Transgene expression of MIC-1 *in vivo* using minicircle DNA results in weight loss and improved glucose homeostasis in mice.
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Macrophage inhibitory cytokine-1 (MIC-1) is a central regulator of energy balance. We constructed a minicircle DNA (mcDNA) plasmid expressing the native signal peptide MIC-1. Another plasmid of human alpha 1 antitrypsin (hAAT) was used as a positive control. Lean male C57/Bl6 mice were administered saline or mcDNA via hydrodynamic tail vein injections. Saline treated animals were maintained on normal rodent chow and mcDNA treated animals were switched to a high-fat diet after injection. Treatment with MIC-1 mcDNA reduced food intake by 20 kcal relative to chow and 40 kcal relative to hAAT at the end of 2 weeks, resulting in a decrease in weight. While the hAAT treated mice gained weight relative to controls, the MIC-1 treated mice showed weight loss. The hAAT treated mice significantly increased body fat stores while MIC-1 treatment produced a significant decrease in both fat and lean masses. Oral glucose tolerance tests revealed that the MIC-1 treated animals had decreases in both insulin and glucose AUCs indicating an improvement in glucose homeostasis. Indirect calorimetry showed that average energy expenditure was elevated in MIC-1 treated mice. Additional measures of body weight taken 4 weeks post-treatment showed that the reduction seen at the 2 week time point was maintained. These results provide evidence that MIC-1 is involved in appetite regulation, body weight and glucose homeostasis and show that minicircle DNA technology may be a valuable technique for target validation studies. Supported by: Eli Lilly and Co.

NTS GLP-1 projections to the mesolimbic dopaminergic reward system reduce food intake
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Peripheral glucagon-like-peptide-1 (GLP-1) signaling is widely investigated for the treatment of type 2 diabetes mellitus and obesity. However, less attention has been devoted to the mechanism by which *central* GLP-1 controls for food intake. While CNS GLP-1 is synthesized almost exclusively in proglucagon neurons of the nucleus of the solitary tract (NTS), GLP-1 receptors (GLP-1R) are widely expressed in the brain, including nuclei in the mesolimbic dopaminergic reward system (MDS), i.e. ventral tegmental area (VTA) and nucleus accumbens. Thus, CNS GLP-1 may regulate food intake in part through a direct hindbrain GLP-1 connection to the MDS. To test this hypothesis, (1) unilateral administration of ventricle-subthreshold doses of the GLP-1R agonist exendin-4 was delivered to the VTA and intake of a preferred food (15% sucrose) and standard chow was measured; (2) double IHC was performed in the caudal brainstem for proglucagon neurons and visualization of the retrograde tracer Fluorogold (2%/100nl) following bilateral VTA injections. Exendin-4 (0.025µg, 0.05µg) in the VTA produced a 46.7% and 56.7% suppression, respectively, in 60min sucrose intake; 0.05µg exendin-4 decreased 24h chow intake by 42.6%. Preliminary IHC evidence indicates that 20-30% of GLP-1-producing NTS neurons project directly to the VTA as they showed double labeling for GLP-1 and Fluorogold immunoreactivity. Data suggest that CNS GLP-1 signaling controls food intake in part through direct NTS GLP-1 modulation of the MDS. NIH-DK085435 (MRH); Merck & Co., Inc. IISP#38723 (MRH). Supported by: NIH-DK085435 (MRH) Merck & Co., Inc. IISP#38723 (MRH).

A new animal model for intestinal lymph sampling for a new look at intestinal physiology
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Standard procedures for intestinal lymph collection involve continuous, quantitative sampling of

lymph fluid and anesthetized or restrained animals that are often sacrificed after 48 h. We here describe a novel technique for the non-occlusive cannulation of the major mesenteric lymph duct in rats that allows for repetitive in-vivo sampling of intestinal lymph from unrestrained, awake and ad libitum-fed animals. The distinctive feature of this novel technique is that a 5-7 mm long piece of VialonTM tubing (OD/ID: 0.8/0.7 mm) with a small hole in its wall is first implanted into the mesenteric lymph duct for stabilization. The tapered tip (OD: 0.1 mm) of the catheter is then inserted into the hole of the tubing and fixed in place with a polyamid suture and a drop of tissue adhesive. In our hands, catheters implanted this way remain patent for up to 6 weeks after surgery. In one experiment we collected lymph from 6 adult rats prior to (0) and 15, 30, 45, 60, 75, 90,120, and 180 min (120 µl, each) after the onset of isocaloric (12 kcal) low fat (LF) or high fat (HF) test meals and measured active glucagon-like peptide-1 (GLP-1). Intestinal lymphatic GLP-1 concentration increased ($p < 0.05$) from »5 pMol (0 min) to a peak of 30 ± 5 (mean ± SEM) or 21 ± 5 pMol at 15 (HF) or 30 min (LF) after meal onset and gradually returned to baseline levels by 180 min. With this new technique few animals suffice to generate physiologically relevant data for various aspects of gastrointestinal physiology that involve the lymphatic system.

Estradiol (E2) increases the acute eating-inhibitory effect of amylin in ovariectomized (OVX) rats

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Cycling female rats eat least on the day of estrus and most on diestrus 2. OVX increases eating throughout the cycle, and cyclic E2 treatment reinstates it. To investigate whether amylin satiation contributes to these effects of E2, OVX Long-Evans rats were cyclically treated with E2 (2 microg SC; cycle D2 models diestrus and D4 estrus) or vehicle (Oil); (1) 10 and (2) 20 µg/kg amylin SC vs. saline were tested on D2 and D4, just before dark onset in 3 h food-deprived rats; (3) 100 µg/kg of the amylin antagonist AC187 or saline were similarly tested on D4; (4) rats were sacrificed 90 min after 20 µg/kg amylin or saline on D4 to assess changes in brain c-Fos expression. Results: (1) 10 and 20 µg/kg amylin decreased food intake more in D4 E2 than D2 E2 rats, suggesting that E2 *cyclically increases* amylin satiation; (2) 20 µg/kg amylin decreased food intake *less* in D2 E2 than Oil rats, suggesting that E2 *tonically decreases* amylin satiation; (3) AC 187 increased food intake more in D4 E2 than Oil rats, indicating that E2 increases the satiating action of endogenous amylin; (4) amylin increased c-Fos expression more in the area postrema (AP) and nucleus of the solitary tract in D4 E2 than Oil rats. E2-induced increases in the satiating potency of exogenous and endogenous amylin contribute to the estrous decrease in eating, which is a new facet of the physiological control of eating by amylin. E2 may act in the AP to affect amylin satiation because amylin acts on its receptors in the AP to inhibit eating in male rats and because some AP neurons express ER-alpha.

Adaptation of mice to imposed meal times and snack episodes tested under various food costs

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The adaptability of meal taking under conditions of working for food was examined in ICR:CD1 mice. In the first experiment, mice were given access to food for either 4, 8 or 16 meal opportunities per day, with the duration of access at each opportunity adjusted reciprocally so that the total time of availability was 160 min in all three groups. When available, food pellets were procured by nose poking responses and an incrementing series of fixed unit prices (FUP: 2,5,10,25). Food demand was comparable in all three groups, and declined by ~50% across the FUP series, an unexpectedly high elasticity. Further, the 16 meal group ate during only about half of the meal opportunities even as total intake declined, and there were changes in the distribution of food intake as FUP increased that were comparable in all groups. Together, these

data show that the decline in intake at higher costs cannot be explained by insufficient time to respond: one possbility is an interaction with circadian factors, although those were not an independent variable in this study. In a second study, using the 8 opportunity protocol, mice were additionally given free sugar cubes (snacks) after the 3rd, 4th, and 5th scheduled meals. Mice ate snacks at each opportunity and at FUP2 showed perfect caloric compensation. At FUP25, when pellet intake was lower, they ate more sugar and more total calories, so did not fully compensate. Thus, the choice for a free snack is influenced by effort and demand for the nutritionally-complete maintenance food. Supported by: NIH.

Insulin Resistance Changes Proportionally to Adiposity After a Stress Test in Obese Humans

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Insulin, an adiposity signal, helps regulate long-term food intake and body weight. Plasma insulin levels increase with adiposity, and obese persons are at risk for developing insulin resistance (Kahn et al., 2000). The stress hormone cortisol, stimulates appetite, and raises glucose levels contributing to weight gain and greater insulin resistance (Epel et al., 2001). High insulin and cortisol levels are associated with adiposity. In the present study, we examined the association between insulin resistance and adiposity in the obese population in relation to the stress-induced cortisol using a Cold Pressor Test (CPT). 23 obese females were measured for adiposity via single slice (L4-L5) MRI for visceral (VAT), subcutaneous (SAT), intramuscular (IMAT), and total slice (TAT) and bioelectrical impedance analysis (BIA). A subset of 7 S's (BMI; 33.8±0.9 kg/m^2 [SEM]) underwent CPT and warm water control, counterbalanced, after an overnight fast. Blood was drawn at –30, 0, 2 (CPT), 5, 15, 30, 45 min, and assayed for cortisol, insulin, and glucose. Insulin resistance was calculated based on QUICKI (Chen et al., 2005). Insulin resistance (baseline to 45 min) increased significantly after the CPT accordingly to IMAT ($p=0.013$), SAT ($p=0.02$), TAT (IMAT +SAT+VAT) ($p=0.028$), and a trend was found for VAT ($p=0.60$), but not for BIA. No significance was found after the warm water control. Cortisol increased after the CPT in all S's ($p=0.039$). Positive correlations were found for BIA (N=23) with SAT ($p<0.001$), VAT ($p=0.007$), and TAT ($P<0.001$). Also, waist circumference positively correlated with VAT ($p=0.01$), and TAT ($p=0.32$) whereas hip circumference correlated with SAT ($p=0.008$), and TAT ($p=0.005$). Intramuscular fat (IMAT) did not correlate with any of the anthropometric measures. Results indicated that after a stress test, insulin resistance changes proportionally to adiposity in obese individuals.

Overeating of sugars and fats: Links to addiction and obesity

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Overeating of palatable food can have powerful effects on brain reward systems. We have developed a rat model to assess whether overeating can produce behaviors and changes in reward-related brain systems that are similar to those seen with some drugs of abuse. In the case of sucrose binge eating, observed behaviors include signs of opiate-like withdrawal, enhanced motivation to obtain sucrose, and a heightened sensitivity to drugs of abuse. Accompanying brain changes include alterations in dopamergic, cholinergic and opioid systems, as well as changes in the levels of DeltaFosB in the nucleus accumbens, which are similar to the effects of some drugs of abuse. While rats bingeing on 10% sucrose show these behavioral and neurochemical signs of addiction, they maintain a normal body weight. These studies addressing overconsumption of sucrose have been extended to compare the effects of overeating of different palatable foods, and the findings suggest that when rats overeat fat-rich diets they can gain excess body weight, but different behavioral signs of addiction are seen. Further, differences between the effects of

overeating sugars and fats have been shown with pharmacological studies targeting GABAergic, opioid and endocannabinoid systems. Collectively, these findings show aberrant behaviors and brain changes that can ensue when rats binge eat palatable foods, and highlight the differences in aspects of addiction that emerge when body weight and the type of palatable food are considered. These findings may be of use in defining and understanding the concept of "food addiction." Supported by: National Eating Disorders Association.

Psychological Stress and Coping Mechanisms: Choices among Food, Physical Activity, and Television

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Chronic stress precedes weight gain. How an individual copes with stress may promote obesity. The purpose was to determine individual difference factors that predict how children cope with stress. It was hypothesized that stress reactive children with greater dietary restraint will choose to spend more time eating and eat more calories after an interpersonal stressor, and that stress reactive children with greater usual TV time will increase TV watching after stress. 30 children (8-12 y) completed 2 visits. On one visit they gave a 5-min stressful speech, and on the other they read. Following both visits, children had a 25 min free-choice period to eat, watch TV, and exercise. The time spent in each behavior was recorded, and the amount of food consumed was weighed. Regression models were used to predict changes in the behavioral choices. Changes in the time spent eating ($p < 0.01$) and calories consumed ($p<0.008$) were dependent on the interaction between dietary restraint and stress reactivity. Children higher for restraint and higher for stress reactivity were predicted to increase their time spent eating by 206 sec and consume 264 more kcal. Changes in the time spent watching TV ($p<0.05$) were dependent on the interaction between stress reactivity and usual TV time. Children higher in usual TV time and stress reactivity were predicted to increase their TV time by 94 sec. It can be concluded that, when stressed, children high in dietary restraint increase their energy intake, and children who watch greater TV increase their TV time. Both of these behaviors would contribute to weight gain.

Observations on the telencephalic control of "non-homeostatic" feeding, with emphasis on opioid mechanisms in the nucleus accumbens and prefrontal cortex

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Telencephalic regulation of feeding involves motivational/affective factors, including taste reward or dysregulated behavioral control. Building on the seminal work of the late Ann Kelley, we focus on descending cortico-striatal regulation of hypothalamic substrates. Critically, stimulating μ-opioid or GABA receptors in the anterior shell of the nucleus accumbens (Acb) promotes voracious feeding, which is associated with a disinhibition of hypothalamic energy-balance control systems. More recently, we found that stimulating μ-opioid receptors in the ventromedial prefrontal cortex (PFC) produces a marked feeding response characterized by many abrupt feeding bouts interspersed with "fragmented" exploration and grooming. PFC-derived feeding appear to arise from glutamate-coded PFC-hypothalamus functional interactions, but that activation of PFC output simultaneously over-stimulates downstream systems (including the Acb) that mediate behavioral switching. We have also studied forebrain plasticity induced by food reward and found that intermittent exposure to palatable feeding produces a marked sensitization of Acb shell GABA systems, which appears linked to Acb opioid but not dopamine release. These results emphasize that telencephalic structures modulating gustatory reward and executive control are intimately linked to hypothalamic systems controlling energy balance and feeding. It is tempting to speculate that disorders of feeding regulation emerge when these telencephalic structures "usurp" control of hypothalamic systems, which may represent an important risk factor for the development of such disorders.

Effects of sucrose added blind to the diet over eight weeks on body mass and mood in men

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The study hypothesises that when there is added energy in the diet, overweight men will partially compensate over a long duration. Additionally, there will be no significant weight gain and no adverse effects of sucrose supplementation found on rated mood or carbohydrate intake. Fat and sucrose intake are negatively correlated in surveys (Raben et al. 1997) but there is controversy over the effects of refined carbohydrate on appetite and weight control (Reid & Hetherington, 1997), based on studies of under 24-hour duration. These studies may provide limited information since adaptation to these sorts of dietary manipulation may take days rather than hours (Astrup & Raben, 1992). Long-term work is important for understanding dietary regulation and obesity. The effects of sucrose drinks (4 x250ml per day; 1800 kJ) on subsequent eating and mood are examined in 40 overweight men (BMI 25-35) (age 30-55), in a between-subjects, blind design, using aspartame sweetened drinks for the control group, over eight weeks. Food intake is measured with a 3-day food diary, over four separate weeks and mood with ten single Likert scales. All participants are informed that they are receiving sugar drinks; half the participants were misinformed. Preliminary results suggest that sucrose supplements significantly reduced voluntary total carbohydrate intake compared to aspartame. Weight is unaffected. It is concluded that within the normal diet of overweight men, inadequate compensation for sucrose and its other suggested adverse effects may be due to cognitive factors. Supported by: The Sugar Bureau.

Chronic administration of low dose bacterial lipopolysaccharide (LPS) inhibits cholecystokinin (CCK)-induced satiation

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The gut microflora is a potential triggering factor in obesity. Diet-induced obese rats exhibit intestinal inflammation and altered tight junctions, and increased plasma levels of LPS. We hypothesized that circulating LPS alters the peripheral control of food intake, resulting in hyperphagia and obesity. **Methods:** Wistar rats fed a low fat (LF) diet were implanted with mini-osmotic pumps delivering low dose LPS (n=9, 300µg/kg/day); controls were fed LF diet. CCK-induced inhibition of food intake (FI) (i.p., 0.3µg/kg) was measured after 5 weeks of treatment.Immunoreactivity for the anorexigenic peptide cocaine-amphetamine regulatedtranscript (CART) and orexigenic neuropeptide melanin-concentrating hormone (MCH) was determined in vagal afferent neurons (VAN) of fasted and fed animals after 6 weeks. **Results:** Energy intake and body weight (BW) were significantly increased in LPS-treated rats (LF 19.4±0.2 vs LPS 20.4±0.2 kcal/100gBW, $p<0.05$; LF 170±8g vs LPS 191±11g, $p<0.05$) and CCK-induced inhibition of FI (42%; <0.05) was abolished by LPS treatment. In VAN of control rats, MCH levels were decreased and CART levels were increased by feeding; in VAN of LPS-treated rats, CART was not upregulated by feeding and MCH was constitutively expressed. **Conclusion:** LPS can alter VAN signaling resulting in lack of CCK-induced satiation and alteration in control of body weight; this may be a mechanism by which gut microflora composition affect control of food intake. Supported by: National Institute of Health Grant DK-41004.

Leptin attenuates mu opioid receptors effect on feeding behavior

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Activation of mu opioid receptors (MOR) makes animals hyperphagic and increases their preference for a high fat diet. Studies from our laboratory have demonstrated that the gene and protein expression of this receptor population is significantly greater in the hypothalamus of obese animals. This warrants the consideration that the increased MOR are potentiating the hyperphagia and the preference for a high fat diet that is associated with obesity. The changes that occur in obesity that contributes to the increased expression of hypothalamic MOR are unknown. Thus, we investigated the hypothesis that hypothalamic MOR are regulated by the anorexic hormone leptin. Utilizing ob/ob mice we were able to demonstrate that in the absence of leptin, hypothalamic MOR are significantly greater than the control C57/B6 mice. When the ob/ob mice were administered an intraperitoneal injection of leptin (5mg/kg), it resulted in a significant decrease in the gene and protein expression of MOR. We also observed that leptin can attenuate MOR effect on feeding behavior. Administering leptin (5ug) into the third ventricle of C57/B6 mice prior to DAMGO (0.025µg), selective MOR agonist, resulted in a significant decrease in food intake. Administering leptin alone did not have any effect on feeding behavior. These data demonstrate that leptin can attenuate the hypothalamic expression of MOR and attenuate MOR effect on feeding behavior. This study was supported by National Institute of Health, NIDDK, grant number DK078588-01A2.

Hypothalamic peptides are altered in rats predicted to consume fat or ethanol.

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Dietary fat or ethanol may be consumed for different reasons, and early determination of vulnerability to consumption is important in preventing disease onset. Our laboratory has recently established two models which, with measures of high locomotor activity in a novel open field or circulating triglyceride (TG) levels after a high-fat meal, identify Sprague-Dawley rats that go on to consume excess high-fat diet or 9% ethanol. In the present study, rats (n=24/group) were tested with these models, classified as low, middle or high responders (n=8/group) and, one week later, sacrificed for analysis of hypothalamic peptide expression using quantitative real-time PCR or digoxigenin-labeled *in situ* hybridization. In the perifornical lateral hypothalamus, the high activity group exhibited higher orexin mRNA (+301%, $p<0.05$), while the high TG group had more melanin concentrating hormone (+108%, $p<0.05$) than the low group. In the paraventricular nucleus, the high activity group showed higher enkephalin mRNA (+82%, $p<0.01$), and both the high activity and high TG groups had more galanin (+139% and +106%, $p<0.05$) than the low groups. In the arcuate nucleus, no groups showed significant differences in neuropeptide Y. These results reveal disturbances in orexigenic peptides in animals prone to consuming fat or ethanol, even prior to exposure to these substances. While the peptides altered may differ depending on the reason for ingestion, such as novelty preference or low TG metabolism, they identify galanin as a common factor and possible target for prevention of overeating or alcohol use disorder. Supported by: USPHS Grant AA-12882.

The role of ghrelin in hippocampal dependent cognitive processes.

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Mild caloric restriction has been demonstrated to improve learning and memory in humans and rodents, where as obesity and metabolic disease is associated with cognitive impairment. Ghrelin is an orexigenic peptide produced by both the gut and brain with the capacity to affect metabolism and behavior. Plasma ghrelin rises before an anticipated meal and it has been suggested that pre-prandial ghrelin increases may be act as a signal to predict meal delivery. Moreover, ghrelin is capable of acting at brain regions involved in the processing of

cognitive-emotional information, suggesting that ghelin may act within these regions to modulate the expectancy of a predicted meal. This talk will present data demonstrating that ghrelin signaling is necessary for the development of food anticipatory activity and intact hippocampal function. Collectively, these results suggest that ghrelin receptor signaling is necessary for adaptations in the anticipatory responses that accompany restricted feeding. Additiionally, they suggest that ghrelin may mediate at least some of the benficial effects of caloric restriction on learning and memory.

Body Fat Deposition: Biological Predictor of Eating Disturbance?

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Although psychological correlates and predictors of the development of eating disturbance have been extensively researched, relatively few studies have focused on biological variables. In the current, two-year study, percent body fat (%BF) and upper abdominal adipose tissue mass (UAAT), as measured by dual energy X-ray absorptiometry, were examined in relation to body image and eating disturbance in 294 initially non-eating disordered women. All analyses controlled for BMI and depression score. Cross-sectionally, total %BF was inversely correlated with body areas satisfaction and positively correlated with frequency of feeling fat and episodes of compensatory behaviors in the last 3 months. UAAT was related to midsection body dissatisfaction, appearance-based self-evaluation, and overweight preoccupation. While %BF was not a longitudinal predictor of the worsening of body image or eating disturbance, baseline UAAT predicted increases in overweight preoccupation over two years. Following data collection completion, further analyses will explore the cross-sectional and longitudinal relationship between percent trunk fat, which has been found to be abnormal in eating-disordered populations, and body image and eating disturbance measures. Our findings suggest that, above and beyond weight status, %BF and UAAT are related to body image and eating concerns and may warrant further investigation as risk factors for the development of eating disorders. Supported by: NIH (NIDDK) .

Viral-mediated overexpression of NPY in the dorsomedial hypothalamus causes hyperphagia and obesity in Sprague Dawley rats

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Previous reports have shown NPY overexpression in the dorsomedial hypothalamus (DMH) in a number of obesity models of rodents. Whether this overexpression plays a causative role in these animal models is not established. To this end, we generated a recombinant vector of adeno-associated virus (AAV)-mediated expression of NPY (AAVNPY) and determined the effect of DMH NPY overexpression on energy homeostasis in adult Sprague Dawley rats. Animals received DMH injections of AAVNPY and food intake and body weight were monitored for 16 weeks. We found that food intake and body weight were significantly increased in NPY overexpression rats compared to rats receiving GFP control vectors. Meal pattern analysis revealed that DMH NPY overexpression specifically increased meal size during the dark period, leading to hyperphagia. NPY overexpression significantly increased fat mass as determined in the areas of inguinal subcutaneous and epididymal white fat and interscapular brown fat. Moreover, while high fat diet access induced obesity in control rats, DMH NPY overexpression exacerbated diet-induced increases in food intake and body weight and resulted in even greater increases in inguinal fat. This overexpression also caused increases in plasma leptin and insulin levels. Together, our results demonstrate that DMH NPY overexpression can

result in obesity and implicates this overexpression as causal in a number of obesity models. Supported by: NIH R01DK074269 (to S.B.).

Inhibitory effects of insulin in the dorsal motor nucleus of the vagus

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Insulin, which is critical to glucose regulation in the body, crosses the blood brain barrier and is transported into the brainstem over twice as rapidly as into whole brain and may affect glucose regulation via central mechanisms. Brainstem nuclei, specifically the dorsal motor nucleus of the vagus (DMV), are essential for visceral parasympathetic function. Pathologies in which insulin is dysregulated, including diabetes, can disrupt this circuit, leading to gastric and other autonomic dysfunction. Insulin receptors (IRs) are expressed in the DMV, and preliminary data indicates that IRs are located in proximity to gastric-projecting DMV cells. We used whole-cell patch-clamp recordings in brainstem slices to identify effects of insulin on synaptic input to DMV neurons. Insulin significantly reduced the frequency of action potential firing (APs), spontaneous excitatory post-synaptic currents (sEPSCs), and miniature EPSCs, with no change in amplitude. Insulin also reduced sEPSC and AP frequency in a subset of identified gastric-related DMV neurons. Insulin activity was dependent on the K_{ATP} channel and PI3-kinase activity, because the effects of insulin on sEPSC frequency were eliminated in the presence of a K_{ATP} channel antagonist, tolbutamide or the PI3-kinase inhibitor, wortmannin. These results suggest that insulin inhibits excitatory input to DMV neurons via a K_{ATP} channel- and PI3-kinase-dependent mechanism. Such regulation may influence glucose metabolism in the DMV and thus, autonomic visceral regulation. Supported by: R01 DK056132, F32 DK089717.

Expectation for palatable food. A process that generates gradually in the brain and correlates with behaviour

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Purpose: Characterize in reward related nuclei such as Nucleus Accumbens and Prefrontal Cortex the process to develop neuronal and behavioural activation anticipating chocolate. **Methods:** Neuronal activation:Male Wistar rats were divided in two groups, those who were sacrificed after ingestion of chocolate and those sacrificed when they were expecting the palatable food. Sacrifice was on days: 1, 2, 3, 5 and 8 of eating chocolate. Brain was processed for c-Fos immunohistochemistry as marker of activation. The positive cells were counted. Behavioral assessment: We designed a wire box cube in which we put the 5 gr. piece of chocolate. It allowed rats to see and smell the chocolate but it was impossible to touch scratch or bite it. The motivation was determined measuring the approaches, contacts and handling of the box during 5 minutes before time for chocolate.**Results:**Rats sacrificed after ingestion of chocolate showed increased neuronal activation in all days tested. The “expectant” group showed progressive neuronal activation that increases depending on the number of days of previous ingestion of chocolate. There was a correlation between the results of the group of expectation and the behaviour of the group of rats that worked to get the chocolate. **Conclusions:** The acquisition of a perseverant behaviour where the animal looks for the pleasurable stimulus develops gradually and it involves both NAcc and PFCx. This study was supported by CONACyT 82462 and PAPIIT UNAM IN-224911. Supported by: CONACyT 82462 and PAPIIT UNAM IN-224911..

Effects of Prenatal Diet on Food Preference and Ethanol Intake in Offspring

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A high-fat diet (HFD) in utero can lead to changes in hypothalamic galanin gene expression as well as hyperlipidemia, preference for fat, and increased body weight. Galanin and circulating triglycerdies (TG) have also been linked to ethanol intake. Thus, offspring of HFD-consuming dams may have avidity for ethanol, and offspring of dams fed other foods that are known to increase TG levels may also have increased body weight, and preference for fat and ethanol. Exp. 1: Dams were fed either a HFD or a control diet. Female offspring were fed standard chow and trained to drink unsweetened ethanol starting on P25. Female rats born to HFD-consuming dams had increased ethanol intake, developed a preference for ethanol over water, and had increased serum TG levels compared to females born to control dams. Exp. 2: Dams were fed standard chow, or standard chow with access to a 16% high-fructose corn syrup (HFCS) or a 10% sucrose solution. Offspring were fed standard chow. As early as P15, rats born to HFCS-consuming dams weighed significantly more than rats born to the control groups, and they showed differences in preference for HFD and HFCS compared with the control groups. Female offspring born to HFCS-consuming dams also showed a preference for ethanol. Collectively, these data suggest prenatal exposure to TG-promoting diets can lead to physiological and behavioral changes related to body weight, food preference and the consumption of ethanol. Supported by: NIDA, NIAAA and National Eating Disorders Association.

Personality as a risk factor for adiposity and hyperinsulineamia

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Personality may be a risk factor for weight gain and insulin resistance. We have studied this in rats that display either a proactive or a passive coping style. We found that passive rats are more prone to develop adiposity, and hyperinsulineamia. Passive rats consumed more of a high fat diet than proactive rats. Subsequently, passive rats have a higher percentages of visceral adiposity. Additionally, baseline insulin levels were elevated in passive rats and in response to a glucose infusion (iv) passive rats showed increased insulin levels at both peak and plateau. Personality may also play a role in the treatment. When allowed to run voluntarily, passive rats display higher levels of running activity. This effect became more pronounced once the rats were switched to a high fat diet; passive rats increased running levels in response to a switch to the high fat diet, whereas proactive rats do not. Running decreased insulin responses in both personalities, although the effects were stronger in the passive rat. Second, treatment with RU486 decreased hyperinsulineamia in passive rats, but had no effect in proactive rats. This suggests that the origin of hyperinsulineamia in the passive rats might be related to enhanced HPA-axis activity. Taken together, these data indicate that passive rats are more prone to develop adiposity and hyperinsulineamia. However, they are also more likely to respond well to a life style intervention program since passive rats voluntarily increase their daily activity when given the opportunity to run, and in this situation, plasma insulin levels are normalized. Supported by: AstraZeneca.

Effect of insulin on dopamine neurons of the Ventral Tegmental Area

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The prevalence of obesity has drastically increased over the last few decades. Exploration into how hunger and satiety signals influence the reward system can help us to understand non-homeostatic mechanisms of feeding. Previous research has implicated mesolimbic dopamine signaling in the incentive, reinforcing, and motivational aspects of food intake. Insulin receptors are expressed in dopaminergic neurons of the ventral tegmental area (VTA) and there is

substantial evidence suggesting that insulin may act in the VTA to suppress feeding. However, the neural mechanisms underlying insulin effects in the VTA remain unknown. We demonstrate that insulin can cause a long-term depression (LTD) of excitatory synapses onto VTA dopamine neurons. This effect requires endocannabinoid-mediated presynaptic inhibition of glutamate release. Insulin-mediated LTD onto VTA dopamine neurons was disrupted in hyperinsulinemic mice. Using fast scan-cyclic voltammetry to measure subsecond dopamine concentrations in the VTA, we found that insulin dose-dependently reduced dopamine concentration by increasing the reuptake of dopamine through its transporter. Finally, insulin administered into the VTA reduces palatable food intake in mice. Taken together, these results demonstrate that insulin acts in the VTA to depress excitatory synaptic transmission of dopamine neurons as well as somatodendritic dopamine concentrations. Furthermore, insulin action in the VTA may serve to reduce palatable food consumption. Supported by: CIHR NSERC.

LPS inhibits ghrelin-excited neurons and food intake via central nitric oxide signaling
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Nitric oxide (NO) is produced by inducible nitric oxide synthase NOS (iNOS). Lipopolysaccharide (LPS) induces high iNOS expression in the arcuate nucleus (ARC). Peripheral administration of the specific iNOS inhibitor 1400W counteracts the anorectic effect of LPS. To evaluate the role of central iNOS signaling we conducted third intracerebroventricular (icv) injections of 1400W in rats receiving LPS (100µg/kg ip). Further, we analyzed the electrophysiological effects of 1400W in ARC preparations that were obtained from rats 4h after peripheral LPS treatment or after in vitro stimulation of the ARC with LPS. We also tested whether LPS induces an iNOS-dependent cGMP formation in the ARC. 1400W (4µg icv) attenuated the LPS-induced anorexia. Superfusion with 1400W (10^{-4}M) increased neuronal activity in 37% of neurons recorded in ARC slices from LPS-treated rats (n=19) but not from control treated animals. Similarly, 1400W induced excitatory effects (45%) after in vitro stimulation with LPS (100ng/ml). 1400W sensitive neurons were excited by ghrelin (10^{-8}M). In vitro stimulation with LPS increased the number of cGMP positive cells in the ARC. This response was blocked by co-incubation with 1400W. In conclusion, central NO signaling contributes to LPS anorexia and seems to inhibit ghrelin-excited ARC neurons via iNOS-dependent NO formation. This effect might be mediated by the NO dependent second messenger cGMP. A pharmacological blockade of NO formation might be a therapeutic approach to ameliorate disease-related anorexia. Supported by: Swiss National Science Foundation (SNF), Krebsliga Zurich .

Mysterious fat: the different impact of fat content on toddlers' and adults' food intake
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Fat content of foods is often incriminated in the high prevalence of overweight and obesity. However, the role of fat on intake and perception is still a matter of debate. This work evaluated the impact of fat content of a creamy white cheese (CWC) on its intake, hedonic rating and sensory characteristics. The CWC variants were commercially available products with 0, 20 or 40% fat and sweetened with 5% added sugar. Study 1: 56 toddlers (2-3 years; 26 ♀-24 ♂) and 51 students (18-25 years;26 ♀-25 ♂) took part to three afternoon snacks (*ad libitum* CWC, biscuits, milk and/or water). Study 2: the same students scored their liking and several sensory descriptors for the three CWC, in a separate sensory evaluation session. Children's intake of CWC was influenced by fat content (P=0.013): 0% and 20% fat CWC were more consumed than the 40% one (196±12, 186±12 and 159±11 g respectively). Fat content had no effect on students' CWC intake (P=0.55; 190±6 g on average). Children maintained an equivalent total energy intake from the three snacks (P=0.58), this was not the case for the students (P=0.006). Students liked the

40% fat CWC more than the 20% and the 0% fat CWC (*P*<0.0001). They differentiated the three CWC according to thickness (*P*=0.04), creaminess (*P*<0.0001), dryness (*P*<0.0001), sourness (*P*<0.0001) and sweetness (*P*=0.0003), but not according to fattiness (*P*=0.43). These results highlight the discrepancy between intake and liking measurements in adults. They also shed light on the poorer ability of adults to maintain their energy intake when fat content varied in a common food contrarily to children. Supported by: The present work was funded by the Nutrition, Chemical Food Safety and Consumer Behaviour Division of INRA (French National Institute for Agronomical Research) and the Regional Council of Burgundy..

Sugar content impacts food intake in toddlers, but could be reduced
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Governmental policies aim at reducing the amount of added sugar in foods, due to its supposed contribution to the rising rates of overweight and obesity. The impact of such a reduction on young children's food intake remains imperfectly known. The present study aims at evaluating 2-3 year-old children's intake of a naturally unsweetened food according to its added sugar level. Fifty children (26 ♀- 24 ♂; age 26 ± 0.5 months; z-BMI -0.28 ± 0.16 SD) attending two nurseries in Dijon (France) were served an afternoon snack once a week for 4 weeks in a crossover design. The target food was a creamy white cheese (CWC) with varying added sugar (0, 5, 10 or 15%). Biscuits, milk and/or water were also provided to children, who could eat *ad libitum* of each item. All foods and drinks were pre- and post-weighed for each child. The CWC intake was affected by sugar addition (*P*=0.001): the 0% added sugar variant was less consumed (166±12 g) than the three other variants (196±10 g, 213±10 g and 197±12 g respectively for the 5, 10 and 15% variants, not different from one another). The individual slopes of intake with increasing added sugar were calculated. These individual slopes were positively correlated to the usual amount of sugar added to dairy products reported by parents (r=0.35; *P*=0.04; n=41), but not to children's z-BMI (r=0.16; *P*=0.26; n=48). It seems possible to lower the amount of added sugar in some dairy foods below the current level which is high in most commercial dairy products (higher observed value around 14 % added sugar) without reducing children's food intake. Supported by: The present work was funded by the Nutrition, Chemical Food Safety and Consumer Behaviour Division of INRA (French National Institute for Agronomical Research) and the Regional Council of Burgundy..

Involvement of the histaminergic system in amylin and leptin action
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Activation of the H1 histamine-receptor (H1r), which is highly expressed in the ventromedial nucleus of the hypothalamus (VMH), suppresses food intake (FI) in rats. Further, amylin and leptin synergize to promote decreased FI, potentially via the VMH. Interestingly, the anorectic effects of single doses of amylin and leptin are reduced in H1r knockout (KO) mice compared with wild type (WT). Here we investigated if higher doses of amylin or leptin would suppress FI in KO mice, and if neuronal activation following treatment with amylin or leptin would differ between KO and WT mice. Fasted mice were treated 2hr prior to (leptin) or at dark onset (amylin), with food returned at dark onset. Unlike WT mice, KO mice did not show an anorexic response to most doses of amylin (5, 20, or 50µg/kg, ip), though FI was suppressed by 200µg/kg amylin. Similarly, leptin (0.5, 1, 5, or 10mg/kg, ip) decreased FI 4 and 6hr after treatment in WT mice, but only 5 and 10mg/kg suppressed FI at 6hr in KO mice. Despite the differential effect on FI, both WT and KO mice showed a significant increase in cFos expression in the AP following amylin (50µg/kg), and a similar level of STAT3 phosphorylation in the arcuate nucleus and VMH following leptin (1.3mg/kg). Our data show that while mice deficient in the H1r are less responsive to eating inhibitory effects of leptin and amylin, neuronal activation in primary receptor sites of these

hormones remains intact, as evident by the increases in pSTAT3 in the hypothalamus and cFos in the AP. Functional H1r therefore seem to be a critical component of networks downstream of amylin and leptin receptors that control FI. Supported by: Swiss National Science Foundation.

'Expected satiation drift' and beliefs about snack foods in children.
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Recently, we have explored evidence for 'expected-satiation drift' – the prospect that familiarity increases the satiation that a food is expected to confer. In the present study we sought to determine whether this drift is evident in children and whether it can be observed in foods that are thought to promote obesity. Using a method of adjustment we quantified the expected satiation of six snack foods. Participants (N= 70; mean age= 11.0 y, 56% female) changed the size of a comparison food to match the satiation that they expected from each snack food. As anticipated, familiarity and expected satiation were positively related (r= .37, p= .002), and this association remained, even after controlling for the palatability of the snack foods. Children who were highly familiar with the snack foods expected them to deliver twice as much satiation as those who never or rarely consumed these foods. In adults, expected satiation is highly correlated with self-selected portion sizes (kcal; r= -0.8). Therefore, familiarity could play an important role in determining the portions of snack foods that are selected and then consumed by children. In the absence of prior experience, the children tended to judge the expected satiation of a snack food based on its perceived volume (an unlearned characteristic). Thus, it would appear that the expected satiation of snack foods changes systematically and this learning can be observed in childhood.

Nutrient induced gut-to-brain signalling in humans
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Gastrointestinal responses to intraluminal nutrients are specific to the type of nutrient present. Lipids have profound effects, slowing the rate of gastric emptying and suppressing food intake. Glucose also influences these, but far less potently. Both processes involve vagal pathways relaying in the brainstem. It has recently become possible to image brainstem activity using 'Blood Oxygenation Level Dependent' signal (BOLD) physiological MRI. This permits detailed comparison of spatiotemporal responses to different nutrient stimuli. Using physiological MRI after lipid and glucose, we have: 1) compared the brain regions responding to these gut-derived signals, and 2) investigated the time course in the key brainstem regions following each nutrient. Healthy fasted subjects were studied in a single blind randomised fashion. Brain activation responses were mapped following intragastric glucose (1M, n=12) or lipid (0.05M dodecanoate, n=10). All subjects underwent control scans (0.9% saline). Both glucose and lipid administration significantly modulated BOLD signal in spatially identical hypothalamic and brainstem areas. However, the time courses were very different. Significant clusters of early activation were identified within these brain regions 5 minutes after lipid infusion, but 19 minutes after glucose infusion. Our data demonstrate the *spatial* pattern of CNS responses is not nutrient specific but that clear differences are observed in *temporal* responses. This may reflect differential elements in endocrine or metabolic responses, or differential effects on gastric function. (Funded by BBSRC) Supported by: Biotechnology and Biological Sciences Research Council Diet and Health Research Industry Club.

Activity-based anorexia mouse model reveals signaling crosstalk between C1q/TNF-

related protein-13 (CTRP13) and Brain-derived Neurotrophic factor (BDNF).
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Anorexia nervosa (AN) shows a high rate of heritability and complex polygenic inheritance patterns. The molecular underpinnings of AN remain largely unknown. We have recently identified a novel family of secreted endocrine hormones, designated as C1q/TNF-related proteins (CTRPs). We have shown that CTRPs play important roles in controlling systemic glucose and fatty acid metabolism. Here, we investigate the mechanism by which CTRP13 acts in the central nervous system (CNS) to modulate whole-body energy metabolism. The activity-based anorexia (ABA) mouse paradigm decreased energy expenditure, lowered circulating levels of CTRP13, and increased BDNF expression in the CNS. To determine the central effects of CTRP13, recombinant protein was injected into the lateral ventricle (LV) of the brain. Central administration of CTRP13 in mice decreased food intake, body weight, blood glucose levels, and whole-body energy expenditure in a manner similar to ABA. In vitro, CTRP13 increased the mRNA expression of BDNF and leptin receptor in mouse hypothalamic cell line (N38). Inversely, central administration of BDNF decreased hypothalamic CTRP13 mRNA expression and lowered circulating levels of CTRP13. Our in vivo and in vitro results suggest reciprocal feedback regulation involving signaling crosstalk between BDNF and CTRP13 in the CNS. We propose that, in a severe state of anorexia nervosa, the BDNF-CTRP13 feedback mechanism may be disrupted.

Functional interactions between the prefrontal and insular cortices during a sucrose-shift procedure
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The goal of this study was to determine if there are functional interactions between the medial prefrontal (mPFC) and insular (IC) cortices during fluid consumption. These cortical areas are reciprocally connected (e.g. Gabbott et al., Brain Res., 2003) and have each been shown to be crucial for incentive contrast effects in sucrose consumption procedures (mPFC: Pecoraro et al., Neurosci., 2008; IC: Lin et al., Behav Neurosci., 2009). We used an incentive contrast procedure to examine neural activity in mPFC and IC. Four rats were maintained at 90% of their free-access body weights and taught to lick at a spout to produce fluid containing 20% sucrose. Then, they were exposed to a "sucrose-shift" procedure, in which the available concentration of sucrose switched from 20% to 2% every 30s during daily 20m testing sessions. Within four sessions, rats came to lick at higher rates for 20% sucrose and stopped licking when the sucrose concentration dropped to 2%. Simultaneous recordings of spike activity and field potentials revealed oscillations in both areas during fluid consumption. These events were coupled to the lick cycle, synchronized between areas, enhanced over the period of learning, and reflected the concentration of sucrose that was consumed (i.e. larger for 20% compared to 2% sucrose). To our knowledge, this study is the first to demonstrate functional interactions between neural processing in mPFC and IC during an incentive contrast procedure. Supported by: NIH Grant AG030004.

Food exposure, cravings, and physiological reactivity in normal-weight subjects
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Food cravings have been characterized as an intense desire to consume a particular food, drink, or taste (Hill, 2007). Research shows that some physiological measures are associated with self-

reported food cravings (Nederkoorn & Jansen, 2002; Nederkoorn, Smulders, & Jansen, 2000). Previous attempts to examine heart rate variability (HRV) as an index of the response underlying craving have lacked a thorough analysis of the sympathovagal response. The aim of this study was to examine the relationship between subjective food cravings and physiological responses during the presentation of palatable food. Participants included six normal-weight adults between the ages of 18-23 (female=83%; Caucasian=17%). Participants were guided through a baseline period, food exposure task, and recovery period and asked to report food craving levels every 30 seconds on a 1-100 scale. HRV, and skin conductance data (GSR) were collected continuously. Pearson correlations indicate significant positive relationships between food cravings and GSR (r=.6; p<.001), HRV-LF/HF (r=.37; p=.02), HRV-LF (r=.48; p= .002), and HRV-VLF (r=.36 p=.02). Subjective food cravings were significantly negatively related to HRV-HF (r=-.35; p= .02). Repeated measures ANOVA analysis found an increase in cravings during exposure, followed by habituation to baseline levels during recovery (F=7; p=.008). Preliminary results support the premise that subjective food cravings are related to a shift from parasympathetic to sympathetic activity. This may be indicative of a stress response and subsequent vagal withdrawal triggered by the desire to eat palatable foods. Full data on 10 subjects will be presented. Supported by: University of California, San Diego.

Role of orexin in effects of food restriction on sucrose self-administration and cue-induced reinstatement to extinguished sucrose-seeking

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The orexin/hypocretin system has recently been implicated in reward-seeking and drug abuse. We examined the involvement of the orexin (ORX) system in operant responding for sucrose, and in cue-induced reinstatement of extinguished sucrose-seeking, using the ORX 1 receptor antagonist SB-334867 (SB). Ad libitum fed or food-restricted male Sprague Dawley rats were trained to self-administer sucrose, and the effects of pretreatment with SB on fixed ratio (FR) and progressive ratio (PR) responding were tested. Reinstatement of extinguished sucrose-seeking was elicited by presentation of cues previously paired with sucrose reward. Finally, Fos expression in ORX neurons was examined following self-administration, late extinction or cue-induced reinstatement to sucrose seeking. Results showed that SB decreased FR and PR responding for sucrose and decreased cue-induced reinstatement to sucrose-seeking in food-restricted but not ad libitum rats. Furthermore, Fos expression was increased in lateral hypothalamic ORX neurons of food-restricted rats compared to ad libitum rats during self-administration. These results indicate that signaling at the ORX 1 receptor is involved in sucrose reinforcement and necessary for reinstatement of sucrose-seeking elicited by sucrose-paired cues and that ORX neurons specifically in the lateral hypothalamus are activated during sucrose self-administration. All of these effects are found only for food restricted rats and lead us to consider that conditioned activation of ORX neurons may increase motivation for sucrose reward during food restriction.

Manipulating the sensory properties and labelling of a beverage preload to enhance satiety.

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Cognitive, oral, post-ingestive and post-absorptive signals have been hypothesized to interact to influence the experience of satiety. Previous research indicates that the satiating power of a beverage preload increases as its oro-sensory properties better predict the delivery of energy. The present studies examined whether explicit satiety messages in the form of food labelling would enhance this effect. We compared the satiating effects of four beverage preloads, differing in energy content (low energy: LE vs. high energy: HE), thickness and creaminess (low sensory: LS vs. high sensory: HS), and presented with either no information, labelling congruent with

energy content, or incongruent. Study 1 (n=72) determined the time at which the HE and LE versions of the preloads caused maximal differences in rated hunger. Study 2 investigated the effect of the preloads on intake of a test meal delivered at this time. In Study 2, 48 healthy non-obese men and women attended the laboratory on two test days where they consumed a LE or HE preload 90 minutes before a test lunch, with energy tested within subjects and label and sensory between. Food intake at lunch was lower after the HE than LE preloads but this effect was moderated by sensory context: intake compensation at lunch for additional energy in the HE preload was greater in the HS context. Labelling did not impact on intake nor moderate these effects. The satiety-relevant sensory quality of a beverage preload improves its satiating power but the effects of satiety-related labelled information are less clear. Supported by: BBSRC.

High protein feeding leads to a decreased postprandial neuronal activation and alterations in neurotransmitters receptor mRNAs within the nucleus accumbens

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High protein (HP) diet induces a decrease of food intake in rats. Mechanisms responsible for this effect are partly unknown but a lower hedonic value of protein is likely to play a significant role in these processes. The nucleus accumbens(NAcc) is a key player in hedonic processes including hedonic responses to food. The aim of this work was to measure the consequences of receiving a HP diet (55% protein as energy) or a normal protein diet (NP, 14% protein as energy) on NAcc function. The levels of neuronal activation in the NAcc and the expression of GABA, opioid and dopamine receptors were monitored. Experiments were performed in male adult Wistar rats. Tested diets were administered either acutely, as preloads, during 2 days or chronically, *ad libitum* for 2 or 15 days. Body weight and food intake were monitored daily. Postprandial NAcc neuronal activation was assessed at the beginning of the daily feeding period by immunolabelling of the c-Fos protein. Quantification by RT-PCR of mRNA coding GABA, opioid and dopamine receptors was performed on rapidly dissected NAcc. Body weight gain and energy intake in rats feed a HP diet decreased while c-fos immunolabelling in NAcc was significantly lower under HP feeding when compared to NP feeding. This effect was concomitant to decreased levels of mRNA coding kappa-opioid-receptor and dopamine 2 receptors. These results suggest that the anorexigenic effect of the HP diet could be due to a decrease of the postprandial activation of Nacc. Supported by: INRA.

Hypothalamic peptide control of alcohol intake: differential effects on frequency or size of drinking bouts

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Orexin (OX) in the perifornical lateral hypothalamus (PFLH) and galanin (GAL) in the paraventricular nucleus (PVN) are both known to increase ethanol intake. Evidence suggests that they may control different aspects of ethanol drinking, with the excitatory peptide OX activating the PFLH to facilitate feeding and appetitive drive and thus initiate drinking and the inhibitory peptide GAL suppressing the PVN satiety system to increase the duration of drinking. The present study tested this hypothesis by examining effects of these two peptides on the microstructure of ethanol drinking. Male Sprague-Dawley rats (n= 6-8/group) were trained to drink 7% ethanol and implanted with guide shafts aimed at the PFLH or PVN. They were then housed in specialized cages with computerized intake monitors (BioDAQ, NJ) and given injections of either saline, OX (1.8 nmol), or GAL (1.0 nmol). Results showed that OX in the PFLH significantly increased ethanol intake and the number of drinking bouts ($p<.05$), while having no effect on the bout duration. In contrast, GAL in the PVN enhanced ethanol intake ($p<.01$) by increasing the average size ($p<.01$) and the duration of bouts ($p<.05$), while having no effect on the frequency of

drinking. These complimentary roles of the two peptides may result from their differential responses to feedback signals, with the OX system negatively regulated by itself and thus initiating bouts of intake and the GAL system functioning in a positive feedback loop that prolongs ethanol drinking. USPHS grant AA-12882. Supported by: USPHS grant AA-12882..

Effect of neuropeptide S receptor antagonists and partial agonists on palatable food consumption in the rat

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Neuropeptide S (NPS) is the endogenous ligand for the previously orphan G-protein-coupled-receptor, now termed NPS receptor (NPSR). NPS has both anxiolytic and pro-arousal properties and decreases food intake. In this work we use a rat model of palatable food (PF) intake to test in vivo different analogs of human NPS characterized in previous in vitro experiments as partial agonists ([Ala^3]NPS and [Aib^5]NPS), or antagonists ([D-Cys(tBu)^5]NPS and [^{t}Bu-D-Gly^5]NPS) [Guerrini et al. Med Res Rev. 2010 Sep;30(5):751-77]. Our results confirmed that intracerebroventricular (ICV) injection of NPS decreases standard chow intake in food restricted rats as well as in freely feeding animals fed with standard diet or PF. [Aib^5]NPS, like NPS, reduced PF intake, thus confirming in vivo its ability to activate NPSR. [Ala^3]NPS did not affect PF intake per se but blocked the anorectic effect of NPS, thus suggesting its ability to function as an antagonist in this model. Finally, [D-Cys(tBu)^5]NPS and [^{t}Bu-D-Gly^5]NPS, described in previous in vitro studies as pure NPSR antagonists, did not affect PF intake when given alone, but fully blocked the anorectic effect of NPS. These results provide an important characterization of the pharmacological properties of these NPS analogs in vivo. Of particular relevance are the data showing that [D-Cys(tBu)^5]NPS and [^{t}Bu-D-Gly^5]NPS behave as pure antagonists at NPSR regulating food intake, indicating that these molecules are suitable tools for further investigation of the physiopharmacology of the NPS/NPSR system.

Effect of prazosin and guanfacine on stress-induced reinstatement of food and alcohol seeking in rats

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Relapse to alcohol use during abstinence or maladaptive eating habits during dieting is often provoked by stress. The anxiogenic drug yohimbine, a prototypical α-2 adrenoceptor antagonist, which causes stress-like responses in humans and non-humans, reliably reinstates alcohol and food seeking in a rat relapse model. Here, we studied the effect of the α-1 adrenoceptor antagonist prazosin and the α-2 adrenoceptor agonist guanfacine on yohimbine-induced reinstatement. In exp.1, we trained rats to self-administer alcohol, and after extinction of alcohol-reinforced lever pressing, we tested prazosin's or guanfacine's effect on yohimbine-induced reinstatement; we also examined prazosin's effect on footshock-stress-induced reinstatement. In exp.2, we trained food-restricted rats to self-administer food pellets and first examined prazosin's or guanfacine's effects on food-reinforced responding, and then, after extinction of lever presses, on yohimbine-induced reinstatement. Prazosin blocked yohimbine-induced reinstatement of food and alcohol seeking, as well as footshock-induced reinstatement of alcohol seeking. Guanfacine attenuated yohimbine-induced reinstatement of alcohol seeking at the highest dose, but its effect on yohimbine-induced reinstatement of food seeking was not significant. Neither prazosin nor guanfacine affected high-rate food-reinforced responding. Results demonstrate an important role of postsynaptic α-1 adrenoceptors in stress-induced reinstatement of alcohol and food seeking.

Stress- and pellet-priming-induced reinstatement of food seeking and neuronal activation in *c-fos-GFP* transgenic female rats: role of ovarian hormones

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Relapse to maladaptive eating habits during dieting is often provoked by stress. Women may be particularly vulnerable to stress-induced relapse due to fluctuations in ovarian hormones. We used ovariectomized (OVX) or sham OVX *c-fos-GFP* (green fluorescent protein) transgenic female rats, which express GFP in strongly activated neurons, to study brain areas involved in stress- and pellet-priming-induced reinstatement as well as the potential role of ovarian hormones in reinstatement and neuronal activation. Food-restricted OVX or sham rats were trained (3 h per day) to lever press for delivery of palatable food pellets, paired with a discrete tone-light cue. Pellet intake was then assessed after systemic injections of the pharmacological stressor yohimbine (0, 0.5, 1 , 2 mg/kg, i.p.). Subsequently, lever pressing was extinguished over 20 sessions and reinstatement of food seeking was assessed after yohimbine injections or pellet priming (0, 1, 2, and 4 non-contingent pellets). Compared to sham rats, OVX rats showed a modest decrease in pellet-priming-induced reinstatement, but not in pellet intake, yohimbine-induced increases in pellet intake or yohimbine-induced reinstatement. In both OVX and sham rats, yohimbine- and pellet-priming induced reinstatement was associated with increased GFP expression in dorsal and ventral mPFC, and nucleus accumbens core and shell. We conclude that ovarian hormones play a role in relapse to food seeking induced by acute re-exposure to food taste and smell but not in stress-induced feeding or relapse in our rat model

Cycles of food restriction increase the orexigenic effect of Nociceptin/Orphanin FQ (N/OFQ) and Neuropeptide Y (NPY) in Female Rats

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Repeated episodes of food restriction/re-feeding, as well as stress, are known to represent key determinants of binge eating towards highly palatable food (HPF) (Cifani et al. Psychopharmacology:2009;204:113-25). However, the reasons accounting for the effect of food restrictions on subsequent eating behaviour is not known at present. This study evaluated the effect of repeated cycles of food restriction/re-feeding on the hyperphagic response to the central administration of the orexigenic neuropeptides N/OFQ and NPY. Female rats were submitted to three 8-day cycles of food restriction/re-feeding (R group). They were given for 4 days 66% of the usual chow intake, followed by 4 days of food *ad libitum*. Control rats (NR) had free access to food pellets for 24 days. Both groups were fed a sweet HPF for 2 h on day 5-6 and 13-14. On day 25 rats received ICV injection of vehicle or of different doses of either N/OFQ or NPY. Doses of N/OFQ in the range of 0.25-1 nmol/rat did not change HPF intake in NR rats, but significantly increased HPF intake in R rats. NPY, 0.2-0.6 ug/rat, did not stimulate HPF intake in NR rats, but elicited a significant hyperphagic response in R rats. In situ hybridization analysis revealed significant increase in mRNA levels for the N/OFQ receptor (NOP receptor) in the ventromedial hypothalamus. Thus, repeated food restrictions sensitize rats to the hyperphagic effect of both N/OFQ and NPY. These findings suggest that yo-yo dieting may alter the regulation of endogenous orexigenic mechanisms.

Ghrelin increases phasic dopamine signals evoked by food reward

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Food consumption is driven by energy need but also by the rewarding properties of food. Ghrelin promotes food consumption and food-seeking behaviors and the presence of its' receptors on

dopamine (DA) neurons, which play a critical role in food reward, suggests that ghrelin may serve as an interface between homeostatic and reward circuitry. Brief changes in DA concentration (phasic) in the nucleus accumbens (NAc) are evoked by unconditioned rewards and phasic DA has been shown to be necessary and sufficient for aspects of reward. Here, we investigated whether ghrelin modulates phasic DA evoked by food reward. Fast scan cyclic voltammetry was used to measure NAc DA in response to the delivery sugar pellets (30 to 90 s ITI) in ad libitum fed rats both before and after either saline (1µL) or ghrelin (1µg) was infused into the lateral ventricle. Consistent with previous findings, DA increased in the milliseconds prior to and peaked at pellet retrieval. Ghrelin significantly and selectively increased this DA response relative to pre-infusion values, as well as relative to data obtained following saline infusions. Rats that received ghrelin infusions also consumed significantly more chow than rats that received saline in a homecage test following the recording session. Our data contribute to a growing literature implicating ghrelin in the regulation of DA signaling. Moreover, they demonstrate that ghrelin may enhance feeding behavior in part by selectively increasing the magnitude of phasic DA signaling to food stimuli. Supported by: NIH Grant DA025634.

The effects of a chronic exercise intervention on appetite and eating behaviors
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Increased physical activity (PA) is associated with successful long-term weight loss maintenance with the mechanisms likely due to more than simply the resulting increased energy expenditure. The effects of PA on energy intake and eating behaviors, however, have been shown to be quite variable. The objective of this pilot study was to examine the effects of a long-term exercise intervention on appetite and eating behaviors. 12 overweight/obese (5 women, 7 men; BMI 33.0±4.4 kg/m^2; age 38.2±9.5 y) otherwise healthy individuals were studied. Questionnaires on eating behaviors (Three Factor Eating Inventory, Craving & Mood), ratings of appeal and desire for foods (ImageRate), and ratings of appetite (hunger, satiety, prospective intake) using visual analog scales were performed at baseline and again after a 6 month progressive exercise intervention (supervised, 5 days per week). Overall, there was a trend for a reduction in body weight (101.5±4.9 to 98.7±5.8 kg, p=0.09). The exercise intervention, however, did not impact any of the measures obtained: eating behaviors, appetite, or food appeal/desire. Interestingly, though, an association was found between change in body weight and change in disinhibition score (r=0.79, p=0.01). In summary, despite adding an exercise intervention resulting in modest weight loss, no changes in eating behaviors were seen except for changes in disinhibition. These findings suggest that chronic exercise may promote weight maintenance and/or weight loss by attenuating the expected changes in eating behaviors and/or by improving disinhibited behaviors. Supported by: NIH.

Addiction and Obesity: insights from functional brain imaging
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The view that hunger is an addiction to food was proposed 100 years ago. Although it often draws criticism, it is worthwhile to view obesity and appetite from the standpoint of addiction neuroscience. The ventral striatum, amygdala, insula and orbitofrontal cortex form a network for appetitive behaviors. These interconnected brain regions, which are implicated in addiction and are a major target of mesolimbic dopamine, attribute value and incentive salience to available stimuli and actions, and are crucially involved in motivated decision making. We will present cue-reactivity studies of food and cigarettes using functional MRI. Food cues contribute to the obesogenic environment. First we demonstrate, using a voxel based meta-analysis, that food and cigarette cues activate an overlapping set of brain regions, notably the appetitive system identified above. Second we will show imaging studies demonstrating that cue-reactivity is

enhanced by psychosocial stress. Third, we will provide evidence that brain regions that respond to drug and food cues are involved in valuation and motivated choice, and that they are amenable to modulation by self-control mechanisms involving the lateral prefrontal cortex. Finally, we will present evidence that the homeostatic peptide hormone ghrelin increases the neural response to food cues in the brain appetitive system. We will also present preliminary evidence that ghrelin may also be a stress hormone, which would make it a potential link between psychosocial stress and weight gain. We will discuss the potential lessons from tobacco policy for the obesity epidemic.

Endogenous GLP-1 is necessary for the inhibition of food intake by jejunal linoleic acid infusions.

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Roux-en-Y surgery results in sustained decreases in food intake and weight loss. A key component is likely the direct delivery of undigested nutrients to the jejunum and resulting changes in levels of gut peptide secretion. Prior work modeling this aspect of the surgery has shown that small volume, prolonged jejunal infusions of linoleic acid (LA) produces sustained decreases in food intake and weight loss. LA infusions also significantly elevated plasma GLP-1 levels. In order to assess a role for increased circulating GLP-1 in the feeding suppression, we examined the effect of prolonged minipump administration of the GLP-1 antagonist exendin 9-39 on the feeding suppression produced by LA. Rats were equipped with both a jejunal cannula and an ip minipump. Using a 2x2 design we infused either saline or LA in the jejunum (7h/day, 11.4kcal) for 5 days with a subset of animals from each group receiving either saline or exendin 9-39 (25pmoles/kg/min) continuously via a minipump. The antagonist had no effect on food intake in the saline infusion condition. LA reduced daily food intake greatly in excess of the kcal infused. Exendin 9-39 completely blocked the feeding suppression produced by the jejunal LA infusion. These data demonstrate that endogenous GLP-1 action is necessary for the reduction in food intake produced by jejunal LA infusions. Whether increased secretion of additional gut peptides is also necessary for such suppressions remains to be determined. (DK19302) Supported by: DK19302.

'Food Addiction' is a Valid Phenotype of Obesity

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While the term food addiction (FA) is widely accepted among the general population, there has been little human study of this construct. The recently developed *Yale Food Addiction Scale* (YFAS) is the first attempt to operationalize FA using the diagnostic criteria for substance dependence. Preliminary research indicates that it may be a useful tool for identifying those with addictive tendencies towards food. We recruited 70 overweight adults who completed the YFAS and relevant psychological measures, underwent a psychiatric screening interview, had height and weight measured, and provided a blood sample for DNA extraction. The YFAS identified 17 who met criteria for FA. Importantly, there were no differences in BMI, age, or gender between the two groups. However, 76% of the FA group was co-morbid for Binge Eating Disorder compared to 19% of the non-FA group. The former was also more impulsive (p=.02), more depressed (p=.01), had more addictive personality traits (p=.004), and reported greater food cravings (p<.0001). C957T is a functional marker of the D2 dopamine receptor gene (DRD2) where the T allele is associated with reduced receptor density and has been linked to addictions like alcoholism. Half the FA group was homozygous for the T allele compared to 12% of the non-FA group. These results provide good evidence that FA has psychobiological similarities to other

addiction disorders and is a valid phenotype of obesity. Supported by: Canadian Institute of Health Research.

Gastric Bypass surgery modifies ethanol consumption in rats

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Surgical treatment of obesity is the only therapy that reliably produces substantial weight loss that is sustained over many years. The Roux-en-Y gastric bypass (RYGB) is the gold-standard of bariatric surgery and the number of these procedures performed has risen dramatically in recent years. New data suggest that the sensitivity to ethanol (ETOH) is augmented following RYGB and that bariatric patients begin to abuse ETOH following surgery. Here we utilized a rat model of bariatric surgery to investigate the effects of RYGB on ethanol intake. We performed sham or RYGB surgery on male Long Evans or male Alcohol Preferring (P) rats (n=10/group). Following recovery rats were exposed to a 10% ETOH solution in their home cage every two days for a period of fourteen days. LE rats exhibited a modest increase in ETOH consumption whereas P rats exhibited ETOH abstinence. That is, rats bred to consume ETOH, stopped drinking after the RYGB procedure. Consistent with previous reports we also observed that ghrelin increased ETOH intake in normal and P rats with RYGB. These behavioral data were associated with altered transcription of within CNS circuits that mediate hedonics and motivation. Collectively, these data suggest that RYGB may alter ETOH intake and critically depend on genetic background or pre-surgical ETOH preference. Supported by: Ethicon Endosurgery.

Metabolic Sensing in Brain Dopamine Systems

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Animals rely on chemoreceptor systems, such as gustation, to establish consummatory preferences among available food sources. However, several lines of evidence indicate that nutrient intake is also under the control of physiological factors even in the absence of normal taste receptor signaling. Current investigations aim at determining the identity of the physiological signal that regulates taste-independent behavioral and neurochemical responses during nutrient intake. Of particular interest is the potential role for brain nutrient sensing as a rewarding physiological signal controlling carbohydrate and fat intake independently of sweetness or fattiness perception. Recent investigations reveal increased dopamine release in striatum in taste-blind mice as well as upon intra-gastric infusions of nutrients, with such nutrient-driven dopaminergic responses appearing to depend on normal brain metabolism. These findings suggest that preferences for nutritive sugars can develop independently of sweetness perception, and that metabolic signals generated during the catabolism of ingested nutrients regulate the activity of brain dopamine pathways. Future research must characterize the nature of the association between neuronal nutrient utilization/sensing, neurotransmitter release, and the formation of nutrient preferences. Supported by: NIH-NIDCD.

POMC-PTP1B-/- mice show increased sensitivity to hindbrain MTII-induced reductions of food intake.

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Leptin regulates energy balance in part through activation of proopiomelanocortin (POMC)

neurons. Protein tyrosine phosphatase 1B (PTP1B) is an important intracellular negative regulator of leptin signaling. POMC neuron-specific deletion of PTP1B in mice results in reduced high-fat diet-induced body weight due to increased energy expenditure and leptin sensitivity. The contribution of specific POMC neuron populations to these effects is unknown. Therefore, POMC-PTP1B-/- and control PTP1B+/+ mice were implanted with chronic 4th ventricle cannulae to permit local activation of hindbrain neurons, as well as telemetric transponders to continuously measure core temperature and physical activity. Using a within subjects design, mice received 4th icv injection of either leptin (3ug; 6ug/200nl), the melanocortin 3/4 receptor (MC3/4R) agonist Melanotan II (MTII; 0.2nM/200nl), or vehicle. Food intake and body weight were measured 6 and 24hr post-injection. MTII-induced reductions in food intake were significantly suppressed at 6 hr in both POMC-PTP1B-/- and control mice, while only POMC-PTP1B-/- mice showed suppression at 24 hr. Leptin significantly decreased intake in both genotypes, although knockout mice showed a trend for enhanced intake suppression. These data suggest that food intake regulation by hindbrain MC3/4R activation involve PTP1B-mediated mechanisms in POMC neurons. Analyses of core temperature and physical activity are underway. Support: NIH DK082417 (KKB) & DK21397 (HJG), AHA 10POST3910000 (BCD).

The role of the adipocyte glucocorticoid receptor in energy metabolism and HPA axis regulation

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Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis contributes to metabolic disorders. Moreover, metabolic disorders are often accompanied by psychopathology. Accumulating evidence suggests that these interactions are mediated, in part, by direct effects of glucocorticoids (CORT) on adipose tissue. The glucocorticoid receptor (GR) is highly expressed in adipocytes and mice with elevated adipose tissue CORT have increased adiposity. Although it is clear that CORT influences energy balance and HPA axis regulation, the actual role of adipocyte GR in these processes is not clear. We utilized the mouse cre/lox system to delete GR selectively in adipocytes in order to determine the role of adipocyte GR in energy metabolism and HPA axis activity. We hypothesized that deletion of adipocyte GR would attenuate diet-induced adipose mass gain, but would facilitate HPA axis-responding. Adiponectin is expressed almost exclusively in adipocytes. Co-expression of the adiponectin-cre and GR-lox transgenes led to a reduction in GR expression selectively in adipocytes. When given a high-fat diet, mice with reduced adipocyte GR consumed less diet and gained less body mass and adipose mass than littermate controls. Although basal CORT levels were not affected by adipocyte GR deletion, mice lacking GR in adipocytes had an augmented CORT response to restraint. Taken together, the results suggest that adipocyte GR contribute to the development of diet-induced obesity and blunt activation of the HPA axis. Supported by: F31 NS 068122.

Neuropeptide transmitters released from VAN into the NTS play an important role in regulating food intake

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Vagal afferent neurons (VAN) convey information from the gastrointestinal tract important in the regulation of food intake (FI) to the nucleus tract solitarius (NTS) and play a major role in the regulation of meal size and duration. During fasting, VAN express the orexigenic neuropeptide transmitter melanin concentrating hormone (MCH). Conversely, in response to a meal MCH expression is downregulated and the anorexigenic neuropeptide transmitter cocaine and amphetamine regulated transcript (CART) is elevated. The aim of this study was to determine the physiological role of CART and MCH on feeding behavior at the level of the medial NTS, the main site of vagal afferent nerve terminals. **Methods**: Male rats were implanted with cannulas at a

medial location in the commissural part of the NTS. 2hr feeding tests with chow were performed in response to saline, CART alone (80pg/kg), MCH1 receptor antagonist (SNAP 94847) alone (5-5000nM), or CART and SNAP 94847(80pg/kg, 50nM) together after a 6hr fast. **Results**: SNAP 94847 inhibited FI in fasted rats in a dose-dependent manner when injected into the NTS compared to saline. CART alone injected into the NTS had no effect on FI in fasted rats compared to saline (8.37 ± 0.79 vs 9.23 ± 0.47g; P>0.05). However, CART significantly inhibited FI in fasted rats when injected into the NTS in combination with SNAP 94847 compared to saline, CART alone, or SNAP 94847 alone (5.12 ± 0.43 vs 9.23 ± 0.47g, 8.37±0.79g, 7.61±0.73g; P<0.001). **Conclusion**: Endogenous MCH release from VAN into the NTS stimulates FI in fasted rats. Endogenous MCH masks the inhibitory effects of exogenous CART on FI at the level of the NTS, but in the absence of MCH, CART plays an important role in satiation. Supported by: NIH.

Hunger fluctuates during the interdigestive state in man

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Background: It has been suggested that phase (ph) 3 contractions of the migrating motor complex are associated with hunger feelings. In this study we investigated whether, in the interdigestive state, 1) hunger fluctuates, resulting in 'hunger peaks'; 2) ph3 contractions are associated with hunger peaks and 3) hunger peaks result in spontaneous food intake. Methods: In 9 healthy volunteers (5 males; 24±7 years) antroduodenal motility was measured using high resolution manometry for 7 hours after an overnight fast. Subjects were blinded towards time of the day. Hunger scores were rated every 5 minutes on 10cm visual analog scales (VAS). Hunger scores were scanned for peaks using a peak-sensitive algorithm. Ph3 contractions were visually identified on the manometry tracings using standard criteria. During the measurements volunteers were allowed to ingest a low-caloric soup twice at time points of their choice. Results: 1) Hunger scores fluctuated: on average 4±2 hunger peaks were identified, with a median interval of 75±62 min. 2) Subjects had 3±1 ph3s (80% of gastric origin), with a median interval of 133±77 min and a mean duration of 8±3 min. 52% of ph3s (82% with gastric origin) were followed by a hunger peak after a mean interval of 2±3 min. 3) 50% of the spontaneous food intakes followed a hunger peak with a mean interval of 4±2 min. Conclusions: Interdigestive hunger ratings fluctuate during an interdigestive period with the formation of hunger peaks. A close correlation exists between ph3 contractions of gastric origin and hunger peaks. Hunger peaks appear to be major determinants for food intake. Supported by: None.

Obesogenic diets with fat and sugar reduce site specific sensitivity to insulin

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We previously showed that rats on a free-choice high-fat high-sugar (fcHFHS) diet become rapidly obese and develop glucose intolerance (GI) within a week. Interestingly, neither rats on a free-choice high-fat diet (fcHF), although equally obese and hyperphagic, nor rats on a free-choice high-sugar (fcHS) diet that consume more liquid sugar, develop GI. We here investigated whether changes in (hepatic) insulin sensitivity (IS) contribute to the observed GI. Rats received either a fcHFHS, fcHF, fcHS or a chow diet for one week. We performed a hyperinsulinemic-euglycemic clamp, with two times basal insulin values, combined with stable isotope dilution to measure endogenous glucose production (EGP) and glucose disappearance. Rats on all free-choice diets were hyperphagic and gained more fat mass compared to rats on chow. EGP suppression by hyperinsulinemia in rats on a fcHFHS was 40% less compared to suppression in rats on a fcHS or chow diet. In rats on a fcHF diet, insulin did not suppress EGP at all. Interestingly, the rate of disappearance for glucose was only affected in rats on a fcHFHS diet (70 vs 90 µmol/kg·min in chow controls). Thus, consumption of saturated fat alone or in combination

with liquid sugar decreased hepatic IS. The combination of saturated fat and liquid sugar also reduced peripheral IS. We therefore hypothesize that saturated fat alone affects mainly the liver and that the combination of saturated fat and liquid sugar also reduces peripheral glucose disappearance which is important for the previously observed GI in fcHFHS. Supported by: ZonMW.

Intestinal endocannabinoid metabolism mediates the cephalic control of dietary fat intake

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We have recently shown that central signals, elicited by the sham intake of dietary fat, activate an endocannabinoid (eCB)-mediated mechanism in the small intestine, via the vagus nerve, which promotes the intake of fat-rich foods. This occurs in a macronutrient-specific manner, because sham intake of sucrose or protein failed to alter intestinal eCB levels, and is tissue-specific, because sham intake of fat failed to alter eCBs in other peripheral organs or brain regions controlling food intake, energy balance, or reward. Here, we extend these studies and investigate the biochemical mechanisms underlying the regulation of intestinal eCB signaling by dietary fat. Fat sham feeding markedly lowered jejunal monoacylglycerol lipase activity, which catalyses 2-AG hydrolysis, without affecting levels of the 2-AG precursor, 1-stearoyl-2-arachidonoyl-*sn*-glycerol (DAG), or activity of the enzyme responsible for converting DAG into 2-AG, DAG lipase. Furthermore, fat sham feeding reduced jejunal activity of the anandamide-degrading enzyme, fatty acid amide hydrolase, and increased levels of the anandamide precursor, N-arachidonoyl-phosphatidylethanolamine, and activity of an enzyme involved in anandamide biosynthesis, N-acylphosphatidylethanolamine-specific phospholipase D. Together, the results indicate that the cephalic component of fat intake, communicating via the vagus nerve, mobilizes jejunal eCBs by regulating both biosynthesis and degradation of these lipid mediators, and this signaling controls dietary-fat intake. Supported by: NIH DK073955 to DP.

Host-microbe interactions in neonatal intestinal development: Role of early nutrition

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During the first 4-6 months, the infant transitions from intravenous to enteral nutrition and from a sterile gut to one colonized by a complex microbiota, while human milk or formula is being consumed as sole source nutrition. Herein, non-invasive approaches were used to study how nutrition influences intestinal development and shapes host-microbe interactions. Stool samples were collected from 3-month-old formula- (FF; n=6) or breast-fed (BF; n=6) infants. Infant gene expression was assessed by microarray analysis of intact sloughed epithelial cells isolated from stool (*AJP* 2010;298:G582-9). Microbial composition and gene expression was assessed by Roche 454 metagenomic pyrosequencing. Host mRNA and microbiome phylogenetic profiles independently classified BF vs. FF. Integrating the two data sets in a linear model demonstrated that the % of *Firmicutes* and *Actinobacteria* in stool as covariates predicted the expression of 394 of 16,853 infant genes (R^2 >0.7; q-values <0.25). Further, the % of Carbohydrate, Virulence, Cell Wall-Capsule, and RNAmetabolic pathways in the metabiome (SEED level 1 biological processes) was correlated (R^2 > 0.7, q-values <0.2) with 20 of 519 infant Immunity and Defense genes (PANTHER biological processes). A systems biology approach identified important gut microbiome pathways affecting intestinal development. Funded by: NIH CA129444, HD061929 and DNS Vision 20/20. Supported by: NIH.

Nucleus Accumbens glucagon-like peptide-1 receptor activation suppresses food intake.
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Hindbrain glucagon-like peptide 1 (GLP-1) neurons project to a number of brain areas that express GLP-1 receptors (GLP-1R). One of these targets is the Nucleus Accumbens (NAc), known for its role in reward and motivated behavior. Injection of GLP-1 into the lateral, 3rd, or 4thventricle reduces food intake, so we hypothesized that activation of NAc GLP-1R would suppress feeding. The NAc lies just ventral to the lateral ventricle, so we examined the dose response for intra-lateral ventricle (lat-icv) GLP-1. Saline or one of 5 doses of GLP-1 was delivered lat-icv 30 min before dark cycle onset (n = 10). Doses of 0.33, 1 and 3 mg GLP-1 significantly reduced food intake by ~30% relative to vehicle 2 h into the dark (p's <0.05); lower doses were ineffective. We chose ventricle-subthreshold doses to inject into the NAc: 0.025 and 0.1 mg GLP-1 vs. saline (n = 8-9/group). Both significantly reduced food intake at 1 (25-37%), 2 (18-32%) and 24 h (7-8.5%) post-treatment (p's <0.05). We next examined the effect of the GLP-1R antagonist exendin 3 (9-39) (Ex9) delivered lat-icv. Ex9 (20 mg) significantly increased intake from 1 (43%) to 24 h (18%) post-treatment (n = 9, p <0.05), whereas we have previously observed no effect of this dose injected 3rd-icv. We are currently examining the effects of a ventricle-subthreshold dose of Ex9 in the NAc. We conclude that that exogenous activation of GLP-1R in the NAc can suppress intake, and suggest that the rostral forebrain contains potentially important sites of action for endogenous GLP-1 stimulation.

Changes in satiation signaling in diet-induced obese (DIO) rats: diet versus phenotype
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Altered sensitivity to satiation signals has been proposed to be partly responsible for increased consumption and weight gain in both animals and humans. Indeed dietary- and genetically-induced obese rats exhibit peripheral and central deficits that have been associated with hyperphagia and obesity. We recently showed that diet-induced obese (DIO) rats are more sensitive to the anorexigenic effects of CCK-8 when fed regular chow, compared to diet resistant (DR) controls. However, whether this effect manifests when animals are on a HF diet is not known. Also, it is not known whether DIO animals exhibit differential responses to the inhibitory effects of intragastric nutrient loads. Therefore, to examine whether these effects are determinants of diet and/or phenotype, DIO and DR rats maintained on either chow or HF/HE (4.41 kcal) diet received CCK-8 (0, 1, 2, 4 µg/kg, IP), intralipid (IL) 20% (10 kcal, 5 ml, IG) glucose 50% (10 kcal, 5 ml, IG) or 0.9% saline (5 ml, IG) after an overnight fast. We found that, compared to DR, DIO rats were more sensitive to the suppressive effects of CCK irrespective of the maintenance diet. On the other hand, DIO rats suppressed food intake less than DR following IG delivery of IL or glucose only when on HF but not chow. This effect was associated with upregulation of vagal LepR and CCK-1R and downregulation of lingual T1R3 and CD-36. These results together with prior findings suggest that DIO rats exhibit a host of signaling deficits contributing to excess intake and body weight.

Absence of gut microbiota increases lipid consumption in C57BL/6J germ-free mice
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A role of gut microbiota in energy and fatty acid storage has been recently shown. As such, mice

devoid of gut microbiota (GF) C57BL/6J (B6) are protected against high fat diet induced obesity and dramatically increase fat accretion when reverted to a microbial environment. We have recently shown that GF mice consume more nutritive (sucrose) but not non-nutrient (saccharin) sweet solutions than normal B6 mice. This was associated with upregulation of intestinal T1R3 and SGLT-1 expression. To test whether elevated sucrose intake in GF mice extends to other palatable stimuli we compare the ingestive responses of GF and control mice to fat emulsions (IL, 0.156, 0.313, 0.626, 1.25). We found that GF mice consume more IL than controls, with increasing intakes as a function of IL concentration. When preference was tested using 48 two-bottle preference test, GF mice preferred the lowest concentration of IL more than control mice. The behavioral data were correlated with expression of nutrient receptors in the lingual and intestinal epithelium. These results show that an absence of gut microbiota results in overconsumption of palatable, nutritive solution that could be due to a compensatory mechanism to account for microbiota-derived energy and/or altered lipid metabolism in GF animals.

The Rostromedial Tegmental Nucleus Provides Inhibitory Tone to Dopamine Neurons

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Dopamine (DA) projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) have been shown critical for motivated behavior, including feeding. Brief, subsecond (phasic) changes in DA concentration have previously been demonstrated not only necessary, but sufficient for associative learning involving food and reinforcement in general. While previous research demonstrated phasic increases and pauses in DA signaling in response to associative learning involving food, the neural substrates responsible for regulating these changes remain unknown. Recent studies suggest the rostromedial tegmental nucleus (RMTg) as a putative inhibitor of VTA DA neuron activity during associative learning. Here, we investigate the role of the RMTg as a potential inhibitor of DA activity using circling, a well validated behavioral model of DA activity in which animals circle towards the side with less DA. We hypothesized that if the RMTg provides significant inhibitory tone on DA neurons, then temporary unilateral inactivation of the RMTg would create an imbalance in DA levels and result in contralateral rotation. As predicted, contralateral rotations increased when the RMTg was inactivated with lidocaine (175nmol: 30.0±10.7; 350nmol: 79.0±18.7) or muscimol (0.05ug: 538.0±234.1; 0.1ug: 581.0±172.5) compared to saline (8.5±6.0). Currently, we are assessing the effects of RMTg activation and inactivation on phasic DA release in the NAc. Our results support the RMTg as a major source of inhibitory tone on DA neurons and hence a key regulator of motivated behavior.
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The metabolic effects of Olanzapine and Topiramate in rats and humans.

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In humans the anti-psychotic Olanzapine (OLZ) has negative side effects on metabolism: it causes weight gain and increases the risk of developing type 2 Diabetes. The anti-convulsant Topiramate (TPM) has the opposite effects: it reduces body weight and improves insulin sensitivity. Because of this, it has been proposed to use TPM to counteract OLZs side effects. The underlying mechanisms by which OLZ and TPM influence metabolism are unknown. To study this, we performed a series of studies in both rats and humans. In rats we administered OLZ and TPM via a permanent intragastric cannula, to mimic oral drug administration, and found that chronic OLZ treatment stimulates weight gain and causes insulin resistance reflected by increased insulin responses during an intravenous-glucose tolerance test OLZ also decreased locomotor activity and core temperature, pointing to a reduction in energy expenditure. OLZ also increased weight gain in humans, accompanied with decreased daily physical activity, reduced body temperature and increased baseline and glucose-stimulated insulin levels during an oral

glucose tolerance test. TPM reduced the OLZ-induced overeating and weight gain in both rats and humans combined with an increased postprandial satiety rating (in humans). We conclude that, in both rats and humans, a reduction in energy expenditure may explain, at least in part, the OLZ effects on weight gain and that the OLZ-induced effects on insulin resistance has a peripheral side of action. We also conclude that TPM may prevent the negative metabolic side effects induced by OLZ. Supported by: Top Institute Pharma.

Maternal high-fat diet during gestation and lactation alters hepatic gene expression in male rat offspring

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Maternal high fat (HF) diet through gestation and suckling has long term consequences on rat offspring and predisposes the pups to diet-induced obesity. In this experiment, we examined hepatic gene expression in postnatal day (PND) 21 male rats. Pregnant female Sprague-Dawley rats were randomly assigned to receive either standard chow (CHOW) or HF diet (60%) from day 2 of gestation through weaning. Pups born to HF-fed dams had significantly higher body weight throughout the post weaning period. On PND 21, HF pups had greater adiposity, plasma leptin concentration, and impaired glucose tolerance compared to CHOW pups. Liver samples were collected on PND 21 and gene expression was measured by RT-PCR. Genes associated with glucose homeostasis and fatty acid oxidation (*Pck1, Ppar-α, Nr3c1, Cpt1a*) had significantly higher levels of expression in HF male pups (increases of 48.9%, 52.3%, 30.7%, and 239.7%, respectively) compared to CHOW pups at weaning. These data suggest that genes that increase hepatic gluconeogenesis (*Pck1* and *Nr3c1*) and fatty acid oxidation (*Ppar-α* andCpt1a) are upregulated. Thus, the expression of genes associated with both glucose homeostasis and fatty acid oxidation are altered and may contribute to the long-term consequences of maternal HF diet during gestation and lactation. Supported by DK077623, HD055030. Supported by: DK077623, HD055030.

Physiological role of leucine in the response to low and high protein diets

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Direct brain (icv) injections of leucine are sufficient to suppress food intake, but it remains unclear whether brain leucine signaling represents a physiological signal of protein balance. We therefore tested whether variations in plasma and brain leucine might contribute to the detection and/or response to low and high protein diets. When rats were placed on isocaloric low (10% Protein Energy; LP) or high (35% Protein Energy; HP) protein diets, food intake diverged within 2 days, with increased consumption of LP and a transient (Days 2 and 3) reduction in consumption of HP ($P < 0.05$). Icv injection of leucine (10ug) significantly reduced food intake in rats consuming the LP diet, but had no effect in rats consuming HP, consistent with the hypothesis that brain leucine differentially signals low vs. high protein. To test whether plasma leucine was altered by dietary protein, rats were transitioned from chow to either a LP or HP diet, and circulating amino acids measured on days 0, 1, 2 and 4. Within 24hrs of HP, leucine levels were significantly increased ($P < 0.05$), and remained elevated for the duration of the experiment. In contrast, plasma leucine was unchanged by exposure to LP. These data indicate that icv leucine differentially influences consumption of LP vs. HP diets, that increased leucine may contribute to the response to a HP diet, but that LP-induced hyperphagia is not associated with a fall in circulating leucine. Supported by: NIH.

Adaptive memory for food: behavioural evidence for a hunter-gatherer mind?
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Memory promotes efficient foraging. Foods that confer a biological advantage will be remembered, together with strategies associated with their procurement. We tested the hypothesis that the same memory bias exists in modern humans and that this is expressed as enhanced memory for foods that are energy dense and/or those that promote satiation. In Experiments 1 and 2, we adapted the delayed-match-to-sample colour-memory paradigm to assess memory for food. In turn, participants were exposed to images of 30 foods on a computer screen. For each food, they provided ratings of liking and expected satiation. In a subsequent incidental-memory task, the participants recalled the hue of each food using a psychophysical colour-matching procedure. Our analysis revealed a significant positive correlation between colour-memory accuracy and the expected satiation of the foods. In Experiment 3, we manipulated 'biological significance' directly. Sixty participants consumed either a novel high (414 kcal) or moderate (275 kcal) energy-dense breakfast. These were matched for their sensory characteristics and expected satiation. Participants tasted the food, rated 18 of its sensory properties, and then consumed the meal. One week later, and without prior warning, they repeated this sensory evaluation, this time based on their memory of the food. The difference between actual and recalled sensory ratings was significantly smaller in the high energy-dense condition. Collectively, these studies are the first of their kind to demonstrate 'adaptive memory' for food in humans. Supported by: Economic and Social Research Council (U.K.).

Strategies for Increasing Children's Knowledge and Liking of Healthful Foods
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From a public health perspective, it is a priority to develop strategies that encourage children to consume a diet rich in fruits and vegetables from an early age. In order to address this important health issue, a variety of nutrition programs have been implemented across the country, many of which promote healthy eating at home. Our research has investigated how exposure to age-appropriate information about healthy eating and the opportunity to sample a variety of fruits and vegetables affects 4-8 year-old children's knowledge about nutrition, and their willingness to try healthy foods. Within controlled laboratory and applied settings, children's knowledge of and willingness to try healthy foods were assessed before and after either a home exposure period or a school nutrition program. Overall, children who were more food neophobic consumed fewer healthy foods at home, were less knowledgeable about healthy foods, and were less likely to try foods presented during testing. Children who were exposed only to information about healthy eating became more knowledgeable about nutrition, but were not willing to try more of the foods during the post-tests. Children, who were exposed to fruits and vegetables, tried more pre-exposed foods than novel foods. Thus, while limited exposure to healthy fruits and vegetables increased consumption of those specific foods, such exposure did not generalize to other foods. These findings demonstrate the challenges involved in enhancing children's fruit and vegetable consumption and highlight the need for strategies that allow children to sample a wide variety of healthy foods. Supported by: The College of William & Mary.

Solid Food Intake Regulation in Infants
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From an early age, the feeding environment involves a complex interaction between the infant

and caretaker, each of whom brings their own set of innate characteristics, experiences, and attitudes about food to the table. Due to the rising concern about childhood obesity and the prevalent belief that children are not able to regulate their own food consumption, many parents limit their infants' food intake. The goal of the present study was to determine whether 4-8 month-old infants would regulate intake of a highly palatable fruit and a less palatable green vegetable of equal calories. To this end, 34 mother-infant dyads were tested under naturalistic conditions in which the infants determined the pace and duration of the feeding. On separate test days, mothers fed their infants the target food while either moderately hungry or after a pre-feeding of infant cereal. Acceptance and liking of the foods were assessed using a variety of measures, including amount and rate of consumption and the frequency of facial distaste expressions. The extent to which mothers used controlling feeding strategies was also measured. Results indicated that the relationship between infants' hunger level and intake was moderated by the palatability of the target food. When fed while hungry, infants ate roughly twice as much fruit than after a pre-feeding of cereal, however consumption of a green vegetable was the same regardless of whether they were fed hungry or full. Moreover, mothers' controlling feeding strategies were not related to intake, suggesting that at this age food consumption is regulated primarily by internal rather than external factors.

Subcutaneous Adipose Tissue Transplantation to the Visceral Cavity in Obese mice: Mechanisms for Metabolic Improvements

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Visceral adipose tissue accumulation is thought to predispose individuals to adverse health consequences. We, however, have demonstrated, via adipose tissue transplantation from lean rodents to the visceral cavity of lean recipients, the opposite is true. We hypothesize that adipose transplantation enhances the capacity of visceral fat to sequester fatty acids (FA) from the blood, thereby reducing FA flux into and triglyceride (TG) storage in the liver, consequently improving glucose tolerance. To assess this ~30 gram high fat diet (HFD)-induced obese mice were sham operated or received autologous (excision of adipose tissueand subsequent relocation withinanimal)inguinalWAT transplantation. Glucose tolerance (GT) waspreformed pre-surgery and4 wks post surgery,while fat pads, liver and portal blood were collected terminally. Though animals remained on HFD post-surgery autologous transplantation significantly improved GT and significantly decreased portal TG and FA acid concentration. In a subsequent experiment we investigated the individual components of autologous transplantation, specifically subcutaneous fat removal vs. transplantation and determined that only transplantation significantly improved glucose tolerance, increased hepatic insulin sensitivity and decreased circulating portal lipids and liver TG storage. Taken together these experiments demonstrate portal lipid delivery plays a role in the metabolic complications of visceral obesity. Supported by: NIH NIDDK.

Vagal GI Afferents in Early Postnatal Overnutrition

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Contributors to the increased prevalence of obesity may include perinatal under- or overnutrition. The obesity that develops in humans and rodents raised under these conditions has been associated with increased meal size. As vagal GI afferents contribute to regulation of meal size, abnormal perinatal nutrition could increase meal size by altering them, possibly through changes in expression of factors that control their development or function. A candidate factor is BDNF as its GI tract expression pattern and the effects of its loss on vagal GI afferents are consistent with such a possibility. We found that BDNF, which regulates survival of over 50% of vagal sensory neurons, is expressed in developing GI tissues innervated by vagal afferents and contributes to survival or differentiation of subsets of vagal gastric mechanoreceptors. Further, GI BDNF

appears to be required for normal gut-to-brain negative feedback and vago-vagal reflex function of as yet unspecified vagal GI afferents. However, in young adults, prior to development of obesity, we found mice that experienced early postnatal overnutrition (EPO) exhibit modest hyperphagia due to a small decrease in satiety, but meal size and intestinal vagal mechanoreceptor density and structure are not significantly altered. Aging or obesity may be required to reveal increased meal size and a vagal contribution. In fact, the effects of GI BDNF on vagal afferents suggest a model that could explain why high-energy diet consumption produces increased obesity in organisms exposed to EPO, and why high-energy diet consumption may be required to increase meal size and reveal altered vagal function in young adults.

Body Mass Index and Externalizing Behavior as Early as Age 3 Predict Disordered Eating Characteristics at 15 Years

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Externalizing behavior (e.g., conduct disorder) has been associated with weight status and rapid weight gain in childhood and adolescence. The objective of this study was to examine body mass index (BMI) and externalizing behavior in early childhood (starting at age 2) as predictors of disordered eating characteristics in adolescence (age 15). Longitudinal data were drawn from the National Institute of Child Health and Human Development's Study of Early Child Care and Youth Development. Data were available for 940 families, collected when children were ages 2, 3, 5, 7, 9, 11, 12 and 15 years. BMI was calculated at all time points from measured height and weight measurements; externalizing behavior was reported by parents at all time points. Adolescents completed the Eating Attitudes Test at age 15. Results showed that BMI and externalizing behavior measured as early as age 3 (and at all time points thereafter) were consistently, positively associated with disordered eating characteristics at age 15. Adolescents who exhibited greater gains in BMI from age 2 to age 15 reported higher levels of disordered eating characteristics at age 15. After accounting for the influence of externalizing behavior at age 15, earlier reports of externalizing behavior did not predict disordered eating characteristics at age 15. There is a need to develop a better understanding of the mechanisms by which these relations exists. Supported by: National Institutes of Health/NICHD - R03HD60013.

SYNERGISTIC POST-PRANDIAL DEREGULATION OF THE OREXIGENIC ENDOCANNABINOID ANANDAMIDE AND THE ANOREXIGENIC PEPTIDE YY IN OBESITY

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Obese subjects have increased circulating anandamide (AEA) and 2-arachidonoylglycerol (2-AG) levels, although there is no information on how these endocannabinoids might contribute to the human obese phenotype. We measured plasma AEA, 2-AG and peptide YY (PYY) in 12 normal weight and 12 obese subjects in response to a calorically balanced meal. Endocannabinoids were measured using a highly sensitive triple-quadrupole mass spectrometry method. Immediately before the meal, plasma AEA significantly increased in both groups. 1 hour after the end of the meal, AEA levels significantly decreased in controls only. 2-AG did not change. Post-prandial PYY significantly increased in controls only. Post-prandial AEA and PYY changes inversely correlated with waist circumference (WC) and independently explained 20.7% and 21.3% of WC variance. Multiple regression analysis further showed that post-prandial AEA and PYY change together explained 33.9% of WC variance ($r = 0.582$, $r^2 = 0.339$, $P = 0.029$). Each of them respectively justified 12.5% and 13.2%, while they commonly explained 8.2% of WC. These data suggest that AEA might have a role in meal initiation. Furthermore, they imply

that anti-obesity therapies should target both orexigenic and anorexigenic mechanisms to be effective.

Impact of Ostracism and Psychosocial Factors on Food Consumption
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The experience of being ostracized impairs youths' abilities to self-regulate, which in turn, leads to increased unhealthy eating. This study tests whether appearance-based rejection sensitivity (ARS) and friendship conflict moderate the effect of ostracism on eating in adolescents. Eighty adolescents(40 girls; *M* age = 13.29 years) completed self-report measures of ARS and perceived friendship conflict. During the study session, participants were either included or ostracized when playing a computer game, Cyberball. Participants then had 30 minutes of free access to various snack foods and sedentary activities. Foods were weighed to determine the amount of food consumed and total kcal, kcal from healthy, and kcal from unhealthy snacks were used as dependent variables. Overall, included girls consumed significantly more healthy kcal than included boys $t(7,32) = -2.63$, $p = 0.01$). A number of significant moderating effects were also found. Included boys who scored high on ARS ($t(2,16) = -1.31$, $p = .04$) and those with greater friendship conflicts ($t(1,19) = 0.12$, $p = .04$) had greater unhealthy and total kcal intake. In contrast, excluded girls with higher friendship conflict had significantly greater total kcal intake ($t(2,17) = -1.09$, $p = .03$). Findings suggest that ARS and friendship conflict differently moderate the relationship between ostracism and food consumption for male and female youth. Findings are discussed according to theory regarding the interface between peer relationships, sex, and eating. Study limitations, as well as clinical implications, are described.

The Effects of Hunger in the Absence of Caloric Restriction in a Mouse Model of Alzheimer's disease
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Caloric restriction (CR) has been shown to slow aging. Here we test the novel hypothesis that the neuroendocrine cascade colloquially known as 'hunger' will ameliorate the pathology and cognitive deficits in the Tg-SwDI transgenic Alzheimer's disease (AD) mouse model. Three groups of 12 mice were used in this experiment. One group was fed *ad libitum* (control) while a second group (CR) was restricted to 80% of the control groups' diet. A third group (LY) was allowed the same intake as controls and was treated daily with the oral ghrelin agonist LY444711 (Eli Lilly) to induce mild chronic hunger. Treatment was started at 8 weeks of age and continued for 16 weeks. During the last 2 weeks of treatment mice were tested for cognitive functioning. All data were analyzed using ANOVA with Fisher's LSD for post hoc comparisons. Behavioral testing did not show differences among groups. Aβ deposition was not different among groups. Analysis using microglia as a marker of neuroinflammation revealed significant differences among groups [$F(2,34) = 5.967$, $p > 0.01$] however post hoc testing showed that only CR animals exhibited significantly less microglia than controls. In contrast, ELISA revealed significant differences among groups in amount of insoluble Aβ40, [$F(2,36) = 3.17$, $p = 0.05$], and Aβ42, [$F(2,36) = 5.291$, $p = 0.01$]. Post hoc tests indicate that the amount of Aβ proteins is higher in controls compared to both CR and LY animals. These results indicate that hunger itself may have some ability to attenuate the pathology associated with AD. Supported by: Alzheimer's of Central Alabama.

Linkages between biology, behavior, and environment in the development of obesity.
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While observational research suggests an association between obesity-related social and physical environment factors with obesity, very little research has addressed the specific factors and pathways linking the wider social and physical environment to obesity. Furthermore, investigations related to environmental influences on health behaviors are complicated by intricate relationship between preferences and choices related to outcomes of interest as people make choices about diet and physical activity based on biological conditions, innate preferences, and a wealth of other factors. For example, few studies directly address the fact that individuals who wish to engage in healthy lifestyles may choose healthy environments. Innovative statistical models that allow examination of each piece of the time-dependent, complex system are clearly needed. There are also differential susceptibilities to variation in environmental conditions that have not been adequately addressed. For example, there is little research on the complex interplay between genes and environment influencing weight gain across the lifecycle. Determining whether people are susceptible to different aspects of the environment may inform current efforts to curb the rising trend of obesity.

Lack of Evidence of Sucrose or Saccharin Addiction Based on Naltrexone Effects on Locomotor Activity

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There is some evidence that sugar can be addictive. For example, naloxone produced some signs of an opioid-like withdrawal in rats given cyclic exposure to sucrose or glucose. Locomotor activity is also thought to be sensitive to opioid withdrawal, in that opioid antagonism is more effective in reducing activity in rats receiving chronic or acute morphine than in opioid-naïve rats. We therefore placed rats on a schedule in which food availability was restricted to a 6 hr/day period that occurred during the dark portion of the light cycle. During this period, rats were given water, 0.1% saccharin solution, or 10% sucrose solution; only water was available for the remaining 18 hr/day. Locomotor activity was measured in 60 min sessions twice prior to the restriction schedule, and again on days 14 and 28 of the schedule. On these days, rats were given injections of saline or naltrexone (NTX, 3 mg/kg) 15 min prior to the session. During the final week of measurement, rats receiving sucrose or saccharin consumed significantly more fluid in the 6 hr period than rats receiving water, and the sucrose rats consumed significantly less food than the water or saccharin groups. On the final trial, NTX caused significant reductions in locomotor activity. However, there were no significant effects of fluid type or fluid x drug interaction. Under these experimental conditions, therefore, we found no evidence of an opioid-like withdrawal produced by cyclic access to sucrose/sweet solutions. Supported by NIDA R01DA021280 and NIDCR T32DE007288 Supported by: NIDA R01DA021280 and NIDCR T32DE007288.

Molecular adaptation in brain reward circuits in response to food restriction

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While manipulations of mesolimbic regions can alter food intake, it is not clear how these neuronal circuits adapt during relevant behavioral states. Likewise, while it has been widely recognized that food restriction enhances learning, motivation, and drug intake, the neural mechanisms underlying these behavioral changes are not well defined. To identify changes in gene expression that may mediate relevant behavioral plasticity, microarray analysis was completed after five days of food restriction. Gene expression was assessed within the hypothalamus, as well as three brain regions within the mesocorticolimbic circuitry, the ventral tegmental area, nucleus accumbens and the medial prefrontal cortex. Validated genes were

shown to be up-regulated across multiple brain regions, and time course studies suggest rapid and persistent induction following restriction. Pharmacological manipulations of corticosterone suggest that it is a key signal leading to changes in expression and that it can potentiate the motivation to seek food in a restricted state. Regulation of NF-kB components are of particular interest since this pathway is known to regulate inflammatory processes in cells, and can influence responses to drugs of abuse and stress. These data suggest stress-hormone mediated transcription as one mechanism by which the food restricted state leads to changes in animal behavior, including enhanced learning and motivation.

alpha-MSH reactive IgG are associated with delayed body weight recovery after MTX induced mucositis

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Methotrexate (MTX) chemotherapy induces mucositis, anorexia and body weight loss. Autoantibodies against the anorexigenic neuropeptide alpha-melanocyte-stimulating hormone (α-MSH) are involved in the physiological regulation of feeding. To investigate if mucositis may influence α-MSH autoantibodies production relevant to food intake and body weight, Sprague-Dawley rats received MTX 3 days (D1-D3), 2.5 mg/kg/day s.c. or saline as pair-fed and control groups.The serum levels of free and total IgG α-MSH were decreased at D5 during MTX-induced anorexia and mucositis while they were elevated at D19 after recovery.MTX group showed delayed body weight recovery by at least one week as compared to the pair-fed group and α-MSH IgG autoantibody levels correlated negatively with food to water intake ratios. The intraperitoneal injections of anti-α-MSH IgG (3 or 10 µg/day/rat) induced a dose-dependent attenuation of food intake and body weight regain in MTX-treated rats accompanied by increased concentrations of α-MSH peptide which correlated positively with plasma levels of α-MSH autoantibodies. Our data show that intestinal inflammation, independently from food restriction, affects general humoral immune response which may influence food intake and body weight control via modulation of α-MSH plasma concentration by α-MSH reactive autoantibodies.

Calorie Labeling on Restaurant Menus: A Useful Public Health Strategy for Obesity Prevention?

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The U.S. health care reform bill approved in March 2010 includes a national requirement for point of purchase calorie labeling at chain restaurants. Consequently, in the near future calorie information for restaurant menu items will be widely available to consumers. Will this information be noticed and used by consumers to choose lower calorie meals? Might restaurants improve the nutritional quality of menu offerings as a result of mandatory calorie labeling? Are there any potential unintended consequences? In this presentation findings from research conducted to date will be drawn upon to address these important questions. In addition, potential strategies for maximizing public health benefit of point of purchase calorie labeling in restaurants will be discussed, and future research needs will be described. Supported by: National Institute of Health, Robert Wood Johnson Foundation Healthy Eating Research Program.

Leptin responsiveness and insulin sensitivity are influenced by the availability of dietary choice independent of body fat or total fat or energy intake.

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Rats offered chow, lard and 30% sucrose solution (choice) are hyperphagic and rapidly become obese. They are resistant to peripheral and central leptin by Day 18, earlier than reported for rats fed a composite high fat diet. We compared leptin responsiveness and glucose tolerance in rats fed chow, choice, chow plus lard or chow plus 30% sucrose with those fed low fat (LFD: 10% kcal fat: Research Diets 12450B) or high fat (HFD: 60% kcal fat: Research Diets 12492) diet. Energy intake was highest in rats fed choice or chow plus sucrose. HFD rats ate less than choice rats, but the same as chow plus lard rats. LFD rats ate less than those fed HFD, but more than those fed chow. Energy consumed as fat was the same (59%) for rats fed chow plus lard as rats fed HFD. Chow plus sucrose rats consumed 60% of energy as sucrose. Energy intake of choice rats was 35% chow, 35% lard and 30% sucrose. On Day 18 an i.p. injection of 2 mg leptin /kg inhibited food intake and weight gain of all groups except choice or chow plus lard rats. Glucose clearance was the same for all rats during a glucose tolerance test (1 mg/kg glucose i.p) on Day 21, but insulin release was exaggerated in choice, HFD and chow plus sucrose rats. Carcass fat on Day 22 was greatest in choice rats. Carcass fat was the same for HFD, chow plus lard and chow plus sucrose rats, but higher than for LFD or chow rats. These results show that leptin responsiveness and insulin sensitivity are influenced by the form in which dietary components are offered, independent of energy intake, fat intake or body fat mass. Supported by: NIDDK grant DK053903.

Opposing effects of low dose leptin infusions into the 3rd or 4th ventricle on energy intake and body fat mass.

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Peripheral infusions of physiologic doses of leptin increase body fat in chronically decerebrate rats, implying that receptors in the hindbrain oppose the catabolic activity of leptin in the forebrain. To test this hypothesis, low doses of leptin were infused into the 3rd or 4th ventricle of Sprague Dawley rats for 12 days from Alzet pumps. As expected, 3rd ventricle leptin (0.15, 0.3 or 0.6 ug/day) inhibited food intake and reduced body fat. By contrast, 0.6 ug leptin /day in the 4th ventricle increased body fat by 20% without changing food intake. To test whether both 3rd and 4th ventricle leptin receptors influenced activity of peripheral leptin, rats were infused with PBS or 40 ug leptin/day from i.p. Alzet pumps and leptin receptor antagonist (leptin mutein protein: PLR Ltd) into the 3rd or 4th ventricle. Peripheral leptin reduced body fat by 25%. This was prevented by 2 ug mutein /day in the 3rd ventricle and 3 ug mutein /day increased body fat of leptin- and PBS-infused rats by 50%. Peripheral leptin reduced 12 day food intake by 6% and 3 ug mutein /day increased intake of PBS-, but not leptin-infused rats by 7%. By contrast, 4th ventricle mutein (1.5, 2.0 or 3.0 ug/day) exaggerated the inhibitory effect of peripheral leptin on food intake, but did not change leptin-induced fat loss. There was no effect of 4th ventricle mutein on food intake of PBS-infused rats, but 3 ug /day decreased body fat by the same amount as peripheral leptin. These data show that 3rd and 4th ventricle leptin receptors have opposing effects on body fat mass and energy intake of rats. Supported by: NIDDK grant DK053903.

Central and vagal mechanisms of glucagon-like-peptide-1 receptor-mediated suppression of food intake

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The glucagon-like-peptide-1 (GLP-1) system is important for energy balance regulation and glycemic control. The development of pharmacological, surgical, and behavioral treatments for obesity and type II diabetes will benefit from a deepened understanding of physiological mechanisms, GLP-1 receptor (GLP-1R) populations, and neuronal intracellular signaling pathways that mediate food intake inhibitory and incretin effects produced by GLP-1R ligands. While research supports a role for vagal GLP-1R signaling in energy balance control, the

presence of central GLP-1R in many nuclei critical to homeostatic- and non-homeostatic-regulation of energy balance highlights the need for research examining individual and combined contributions of vagal and CNS GLP-1R. Indeed, recent findings show intake inhibitory effects of GLP-1R agonists, exendin-4 and liraglutide, are mediated by activation of GLP-1R expressed on subdiaphragmatic vagal afferents and in the brain. Within the CNS, the nucleus tractus solitarius (NTS) is a site-of-action for endogenous GLP-1R-mediated control of feeding. NTS GLP-1R activation suppresses intake and body weight through coordinated intracellular signaling: PKA-mediated suppression of AMPK and activation of MAPK. Further, endogenous GLP-1 is synthesized by NTS proglucagon neurons that project locally and throughout the brain. Recent data show that direct NTS GLP-1 projections to the mesolimbic dopaminergic system may affect food intake by modulating the rewarding value of food. These findings suggest that peripheral and central GLP-1R offer great potential for obesity treatments. NIH-DK085435. Supported by: NIH-DK085435.

Exenatide regulates short-term control of food intake by different neuronal pathways.
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We have shown that exenatide, a synthetic agonist of glucagon like peptide-1 (GLP-1), reduces food intake by activating enteric and dorsal vagal neurons. Here, we investigated the role of various neuronal pathways in this reduction by exenatide. Five, overnight food-deprived, groups of rats (n=8 rats per group): vagotomy (VGX), celiaco-mesenteric ganglionectomy (CMGX, which destroys sympathetic / spinal afferent innervation to the gut), VGX/CMGX, duodenal myotomy (MYO, which destroys the enteric nervous system of the gut) and sham surgery received exenatide (0.5ug/kg, i.p) and the first meal size (MS, 10% sucrose solution) and intermeal interval (IMI, time between first and second meals) were determined. We found that (1) exenatide reduced meal size and prolonged IMI. (2) Vagotomy attenuated reduction of meal size by exenatide and (3) VGX, CMGX and MYO attenuated prolongation of the IMI. Therefore, these data suggest that reduction of meal size by exenatide requires an intact vagus nerve, but prolongation of the IMI requires intact vagus, sympathetic / spinal afferent and enteric nerves. **Supported by Amylin Inc. grant.** Supported by: Supported by Amylin Inc. grant..

Intragastric administration of the bitter agonist denatonium benzoate (DB) increases satiation in healthy volunteers.
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Aim: In mice intragastric administration of bitter receptor agonists decreased food intake (PNAS 108: p2094). We set out to investigate the effect of DB on satiation and intragastric pressure (IGP) during intragastric nutrient drink infusion in humans. **Methods:** 10 healthy volunteers were recruited in a blinded crossover study. After an overnight fast an infusion catheter and a manometry probe were positioned in the proximal stomach. After a stabilization period DB (±0.15 and 1 µmol/kg) or vehicle was infused intragastrically; 30 minutes later a nutrient drink (1.5 kcal/ml) was intragastrically infused at 60 ml/min. Satiation and gastrointestinal symptoms (e.g. nausea) were scored every minute. The experiment ended when subjects scored maximum satiation. Results are expressed as mean±S.E.M. and compared using ANOVA. **Results:** Volunteers did not report any symptoms after DB treatment, however satiation scores were increased during nutrient drink infusion (P=0.51 and 0.015 for 0.15 and 1 µmol/kg DB respectively). At maximum satiation the ingested volume after treatment with 0.15 µmol/kg DB (848±103 ml) and 1 µmol/kg DB (791±76 ml) was lower than after placebo treatment (920±74ml; P=0.06 and 0.02 respectively). IGP during nutrient drink infusion tended to be elevated after treatment with the highest dose of DB (P=0.25; n=6). **Conclusion:** The bitter agonist, DB, dose-dependently increased satiation and reduced the volume of nutrients ingested

upon maximal satiation. The contribution of bitter taste receptors (T2Rs) and changes in gastric motor physiology requires further investigation.

Peripheral Y_2 receptor activation inhibits gastric accommodation during intragastric nutrient infusion in rats.

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Aim: PYY_{3-36} inhibits food intake in rats. We set out to determine whether Y_2 receptors are involved in the regulation of gastric accommodation in conscious Wistar HAN rats by measuring the intragastric pressure (IGP) during intragastric nutrient infusion. **Methods:** After an overnight fast, a previously implanted gastric fistula was connected to a nutrient drink infusion system and a manometer to measure IGP (n=27). IGP was measured before and during the infusion of a nutrient drink (0.5 ml/min; 1.5 kcal/ml) until 10 ml was infused. Rats were treated with 0, 33 and 100 pmol/kg/min PYY_{3-36} (intravenous infusion during the whole experiment) in combination with the Y_2 receptor antagonists JNJ31020028 (JNJ; 10 mg/kg), BIIE0246 (2 mg/kg) or vehicle which were given subcutaneously before the start of the experiment. Tests were also performed after subdiaphragmatic vagotomy. IGP during nutrient drink infusion was compared by calculating the area under the IGP curve; data were represented as mean±S.E.M. and compared using ANOVA. **Results:** PYY_{3-36} elevated IGP during nutrient drink infusion (94±6, 114±10 and 146±14 mmHg.min for 0, 33 and 100 pmol/kg/min PYY_{3-36}; P=0.11 and 0.01 vs. placebo respectively). BIIE0246 and JNJ significantly suppressed the PYY_{3-36}-induced IGP increase during nutrient drink infusion (P<0.05 and <0.01 respectively). Also in vagotomized rats the effect of PYY_{3-36} was significantly inhibited by JNJ (P<0.05). **Conclusion:** PYY_{3-36} enhanced the IGP increase during nutrient drink infusion before and after vagotomy. Y_2 receptor antagonists decreased this IGP increase. These results indicate that PYY_{3-36} inhibits gastric accommodation during nutrient drink infusion through activation of peripheral Y_2 receptors and this might provide an alternative explanation for its effect on food intake.

Intragastric pressure is a major determinant of satiation.

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Aim: We previously showed a correlation between intragastric pressure (IGP) and satiation scores during intragastric nutrient drink infusion. Our aim is to investigate the relation between IGP and satiation during intragastric nutrient infusion while artificially increasing the IGP. **Methods:** In 11 fasted healthy volunteers an infusion catheter and a manometry probe were positioned in the proximal stomach. Using a custom-made system we could increase the pressure on the stomach (increasing the IGP) or on the lower abdomen (control; no effect on IGP). During the baseline period we determined the pressure on the stomach necessary to obtain an IGP increase of 5 mmHg (=maximum pressure applied; the same pressure was maximally applied on the lower abdomen). After a stabilization period a nutrient drink (Nutridrink; 1.5 kcal/ml) was intragastrically infused at 60 ml/min. The pressure on the stomach/abdomen was progressively increased during this infusion until the previously determined maximal pressure. The subjects scored satiation using a 6-point Likert scale until maximum, when the experiment ended. Results are presented as mean±S.E.M. and compared using a paired t-test. **Results:** At maximal satiation the volume nutrient drink ingested was significantly smaller when external pressure was applied to the stomach (939±71 ml) vs. the control situation (1084±75 ml; P<0.05). During nutrient drink infusion IGP increased significantly faster when external pressure was applied to the stomach (0.41±0.05 vs. 0.29±0.05 mmHg/60 ml respectively; P<0.05). However, the satiation score increase per mmHg IGP increase was similar in both groups: 0.85±0.09 vs. 0.84±0.10 satiation score point increase per mmHg IGP increase. **Conclusion:** We observed a

close correlation between IGP and satiation score increase. These observations indicate that IGP is a major determinant of satiation.

Toll-like receptor 2 is involved in sickness responses induced by acute inflammation in the brain

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Sickness responses such as anorexia, fever and hypoactivity are closely associated with inflammatory diseases. Especially, acute inflammation in the brain elicits a profound negative energy balance. Previous evidences have shown that a number of cytokines and pathogens induce sickness responses by activating inflammation in the brain. Moreover, recent studies have suggested that toll-like receptor 4 (TLR4) and MyD88 play critical roles for the mediation of anorexia and/or metabolic disorders induced in the acute and chronic inflammatory conditions in the brain. In this study, we tried to identify TLR2 action in the sickness responses induced by acute inflammation. Adult male mice were intracerebroventricularly injected with Pam3CSK, a synthetic TLR2 ligand, and change in their sickness behaviors was observed. Administration of Pam3CSK induced decreases in food intake, body weight and locomotor activity, but resulted in an increased body temperature. However, TLR2 and MyD88 knockout mice showed mitigated responses to the Pam3CSK injection. These results suggest that TLR2 might be a critical mediator of sickness responses to inflammation in the brain.

Melanin Concentrating Hormone (MCH) influences cue-driven food intake under conditions of satiety.

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We are bombarded with cues for food, such as signboards and media advertisements, which likely drive food intake and weight gain. From the perspective of associative learning, these cues can influence overeating by inducing endogenous appetitive states that enhance pleasurable sensations of food, and/or overriding cues for satiety that would normally induce meal termination. In the laboratory the influence of food-paired cues on intake can be assessed using the cue-potentiated feeding paradigm. In this task, mice are trained under food-restriction conditions to discriminate between presentations of a food-paired CS+ and an unpaired CS-. Mice then receive *ab-libitium* access to their maintenance diet prior to food consumption tests in the presence of the cues. Presentation of CS+ but not CS- leads to significant overeating during the test stage, suggesting that food-paired cues can drive food intake under conditions of satiety. While the neural structures and behavioral basis for cue-potentiated feeding have been characterized, the role played by neuropeptides is yet to be determined. Due to its expression in portions of brain circuitry responsible for this phenomenon, gene-targeted mice lacking the MCH-1R receptor underwent Pavlovian training followed by tests for cue-potentiated feeding. Notably, deletions of MCH-1R disrupted potentiation of feeding by the CS+. As a comparison we also examined intracranial 3CV disruption of MCH-1R, using pharmacological agents designed to antagonize the receptor. These results suggest MCH plays a role in both endogenous and exogenous controls of feeding. Supported by: NIDDK.

Intact Catecholaminergic Projections to the Forebrain Attenuate Diet-Induced Obesity and Contribute to the Maintenance of Normal Glucose Homeostasis.

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Hindbrain catecholamine-containing neurons provide extensive projections to many forebrain regions. They encode a variety of viscerosensory signals, including those essential for feeding and adrenocortical responses to glycemic challenges. Here we use an immunotoxin consisting of an antibody to dopamine-ß-hydroxylase (DBH) conjugated to saporin—a ribosomal toxin—(DSAP) to show that intact catecholaminergic projections help restrain the increased adiposity that can follow eating a high calorie diet. Male Sprague-Dawley rats (~300g BW) were injected with DSAP or mIgG-SAP (control) bilaterally into the paraventricular hypothalamic nucleus (PVH). Control and lesioned animals were then offered either chow (Teklad rodent chow 8604), or a high-calorie diet (Reseach Diets D12492 [60% fat/20% sucrose/20% protein] plus 30% sucrose solution) plus chow for 49 days. Mean 24h food intakes were determined for the final 5 days, and fasting glucose was determined in week 6. Lesions were assessed by examining the DBH innervation of the PVH. Lesioned animals showed significantly increased fasting blood glucose irrespective of diet, and markedly increased caloric intake, body weight, and abdominal adiposity compared to intact controls after consuming the high-calorie diet. This suggests that intact catecholaminergic projections to the forebrain significantly attenuate diet-induced obesity and are important for maintaining normal glucose homeostasis. Supported by: NS029728 and a JDRF research grant..

Leptin modulates sweet sensitivities in enteroendocrine STC-1 cells.
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Leptin is a multifunctional hormone that acts not only on central hypothalamic nuclei crucial for regulating food intake but also on peripheral various organs with different physiological functions. The taste organ is one of the peripheral targets for leptin and the hormone selectively suppresses sweet taste responses via its receptor, Ob-Rb expressed in taste cells. Recently, gut enteroendocrine cells are shown to express sweet taste receptors (T1R2/T1R3) and Ob-Rb and respond to sweet compounds followed by hormone release and glucose absorption. However, little is known about leptin effects on the responses. Here, we used enteroendocrine STC-1 cells and examined intracellular Ca^{2+} responses to sweet compounds and modulation of leptin on the responses. The results showed that Ca^{2+} responses to sweet compounds (glucose, sucralose, sucrose, SC45647) were selectively suppressed by leptin without affecting responses to bitter (denatonium) and umami (L-glutamate) compounds. Leptin suppression on sweet responses disappeared after treatment with a leptin receptor antagonist (L39A/D40A/F41A), suggesting the effect is mediated by leptin receptors. Responses to sweet compounds were suppressed by grumarin, a selective inhibitor for mouse sweet taste receptor (mT1R2/T1R3), suggesting sweet responses in STC-1 cells occurred through mouse T1R2/T1R3. These observations suggest a possibility that leptin may influence the sensing and the absorption of nutrients in the gut by modulating sweet sensitivities of the gut cells.

A mediation analysis predicting body fat percentage with sleep and disinhibited eating in women
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Recent studies indicate a U-shaped relationship between sleep duration and body fatness. There are several possible mechanisms explaining how sleep deficit may contribute to weight gain. Some studies indicate race and gender differences in this relationship. We examined sleep and eating patterns as predictors of body fat in women. This study of 206 non-eating disordered African American (47%) and Caucasian women examined the relationship of disinhibited eating (DE, Eating Inventory, ©1983) and self-reported hours of sleep to body fat percentage (BF%,

Tanita BC-418). Standard regression mixed models were evaluated with all participants (N=206) and only with those reporting <7.5 hours of sleep per night (n=144). BF% ranged 13-57. In those reporting <7.5 hrs/night, both increased DE (β= .413, *p*<.001) and fewer hours of sleep (β= -.23, *p*= .002) were significant predictors of increased BF%, *F*(2,143)= 20.68, p<.001. In the model including all women,*F*(2,205)= 26.26, p<.001, sleep (β= -.142, *p*= .025), as well as DE (β=.419, *p*<.001) was still a significant predictor of BF%. Shared variance (sleep and DE) = .011, (N=206). No race effect was observed. Women reporting fewer hours of sleep and higher disinhibited eating patterns had a higher BF%. The relationship between the two predictor variables appears to be largely independent. Treatment of sleep deficiency may facilitate weight management in women regardless of eating patterns that are also associated with increased weight. Supported by: not applicable.

Neurohormonal and dietary influences on hippocampal-dependent inhibitory controls of food intake

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Excessive food intake accompanying human obesity is generally not driven by metabolic need. Thus, it is critical to better define the neural basis of non-homeostatic controls of energy balance. Emerging evidence highlights the hippocampus, traditionally linked with learning and memory, as a forebrain structure of importance in the inhibitory control of food intake. The hippocampus integrates internal energy status signals (e.g., leptin, ghrelin) with previous behavioral experiences to modulate food-directed behaviors. In the absence of appetitive behaviors (e.g., satiety), the hippocampus functions to suppress the activation of food-related memories triggered by environmental cues. Consistent with this notion, selective hippocampal lesions increase appetitive responding to discrete and contextual cues previously associated with food, and ultimately increase energy intake and body weight gain in rats. This hippocampal-dependent inhibitory control of food intake is compromised by consumption of saturated fats and simple carbohydrates, both of which impair hippocampal-dependent memory function and increase behaviors directed at food procurement. Recent data show hippocampal subnuclei control of food intake and food-related memory inhibition is modulated by neurohormonal signals, such as leptin, that inform the brain about energy status. These findings support an anatomically distributed control of energy balance that extends beyond the hypothalamus and hindbrain and includes the hippocampus and other brain regions that control higher-order function. DK089752 and ECRG (The Obesity Society). Supported by: DK089752 and ECRG (The Obesity Society).

Food Branding and Childhood Eating Behavior and Obesity

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Food branding is a marketing strategy that creates strong emotional attachments with a food product logo in children as young as 2 years-old. Research from our laboratory suggests that children who are overweight are more responsive to food branding than non-overweight children, and they eat more when food brands are present than when they are not. In order to determine which children are more responsive to food brands, we created a Food Brand Based Stroop task to assess attentional bias toward common food brand images and tested this instrument in a diverse cohort of 7-9 year-old children (n=40). We also tested the relationship between children's response on the Food Brand Stroop task and their intake at laboratory buffet meals that were served with vs. without brand logos from a fast food restaurant. As predicted, children who were overweight showed an attentional bias toward food brand images, as evidenced by a longer response time on the Stroop task (p<0.05). In addition, response on the Stroop task was associated with an increased intake when foods were served to children packaged in containers

with a fast food logo ($p<0.05$), but was unrelated to intake at the unbranded condition. Because overweight children appear to be more responsive to food branding, other studies in our laboratory have begun to use food marketing strategies to increase intake of healthy foods, like fruits and vegetables. In an 8-week intervention, we have found that packaging fruits and vegetables in fun, child-friendly containers decorated with the child's favorite cartoon characters is a particularly effective strategy to increase intake of these foods. Future studies will determine the policy implications of these findings. Supported by: St. Luke's Roosevelt Hospital Pilot Grant Program.

Paradoxical roles for hypocretin (orexin) transmission in regulating drug consumption and feeding intake

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Hypocretin peptides 1 and 2, also known as orexin A and B, are lateral hypothalamic (LH) neuropeptides that are emerging as important regulators of reward and motivation. In particular, hypocretin systems are thought to play a key role in regulating food consumption to maintain energy balance, and also to regulate the motivation to consume drugs of abuse. Here, I will present new evidence, from rats and knockout (KO) mice with null mutation in the hypocretin-1 receptor (Hcrt-1-R), showing that Hcrt-1-R transmission plays a critical role in regulating nicotine and cocaine self-administration behavior, and cue-induced reinstatement of extinguished drug-seeking during periods of abstinence. As such, Hcrt-1 transmission likely plays a key role in drug addiction. In contrast to the diminished motivation to consume addictive drugs that we detected in Hcrt-1-R KO mice, we found that these mice demonstrated significantly greater motivation to seek and consume food. This enhanced food intake was detected most reliably when animals were tested under conditions of negative energy balance. Ongoing studies are seeking to clarify the underlying neurobiological substrates that regulate these dissociable roles for Hcrt-1-R transmission in drug and food seeking behaviors. Taken together, these findings demonstrate that Hcrt-1-R transmission is central to regulating drug intake, but that these receptors may actually protect against overconsumption of food in hungry animals.

Compound K induces GLP-1 release from the human enteroendocrine cell line NCI-H716

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Glucagon-like peptide-1 (GLP-1), a neuropeptide endogenously produced from L cells in the gastrointestinal tract, plays an important role in glycemic regulation and energy balance. Compound K (CK; 20-O-beta-D-glucopyranosyl-20(S)-protopanaxadiol) is an active metabolite of rotopanaxadiol-type saponins in the intestine after oral administration and is the major form of protopanaxadiol saponins of ginseng (*Panax ginseng* C.A. Meyer, Araliaceae) absorbed. The aim of this study was to investigate whether CK affected GLP-1 release in NCI-H716 cells. Prohormone convertase (PC) 3 gene regulating GLP-1 maturation was analyzed by RT-PCR. Effects of inhibitors for G protein-coupled receptor-related signaling components on CK-mediated GLP-1 release were studied. CK at the concentrations from 1 to 100 micromolar stimulated GLP-1 release in the cells dose-dependently ($p<0.001$). CK promoted PC 3 mRNA expression. The data suggested that CK showed its stimulation on GLP-1 release via the maturation of prohormone form of GLP-1. CK-stimulated secretion of GLP-1 was reduced when G proteins and TRPM5 were blocked with GDP-beta-S and triphenylphosphine oxide, respectively, suggesting that the secretion was activated by G-proteins and TRPM5. Supported by NRF 2010-0024475 and KFRI E0111503. Supported by: KRF and KFRI.

Effects of early postnatal environment on hypothalamic gene expression in OLETF rats

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Previous reports have shown that the early postnatal environment altered the obesity phenotype of Otsuka Long-Evans Tokushima Fatty (OLETF) rats. To determine whether this early postnatal environment affects hypothalamic signaling systems involved in energy balance, OLETF pups and lean control LETO pups were cross-fostered to same or opposite strain Dams (designated as LdLp: LETO pups with LETO dams; LdOp: OLETF pups with LETO dams; OdLp: LETO pups with OLETF dams; and OdOp: OLETF pups with OLETF dams) on postnatal day 1 (PND 1) and sacrificed at PND 23 or PND 90 for examination of hypothalamic gene expression. Rats had access to regular chow throughout the study. On PND 23, NPY gene expression was significantly increased in the DMH in both LdOp and OdOp pups compared to LdLp pups. DMH NPY expression did not differ between OdLp and LdLp pups. On PND 90, DMH NPY expression was significantly increased in both OdOp and OdLp rats, but was unchanged in LdOp rats compared to LdLp controls. In contrast to DMH NPY, gene expression for NPY and proopiomelanocortin (POMC) in the arcuate nucleus appeared to appropriately respond to alterations in body weight and plasma leptin levels. Together, our results demonstrate the effects of both genotype and early postnatal environment on obesity of OLETF rats and further suggest an important role of DMH NPY in the development of obesity of OLETF rats. Supported by: DK57609.

Lithium chloride induces nuclear activation of transducer of regulated CREB (TORC) in the rat hindbrain.

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Visceral or toxic stimuli such as lithium chloride induce c-Fos in the nucleus of the solitary tract (NTS) and parabrachial nucleus (PBN; e.g. Houpt et al. 1994). Induction of c-Fos can occur when the phosphorylated transcription factor cAMP response element-binding (pCREB) binds to the CRE in the c-Fos promoter. However, basal levels of pCREB are very high in the NTS and PBN even in the absence of stimulation(e.g. Houpt 1997). Therefore, the presence of pCREB is not sufficient for c-Fos induction. There are several additional factors that together with pCREB might lead to c-Fos induction after stimulation: activation of other transcription factors such as serum response factor (SRF); modification of histones by acetyl transferases such as CREB-binding protein (CBP); or recruitment of obligatory cofactors such as transducers of regulated CREB (TORCs). To test if an obligatory cofactor is recruited to the nucleus after LiCl stimulation, we examined TORC1 staining in the NTS and PBN of rats. Adult male Sprague-Dawley rats were injected with 12 ml/kg 0.15M LiCl (n=4) or NaCl (n=3). One hour following injection the rats were perfused and hindbrain sections processed for TORC1 immunohistochemistry (Cell Signaling). There was a significant elevation of nuclear TORC1 staining in the NTS 1 h after LiCl (159±8.5) compared to NaCl (93.4±15.2; $p<0.05$). No difference was found in nuclear TORC1 staining in the PBN. Thus, increases in nuclear TORC1 levels may act with pCREB to induce c-Fos in the NTS. We hypothesize that TORC1 is not synthesized upon neuronal activation, but instead is sequestered in the cytoplasm and translocates to the nucleus after stimulation. The high levels of TORC1 after NaCl injection and the failure of LiCl to increase nuclear TORC1 in the PBN suggests that additional factors may also regulate c-Fos expression. Supported by NIDCD T32-00044. Supported by: NIDCD T32-00044.

Leptin in Anorexia Nervosa: Relationship to Physical Activity and Weight Suppression

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Anorexia Nervosa (AN) is a life-threatening disorder of self-starvation. Multiple neuroendocrine abnormalities are known but the extent to which they are an effect and/or cause of starvation remains unclear. We investigated clinical correlates of leptin levels in patients with AN. Methods: Forty-four women with AN had fasting serum leptin levels measured both before and after beginning inpatient weight restoration therapy. Physical activity was monitored twice using an accelerometer, and Weight Suppression was calculated as the difference between lifetime highest weight and current weight. Results: Leptin levels at weight restoration ranged from 0.2 to 33.5 ng/ml, despite similar BMI across patients. Leptin measured at weight restoration was inversely associated with both physical activity measures and weight suppression. Leptin level at weight restoration itself significantly predicted resumption of menses. Conclusions: Data are preliminary, but suggest that patients with AN may have different physiological "set-points," as reflected by menstrual status, depending on lifetime highest weight. Hypoleptinemia appears to be a marker of, and may also serve to perpetuate, behavioral and physiological dysregulation in AN. Implications for further research and treatment are discussed. Supported by: NARSAD, NIMH.

Energy Deficits Dissociate Motivation from Performance and Reward

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Animals switch their behavioral priorities from ingestive to sex behavior to optimize reproductive success in environments where energy availability fluctuates. We hypothesized that energy availability differentially affects each of the components of behavior: motivation, performance, and reward. In Syrian hamsters (n=16), 7-11 days of 25% food restriction significantly affected the motivation for food and sex by increasing food hoarding and decreasing vaginal scent marking and the preference for spending time with male hamsters, but had no significant effect on performance (food intake and lordosis). A similar level of food restriction failed to dissociate sexual motivation from sexual reward (as measured by the formation of a conditioned place preference (CPP)). The formation of a CPP to mating is reflected in the nucleus accumbens (NAc) as increased neural activation of the immediate early gene, c-fos. Mating-induced neural activation in the NAc did not differ between food-restricted and fed hamsters (n=24). Both food-restricted and ad libitum-fed females formed a CPP in response to 4 copulatory experiences despite the fact that food restriction significantly inhibited sexual motivation (n=24). Together these data are consistent with the idea that mild food restriction inhibits sexual motivation while it fails to attenuate sexual performance and the rewarding consequences of mating. This likely ensures vigilant food hoarding in preparation for possible reproductive opportunities during the more fertile periods of the females' estrous cycle.

Hydration state controls stress responsiveness and social behavior.

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To test neural mechanisms underlying stress integration within the context of homeostatic adversity, we evaluated the impact of a pronounced physiological (hypernatremia) challenge on hypothalamic-pituitary-adrenal (HPA), cardiovascular and behavioral responses to an acute psychogenic stress. Relative to normonatremic controls, rats rendered mildly hypernatremic had decreased HPA activation in response to physical restraint, a commonly used rodent model of psychogenic stress. In addition, acute hypernatremia attenuated the cardiovascular response to

restraint and promoted faster recovery to pre-stress levels. Subsequent to restraint, hypernatremic rats had significantly more c-Fos expression in oxytocin and vasopressin containing neurons within the supraoptic and paraventricular nuclei of the hypothalamus. Hypernatremia also completely eliminated the increased plasma-renin-activity that accompanied restraint in controls, but greatly elevated circulating levels of oxytocin. The endocrine and cardiovascular profile of hypernatremic rats was predictive of decreased anxiety-like behavior in the social interaction test. Collectively, the results indicate that acute hypernatremia is a potent inhibitor of the HPA, cardiovascular and behavioral limbs of the stress response. The implications are that the compensatory responses that promote renal-sodium excretion when faced with hypernatremia also act on the nervous system to decrease reactivity to psychogenic stressors and facilitate social behavior. Supported by: : NIH HL096830 (EGK) AHA 09PRE2250169 and NIH F31 NS068122 (ADdK) NIH DK66596-05A2S1 (RRS) NIH DK66596 (RRS) NIH MH49698 (JPH) .

Pleasure principles for food intake

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The hedonic component of eating is an underexplored topic within neuroscience, which is surprising given its importance for our survival and general well-being, as well as the obvious links to obesity and eating disorders. Based on findings from animal models and human neuroimaging, this lecture will give an overview of established principles, neural mechanisms and functional neuroanatomy of the primate and human brain processing systems involved in controlling eating. This overview will survey topics related to food intake including subjective pleasure versus objective hedonic reactions; pleasure cycles and satiety cascades; liking, wanting, and learning components of reward; subcortical hedonic hotspots for pleasure generation; and the role of higher cortical regions such as the orbitofrontal cortex.

Modulation of taste sensitivity and feeding by Oral PYY signaling

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Recent findings suggest that the gustatory system shares a number of common features with the gastrointestinal system. Indeed, many metabolic polypeptides have been shown to be expressed in taste cells (TCs) or to be present in saliva. Peptide YY (PYY) is a satiation hormone released postprandially into the bloodstream from enteroendocrine L-cells in the gut epithelia. We recently reported that PYY_{3-36} is also present in the oral cavity, in particular in saliva. In addition, we found that 1) PYY is synthesized in the TCs and 2) that Y receptors are abundantly expressed in the tongue epithelia as well as in the salivary ducts of the Von Ebner's gland. The objective of the current report was to investigate whether PYY_{3-36} modulates taste perception and/or food intake. In a PYY KO mice model we showed that PYY modulates taste sensitivity. Experiments are under way to extend these findings in a WT mouse model and to map PYY-positive taste cells in the circumvallate papilla using GFP as a surrogate marker for PYY. We also chronically augmented salivary PYY in mice and these animals lost a significant amount of body weight. In summary, these data suggest a role for PYY signaling in the modulation of taste sensitivity and suggest that this system could be targeted as an alternative therapeutic approach for the treatment of obesity. Supported by: NIDCD (P30 DC010763) and, in part, by the Children's Miracle Network Foundation..

Modulation of gastrin-releasing peptide signaling by neuropeptide Y.
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We, and others, found that the ability of peripherally administered cholecystokinin to suppress feeding and induce hindbrain c-fos activation was blunted by prior central administration of neuropeptide Y (NPY). To evaluate whether this generalized to other peripheral satiety signals, we examined the effect of NPY pretreatment on gastrin-releasing peptide (GRP)-induced feeding suppression and c-fos activation. Male Sprague-Dawley rats (n=11) with third ventricular (3V) cannulas were the experimental subjects. Food was removed 5 h before the start of the experiment and rats received either 3V 0.9% saline or 1.0 nmol NPY 2 h prior to lights out. At lights out, rats were given either ip 0.9% saline or GRP18-27 (10, 32 and 100 nmol/kg). Food was immediately returned and intake was measured 15 and 30 min after food access. To determine the effect of NPY pretreatment on GRP-induced neuronal activity, c-fos activation was examined in the NTS after 3V NPY (1.0 nmol) given 2 h prior to ip administration of 32 nmol/kg GRP18-27. Our results showed that GRP18-27 produced a dose-related suppression of food intake in both the presence or absence of NPY ($p<0.05$). While there was a trend towards reduced suppression with NPY pretreatment, it did not reach statistical significance. However, 3V injection of NPY significantly reduced the number of c-fos positive nuclei in the NTS induced by ip GRP18-27 ($p<0.05$). These data suggest that GRP signaling can be modulated by NPY pretreatment and further supports an interaction between brainstem responses to peripheral satiety signals and signals involved in energy balance. Supported by: DK19302.

Peripheral glucagon-like peptide-1 (GLP-1) in energy homeostasis
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Enteroendocrine L-cells release GLP-1 in response to luminal nutrient (primarily carbohydrate and fat) stimulation. GLP-1 receptors (GLP-1R) are expressed in the periphery and in brain areas implicated in the regulation of energy homeostasis. GLP-1 has potent insulinotropic and glucoregulatory effects, and peripheral administration of GLP-1 inhibits eating. This may reflect a physiological satiating function of endogenous GLP-1, but the exact stimuli of GLP-1's release and the site(s) and mechanism(s) of its action are unresolved. Data collected in our laboratory indicate that: 1) high fat meals are a more potent stimulus for intestinal GLP-1 release in rats than isocaloric low fat meals, as measured by changes in intestinal lymph GLP-1 levels; 2) intestinal triglyceride re-synthesis directly or indirectly modulates dietary fat-induced GLP-1 release; 3) hepatic degradation prevents a systemic increase in endogenous GLP-1 during chow meals in rats; 4) the area postrema and hindbrain GLP-1R activation are involved in mediating a possible endocrine eating-inhibitory effect of GLP-1, whereas abdominal vagal afferents are involved in its putative paracrine satiating action; and 5) GLP-1 can promote adipocyte proliferation and triglyceride synthesis through a direct, GLP-1R-mediated effect. Further studies should a) examine under which conditions a systemic endocrine or a local paracrine action of GLP-1 in the intestine is physiologically relevant for satiation, b) identify the neural mechanisms mediating these effects, and c) test whether GLP-1 released into the intestinal lymph may have direct access to intra-abdominal adipose tissue. Supported by: ETH Zurich.

TRPM5 KO-mice develop less insulin resistance compared to wt-mice after diet induced obesity
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TRPM5 is a Ca^{2+} activated cation channel with a central role in taste signaling, acting downstream of taste receptors. This system is also found in the gut, where taste receptor activation has been shown to regulate GLP-1 release and glucose homeostasis. In addition TRPM5 is found in pancreatic b-cells. The aim of the present study was to investigate the effects of TRPM5 gene knock out on body weight, insulin sensitivity and other metabolic parameters in diet induced obesity. Two experiments were performed in female mice, one where TRPM5 KO mice and wild type (WT) littermates were fed a café diet (chocolate ball, chocolate bar, nougat and cheese) for 40 weeks (n=5-8), and a second experiment where KO and WT mice were fed a 60% high fat diet for 39 weeks (n=13-15). An oral glucose tolerance test was performed at the start of the experiment and after 21, 27 (exp 1) and 37-39 w on the diet. In exp. 2 food intake was followed at w1, w6 and w13. Both WT and KO mice became obese on the diets, but KO mice gained significantly less body weight and fat mass although no difference in food intake could be demonstrated. The TRPM5 KO mice showed increased insulin sensitivity, which was largely independent of body weight. At termination the KO mice had significantly reduced brown adipose and liver weight as well as lower liver triglycerides. The main finding is the clearly improved insulin sensitivity in TRPM5 KO mice compared to wild type mice on café diet, which to a large degree is independent of body weight. When on a high sugar containing diet TRPM5 KO mice are less diabetic prone, suggesting a role for TRPM5 in diet induced insulin resistance. Supported by: AstraZeneca R&D, Molndal, Sweden.

Eating-Inhibitory effect of the PPAR-α agonist Wy-14643 in rats

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Peroxisome proliferator-activated receptor-α (PPAR-α) is implicated in the regulation of absorption, storage and utilization of dietary fats. PPAR-α agonists are used as hypolipidemic drugs and have been shown to reduce food intake through as yet unknown mechanisms. We investigated the effect of the synthetic PPAR-α agonist Wy-14643 on food intake in rats and started to characterize its mechanism of action. Wy-14643 was injected (40 mg/kg body weight) through intraperitoneal catheters at the onset of the dark phase in male, adult Sprague-Dawley rats fed a high fat (49 kcal% from fat) diet ad libitum. Food intake was recorded automatically for 12 h and analyzed for meal patterns (meal size, duration and frequency). Wy-14643 reduced food intake through an increase in the latency to eat and a decrease in first meal size, without affecting subsequent parameters. Wy-14643 did not induce a taste aversion in a two-bottle preference test of saccharine solution vs. water. In addition, Wy-14643 induced an increase in the number of c-Fos protein expressing cells in the area postrema (AP), the nucleus tractus solitarii (NTS) and in the hypothalamic paraventricular nucleus (PVH), but not in the hypothalamic arcuate nucleus and the central area of the amygdala. The results suggest that Wy-14643 enhances both satiety and satiation without causing illness through an eating-inhibitory neuronal network involving the AP, NTS and PVH, which may be recruited by direct actions on the AP or through a peripheral action and afferent nerve signaling.

A delivered satiating claim influences short-term appetite in high disinhibited low restraint women without influence on food intake

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The relationship between food behaviour and perceived food label is often unclear as it could vary according to individual differences. Several studies showed conflicting results. The aim of our work was to evaluate the psychological influence on satiety of a message delivered before eating and to analyze whether this result will vary according to volunteers' disinhibition and

restraint levels. In a crossover randomized design, 81 lean women attended the laboratory on 2 days to test the same control biscuit as a fixed breakfast with either a satiating or a control claim. Five groups of subjects were recruited according to their combined restraint and disinhibition scores, including high restraint high disinhibited (HRHD), low restraint low disinhibited (LRLD), high restraint low disinhibited (HRLD) and low restraint high disinhibited (LRHD). There was no significant effect of the satiating claim on food intake at the next meal. However, concerning appetite sensations, LRHD group had both lower desire to consume 2.5h and 3h after breakfast and lower prospective consumption 3h after breakfast with the satiating claim. Independently of the message, appetite, prospective consumption and desire to eat were higher for HD vs. LD volunteers. These results showed a claim effect on appetite for LRHD women who might be the more receptive to environmental cues. This conclusion highlights the importance of high disinhibition scores on appetite sensations.

Food ads increase snack eating but not meal eating.

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Two studies were performed to evaluate the effects of viewing TV ads on food intake. The first study (n=30) assessed the influence of television commercials on food consumption in a lunch meal setting. Undergraduates at Cornell University were asked to evaluate three television advertisements on three separate days separated by one week. The video's were either TV advertisement depicting (1) people eating food, (2) food was present but not consumed, or (3) car commercials. The participant completed a short survey following each video. Following this exercise, lunch was served and measured. The particular video watched had no effect on the consumption of the lunch. The second study (n=28) was performed that was quite similar to the previous study, but used only the food ad and the car ad and instead of feeding lunch, provided commercial snacks while the participants evaluated the ads. Viewing food ads significantly increased the amount of snack food consumed ($p<0.04$). It appears from these data that eating snacks is more vulnerable to the priming effects of watching food ads than is meal eating.

Synphilin-1 activates AMPK via ATP binding

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Synphilin-1 is a cytoplasmic protein enriched in brain with unclear function. We recently generated a human synphilin-1 transgenic mouse model that displays some key features of obesity including increased food intake, body weight and body fat. To investigate the molecular basis of synphilin-1 in controlling food intake and body weight, we have used in vitro cultured neuronal cell systems. We generated a stable pool of N1E-115 cells expressing human synphilin-1. We found that over expression of synphilin-1 significantly increased AMP-activated kinase (AMPK) phosphorylation and cellular ATP levels. Activation of AMPK in hypothalamic sites can play a role in reducing food intake. Furthermore, synphilin-1 bound with ATP. To map potential sites of these interactions on the synphilin-1 protein, we identified 5 predominate ATP binding sites. Site mutagenesis was used to alter amino residue, K to A in each of these five binding sites. The resulting construct reduced synphlin-1 binding with ATP, almost totally blocked synphilin-1-induced AMPK activation, and decreased ATP levels. These data suggest that synphlin-1 is an ATP binding protein and regulates AMPK activity via ATP binding. These studies may provide novel insights into synphilin-1's biological functions and potential mechanism for affecting energy balance.

Combinations of the GLP-1 agonist exendin-4 and the opioid antagonist naltrexone inhibit food intake to a greater degree than either alone.

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The glucagon-like peptide-1 (GLP-1) analog exendin-4 (Ex4) and the opioid receptor antagonist naltrexone (Nal) respectively affect food intake via the energy homeostasis feedback control and reward systems. This study examined the effects of individual or combined doses of Ex4 (0, 1, 3.2, and 10 μg/Kg) and Nal (0, 0.32, 1, 3.2 mg/Kg) on food intake in male Sprague-Dawley rats (n=8). On a test day, food was removed 4 hrs before the onset of the dark cycle. An ip injection of a dose of individual or combined drugs was given 15 min before lights out. Food was returned to rats immediately at dark onset. Food intake was measured at 1, 4, and 20 hrs. The results revealed significant dose dependent suppressions of food intake when Ex4 or Nal was administered separately. Surface plots of hourly intake indicated a synergistic interaction at lower doses of Ex4 and Nal during the first 4 hrs of feeding and additive effects during 20 hrs. Furthermore, the effects of consecutive administration of Ex4 (3.2μg/Kg) and Nal (1mg/Kg) combination on food intake were tested when the rats became obese. Such dose combination produced a synergistic reduction in food intake. These results suggest that simultaneously targeting homeostatic and reward systems maybe an effective method to reduce food intake and body weight. Supported by NIH grant DK19302.

Expression of the fatty acid sensors, CD36, GPR119 and GPR120, in the duodenum of humans: relationships with obesity.

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The molecular mechanisms underlying gastrointestinal (GI) fatty acid (FA) sensing are unclear. In animal and cell-line models the G-protein coupled receptors, GPR119 and GPR120, are expressed on enteroendocrine cells, where their activation mediates FA-induced GI peptide secretion. The FA sensor, CD36, which is expressed on enterocytes in the proximal small intestine, also plays an important role by mediating FA absorption and subsequent mobilisation of oleoylethanolamine, which reduces food intake and body weight in rodents. The expression of these FA sensors in the human intestine has not been well characterised. Here, we investigated duodenal expression of CD36, GPR119 and GPR120 in humans and explored relationships between their relative expression and body mass index (BMI). Duodenal biopsies were obtained from 11 patients (BMI: 27.2±2.2, age: 50.5±5.4)) undergoing surveillance endoscopy. RNA was extracted from the tissues and the expression of CD36, GPR119 and GPR120 transcript calculated relative to β-actin using RT-PCR. GPR119, GPR120 and CD36 were found in the duodenal biopsies indicating that they all are expressed in human small intestine and, thus, may play a role in intestinal fat sensing in humans. In addition, CD36 expression, in particular, was positively related to BMI (R^2=0.6, P<0.05). Our data, therefore, suggest that CD36 expression is modulated by body weight and may be involved in mediating the changes in GI fat sensitivity that have recently been established in obesity. Supported by: Grant funding..

A novel obesity model: human Synphilin-1 transgenic Drosophila

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Obesity and its related disorder are increasing at an alarming rate worldwide. The molecular mechanisms underlying obesity remains incompletely understood. Here we generated a

transgenic Drosophila model, in which overexpression of human synphilin-1 induced obesity-like phenotypes. Synphilin-1 is a cytoplasmic protein and interacts with alpha-synuclein and other proteins and has implication in Parkinson's disease. In this study, we used UAS/GAL4 system to express human synphilin-1 in various fly neurons that regulate energy balance, including fruitless-gal4, dopaminergic, serotonergic and pan neurons. We also expressed human synphlin-1 in fat body and insulin-like peptide secretory cells in flies. We found that expression of human synphlin-1 significantly increased fly body weight in female flies compared with non-transgenic controls. Moreover, synphilin-1 increased the size of fat body cells in the 3rd larvae stage, indicating that synphlin-1 increased lipid-fat disposition in flies. Behavioral studies showed that synphilin-1 transgenic flies increased food intake and are resistant food deprivation. These results demonstrated that human synphilin-1 regulates food intake and body weight in flies. The synphilin-1 transgenic drosophila can be a valuable model for future pathogenesis and therapeutic studies. Supported by: NIH.

Cholecystokinin knockout mice are resistant to high-fat diet-induced obesity

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Background & Aims: Cholecystokinin (CCK) is a satiation peptide released during meals in response to lipid feeding and regulates pancreatic digestive enzymes vital to the absorption of nutrients. We hypothesized that mice lacking the CCK gene and fed a 20% butter diet fat would have alterations of fat metabolism. **Methods:**We used quantitative magnetic resonance imaging to determine body composition and monitored food intake of CCK knockout (CCK-KO) mice in an automated measurement system. Additionally, intestinal fat absorption and energy expenditure were determined by utilizing a non-invasive assessment of intestinal fat absorption and an open circuit calorimeter, respectively. **Results:** After consumption of a high-fat diet for 10 weeks, CCK-KO mice exhibited reduced body weight gain and body fat mass, and enlarged adipocytes, despite normal food intake. CCK-KO mice had defective fat absorption, especially for long-chain saturated fatty acids, but pancreatic triglyceride lipase (PTL) did not play a critical role in the fat malabsorption. Energy expenditure was higher in CCK-KO than wild-type (WT) mice, and CCK-KO mice displayed greater carbohydrate oxidation during high-fat feeding. **Conclusion:** We conclude that CCK is involved in regulating metabolic rate and is important for lipid absorption and the control of body weight during high-fat feeding. Supported by: NIH NIDDK.

Central GLP-1 receptor signaling directly controls brown adipose tissue thermogenesis

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Proglucagon gives rise to a number of biologically active peptides by site specific posttranslational processing. GLP-1, oxyntomodulin (OXM) and glucagon have all been implicated in controlling energy balance. OXM binds to both the GLP-1 and glucagon receptors (GLP-1R and GCGR) and little is known about which receptor mediates its effects. Chronic administration of GLP-1, OXM or a soluble, anionic glucagon full agonist (IUB94) into the lateral ventricle via osmotic minipump significantly decreased body weight. Acute ICV administration of all peptides significantly increased both activity of the sympathetic nerves innervating the interscapular brown adipose tissue (BAT) and BAT temperature. The effect of OXM on BAT thermogenesis persisted with chronic ICV infusion in WT mice, an effect absent in GLP-1R KO mice, showing the effect is dependent on GLP-1R signalling. Chronic ICV infusion of OXM did not

affect peripheral insulin sensitivity measured by euglycemic-hyperinsulinemic clamp. These data demonstrate a role for central GLP-1R and GCGR signalling in controlling BAT thermogenesis. Our results suggest that the increase in non-shivering thermogenesis may contribute to the anti-obesity benefits of therapies based on GLP-1R and GCGR agonism.

Sucralose preferring and avoiding rats perceive the taste of sucralose as qualitatively different

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Sucralose, an artificial sweetener, elicits a robust bimodal preference response in rats. About 70% of rats tested in a two-bottle preference test display clear avoidance responses to concentrations ≥ 0.01g/L (sucralose avoiders, SAs), while the remaining rats display preferences over water at these same concentrations (sucralose preferrers, SPs). It is unclear, however, whether the functional basis underlying these different phenotypes relates to the qualitative perceptual properties of sucralose or only its evaluation by so called “reward” circuits. In humans, some artificial sweeteners elicit bitter side tastes depending on concentration and some bind with members of the T2R taste receptors that are activated by bitter tasting ligands. To test the hypothesis that SAs and SPs differ with respect to their perception of a quinine-like taste quality of sucralose, we trained SPs and SAs in a two-response operant taste discrimination task to lick one response spout if the sampled stimulus was sucrose and a different response spout if it was quinine hydrochloride. We then assessed which response spout the rats licked when given nonreinforced test trials with sucralose. SPs treated sucralose as if it were perceived as more sucrose-like, and thus less quinine-like, compared to SAs, with this difference peaking at the 16.0 g/L concentration (91.7% ± 8.2 & 51.8% ± 15.0, respectively; P <0.05). We conclude that SAs and SPs perceive the taste of sucralose differently, which likely contributes to the difference in their preference phenotype.

Differential neuronal encoding in the nucleus accumbens is associated with behavioral indices of conditioned taste aversion learning.

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Our lab has found that, in a Pavlovian conditioned taste aversion (CTA) paradigm, responses of NAc neurons encode the change in hedonic value of a taste stimulus. Here, we tested whether the NAc could track the hedonic value of cues associated with taste stimuli gradually made aversive through CTA learning. Rats (n=10) were trained to press one of two levers for an intra-oral infusion of either orange- or grape-flavored sucrose. Different cues (tones) preceded each lever presentation. During conditioning, only one cue-lever-flavor combination was presented on each day, followed by an injection of either LiCl or saline. After conditioning (6-10 sessions), rats were tested in a session in which both cue-lever-flavor combinations were presented pseudo-randomly. During all sessions the electrophysiological activity of single NAc neurons was recorded. While operant responding for both flavors was equally high at the beginning of the conditioning sessions, responding for the LiCl-paired flavor significantly decreased by the end of training in 9 of the 10 rats. Likewise, during the test session rats avoided responding on the LiCl-paired lever and preferentially responded for the saline-paired flavor. Initial electrophysiological results suggest the NAc differentially responds to the two cues after conditioning and during the test session - where the saline-paired cue evoked significantly more activity relative to the LiCl-paired cue. This differential activity may direct behavior towards ‘safe’ flavors and away from ‘harmful’ ones. Supported by: UIC Chancellor's Supplemental Graduate Research Fellowship (ALL) DA025634 (MFR).

Current Dieters Consume Fewer Beverage Calories – but Not Fewer Food Calories – Than Unrestrained Eaters in the Natural Environment

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Restrained eaters do not consume fewer calories than unrestrained eaters in the natural environment. However, current dieting to lose weight has been shown to be conceptually and empirically distinct from restrained eating. We compared the naturalistic caloric intake of four groups: Current weight loss dieters (CDs), those currently dieting to prevent weight gain(CD-P), restrained eaters who are not currently dieting (R-ND), and unrestrained non-dieters (UR-ND). It was predicted that there would be a significant difference in nutritional intake among the four groups, with energy intake lowest in CDs and highest in UR-NDs. Analyses were performed with 293 freshman females enrolled in a weight gain prevention study. Scores on the TFEQ Cognitive Restraint scale, current dieting status, and three 24-hour food recalls were collected at baseline. For total daily intake, results were in the expected direction, but were not statistically significant. CDs reported the lowest caloric intake (M=1530.25, SD=417.98), followed by CD-Ps (M=1590.93, SD=552.60), RNDs (M=1666.20, SD=462.22), and UR-NDs (M=1686.75, SD=430.34). A significant difference was found for calories from beverages only, (F(3,131)=4.71, p=.004): CDs consumed fewer beverage calories (M=197.22, SD=134.20) than UR-NDs (M=336.75, SD= 183.24). These are the first results indicating a relationship between self-reported restrained eating or dieting and measured caloric intake. The findings suggest that modifying beverage intake may be a relatively easy way to reduce energy intake to lose weight. Supported by: NIH.

Hemopressins are novel peptide ligands at CB_1 cannabinoid receptors that can act centrally to affect appetite

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Hemopressin (Hp) is a short, nine-amino acid peptide, derived from the alpha chain of haemoglobin, which has previously been shown to cause negligible decreases in blood pressure and to have non-opioid antinociceptive effects (Heimann *et al*., 2008). We have since shown that injection of Hp causes a decrease in normal, night-time feeding via CB_1 receptors, without disrupting the behavioural satiety sequence and without causing any obvious adverse events (Dodd *et al.*, 2010).Thus, the hypophagic response is lost in $CB_1^{-/-}$ mice. Here, we present data from both functional MRI in rats and functional immunohistochemistry in mice, to demonstrate sites of action of Hp within the brain, including the hypothalamus and the periaquaductal grey. Interestingly, a slightly extended form of the peptide, RVD-Hp, has recently been discovered in the rodent brain (Gomes *et al*., 2009). We used cells transfected with GFP-tagged CB_1 receptor to show that while Hp behaves *in vitro* as a receptor inverse agonist, RVD-Hp acts as an agonist. To date, however, *in vivo* feeding experiments using RVD-Hp have proved inconsistent. Dodd *et al*., J Neurosci, 30: 7369-7376 (2010) Gomes *et al*., FASAEB J, 23: 3020-3029 (2009) Heimann *et al*., Proc Natl Acad Sci, 104: 20588-93 (2007) Supported by: BBSRC.

Energy state cues overshadow auditory cues for the discriminative control of behavior.

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Previously we showed that rats can use interoceptive stimuli arising from different levels of food deprivation as signals for the delivery of appetitive reinforcement. These cues have been shown to have sensory properties that generalize to stimuli produced by hormonal manipulations that

promote (e.g., Davidson et al, 2005) or inhibit (Kanoski, et al, 2007) food intake. Furthermore, the ability of rats to solve such "food deprivation intensity discriminations" depends on functional integrity of the hippocampus (Davidson et al, 2010). The goal of the current study was to assess the ability of interoceptive food deprivation intensity stimuli to compete with exteroceptive auditory cues for the discriminative control of appetitive conditioned responding. We trained rats to use interoceptive cues (0- and 24-hr food deprivation) and distinct auditory stimuli as compound discriminative signals for delivery of sucrose pellets. After asymptotic discrimination performance was achieved, the rats were tested in extinction with only deprivation intensity cues. Next, the rats were tested on trials in which the identity of the auditory cues that were paired with deprivation cues were either the same or the opposite compared to original training. The results of these tests showed that learned control by deprivation intensity cues strongly overshadowed that by auditory cues. This outcome is consistent with the view that learning about deprivation cues and auditory stimuli involve the establishment of different types of associative relationships. Supported by: R01 HD 028792.

CD36 is regulated by dietary lipids in mouse circumvallate papillae: impact on spontaneous fat preference

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Recent data of our lab indicate that lingual CD36 is a gustatory lipid-sensor involved in the preference for fat in the mouse. CD36 gene expression is regulated by lipids in different tissues such as the intestine, adipose tissue or muscle. The aim of this study was to determine if lingual CD36 is also regulated by dietary lipids in the mouse circumvallate papillae (CVP) and the impact on fat preference. Using mice subjected to different nutritional status, we showed that CD36 mRNA levels are down-regulated during the dark period compared to the light period.This change is related to the food intake and is lipid-dependent.CD36 protein levels are also down-regulated by the food intake and it is a rapid but transient regulation. Indeed, there is a 2-folddrop in CD36 protein levels 1h after refeeding compared to fasted controls, followed by a progressive return to the fasting levels. To explore whether CD36 protein levels can affect fat preference, $CD36^{+/+}$, $CD36^{+/-}$and $CD36^{-/-}$mice were subjected to a short term double-choice preference test. Linoleic acid preference found in $CD36^{+/+}$ animals was fully abolished not only in $CD36^{-/-}$ mice but also in $CD36^{+/-}$ animals in which CD36 protein expression is 2-fold lower in CVP compared to wild-typemice. These data suggest that CD36 protein down-regulation by the food intake seems sufficient to affect fat preference. As a lipid-sensor, CD36 might modulate the motivation for fat during a meal. This short-term effect is reminiscent of sensory-specific satiety. Supported by: French Research Agency (ANR) and Vitagora cluster (SensoFAT project to P.B.) and the Burgundy Council and Centre National Interprofessionnel de l'Economie Laitière (CNIEL) (HumanFATaste project to P.B.

Impact of long chain fatty acids on sweet taste sensitivity in mice: role of the GPR120/GLP-1 signaling

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GPR120 was identified as a candidate for oral lipid detection. It's a receptor abundantly expressed in gut endocrine cells. Its activation by long chain fatty acids (LCFA) induces the release of glucagon-like peptide-1 (GLP-1). GPR120 is also expressed in rodent taste buds. In an interesting way, GLP-1 and its receptor are found in mouse tongue and GLP-1R KO mice have a reduced sweet taste sensitivity. The goal of our work was to determine if there is a functional link between LCFA, GPR120 and GLP-1 in the tongue and the impact of this system on sweet taste

sensitivity in the mouse. By immunohistochemistry, we showed that GPR120 and GLP-1 are co-localized in the circumvallate papillae (CVP). Moreover, the stimulation of CVP explants in culture by LCFA or a specific GPR120 agonist induced GLP-1 secretion in the culture medium. Using short-term behavioral tests, we showed that the addition of LCFA (200µM) in a sucrose solution (62mM) increases sweet taste sensitivity in wild-type but not in GLP-1R KO mice, suggesting the involvement of GLP-1 signaling in this response. Our current objective is to determine the role of GPR120 in this behavior. These results suggest that there is an oral detection of LCFA in the mouse which can have a direct impact on sweet taste preference, probably *via* the GPR120/GLP-1 signaling. Supported by: French Research Agency (ANR) and the Vitagora cluster (SensoFAT project to P.B.) and the Burgundy Council and Centre National Interprofessionnel de l'Economie Laitière (CNIEL) (HumanFATaste project to.

Microstructural analysis of water and sucrose intake by rats after systemic administration of the glucagon-like-peptide-1 (GLP-1) receptor agonist Exendin-4.

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The GLP-1 receptor agonist Exendin-4 (Ex4) decreases volume consumed in feeding tests, but the behavioral patterns leading to intake outcomes have yet to be determined. Therefore, we examined in male Sprague-Dawley rats (n=11) the effects of Ex4 (1 µg/kg ip) on the microstructure of fluid ingestion in 60-min sessions. First we assessed the effect of Ex4 and vehicle on lick patterns to water when the rats were ~23-h water-deprived, and then to sucrose solutions (0.03, 0.1, 0.3, and 1 M, presented individually in ascending order) while rats were ~23-h food-deprived and while nondeprived. The temporal distribution of licks taken during these sessions was organized into bursts (licks separated by pauses of ≥ 1 s) and meals (licks separated by a pause ≥ 5 min). In the first meal of the sessions, Ex4 decreased licks to water while the rats were water-deprived via a decrease in burst number. In contrast, Ex4 decreased licks taken to sucrose while the rats were food-deprived via a decrease in burst size. Ex4 did not affect the size of the first burst or the number of licks during the first minute of sampling of the rats in any deprivation state. Finally, Ex4 increased the mean interlick interval (pauses of 50-250 ms) independent of stimulus or deprivation state. These results suggest that agonism of GLP-1 receptors decreases ingestion through multiple mechanisms, including direct or indirect modulation of central oromotor circuits, but likely not through those derived from orosensory stimulation. Supported by: 1F32DC010517-01 to CMM.

Phasic dopamine signaling evoked by unexpected food reward differs with respect to striatal subregion and preference

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Phasic activation of dopamine neurons is evoked by unexpected reward and is important in motivating behavior towards food. However, the degree to which different pools of dopamine neurons are recruited in this way is unclear. So far the output of these cells after unexpected reward, i.e. a phasic elevation in dopamine, has only been measured in nucleus accumbens (NAc) core while other striatal regions have not been formally examined. Here, we used fast-scan cyclic voltammetry in rats to record the dopamine response to delivery of unexpected sugar pellets across the striatum. In all rats, we find robust pellet-evoked elevation of dopamine in the NAc core. In contrast, in NAc shell, dorsomedial and dorsolateral striatum no pellet-evoked dopamine was observed. Furthermore, we find that the magnitude of the response in NAc core is linked to preference. As such, flavored sucrose and saccharine pellets, both of which are readily consumed by rats, evoke a dopamine response. However, the dopamine response to sucrose

pellets is far greater than that to saccharine, reflecting the rat's preference. Current studies are determining if this preference results from nutritional or sensory differences between the sweeteners. In summary, we find that the dopamine response to unexpected food reward is specific to NAc core and its magnitude is modulated by preference. Supported by: DA025634.

Glucagon-like peptide-1 receptor agonists suppress water intake

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Activation of the glucagon-like peptide-1 (GLP-1) system decreases food intake and body weight. Previous studies demonstrated that GLP-1 receptor (GLP-1R) agonists also suppress water intake, but most of these studies failed to adequately dissociate the decreased fluid intake from the hypophagic response. Additionally, it is unknown whether forebrain and/or hindbrain GLP-1R populations mediate the anti-dipsogenic effects of the ligands. To address these issues, we examined the effects of peripheral administration of GLP-1(7-36) and the longer-acting GLP-1R agonists, exendin-4 and liraglutide, on water intake (recorded continuously for 24h in automated chambers) in rats with and without access to food. Water intake was suppressed by IP administration of all three ligands whether food was present or not, suggesting that the anti-dipsogenic effects were not secondary to effects on food intake. Central application of the ligands into either the lateral or the fourth ventricle also suppressed water intake when food was absent, suggesting that stimulation of hindbrain GLP-1Rs in the absence of forebrain stimulation is sufficient to suppress water intake. These experiments demonstrate anti-dipsogenic effects of GLP-1R ligands that are mediated, at least in part, by hindbrain GLP-1Rs and occur independent from any effects on food intake. Support: NIH awards DK-89752 (SEK), DK-85435 (MRH), DK-73800 (DD), and HL-91911 (DD). Supported by: NIH.

Dissimilar effects of Na depletion and dehydration on the differential intake of salted and unsalted food in rats

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We investigated the effect of Na or water depletion on the intake of NaCl in food. Sprague Dawley rats had a choice of 2 foods that were deficient (0.02% Na; unsalted food) or sufficient (0.5% Na; salted food) in Na. In some experiments unsalted and salted foods were otherwise identical; in others several constituents of the foods, including sucrose, differed considerably between unsalted and salted food. Rats (n = 5 or 6) were Na depleted by furosemide (20 mg/kg) injection on days 1 & 2. Intake of preferred unsalted food fell on day 1 & 2 of treatment (22.1± 1.9 to 13.5 ± 1.9 & 10.6 ± 1.4 g), but intake of salted food was unchanged on day1 (5.3 ± 1.2 to 7.0 ± 1.8 g), and increased on day 2 (to 12.3 ± 3.1 g) of Na depletion. Intakes returned to pre-treatment levels by day 5. By contrast, water deprivation for 2 days resulted in intake of salted food falling (12.3 ± 2.3 to 6.0 ± 2.2 & 1.3 ± 0.7 g on days 2 & 3). Intake of unsalted food fell ($p < 0.01$) only on day 2 (19.8 ± 1.7 to 17.0 ± 1.6 & 13.1 ± 1.1g). These effects of Na depletion and dehydration were seen regardless of changes in other constituents of the foods. We suggest that an early reduction in preference for unsalted food may be a homeostatic response leading Na depleted animals to seek out and consume salted food. On the other hand, by reducing intake of salted food more than unsalted food, water deprived animals reduce their ingested osmotic load thereby ameliorating dehydration-induced hypertonicity. Supported by: NHMRC of Australia & L.Y. & GH Mathers Trust.

Regional Brain Metabolic Responses to Food Expectation Predict Food Preference

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Brain glucose metabolism (BGluM) is used to map regional brain function to behavior. Using [^{18}F]-fluoro-2-deoxyglucose (FDG) and small animal positron emission tomography (μPET) we correlated changes in BGluM following the expectation of two food stimuli with conditioned place preference (CPP) for each stimulus. Male adult rats were conditioned to expect either 5g of chow or cooked bacon in contextually distinct chambers. Rats were then tested for CPP, and afterwards BGluM was assessed twice, once following exposure to the bacon-paired chamber, and once to the chow-paired chamber. Rats showed variability in CPP, suggesting that some rats preferred bacon, whereas others preferred chow. Regression analysis showed that individual CPP for the bacon- but not chow-paired environment was correlated with BGluM in regions associated with saliency (nucleus accumbens), motivation/drive (caudate putamen, orbital cortex, hypothalamus), and interoception (thalamus). Our findings show that there are individual variations in regional brain responses and behaviors related to food reward and suggest that food preference may be influenced by individual differences in sensitivity of the food-reward circuitry to conditioned food stimuli, which may in turn contribute to compulsive eating and obesity.

Effect of the orexin receptors antagonists in an animal model of binge eating

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There is evidence supporting a role of the orexin system in the modulation of feeding behavior. Injection of orexin-A, into the lateral ventricle of rats, induces a dose-related increase in food intake that is blocked by pre-treatment with SB-334867, an orexin 1 receptor (OX1R) antagonist. Moreover, lateral hypothalamus orexin neurons are activated by cues associated with food. In this work we tested GSK1059865, a selective OX1R antagonist; JNJ10397049, a selective OX2R antagonist and SB-649868, a dual OX1/OX2R antagonist in a binge eating model in rats recently described by Cifani et al. (Psychopharmacology 2009). We used topiramate as a reference compound because it was shown to selectively block binge episodes in humans. The pharmacokinetic profiles of tested compounds were also investigated. Results showed that SB-649868 did not affect feeding in rats with no history of restriction and not exposed to stress (NR+NS). Conversely it selectively reduced highly palatable food (HPF) intake in rats previously exposed to 3 cycles of food restriction and then exposed to stress (R+S) (binge eating group). JNJ10397049 did not affect HPF intake either in NR+NS or in R+S. The selective OX1R antagonist did not affected HPF intake in NR+NS but completely prevented the occurrence of binge eating in R+S. Results indicated that orexin receptor antagonists selectivity prevent binge eating behavior and that this effect is mediated by OX1R. These findings suggest that OX1R may represent an interesting target for the pharmacological treatment of binge eating

Effect of the CRF-1 receptor antagonist R121919 on binge eating

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Stress is a key determinant of binge eating (BE).The present study evaluated the effect of the corticotrophin releasing factor 1 receptor (CRF-1R) antagonist R121919 in female rats, in which BE for highly palatable food (HPF) was evoked by stress and repeated food restrictions (Cifani et

al. Psychopharmacology:2009;204:113-25). Four groups of rats were used: NR+NS was normally fed and not stressed on the test day (d25); NR+S was fed as NR+NS and stressed on d25; R+NS was exposed to 3 cycles of yo-yo dieting but not stressed; R+S was fed as R+NS and stressed on d25. All groups were fed HPF for 2 h on day 5-6 and 13-14. Stress was induced by preventing access to HPF for 15 min, while rats were able to see and smell it. R121919 was injectioned s.c. 1 h before access to HPF. BE was selectively observed in R+S, that showed a marked increase in HPF intake in comparison to NR+NS. HPF intake in R+NS and NR+S was not significantly different from that of NR+NS. R121919 (10-20 mg/kg) significantly reduced HPF intake in R+S, but had no effect in the other 3 groups. After the stressful procedure, rats showed increased serum corticosterone (CORT) levels. To asses whether CORT is involved in the BE response, R+S and NR+NS were treated with metyrapone, a CORT synthesis inhibitor. It failed to prevent BE. Lastly, CORT did not induce BE in R+NS, in comparison to NR+NS. These findings suggest that CRF-1R mechanisms are involved in the BE response following stress and food restrictions; this effect is likely related to its extrahypothalamic functions rather than to its regulatory role in HPA axis activity

Ghrelin reduces hypertonic saline intake under a variety of natriorexigenic conditions
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A relatively new area of research has explored how ghrelin, a peptide hormone most commonly studied in the context of feeding, affects fluid balance. Recent publications have described an anti-dipsogenic action of ghrelin under several conditions that increase water intake, including icv angiotensin II (AngII) and sc hypertonic saline. Fluid balance involves the coordination of water intake as well as NaCl intake, but our previous studies focused exclusively on the role of ghrelin in water intake. Therefore, the present set of experiments was designed to test the effect of icv ghrelin on hypertonic saline intake under several natriorexigenic conditions. Rats were stimulated to drink saline by icv AngII, water deprivation with or without partial rehydration, sc polyethylene glycol (PEG), or dietary sodium deficiency. Rats were injected with ghrelin (0.5 µg) or vehicle (1 µL aCSF) immediately before a two-bottle test measuring water and 1.8% NaCl intake. Ghrelin reduced saline intake in all conditions except water deprivation without partial rehydration. Ghrelin also reduced water intake, but the effect was more variable between experiments. Accordingly, the data suggest a more reliable and prominent effect of ghrelin on saline intake than on water intake. Further examination of the physiological basis and underlying mechanism of action of this effect is necessary to understand more fully how ghrelin coordinates fluid and food intake.
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Melanin Concentrating Hormone (MCH) gene expression changes in conditioned taste aversion (CTA), however MCH administration does not block CTA.
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MCH stimulates feeding driven by energy needs and reward. Orexigenic peptides like nociceptin/orphanin FQ, agouti-related peptide and opioids, also increase consumption by reducing avoidance of potentially tainted food in animals displaying a CTA. Using real-time PCR, we assessed whether expression of genes encoding MCH and its receptor MCHR1, were affected in CTA in the rat. We also investigated whether injecting MCH centrally during the acquisition and retrieval of LiCl-induced CTA, would alleviate aversive responses.MCHR1 mRNA was upregulated in the brain steam, as well as in the hypothalamus together with MCH mRNA; and there was a strong trend suggesting upregulation of both in the amygdala. Despite these

expression changes associated with aversion, MCH injected prior to the induction of CTA well as later, during the CTA retrieval did not reduce the magnitude of CTA.We conclude that MCH and its receptor form an orexigenic system whose expression is affected in CTA. However exogenous administration of MCH peptide was insufficient to prevent the onset or facilitate extinction of LiCl-induced CTA. This designates MCH as one of many accessory molecules associated with shaping an aversive response, but not a critical one for LiCl-dependent CTA to occur. Funded by Swedish Research Council, The Novo Nordisk Foundation, the Brain Research Foundation, NIDA R01DA021280, NIDDK P30DK50456, NIDCR T32DE007288.

Cholinergic mechanisms and the behavioral effects of dietary fat consumption

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Recent reports suggest a positive association between fat consumption and various behavioral disturbances. To understand the mechanisms underlying these disturbances, the present study investigated, in Sprague-Dawley rats, the influence of short-term consumption of a high-fat diet (HFD) compared to chow diet on anxiety, novelty-seeking and exploratory behaviors and on acetylcholine (ACh) neurotransmission in the brain that may mediate these behaviors. In animals with similar caloric intake and body weights, HFD intake increased serum fatty acids and stimulated novelty-seeking and exploratory behavior while reducing anxiety. The consumption of a HFD also significantly reduced the activity of ACh esterase (AChE), an enzyme that breaks down ACh, in the frontal cortex, hypothalamus and midbrain area. With measurements of [125I]-epibatidine or [125I]-bungarotoxin binding to nicotinic ACh receptors (nAChRs) containing β2 or α7 subunits, respectively, the results showed HFD consumption to increase β2-nAChR binding in the medial prefrontal cortex and substantia nigra, while increasing α7-nAChR binding in the lateral and ventromedial hypothalamus. Further, with measurements of behavioral sensitivity to an acute nicotine challenge, the rats consuming the HFD exhibited increased ambulatory behavior, which was not evident in rats consuming chow. These findings suggest that the behavioral consequences of short-term HFD consumption may be mediated by enhanced cholinergic activity, along with stimulation of β2-nAChR in cortical and midbrain regions and of α7-nAChRs in hypothalamic regions. Supported by: USPHS grant DA 21518.

The learned shift in flavor palatability evaluation produced by flavor-nutrient conditioning is susceptible to rapid extinction.

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Learned association between a cue flavor and positive nutritional consequences sensed postingestively can produce long-lasting increased preference for that flavor, as measured by intake in a choice test. Such learned preferences are fairly persistent (i.e., resistant to extinction) even once the flavor is divorced from its prior nutritional consequences. Given evidence that the learned preference can be attributed, at least partly, to a positive hedonic shift in palatability evaluation, that has been suggested as the psychological basis for resistance to extinction. In this experiment, rats were trained with four 8-hr sessions in which consuming a CS+ cue flavor (orange or lemon-lime in saccharin) was paired with intragastric glucose infusion, alternating with four sessions of the opposite flavor (CS–) paired with water infusion. This training established a powerful preference for the CS+ flavor in a choice test, and enhanced CS+ palatability as measured by lick microstructure pattern analysis. Next, extinction training involved a series of twice daily 30-min sessions alternating between the two flavors, each unpaired with IG infusion, lasting 14 days. The CS+ preference was resistant to extinction, as that flavor remained significantly preferred over CS– in a choice test. But differential CS+ and CS– palatability, measured by lick microstructure, extinguished rapidly. Thus a lasting hedonic shift is not the basis for persistent preference after extinction of flavor nutrient-conditioning.

Preferences for fat and basic tastes and in 3-, 6- and 12-month-old infants

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Fat perception received recent interest, but fat preference in human infants is a matter of debate. The objective here was to investigate fat and taste preferences in the same infants (N=66) at 3, 6 and 12 months. Preference for a fat solution (sunflower and rapeseed oils mixed with soy lecithin) and for taste solutions (sweet, lactose; salty, NaCl; bitter, urea; sour, citric acid; umami, sodium glutamate) was evaluated. The same method was applied at each age. Mothers and their infant participated in 2 videotaped sessions, during which the 5 taste and fat solutions were assessed in a balanced order. For each taste, 4 bottles (water, tastant, tastant and water) were presented by the experimenter. Two global indices were calculated to represent acceptance of the tastant relatively to water (W), based on ingested volumes and on facial expressions. At 3 and 6 mo, the fat solution was as consumed as W; but less than W at 12 mo; at all ages it elicited 'negative' expressions. For taste solutions, at 3 mo the sweet solution was more and the bitter one was less consumed than W; the bitter and the sour solutions elicited 'negative' expressions. At 6 and 12 mo, the sweet and salty solutions were more consumed than W and elicited 'positive' expressions; the bitter and sour solutions elicited negative expressions. Infants were indifferent to the umami solution. These findings are in accordance with the literature on taste preference but the indifference or rejection of the fat solution raise questions about an 'innate' preference for fat. The olfactory component of fat might be involved in this rejection. Supported by: ANR 2006-PNRA-OPALINE & Regional Council of Burgundy. .

Modulation of sweet taste responses by antagonists for leptin and endocannabinoid receptors in normal lean and *db/db* mice.

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The taste organ is a peripheral target for both leptin (Lep), an anorexic mediator and endocannabinoids (EDs), orexigenic mediators. In mice, Lep selectively inhibits behavioral, taste nerve and taste cell responses to sweet compounds. Opposing the action of Lep, EDs enhance the sweet taste responses. Such modulation disappeared in *db/db* mice with defects in Lep receptors or mice genetically lacking ED receptors, suggesting that exogeneous Lep or EDs affects sweet taste via activation of their cognate receptors in taste cells. However, potential roles of endogenous Lep and EDs in sweet taste remains unclear. Here, we examined effects of antagonists for Ob-Rb (L39A/D40A/F41A) Lep and CB1 (AM251) ED receptors on the chorda tympani (CT) nerve responses in lean control and *db/db* mice. The results demonstrated that lean mice exhibited significant increases in CT responses to sweet compounds after i.p. administration of L39A/D40A/F41A, while they showed no significant changes in the CT responses after AM251. In contrast, *db/db* mice showed clear suppression of CT responses to sweet compounds after AM251, and exhibited enhanced expression of a biosynthesizing enzyme (DAGL) of ED in taste cells. These findings suggest a possibility that circulating Lep may act as a modulator in lean mice that tonically affects basal sweet sensitivity, whereas EDs whose production may be potentiated under defects in the Lep system, may lead to increased basal sweet sensitivity in Lep receptor-deficient db/db mice.

Emotional eating and night eating syndrome in college students

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The night eating syndrome (NES) is a stress-related eating disorder consisting of morning anorexia, evening hyperphagia, insomnia, and nocturnal awakening to eat. It has been associated with depressed mood which worsens in the evening but is not consistly related to elevated BMI. The present study was conducted to examine whether a relationship exists between emotional eating and NES symptoms as measured by the Night Eating Diagnostic Questionnaire (NEDQ). A sample of students (*N*=246) completed the DEBQ, NEDQ, Night Eating Syndrome History and Inventory and provided demographic information including height and weight. Participants were grouped by severity of NES symptoms using the NEDQ: normal (*n*=166), mild night eater (*n*=37), moderate night eater (*n*= 29), and full syndrome (*n*=14). MANOVA was used to compare DEBQ scores for the groups; those in the full syndrome category had significantly higher emotional eating scores [$F(3, 240)=4.5$, $p=.004$] and higher external eating scores [$F(3, 240)=7.8$, $p=.000$] than those in the normal and mild categories. The trend for both was higher mean scores as symptoms increased. The pattern in dietary restraint was less clear: those in the moderate night eater category had significantly lower scores than those identified as normal or full syndrome [$F(3, 240)=4.8$, $p=.003$]. No significant relationship was found between BMI and NEDQ [$F(3, 241)=1.04$, $p=.374$]. The results suggest that NES is associated with higher emotional eating in college students. Supported by: Wagner College.

Jejunal infusion of glucose decrease food intake in non-human primates through changes in meal frequency.

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Roux-en-Y gastric bypass (RYGB) involving gastric restriction, bypass of the upper intestine and direct delivery of nutrients from the stomach to the duodenum is the most effective obesity treatment. Experiments in rats aimed at understanding the mechanisms underlying the efficacy of RYGB have shown that jejuna nutrient delivery is itself a potent inhibitor of food intake. The aim of this study was to generalize these effects from rats to nonhuman primates. We examined the effects of jejuna infusions of glucose on the food intake and meal patterns of adult male rhesus monkeys. Monkeys received a jejuna infusion of glucose at a rate of 1 kcal per minute (75 kcal/75min). Infusions were done at the start of a 6-hour daily access to food (mid-day). To futher characterize the effects of the jejunal nutrient, we repeated infusions for 5 consecutive days. Similar to finding in the rat, glucose infusions suppressed food intake beyond their caloric load. Meal pattern analysis revealed that glucose infusions significantly reduced intake through changes in meal frequency. Jejunal glucose infusions maintained their efficacy across the 5 consecutive days with no compensatory increase in food intake on the following days. These results demonstrate that nutrients infused directly into the jejunum can significantly decrease food intake by means of decrease meal frequency and suggest that this aspect of the RYGB procedure contributes significantly to the overall efficacy of the surgery. Such findings could further advancements in obesity therapy. Supported by: DK19302.

CALORIC TITRATION METHOD FOR WEIGHT LOSS IN OBESE AND OVERWEIGHT ADULTS: PRELIMINARY SIX MONTH RESULTS

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The average American has experienced a steady increase in body weight for several decades. The purpose of this study is to investigate the efficacy and feasibility of pairing frequent self-weighing with visual feedback from a web-based program to produce a 10% reduction in body weight over one year. One-hundred and fifty-two adults with a Body Mass Index (kg/m^2) greater than 27.0 were randomized to an experimental or control group. All participants attended an initial meeting where research-based weight loss strategies were presented. The experimental group

was also given a scale and access to a website to log their weight at least 3 times per week. As part of a crossover design, the control group will be given access to the experimental intervention after one year. Participants were weighed using a LifeSource MD Precision Scale (model: UC-321P) at baseline and six months after baseline. Six month weigh information has been collected from 53 participants as of March 15th, 2011. Available data were analyzed using PASW Statistics 18. The average weight loss was 2.4 ± 9.1 lbs. Participants in the control group lost an average of 2.5 ±9.1 lbs (n = 21) and participants in the experimental group lost an average of 2.4 ±9.2 lbs (n=32). Currently, results do not support the hypothesis that the use of this behavioral web-based program provides a unique benefit for weight loss when compared with not using this program.

Prenatal Immune Priming of Metabolic Dysfunctions Related to Schizophrenia

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Gestational (G) infection increases the offspring's risk of neurodevelopmental disorders, such as schizophrenia (S), which supports the concept of early-life programming (ELP). In addition to its complex neurological profile, S is associated with increased adiposity and insulin resistance. Here we used a well-established murine SELP model (Meyer et al, Prog Neurobiol, 2010, 90: 285-326) based on G poly(I:C) inoculation to test whether ELP may promote these metabolic dysfunctions. We examined the metabolic effects of ELP at two maturational stages, puberty and adulthood (postnatal weeks 4-6 & 10-12, respectively). As programing effects depend on G timing, we included offspring exposed to poly(I:C) early (G day 9 = GD9) and late (GD17). ELP-mice (GD9 & GD17) were undistinguishable from controls (Ctrl) in body length, weight & growth, but GD17 mice showed increased adiposity (5.0 ± 0.4 vs. Ctrl 3.6 ± 0.3 fat [% body mass], $P < 0.05$) at puberty and GD9 mice in adulthood (22.2 ± 2.2 vs. Ctrl 16.0 ± 1.4, $P < 0.05$). Also, GD17 mice showed increased fasting glycemia at puberty (7.7 ± 0.3 vs. Ctrl 7.0 ± 0.2 mmol/L, $P < 0.05$) and reduced insulin sensitivity in an oral glucose tolerance test in adulthood (AUC 0-150 min, 631 ± 54 vs. Ctrl 528 ± 31, $P < 0.05$). Hyperphagia (GD17 = Ctrl +15%) and high metabolic rate (GD17 = Ctrl +33%) around puberty and hypoactivity in adulthood (GD9 = Ctrl -12%) may contribute to the observed pre-diabetic phenotype in ELP mice. These are the first experimental data suggesting that ELP can be a causal factor in the development of S metabolic abnormalities.

Decreased weight gain and depression-like behaviors with free access to highly palatable food in rats

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We have reported that a long-term limited access to highly palatable food shortens, but free access prolongs, the hypothalamic-pituitary-adrenal (HPA) axis response to restraint stress in rats. Psycho-emotional disorders frequently involve dysfunctions in the HPA axis activity. In this study, rats received chocolate cookies for 1 h daily (limited access; LA) or freely (free access; FA) with *ad libitum* chow access for 7 days, and then were subjected to behavioral tests. Control group received chow only, and all food conditions were continued throughout the whole experimental period. Daily caloric intake increased with cookie access; interestingly, the increase was observed only on the first day in LA group, but persisted in FA group. Body weight gain did not differ between LA and control group; however, suppressed in FA group. Ambulatory activity of LA or FA rats, especially entry number to center area, tended to be increased, but statistical significance was not found. Number of groomings decreased, but fecal boli increased, in LA rats compared with chow controls. Scores in the elevated-plus maze test did not differ among the experimental groups. In the porsolt swim test, immobility duration was increased in FA rats, but not in LA, compared with chow controls. Results suggest that a long-term free access to highly palatable food may lead to the development of depression-like behaviors in rats, likely in relation

with prolonged stress responsivity. Supported by MOEST(2009K001269; 2010-0003642) Supported by: MOEST(2009K001269 2010-0003642).

Hypothalamic serotonin receptors expression associated with sodium appetite enhancement produced by dehydration.

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Sodium appetite is a behavior that increases by repeated episodes of water deprivation-partial rehydration (WD-PR). We investigated the status of the serotonin (5-HT) system in the hypothalamus of rats under different cycles of repeated WD-PR. Adult male Holtzman rats were individually housed with chow, water, and 0.3 M NaCl available. Rats were submitted to cycles of 36 hours of WD followed by 2 hours of PR, with water only, at 7-day intervals and sodium appetite tests were performed after each cycle. The intake of 0.3 M NaCl was significantly increased after cycle 3 (17.3 ± 1.4 ml) versus cycle 1 (11.2 ± 1.4 ml) or 2 (12.8 ± 2.4 ml). Different sets of rats were sacrificed and hypothalamus dissected after the cycle 1 or 3 of repeated WD-PR. The amounts of mRNA for all 14 known 5-HT receptor subtypes were determined by RT followed by qPCR in both groups. Transcripts for 5-HT1A, 2A, 3B, and 7 were increased by 62, 111, 145, and 100%, respectively, in the hypothalamus of rats after 3 cycles when compared with 1 cycle of WD-PR ($p<0.05$). Similar mRNA quantity was found for remaining 5-HT subtypes. Immunoreactive protein bands for 5-HT1A and 5-HT7 were elevated by 22% and 15%, respectively, at the end of cycle 3 compared to cycle 1 ($p<0.05$). However, 5-HT2A did not alter. Our data suggest that increased density of selective hypothalamic serotonin receptors may play a role in mechanisms related to the elevated sodium appetite induced by dehydration. Funded by CNPq and FAPESP. Supported by: CNPq and FAPESP.

Exploring urocortin-responsive circuits in forebrain and hindbrain

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Administration of urocortin I (UcnI), into the lateral (LV) or fourth (4V) ventricle, leads to behavioral, physiological, and neuronal changes relevant to energy homeostasis. These changes include decreased food intake, increased blood glucose, and expression of Fos in the paraventricular hypothalamic nucleus (PVN) and the nucleus of the solitary tract (NTS). To explore the interactions between these UcnI responsive structures, we administered UcnI to the LV, 4V, PVN, or NTS. Consistent with previous studies, ventricular application of UcnI (1µg) decreased food intake, increased blood glucose, and increased Fos expression in the PVN and NTS. The responses to 4V injections were remarkably similar to the responses after LV injections, suggesting a critical role for hindbrain structures or for UcnI-sensitive ascending projections. To test the sufficiency of the NTS for the observed responses, we made injections of UcnI (0.1µg) directly into the NTS. These injections, however, did not affect food intake or blood glucose. In contrast, rats injected with UcnI directly into the PVN (0.01µg) ate less than controls, but these injections did not stimulate a hyperglycemic response nor did they stimulate Fos expression in the NTS. Collectively, these findings suggest that the NTS is not sufficient for the observed effects of UcnI and that the PVN, although an effective site for the hypophagic responses, is not sufficient to stimulate changes in blood glucose after UcnI administration. The divergence of the glycemic and ingestive responses to UcnI in the PVN warrants further investigation. Supported by: NIH.

Amylin induced ERK 1/2 phosphorylation may contribute to its eating inhibitory effect
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Peripheral amylin inhibits food intake via activation of the area postrema (AP). Because amylin activates the extracellular-signal regulated kinase 1/2 (ERK) pathway in some tissues, and because ERK1/2 phosphorylation (pERK) leads to acute neuronal responses, we postulated that the ERK pathway may be involved in the fast eating inhibitory effect of amylin, similar to CCK (Sutton et al., 2004). First, we investigated the temporal pattern of amylin activated pERK and the implication in amylin's anorectic action. Because part of amylin activated neurons in the AP are noradrenergic, we also phenotyped the pERK-positive AP-neurons using dopamine-beta-hydroxylase as marker. We injected 24h fasted rats with saline or amylin (5-20 ug/kg SC) and perfused the rats 10-30 min later. The peak of pERK in the AP was 10-15 min after amylin; the effect was dose dependent, and 22% of pERK-positive AP neurons were noradrenergic. The MEK1/2 inhibitor U0126 was injected into the 4V to inhibit ERK1/2 signaling in the AP; 24h fasted rats received U0126 (7ug) or vehicle 30min before dark onset, and saline or amylin (5 ug/kg) at dark onset. Amylin significantly reduced 60min food intake; U0126 blocked this effect, and U0126 also tended to reduce amylin induced pERK in the AP. These results show that amylin stimulates pERK in the AP and that a subpopulation of amylin-responsive AP neurons is noradrenergic. Because local 4V administration of U0126 attenuated amylin's feeding effect, ERK phosphorylation may be a necessary part in the signaling cascade that mediates amylin's eating inhibitory effect. Supported by: N/A.

Prenatal environment vs. genetic predisposition vs. dietary history: is (hedonic) obesity the parents' fault?
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Central dopamine codes for the hedonic value of food and may override the homeostatic control of energy balance. In this work, we use a multi-level approach from the living animal to the single neuron to study the role of pre- and postnatal brain dopamine in obesity in dietary obese (DIO) and inbred obesity-prone (OP) rats. In DIO and OP adult females, we show decreases of approximately 50% in basal and stimulated dopamine release in the accumbens, striatum and prefrontal cortex. Deficits in dopamine signaling are linked to an attenuated response to amphetamine and reductions in tyrosine hydroxylase and vesicular monoamine transporter mRNA and protein expression. Obesity-resistant (OR) embryos transplanted to OP dames on day E1 show equivalent postnatal deficits in dopamine neurotransmission that are linked to accelerated body weight gain and decreased spontaneous activity during the pre-pubescent period. Dopamine replacement in OP females results in a 10% decrease in both food intake and body weight and more than 2-fold stimulated dopamine release in the nucleus accumbens than in OP control animals. In conclusion, depressed dopamine release can be induced by exposure to an obesogenic intrauterine environment. Sustained deficits in dopamine during the pre-pubescent period may lead OP animals to compensate by overeating. Selective targeting to upregulate dopamine exocytosis constitutes a promising approach for both the prevention and treatment of dietary obesity. Supported by: DK065872, ARRA 3R01DK065872, F31 DA023760, The Medical Foundation.

Neural mechanisms of the eating-inhibitory effect of circulating glucagon-like peptide-1 (GLP-1) in rats
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We have shown that the eating-inhibitory effect of hepatic portal vein (HPV) GLP-1 infusions in rats is a) independent of intact abdominal vagal afferents, b) blocked by intra 4th ventricular infusion of the GLP-1 receptor (GLP-1R) antagonist exendin-9, and c) accompanied by an increase in the number of c-Fos expressing cells in the area postrema (AP) and nucleus tractus solitarii (NTS), indicating that hindbrain GLP-1R are involved. Here we used remotely controlled HPV GLP-1 infusions (1 nmol/kg body weight) during the first nocturnal meal in adult male rats to further explore the neural mediation of circulating GLP-1's eating-inhibitory effect. We found 1) HPV GLP-1 failed to reduce meal size in AP lesioned rats [Sham/Veh: 3.3 ± 0.8; Sham/GLP-1: 2.6 ± 0.8 ($P < 0.05$); Lesion/Veh: 3.8 ±1.1; Lesion/GLP-1: 4.2 ± 1.0 (n.s.) (g, mean ± SEM)] and 2) that HPV GLP-1 infusion increased phosphorylation of extracellular signal-regulated kinase-2 (ERK-2) compared to vehicle 15 min post-infusion in the NTS (by 45%, $P < 0.05$) and of ERK-1 and ERK-2 (by 25 and 35%, respectively, $P < 0.05$) in the central nucleus of the amygdala (CeA) as revealed by standard Western-blotting technique. These data indicate that circulating GLP-1 inhibits eating by acting on the AP, and that this effect may involve the subsequent activation of NTS and CeA. Whether ERK phosphorylation in these areas is involved in the eating-inhibitory effect of GLP-1 is under investigation.

Short- and long-term effects of olanzapine on food intake and hypothalamic gene expression in female rats

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Olanzapine is an atypical antipsychotic drug shown to have severe metabolic side-effects in humans. The mechanisms responsible for these effects remain unclear. Here, we examined the effects of both short- (5d) and long-term (3wk) olanzapine treatment in adult female Sprague Dawley rats. We found that a daily oral (3 mg/kg) dose of olanzapine (OLZ) led to hyperphagia and increased weight gain which begins within a few days. OLZ rats remained hyperphagic for 2 weeks then food intake returned to control levels although increased body weight was maintained. Short term OLZ had no effect on glucose tolerance but by 3 weeks, OLZ rats had impaired glucose tolerance and increased adiposity. Pair-feeding OLZ rats to control food intake was sufficient to prevent differences in body weight and glucose tolerance. Gene expression studies revealed a short-term orexigenic profile consistent with OLZ food intake patterns. We found significantly increased NPY and decreased POMC expression in the arcuate nucleus at 5 d but not 3 wks. At each time point, fasting plasma leptin and insulin levels did not differ from controls. Altered glucose homeostasis is likely a consequence of increased body weight resulting from hyperphagia associated with OLZ treatment. Higher expression of NPY and lower POMC may initially serve to drive hyperphagia and greater weight gain with OLZ treatment.
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How can lipid decrease food and energy intakes ?

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In the past few years, lipid's satiating capacity has been less explored than its obesogenic properties. It is known that infusing poly-unsaturated-fatty acid (PUFA) in the small intestine with a slow rate decrease food intake in humans and in rats. This work aimed at understanding whether mixing lipid rich in PUFA with a food component which can reduce gut transit rate such

as dietary fiber can affect feeding. Different mixtures of lipid (rapeseed oil) and fiber (guar gum and fructo- oligosaccharide) were tested in mice. We found that high viscous fiber and mixture of lipid and high viscous fiber reduce diet (14% protein/energy, 10% lipid/energy) and energy intake from 3h to 9h after administration. The decrease of energy intake was of 40% (3h) and 22% (9h) for viscous fiber and 19% (3h) and 15% (9h) for viscous lipid- fiber mixture. This effect is due to a strong decline of meal size (at 1h, 6h, 9h) and meal duration (at 6h and 9h) and is concomitant with higher expression of the fos proto-oncogene (indicating neuronal activity) in neurons of the nucleus tractus solitarii (structure involved in satiation control). We also observed that the energy intake decrease is dependent of CCK-1R but not GLP-1R signaling. The slowdown of gastric emptying is also involved in viscous lipid-fiber mixture effect. We conclude that lipid can reduce feeding when mixed with viscous fiber. Supported by: INRA.

Can Limiting Dietary Variety Assist with Reducing Energy Intake and Weight Loss?
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Experimental research shows limiting meal variety reduces meal energy intake (EI), and observational research demonstrates less variety consumed within energy-dense food groups is related to greater weight loss. To understand the effect of limiting variety on EI and weight loss, a series of investigations was executed. A lab-based study gave the same energy-dense food, cake, (NV) or different energy-dense foods (V) over 4 days and examined hedonics and EI. On day 4, cake hedonic rating was lower in NV than V (47.8 $\pm$ 18.3 mm vs. 65.0 $\pm$ 14.1 mm, $p<0.05$), with no differences in EI. Next, a prescription limiting snack food (SF) variety to one chosen SF was examined in an 8-week lifestyle intervention. Hedonics of the chosen SF decreased ($p<0.05$), and limiting variety decreased weekly SF EI by 63%, while a control condition reduced weekly SF EI by 51%. Finally, in an 18-month lifestyle intervention, a prescription limiting SF variety to two chosen foods (LV) was compared to a standard intervention (Lifestyle). Intent-to-treat analyses showed LV ate less SF variety than Lifestyle at 6, 12, and 18 months ($p<0.01$). LV ate less kcals/day ($p<0.05$) at 6 months, and less SF kcals than Lifestyle at 6, 12, and 18 months ($p<0.05$). Hedonics of one chosen SF more greatly decreased in LV as compared to a yoked control in Lifestyle ($p<0.05$). BMI significantly decreased ($p<0.001$), with no differences between conditions (18 months: -9.8 $\pm$ 8.3% body weight). Limiting SF variety reduced EI and appeared to reduce liking of SF. Limiting dietary variety in more areas may be needed to reduce EI more so than a standard prescription to produce greater weight loss. Supported by: NIDDK.

Stimulant sensing in Glucagon-like peptide-1 secreting L-cells
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Glucagon like peptide 1 (GLP-1), released from enteroendocrine L-cells in the intestinal epithelium, plays an important role in post-prandial glucose homeostasis and appetite control. Following the therapeutic successes of GLP-1 mimetics and DPP4 inhibitors, attention is now turning towards the L-cell, to address whether it would be both possible and beneficial to stimulate the endogenous release of GLP-1 in vivo. Understanding the mechanisms underlying GLP-1 release from L-cells is key to this approach. In vitro studies on L-cell physiology, that were previously largely restricted to the use of cell lines, can now be performed on primary intestinal cultures in which GLP-1 secreting cells are identifiable by their expression of a fluorescent transgenic marker. It has been found that a range of physiological signalling mechanisms contribute to L-cell activation, including electrogenic nutrient uptake, metabolism and G-protein coupled receptor activation. Examples of the latter include the bile acid sensitive TGR5, a Gs-coupled receptor and the short chain fatty acid sensitive receptors GPR41 and GPR43, which are Gi/q-coupled. Stimulant dependent elevation of Ca^{2+} and cAMP correlate with enhanced GLP-1 release. The ability to analyse and purify primary L-cells provides a route to identify novel

pathways and receptors in L-cells that might be targetable therapeutically in the future. Supported by: Wellcome Trust.

Tiny Tastes: A home based intervention promoting acceptance of disliked vegetables
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The use of rewards to encourage children to eat healthfully is controversial, with some researchers claiming that *liking* for the rewarded food is decreased. However, recent research suggests that the case against the use of rewards may have been overstated. A RCT evaluated the effectiveness of an exposure-plus-reward intervention in increasing *liking* and *intake* of a moderately disliked vegetable, when conducted by parents at home. Preschool children (n=151) were assigned to Exposure + social reward (praise), Exposure + tangible reward (sticker) or Control conditions, after a pre-test assessment at which a disliked target vegetable was selected for each child. Immediately after this, children in the two experimental groups were offered a taste of their vegetable for 12 days and, depending on the condition, were praised or received a sticker for tasting it. The control group received no taste exposures. Assessments were conducted immediately post-test and 1 and 3 months later. Over the test period, children in the praise and stickers groups significantly increased liking and intake of their target vegetable. However, only children receiving stickers differed significantly from children in the control group in liking and intake of their vegetable post-test. Both the reward groups maintained levels of liking and intake, and at 3 month follow-up, liked their vegetable significantly more than the control group, but only the sticker group consumed significantly more than the control group. These findings support the use of stickers with repeated taste exposures to improve children's diets. Supported by: Medical Research Council/NPRI.

Food-associated cues trigger dopamine transients during initial binge episodes
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Fast dopamine release events, or *dopamine transients*, are thought to be neural signals of reward prediction that can activate seeking and appetitive behaviors. We tested whether a food-associated cue was associated with increased dopamine release at initial presentations. Adult male rats received a tasting of Double Stuf Oreo®cookies (4.8 kcal/g, 24% fat, 72% carbohydrate, 3.4% protein) and then were surgically prepared for neurochemical measurements. After recovery, dopamine was measured by using fast scan cyclic voltammetry in the nucleus accumbens core while rats were exposed to a food-associated cue that consisted of a paste of cookies and water inside a metal tea ball that allowed the smell but not the consumption of the food. Eight successful recordings were made in 5 rats: 4 recordings during the first binge cue exposure, and 4 during the second. During the first minute of cue presentation, the rate of dopamine transients increased 3-fold from baseline (5 min preceding the cue), from 0.7 to 2.4 transients per minute. Moreover, the amplitude of the transients was 60% higher during cue presentation than during baseline, from 25 to 41 nM. The cues were followed by 30-min access to cookies and chow, during which rats ate 5.8 ± 0.7g cookies and 0.7 ± 0.2 g chow. These findings suggest that exposure to food-related cues increases dopamine signaling in reward pathways of the brain. This increase in dopamine signaling may act as a trigger for increased consumption of palatable foods, initiating a neurochemical cascade that primes an individual for overconsumption and binge eating. Supported by: NIH, UNC.

Social Influences on Food Choice
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The eating behaviour of those around us has been shown to affect the amount of food we eat. However, less is known about whether our food choices are similarly affected by social influences. If a dining companion is eating healthily, are we more likely to also select healthy food items? The present study examined whether food choices are influenced by the choices of an eating companion. Eighty female participants attended a lunch time study 'examining mood and food enjoyment' and were paired up with another participant (a confederate) on arrival. After completing demographic questions and mood ratings together, the confederate and participant were taken to a buffet consisting of plates of sandwiches, carrot sticks, tomatoes, rice cakes, chips, cocktail sausages and savoury pastries and asked to select a lunch as part of the study. In view of the participant, the confederate selected their lunch first and chose a fixed amount of sandwiches plus a fixed amount of either low energy dense accompanying items (carrot sticks, tomatoes, rice cakes) or a fixed amount of high energy dense accompanying items (chips, sausages, pastries). The participant then selected their lunch and ate it alone. Although both groups selected a similar amount of food (in kcals), participants in the low energy dense confederate condition selected a greater proportion of low energy dense foods and a smaller proportion of sandwiches from the buffet for their lunch than participants in the high energy dense confederate condition. The results suggest that the food choices of those around us influences our own food choices and this may be explained by the operation of social norms. Supported by: University of Birmingham.

Differential encoding of cues in nucleus accumbens predicts behavioral inhibition.
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The failure to inhibit action in response to reward-associated cues can result in engagement in such impulsive behaviors as overeating, smoking or gambling. Often, cues that predict reward lead to approach and consumption, and each aspect of this sequence is capable of driving neural responses in the nucleus accumbens (NAc). To dissociate whether NAc responses are related to reward-prediction or action selection, we recorded the activity of individual NAc neurons while rats (n=11) performed a symmetric Go/NoGo task. In this task, both Go and NoGo cues predict reward, but require either approach or inhibition of a lever press to receive it. All correct trials result in the delivery of a sucrose pellet, while all errors result in a 40s time out. Rats performed at high levels of accuracy for both Go (*M* = 88.6%, *SE* =1.8) and NoGo trials (*M* = 76.8%, *SE* = 6.4). Neurons that responded to cues with transient increases in activity showed larger increases that preceded withholding of lever presses for both correct NoGo and Go error trials. Neurons with transient cue-related decreases showed greater reductions in activity preceding lever presses-both correct Go and NoGo error trials. Treatment with the dopamine D2 receptor antagonist raclopride resulted in elevated NAc activity and a greater proportion of failures to press following Go cues. These findings are compatible with the idea that reductions in NAc activity permit the execution of goal-directed actions, and increasing activity is associated with avoidance. Supported by: R21DA027127, R01DA025634.

Maternal restrictive feeding style and girls' inhibitory control interact to predict changes in BMI from 5 to 7 y
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Mothers employ a variety of restrictive feeding practices (e.g. limiting how often snack foods are purchased, how much snack food children can eat, keeping snack foods out of physical reach); yet, we know very little about the multidimensional nature of restriction and how children's temperament may moderate the effects of restriction on eating behaviors and weight gain. Methods: The sample included 180 non-Hispanic white families. Mothers reported on 5

dimensions of restricted access to 7 palatable snack foods. Girls' height and weight, eating in the absence of hunger (EAH) and dimensions of temperament were assessed. Results: Latent Profile Analysis revealed 4 distinct restriction styles: low restriction (*LR*), and 3 high restriction (*HR*) styles varying by how much snack foods were kept within child's physical reach—*HR-low reach*, *HR-some reach*, and *HR-high reach*. No group differences in girls' BMI were observed at age 5. Among *LR* and *HR-high reach* groups, girls' with lower inhibitory control had greater percent change in BMI from 5 to 7 y.All *HR* mothers had daughters with higher EAH intakes at age 7, relative to *LR* mothers, after adjusting for age 5 EAH. Conclusion: Lower inhibitory control coupled with *LR* or *HR-high reach* predicted greater change in girls' BMI from 5 to 7 y. High maternal restriction overall was associated with greater EAH at age 7. Future work should examine how individual differences in temperament may influence children's response to restriction. Supported by: NIH M01 RR10732, HD32973, and 1 F31 HL092721-01.

Effect of liraglutide on intragastric pressure (IGP) and satiation during intragastric nutrient drink infusion in healthy volunteers

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Aim: Liraglutide, a stable glucagon-like peptide-1 (GLP-1) analogue, is used to treat diabetes and induces weight loss; it is unclear whether a peripheral mechanism of action is involved. We investigated whether liraglutide affects the relation between gastric accommodation and satiation by measuring the IGP during nutrient drink consumption. **Method:** 12 fasted healthy volunteers (HVs) were tested 12-20h after sc injection with placebo, 0.3, 0.6 or 1.2 mg liraglutide. An infusion catheter and a manometry probe were positioned in the proximal stomach. After a stabilization period intragastric infusion of a nutrient drink (Nutridrink; 1.5 kcal/ml) started at 60 ml/min. During the nutrient drink infusion the HVs scored their satiation every minute on a graded scale (0-5) until maximum, when the infusion was stopped. Data is presented as mean±SEM; comparisons were performed with ANOVA ($P<0.05$ was significant). **Results:** Liraglutide was well tolerated except for the highest dose which induced nausea. During nutrient drink infusion IGP decreased as compared to the baseline IGP, indicating gastric relaxation. The average IGP decrease was -2.8±0.6, -1.9±0.3, -0.9±0.3 and -2.1±0.5 mmHg after placebo, 0.3, 0.6 and 1.2 mg liraglutide respectively; $P<0.05$. The maximum tolerated volume was 913±124, 851±145, 848±116 and 695±135 ml after placebo, 0.3, 0.6 and 1.2 mg liraglutide respectively (NS). **Conclusion:** Except for the highest dose which induced nausea, liraglutide dose dependently inhibited gastric relaxation and increased satiation during nutrient drink consumption however the latter did not reach significance.

VOLUNTARY EXERCISE, FOOD DEMAND, AND WEIGHT LOSS IN MIDDLE-AGED MICE WITH DIETARY OBESITY

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We have shown previously that the demand function for food in voluntarily exercising (running wheels) mice is inelastic relative to sedentary mice. Despite the fact that they eat more than sedentary mice at higher unit price for food, the exercising mice lose considerable body weight and fat. In the present study, we examine the effect of antecedent dietary obesity (DIO) on running and food demand. Male C57BL/6J mice (~8 mo of age and 30 g) were given initial 4 day training with running wheels and nose poking for 20 mg nutritionally complete pellets in operant chambers. They then were fed either low fat (LF: 10% energy from fat) or high fat (HF: 60% energy from fat, to induce DIO) diets in their home cages for 9 weeks. At the end of this time, the LF and HF groups had gained ~10 and18 g, respectively ($P<0.01$). Each group was then divided

into three equal subgroups all of whom then lived in operant chambers and performed a nosepoke response to obtain their food (the low fat 20 mg pellets used in the initial training). One subgroup each from the LF and HF groups was maintained on a minimal fixed unit price (FUP: 2 nose pokes per pellet) throughout with no wheels A second subgroup was also sedentary, but food was available at incrementing unit prices (FUP 2,5,10,25,50) with each schedule in place for 4 days. A third subgroup had the same incrementing price schedule with voluntary access to wheels. As expected, the subgroups maintained on FUP2 ate a constant amount throuhout, although the DIO mice lost ~6 g body weight. Also as expected, the incrementing cost sedentary groups showed a decline in food intake as cost increased (the demand function), but that of the DIO group was comparable to that of the non-DIO or former LF group. Also as expected, the exercising mice showed less elastic demand functions, but this also did not differ between DIO and non-DIO groups. Running distance did not differ between diet groups or across the FUP schedules. Weight loss was greater in the DIO runners (- 18 g) than in DIO sedentary (-11 g) or non-DIO runners (-12 g). Thus, despite no difference in food intake or demand as a function of price, voluntary running by middle-aged DIO mice is associated with greater weight loss than in non-obese mice. Supported by: NIH.

Inter-individual relationships between energy balance and percentage SWS + REM sleep of total sleeping time in normal weight men measured over 48h in controlled conditions in the respiration chamber

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Background: Epidemiologically, BMI is inversely related to sleep duration. Intra-individual variance in SWS and REM sleep have been related to variance of metabolic and endocrine parameters that are risk factors for the disturbance of energy balance.
Objective: Investigate inter-individual relationships between energy balance (EB = |Energy expenditure–energy intake|, kJ/48h), percentage SWS+REM sleep of total sleeping time, and relevant parameters in normal-weight men during two 48h stays in the controlled environment at the respiration chamber.
Methods: 16 men (age 23±4y, BMI 23.9±1.9 kg/m2) stayed in the respiration chamber twice for 48h to assure EB. EEG was used to monitor sleep (2330-0730h). Hunger and fullness were scored by VAS; mood was determined by STAI-state; food reward by liking and wanting. Baseline blood and salivary samples were collected before breakfast. Subjects were fed in EB, except for the last dinner, when energy intake was ad libitum.
Results: Percentage SWS+REM sleep showed subject variability (32-61%) and within-subject reliability (first-second 48h stay $r=0.74$, $p<0.05$). A positive EB was achieved by overeating during the ad lib meal, and was related inversely to average percentage SWS+REM sleep ($r=-0.56$, $p<0.004$). Multiple regression analysis showed that positive EB was explained by percentage SWS+REM sleep and ghrelin concentrations ($r=0.73$, $p<0.001$); overeating was positively, and percentage SWS+REM sleep inversely related to relevant hunger-, reward-, stress-, and orexigenic hormone- parameters.
Conclusion: A positive EB due to overeating, was explained by a lower percentage SWS+REM sleep of total sleeping time, mediated by hunger, fullness, STAI state scores, total wanting score, and cortisol concentrations. Supported by: No conflict of interest.

Effects of increasing loads of intraduodenal protein on antropyloroduodenal motility, plasma GLP-1 and energy intake in healthy males

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The presence of nutrients in the small intestinal lumen modulates gastrointestinal (GI) function (including stimulation of isolated pyloric pressure waves (IPPWs), suppression of antral and duodenal pressure waves and stimulation of the release of gut hormones (eg glucagon-like peptide-1, GLP-1)) and suppresses subsequent energy intake (EI). For lipid and glucose, these effects are load-dependent, and fat is more potent than glucose. There is little information about the effects of protein. We hypothesized that intraduodenal protein would modulate antropyloroduodenal (APD) motility, plasma GLP-1 and EI in a load-dependent manner. 16 lean, healthy males (age 27±3 years, BMI 22.1±0.6kg/m^2) were studied on 4 occasions in randomized, double-blind fashion. APD pressures (high-resolution manometry) and plasma GLP-1 (RIA) were measured during 60-minute infusions of equiosmolar, equivolaemic whey protein solutions, delivered at 0.5 (P0.5), 1.5 (P1.5) and 3 (P3) kcal/min (reflecting the range of gastric emptying), or saline (C). EI at a buffet-style lunch, consumed immediately after the infusions, was quantified. There were treatment effects on antral presures and both basal pyloric pressures and IPPWs (all P<0.05) and a trend for a treatment effect on duodenal pressures (P=0.07); P3 and P1.5 suppressed antral (P<0.05), and tended to suppress duodenal (P=0.17), waves compared with C, P3 tended to stimulate basal pyloric pressures (P<0.12), and P3 and P1.5 to stimulate IPPWs (P<0.09), compared with C and P0.5. There was a treatment*time interaction for GLP-1 (P<0.001); P3, P1.5 and P0.5 stimulated GLP-1 compared with control (P<0.001), and P3 and P1.5 stimulated GLP-1 compared with P0.5 (P<0.05) (conc (pmol/l) at t=60min; C: 28±2; P0.5: 30±3; P1.5: 39±3; P3: 48±4). There was also a treatment effect for EI (P<0.01); P3 suppressed EI compared with C, P0.5 and P1.5 (P<0.05) (kcal; C: 1238±111; P0.5: 1191±113; P1.5: 1077±125; P3: 912±120). There were inverse relationships between EI with AUCs for basal pyloric pressure (r=-0.57), IPPWs (r=-0.40) and plasma GLP-1 (r=-0.37) (all P<0.01). In conclusion, it appears that *1*) intraduodenal protein modulates GI function in a load-dependent manner, and *2*) both pyloric pressures and GLP-1 may contribute to the suppressive effect of protein on energy intake.
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Intraduodenal lipid and protein suppress energy intake comparably, but have discordant effects on pyloric motility and GLP-1 release

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The presence of lipid and glucose in the small intestine slows gastric emptying by stimulating isolated pyloric pressure waves (IPPWs), increases glucagon-like peptide-1 (GLP-1) release and suppresses energy intake. When given intraduodenally, lipid is more potent than glucose, so that the combination of lipid and glucose is less effective than the equivalent amount (kcal) of lipid alone. The effects of ID protein, and potential interactions with lipid, on GI function and energy intake, are unknown. We hypothesised that protein and lipid, when infused intraduodenally alone or in 1:2 or 2:1 combinations, would have differential effects on IPPWs, GLP-1 and energy intake. 12 healthy males (age 27±5 years, BMI 21.8±0.5 kg/m2) were studied on 5 separate occasions in double-blind, randomized order. IPPWs and plasma GLP-1 were measured during 90-min ID infusions of *1*) saline (C), *2*) 3-kcal/min lipid (Intralipid; L3), *3*) 2-kcal/min lipid+1-kcal/min protein (L2/P1), *4*) 1-kcal/min lipid+2-kcal/min protein, (L1/P2) *and 5*) 3-kcal/min protein (whey protein; P3). Immediately after the infusion, energy intake from a buffet lunch was quantified. While all nutrient infusions stimulated IPPWs, only the lipid-containing infusions differed significantly from C (P<0.001). L3 stimulated plasma GLP-1 compared with C and the other nutrient infusions (P<0.05), which yielded similar responses (conc (pmol/l) at t=90min; C: 26±5; L3: 76±12; L2/P1: 51±5; L1/P2: 45±3; P3: 46±4). In contrast, both L3 and P3 suppressed energy intake compared with control, while the effects of L2/P1 and L1/P2 did not differ from control (kcal; C: 1254±92; L3: 973±146; L2/P1: 1117±157; L1/P2: 1134±120; P3: 1022±121; P<0.05). We conclude that in healthy males the suppression of energy intake by isocaloric duodenal protein and lipid is comparable, but the mechanisms underlying this effect differ. Furthermore, combinations of the

two nutrients are less effective despite delivering identical caloric loads. Supported by: National Health and Medical Research Council of Australia Grants 565312 and 627002 (to CF-B) .

The Importance of Peers and Friends to Eating, Physical Activity, and Obesity during Childhood and Adolescence.

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The impact of peers and friends has traditionally been given a secondary role, and most current research focuses exclusively on the ways in which peers and friends impact overweight youths' cognitive and psychosocial development (i.e., in the form of prejudice and social isolation as a result of obesity). We believe that a new conceptual approach emphasizing the ways in which social factors directly contribute to positive energy balance or can potentially promote healthful behaviors is required. This talk summarizes studies conducted by our team and offer a conceptual foundation to account for the unique influence of friends and peers on children and adolescent's eating behavior and activity choices. The premise of our socio-developmental model of choice theory is that the extent to which youth's characteristics determine whether they become healthy or maladjusted is contingent on particular peer experiences. Previous studies in our laboratory support this model in indicating that friends and peers increase youth's motivation to be physically active and their actual physical activity, but that an impoverished social network deprives youth, and especially overweight youth, of these "pull-in" factors or incentives which facilitate physical activity. Our research also supports that the presence of peers and friends reduced energy intake, and promoted healthier food choices in youth. The limitations of past studies are described, and future research directions are put forth. In conclusion, we argue that linking the individual to their social network is essential to understand how youth make choices about eating, physical activity and alternative behaviors and that the involvement of children's and adolescents' social networks in prevention and intervention efforts may be critical for promoting and maintaining positive behavioral health trajectories.

Rapid detection of "taste" stimuli in the intestine suppresses ongoing ingestive behavior

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Bitter and sweet taste receptors reside in the GI tract, but whether they produce sensory signals that are integrated in the control of ingestion is unknown. To assess GI taste, thirsty rats licked at a spout for 0.12M NaCl for 30 mins each day. During the first 6 mins of the session, they received a yoked intraduodenal (ID) infusion of 0.12M NaCl. On probe sessions, a bitter 10mM Denatonium Benzoate (DB) or sweet 0.2% Saccharin (Sacc) stimulus was laced in the ID NaCl infusion. Rats suppressed ongoing licking in response to arrival of DB in the intestine and resumed licking when the DB infusion terminated. This pattern emerged after several exposures to ID DB, suggesting the solution's aversive effects promoted the detection of its ID sensory features to inhibit intake and minimize further delivery of the stimulus to the GI tract. To model this taste aversion in the intestine, DB or Sacc was mixed into 0.12M LiCl (instead of NaCl) for ID infusion. This treatment facilitated the emergence of an early lick suppression across sessions and sharpened the response within sessions to ID DB, but did not establish a response to ID Sacc. In a final experiment, rats curbed intake in response to an ID caloric (Sucrose), but not a second ID non-caloric (Sucralose), sweet taste, even after repeated presentations in LiCl. The GI taste aversion protocol yielded rapid and robust changes to ingestion in response to ID DB and Sucrose, but not Sacc and Sucralose. This procedure will be useful for future studies of GI taste. (DK027627; HD052112) Supported by: DK027627 and HD052112.

DGAT-1 inhibition increases plasma glucagon-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY) levels in response to a high fat (HF) meal in rats

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Ingested nutrients stimulate the release of GLP-1 and PYY from enteroendocrine L-cells, but the mechanisms of this effect are still elusive. Triacylglycerol (TAG) synthesis may somehow interfere with GLP-1 and PYY release because mice deficient in diacylglycerol acyltransferase-1 (DGAT-1), a key enzyme in TAG synthesis, showed increased plasma levels of both hormones after oral administration of corn oil (Okawa, 2009). Here we used adult, male rats adapted to a HF diet and to an 8 h feeding/16 h deprivation schedule to investigate the effects of a DGAT-1 inhibitor (DGAT-1i) on hepatic portal vein (HPV) plasma levels of active GLP-1 and total PYY in response to a 3.5 g HF test meal given at the onset of the 8 h feeding time. In response to intragastric (IG) vehicle infusion, plasma levels of GLP-1 and PYY increased ($p < 0.05$) by 84 (GLP-1) and 206 % (PYY) at 60 min after meal onset, respectively. Compared to IG vehicle infusion, IG DGAT-1i (10 mg/kg body weight) enhanced ($p < 0.05$) the meal-induced GLP-1 and PYY response by 46% and 65% respectively (t_{AUC} = 0 – 180 min after meal onset). Under similar conditions, IG DGAT-1i administration reduced food intake (FI; 26.7%; $p<0.05$). These data indicate that pharmacological inhibition of TAG re-synthesis in the small intestine directly or indirectly enhances meal-induced GLP-1 and PYY release. This effect may contribute to the FI reduction in response to DGAT-1i administration. Supported by: AstraZeneca R&D, UK.

Abnormal adaptation to lactation leads to normalization of obesity at the time of weaning in CCK1R deficient rats

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OLETF rats lack CCK_1 receptors and represent a model of hyperphagia induced obesity. We studied adaptation of the dams to the challenges of pregnancy and lactation, when rearing their own or opposite-strain pups. We focused on body weight/adiposity, milk lipid content, intake, maternal behavior and hypothalamic gene expression of NPY and POMC in selected brain areas. We found that: 1) OLETF dams were obese and overate during pregnancy and the post-weaning period, but consumed normal amounts of food during the lactating period. This lead to transient weight loss, while OLETF pups still developed pre-obese symptoms. LETO control dams showed hyperphagia during pregnancy and lactation, but returned to normal intake/ adiposity/weight after weaning; 2) The dams' physiological adaptation was not altered by the pups' strain; 3) OLETF mothers presented more frequent nursing on PNW3, but only when rearing OLETF pups. LETO maternal behavior remained unchanged; 4) OLETF dams presented higher milk lipid levels than controls and 5) NPY levels in the ARC and DMH were not increased as expected for lactating OLETF females, suggesting defective hypothalamic adaptation to the demands of lactation. The results show between-strain differences in the pattern of adapting to the energy-demanding perinatal period. Importantly, OLETF females' "normal" intake during lactation implies that the unique hormonal background characterizing lactation may override the genetic deficiency in the CCK system that usually leads to overeating and obesity. Supported by: NIH-NIDDK.

Neuronal reward processing

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We investigated basic neuronal reward and risk processes that are important for decision making, using neurophysiological and neuroimaging methods. Dopamine neurons are activated by rewards and reward prediction stimuli. The signal reflects reward prediction error which represents a crucial signal for learning. As electrical and optogenetic activation of dopamine

neurons elicits learning and approach behaviour, the data suggest a role for dopamine neurons in reward processing. Reward value appears to depend on the individual decision maker and the environment, and hence is subjective. Dopamine neurons, and likely downstream striatal activations, discount reward value across temporal delays of a few seconds despite unchanged objective reward value, suggesting subjective value coding. Reward predictions inform about probability distributions of reward value and thus the degrees of risk. Dopamine and orbitofrontal neurons code risk distinct from value and utility. The processing of risky outcomes depends on the subjective perception of risk and on individual risk attitude. Human risk signals covary with risk attitudes in subregions of prefrontal cortex, suggesting subjective coding of risk. Together, these data suggest that reward neurons code the key parameters determining the subjective reward values underlying economic decisions. Supported by: Wellcome Trust.

Flavor Conditoning by Nutrients in the Gut

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Food selection and preference are influenced by the flavor (taste, odor, texture) but also by the post-oral actions of nutrients. This is demonstrated by studies in which the intake of a flavored solution is paired with an intragastric (IG) nutrient infusion (e.g., glucose, corn oil), and a different flavored solution is paired with a water infusion. In subsequent choice tests, animals show strong preferences for the nutrient-paired flavor. Flavor-nutrient conditioning can occur in a single training trial, in non-deprived as well as food-deprived animals, and is very resistant to extinction. The magnitude of the conditioned preference varies as a function of flavor quality, nutrient type and energy density. The upper small intestine is a primary site of action for glucose conditioning as indicated by the effectiveness of duodenal and jejunal infusion sites, but not by infusions that bypass the upper intestine (ileal or hepatic-portal). The identity of the nutrient sensors that mediate flavor conditioning is not known. Intestinal sweet taste receptors are not implicated because T1R3 knockout mice show a robust conditioning response to IG sugar infusions. Rather, a glucose-specific sensor is suggested by the conditioning effectiveness of glucose but not fructose, galactose or the artificial sweetener sucralose. Also unknown is the gut-brain pathway that mediates nutrient conditioning. Vagal deafferentation does not block carbohydrate conditioning, which suggests hormonal mediation. Supported by: National Institutes of Health Grant DK031135.

Assisted reproductive techniques alter energy balance of young mice

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It is estimated that at least 3 million children have been born following assisted reproductive technologies (ARTs). The majority of these children appear healthy, although there are reports of altered glucose metabolism in young adults. Because of their relatively short time of use, little data pertaining to the long-term effects of ARTs exist. Therefore, we have utilized a mouse model to investigate the effects of IVF and intracytoplasmic sperm injection (ICSI). We have reported that 8 wk old mice conceived by ARTs have altered responses to glucose tolerance tests (GTT). IVF mice in particular have elevated basal insulin and significantly higher levels in response to GTT. These effects are evident despite similar body weight and body composition. Shortly thereafter, body weights of IVF and ICSI become significantly heavier than controls. Although differences existed 8 wks, no differences in response to GTT were observed at 20 wks. Body weight changes reflect increased adiposity and plasma leptin, and are most prominent in IVF mice. Preliminary data suggest that IVF mice exhibit higher levels of NPY mRNA expression in the arcuate nucleus of the hypothalamus (ARC) at 8 wks of age (prior to development of obesity) than control mice, while POMC and AgRP expression does not differ

between groups. These findings suggest that altered glucose metabolism in young mice is transient, but may play a role in the future development of body weight and composition changes. Supported by: DK 068273.

The relationship between reward contingency and attention to conditioned food cues.
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Previous research indicates that food cues are able to command greater attention in obese vs. lean participants and individual differences in food cue responsiveness predict weight gain over a 12 month period. Here we explore the influence of motivational state on the ability of neutral stimuli to acquire incentive salience through classical conditioning. Participants who were either deprived of chocolate or not (N=30/group) were first trained to associate neutral stimuli (CS) with chocolate using a reward contingency of 0, 10, 50 and 90%. Cue salience was then measured with an attentional blink task where participants had to correctly identify two targets within a stream of 15 distracters. The detection rate for target 2 (T2) is decreased when it rapidly follows target 1 (T1) as processing of T1 causes T2 to be missed. Detection typically improves when T2 is highly salient and in this case the training stimuli were used as T2. We also recorded brain activity using EEG in a subset of participants (N=24) during the task. Preference for the CS after training was significantly related to reward contingency ($P<0.05$). There was a significant main effect of reward contingency on correct detection of T2 ($P<0.001$), with CS associated with 10 and 90% rate of reward showing the highest detection levels ($P<0.001$). Mean percent correct = 49.7 (±0.03), 66.1 (±0.04), 54.7 (±0.02), 65.6 (±0.03) for 0, 10, 50 and 90% reward contingencies respectively. There was no main effect of deprivation condition, nor any interaction between deprivation and reward contingency on T2 detection. ERP analysis of P300 peak amplitude following T2 presentation showed a significant interaction between deprivation condition and reward contingency ($P<0.05$). In non-deprived participants there was a greater brain response to the 10 and 90% contingency cues compared to 0 or 50%. No difference between contingencies was evident in the non-deprived group. These results show for the first time that preferential allocation of attention can be seen in response to neutral cues paired with food reward. Supported by: Swansea University Graduate Teaching Studentship.

Fructose-induced leptin resistance involves impaired AMPK but intact STAT3 signaling
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Specific dietary components may contribute to dietary-induced leptin resistance. We reported 6 months of 60% dietary fructose impairs physiological responses to leptin. The present objective was to determine if dietary fructose is associated with impaired leptin signaling, and if shorter durations and lower concentrations of fructose still induce leptin resistance. Rats were fed 60% fructose for 60 days, followed by acute icv leptin (2ug) injection. Fructose decreased levels of pAMPK and pACC and prevented dephosphorylation of pAMPK and pACC by leptin. In contrast, fructose did not disrupt leptin-mediated STAT3 signaling. In a separate study, STAT3 signaling was impaired with a typical 60% fat/7% sucrose diet whereas with 60% fat/sugar free or 13% fat/60% fructose, STAT3 signaling remained intact. Next, rats were fed 20% fructose, a concentration close to high-end human consumption, for 14 days followed by 7-day icv leptin (1.5ug/day) infusion. Leptin responses (reductions in food intake and body weight) were impaired with fructose feeding. Collectively, these data indicate that fructose-induced central leptin resistance includes disruption in the leptin-mediated AMPK/ACC pathway but the STAT3 signaling pathway remains intact. Moreover, fructose-induced central leptin resistance occurs

rapidly in less than 14 days and with dietary fructose concentrations similar to high-end human consumption. Supported by: Supported by NIH AG-26159, T32AG00196, P30 AG028740..

The role of Melanin Concentrating Hormone (MCH) in reward learning.
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MCH is an orexigenic peptide that is expressed throughout the cortico-limbic-striatal reward circuit. We examined whether systemic treatment with pharmacological agents designed to antagonize the MCH receptor (MCH-1R), or targeted-deletion of MCH-1R in gene-targeted knock-out (KO) mice would disrupt two putative forms of reward learning that rely on different neural circuitries: Pavlovian-instrumental transfer (PIT) and conditioned reinforcement (CRf). In Experiment 1, control mice and MCH-1R KO mice were trained to discriminate between presentations of a reward-paired cue (CS+) and an unpaired CS-. Following normal acquisition of the Pavlovian discrimination in all mice, we assessed whether the CS+ was capable of augmenting ongoing instrumental lever performance (PIT). Neither pharmacological inactivation of the MCH-1R receptor in control mice, nor MCH-1R deletion in KO mice disrupted this form of reward learning, indicating that MCH-1R signaling is not required for attributing incentive motivation to the CS+. In Experiment 2, following Pavlovian training, the ability of the CS+ to reinforce new instrumental nose-poke learning was assessed (CRf). Pharmacological disruption in control mice, and genetic deletion in KO mice impaired CRf test performance, suggesting MCH-1R is necessary for initiating and maintaining behaviors that are under the control of conditioned reinforcers. These results suggest a role for MCH in guiding behavior based on the conditioned reinforcing value of a cue, but not on its incentive motivational value. Supported by: DK84415.

Exendin-4 decreases food reward and directly targets the mesolimbic circuitry
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Glucagon like peptide 1 (GLP-1) system is a new, emerging target for diabetes treatment. GLP-1 in addition to effects on glucose homeostasis also reduces food intake. To date impact of GLP-1 on feeding has only been evaluated on CNS areas classically involved in feeding regulation, the hypothalamus or brainstem. Some aspects of feeding behavior however can be regulated outside of those sites. Recently the mesolimbic system has emerged as a key target for regulation of food reward and motivation, major contributing factors to obesity and overeating. Interestingly, GLP-1 receptors (GLP-1Rs) are expressed in key mesolimbic nodes, the ventral tegmental area (VTA) and nucleus accumbens (NAc). Surprisingly their function is entirely unexplored. Here we hypothesized that GLP-1 can regulate food reward, and act directly on the mesolimbic system. Using two models of food reward, sucrose operant conditioning and conditioned place preference (CPP) in rats, we show that peripheral Exendin-4 (EX4), a stable analogue of GLP-1, powerfully inhibits both of these reward behaviors. We next demonstrate that this effect is mediated centrally, via GLP-1Rs. We further explore the neurobiological substrate underlying this effect, using direct microinjection of EX4, and indicate that EX4 mediated inhibition of food reward can be driven from two mesolimbic nodes, the VTA and NAc. In addition, both VTA and NAc EX4 microinjections reduced chow intake. These data are the first to demonstrate a striking impact of GLP-1 on food reward and to indicate a direct role for GLP-1Rs in the mesolimbic system. FP7-HEALTH-2009-241592; FP7-KBBE-2009-3-245009 & FP7-KBBE-2010-4-266408 Supported by: European Eunion: FP7-HEALTH-2009-241592 (EurOCHIP) FP7-KBBE-2009-3-245009 (NeuroFAST) and FP7-KBBE-2010-4-266408.

Effects of exercise on meal related gut hormone responses and CCK sensitivity
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Wheel running (WR) in rats has been shown to cause transient reductions in body weight (BW) and food intake and to increase leptin sensitivity. We hypothesized that exercise affects food intake by changing either gut hormone secretion or sensitivity. The effects of acute and long-term exercise on BW, food intake, gut hormone release and CCK sensitivity were examined in male Sprague-Dawley rats. The rats were divided (n=6/group) into sedentary (Sed) and (WR) with food intake, BW, and WR activity monitored daily. A meal test was performed prior to, 3 days and 2 weeks after wheel access. Rats were food deprived for 4 hrs then given a meal of Ensure (~9.5kcal) through oral gavage at lights out. Blood samples were collected for gut hormone analysis 15 min before the meal and up to 4 hrs post meal. After 2 weeks of running wheel access the effect of exercise on CCK (0.32, 0.56, 1 and 3.2 nmol/kg) sensitivity was tested. Rats were food deprived for 4 hrs and given an IP injection of CCK 15 min prior to lights out and Ensure access. Compared to Sed, exercise significantly decreased BW, food intake, and meal size after 3 days WR. Long-term exercise caused a significant increase in post-meal amylin and a significant rebound of ghrelin at the 4 hr timepoint. Furthermore, 1 nmol/kg CCK reduced Ensure intake significantly greater in WR than in Sed rats . Together these results suggest exercise affects food intake by changing gut hormones release patterns as well as increasing sensitivity to gut feedback signaling. Supported by NIH grant DK19302. Supported by: NIH grant DK19302..

Hepatic portal vein (HPV) peptide tyrosine-tyrosine (PYY) and meal-taking in rats
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Peripheral administration of PYY inhibits eating, but the site, mechanism, and physiological relevance of PYY's eating-inhibitory action are unclear. Here we equipped adult male rats (n=8) kept on a medium-fat diet with HPV catheters and infused (0.2 ml/min) glucagon-like peptide-1 (GLP-1), PYY (1.0 nmol/kg BW, each) or vehicle (V) by remote control during the first spontaneous nocturnal meal. Either peptide reduced ($p < 0.05$) ongoing meal size (V: 4.1 ± 0.2, PYY: 2.4 ± 0.2, GLP-1: 1.6 ± 0.1 g; mean ± SEM). Subsequent meal sizes and cumulative food intake (2 h and beyond) were unaffected. In 10 other rats kept on chow intra-meal HPV PYY (1.0 and 3.0 nmol/kg BW) infusions also reduced ($p < 0.05$) meal size (V: 2.6 ± 0.2, 0.33 nmol: 2.5 ± 0.4, 1.0 nmol: 1.8 ± 0.2, 3 nmol: 1.8 ± 0.2 g). Intragastric nutrient infusions usually stimulate intestinal PYY release, but so far circulating PYY has not been measured in relation to real meals in rats. We did so and found that an isocaloric chow or high fat (HF) meal (12.5 kcal) given at dark onset after 3 h food deprivation increased ($p < 0.05$) HPV plasma PYY concentration from 70 ± 6 (0 min) to 104 ± 9 pg/ml (chow) and from 56 ± 9 (0 min) to 85 ± 9 pg/ml (HF) at 15 min after meal onset. Plasma PYY did not increase under control conditions without a meal. These findings show that HPV PYY increases during normal meals in rats and that experimentally induced prandial increases in HPV PYY can acutely inhibit eating. Further studies should examine whether PYY administrations that mimic the meal-induced increase are sufficient to inhibit eating.

Antipsychotic drug induced metabolic dysfunction and its amelioration using zonisamide
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The use of antipsychotic drugs (APDs), including olanzapine, in the treatment of schizophrenia is associated with pronounced weight gain and dysregulation of glucose metabolism. These studies aim to determine whether companion administration of olanzapine and zonisamide can be

used to prevent these metabolic disturbances. The experiments involve female Sprague Dawley rats, administered olanzapine, in combination with zonisamide. Chronic olanzapine administration increased the size of visceral and subcutaneous adipose tissue depots, associated with a reduction in β adrenergically stimulated lipolysis driven by lipases including ATGL and HSL. Subchronic olanzapine treatment was associated with a preferential shift to carbohydrate oxidation and a reduction in locomotor activity. Acute olanzapine administration caused rapid hyperglycemia, in addition to a reduction in glucose tolerance and insulin sensitivity. Chronic administration of olanzapine is associated with significant hyperinsulinemia during a glucose challenge, in addition to a significant reduction in insulin sensitivity. Co-administration with zonisamide ameliorated a range of metabolic changes induced by olanzapine resulting in a normalization of APD induced weight gain and dysregulated lipid metabolism. These findings suggest that a combined olanzapine and zonisamide approach in the treatment of psychoses might reduce the adverse effect profile seen in some patients, and may provide opportunity for better long term outcomes in schizophrenia.

Wheel running and caloric restriction recruit distinct hypothalamic transcriptional profiles in wildtype and leptin receptor deficient mice

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The hypothalamus is an essential relay in the neural circuitry underlying energy metabolism. In the current report, we have manipulated energy intake and expenditure using restricted feeding and voluntary wheel running. We performed these experiments in male wildtype (C57Bl/6) mice, and in db/db mice, which lack functional leptin receptors. After running or caloric restriction, we simultaneously assessed multiple gene expression profiles in the hypothalamus. This analysis revealed that, under basal sedentary conditions with ad libitum feeding, genes associated with embryonic development, reproduction, and carbohydrate metabolism were differentially expressed in the hypothalamus of db/db mice. After running, a wider array of functional gene sets met statistical criteria for differential expression in wildtype mice, relative to db/db mice, in a manner consistent with the higher activity levels exhibited by wildtype mice. However, following caloric restriction, a more varied set of transcripts reached expression criteria in db/db mice, relative to wildtype mice. Both quantitatively and qualitatively, caloric restriction and physical exercise are associated with distinct transcriptional signatures that differ between wildtype and leptin receptor deficient mice. Supported by: National Institute on Aging Intramural Research Program.

Maternal high fat diet during gestation or suckling alters offspring leptin sensitivity prior to weaning.

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Maternal high fat (HF) diet through gestation and suckling has long term consequences on offspring's metabolism. In this experiment, we used a cross-fostering paradigm to determine whether maternal HF diet affects offspring leptin sensitivity before weaning. Female Sprague Dawley rats arrived on gestation day 2 and were divided randomly to receive chow (CH) or HF diet through gestation and suckling. On PND1, all litters were cross-fostered to a CH or HF dam resulting in four groups of pups according to their dams' diet: CH-CH, CH-HF, HF-CH and HF-HF. Pups cross-fostered to HF dams had greater body weight, more subcutaneous and visceral adiposity and higher plasma leptin than CH-CH or HF-CH group on PND10 and PND21. Pups were challenged with saline or leptin (3mg/kgbw, ip) and p-STAT3 protein was measured in the

ventral hypothalamus on PND10 or arcuate nucleus on PND21. On PND10, male pups with prenatal or/and postnatal HF diet had lower p-STAT3 after leptin challenge relative to the CH-CH group while female pups with prenatal HF diet had lower p-STAT3 after leptin challenge. On PND21, both male and female pups with postnatal HF diet had lower p-STAT3 after leptin challenge while HF-CH pups had similar p-STAT3 compared to the CH-CH group. Taken together, these data suggest that maternal HF diet during gestation or suckling alters offspring leptin sensitivity before weaning. Supported by: NIH grants DK077623, HD055030.

Ghrelin administration in humans increases bids for food items while decreasing bids for non-food items

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Previous research has shown that activity in the ventromedial prefrontal cortex (VMPFC) correlates with people's willingness to pay for goods, and that the orexigenic peptide ghrelin enhances activity in the VMPFC while subjects view food pictures. In this we investigate the impact of ghrelin in the values that the vmPFC assign to foods at the time decision-making. We hypothesized that the administration of ghrelin would increase subjects' willingness to pay for food items as well as the value signals encoded in vmPFC, but this will not be the case for non-food items (trinkets). We scanned 29 normal weight participants using fMRI and asked them to bid for the right to get food items and trinkets of comparable value in two different conditions: following either a ghrelin or a saline control injection. Behaviorally, ghrelin significantly increased the willingness-to-pay for food items ($2.09 ghrelin, $1.82 saline, $p < 0.05$), abut it marginally reduced the willingness-to-pay for trinkets ($1.32 ghrelin, $1.58 saline, $p = 0.052$). Neurally, we found greater activity in the VMPFC after ghrelin administration when brain response to food was modelled as a function of bid value. Conversely, the VMPFC bid effect for trinkets was greater in the saline condition. Results suggest that ghrelin increases the motivational value of foods by increasing the value assigned to food stimuli in the VMPFC.

3rd ventricular co-injection of sub-threshold doses of NPY and AgRP stimulate food hoarding, foraging and intake and neural activation.

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Obesity is a growing concern in industrialized nations, with ~60% of Americans classified as overweight/obese. We previously showed that 3rd ventricular (3V) neuropeptide Y (NPY) and agouti-related protein (AgRP) injection potently stimulates food foraging/hoarding/intake. Here we tested whether sub-threshold doses of NPY and AgRP, alone or together stimulates food foraging/hoarding/intake and neural activation [Fos immunoreactivity (ir)] in Siberian hamsters housed in our foraging/hoarding apparatus. Each hamster received each of four treatments: 1) NPY (0.0176 nmol), 2) AgRP (0.01 nmol), 3) NPY + AgRP and 4) saline with a 7-d washout period between treatments. Doses were shown previously to be sub-threshold for all ingestive behaviors. Foraging (pellets earned), food intake and hoarding were measured 1, 2, 4, and 24 h post-injection. 3V injection of NPY + AgRP stimulated food hoarding, foraging and, to a lesser extent, food intake, whereas other treatments did not. After identical treatment in separate animals, cFos-ir was assessed at 2- and 14-hr post-injection, times when food intake (0-2 h) and hoarding (4-24 h) were uniquely stimulated, cFos-ir was increased in several hypothalamic and hindbrain nuclei (including the arcuate, magno- and parvocellular paraventricular, and area postrema) previously shown to be involved in ingestive behaviors, but only in NPY + AgRP treated animals. These results suggest that NPY and AgRP can interact to stimulate ingestive behaviors and neural activation at distinct time points. Supported by: NIDDK.

CRF1R ANTAGONISTS AND NPY AGONISTS PROTECT AGAINST BINGE-LIKE ETHANOL DRINKING IN C57BL/6J MICE BUT FAIL TO INFLUENCE LOW ETHANOL INTAKE

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Binge drinking, defined as excessive ethanol intake over a short period of time that generates elevated blood ethanol levels (80 mg/dL or greater), has become a serious health problem world-wide. Longer-term binge drinking has been implicated in the subsequent development of ethanol dependence. Here we provide evidence showing that various CRF1R antagonists protect against excessive binge-like drinking of a 20% (v/v) ethanol solution (associated with blood ethanol concentrations [BECs] of >100 mg/dL) in non-dependent mice but do not alter drinking in mice consuming moderate amounts of ethanol (associated with BECs <25 mg/dL). Similarly, NPY protects against binge-like ethanol drinking but does not reduce non-binge-like ethanol intake. Follow-up studies showed that a selective NPY type-1 receptor (Y1R) agonist and type-2 receptor (Y2R) antagonist blunt binge-like ethanol drinking, and that binge-like ethanol consumption causes a significant increase of CRF and decrease of NPY immunoreactivity (IR) in the central nucleus of the amygdala (CeA). The present results suggest that binge-like ethanol drinking in non-dependent mice triggers alterations within central CRF and NPY pathways analogous to what occurs in ethanol-dependent rodents. Thus, CRF1R antagonists, Y1R agonists, and Y2R antagonists are potential attractive therapeutic targets for treating problem binge drinking in the human population. (Supported by grants from NIAAA and the Department of Defense). Supported by: NIAAA and the Department of Defense.

Neither basal energy expenditure under low fat feeding nor TEF and RQ responses to a low- or high-fat test meal identify high fat sensitive rats.

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Individuals challenged by a high fat diet (HFD) are known to present differences in sensitivity to body fat (BF) gain. We previously observed that fat sensitive (FS) rats can be segregated from fat resistant (FR) ones from their larger meal number under low fat diet (LFD), and, when switched to a HFD, a larger decrease in total energy expenditure (EE) and a smaller one in respiratory quotient (RQ). In this study, EE and RQ were measured in LFD fed rats in the basal state and in response to ingestion of a test meal of either the LFD or a HFD. The rats were separated between FS and FR according to their BF gain later measured by MRI during 3wks of HFD. Basal EE, TEF, resting- and movement-RQ values in response to the test meals were similar in FS and FR rats. To test the lack of association between BF gain and these components of EE, BF gain was analyzed after grouping of rats into those of low or high (i) basal EE, (ii) TEF, (iii) resting-RQ and (iv) movement-RQ. This study showed that large individual differences in these parameters did not result in significant differences in HFD-induced BF gain. In conclusion, FS rats fed a LFD cannot be distinguished from the components of their EE nor in response to an acute challenge with a LFD or HFD meal. Interestingly, individuals that exhibit large metabolic differences appear eventually to exhibit the same sensitivity to HFD. Thus development of the FS phenotype is expressed after medium/long exposure to the HFD. Supported by: INRA.

Meal-induced increase in respiratory quotient but not basal energy expenditure or thermic effect of feeding can predict body fat gain sensitivity of rats to a low fat high carbohydrate diet

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Individuals challenged by a high fat diet present large differences in sensitivity to body fat (BF) gain, but BF gain can also vary substantially in rats fed a low-fat high carbohydrate diet (HCD). This led us to define the concept of carbohydrate sensitive (CS) vs carbohydrate resistant (CR) rats in opposition to the usual concept of fat sensitive vs fat resistant rats. In the present study energy expenditure (EE) and respiratory quotient (RQ) were measured in 24 HCD-fed rats in the basal state and in response to ingestion of a test meal of the usual HCD. The rats were separated between CS and CR according to their 3 wk BF gain measured by MRI. Data were compared between the 8 rats that gained the least fat and the 8 that gained the most. Basal EE corrected for lean body mass and the thermogenic response to the meal were similar in CS and CR rats. In contrast, post-meal RQ was significantly higher in CS rats (from 60 to 225 minutes post meal) suggesting a defective fat oxidation. To test the potential predictive power of post-meal RQ, the 24 rats were re-ordered according to their RQ response to feeding and BF gain measured in the 2 groups composed of the 8 rats with the lowest post-meal RQ values and the 8 with the highest values. The two groups thus formed revealed a significant difference in BF gain suggesting that post-meal RQ can be a simple non-invasive means to discriminate between CS and CR rats.

Rats display behavioral adaptation to a diet containing tannic acid

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Animals, including humans, regularly consume tannins in their diet. Previous studies have demonstrated that salivary proline-rich proteins (PRPs) can bind to tannins and increase the acceptability of tannin- containing diets. It has been hypothesized that this change in acceptability is due to PRPs preventing tannic acid from binding to bitter taste receptors. Since rats do not constitutively produce high levels of PRPs, but induce production when challenged with a tannin diet, they are an ideal model for studying the effects of PRPs on feeding behavior. We measured the spontaneous feeding behavior of 8 rats consuming a control diet (5 days) followed by a diet containing 3% tannic acid (6 days). Total intake was reduced during the first three days of exposure to the tannin diet ($p<0.001$) dropping from 28g/day on control diet to 19 g/day at first exposure to tannic acid. This reduction was due entirely to a decrease in meal size ($p<0.001$) with no alteration in meal number. Total intake and meal size recovered to baseline levels by the fourth day of exposure to the tannin diet, presumably due to the induction of PRPs. Consumption of the tannin diet also decreased rate of feeding and increased meal duration (from 9 to 15 minutes) but these measures, which reflect diet palatability, did not return to baseline levels. We conclude that alterations in the acceptability of the diet are not due to a change palatability of tannin containing diets in rats. Supported by: NIH 5 T32 DC000044, DK73936 and DC-004785 .

The role of reinforcer exposure and diet duration in high-fat diet-induced motivational deficits

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Previous work indicates that obese rats chronically consuming a high-fat diet (HFD) bar press at lower rates relative to lean rats maintained on chow, as well as showing alterations in dopamine function (Davis et al., 2008). The goal of the current studies was to assess factors related to dietary experience to elucidate mechanisms underlying this observed behavioral change. In Experiment 1, half the rats in each diet group (HFD or chow) were exposed to sucrose pellets prior to dietary manipulation. After 12 weeks on the assigned diet, rats underwent operant conditioning with the same sucrose reinforcer. Results indicate that exposure to sucrose prior to

receiving HFD attenuated the suppression of responding (on both FR and PR schedules) in the HFD condition. In Experiment 2, rats were maintained on HFD or chow for 3 weeks prior to operant conditioning. Following conditioning, half the rats in each diet condition were switched to the other diet and half remained on the initial diet. Results show that 3 weeks of HFD had no effect, while 6 weeks of HFD significantly reduced bar pressing. These studies support the hypothesis that physiological changes develop over time during chronic HFD consumption and accumulation of body fat that may be responsible for the motivational deficits observed. Further, these results suggest that the encoded value of the reinforcer depends on initial exposure to the reinforcer relative to the HFD and/or the physiological changes associated with the development of obesity. Supported by: NIH (DK066223), Grinnell College, University of Cincinnati (URC Post-doctoral fellowship).

INTESTINAL CD36: A LIPID-SENSOR INVOLVED in the PROCESSING of CHYLOMICRONS in RODENTS.

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CD36 is a multifunctional glycoprotein which binds nanomolar concentrations of long-chain fatty acids (LCFA) and is highly expressed on the luminal surface of enterocytes. Despite of its implication in oleoylethanolamide (OEA) and chylomicron synthesis, CD36 function in small intestine remains incompletely understood. Our *in vivo* data demonstrated that CD36 gene deletion in mice did not affect intestinal LCFA uptake. CD36 protein disappeared early from the luminal side of intestinal villi during the post-prandial period but only when the diet contained lipids. This drop was significant 1h after a lipid supply and was associated with ubiquitination of CD36. Using CHO cells expressing CD36, it was shown that the digestion products, LCFA and diglycerides, trigger CD36 ubiquitination. *In vivo* treatment with a proteasome inhibitor prevented the lipid-mediated degradation of CD36. *In vivo* and *ex vivo,* CD36 was required for dietary-lipid activation of ERK1/2 which is associated *ex vivo* with an increase of ApoB48 and MTP, proteins involved in chylomicron formation. Therefore, intestinal CD36 through ERK1/2 mediated signaling displays features of a lipid sensor involved in the adaptation of intestinal metabolism to the postprandial lipid challenge by promoting the production of large chylomicrons rapidly cleared in the blood. Supported by: National Institute of Health and Medical Research (INSERM) and the National Institute of Agronomic Research (INRA) and by grants from the Research Program in Human Nutrition SensoFAT, French National .

In Contrast to Sucrose, Normal Taste Sensitivity to Polycose in Mice Does not Depend on the Combined Presence of T1R2 and T1R3

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The T1R2 and T1R3 proteins form a heterodimer binding with “sweet” tasting compounds. Here, we tested the necessity of these subunits in the detection of various compounds. We trained T1R2 knock-out (KO), T1R3 KO and their wild-type (WT) littermate controls (n=7-9/group) in a two-response operant discrimination procedure to lick a response ball upon sampling a taste solution and to lick another response ball upon sampling water. Correct responses were reinforced with water and incorrect responses were punished with a time-out. Testing was conducted with a modified descending method of limits procedure across 25-min sessions. The KO mice failed to discriminate 1 M sucrose from water. These same mice showed normal NaCl sensitivity (EC_{50} of the concentration-% correct curve). KO and WT mice did not differ in the EC_{50} of their Polycose psychometric functions, but Genotype x Concentration ANOVAs revealed

significant interaction effects largely due to slightly poorer performance of KOs at higher concentrations. There was evidence that the KO (especially T1R2) mice could detect maltose at high concentrations, but their performance was overall significantly worse than their WT counterparts. Our findings provide strong evidence that in contrast to sucrose, the combined presence of T1R2 and T1R3 is unnecessary for relatively normal orosensory detection of Polycose, at least in this task. Some detectability of maltose might be mediated by the putative polysaccharide taste receptor, potential T1R homodimers, or non-taste orosensory cues.
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Lateral Hypothalamic NMDA and $GABA_A$ Receptors Mediate Feeding Elicited by Ipsilateral Nucleus Accumbens Shell Inhibition

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Food intake can be elicited by NMDA receptor stimulation or $GABA_A$ receptor blockade in the lateral hypothalamus (LH). Similarly, $GABA_A$ receptor stimulation or AMPA receptor blockade in the nucleus accumbens shell (AcbSh) can produce feeding. Although a feeding-relevant functional relationship between these nuclei has been demonstrated, it is unclear whether this interaction is ipsilateral or contralateral. To explore this interaction, adult male Sprague-Dawley rats were implanted with three chronic indwelling cannulas, one into the AcbSh and two bilaterally into the LH. To evoke food intake, the $GABA_A$ receptor agonist muscimol (0.1 µg) or the AMPA receptor antagonist 6,7-Dinitroquinoxaline-2,3-dione (DNQX, 1.25 µg) was injected into the AcbSh. To suppress the AcbSh inhibition-induced feeding, the NMDA receptor antagonist D-(-)-2-Amino-5-phosphonopentanoic acid (D-AP5, 2.0 µg) or muscimol (25 ng) was injected into the LH either ipsilateral or contralateral to the AcbSh injection site. AcbSh muscimol and DNQX separately caused increased eating within 2 hours of injection and ipsilateral LH injections of D-AP5 or muscimol suppressed or blocked this increase. In contrast, injection of D-AP5 or muscimol into the contralateral LH had little or no suppressive effect. These results suggest that there is a strong ipsilateral bias in the feeding-relevant functions of the glutamate and $GABA_A$ receptor-modulated AcbSh-LH circuit.

Neuropeptide Y sensitivity in an animal model of diet induced obesity

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Neuropeptide Y (NPY) is a hypothalamic hunger peptide, which is downregulated upon food ingestion. Interestingly, rats on a free choice high-fat high-sugar (fcHFHS) diet for 1 week show paradoxically increased NPY mRNA levels despite profound hyperphagia. After 4 weeks, mRNA levels are similar to chow, but hyperphagia remains. As the mRNA levels do not explain the sustained hyperphagic behavior, we hypothesized that NPY sensitivity increases in rats on the fcHFHS diet over the course of 4 weeks. For 4 weeks, rats were subjected to chow only, a fcHFHS diet or a choice diet of fat and chow (fcHF). After 1 and 4 weeks, rats received an intracerebroventricular (ICV) injection of 1µg NPY or vehicle. Total caloric intake and individual food components (chow, fat and sugar) were determined 2 hours after ICV injection. We showed that after 1 week both fcHF and fcHFHS groups overate and showed increased response to NPY compared to chow. After 4 weeks, only fcHFHS remained hyperphagic and showed increased responsiveness to NPY compared to fcHF and chow. Moreover, in rats on fcHFHS, NPY mainly increased the preference for lard and chow, but not sugar, after both 1 and 4 weeks on the diet. In conclusion, the higher NPY responsiveness in rats on a fcHFHS diet explains their continuing hyperphagic behavior and may result from increased NPY receptor availability since NPYmRNA

levels were not increased. Interestingly, NPY increased the hedonic fat component as well as the healthy chow component in the fcHFHS diet.

Investigation into the specificity of the behavioral desensitization observed after repeated angiotensin II administration.

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Central injection of angiotensin II (AngII) robustly increases intake of water and saline, but multiple icv injections of AngII reduce its dipsogenic efficacy, without affecting saline intake. The present experiments were designed to rule out several potential non-specific effects that could possibly account for the decreased dipsogenic potency of AngII. To test for aversive properties of the desensitizing paradigm, we paired a novel flavor (vanilla or almond) with the procedure used to generate behavioral desensitization to AngII (3x 300 ng AngII, icv) or its control manipulation (3x TBS, icv). Subsequent preference tests did not detect differences in intake of the two fluids, suggesting an absence of a conditioned taste aversion. Additional studies evaluated changes in blood pressure to test for different pressor responses to AngII in control and behaviorally desensitized rats. Tail-cuff pressure recordings detected an increased pressor response by AngII, but this was not significantly different between these groups at the time that corresponds with the observed behavioral effect. Further testing showed that the behavioral desensitization that occurs after repeated AngII is specific to the angiotensin system because water intake stimulated by a test injection of AngII was reduced, but carbachol-induced drinking was unaffected. These data are consistent with a desensitization of the response rather than a less selective suppression of behavior. Supported by: NIH.

Aging of vagal afferent glutamatergic neurons in the rat

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It is well known that vagal afferent neurons in nodose ganglion (NG) provide a direct connection between the gastrointestinal tract and the hind brain, and glutamate plays the major role in vagal neurotransmission. However, there has been surprisingly little known on aging of vagal afferent neurons with respect to neurochemical phenotype and function. Our previous results indicate that vagal afferent neurons in NG from 6-week-old rats express NMDA receptors composed of NR1, NR2B, NR2C and NR2D subunits. It has been also shown that CCK reduced food intake by acting on vagal afferent neurons and that the non-competitive NMDA-type glutamate receptor antagonist, MK-801, increased food intake in adult rats. In order to determine the age-related changes in subunit composition of NMDA receptors, we employed immunocytochemical techniques in NG from 6-week-old, 30-week-old and 60-week-old male Sprague-Dawley rats. To address age-related functional changes in vagal neurotransmission, we studied food intake at different ages following CCK and MK-801 administration. Results of the study revealed the age-related reduction of NR2B and NR2C subunit expression in NG. Moreover, CCK reduced food intake in all studied groups and there were no significant age-related differences. In 6-week-old rats,MK-801 increased food intake by about 20% while in older rats this effect was doubled. Results of our study show that vagal afferent glutamatergic regulation of food intake changes with age, and subunit-composition of NMDA receptor of vagal afferents contributes to the changes in the glutamatergic control of food intake. Supported by: NIH/NIDDKD R01 DK052849.

Effect of ghrelin administration into the ventral tegmental area (VTA) on food-reinforced behavior in dopamine intact and depleted rats.

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Recent evidence suggests that the gut-brain peptide ghrelin acts via the mesolimbic system to alter appetitive motivation. In the present study, rats were trained to operantly respond for food on a progressive ratio PR5 schedule and stable breakpoints were established. Ghrelin was then microinjected into the ventral tegmentum at doses of 30 and 300 pmol, eliciting an increase in breakpoint. The neurotoxin 6-hydroxydopamine (6-OHDA) was subsequently administered into the VTA resulting in a 77% depletion of forebrain dopamine. Stable breakpoints were again established. We then assessed ghrelin's ability to alter operant responding for food and found that the effect of ghrelin on food-reinforced behavior was diminished. Our findings indicate that ghrelin alters food-motivated behavior by acting within the VTA and that this effect is dependent on intact dopaminergic neurons.

Molasses extract decreases diet-induced obesity

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Obesity, the excess accumulation of adipose tissue, is associated with over 30 medical conditions and is a major health problem worldwide. Polyphenols are plant chemicals that have antioxidant properties, with some being shown to reduce body fat deposition. Our aim was to investigate the effect of supplementation with 0, 2 or 4% molasses extract (ME) in male C57BL/6J mice fed a high fat (21%) diet for 10 weeks (*n*=15 mice/group). Body weight, food and water intakes were measured daily. At the end of the 10 week period, body composition (DEXA, MRI); plasma adiponectin and leptin (ELISA); faecal energy content (bomb calorimetry), adipose (adiponectin, PPARγ2, FAS) and liver (PPARα, FAS, PGC1α, UCP2) mRNA expression were examined. The results indicated that relative to the control group, food intake was not altered by ME supplementation. At 10 weeks, the 4% ME group had a lower ($p<0.05$) body weight than the control group, due to a lower ($p<0.05$) amount of body fat. Plasma leptin was lower ($p<0.05$) in the 4% ME group but adiponectin was not altered. Compared to control, energy digestibility was decreased ($p<0.05$) in both ME groups. In adipose tissue, gene expression of adiponectin, PPARγ2 and FAS and in liver, gene expression of PPARα and UCP2 were increased ($p<0.05$) by ME. In conclusion, the addition of ME to a high-fat diet reduced diet-induced obesity, primarily via increased energy excretion and possibly via increased energy expenditure, suggesting their potential use as supplements to ameliorate current trends in overweight and obesity.
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Ambien-induced hyperphagia and adiposity in rats

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Ambien is a nonbenzodiazepine drug that has been shown to have high affinity for the alpha-1 and reduced affinity for the alpha-2 and alpha-3 subunits of the GABA-A receptor complex. The role of Ambien in the development of hyperphagia is controversial. In the present study, Ambien was placed in a "treat" of condensed milk to ensure complete consumption of the drug at a specified time. Twelve male Long Evans rats were assigned to either a control or experimental group and were subjected to a seven-day habituation period in which they received 500µL of condensed milk daily. Following habituation, six experimental rats received a daily dose of 10 mg/kg Ambien dissolved in distilled water in the milk, while control rats received only water in the milk. The drug period lasted for three weeks and a three-day withdrawal period ensued, during which time both groups received only the condensed milk. Animals receiving Ambien ate significantly more food, had a significantly higher body weight and relative food intake, and had a significantly more positive feed efficiency than control animals at the end of the experimental

period. During the withdrawal period, rats that had been exposed to Ambien had a significant drop in food intake, body weight, and relative food intake compared to the experimental period. Also, during the withdrawal period, experimental rats demonstrated a negative feed efficiency. At the conclusion of the experiment, rats ingesting Ambien showed significantly more adiposity than control rats. An altered state of metabolism may account for the increased adiposity in experimental animals.

Sensory-specific satiety in humans: More than 'just' habituation?
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The prevailing view is that sensory-specific satiety (SSS) is an example of habituation. However, the extent to which this phenomenon results solely from a low-level process has remained unclear. For the first time, we sought to isolate the relative contribution of habituation from forms of 'high level' cognitive activity. In three studies (*N*= 60, 60, and 48, respectively) we manipulated beliefs about the availability (to consume) of uneaten foods to determine their role in the devaluation of the eaten food. Specifically, participants were told that they either would or would not be granted access to other uneaten foods at the end of a fixed or *ad libitum* meal. In study 2 (a fixed meal) we found that restricted access to an uneaten food promoted a greater reduction in the palatability of an eaten food. In a final study (*N*= 80) we assessed SSS after covertly and independently manipulating the perceived and actual amount of food consumed (using a slow self-refilling/draining bowl). In this context, we find that SSS is influenced not by the perceived amount but by the actual amount consumed. Overall, these findings demonstrate that SSS is governed by separate and dissociable processes. Supported by: EPSRC/ESRC.

High-fat diet induced impairment in exendin-4-induced anorexia emerges quickly and is reversed by return to chow diet.
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Previously, we showed that chronic high-fat (HF, 60%) diet impairs the anorexic response to ip injection of glucagon-like peptide 1 (GLP-1) and the potent GLP-1 agonist exendin-4 (Ex4) relative to the responses of low-fat (LF, 10%) diet-fed rats. After 6 weeks on LF or HF diets, LF-fed rats showed a significant 15% reduction in intake and a significant weight loss after 1 ug/kg Ex4 relative to vehicle, whereas HF rats showed no effect of the same dose at 24 h post-treatment. Here we returned 8-week LF- and HF-fed rats to a chow diet and assessed response to Ex4 to determine if the HF diet-related impairment is reversible. At 4 and 6 weeks on chow diet, both groups of rats were given 1 ug/kg Ex4 and 24-h intake was measured. Formerly LF-fed rats responded with significant anorexia as expected, and formerly HF-fed rats showed a significant response of the same magnitude (8%) during both tests. Next, we examined the time course of the development of the impairment. Another group of rats was tested for response to 1 ug/kg Ex4 while on chow diet; all were responsive. They were then put on HF diet and the Ex4 response was tested again 3, 7, 14, and 21 days later. The 1 ug/kg dose of Ex4 significantly reduced 24-h food intake after 3 days on HF diet, but the effect was marginal at 7 days ($p = 0.05$), and no longer present after 14 and 21 days on HF diet. We conclude that the mechanism for this impairment must be an effect of HF diet maintenance that is not immediate but emerges within 2 weeks, and that it is reversible with return to LF feeding. Supported by: NIH DK078779.

Modeling impulse controls deficits: relevance for addictive behaviors?
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A growing body of evidence indicates that high levels of impulsivity are a significant risk-factor for the development of substance abuse, particularly with regards to stimulant drugs. However, recent data also suggest an important link between deficits in impulse control and other putative addictions, such as problem gambling, and overeating. Regarding these conditions, it can be difficult to determine whether high trait impulsivity is predictive of engagement in problem behaviors, or whether the development of the addiction itself exacerbates impulsive responding. Such questions are difficult to resolve using clinical populations, and animal models could make an important contribution in this regard. For example, the rodent five-choice serial reaction time task has been developed as an analogue for the human continuous performance test, and both provide measures of premature responding i.e. the inability to withhold from making a prepotent motor response, also known as impulsive action. Research using this model suggests that high levels of this form of impulsivity increases vulnerability to cocaine addiction, and also that self-administration of cocaine can lead to impulse control deficits during withdrawal. Ongoing research is exploring whether similar relationships exist between poor inhibitory control and other addictive behaviors, such as gambling. In addition, we have found that the level of impulsive action varies depending on the number of sugar pellets at stake, such that larger rewards may be capable of inducing higher levels of impulsivity. Supported by: CIHR, NSERC, MSFHR.

Flip-flop memory circuit uses a synaptic AMPK-dependent positive feedback loop and is switched by hunger state

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Synaptic plasticity in response to changes in physiologic state is coordinated by hormonal signals across multiple neuronal cell types, but the significance and underlying mechanisms are unclear. Here, we combine cell type-specific electrophysiological, pharmacological, and optogenetic techniques to dissect neural circuits and molecular pathways controlling synaptic plasticity onto AGRP neurons, a population that regulates feeding. We find that food deprivation elevates excitatory synaptic input, which is mediated by a presynaptic positive feedback loop involving AMP-activated protein kinase. Potentiation of glutamate release was triggered by the orexigenic hormone ghrelin and exhibited hysteresis, persisting for hours after ghrelin removal. Persistent activity was reversed by the anorexigenic hormone leptin, and optogenetic photostimulation demonstrated involvement of opioid release from POMC neurons. Based on these experiments, we propose a memory storage device for physiological state constructed from bistable synapses that are flipped between two sustained activity states by transient exposure to hormones signaling energy levels Supported by: Howard Hughes Medical Institute.

The Leptin Signaling Cascade and Pediatric Obesity.

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The prevalence of overweight and obesity in children has tripled during the past 40 years. This alarming rise in body weight has likely occurred because the current environment affords easy access to calorie-dense foods and requires less voluntary energy expenditure. However, this environment has not led to severe obesity in all children; rather, it has unmasked a select group of individuals whose body weight regulatory systems are not able to control body adiposity with sufficient precision in our high calorie/low activity environment. This presentation will review genetic syndromes affecting the leptin signaling cascade that have been demonstrated to be associated with pediatric-onset obesity, concentrating on genes other than leptin and the melanocortin 4 receptor. This research was supported by the Intramural Research Program of the NICHD, NIH.

Understanding the nature of the reinforcer in human flavour-nutrient learning.
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In flavour-nutrient learning (FNL), repeated experience of a novel flavour and subsequent ingestion of nutrients has been hypothesised to increase subsequent flavour liking and consequent intake. However, although there are published studies consistent with this effect, other studies have failed to find evidence of changes in liking or intake through flavour nutrient associations. Here a series of recent studies attempted to clarify the nature of the reinforcing effects of ingested nutrients and whether this could explain variability in human FNL. First, the importance of nutrient load is considered. A simple FNL model would predict greater liking as energy intake increases. However, excessive nutrient intake could be aversively over-satiating, implying an inverted U-shape function between ingested nutrients and change in liking, and evidence is presented consistent with this latter view. Second, the issue of nutrient relevance is considered. If a person's primary control of intake was based on cognitive rather than physiological signals, then FNL effects would be weaker. Evidence that restrained eaters show weak liking changes through FNL is consistent with this view. Finally, whether nutrients are expected or not is considered, with evidence that prior expectation that a food is high calorie preventing liking change through FNL. Together these data suggest that FNL operates most effectively where ingested energy matches short-term needs, is unexpected and does not contradict restrained attitudes. Together these findings imply considerable cognitive influence on FNL in humans.

Loss of control of food intake among children during the school lunch
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In an observational and experimental study in a secondary school in Stockholm the cumulative food intake was studied in 18 girls and 12 boys individually and after experimentally increasing or decreasing the speed of eating or maintaining its control level by computer during the school lunch. All children had their school lunch in a shorter period of time than when eating individually (girls: 5.6 (1.2) min vs 10.7 (2.1) $P<0.001$; boys: 6.8 (1.3) min vs 8.8 (1.8), $P=0.003$). Only two girls and one boy maintained their food intake at the individual level when eating their school lunch; nine girls ate 30% less food and seven girls ate 33% more food and 11 boys ate 35% more food. These changes were prevented by providing feedback via computer to maintain the control pattern of eating during the school lunch and they were replicated by experimentally increasing the speed of eating by computer feedback. The conditions at the school lunch increased the speed of eating such that the children were unable to maintain their individual pattern of food intake. Interestingly, the increase and decrease in food intake which emerged are comparable to those previously reported after administration of orexigenic (ghrelin) and anorexigenic (PYY) peptides in humans. While the former changes could be prevented by feedback on how fast to eat during the course of the lunch, the latter effects have never been reversed. Supported by: Mando Group AB.

NTS leptin signaling contributes to meal size control and suppression of food intake by intestinally-derived satiation signals
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Leptin receptors (LepR) expressed in the medial nucleus tractus solitarius (mNTS) are required

for normal energy balance control. Here, the contribution of mNTS LepR signaling to the mediation of the intake suppressive effects of intraduodenal nutrient infusion and meal parameter (meal size and frequency) control is evaluated. Intestinal nutrient (Intralipid; 8ml at 0.5kcal/ml) infusion at a subthreshold concentration for intake suppression and a subthreshold dose of 4th ventricle leptin (5µg), combined to significantly decrease food intake in rats. To assess the roleof *endogenous* mNTS LepR signaling in mediating the intake suppressive effects of intestinal nutrient delivery, knockdown of LepR in the mNTS and area posterma (AP) (mNTS/AP LepRKD) via adeno-associated virus short hairpin RNA-interference (AAV-shRNAi) was employed. Rats with LepRKD in the mNTS showed attenuated 30 and 60m food intake suppression by intraduodenal infusion of a complete liquid meal (Ensure) in a concentration dependent fashion. The endogenous role of mNTS LepR signaling in control of within-meal satiation signaling was further examined following LepRKD by analysis of *ad libitum* meal parameters. mNTS LepRKD increased daily food intake by increasing average meal size but not frequency, whereas LepRKD restricted to the AP did not influence overall energy intake. Current findings demonstrate an endogenous contribution of mNTS LepR signaling in sensitivity to intestinal satiation signals and meal size control. DK21397. Supported by: NIH DK21397.

Structural and functional dissection of the central connections of hindbrain A1 and A2 noradrenergic (NA) cell groups

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NA signaling pathways are implicated in diverse autonomic, endocrine, and behavioral adjustments associated with the central control of food intake and energy homeostasis. NA neurons within the nucleus of solitary tract (A2) and caudal ventrolateral medulla (A1) appear to innervate similar regions of the brainstem, hypothalamus, and limbic forebrain, and also appear to share central sources of axonal input. However, some evidence suggests that A1 and A2 projection fields are discrete. To determine the extent to which A1 and A2 regions participate in similar or discrete neural circuits, we employed a double co-injection neural tracing paradigm (Thompson and Swanson, PNAS, 2010). A cocktail of phaseolus vulgaris leucoagglutinin/cholera toxin B was delivered iontophoretically into either the A1 or A2 region, and in the same rat a combination of biotinylated dextran amine/FluoroGold was delivered into the alternate region. Two weeks later, rats were injected with cholecystokinin (CCK) and perfused with fixative. Tissue sections were processed for immunocytochemical detection of nuclear cFos together with various combinations of tracers. Results confirm the utility of the quadruple neural tracing approach, and have revealed that ascending projections arising from the A1 and A2 regions tend to target discrete subregions of the parabrachial nuclei, paraventricular hypothalamus, and bed nucleus of the stria terminalis. Ongoing analyses will probe for potential areas of collateralized or discrete inputs to the A1 and A2 regions, together with identification of inputs that are activated by CCK. Supported by: NIH #MH59911.

CAFFIENE CONDITIONS FLAVOR PREFERENCES IN ADOLESCENTS.

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Beverage manufacturers say that caffeine is added to drinks to enhance their flavor, but many researchers speculate that caffeine is added to enhance preferences for these drinks. Previous studies in adults have shown that caffeine can condition flavor preferences for novel flavored teas, but similar studies involving adolescents have not been conducted. The purpose of this study was to test the hypothesis that caffeine added to novel flavored drinks would increase liking and preference in adolescents. Adolescents (n=112) between the age of 12 and 17 were brought into the laboratory for 6 visits. They tasted 7 novel soda drinks and provided liking ratings and ranked the beverages in order from most to least liked. The drink ranked #4 was chosen as the

target beverage. Participants returned to the lab for 4 consecutive conditioning trials, during which they were randomly assigned to consume the target beverage with either caffeine (1 mg/kg or 2 mg/kg) or placebo. On the final visit, participants re-tasted the 7 soda beverages and provided liking ratings and rankings. Participants in the caffeine group increased their liking of the target beverage over the exposure period, but there was no change in liking for those in the placebo group. These findings indicate that caffeine added to novel-flavored beverages increases liking and preferences of these beverages relative to those without caffeine. This conditioned preference represents an alternative mechanism for increased consumption of caffeinated beverages over time. Supported by: NIH.

The sensitivity of AP neurons to amylin and GLP-1 is modulated by the feeding status

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The AP is sensitive to the anorectic hormones amylin and glucagon-like peptide 1 (GLP-1). Amylin-induced c-Fos expression and amylin's hypophagic effect is decreased by protein while 24h fasting increases amylin-induced AP activation (c-Fos). Here we investigated whether the responsiveness of AP neurons to GLP-1 is also increased after 24h fasting and whether the angiotensin II (AngII) mediated AP activation is independent of the feeding status because AngII primarily modulates cardiovascular function via the AP. Moreover, we analyzed whether GLP-1 and AngII responsive AP neurons express the calcitonin receptor (CTR), the core component of the amylin receptor. While in ad libitum fed rats GLP-1 (100 µg/kg ip) failed to induce a c-Fos response, fasted rats showed a significant increase in the number of c-Fos positive cells. Interestingly, only 5h of food deprivation was sufficient to significantly increase the amylin-induced (5 µg/kg sc) c-Fos response. In contrast to amylin and GLP-1, the AngII-induced (50 µg/kg sc) AP activation was not enhanced by fasting. After amylin treatment, 68% of all c-Fos positive neurons co-expressed the CTR but there was no co-localization between c-Fos and the CTR after GLP-1 or AngII. The results suggest that CTR expressing neurons activated by amylin do not seem to represent target cells for GLP-1 or AngII. It remains to be established whether the increase in neuronal AP responsiveness to GLP-1 by fasting is also protein-dependent and whether protein intake attenuates AP dependent in vivo effects of GLP-1, similar to amylin.