controls. The effect of portion size on intake persists in both children and adults even when they are allowed to select their own portions. Portion size affects intake not only of foods with an amorphous shape but also of those that come in defined units or packages. Attempts to moderate the portion size effect by providing cues such as plate or utensil size have had mixed results. The effect of portion size is sustained over multiple meals, but varies between foods. In a meal with several items, foods ranked higher in taste show the strongest effect of portion size. A robust finding is that when portions offered are kept constant while energy density is increased, both children and adults eat a consistent amount of food by weight so that they consume more energy. Physical properties of food that affect the perceived portion, such as aeration, influence the amount people serve and eat, while they estimate they have taken the same number of calories. These studies show that portion size and energy density influence meal size from an early age and these effects persist in adults despite increased experience with choosing meals to meet their energy needs. Questions raised by these findings about the cognitive control of meal size will be considered.

Body composition changes following sugar and food restriction with exercise in a sugar-sweetened beverage rat model of obesity

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Following sugar and food restriction, sugar-induced adiposity can persist despite similar losses in body mass to controls. This experiment investigated 3 questions. What is the effect of sugar restriction only on body composition? Does exercise have a synergistic effect with sugar and food restriction on reducing adiposity? And, is lean muscle tissue lost following sugar and food restriction? 32 male Wistar rats were provided free access to chow, water and a 10% (w/v) sucrose solution for 42 days. On d43 animals were matched for body mass and previous sucrose consumption and assigned to 1 of 4 groups: S, NS (sustained free access to chow, water with or without sucrose respectively), NSFR or NSFRE (no sucrose, food restriction (60% intake) with or without free access to running wheels (2h/day, 5 days/week) respectively). Animals were culled on d79, visceral fat pads and hindlimb muscles were dissected and weighed. Groups S and NS were heavier ($p=0.003$) with greater total fat mass ($p<0.001$) than NSFR and NSFRE. There were no differences in body mass between S and NS or between NSFR and NSFRE. Absolute muscle weights were similar between all groups, however when expressed relative to body mass Soleus ($p=0.004$) and EDL ($p=0.007$) of NSFR and NSFRE groups were larger than those of S and NS. The main findings are: Removing only sugar did not result in beneficial effects on body or fat mass; sugar and food restriction reduced total body and fat mass, but not muscle mass; exercise did not further reduce adiposity over the effects of restricting sugar and food.

Nicotine differentially impacts body weight gain and reinforcement in obese-prone and –resistant rats

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Nicotine (NIC) suppresses body weight (BW), a factor impacting smoking initiation and the failure to quit. The FDA is considering a policy of markedly reducing the allowable NIC content in cigarettes; NIC may prevent the onset of obesity and NIC reduction may result in dramatic weight gain, an issue that must be considered in tobacco regulatory policy. We previously demonstrated that self-administered (SA) NIC, even at doses below the reinforcing threshold, suppresses BW independent of food intake. The present study examined, in obese-prone and –resistant rats: 1) NIC’s BW-suppressant effects; and 2) the impact of obesity on NIC reinforcement. BW gain of adult male rats maintained on high fat diet (HFD; 31.8% kcal from fat) distributed into diet-induced obese (DIO) and DIO-resistant (DR). These rats SA NIC (0 or 60 µg/kg/infusion, a standard SA dose); NIC suppressed BW gain but not food intake in DIO rats. NIC had no effect on BW in DR rats, indicating that obesity-resistant rats are also resistant to NIC’s BW-suppressive effects. Modeling current smokers transitioning to reduced NIC content cigarettes, NIC dose was reduced to 3.75 µg/kg/infusion. Dose reduction resulted in increased BW gain in DR, but not DIO rats. No differences in infusions taken emerged between groups at 60 µg/kg/infusion. Following NIC reduction, the DR group took more infusions, indicating lean individuals may compensate their smoking behavior during NIC dose reduction. Together, these data indicate the obese as a subpopulation of risk in the consideration of a NIC reduction policy.

Brown Adipose Tissue (BAT) Sensory Innervation Monitors Lipolysis

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BAT, an important effector of thermogenesis and lipolysis, is exclusively dependent on its sympathetic nervous system (SNS) innervation for most of its functions. BAT also has sensory system (SS) innervation for BAT regulation. BAT stimulation increases SNS drive producing more fatty acids (FAs) than can be used for heat; however, the physiological role of surplus FAs remains unknown. Therefore, we tested whether BAT SS senses the SNS-induced lipolytic output by injecting the FA arachidonic acid (AA), the most abundant polyunsaturated fatty acid in lipids of the CNS, and β3-adrenoceptor agonist CL316,243, intra-left BAT of Siberian hamsters with intra-right BAT injections of vehicle as controls. We first prelabeled the dorsal root ganglia (DRG) for the sensory nerves innervating BAT with Fast Blue (FB) and after injections prelabeled the c-Fos immunoreactivity (-ir) to the DRG with FB to identify BAT afferent neurons that possibly underlie BAT thermogenic and lipolytic responses. Both AA and CL316,243 significantly raised BAT and activated C2-C4, T1-T4 DRG (c-Fos-ir+FB) ipsilaterally versus the contralateral counterpart. A warmth-sensing transient receptor potential channel V3 (TRPV3)-ir was significantly increased within C4-T4 DRG by AA and CL316,243 versus contralateral fat pad with slightly larger increases after CL316,243. Cold-related TRPM8-ir was also increased by either AA or CL316,243. Collectively, this evidence favors stimulation of lipolysis that can directly activate BAT-associated DRG in a feedback fashion and temperature-sensitive TRPV3 and TRPM8 channels that may contribute to energy balance control.

Western diet intake disrupts learning mechanisms involved in externality

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Food-related cues in the obesogenic environment constantly elicit intake, but satiety cues typically suppress responding to these cues. An overwhelming of satiety cues by external cues has been suggested as a key contributor to the obesity pandemic. The current research explores a mechanism for how a shift from internal to more external control of appetitive behavior might develop. For Group Dep+, interoceptive
signals arising from 0- and 4hr food deprivation in compound with external light and tone cues predicted sucrose, while for Group DepR, external cues, but not deprivation cues, predicted sucrose. When asymptote was achieved, external cues were removed to evaluate learning about deprivation cues alone, and then deprivation was held constant to assess external cue control. Performance on the compound discrimination was then reestablished, and half of the Dep+ rats received a high-fat, high-sugar Western diet (WD) while the others remained on chow. The day after the diet switch, external cues were again removed, and lastly, external cues were reintroduced. Like Group DepR, Dep+ WD rats were impaired in using deprivation cues compared to Dep+ chow rats, but WD rats recovered discrimination when external cues were again present. These results suggest a selective, WD-induced deficit in the ability to use interoceptive satiety cues, which would be expected to further promote excess intake and obesity. WD intake may initiate a vicious cycle of obesity and its associated cognitive decline by disrupting major substrates for learning and memory.

Targeting the Alpha Cell in Hypoglycemia

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Severe hypoglycemia reported in type 1 and insulin-dependent type 2 diabetics is associated with a greater than 3 fold increase in 5-year mortality. Iatrogenic hypoglycemia compromises a patient’s endogenous defenses (sympatho-adrenal and counter-regulatory mechanisms) predisposing to recurrent hypoglycemic events. We studied the pancreatic alpha cell to gain insight into the intra-islet mechanisms controlling glucagon production and secretion and uncovered a novel paracrine mechanism by which the delta cell influences alpha cell function. Encoded in the pro-somatostatin prohormone we discovered a second biologically active peptide, neuronostatin (NST), that exerts potent actions independent of those of somatostatin in brain, gut, heart and pancreas. We have demonstrated in transformed alpha cells and isolated mouse and rat islets that NST increases proglucagon mRNA levels and glucagon release under low glucose conditions. In addition to these direct alpha cell actions, NST when added to whole islets indirectly inhibits glucose stimulated insulin secretion, an effect that is mirrored by NST infusion prior to an in vivo glucose challenge. The alpha cell actions of NST require the presence of the G protein coupled receptor GPR107, as do the sympatho-stimulatory effects of the peptide, and post-receptor signaling through non-cAMP dependent activation of protein kinase A and the NFKB/IkkB complex. We suggest that this novel paracrine interaction of delta cell-derived NST with GPR107 on the alpha cell provides a druggable target for enhancing glucagon secretion to prevent recurrent hypoglycemic events.

Hedonic hunger’s relation to neural, behavioral & perceptual responses to food stimuli: Evidence from three studies

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The Power of Food Scale (PFS) seeks to identify individuals with high susceptibility to environmental cues that promote food intake; a construct characterized as hedonic hunger. This purpose of study was to directly test correlates of PFS scores to various measures of food responsivity. Data from 3 studies (Study 1, n=44; Study 2, n=398; Study 3, n=99) including the PFS, neural responsivity during intake and anticipated intake of milkshake, behavioral food reinforcement, perceptual hedonic ratings of food images, and BMI and binge eating over time were analyzed. PFS scores were strongly related to bilateral brain response in regions implicated in oral somatosensation processing during cue-elicited anticipation of milkshake receipt (r = .67, .64). PFS scores were also positively correlated with behavioral food reinforcement (r = .31, p=.03) and perceptual hedonic ratings of food appeal (r =.24, p=.02), in particular appeal of energy-dense foods (r = .32, p=.001). Lastly, PFS scores were not associated with baseline BMI (Studies 1-3: p = .14-.21) or change in BMI over two-year follow-up (Studies 1,2: p=.14, .37), but were significantly correlated with
baseline in binge eating in two samples (Studies 1,2: r = .58, .31, p< .001, p =.02). Results indicate that
hedonic hunger is not indicative of weight regulation and/or long-term energy intake. Instead, those that
report high hedonic hunger are likely to show increased neural and perceptive responses to cues of
palatable foods, an increased motivation to consume such foods, and greater likelihood of current binge
eating.

Sex differences in angiotensin II-induced behavioral desensitization

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Previous in vivo studies from our laboratory and in vitro studies by others demonstrate that the angiotensin
type 1 receptor (AT1R) rapidly desensitizes after repeated exposure to angiotensin II (AngII). To date, one
behavioral effect of this desensitization, a decrease in the dipsogenic potency of Ang II treatment, has been
studied exclusively in male rats. Because sex differences in the dipsogenic potency of AngII are well
established, it is plausible to hypothesize that sex differences exist in the desensitization of the AT1R. Here
we tested the influence of sex and hormone treatment on water intake after repeated AngII treatment. As
expected, when male rats were pretreated with three 300 ng injections of AngII spaced 20 min apart they
drank less water after a 100 ng test injection of AngII than did rats pretreated with vehicle, p < 0.05. Next,
female rats were ovariectomized, treated with either oil or 20 µg estradiol benzoate (EB) for two
consecutive days and 48 h after the second hormone treatment underwent our behavioral desensitization
paradigm. After repeated injections with AngII, water intake was no different from the intake in control-
treated rats, regardless of hormone treatment. Furthermore, preliminary data suggest that progesterone does
not influence the female rat’s inability to show behavioral desensitization. Follow-up studies are underway
to test if testosterone is the key gonadal hormone necessary for mediating this sex difference. These data
reveal a striking sex difference in the response to elevated AngII that may shed light on the disparate levels
of cardiovascular disease in males and females.

Rats learn to prefer the orosensory properties of glucose over those of fructose

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Postoral signals modulate the hedonic value of associated taste stimuli, but whether these affect the
sensory-discriminative aspects of taste function is unknown. Fructose (F) and glucose (G) appear to elicit
the same sweet taste quality, but engage different postoral pathways. Here, we assessed whether food-
deprived rats can discriminate G from F on the basis of their orosensory features if first given the
opportunity to consume each sugar alone and experience the differential postoral effects. One group (GvF,
n=9) had randomized access to 3 concentrations of G and F (0.316, 0.56, 1.1M) in separate 30-min 1-bottle
training sessions (18 sessions). Control groups received equivalent exposure to either the 3 G (n=6) or F
(n=5) concentrations only, or remained sugar naïve (n=8). The GvF group had increased burst sizes, longer
meals, and licked at a faster rate for G, even within the 1st min of the session, compared to F (ps< 0.02).
Consistent with this, during post-training 30-min brief-access tests, in which the 3 concentrations of G and
F were randomly presented in 20-s trials in the same session, GvF rats had higher lick scores to G than F
(p<0.05), while the other training groups licked comparably to both sugars. Additional testing suggested
enhanced G responsiveness in the GvF rats was quite specific to G, but, interestingly, they generalized this
to a maltodextrin as well. Thus, rats can use oral cues to discriminate G from F following the opportunity to
experience both individually in 1-bottle sessions, but the receptors mediating this sugar discrimination
remain to be identified.
Ghrelin signaling is not essential for sugar or fat conditioned flavor preferences in mice

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The post-oral actions of sugar and fat stimulate intake and condition flavor preferences in rodents. Mice acquire strong preferences for flavors paired with intragastric (IG) infusions of glucose or fat (Intralipid). This post-oral conditioning response is mediated, in part, by gut nutrient sensors. Visceral deafferentation does not block IG nutrient conditioning, which implicates a gut-brain hormonal pathway. Ghrelin is the only hormone known to stimulate feeding and enhance food reward. This study investigated the involvement of ghrelin signaling in nutrient conditioning in mice. In Exp. 1 ghrelin receptor knockout and C57BL/6 (B6) wildtype mice were trained to drink a flavored saccharin solution (CS+) paired with IG 16% glucose and a different flavored solution (CS-) paired with IG water. Both groups drank more CS+ than CS- in training and preferred the CS+ to CS- in a two-choice test. In Exp. 2 both groups learned to prefer a new CS+ flavor paired with IG fat (Intralipid) over a new CS- flavor. In Exp. 3 B6 mice learned to prefer a flavor mixed into 8% glucose over another flavor mixed into a "sweeter" 0.1% sucralose + saccharin solution. Treating mice with a ghrelin receptor antagonist [(D-Lys3)-GHRP-6] during flavor training did not attenuate the glucose-conditioned preference. Together, these results indicate that ghrelin receptor signaling is not required for post-oral sugar and fat conditioning. Post-oral nutrient conditioning appears to involve a different gut hormone with orexigenic and reward actions.

Dietary Modulation of Striatal D2 Receptor Binding Potential and Stress Responses in Adult Female Macaques

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Both social stress and Western diet patterns increase disease risk. Here we test the hypothesis that diet composition modulates physiological stress responses in socially housed macaques. In those consuming a Western diet, subordinates (SUBS, n=21) had higher cortisol responses to adrenocorticotropin (ACTH) than dominants (DOMS, n=18, p=0.03), whereas in those consuming a chow diet, SUBS (n=24) had lower cortisol than DOMS (n=16, p=0.02). In another study, 24 hr heart rates (HRs) were recorded longitudinally in 42 macaques after 6 mos of chow diet, and after 18, and 34 mos of Western diet. There were no social status differences while consuming chow (p=0.34). Social status differences emerged with time consuming the Western diet (18 mos p=0.13, 34 mos p=0.002). SUBS also lost much of their HR circadian rhythm by 34 mos (time X status interaction p=0.005). Both stress and cortisol can reduce striatal dopaminergic function which is associated with reward deficiency, substance abuse, and obesity. We assessed striatal D2/3 receptor binding potential (D2/3RBP) in DOMS (n=14) and SUBS (n=16) consuming a Western diet, compared it to DOMS (n=4) and SUBS (n=4) consuming a chow diet, and found a social status X diet interaction (p=0.007). Chow-consuming DOMS had higher striatal D2/3RBP than their subordinate counterparts and all macaques consuming the Western diet. These data suggest that diet composition modulates physiological stress responses and may have deleterious effects on the function of the striatal reward system.

Binge-like high-fat diet intake enhances preference and motivation for highly palatable food.

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Binge eating disorder (BED), characterized by excess caloric intake in a short period of time is associated with loss of behavioral control coupled with increased motivation to obtain palatable foods. Heightened impulsivity for palatable foods can initiate compulsive feeding in rodents, however it is unknown if prolonged bouts of binge-like feeding enhance motivation for palatable foods. We predicted rats exposed to a binge feeding regimen would display augmented motivation for sucrose. To do this, male Long Evans rats, received two hour (binge sessions) access to HFD (4.54 kcal) every day (HFD-ED) or every third day (HFD-3D) for a period of six weeks. Controls received a novel hopper of chow during each binge session. Standard rodent chow and water were available ad libitum for all groups throughout the study. Following binge exposure, all groups underwent motivational testing where operant responses detected by a touch screen delivered a 45mg sucrose pellet. HFD-3D rats displayed typical binge-like intake as evidenced by increased 24-hr caloric consumption relative to controls. In contrast, both HFD-3D and -ED rats displayed compensatory underfeeding following HFD exposure. Interestingly, both HFD-3D and -ED groups displayed enhanced acquisition of operant responding and subjective preference relative to controls. Taken together, these data suggest that binge-like feeding affects behavioral variables which may contribute to the maintenance of BED in the clinical population.

Estrogen effects on oxytocin in the forebrain and hindbrain of ovariectomized rats: Implications for eating behavior?

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Central oxytocinergic systems have been proposed to have inhibitory effects on food intake. Moreover, the hindbrain receives projections from oxytocin (OT) neurons, which may indirectly influence feeding by affecting gastric function. Estrogen is well known to reduce food intake, and estrogen receptors (ERs) are present in OT neurons of the Paraventricular nucleus (PVN) and Supraoptic nucleus (SON) of the hypothalamus. The presence of ERs in oxytocin-producing neurons suggests that the regulation of OT by estrogen may contribute to estrogen-induced reduction of food intake. Our goal was to assess estrogen effects on OT by comparing OT levels in the SON, PVN, and the hindbrain of ovariectomized rats with or without estrogen by the use of standard immunohistochemical labeling. Semi-quantitative assessment of OT labeling showed that estradiol benzoate (EB)- and vehicle-treated rats (n = 3/group) had similar levels of labeling in the PVN, but EB-treated rats demonstrated more robust labeling in the SON and in the hindbrain. These results suggest an interaction between estrogen and central oxytocinergic systems that may play a role in the control of eating behavior.

CCK response deficiency in synphilin-1 transgenic mice

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Previously, we have identified a novel role for a cytoplasmic protein, synphilin-1, in the controls food intake and body weight in mice and Drosophila. Ubiquitous overexpression of human synphilin-1 in brain neurons in transgenic mice results in hyperphagia expressed as an increase in meal size. However, the mechanisms underlying this action of synphilin-1 remains to be determined. Here we investigate a potential role for altered gut feedback signaling in the effects of synphilin-1 on food intake. We examined responses to peripheral administration of cholecystokinin (CCK), amylin and the glucagon like peptide-1 (GLP-1) receptor agonist, exendin-4. Intraperitoneal administration of CCK at doses ranging from 1-10 nmol/kg significantly reduced glucose intake in non-transgenic mice, but failed to affect intake in synphilin-1
transgenic mice. Moreover, CCK administration strikingly increase c-Fos expression in the NTS in non-transgenic mouse, but there was a significantly attenuation of CCK-induced c-fos expression in synphilin-1 transgenic mice. In contrast, both non-transgenic and synphilin-1 transgenic mice were similarly responsive to amylin and exendin-4 treatment. These studies demonstrate that synphilin-1 results in a CCK response deficiency that my contribute to the increased meal size and overall hyperphagia in synphillin-1 transgenic mice.

Nerve damage obscures links between oral anatomy and sensation that guide dietary health

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Oral sensory variation exists, but debate persists about its physiological basis and dietary health impact. For example, multiple reports show that taste perception rises with fungiform papilla (FP) density, yet three recent studies find no such association. This discrepancy may arise when oral sensory evaluation fails to assess nerve damage, which can alter taste sensation without affecting oral anatomy. To illustrate, 591 people provided health information relevant to taste damage (i.e., otitis media, tonsillectomy, head trauma, taste phantoms), took a spatial taste test, and sampled a filter paper infused with 6-n-propylthiouracil (PROP, 1.6 mg). FP density was measured in a circle (6 mm diameter) adjacent to the tongue tip and midline. We found a significant correlation between FP density and the intensity of anterior taste cues and PROP paper, but only in participants without health conditions related to taste damage; those with taste-related pathology showed no such effect. We also examined a functional measure of anterior vs. whole-mouth bitter taste: Individuals with ratios above the median (i.e., healthy anterior taste) showed a significant correlation between FP density and anterior taste intensity, but those with ratios below the median (i.e., anterior taste loss) showed no such association. These data verify that oral sensory nerve damage distorts the relationship between FP density and taste perception, which may contribute to discordant food-related effects of oral sensory variation.

Maternal high-fat diet during gestation or lactation differentially impairs offspring hypothalamic neurocircuit development

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Maternal high-fat diet (HF) during gestation and lactation results in obesity, impaired glucose tolerance and leptin resistance in rat offspring. Leptin and insulin levels are elevated in offspring of HF fed rat dams and proper levels of these hormones are required for normal development of pathways from the arcuate nucleus (ARC) to other hypothalamic areas. We hypothesized that the development of projections from agouti-related peptide (AgRP) and proopiомelanocortin (POMC) expressing neurons to the paraventricular nucleus (PVN) are impaired in offspring from HF fed rat dams. Pregnant Sprague Dawley rats were fed chow (CH) or HF diet throughout gestation and lactation. On postnatal day (P)1, litters were cross-fostered to a CH or HF dam resulting in 4 groups according to the dams’ diet: CH-CH, CH-HF, HF-CH, and HF-HF. On P21, there was a significant reduction in AgRP fiber densities in the PVN of CH-HF and HF-HF pups. The density of α-MSH (contained in POMC neurons) labeled fibers in the PVN was significantly lower in CH-HF and HF-CH compared to CH-CH, but not in HF-HF pups. STAT3 signaling is decreased in CH-HF and HF-HF pups on P21. The data suggest that maternal HF diet during gestation and/or
lactation may lead to impaired development of AgRP/NPY and POMC projections from ARC to PVN, which is likely, due to deficits in STAT3 signaling.

**Eating Disorders, Gene-Environment Interactions and the Epigenome: Roles of nutritional status stress exposures**

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It is an obvious point that the environment shapes our personalities and the expression of our inherent behavioral and emotional tendencies. However the answer to the question “How exactly do these things occur?” is not so obvious. Epigenetic mechanisms are believed to link environmental exposures to gene expression, and in so doing, to provide a physical basis for the activation, by life experiences, of mental-health problems--among them, eating disorders. This presentation is about gene-environment interactions and epigenetic processes in the eating disorders. The talk provides a background on molecular (genetic and epigenetic) mechanisms that are believed to bridge the gap between life stresses (perinatal factors, childhood adversities, performance pressures, and especially, effects of malnutrition) and eating disorders. New findings will be presented that indicate altered epigenetic marks (some secondary to prolonged illness) at genomic regions pertinent to social-emotional problems and physical sequelae that are common in AN. It will be argued that an epigenetically informed understanding of eating disorders blames affected people and their families less, helps explain why eating disorders are triggered by excessive caloric restraint, and may clarify why eating disorders (once established) become so strongly entrenched. Finally, the talk will examine the potentials of an epigenetically informed model to contribute to the development of more effective, person-centered treatments.

**Investigation into the Central Actions of Adropin**

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Adropin is a newly described peptide encoded by the Energy Homeostasis Associated (Enho) gene produced primarily in liver and brain. While several studies have examined its role in the periphery (specifically metabolic function), little is known about its action in the brain. Therefore, the purpose of this study was to determine the possible central actions of adropin on food and water intakes in rats. Male Sprague-Dawley rats were housed in metabolic cages with free access to lab chow and water (lights out 1800-0600 h). We recorded daily ad libitum feeding and drinking behavior prior to and following testing. On the day of testing, rats were given a 2μL intracerebroventricular injection of saline (n=12), 1nM adropin (n=7), or 3nM adropin (n=9) at 1730 h. Food and water intakes were monitored at 30-minute intervals until 1930 h and again the next day at 0800 h. We did not observe any significant difference in food intakes between rats given saline and those receiving adropin injections. Conversely, there was a significant decrease in cumulative water intake between saline- and adropin-treated rats during the early dark phase, which resolved 2 hours post injection. Although adropin did not appear to affect feeding behavior, these results do suggest a potential role in the CNS regulation of water drinking. Importantly, we recently have identified a putative receptor for adropin and are currently examining the effect of siRNA-induced compromise of its production on the cellular actions of the peptide, with the goal of determining the physiologic relevance of adropin’s CNS actions.

**Thylakoid consumption reduces wanting and liking for palatable food - treatment effects are correlated to a reduced food intake**
The purpose of this study was to investigate how treatment with thylakoids from green leaves, previously found to affect appetite-regulating hormones, affects hunger, satiety, liking and wanting for palatable food as well as intake of palatable food. Associations with scores for eating behavior were also examined. 22 middle-aged female participants received either thylakoids (5 g) or placebo with a standardized breakfast on two separate days in a crossover design. VAS-questionnaires about hunger, satiety and cravings for palatable food were filled out hourly, the last time point after an ad libitum snack buffet in the afternoon. This time, the questionnaire included questions about liking. Thylakoid treatment increased ratings of satiety, decreased ratings of hunger and decreased cravings for snacks and sweets during the day compared to placebo. In addition, there was a decreased liking for sweet after treatment. The effects of thylakoids on scores for wanting and liking were correlated to a reduced intake by treatment, even though food intake was not affected significantly. The treatment effects on wanting all snacks, sweet-and-fat snacks in particular, were positively correlated to higher emotional eating scores. Thylakoids may be used as a food supplement to reduce wanting and hedonic hunger, associated with overeating and obesity.

Pressure to be Thin Predicts Body Weight and Fat Gain in Adolescence

Overweight (OW) adolescents report more sociocultural pressure to be thin than non-OW teens. Whether such pressure affects weight gain has not been evaluated prospectively. We studied associations of parental & peer pressure to be thin with weight & fat mass gain in 198 teens (65% F; 39% OW) over 1y. At baseline, pressure to be thin was assessed by teen- & mother-report on the Pressure to be Physically Attractive Questionnaire. Maternal perception of child weight was measured on the Child Feeding Questionnaire. At baseline & 1y later, height & fasting weight were used to compute BMI; fat mass was assessed with air displacement plethysmography. Controlling for baseline BMI or fat mass, puberty, sex, age, race, Δheight, & time to follow-up, teen-reported pressure to be thin from mothers, fathers, & peers predicted ΔBMI & Δfat (βs=.19-.26, p<.05), such that more pressure related to greater gain. Mother-reported pressure predicted ΔBMI & Δfat (βs=.20, p<.04), & maternal perception of child OW predicted Δfat (β=.28, p<.01). OW status was a moderator; pressure to be thin was a stronger predictor of ΔBMI & Δfat gain for OW teens (p<.05). We conclude parental & peer messages about thinness are associated with BMI & fat gain in adolescence, particularity in OW teens. Further research must determine if these relations are bidirectional & through what mechanisms (e.g., dieting, disinhibited eating, stress response) sociocultural pressure affects body weight & fat.

BMI positively correlates with amygdalo-hypothalamic effective connectivity in the absence of hunger

Animal models indicate that basolateral amygdala (BLA) input to the hypothalamus (HYP) is essential for external food cues to trigger feeding in the absence of hunger (Petrovich et al. 2002). Obese humans are particularly prone to externalized eating behavior (Schacter 1968). It is unknown if enhanced BLA-HYP
connectivity in the absence of hunger is a feature of human obesity. 32 humans across a range of BMIs (15 male; BMI M\(=25.3 \ SD=4.5 \ range=19.5-37\)) tasted milkshake and tasteless solutions during fMRI scanning when hungry (4h fast) and when full (after fixed-portion or ad libitum meal). The 3 scans took place in randomized order on separate days. We used dynamic causal modeling to evaluate BLA-HYP connectivity as a function of internal state and BMI. Bayesian model selection showed that at the fixed and ad libitum scans, the model where taste inputs enter the BLA and flow unidirectionally to the HYP best fit the observed data. In contrast, in hunger the best model featured taste inputs entering the HYP with bidirectional connections to the BLA. This suggests that the BLA exerts greater influence on HYP circuits when full, while in hunger processing in the HYP drives the system. Connection strengths from BLA to HYP when full also positively correlated with BMI. These data support the hypothesis that BLA-driven responses to taste inputs exert greater influence on homeostatic circuits in the HYP in the absence of hunger. They also suggest that this influence is greater in obesity.

The relationship between obesity, quality of life, and psychopathology in primary care settings

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In clinical practice, behavioral approaches to obesity primarily focus on diet and exercise. Little is known about the prevalence of psychopathology in obese persons in primary care (PC), or whether this pathology affects clinical outcomes. As BMI increases, quality of life (QoL) decreases, and the prevalence of psychopathology is greater than in normal weight individuals. To explore the psychological and social impacts of obesity on individuals in PC. This cross sectional study consisted of 153 individuals who were referred from PC providers who were identified as having a BMI >30 kg/m\(^2\), and responded to a request for volunteers. Each individual completed a demographic questionnaire, Impact of Weight on QoL assessment tool, and the Hospital Anxiety and Depression Scale (HADS). Data were analyzed using T-tests, cross-tabulation, chi\(^2\), and ANOVA. Linear regression coefficients were calculated to assess the relationship between BMI and QoL, while logistic regression models were used to analyze HADS data. The sample was predominantly female (68%), mean BMI of 38.2 kg/m\(^2\). A higher BMI value was significantly negatively associated with QoL, with an increase of 1 BMI translating to decreases of 1.93 in physical function (\(p< 0.001\)), 1.62 in self-esteem (\(p< 0.05\)), 2.69 in public distress (\(p< 0.001\)), and 1.33 in work (\(p< 0.001\)). The prevalence of anxiety (62.4%) and depression (54.9%) was significantly higher, compared to the US population of 18.1% and 6.9%, respectively. This study identified a significant inverse relationship between higher BMI scores and QoL, as well as increased psychopathology in obese individuals in PC settings.

GLP-1 receptors in lateral septum influence sucrose and corn oil intake

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Our recent data support the idea that the GLP-1 receptors (GLP-1R) in the lateral septum (LS) play a physiologic role in the control of food intake. Using immunohistochemistry and retrograde tracing, here we describe the projection from GLP-1 cells in the caudal brainstem to the LS. To further investigate the effect of LS GLP-1R on feeding, we administered the GLP-1R antagonist exendin-(9–39) (Ex9), at a dose subthreshold for effect when delivered to the lateral ventricle. Different groups of LS-cannulated rats were trained to drink 0.25 M sucrose or 4% corn oil in 2-h home cage test sessions. Intra-LS Ex9 significantly increased sucrose (13%) and corn oil (62%) intake relative to vehicle. To determine the mechanisms through which endogenous activation of LS GLP-1R reduces sucrose intake, we examined the effect of intra-LS Ex9 on meal pattern and licking microstructure in a group of rats licking for 0.25M sucrose during
2-h tests in lickometer-fitted chambers. Ex9 treatment significantly increased first meal size (24%) and meal duration (25%) relative to vehicle. Microstructural analysis revealed that within the first meal, LS Ex9 significantly increased the average size (35%) and duration (32%) of licking bursts, particularly during the early portion of the meal. This suggests that blockade of LS GLP-1R increases meal size in part by increasing food palatability. Together, our findings continue to support the hypothesis that GLP-1R in the LS play a physiologic role in the control of feeding and suggest that LS GLP-1R may influence taste evaluation.

Central ghrelin administration increases food foraging/hoarding that is blocked by GHSR1a antagonism and attenuates PVH neuronal activation

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The stomach-derived “hunger hormone” ghrelin increases in circulation in direct response to time since the last meal. We previously demonstrated peripheral injection of ghrelin potently stimulates food foraging (FF) food hoarding (FH) and food intake (FI) in Siberian hamsters. It remains, however, unknown if central ghrelin is necessary and sufficient to increase these behaviors regardless of peripheral manipulation. Here, we injected three doses (0.01 µg, 0.1 µg, and 1.0 µg) of ghrelin into the third ventricle (3V) of Siberian hamsters and measured FF, FH, and FI. To test the effects of 3V ghrelin receptor blockade, we used GHSR1a antagonist JMV2959 to block these behaviors in response to food deprivation or a peripheral ghrelin challenge. Finally, we examined neuronal activation in the arcuate nucleus (Arc) and paraventricular hypothalamic nucleus (PVH) in response to peripheral ghrelin administration and 3V antagonism. Ghrelin 3V stimulated food intake at 2-4 h and food hoarding through day 4. JMV2959 3V pretreatment successfully blocked peripheral ghrelin-induced increases in FF, FH and FI and food deprivation-induced increases in FF, FH and FI up to four hours. c-Fos-immunoreactivity (ir) was significantly reduced in the PVH but not the Arc following pretreatment with JMV2959. Collectively, these data suggest central GHSR1a activation is both necessary and sufficient to increase appetitive and consummatory behaviors in Siberian hamsters.

Effects of age and ovariectomy on thirst and salt appetite in rats.

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We tested the effects of age and Estrogen (E2) deprivation on thirst and salt appetite responses of female rats aged 5 (n=8) and 25 (n=10) months maintained on water, 0.3 M NaCl and standard diet. In one test, rats were water deprived for 20 hr by removing the drinking fluids. Then burettes of water were provided and intakes were recorded for 90 min. In another test, rats were depleted of sodium by injections of the diuretic, furosemide (10 mg/kg, sc) and access only to water and sodium deficient diet for 22 hr. Then burettes of water and 0.3 M NaCl solution were provided and intakes were recorded for 90 min. Young and aged rats were tested before and again 2 wks after ovariectomy (OVX). After water deprivation, the rats drank nearly identical amounts of water pre and post OVX, and age had only small effects. After sodium depletion, young rats drank substantial amounts of sodium pre OVX (2.1±0.4 ml) and significantly less post OVX (0.9±0.3 ml). Aged rats drank trivial amounts of sodium both pre (0.3±0.2) and post (0.3±0.1) OVX. The results suggest that deprivation-induced thirst is largely intact both with advanced aged and loss of E2. However, depletion-induced salt appetite is greatly reduced in aged compared with young rats with
loss of E2 accounting for ~2/3, and other age-related effects accounting for ~1/3, of the difference in intakes between the ages.

Water intake and central activation stimulated by Isoproterenol in ovariectomized young and aged female rats

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Changes in thirst, cardiovascular function, and hormones such as angiotensin II (AngII) in reproductively senescent females suggest a role for estrogen in body fluid balance. However, it is unclear whether such changes are due to loss of estrogen or to aging, per se. These studies used young (5 mo; n=9) and aged (25 mo; n=9) ovariectomized (OVX) female rats to examine water intake and central activation in response to isoproterenol (ISOP; 30 mg/kg, sc). Water intake by aged OVX rats was reduced by ~40% in the first 30 min after ISOP (aged OVX rats: 0.7 ± 0.1 ml/100g BW; young OVX rats: 1.6 ± 0.2 ml/100g BW) and remained suppressed throughout the 90-min test. Fos immunolabeling was increased by ISOP in both young and aged OVX rats. However, the increase was selectively blunted in aged OVX rats: labeling in the organum vasculosum of the lamina terminalis, subfornical organ, and paraventricular nucleus was ~40% of that in young OVX rats. In contrast, fos labeling was comparably increased in the supraoptic nucleus. Thus, aging affects responses to body fluid challenges independent of—or in addition to—the loss of estrogen. Blunted central activation may contribute to the reduced water intake by aged OVX rats in response to ISOP, but whether these effects reflect decreased circulating AngII or decreased central sensitivity to AngII remains to be determined.

The taste of P

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Rats and cattle have a specific appetite for phosphorus (P) but how they recognize it is unknown. Cats and dogs are strongly attracted to P salts—phosphates and pyrophosphates—but why is also unknown. Could there be a P taste? To investigate, we used 5-sec brief-access gustometer tests and 48-h two-bottle choice tests to assess the taste responses to P salts of mice with knockout of genes required for taste transduction. Controls, including C57BL/6J and wild-type mice, had modest preferences for millimolar concentrations of trisodium pyrophosphate and other P-containing sodium salts. However, mice with genetic knockout of ITPR3 or CALHM1 did not prefer these salts. ITPR3 and CALHM1 are integral to GPCR-mediated taste transduction so this implies that the preferred component of P taste is detected by one or more GPCR. Next, we assessed the avidity of T1R3 knockout mice for various P and non-P salts. Counterintuitively, these mice had elevated preferences relative to wild-type controls for tri- and tetra-sodium pyrophosphate, and other P-containing sodium salts. However, mice with genetic knockout of T1R3 did not show these preferences. Thus, the strong preferences for P salts of T1R3 knockout mice are P-specific and distinct from the paracellular gap-mediated taste transduction mechanism. We conclude that P is detected by at least two GPCRs, with one being T1R3 and the other(s) unknown. The involvement of taste GPCRs implies that mice can taste P.

Conditioned avoidance of a high fat/high sucrose diet differentially generalizes to orosensory stimuli

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Orosensory characteristics of diets play a role in food acceptance and rejection. The current study was designed to investigate the gustatory components that contribute to the intake of a palatable, high-energy diet (HE; 45% fat, 17% sucrose). Here, rats were conditioned to avoid HE diet by pairings with i.p. injections of LiCl and subsequently tested to an array of taste compounds in a brief-access lick procedure (10-s trials, 30-min sessions). Compared to NaCl-injected controls, LiCl-injected rats suppressed licking response to 100% linoleic acid and 20% intralipid, and to a lesser extent 17% sucrose. There was more variability in the lick responses to sucrose among the LiCl-injected rats. Rats that tended to suppress licking to sucrose generalized this response to glucose, fructose and Na-saccharin but not to Polycose. In contrast, LiCl-injected rats did not significantly suppress lick responses to water, NaCl, citric acid or quinine compared to controls rats. The brief access feature of this procedure, allows for behavioral measures in which postingestive factors are minimized. These findings support a role for gustatory cues in the detection of high fat/high sugar diets. Furthermore, it appears that the fat component is a more salient orosensory feature of the HE diet.

A role for Vitamin D3 signaling in obesity and dopamine-related behaviors

Vitamin D3 deficiency rates have increased concurrently with obesity rates, and evidence suggests an inverse relationship between circulating vitamin D3 levels and body mass index (BMI). In mice, we show a causative role for reduced dietary vitamin D3 high fat diet (HF-D)(cholecalciferol, ~11% of normal HF diet) in promoting diet-induced obesity (DIO). Chronic exposure to the HF-D diet caused a gain in body weight and food intake (n=10,10 p< 0.05). Dopamine neurons in the midbrain and their target neurons in the striatum were found to express vitamin D3 receptor protein (VDR). VDR functions as a transcription factor, and treatment with fully active D3 (calcitriol, 10µg/kg ip) was used to explore effects on dopamine circuits. Calcitriol increased: 1) dopamine-related gene expression (n=5,5 p< 0.05), 2) dopamine release (n=6,6 p< 0.05), and 3) amphetamine-induced (2.5 mg/kg) locomotor activity (n=8,8 p< 0.05). However, mice trained to orally consume amphetamine showed a reduction of intake after calcitriol treatment (n=12,12 p< 0.05). In complement, HF-D mice had reduced locomotor activity after amphetamine, yet consumed more oral amphetamine (n=5,5 p< 0.05). Finally, calcitriol treatments reduced body weight and food intake in DIO mice. These data support a role for vitamin D3 signaling on dopamine sensitivity and regulating consummatory behaviors.

Reproducibility and validity of satiety measures in healthy women

Reproducibility and validity testing of appetite ratings and energy intakes is needed. Healthy women with unrestrained eating behaviors (23.0 ± 2.6y, n=18) consumed a yogurt breakfast (190 kcal) for 8 d, and on days 1 and 8, rated their appetite (Hunger, Fullness, Desire to Eat, Prospective Food Consumption (PFC)) every 30 min over a 3.5 h period using visual analogue scales (VAS) in a research setting. At 180 min,
participants consumed an *ad libitum* pizza lunch and at 210 min, left the research center and recorded their food intake for the remainder of the day. Ratings from fasting, 180 and 210 min time points, total area under the curve (AUC) for 0-180 min, and lunch and total day energy intakes were compared. Reproducibility within satietiy measures was evaluated using coefficients of repeatability (CR), coefficients of variation (CV) and intra-class coefficients ($r_i$). Correlation analysis was used to examine validity between satietiy measures. Appetite ratings were reproducible for Hunger, Desire to Eat and PFC at 180 min (CR=17.5-25.5mm; CV=5.7-8.5%; $r_i=0.65-0.72$), and Fullness at 210 min (CR=14.1mm; CV=4.0%; $r_i=0.71$). AUCs for Hunger, Desire to Eat and PFC, and *ad libitum* energy intakes were reproducible, but fasting ratings and total day energy intakes were not. AUCs for Hunger, Desire to Eat and PFC, and PFC at 180 min, were correlated to total day energy intakes ($r=0.49-0.60$, P< 0.001), but no appetite ratings were correlated to lunch intakes. PFC ratings may be useful predictors of total energy intake in young women, but ratings of satiety did not concur with next meal intake, a measure of satiation.

Effects of monotonous versus varied (“junk food”) high-fat diet on obesity and food motivation

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Prior work in our lab suggested that a monotonous high-fat diet reduced motivation to obtain and consume palatable foods compared to a monotonous low-fat diet in rats. However, work from other laboratories found the opposite results using diets that were more varied, or more similar in taste (i.e., sugar content) to the test food. More varied diets (“cafeteria diet”) allow rats to experience a variety of tastes, textures, and nutritional composition in a way that better models human food consumption than standard commercially available high-fat diets. While prior studies have used this model to induce obesity or assess the effects of diet on physiological and behavioral measures, these studies have not typically compared the effect of these diets to monotonous diets. The goal of the present study was to compare three diets: a “junk food” or cafeteria diet consisting of three weekly100-calorie supplements of a variety of processed foods high in fat and refined carbohydrates (cookies, chips, candy), a commercially available diet with 45% saturated fat, and standard rat chow with 4% fat. The goal of introducing this “junk food diet” is first, to model human eating better, and, second, to familiarize animals with foods of varying physical properties and nutrient content. We hypothesize that this food variety will increase responding for novel palatable foods in an operant conditioning progressive ratio task, allowing us to better generalize this behavior to human obesity. Data on free intake of novel palatable foods, weight gain and blood leptin levels will also be presented.

Optogenetic Manipulation of Posterior Paraventricular Thalamic Circuits Alters Chocolate Intake


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Prior studies implicate the posterior paraventricular thalamus (pPVT) in controlling food intake; those data show that pPVT lesions and inhibition with muscimol increase intake. Paradoxically, pPVT excitation with orexin A also increases intake. Therefore, we sought to explore how optogenetic excitation or inhibition of the pPVT may similarly alter intake of normal chow and highly palatable food. Two groups of four adult Long Evans rats received pPVT microinjection of adeno-associated viruses coding for channelrhodopsin or halorhodopsin, and optic fiber implants were aimed at the pPVT, central amygdala (CeA), and nucleus accumbens shell (AcbSh). Rats were tested for one hour in an open field chamber with access to water, chocolate fragments, and chow. Yellow laser-mediated inhibition of the pPVT increased chocolate intake (10.3 +/- 0.8 g) relative to intake without laser (6.4 +/- 1.1 g; p = .049), but blue laser-mediated excitation of the pPVT did not significantly alter intake. Excitation of pPVT to AcbSh projections suppressed chocolate intake (0.9 +/- 0.9 g) relative to intake without laser (4.0 +/- 0.0 g; p = .023), but inhibition of this
projection did not significantly alter intake. Manipulations of pPVT to CeA projections did not significantly alter intake. Chow intake remained unchanged in all tests. These data suggest that 1. pPVT optogenetic inhibition may mimic the appetitive effects of muscimol microinjections, and that 2. excitation of the pPVT to AcbSh circuit suppresses appetitive behavior.

Optogenetic inhibition of ventral tegmental area dopamine neurons reduces reward-seeking

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Ventral Tegmental Area (VTA) dopamine neuron (DA) activity is important for responding to reward-predicting cues and the expression of motivated behavior. Previously we showed that VTA GABAergic neuronal activity attenuated the consummation of a cued reward, possibly through inhibition of DA neurons. Here we explore the need for DA neuron activity during both reward-seeking and consumption. Mice learned to associate a light cue with the delayed delivery of a sucrose reward. Subsequently we made use of optogenetic inhibition of VTA DA neurons during task execution to assess the consequences of this inhibition during cue presentation and reward delivery on anticipatory licking activity and reward consumption. We find that inhibition of VTA DA activity decreases task performance during anticipatory licking and reward consumption. This contrasts with our previous finding that activation of VTA GABA only attenuated consumption of the reward. Importantly, related licking motor responses, as well as locomotor activity are unimpaired. Thus direct inhibition of VTA DA neurons decreases performance on cue-reward seeking tasks. What remains unsolved is how modulation of reward value and DA neuron activity affect reward-seeking. To this end we have developed a choice paradigm in which rewards of varying value can be obtained. The modulatory role of DA in such a task will be discussed.

Stress effects on taste preferences in male and female Rats

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A majority of males and females in the US are overweight and stress is known to affect food intake. The goal of this study was to determine whether there are sex differences in food preferences after exposure to stress. In our survey of men and women, women reported a preference for sweet foods when they are stressed while men report preferring salty foods. We next examined sex differences in taste preferences by male and female rats that were exposed to stress. Six male and six female rats were placed in cages that allow continuous monitoring of food and fluid intake. Rats were given two-hour, two-bottle tests on 2 consecutive weeks to determine baseline preferences for 0.15 M NaCl (salt), or 10% sucrose (sweet) solutions. The following week, rats underwent restraint stress for 15 minutes, then were returned to their cages where a two-bottle test (salt and sweet solution) was conducted. On the final week, a post-stress preference test was conducted. Preference testing before stress showed that both male and female rats preferred salt or sweet to water, but preferred sweet over salt. Immediately after restraint stress, male and female rats preferred sweet over salt, and this trend continued in the post-stress test. Thus, unlike humans, male and female rats prefer sweet tastes before, during, and after stress, though direct tests of food preferences by humans will be necessary to make definitive conclusions.
A modified Roux-en-Y gastric bypass procedure alters the feeding responses evoked by exogenous gastrin releasing peptides

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To test the hypothesis that Roux-en-Y gastric bypass (RYGB) alters meal size (MS) and intermeal interval (IMI) length by exogenous gastrin releasing peptides (GRP) and changes the gastrointestinal sites of actions regulating them, we measured MS and IMI length by infusing exogenous GRP-10, GRP-27 and GRP-29 in the celiac artery (CA, supplies stomach and upper duodenum) and the cranial mesenteric artery (CMA, supplies small and part of the large intestine) in modified RYGB (in which part of the stomach is removed) and sham-operated rats. We found that (1) GRP-10 given in the CA reduced MS and prolonged the IMI only in the RYGB group. (2) GRP-27 given by both routes reduced MS in the sham group, and by the CMA it reduced MS in the RYGB group but more so in the sham rats. GRP-27 given by the CA prolonged the IMI only in the sham group. (3) GRP-29 given by both routes and in both groups reduced MS, more so in the sham group, and when given by the CA in both groups it prolonged the IMI, and more so in the RYGB group. In conclusion, modified RYGB alters MS and IMI length by exogenous GRP and the gastrointestinal sites of actions regulating them. Changes in the architecture of the gut, which leads to possible redistribution of the GRP receptors following the RYGB surgery, may explain some of these findings.

Effect of cholecystokinin-8 and cholecystokinin-33 on meal size and intermeal interval and the gastrointestinal site of action regulating them in diet-induced obese rats maintained on normal rat chow

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The feeding responses by various gut peptides change in diet-induced obese (DIO) rats maintained on different diets. Here, we tested the hypothesis that meal size (MS) and intermeal interval (IMI) length by exogenous cholecystokinin (CCK)-8 and CCK-33 and the gastrointestinal site(s) of action regulating them change in DIO rats by measuring these feeding responses following infusion of the peptides (0.01 and 0.05nmol/kg) in the celiac artery (CA, supplies stomach and upper duodenum) and the cranial mesenteric artery (CMA, supplies small and part of the large intestine) in DIO prone (DIO-P) and DIO resistant (DIO-R) rats maintained on normal rat chow. We found that (1) CCK-8 0.05nmol given by the CMA reduced MS and CCK-8 0.01nmol given by the CA prolonged the IMI only in DIO-R rats, (2) CCK-33 0.01nmol given by both routes reduced MS in DIO-P rats and prolonged the IMI by the CMA route in both rat groups and (3) CCK-33 0.05nmol given by both routes and in both groups of rats reduced MS but only by the CMA it prolonged the IMI in the DIO-R group. We conclude: (A) at these doses only DIO-R rats are responsive to CCK-8 and the two feeding responses are regulated by different sites in the gut, (B) DIO-P rats are more sensitive to CCK-33 than DIO-R rats and (C) in both rats MS and IMI length by CCK-33 are regulated by different sites, CA and CMA supplies sites regulating MS while CMA supplies sites regulating IMI.

Forebrain Catecholaminergic Projections Restrain High Calorie Diet-Associated Hyperphagia and Adiposity

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Hindbrain catecholaminergic (CA) neurons provide metabolic and energy information to the hypothalamus. To determine their role in long-term food intake and body weight regulation we ablated those CA neurons with projections to the hypothalamic paraventricular region with an anti-dopamine-b-hydroxylase (DBH)-saporin conjugate (DSAP). Bilateral paraventricular injections of DSAP or control (MSAP) were made in male Sprague-Dawley rats (300g BW). Rats were then offered either a combination of chow, 60% fat diet (Research Diets), and a 30% sucrose solution (HiCal), or chow alone. Six weeks later food daily intakes were measured for 5 days along with fasting glucose. Body weights were measured throughout. Iv glucose tolerance was measured in 2 separate groups of chow DSAP/MSAP rats. Rats were anesthetized, blood samples taken, and perfused with 4% buffered paraformaldehyde. Abdominal fat pads and thymus glands were weighed. Rats were assigned as lesioned or sham-lesioned depending on residual hypothalamic and hindbrain immunoreactive DBH. All HiCal variables for both groups except thymus weights were increased above those in chow rats. HiCal DSAP rats had significantly elevated caloric intakes, abdominal fat, and plasma leptin, compared to HiCal shams. Thymus weights were significantly reduced only in HiCal DSAP rats. Chow DSAP rats also had small but significantly elevated fasting glucose and insulin. Glucose tolerances were unaffected. CA projections therefore help maintain glycemic control and central glucocorticoid feedback during a HiCal diet thereby restraining hyperphagia and adiposity.

Nutraceuticals for body-weight management: the role of green tea catechins

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Body-weight management after body-weight loss is a challenging task. The objective of this presentation is to highlight the role of green tea catechins herein. Observations in this respect are that in habitual low caffeine consumers, a green tea-caffeine mixture improves body-weight maintenance, partly through thermogenesis and fat oxidation (Obes Res 2005). This body-weight maintenance does not show a synergism with a similar effect of a protein diet (AJCN 2009). A meta-analysis showed a small effect on weight loss and subsequent weight maintenance from catechins or an epigallocatechin gallate (EGCG)-caffeine mixture. Habitual caffeine intake and ethnicity were identified as moderators. (Int J Obes 2009). The main mechanisms are energy expenditure and fat-oxidation (Obes Rev 2011), with a possible role for catechol_O-methyl transferase Val(108/158)Met polymorphism (rs4680) (PLosOne, 2014). The latter may explain the ethnicity effect. However, without an initial decrease in body-weight, long-term green tea extract supplementation does not affect fat absorption, resting energy expenditure, and body-composition in adults (J Nutr 2015), nor the diversity or composition of the gut-microbiota. In conclusion, after an initial body-weight loss green tea catechins support body-weight maintenance in habitual low caffeine consumers, based upon energy expenditure and fat oxidation.

Adverse social experience sustains emotional feeding in females

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Chronic exposure to social stressors can have bidirectional effects on appetite. However, an emerging body of work indicates that stress-induced emotional feeding of palatable diets may increase the risk of developing an obese phenotype. Using socially housed female rhesus monkeys, studies are testing the hypothesis that adverse social experience, imposed by social subordination, increases preference for and consumption of a palatable, high caloric diet. Socially subordinate females show deficits in stress hormone feedback regulation as well as a distinct behavioral profile that includes more anxiety like behavior in standardized tests of emotional reactivity. In addition, subordination produces widespread deficits in function of reward circuitry. While subordinate females show mild inappetence when fed a low fat and
sugar, high fiber chow diet, these females consume significantly more calories compared with more dominant animals when both the prudent diet and a highly palatable high caloric diet are available. The hypothesis that this emotional feeding phenotype is maintained by increased stress hormone signaling is supported by observations that acute administration of a corticotropin releasing factor type 1 receptor antagonist (Antalarmin) decrease calorie consumption in subordinates to quantities consumed by dominant females. Together, these data suggest that the emergence of emotional feeding is dependent on the dietary environment and is likely the result of stress-induced changes in reward circuitry leading to a preference for palatable, calorically dense diets. Supported by by NIH R01DK096983 and OD-P51011132

Hedonic Hunger Predicts Left-Sided Activity and Restrained Eating Predicts Right-Sided Activity in the Prefrontal Cortex

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Asymmetrical alpha activation in the prefrontal cortex (prefrontal asymmetry) in electroencephalography (EEG) has been related to eating behavior. Prior studies linked dietary restraint with right prefrontal asymmetry (Silva et al., 2002) and disinhibition with left prefrontal asymmetry (Ochner et al, 2009). The current study simultaneously assessed restrained eating and hedonic hunger (drive for food reward in the absence of hunger) in relation to prefrontal asymmetry. Resting-state EEG and measures of restrained eating (Revised Restraint Scale; RRS) and hedonic hunger (Power of Food Scale; PFS) were assessed in 61 non-obese adults. When entered individually, hedonic hunger predicted left asymmetry. However, PFS and RRS were correlated ($r = 0.32, p < .05$). When entered simultaneously there was a significant interaction between PFS and RRS on prefrontal asymmetry, $p < 0.01$. Results indicated that those high in hedonic hunger exhibited left asymmetry irrespective of RRS scores; among those low in PFS, only those high in RRS showed right asymmetry. Results were consistent with literature linking avoidant behaviors (restraint) with right-prefrontal asymmetry and approach behaviors (binge eating) with left-prefrontal asymmetry. It appears that a strong drive toward palatable foods predominates at a neural level even when restraint is high. Findings suggest that lateralized prefrontal activity is an indicator of motivation both to consume and to avoid consuming highly palatable foods.

The influence of eating frequency on appetite during weight loss

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Eating frequently is thought to assist with managing hunger and fullness, which may improve dietary adherence to a hypocaloric diet. This study examined the effect of eating frequency (EF) on appetite, energy intake (EI), and weight loss in an 8-week lifestyle intervention. Twenty-two participants (42.6±13.5 yrs, 32.2±3.9 kg/m$^2$, 86.4% female and white) were randomized to Three Meal (three meals/day; n=11) or Grazing (eat $>$100 kcals every 2-3 hrs; n=11). Groups received a lifestyle intervention (weekly individual sessions; diet = 1200–1500 kcal/day, < 30% kcal from fat; physical activity = 200 mins/wk). Hunger and fullness via Ecological Momentary Assessment (EMA), EI, and weight were collected at 0 and 8 weeks. EMA was sampled using semi-random prompts occurring outside of eating bouts, and event contingent prompts occurring after eating bouts. For EF, a significant interaction was found, with Three Meal having lower EF than Grazing at 8-weeks (2.9±0.2 eating bouts vs. 5.5±0.2 eating bouts, $p<0.001$). EMA from semi-random prompts showed no significant group differences across time. EMA from event contingent prompts showed no difference in hunger, however fullness showed a significant interaction, with Three Meal having higher fullness ratings than Grazing at 8-weeks (3.6±0.1 vs. 3.1±0.1, $p=0.017$). While no significant group differences occurred, EI and weight significantly lowered ($-719±124$ kcal/day and -
9.8±1.2 lbs, respectively). Lower EF may increase feelings of fullness when a hypocaloric diet is consumed. Higher EF may not assist with adherence to a hypocaloric diet or improve weight loss.

Reduced sensory-evoked activity of locus coeruleus-norepinephrine neurons following dietary-induced binge eating and relationship to NPY

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A major component of the stress neuraxis is the locus coeruleus-norepinephrine (LC-NE) system. Neuropeptide Y (NPY) in the LC-NE system has a purported anxiolytic effect. The role of the LC-NE system, as well as the interaction with NPY, in binge eating is largely unexplored. We used a dietary-induced binge eating protocol in young adult female rats exposed to 5 episodes of intermittent chow deprivation (24h) followed by sweetened fat (vegetable shortening with 10% sucrose; Restrict Binge). Additional groups included intermittent deprivation only (Restrict), intermittent sweetened fat only (Binge) or standard fed controls (Naive). Single unit electrophysiological recording under isoflurane anesthesia revealed differences in sensory (sciatic nerve stimulation; 50 stimuli, 3.0 mA, 0.5 ms) evoked LC activity [F (3, 93) = 7.1, p < 0.05]. Restrict Binge (6 animals; 20 cells) and Binge (6 animals; 27 cells) had a reduced rate compared with Naive (7 animals; 22 cells, p< 0.05), whereas Binge also had rate reductions compared with Restrict (6 animals; 22 cells, p < 0.05). In a separate set of animals (n = 5-7/group), LC region gene expression revealed NPY differences [F (3, 22) = 4.1, p< 0.05]. Restrict showed a 2-fold increase in NPY compared with all groups (p < 0.05). Additional results suggest a different pattern of evoked LC activity following intra-LC NPY injections. Such findings suggest NPY is not likely involved in the pattern of LC neural activity produced by dietary-induced binge eating.

Individual differences in flavour-based learning: a microstructural analysis.

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Studies of human ingestive behaviour have built on techniques arising from the study of animal behaviour, such as the use of detailed analysis of eating microstructure pioneered by the use of the universal eating monitor (Kissileff, 1980). This approach has helped dissociate mechanisms underlying different components of ingestion: e.g. how palatability and satiation interact to determine meal-size. Similar approaches have since been used to explore how associations between cues and aspects of food ingestion modulate flavour liking, and what underlies individual differences in liking expression. Associations between novel odours and the oral experience of sweetness increase perceived odour sweetness. For sweet-likers, this association also increases odour liking, but this effect is greater, and the impact of this odour change on behavioural measures (“sniffing”) is more pronounced, for those prone to uncontrolled eating (high scores on disinhibition scale of the Three Factor Eating Questionnaire, TFEQD). High TFEQD scores are correlated with behavioural measures of reward reactivity and these moderate the sweet-driven changes in odour liking. In contrast, liking for flavours acquired through associations with ingested nutrients are unaffected by differences in reward sensitivity but are blunted by a history of dietary restraint. Together these findings imply that sensitivity to reward may enhance reactivity to sweetness and associated flavours, but that attempts to restrain eating may reduce sensitivity to the controlling effects of satiety, so increasing the potential for uncontrolled eating.

Physiological basis of sensory-enhancement of satiety: a role for CCK and PP
Increasing the expectation that a drink will be filling by making it thicker and more creamy greatly increases post-ingestive satiety (sensory-enhanced satiety, SES). It is also known that cues associated with ingestion trigger preparatory physiological changes (cephalic phase responses: CPR). To test the potential role of CPR in SES, 24 healthy volunteer men consumed one of four test drinks 90 minutes before a test lunch, with blood samples drawn to assay blood glucose, insulin, pancreatic polypeptide (PP) and cholecystokinin (CCK) before and periodically after drink consumption. The test drinks combined two levels of energy (LE: 78 or HE: 274kcal) combined with two levels of sensory (thin, LS or thick and creamy, HS). Participants consumed least after the HEHS preload, and most after the two LE preloads, and this was mirrored by greater suppression of hunger in the HEHS condition. Blood glucose and insulin were greater after HE than LE drinks, and were unaffected by the sensory manipulation. PP levels increased more after HS than LS drinks but were unaffected by energy content, whereas the only significant increase in CCK was after ingestion of the HEHS condition. These data imply that down-down signalling allows integration of sensory information with nutrient sensing to generate an appropriate satiety response and offer novel approaches to future development of satiating products.

Hindbrain prolactin-releasing peptide (PrRP) neurons are not closely linked to motor circuits controlling intrinsic tongue muscles

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PrRP is expressed by noradrenergic neurons in the caudal nucleus of the solitary tract (cNTS). In rodents, PrRP neurons express cFos in direct proportion to feeding-induced gastric distension, and central PrRP signaling limits meal size. PrRP neurons innervate brainstem regions that control oral consummatory behaviors, and forebrain regions that modulate food intake. Thus, PrRP neurons may control feeding motor programs via multisynaptic circuits. The current study combined pseudorabies virus (PRV) transport with immunofluorescent labeling to determine whether PrRP neurons are synaptically linked to pre-motor neurons that control tongue shape (intrinsic muscles). Sprague-Dawley rats were sympathectomized to prevent central autonomic infection, and then injected with PRV unilaterally into the anterior tongue. 4 days later, rats were perfused and brain sections processed to colocalize PRV, PrRP, and other neurotransmitter markers. As previously reported, infected motor neurons were located unilaterally within the hypoglossal nucleus, and infected pre-motor neurons were located bilaterally within the cNTS, area postrema, medullary and pontine reticular formation, midbrain, hypothalamus, and limbic forebrain. Although infected cNTS neurons often intermingled with PrRP-positive neurons, very few were double-labeled, suggesting that PrRP neurons are not closely linked to motor circuits that control the shape of the tongue. Ongoing studies are exploring whether PrRP neurons are linked to motor neuron pools that position the tongue and/or control other consummatory ingestive behaviors.

Nutrient induced changes in intestinal epithelial crypt and stem cell metabolism

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The intestinal epithelium plays an integral role in ingestive behaviors. Maintenance of the epithelium is driven by continuous stem cell proliferation and differentiation. The amount and type of diet influence
these processes and result in changes in the size and cellular make-up of the tissue. The mechanisms underlying the nutrient-driven changes in proliferation and differentiation are not known, but may involve a shift in intracellular metabolism. A shift in the metabolic flux of stem cells from the use of oxidative phosphorylation to glycolysis has been used as an indicator of an increase in abnormal mammalian tissue growth, but it is not known if this shift also occurs under normal nutrient-driven increases in intestinal epithelial size. In order to test if nutrient availability drives a shift in metabolism, we used 1) fluorescence-activated cell sorting to analyze intestinal epithelial stem cells isolated from mice that express a green fluorescent protein stem cell marker (LGR5-GFP mice) and 2) primary intestinal crypt cultures generated from wild type mice. We treated these cells with 0mM, 5mM or 20mM of glucose and found that lactate production increased in both nutrient conditions and across time from 30, 60, 120 and 240min. These data indicate that nutrients are able to drive an increase in glycolysis and that there may be a shift in metabolism that occurs under normal intestinal epithelial stem proliferation and tissue growth. Utilizing this model, we can test the intracellular signaling involved in metabolic changes in stem proliferation and differentiation.

**Food odors and attentional bias for visual food cues**

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Odors play an important role in cognitive and behavioral responses to foods, often acting as primes that influence attention. The present study examined whether acute exposure to a high fat odor affected attentional bias for visual food cues. Female participants (N= 78; mean age= 19.7 years) were exposed to either a high fat or neutral odor (clean air) before engaging in a flanker task. In this task, high and low fat food images were presented as central targets or flanking distractors, and participants were instructed to categorize the central target while ignoring the flankers. Reaction times were recorded over 136 trials and data from participants who correctly identified the odor stimuli (N = 45) were entered into a repeated measures ANOVA. Preliminary results revealed a target x flanker interaction (p < 0.01) and a target x flanker x odor interaction (p = 0.03). Subsequent breakdown of these interactions showed that the neutral odor group exhibited slower reaction times when a high fat, but not low fat, target was presented with high fat flankers (p = 0.076). No effects were observed, however, for the high fat odor group. These findings suggest that acute exposure to a high fat odor may reduce attentional biases to foods.

**Stress, Depression and Obesity: The Ghrelin Connection**

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The peptide hormone ghrelin has both orexigenic and antidepressant actions, positioning it to mediate the strongly interconnected eating and mood-related manifestations of conditions such as anorexia nervosa and obesity. Here, I will review some of our pre-clinical work on mechanisms underlying the contributions of the ghrelin system to these behaviors. We have adapted several behavioral tasks with which to study complex eating behaviors in mice, including conditioned place preference for high-fat diet. When the latter is coupled to the chronic social defeat stress model of prolonged psychosocial stress, we also can study stress-based comfort food eating. These behavioral models are used in conjunction with standardized measures of depressive-like behavior. Testing these models with mice in which we have manipulated the ghrelin system genetically, physiologically or pharmacologically has helped demonstrate that an intact ghrelin system is essential for some key behavioral responses to chronic stress and to caloric restriction, both of which increase ghrelin secretion. For example, ghrelin receptor deletion in mice exaggerates depressive-like behavior following chronic stress, blocks the usual food reward behavior induced by stress and prevents the usual antidepressant-like behavioral response to caloric restriction. Ghrelin's
antidepressant effect during stress involves protection of adult hippocampal neurogenesis. Recent work has moved us closer to confirming an essential role for beta 1-adrenergic receptor signaling in mediating the effects of caloric restriction and stress on ghrelin secretion.

Orexin neuron activation drives spontaneous physical activity and promotes healthy body weight.

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Spontaneous physical activity (SPA) is a promising therapeutic target for improving multiple clinical outcomes in obesity and metabolic syndrome. Low levels of the neuropeptide, orexin, are correlated with reduced SPA and pathological body weight in humans and animals. We used a pharmacosynthetic approach (Designer Receptors Exclusively Activated by Designer Drugs; DREADDs) to stimulate orexin neurons in adult male mice. Selective targeting was achieved by bilateral virus injection into the lateral hypothalamic area of transgenic mice expressing the DNA-recombinase, Cre, in orexin neurons. In the presence of Cre, viruses expressed an excitatory, Gq-coupled, DREADD. A single systemic dose of the Designer Drug, Clozapine-N-Oxide (CNO; 5mg/kg; IP), activated DREADD-containing orexin neurons and increased SPA 3-fold in the 2hrs post-injection compared to vehicle (N=8, p< 0.001). Under standard chow conditions, CNO did not alter body weight or food intake. To test if elevated SPA protects against an obesogenic diet, animals were housed on 40% high fat diet (HFD) and given daily injections of CNO or vehicle. Five consecutive days of CNO resulted in body weights (25.75g+/−0.38; Mean+/−SEM) that were not significantly different from pre-HFD levels (25.20g+/−0.49); whereas, animals that received control injections continued to gain weight (27.12g+/−0.35) and adiposity. This study demonstrates the ability of SPA to counteract HFD-induced weight gain. Many medical conditions, in addition to obesity, stand to benefit from enhanced physical activity.

Brain reward responses to olfactory food cues in obese participants – preliminary fMRI results

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Heightened neural responsivity to olfactory food cues may increase craving in the absence of hunger, leading to overeating and eventually obesity. Olfactory cues of palatable energy dense foods are omnipresent in our environment. This study aimed to disentangle brain reward processing in obese participants during exposure to olfactory cues of high energy and low energy dense foods. Functional and anatomical MR images of nine obese participants (age 37±10 yrs; BMI 41±3 kg/m²) were acquired using a 3T MRI scanner. During scanning, olfactory cues of high energy dense food, low dense food and non-food (30 per category, 2s each) were presented in pseudo randomized order. Preliminary ROI analyses in SPM8 revealed increased activation in the left inferior orbitofrontal cortex (z=3.33) in response to high energy compared to low energy odours. The left medial (z=3.25) and middle orbitofrontal cortex (z=3.34) were activated more during exposure to low energy compared to high energy odours. These results suggest a distinction between lateral and medial orbitofrontal cortex activation related to the reward value (respectively high/low) signalled by the cue, as previously suggested by others (e.g. Yokum et al., 2012). This study will be extended with measurements in a larger sample, before and after gastric bypass surgery.

Is it good to have options? The effect of offering a choice of portion sizes on intake at a meal
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When served larger portions at a meal, people consume more energy. We tested whether giving individuals a choice of portion sizes for a meal affected either the amount selected or consumed. In a crossover design, 24 women and 26 men ate lunch in the lab once a week for 3 weeks. At each meal, subjects were shown 3 portions of pasta, then chose one and consumed it ad libitum. Across the meals, 3 sets of portions were offered in a counterbalanced design; for women the sets by weight (g) were: 300/375/450, 375/450/525, and 450/525/600. Men’s portions were 33% larger than those offered to women. The results showed that increasing the size of portion choices did not significantly affect the relative size selected at all 3 meals: 18 subjects chose the smallest portion within each set, 2 chose the medium, and 1 chose the largest. The size of portion choices did, however, significantly influence intake for both women and men (P<0.0001). Meal intake was 16% greater when the largest set of portions was offered (mean ± SEM: 661±34 kcal) compared to the medium and smallest sets (mean ± SEM for both: 568±18 kcal). These results confirm the robust effect of portion size on intake and suggest that while offering a choice of portions can help to moderate intake, the sizes of the available portions are a critical determinant of energy intake. Thus, offering more portion choices could be a useful tool to counter the portion size effect, as long as the portions fall within an appropriate range for energy needs.