Appetite 54 (2010) 631–683

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Abstracts

Society for the Study of Ingestive Behavior Annual Meeting 13–17 July 2010, Pittsburgh, PA, U.S.A.

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Flavor preferences conditioned by post-oral infusion of monosodium glutamate in rats

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Monosodium glutamate (MSG), the prototypical umami source, can enhance the preference for associated flavors in humans and rodents. Although MSG preference has been attributed to its taste, vagally mediated post-oral detection has also been demonstrated. Recently, Uematsu et al. (2009) trained a preference for a flavor paired with intragastric (IG) infusion of 60 mM MSG in water-restricted rats. The present study extends this work by comparing MSG-based flavor conditioning in water- and food-restricted rats and testing the persistence of flavor preferences. Adult male Sprague–Dawley rats with IG catheters drank grape or cherry flavored solutions paired with volume-matched infusions of 60 mM MSG or water in daily 30-min sessions. To stimulate drinking in the food-restricted rats, their flavored solutions were sweetened with saccharin. Two training/test cycles were conducted, each with eight 1-bottle training sessions followed by two 2-bottle preference tests without infusions. Food- and water-restricted groups displayed similar preferences for the MSG-paired flavor in the first (68–77%) and second (64–70%) cycles. When this extinction testing was continued after the second cycle, the food-restricted group sustained its preference across four 2-day tests, but water-restricted rats lost their preference. This study demonstrated that flavor conditioning with post-oral MSG can be obtained with both food and water restriction, and revealed greater resistance to extinction for preferences trained and tested under food-restricted conditions. Supported by the Ajinomoto Amino Acid Research Program.
doi:10.1016/j.appet.2010.04.011

The effects of diet on the consumption of sucrose solution and lard and the development of obesity

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This study tested the effect of diet on the consumption of a 30% sucrose solution (SS) and lard on energy intake, body fat, insulin tolerance and serum triacylglycerol (TG). Male 300 g Sprague–Dawley rats ($n = 10$) were offered chow, chow + SS, chow + SS and lard (chow choice), low-fat diet (LFD: D12450B Research Diets, Inc.), LFD + SS, LFD + SS and lard (LFD choice) or a dry high-sucrose diet (70% kcal sucrose, 10% fat). Energy intakes of rats fed chow, LFD and high-sucrose diets were similar but were increased by 16% in chow + SS, 15% in LFD + SS, 11% in LFD choice and 23% in chow choice rats. Chow choice rats consumed 142% more lard than LFD choice rats. Fasting glucose was increased in chow choice and LFD choice rats compared to the chow and high-sucrose diet rats after 14 days, but insulin tolerance remained the same for all groups. Fasting TG increased only in LFD choice rats and were 75% higher than those of chow, LFD or high-sucrose rats. After 21 days, there was no significant difference in carcass fat content of LFD, chow + SS, LFD + SS or high-sucrose rats. Carcass fat increased in both groups of choice rats compared with their controls, but this was significant only for the chow choice rats (LFD, 5.8% vs. 4.2%; chow, 7.8% vs. 3.0%). A second study confirmed that rats offered the choice of SS and lard consumed more lard when given chow compared to LFD diet (1161 ± 210 vs. 449 ± 87 kcal/31d). Thus the dry diet offered to rats influences macronutrient self-selection, the development of obesity and certain aspects of the metabolic syndrome. Supported by NIH R01 DK53903.
doi:10.1016/j.appet.2010.04.012

0195-6663/$ – see front matter
doi:10.1016/j.appet.2010.04.010

Neuronal activation in response to isoproterenol (Iso) in 6-day-old rat pups

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The purpose of the present study was to characterize the neural systems controlling drinking in neonates using Fos expression in brains from rat pups treated with the beta-adrenergic agonist isoproterenol. 6-day-old pups each from different litters were injected with a dipsogenic dose of Iso (500 μg/kg), and a sibling from each litter was injected with 0.15 M NaCl (control). All s.c. injections were made over the scapulae at a volume of 1.25 ml/100 g body wt (approx. 0.1 ml vol/pup). Pups were maintained at 33 °C and 90 min later anesthetized with pentobarbital and perfused transcardially with 10 ml of 0.1 M PBS followed with 10 ml of 4% paraformaldehyde (PFA) in PBS. The brains were removed and immersed in PFA overnight and then 30% sucrose-PBS for 24 h. 40 nm coronal frozen sections were cut and processed for Fos immunoreactivity (FOS-ir) by the ABC technique. In control pups, there was little or no Fos-ir. However Iso induced increased levels of Fos protein in the forebrain of the 6-day-old pups. These areas of intense Fos-ir in the pup brain included the OVLT, MnPO, SON, PVN and SFO. This study shows that in suckling rats when treated with an Iso thirst-inducing challenge there is an adult-like pattern of Fos expression. This is present before pups display independent drinking behavior. The results demonstrate that CNS pathways mediating body fluid homeostasis are responsive to a thirst stimulus and mature early, while motor capacities for drinking appear later in life.

doi:10.1016/j.appet.2010.04.013

Knock-down of estrogen receptor-α (ERα) neurons in the nucleus tractus solitarii (NTS) eliminates CCK-induced c-Fos expression in the paraventricular nucleus of the hypothalamus (PVN)

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Eating is inhibited by estradiol (E2) in many animal species and in women. We demonstrated that, in rats, ERα neurons in the NTS just caudal to the AP (cNTS) are necessary and sufficient for this effect and an increase in the satiating action of CCK is part of the mechanism. Here we determined how RNAi silencing affects CCK-induced cFos expression in the cNTS and the PVN. An adeno-associated viral vector expressing small hairpin RNA silencing ERα(ERV) or the same vector expressing luciferase (LUC) was bilaterally injected into the cNTS of OVX rats. Rats were then SC injected once every 4d with 2 μg E2 or oil. E2 failed to increase CCK's satiating potency or to restrain weight gain in ERV rats. After 40 d rats were injected IP with 4 μg/kg CCK, perfused, and the cNTS and PVN examined for ERα and c-Fos expression. ERα staining was absent in the cNTS of ERV rats, but normal in the forebrain. CCK increased c-Fos expression in the cNTS and in the PVN in E2-treated LUC rats, but not in E2-treated ERV rats or oil-treated rats. These data indicate that activation of cNTS ERα cells is necessary for CCK-induced cFos expression in the cNTS and PVN. This suggests that cNTS and PVN cells expressing cFos after CCK are downstream of cNTS ERα cells and that estrogenic signaling is necessary for CCK-induced satiation and c-Fos brain activation in female rats.

doi:10.1016/j.appet.2010.04.014

Effects of exercise and diet-induced obesity on food demand characteristics in mice

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The purpose of the present work is to characterize in mice the effect of voluntary physical activity on energy balance, body composition, meal patterns and demand functions for food intake under various economic conditions. Two experiments were performed. In the first experiment, the effects of voluntary running wheel activity on food intake and meal patterns were measured under unit prices for food in CD1 mice. In the second experiment, in addition to the voluntary exercise, we examined the effects of diet-induced obesity on demand functions for food intake and meal patterns in B6 mice. The results from both experiments indicated that voluntary wheel running activity increases daily food intake and that running animals consumed bigger but fewer meals compared to the sedentary. Although they ate more, running mice had significantly lower body fat compared to sedentary animals, especially in subcutaneous depots. The results from the second protocol showed that the effects of exercise under the conditions of diet-induced obesity resulted in less weight loss during the economic protocol compared to sedentary diet-induced obese animals. For non-obese controls, the effects of exercise agreed well with the results of Experiment 1, and running mice weighed less than sedentary counterparts. Thus, although we found a preventative effect of exercise on body fat accumulation, exercise actually slowed weight loss in mice with a precondition of obesity.

doi:10.1016/j.appet.2010.04.015

Effects of certainty of cue-food associations on binge behavior in rats

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We predicted that binge size and escalation would be attenuated when the association between cues and opportunities to binge were highly predictable. 3 groups of male Sprague–Dawley rats ($n = 12$ each) were housed individually and given continuous access to chow throughout. Two groups were housed in the same room and 1 group in a separate room. The groups in the same room were maintained on 2 protocols: (1) daily (D): 30-min access to shortening daily; (2) intermittent (INT-U): 30-min access to shortening on Mon, Wed, and Fri. Thus, INT-U was exposed to uncertain (unpredictable) binge–cue associations, since the cues predicting binge opportunities (investigator in room, etc.) were present every day. The isolated group (INT-C) was also maintained on the INT protocol, but binge–cue associations were certain (predictable), as investigators only entered the INT-C room when shortening was provided. Escalation of shortening intake was most rapid in INT-C ($p < 0.05$). Specifically, INT-C shortening intake was 226% and 247% of day 1 on the 2nd and 3rd shortening access periods, respectively. INT-U intake was only 170% and 151%, respectively, of day 1; D intake was 118% and 105%, respectively, of day 1. Binge size, however, did not differ significantly between INT-C and INT-U. Furthermore, from wk 2 on, INT-C and INT-U both consumed significantly more shortening during the 1-h period than did D ($p < 0.01$). This study shows that binge eating in rats occurs regardless of the certainty of association between cues and binge opportunities. Funding: RO1-MH67943 (RC).

doi:10.1016/j.appet.2010.04.016

Parabrachial Y1/Y4 receptor stimulation increases licking for sucrose

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The hindbrain parabrachial nucleus (PBN) processes taste and visceral sensory signals and has numerous connections with nuclei implicated in feeding control, including input from hypothalamic NPY/AGRP/GABA neurons. We evaluated the dose effects of the NPY Y1 antagonist 1229u91 on licking for 0.1 M sucrose after bilateral injection into the lateral PBN (0.0 nM, 0.05 nM, 0.5 nM, and 2.5 nM per side; $n = 8$). Meal size was significantly increased by the 1.0 nM and 5.0 nM/brain doses. At these doses, there was no significant effect on meal frequency, initial lick rate or mean lick burst size, suggesting that appetitive and taste evaluation processes were not affected. Meal size was enhanced by a significant increase in the lick-burst count and a reduction in pause time between bursts. A moderate but non-significant increase in meal duration was also observed. Results suggest that 1229u91 influenced food intake through effects related to the processing of visceral stimuli, consistent with observations of neural responses to gastrointestinal stimuli in the lateral PBN. The results, however, are less consistent with reports that 1229u91 blocks the hyperphagic effects of ventricular NPY/ghrelin when infused into the brain ventricles. 1229u91 elicited hyperphagic responses either through antagonist function at Y1 receptors which have been identified within lateral PBN, or possibly through its agonist effects at Y4 receptors. Pancreatic polypeptide, which induces hyperphagia after brain injection, exhibits high affinity for Y4 receptors and it has been shown to bind within the PBN. Further study will be necessary to evaluate this hypothesis. Supported by DC07389.

doi:10.1016/j.appet.2010.04.017

Effects of fasting/refeeding on brown adipose tissue thermogenesis in lean and obese mice

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It is speculated that diet-induced obesity (DIO) is associated with a defect in Brown Adipose Tissue (BAT) thermogenesis. To compare BAT thermogenesis in lean and DIO mice, we surgically implanted thermal probes into the interscapular BAT (iBAT) of 3 mo male C57/bl6 mice kept on either chow (LFD, $n = 12$) or high-fat (HFD, $n = 12$) diets. After recovery from surgery, the iBAT temperature was remotely recorded (at week 9 of HFD) at regular hourly intervals in free-feeding mice during the light and dark periods. Both groups had similar circadian profiles of iBAT temperature and similar calorie intake. Next, we determined whether DIO mice can regulate iBAT thermogenesis in response to changes in energy status. We fasted mice for 24 h, then refed them 2 h after the onset of dark. In LFD mice, fasting caused a marked decrease in iBAT temperature in both light/dark phases, which was rapidly restored to normal by refeeding. By contrast, the effect of fasting and refeeding on iBAT temperature of HFD mice were markedly attenuated. These data indicate that, although DIO mice do not show any defect in the basal profile of BAT thermogenesis, they fail to appropriately modulate BAT thermogenesis in response to nutritional signals. These results suggest the presence of "metabolic inflexibility" in BAT of DIO mice that impairs nutrient-dependent regulation of thermogenesis.

doi:10.1016/j.appet.2010.04.018

Early life experience shapes the functional organization of stress-responsive visceral circuits

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The amount and quality of maternal care received by infants impacts their physiological and emotional development. In rat pups, daily brief (i.e., 15 min) maternal separation (MS15) during the first 1–2 postnatal weeks increases active maternal care, which is associated with later reductions in stress responsiveness and anxiety-like behavior in the offspring. Stress and emotional responses prominently feature altered gastrointestinal (GI) function, and we have shown that the developmental assembly of central neural circuits underlying gastric control is modified during the neonatal period by MS15. When rats with a developmental history of MS15 are examined as adolescents, they display significantly increased retrograde transneuronal viral transport from the stomach wall to the paraventricular nucleus of the hypothalamus (PVN), suggesting that PVN-mediated effects on GI function and stress responsiveness may be sensitive to early life experience. Indeed, the ability of restraint stress to activate stress-sensitive noradrenergic (NA) neurons within the dorsal vagal complex depends on a descending pathway from the PVN, and NA activation after restraint and other stressors is blunted in MS15 rats. We also have shown in adult rats that the anxiolytic behavioral effect of neonatal MS15 is reversed by concurrent neonatal antagonism of CCK-1 receptors, suggesting endogenous gut hormone receptor signaling in infants as a potential pathway through which maternal care might regulate the development and functional organization of emotional/visceral circuits that control stress responsiveness and anxiety.

doi:10.1016/j.appet.2010.04.019

Positive relationship between hypothalamic enkephalin and ethanol

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Ethanol is not just a drug of abuse but is also a food containing calories. With evidence suggesting a positive, bidirectional relationship between fat consumption and the opioid, enkephalin (ENK) in the hypothalamic paraventricular nucleus (PVN), this study investigated whether this relationship also exists for ethanol. Using Sprague–Dawley rats, we have found that PVN injection of the ENK analogue D-ala^2-met-enkephalinamide (DALA; 14.2 nmol) vs saline increases 1-h intake of 7% ethanol (0.7 ± 0.1 g/kg vs 0.3 ± 0.1 g/kg, $p < 0.05$, $n = 5$). In turn, rats chronically drinking 3 g/kg/day of 9% ethanol vs water show enhanced ENK mRNA expression in the PVN (+46%), as assessed by quantitative real-time PCR (qRT-PCR), radiolabeled in situ hybridization, and digoxigenin-labeled in situ hybridization ($p < 0.05$, $n = 5$/group). Further, rats predicted to be high vs low consumers of ethanol, by their increased locomotor activity in a novel open field, also show increased PVN ENK mRNA expression (+18%, $p < 0.001$, $n = 5$/group, qRT-PCR). As with fat, this relationship between ENK and ethanol may be related to circulating triglycerides (TG) that are increased by ethanol intake similar to fat intake. In rats drinking 7% ethanol, the drug gemfibrozil (50 mg/kg, i.g.) that reduces TG levels both decreases ethanol intake over 4 h (2.2 ± 0.1 g/kg vs 1.8 ± 0.1 g/kg, $p < 0.01$) and decreases ENK mRNA expression prior to daily ethanol access (-12%, $p < 0.05$, $n = 15$, qRT-PCR). This evidence suggests that, similar to dietary fat, a positive feedback relationship exists between PVN ENK and the consumption of ethanol.

doi:10.1016/j.appet.2010.04.020

Dietary omega-3 fatty acid deficiency, hypertension and the renin–angiotensin system

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Deficiency of dietary omega-3 polyunsaturated fatty acids induces an elevation of blood pressure in the rat observable from approximately 6-months of age. However, the aetiology of this hypertension remains unknown. We examined the role of the renin–angiotensin system (RAS) in the hypertension caused by life-long deficiency of dietary omega-3 fatty acids. In study one, genes related to the RAS were analyzed in hypothalamic tissue in omega-3 fatty acid deficient and sufficient animals prior to (3-months-old), and following (9-months-old), the development of hypertension. In study two, an angiotensin converting enzyme (ACE) inhibitor, perindopril, was chronically administered to 9-months-old animals that were life-long deficient or sufficient in omega-3 fatty acids. Blood pressures were measured by tail cuff sphygmomanometry and gene expression using RT-PCR. At 3-months angiotensin II receptor 1a (AT1a) expression was up-regulated, however, by 9-months AT1a was no longer over-expressed. Administration of perindopril reduced the hypertension (systolic and diastolic blood pressure) in deficient animals, without affecting the blood pressure of sufficient animals. Overall, these findings demonstrate the involvement of the RAS in hypertension related to omega-3 fatty acid deficiency and indicate that early programming may be involved. Furthermore, reducing RAS activity can effectively treat the blood pressure increase caused by omega-3 fatty acid deficiency.

doi:10.1016/j.appet.2010.04.021

Chronic high fat feeding decreases chow and sweet food consumption. Investigating the role of BDNF

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Diet influences brain mesolimbic functioning. For instance, chronic high fat diet (HF-diet) alters the expression of dopamine (DA)-related genes and turnover in these areas. BDNF influences hedonic feeding by modulating the mesolimbic DA system. Little is known about the impact of HF-diet over the consumption of palatable foods and the possible involvement of circulating BDNF, therefore this was our aim in this study. Female rats received either control (C-rats) or high fat diet (HF-rats, 45% calories from fat) for 5 weeks. Body weight and chow consumption were accompanied weekly. Afterwards, they were habituated to Froot Loops (FL) for 4 days. In the day of the experiment, they were fasted for 4 h and received only FL ad libitum for 1 h, being sacrificed immediately after. Over the 5 weeks period HF-rats ate less food than C-rats ($p < 0.001$), which yielded a lower caloric intake ($p = 0.029$). Sweet food intake was also decreased in HF rats ($p < 0.001$) in the 1-hour test. HF-rats had a tendency to gain more weight ($p = 0.062$), and had more abdominal fat ($p = 0.032$). There were no differences in serum BDNF or glucose. We suggest that high fat diet decreases chow and sweet food consumption, probably by acting on satiety mechanisms and/or hedonic aspects of feeding. Serum BDNF does not seem to be related to these findings.

doi:10.1016/j.appet.2010.04.022

Binge eating of a sweet-fat diet does not result in opiate-like withdrawal as seen with sugar solutions

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Previous studies indicate that binge eating sugar leads to behavioral and neurochemical changes similar to those seen with drug addiction, including signs of opiate-like withdrawal. Studies are emerging that show indices of addiction when animals overeat a fat-rich diet. The goal of the present study was to utilize liquid or solid diets high in sugar and fat to determine whether opiate-like withdrawal is seen after binge consumption of these diets in Sprague–Dawley rats. Control groups were given ad libitum access to the sweet-fat food or chow. All rats were then given a battery of tests to measure signs of opiate-like withdrawal, which included somatic signs of distress, elevated plus-maze anxiety, and locomotor hypoactivity. Neither naloxone (3.0 mg/kg) nor fasting induced withdrawal was observed in rats that were maintained on a nutritionally complete pelleted sweet-fat diet, a sweet, high-fat diet supplemented with standard rodent chow, or a liquid sweet-fat diet. Further, body weight reduction to 85%, which is known to potentiate the reinforcing effects of substance of abuse, did not affect naloxone-precipitated withdrawal. Thus, unlike findings that have been previously reported from this laboratory for rats with binge access to a sucrose solution, rats that binge eat sweet-fat combinations do not show signs of opiate-like withdrawal under the conditions used. This may have clinical implications for interpreting the symptoms seen in patients who binge eat.

doi:10.1016/j.appet.2010.04.023

Regulating energy balance. What is the regulated parameter?

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Over the course of an average person's adult life they will consume more than 15,000 lbs of food while gaining only 20–30 lbs of body weight, most as body fat. These numbers demonstrate the remarkable precision of the regulatory system that governs body weight even in the face of what is considered clinically meaningful weight gain. This is striking given that the body does this despite dramatic day to day fluctuations in both energy intake and expenditure, two parameters that have proven to be extremely difficult to measure accurately in free living humans. It seems that the body can do a better job of quantifying energy balance than researchers can. But what is the body regulating? The available evidence suggests that it is not body weight or body fat. It is not insulin or leptin or ghrelin or any of a number of other important signals. Studies performed in rodents and humans of varying phenotypes imposing states of positive or negative energy balance by over or underfeeding or increasing or decreasing physical activity can help inform our thinking about this fundamental question. The results of these studies to date support the idea that within a range of nutrient stores that are "biologically acceptable" energy balance is regulated through the modulation of meal size and number in the context of the availability of circulating and stored nutrients. A unifying hypothesis is that the body regulates the transition point between the assimilation of exogenous fuels and the need to release endogenous nutrients. This cyclic process takes place over hours, but is regulated by factors such as learning and insulin sensitivity that develop over longer periods of time and reflect changes in nutrient stores that occur over days and weeks. One of the great challenges in this field remains understanding how short and long term signals of energy balance are interpreted and integrated by the brain.

doi:10.1016/j.appet.2010.04.024

Setting a social norm regarding food intake in children

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People use other's food intake as a social norm indicating how much they are 'allowed' to eat. Ample experimental research showed the impact of peer modeling on food intake in adolescents and adults, whereas few studies focused on young children. This study used an innovative design in a naturalistic setting to investigate whether a social norm in food intake that was set by a confederate peer would still be followed by the participant a few days later. Therefore, we made use of two sessions in which the participants ($N = 221$) were asked to perform a cover task, i.e. solving a puzzle in 10 min. In the first session, they had to cooperate with a same-sex normal-weight confederate that was instructed to either consume nothing, a small (3) or a large (10) amount of chocolate-coated peanuts. In the second session (at least two days later), the participant was left alone with a variety of foods. An ANCOVA, with hunger and liking of the chocolate-coated peanuts as covariates, revealed significant main effects for eating condition on kcal consumed in the first session $F(2,217) = 12.34$, $p < 0.001$ as well as in the second session $F(2,218) = 6.26$, $p < 0.001$. Post-hoc Bonferroni tests showed a significant difference in food intake between children in the no-intake and high intake condition in both sessions. This suggests that a social norm was being set during the first session which still served as a norm for the participant in the second session. No differences were found in effects between children with a low or high BMI. In sum, our findings showed that children are strongly affected by a peer's food intake.

doi:10.1016/j.appet.2010.04.025

High-fructose corn syrup leads to obesity in rats. Increased body weight, body fat and triglyceride levels

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High-fructose corn syrup (HFCS) accounts for as much as 40% of caloric sweeteners used in the United States. Some studies have shown that short-term access to HFCS causes increased body weight, but findings are mixed. The current study examines both short- and long-term effects of HFCS on body weight, body fat, and circulating triglycerides (TG). In Experiment 1, male Sprague–Dawley rats were maintained for short-term (8 wks) on (1) 12-h/day of 8% HFCS, (2) 12-h/day 10% sucrose, (3) 24-h/day HFCS, all with *ad libitum* rodent chow, or (4) *ad libitum* chow alone. Rats with 12-h access to HFCS gained significantly more body weight than animals given equal access to 10% sucrose (502 ± 11 g vs. 477 ± 9 g), even though they consumed the same number of total calories from chow and sugar each day and fewer calories from HFCS than sucrose. In Experiment 2, the long-term effects of HFCS on obesogenic parameters and gender differences were explored. Over 6 months, both male and female rats with access to HFCS gained significantly more body weight than control groups. Over the course of the study, males with HFCS access gained 257% of their baseline weight, compared to chow-fed controls that gained 175%. Females with HFCS access gained 199% of their baseline weight, while chow-fed controls gained 177%. This increase in body weight with HFCS access was accompanied by an increase in abdominal adipose fat and circulating TG levels. Translated to humans, these results suggest that excessive consumption of HFCS may contribute to the incidence of obesity.

doi:10.1016/j.appet.2010.04.026

Brain representation of liking and wanting as a function of hunger and satiety

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Background: Eating in the absence of hunger (EAH) is a likely factor in the etiology of obesity. Liking and wanting may be important determinants of EAH. *Aim*: Assess the brain representation of liking and wanting as a function of hunger. *Methods*: 15 subjects (female, age = 21.5 ± 0.4 y, BMI = 22.2 ± 0.4) completed 2 fMRI scans, one fasted (pre-meal), one satiated (post-meal). During each scan, subjects rated food images for liking and wanting on a 4-point scale. Food choice was defined as items with average wanting >2.5, which were offered to eat. Everything had to be sampled. Visual analog scales (VAS) for hunger and satiety; energy intake (EI) and energy density (ED) were assessed. *Results*: Fasted and satiated conditions were confirmed by decreased post-meal hunger (-52 mmVAS; $p < .001$). Average rating for liking was not different over time, whereas rating of wanting was decreased post-meal (-0.6, $p < .001$). Wanting was specifically represented in the caudate while liking was represented in the insulae. Liking and wanting related brain activation was significantly higher pre-meal than post-meal. Only EI post-meal (EAH) was related to ED ($r2 = .803$, $p < .001$). *Conclusion*: Liking and wanting were represented in specific areas namely the insulae and the caudate, respectively. Although rated liking remained constant during satiation whereas rated wanting decreased, both showed decreased brain activation during satiety.

doi:10.1016/j.appet.2010.04.027

Pilot study evaluating Pavlovian conditioning of swallowing to innocuous cues in humans

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The purpose of this pilot study was to evaluate acquisition of learned physiological responses to neutral cues paired with hedonic food cues, in preparation for studies on extinction of physiological responses to food cues. This pilot study was a within subject design with six young adults. Sixteen conditioning trials were presented, half of which paired the presentation of a green square on a computer screen (CS+) with the delivery of 1 ml of chocolate milkshake (US). The other 1/2 of the trials paired a red circle on the screen with no US delivery (CS−). Presentation of trials was randomized. Immediately after the conditioning trials, learning was assessed by the presentation of 3 trials of each CS type without US delivery. Swallowing was measured by electromyography (EMG) recordings obtained from two small Ag/Ag-Cl cup electrodes placed 1 cm apart at the *musculus digastricus* under the jaw (Nederkoorn et al., 1999). The mean sum of swallows during the CS+ conditions (8.33) was significantly greater than that during the CS− conditions (3.00) in the test phase across 6 subjects ($t_5 = 2.02$, $p < 0.05$). These pilot results suggest that swallowing can be conditioned in humans to innocuous cues. Future studies will evaluate the extinction of swallowing and additional physiological responses in order to translate these basic learning principles to exposure-based obesity interventions.

doi:10.1016/j.appet.2010.04.028

Diet-induced obesity, hyperamylinemia and amylin sensitivity

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Amylin is co-secreted with insulin from the pancreas to control nutrient flux after a meal. Though amylin is a promising treatment of obesity and diabetes, it has been reported that obese animals are less responsive to amylin administration, suggesting that adiposity might render amylin less therapeutically effective. The first aim of our study was to assess the acute anorectic response to amylin in rats that were chronically fed a high fat diet (HF). We also tested if hyperamylinemia modifies amylin sensitivity independently of obesity. Male rats were maintained on standard chow or HF (60% kcal from fat) for 14 wk. At 9 wk, rats maintained on HF had elevated fasting levels of amylin and leptin, and at the time of sacrifice at 14 wk showed significant increases in visceral and subcutaneous adipose tissue. During the study, sensitivity to the anorectic effect of amylin was determined by injecting vehicle or amylin (5, 20, or 50 μg/kg, s.c.) to non-fasted rats and monitoring food intake for 2 h. In the first 6 weeks, HF did not initially alter amylin-sensitivity; however, by wk 11, low doses of amylin only significantly suppressed food intake in the chow-fed rats. This suggests that amylin's ability to inhibit food intake is reduced following long-term access to HF and the development of obesity. Our results demonstrate that amylin's potency as an anorectic agent can be modified by chronic HF consumption. Though we cannot presently speak to underlying mechanisms, we have recently found that chronic hyperamylinemia alone, which is typically associated with obesity, does not cause amylin insensitivity in rats.

doi:10.1016/j.appet.2010.04.029

Short-term, but not extended, access to palatable diet diminishes amylin responsiveness in rat

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The pancreatic hormone amylin, which acts via the area postrema (AP) to reduce food intake, is reportedly less effective in obese humans and some rodent models of obesity. However, it is unknown what aspects of obesity alter amylin sensitivity. Here we test the hypothesis that short-term intake of a high-energy, palatable diet (Ensure chocolate), independent of obesity, is sufficient to cause amylin insensitivity in rodents. Male rats were offered Ensure liquid diet for either 3 days or 3 weeks, following which the responsiveness to both central (5 pmol, i3V) or peripheral (5 μg/kg, ip) amylin were examined. Three weeks access to Ensure resulted in hyperphagia and weight gain, but sensitivity to the anorectic effects of amylin remain intact. Interestingly, when Ensure was only offered for 3 days, neither central nor peripheral administration of amylin attenuated food intake. However, amylin responsiveness was restored by placing the rats back on chow for 3 days, or increasing the dose of amylin (10 or 100 pmol, i3V). Finally, we examined if 3 days of Ensure-feeding modifies peripheral amylin-induced cFos activation, and found Ensure does not alter expression in the AP, amylin's central target site. These results suggest that the amylin insensitivity following short-term intake of palatable diet is reversible, dose-dependent, and may involve altered neuronal activation in central brain sites downstream of the AP.

doi:10.1016/j.appet.2010.04.030

Effect of sympathectomy and sympathectomy/vagotomy on reduction of food intake by cholecystokinin-8 and 33

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Reduction of food intake by CCK is vagally mediated. However, the role of the sympathetic innervation of the gut in this reduction has not been tested. We used three groups of rats, sympathectomy (SYMPX, celiaco-mesenteric ganglionectomy), sympathectomy/vagotomy (SYMPX/VGX) and sham rats injected with CCK-8, 33 (1, 3, and 5 nmol/kg) or saline i.p. followed by measuring the intake of 10% sucrose for a total of 120 min. In the SYMPX group, CCK-8 and -33 reduced meal size and increased the satiety ratio. In the same group, CCK-8 reduced the intermeal interval (IMI) but CCK-33 increased it. Devazepide, a CCK_1 receptor antagonist failed to block this reduction. In the SYMPX/VGX group, both peptides reduced meal size, and CCK-33 reduced it more than CCK-8. Both peptides increased the IMI and satiety ratio. Devazepide blocked this effect while L365, 260 did not. In conclusion, removal of the sympathetic or combined sympathetic and parasympathetic innervations of the gut did not affect reduction of food intake by CCK-8 and 33. Therefore, another pathway(s) may mediate the reduction of food intake by CCK.

doi:10.1016/j.appet.2010.04.031

Racial differences in ghrelin response to glycemic load

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This study evaluated glycemic load (GL) effects on ghrelin and whether any observed effects of GL on ghrelin differed as a function of race. Twenty Black and 20 age- and body mass index-matched White women (10 each group normal weight vs. obese) completed in randomized order two 4-day weight-maintenance, mixed macronutrient high (212.5 ± 31.2) vs. low GL (107.5 ± 25.2) diets, each followed by an overnight fast and a test meal of similar composition (high GL = 59.1 ± 5.9; low GL = 31.3 ± 3.6). Blood samples were obtained before and for 3 h after each test meal and later assayed for total ghrelin (TG), insulin, and glucose. Postprandial TG area under the curve (AUC) was significantly less after the high vs. low GL meal ($p < 0.0008$), with this effect tending to differ by race (White women, $p < 0.004$ vs. Black women, $p > 0.14$). $Glucose_{AUC}$ ($p < 0.03$) and $insulin_{AUC}$ ($p < 0.02$) were significantly greater after the high vs. low GL meal, with these effects being more pronounced in White (ps < 0.005) compared to Black (ps > 0.70) women. These findings are consistent with: (1) observations linking high GL to greater insulin response, (2) an inverse relationship between postprandial insulin and ghrelin levels, and (3) ghrelin downregulation with prolonged high GL dietary intake. Future studies should consider race as a potentially important modifier of GL effects on appetite hormones.

doi:10.1016/j.appet.2010.04.032

Expected satiety influences actual satiety

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We explored the hypothesis that the satiety that we expect a food to confer can influence the actual satiety that is experienced after it has been consumed. In Experiment 1 we manipulated 'expected satiety' by telling participants ($N = 32$) that a 'fruit smoothie' contained either a small or a large amount of fruit. All participants consumed the same smoothie. Nevertheless, those in the 'large amount' condition reported significantly lower hunger, 0, 1, 2, and 3 h after meal termination. In Experiment 2 we manipulated information about the volume of soup consumed in a meal. Before lunch, participants were shown either 300 ml or 500 ml of soup. Orthogonal to this, half consumed 300 ml and half consumed 500 ml. This process yielded four separate groups (25 participants in each). Covert and independent manipulation of the 'actual' and 'perceived' soup portion was achieved using a computer-controlled peristaltic pump. Immediately after lunch, self-reported hunger was predicted by the actual and not the perceived amount of soup consumed. However, 2 and 3 h after meal termination this pattern was reversed. Hunger was predicted by the perceived and not the actual amount. Together, these findings confirm a role for 'expected satiety' and show how memory for a recent eating episode can affect satiety in the inter-meal interval. This research was supported by a BBSRC-DRINC grant (ref: BB/G005443/1).

doi:10.1016/j.appet.2010.04.033

Hypothalamic neuron derived neurotrophic factor (NENF) regulates food intake

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Identification of novel hypothalamic-expressed secreted factors may help identify novel drug targets for treatment of obesity and eating disorders. We developed a screen to identify novel candidate hypothalamic secreted proteins meeting the following criteria: (1) expression in hypothalamic nuclei known to regulate body composition, hunger or satiety, (2) residing in a genomic locus containing a QTL that regulates body composition or food intake, (3) possessing a signal peptide sequence, (4) showing altered gene expression under fed, fasted and DIO conditions and (5) no prior implication for these processes. Recombinant proteins were generated, injected into the lateral ventricle (LV) and body weight and food intake measurements taken. We characterized one candidate protein further, NENF. A single NENF LV injection (30 nm) once per week partially reversed a chow-induced obese phenotype by decreasing food intake, but this was not observed with obesity induced by a high-fat (HF) diet. The NENF protein injection altered hypothalamic gene expression patterns in a direction that resembled DIO animals. This suggests that the NENF protein may be effective to alleviate obesity induced by a chow diet, but not on a HF diet. Finally, these results demonstrate that we have successfully initiated a screen to identify novel hypothalamic secreted neuropeptides that regulate food intake and body weight.

doi:10.1016/j.appet.2010.04.035

Melanocortin-3 receptors and synchronization of rhythms to meal entrainment

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Adaptation to nutrient scarcity involves the expression of behavioral and metabolic programs that maximize survival. This process includes the entrainment of the circadian rhythm to facilitate the anticipation of nutrient availability. Determining exactly how temporal restrictions in nutrient availability force changes in the circadian rhythm and the involvement of the molecular clock is unclear. We entered the field with the simple hypothesis that hypothalamic melanocortin neurons are involved in the entrainment of rhythms to food presentation, and regulate inputs into the "food entrainable oscillator". The hypothalamic melanocortin system coordinates the homeostatic response to variable calorie intake, integrating signals of metabolic status with outputs affecting ingestive behaviors and metabolism. In this presentation I will summarize results from studies showing that C57BL/6J mice lacking functional melanocortin-3 receptors (*Mc3r*−/−) are a unique genetic model unable to efficiently express food anticipatory activity (FAA) (J. Neurosci., 2008 28(48), 12946–12955). While ad libitum fed *Mc3r*−/− mice exhibit modest changes in energy homeostasis, they develop a metabolic phenotype involving mixed insulin resistance and altered substrate preference (FASEB J., 2010, 24(3), 862–872). Collectively, these data suggest that Mc3r regulate both behavioral and metabolic adaptation to temporal restrictions in food availability. This is associated with altered rhythmicity in the expression of clock genes in the brain and liver. However, whether this phenomenon is causative or results from metabolic dysregulation is unclear.

doi:10.1016/j.appet.2010.04.034

Effect of chronic variable stress on central regulation of food intake and neurogenesis

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Chronic stress alters several central mechanisms including those of food intake regulation and neurogenesis. Our goal was to determine the effect of chronic variable stress (CVS) on these two systems. Two experiments were performed using 2 weeks CVS in male Wistar rats. CVS consisted of daily unpredictable exposure to a variety of stressors. In the first experiment, food intake and body weight were measured daily. At the end of CVS, hypothalamic neuropeptide mRNA expression, basal plasma hormone levels and body composition were measured. In the second experiment, the effects of CVS on brain morphology were assessed by MRI, and at the cellular level by staining. Rats exposed to CVS displayed greater corticotropin releasing factor (CRF) and a tendency towards lower neuropeptide Y (NPY) expression, plus a decreased body weight due to diminution of adipose tissue mass compared to control rats. A decrease in food intake only partly explained this decrease since stressed rats also showed a reduced weight gain per kJ ingested. Stressed rats had a 2-fold increase in basal corticosterone levels. The effects of CVS on neuroanatomy of the brain are currently being analysed. In conclusion, CVS affected central food intake regulation. CVS induced a decrease in food intake, probably due to CRF inhibition of orexigenic NPY neurons. The lowered body weight of stressed rats could be explained by an inhibition of food intake and, since CVS only lasted 2 weeks, an acute lipolytic effect of corticosterone.

doi:10.1016/j.appet.2010.04.036

"Snack" and "meal" food categories and their frequencies in college students

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The cognitive representation of food as belonging to a "snack" or a "meal" influences eating behavior. Capaldi and Privitera (2008) showed that subjects who considered a particular food to be a "snack" ate significantly more calories later than subjects who considered the same foods as a meal. Since snacks contribute to increased caloric intake, we surveyed 612 college students (48% males and 52% females) asking them to categorize 143 foods as "snacks" or "meals". The students varied extensively in their classification of foods indicating the importance of cognitive factors on eating. For example, for each of the following foods half the respondents viewed the food as a snack, and half as a meal: potato salad, toast with jam, English muffin, French fries and fruit and yogurt parfait. On the other hand, potato chips, crackers, cookies and roasted peanuts were consistently viewed as snacks, while soups, pasta, pizza and scrambled eggs were consistently viewed as meals. Meats and poultry fell mostly in the meals category while, foods in the fats and sweets as well as breads, cereals and pasta group fell mainly in the snacks category. Foods high in carbohydrate and fat (poptarts, doughnuts, cheese sandwich, cinnamon rolls, nachos and muffins) were considered as snacks more often by males than females. The data provide a source for those wishing to investigate the effects of categorizing foods as snacks or meals on eating behavior. Also, since whether a food is considered a snack or meal is learned, the study is part of a large body of literature showing the importance of prior experience with food on eating behavior.

doi:10.1016/j.appet.2010.04.037

Knockdown of NPY expression in the dorsomedial hypothalamus ameliorates high-fat diet-induced obesity in rats

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We have previously demonstrated that knockdown of NPY expression in the dorsomedial hypothalamus (DMH) via adeno-associated virus (AAV)-mediated RNAi (AAVshNPY) ameliorated the hyperphagia, obesity and diabetes of OLETF rats that had elevated Npy gene expression in the DMH. From these data, we have suggested that DMH NPY plays an important role in modulating food intake and energy balance. To extend these findings, we examined whether knockdown of NPY expression in the DMH prevents high-fat diet-induced obesity in Sprague–Dawley rats. We found that while high-fat diet induced increases in food intake and body weight gain in rats receiving control vector (AAVshCTL), DMH NPY knockdown significantly attenuated these increases. Glucose tolerance test revealed that while high-fat diet access caused glucose intolerance and hyperinsulemia in AAVshCTL rats, DMH NPY knockdown ameliorated these alterations. Moreover, while high fat diet access resulted in increased fat mass and leptin levels, DMH NPY knockdown attenuated these increases. Overall, these results provide additional evidence for an important role of DMH NPY in the modulation of energy balance and suggest that DMH NPY may become a potential target for preventing obesity. Supported by NIH DK074269.

doi:10.1016/j.appet.2010.04.039

Effects of not predictable alternative overcrowding and isolation on food intake and body weight gain in male and female rats at weaning or adulthood

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Feeding behavior and body weight can be modulated by stressful social factors, but in a way unclear stress has been associated with factors like genre and age that may influence the susceptibility of subjects. The aim of this study was to evaluate the effects of exposure to unpredictable alternative overcrowding and isolation stress paradigm on food intake and body weight gain in rats, and to compare between male and female in two ages. 10 male and 10 female *Wistar* rats of 22 days old (weaning experimental subjects), and 10 male and 10 female of 70 days old (adulthood experimental subjects) with respective control groups, were exposed by 15 days to unpredictable alternative overcrowding-isolation. Animals remained in constant conditions: 21 °C, 60% humidity and 12:12 h dark–light cycles, with *ad libitum* access to standard rat chow and water. Food intake and body weight gain were registered during stress and for 20 days after stress. The experimental groups show differences respect to control groups most evident at second week during stress, food intake and body weight gain were affected in a sex-specific manner in both groups of age, some effects persisting after the stressor exposure and other were reverted at different times related with gender and age. The results show the influence of gender and age factors on the effects of this model of chronic stress.

doi:10.1016/j.appet.2010.04.038

Influence of intracerebroventricular obestatin on colonic motility and secretion in conscious rats

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Obestatin, a novel 23 amino acid peptide, is derived from mammalian preproghrelin gene via a bioinformatics approach. Though obestatin regulates thirst, sleep, memory, anxiety, activates cortical neurons in the brain and stimulate proliferation of retinal pigment epithelial cells, there is no study to explore its central impacts on the lower gut motility and secretion. We investigated the influence of intracerebroventricular (ICV) injection of obestatin on rat colonic motor and secretory functions. Colonic transit time, fecal pellet output and fecal content were assessed in freely fed, conscious rats, which were implanted with ICV and colonic catheters. Human/rat corticotropin-releasing factor (h/rCRF) was applied as a stimulatory inducer of colonic motility and secretion. ICV injection of obestatin (0.1, 0.3, 1.0 nmol/rat) did not modify the colonic transit time, whereas ICV injection of h/rCRF (0.3 nmol/rat) significantly shortened colonic transit time. ICV obestatin did not affect the fecal pellet output, frequency of watery diarrhea, total fecal weight, fecal dried solid weight, or fecal fluid weight in the first hour post injection, either. Contrary, ICV injection of h/rCRF effectively stimulated fecal pellet output, as well as increased total fecal weight, fecal dried solid weight and fecal fluid weight during the first hour post injection, compared to ICV saline controls. In conclusion, acutely central administration of obestatin exhibits no influence on colonic motility and secretion in conscious rats.

doi:10.1016/j.appet.2010.04.040

Glutamate agonists injected in the lateral hypothalamus stimulate ethanol intake

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Glutamate inputs to the hypothalamus are important in initiating ingestive behavior. The question is whether this includes ethanol intake, with a possible role in alcohol abuse. Male Sprague–Dawley rats ($N = 50$; $n = 12$–13 subgroup) were trained to drink 9% ethanol ad libitum and implanted with cannulas aimed at the lateral hypothalamus (LH). Microinjections of the glutamatergic agonist NMDA dose-dependently increased ethanol consumption, relative to vehicle injections given in counterbalanced order. Ethanol intake was significantly enhanced for 1 h after the 5.5 nmol dose (vehicle: 0.41 ± 0.08 g/kg; NMDA: 0.66 ± 0.15 g/kg) ($p < 0.05$) and for 6 hr after the 11 nmol dose (vehicle: 1.05 ± 0.22 g/kg; NMDA 2.01 ± 0.34 g/kg) ($p < 0.05$). Compared to the long-lasting effect of NMDA, the glutamatergic agonist AMPA produced milder but similar results in the LH. At 1.07 nmol, AMPA significantly enhanced ethanol consumption for 4 h post-injection (vehicle: 0.70 ± 0.11 g/kg; AMPA: 1.04 ± 0.15 g/kg) ($p < 0.05$). Water and food intake were unaffected in all tests. These results show that glutamate, which also stimulates feeding when injected into the LH (Stanley et al., 1993), can instead induce 9% ethanol intake in rats that have learned to drink it, having an effect that lasts up to 6 h. Thus, glutamate inputs to the LH have excitatory control over the initiation and maintenance of ethanol intake and thus may be a site where glutamatergic drugs, e.g., acamprosate, act to control ethanol consumption.

doi:10.1016/j.appet.2010.04.041

Increased amygdala response and decreased influence of internal state on amygdala response to food in overweight compared to healthy weight individuals

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Neuroimaging studies in healthy weight (HW) individuals have demonstrated that the amygdala responds to food cues and that this response is attenuated by feeding to satiety, suggesting that the value of the food cue is represented there. To test the hypothesis that amygdala response to food is greater in overweight (OW) compared to HW individuals, we used fMRI to examine brain response to the taste and smell of highly palatable milkshakes in 26 individuals (13 HW and 13 OW). Perceptual ratings of the stimuli and of internal state were collected before and after scanning. Between group analyses of variance based on random effects models were performed in SPM5. Peaks were considered significant following correction for multiple comparisons across all voxels in the amygdala. Greater amygdala response was observed in the comparison of milkshake vs. tasteless and of food aromas vs. odorless in OW compared to HW individuals. This response did not vary as a function of stimuli pleasantness. However, hunger, which did not differ between groups, was positively associated with amygdala response to milkshake in the HW group, whereas no association was observed in the OW group. Additionally, amygdala response to the food aromas predicted weight gain one-year post scan. These findings suggest that heightened amygdala response to food, coupled with reduced influence of internal state upon this response, may lead to overeating.

doi:10.1016/j.appet.2010.04.042

Role of dopamine in dorsal medial prefrontal cortex in yohimbine-induced reinstatement of food seeking in rats

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In humans, relapse to maladaptive eating habits during dieting is often provoked by stress. We adapted a drug relapse-reinstatement model to study the role of stress in relapse to food seeking (Nair et al., Prog. Neurobiol., 2009). In our model, the anxiogenic drug yohimbine, an alpha-2 adrenoceptor antagonist, that causes stress-like responses in humans and laboratory animals, reliably reinstates food seeking. We recently found that yohimbine-induced reinstatement of food seeking is attenuated by systemic injections of SCH23390 (a D1-family receptor antagonist) but not clonidine (an alpha-2 adrenoceptor agonist). Here, we studied the role of the medial prefrontal cortex (mPFC) in yohimbine-induced reinstatement. We trained food-restricted rats to lever-press for 35% high-fat pellets every other day (9–15 3 h sessions). We then extinguished the food-reinforced operant responding for 10–14 days by removing the pellets. Subsequently, we tested the effect of systemic injections of yohimbine (0, 2 mg/kg) on reinstatement of food seeking. In Exp. 1 we found that yohimbine-induced reinstatement was associated with strong induction of Fos (a marker of neuronal activity) in the dorsal mPFC and weaker Fos induction in the ventral mPFC. In Exp. 2 we found that dorsal but not ventral mPFC injections of the D1-family receptor antagonist SCH23390 (0.5, 1.0 μg/side) decreased yohimbine-induced reinstatement of food seeking. Our data indicate a critical role of dorsal mPFC dopamine in reinstatement food seeking induced by the pharmacological stressor yohimbine.

doi:10.1016/j.appet.2010.04.043

Effect of *Rhodiola rosea* extracts on binge eating in female rats

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Stress is a determinant of binge eating. *Rhodiola rosea* (ROR) extracts modulate stress responses. The present study evaluated the effect of ROR dry extract and its active principles in rats in which binge eating for highly palatable sweet food (HPF) was evoked by stress and repeated food restrictions. Female Sprague–Dawley rats were submitted to three 8-day cycles of food restriction/refeeding (4 d 66% of the usual chow intake, 4 d food ad libitum) and to acute stress on d25. Stress was induced by preventing access to HPF for 15 min, while rats were able to see and smell it. 4 groups of rats were used: NR + NS rats were normally fed and not stressed on the test day (d25); NR + S rats were similarly fed but were stressed on d25; R + NS rats were exposed to 3 cycles of yo-yo dieting but not stressed; R + S rats were exposed to 3 cycles of yo-yo dieting and stressed on d25. ROR dry extract (containing 3% rosavin and 3.12% salidroside) or the purified principles were given by gavage 1 h before access to HPF. Food restrictions and stress induced binge eating in R + S rats, increasing HPF intake of about 50% in the first 15 min. 10 mg/kg of ROR extract significantly reduced and 20 mg/kg abolished the HPF binge in R + S rats, but did not modify HPF intake in NR + NS, NR + S or R + NS rats. Rosavin or salidroside, 600 or 636 μg/kg (i.e. the amounts in 20 mg/kg of extract) significantly reduced HPF intake in R + S rats; when given together they completely abolished the binge response. Thus, ROR extracts or its active principles, rosavin and salidroside, may be interesting agents for treatment of bingeing-related eating disorders.

doi:10.1016/j.appet.2010.04.044

Effect of the NOP receptor antagonist UFP-101 in an experimental model of binge eating

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UFP101 is a high affinity peptide antagonist for the nociceptin/orphanin FQ receptor. Since it was reported to influence feeding behaviour, this study evaluated its effect in an animal model of binge eating (BE), in which BE for sweet highly palatable food (HPF) was evoked by repeated food restrictions and stress. Female Sprague–Dawley rats were submitted to three 8-day cycles of food restriction/refeeding (for 4 days 66% of chow intake + 4 days food ad libitum) and to acute stress (on day 25) to evoke BE (R + S group). Stress was induced by preventing access to HPF for 15 min, while rats were able to see it and to smell its odour. Control rats (NR + NS) were normally fed and were not stressed. The combination of cyclic food restriction and stress induced BE that was significantly reduced by ICV injection of UFP101, 20 nmol/rat. HPF intake was also reduced in NR + NS, suggesting a general effect on HPF intake, rather than a selective effect on the binge episode. To further investigate this effect, UFP101 was also studied in freely feeding male Wistar rats familiarized with HPF offered for 1 h at 3-day intervals. UFP101, 15–20–30 nmol/rat but not 7.4, significantly reduced HPF intake. When tested for its effect on chow intake in 24 h food-deprived rats, UFP101 significantly reduced food intake at the same doses effective on HPF. Although it did not significantly affect feeding in sated rats, it showed a clear trend to reduce nocturnal chow intake. The present results indicate that UFP101 exerts a general effect on feeding, independent from the type of food (HPF vs chow) offered to the rat or the conditions in which feeding is evoked.

doi:10.1016/j.appet.2010.04.045

Consumption of a high fat diet affects phasic dopamine release and reuptake in the nucleus accumbens

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The rate of obesity has climbed dramatically over the past several decades as food high in fat content has become more readily accessible. In the US alone, approximately one third of adults are considered obese. Obesity has been correlated with changes in the mesolimbic dopamine (DA) system. Human imaging studies have revealed that DA terminal regions differentially respond to food depending on body mass index. In animal subjects, high fat diet exposure reduces motivated behavior and responses to amphetamine. Thus, high fat diet exposure may lead to obesity, in part, through feed forward mechanisms that suppress mesolimbic DA signaling. Here, we determined the effects of different durations of high fat diet exposure on phasic DA release evoked by electrical stimulation of the ventral tegmental area. Rats were given ad libitum access to either a high fat diet (60% kcal/g from fat; HFD) or a low fat diet (10% kcal/gm from fat; LFD). After different durations on the diet (2, 4 or 6 weeks), rats were anesthetized with urethane. Phasic spikes in DA concentration were evoked once every 2 min by stimulating the VTA and measured using fast scan cyclic voltammetry at a carbon fiber microelectrode in the nucleus accumbens. DA function was assessed by altering the number, frequency, and intensity of current pulses before and up to 1 h after cocaine injection. Cocaine caused a dramatic increase in evoked DA in LFD rats. In contrast, cocaine caused a much smaller increase in evoked DA in HFD rats. The data were modeled to determine if baseline and cocaine potentiated differences in evoked DA between LFD and HFD rats were due to changes in DA release, reuptake or both. The results demonstrate that high fat diet exposure results in dramatic changes in phasic DA signaling. Given its established role in reward, reinforcement and motivation, these changes in phasic DA signaling likely contribute to further imbalance between energy intake and energy expenditure.

doi:10.1016/j.appet.2010.04.046

Is your brain to blame for weight regain?

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The weight-reduced state is associated with a very high propensity for weight regain. The mechanisms responsible for this effect are likely multi-factorial with changes in energy expenditure, substrate metabolism, and energy intake all favoring weight regain. Central mechanisms important in the regulation of energy intake are impacted at multiple levels. Homeostatic mechanisms, such as hormones important in energy balance, have been shown to be impacted by weight loss. Non-homeostatic mechanisms, such as motivation, reward and learned behaviors, are also affected by negative energy balance and the weight-reduced state. Neuroimaging studies have shown that reduced-obese individuals have significantly different responses to food-related cues than obese and normal weight individuals which may further explain their propensity for weight regain. In summary, the weight-reduced state is likely associated with an alteration in the complex interaction between responses to environmental cues, changes in behaviors and reward, and changes in homeostatic signals, resulting in a milieu favoring increased energy intake.

doi:10.1016/j.appet.2010.04.047

Involvement of D2 receptors in the medial agranular cortex in binge consumption of fat in rats

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Prefrontal cortical (PFC) targets of midbrain dopamine neurons may be important to binge-type consumption of fatty foods. Furthermore, D2 receptors have been implicated in compulsive overeating and bingeing. We sought to determine if PFC D2 receptors were critical to binge consumption of fat in rats. Two groups of male Sprague-Dawley rats had either: (1) daily (D): 1-h access to shortening daily; or (2) intermittent (INT): 1-h access to shortening on Mon, Wed, and Fri. All rats had access to chow when shortening was not available. On these protocols, INT shortening intakes gradually escalate until they consistently exceed those of D, i.e. INT rats binge. After 7 weeks, rats were equipped with bilateral cannulae aimed at either the anterior cingulate (AC) or medial agranular (AGm) cortex. 1 wk later, the D2 antagonist eticlopride (vehicle, 0.1, 0.3, 1 μg/0.5 μl/site) was infused and effects on shortening intake assessed. Intra AGm eticlopride (0.3 μg/side) significantly stimulated shortening intake in INT but not D rats ($p < 0.05$). Eticlopride had no effect when infused into the AC. The inverted U-shaped dose–effect function is consistent with pre-synaptic effects. These results indicate that reduced D2 receptor actions in the AGm do not cause bingeing, but can exacerbate bingeing once it is established. This suggests that D2 receptor dysregulation in the AGm occurs as a result of binge consumption of fatty foods. Given the apparent role of the AGm in directed attention, such alterations may serve to focus attention on eating during a binge. Funding: RO1-MH67943 (RC).

doi:10.1016/j.appet.2010.04.048

Baclofen reduces binge frequency

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The GABA-B agonist baclofen showed promise in substance abuse treatment, reduced binge size in rats and reduced binge frequency in an open label trial in humans. This study tested the effect of baclofen (20 mg TID) on bingeing in a randomized, placebo-controlled, double-blind, cross-over trial. 19 subjects who self-reported bingeing ≥3X per week started and 13 (11 F, 2 M) completed the study. Average (±SE) binge duration was 20 (±3) years; age was 45 (±3) years. Binge frequency was significantly lower during baclofen than during placebo ($p < 0.05$), and was reduced by 23% (±10%). Bingeing was not reduced in all subjects and, among responders, reductions ranged from 1% to 80% ($n = 9$). 5 subjects showed reductions of >40%; 3 requested continuation of baclofen. Relative to placebo, baclofen had no significant effect on self-reported binge severity and self-control, Binge Eating Scale score, craving, anxiety, or depression. There were about twice as many reports of side effects during drug compared to placebo, with tiredness/fatigue (TF) and headache (HA) being the most highly represented (baclofen: 4 TF, 4 HA; placebo: 0 TF, 1 HA). The present results indicate that baclofen: (1) can reduce binge frequency and (2) may offer a new tool for the treatment of binge eating. Supported by PSIDO. Thanks to L. Kipp and GCRC staff.

doi:10.1016/j.appet.2010.04.049

Urocortin microinjection into the lateral septal area alters appetite and energy substrate utilization

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Urocortin (UCN) is a 40 amino acid peptide and a corticotropin releasing hormone (CRH)-related ligand. UCN was cloned from the rat midbrain and exhibits a 45% sequence identity to CRH and a 63% sequence identity to urotensin. The peptide shows high affinity for CRHr1 and CRHr2 but appears to exhibit greater affinity for the CRH2 type receptor. Recent work has implicated UCN in various endocrine and physiologic functions including appetite suppression. We have previously reported that UCN inhibits food intake and alters energy metabolism when injected into discrete regions of the hypothalamus. Other work suggests that UCN may inhibit eating when injected into the lateral septal area (LSA) of the limbic system. In the present study, we investigated both the eating and metabolic effects of UCN microinjected into the LSA. Rats ($n = 10$) were injected with UCN (6.25–100 pmol) or vehicle directly in the LSA at the onset of the dark cycle. The metabolic effects ($n = 10$) were monitored using an open circuit calorimeter which measured oxygen consumption and carbon dioxide production (RQ; respiratory quotient). UCN reliably decreased food intake and RQ over a 4 h post-injection period. The lowest effective dose was 12.5 pmol. These results suggest that the LSA is sensitive to UCN mechanisms regulating energy substrate utilization in addition to a role in stress and appetite regulation.

doi:10.1016/j.appet.2010.04.050

Gut peptides are not necessary for food anticipatory activity induced by a highly palatable meal

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Animals learn to anticipate a meal as evidenced by increased activity prior to a scheduled mealtime. This learned response appears to be independent of nutrient status because food anticipatory activity (FAA) can be seen after entrainment by a highly palatable food when rats remain ad lib on chow. Mealtime feeding not only induces an increase in activity, but also appears to entrain the secretion of various peptides prior to a meal including insulin, ghrelin and glp-1 when rats are conditioned to a 4 h meal each day. It is not clear if these meal anticipatory increases in gut peptides are also associated with FAA or those induced by a highly palatable food. In order to assess if these preprandial peptide changes are associated with the FAA that occurs with palatable meal entrainment, rats were conditioned to receive a 2 h access of chocolate in the middle of the light cycle while remaining ad lib on chow. FAA was measured for 4 h prior to the chocolate meal. Rats were then sacrificed at 90, 60, 30 min prior to the chocolate mealtime and plasma was collected. Although the chocolate-entrained rats showed FAA compared with the non-chocolate entrained animals, they did not show anticipatory increases in the ghrelin or glp-1. In fact, chocolate entrained animals had significant decreases in insulin prior to mealtime. Thus, FAA can occur without increases in insulin, ghrelin or glp-1. This suggests that separate mechanisms may underlie the meal entrainment to chow versus entrainment to a palatable food when freely feeding.

doi:10.1016/j.appet.2010.04.051

The effect of orexin A on food intake and spontaneous physical activity in the paraventricular nucleus and ventral tegmental area

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Differences in neurological control account for much of the observed variation in motor and feeding behavior. Orexin A (OxA) is a neuropeptide that increases spontaneous physical activity (SPA) and food intake, which influence the development of obesity.

In this study the effect of OxA injection into the paraventricular nucleus of the thalamus (PVT) and the ventral tegmental area (VTA) in rats on SPA and FI was assessed. Both of these areas were chosen because of their known roles in the regulation of motivational behaviors such as feeding and activity. Vehicle or OxA (50, 100 and 250 pmol) were injected into each site. Spontaneous physical activity (SPA) was measured using activity-sensing chambers. Food intake was measured through changes in hopper-container weight. Repeated measures ANOVA was used to assess differences between response to OxA in each brain site. OxA significantly increased time spent ambulating in the first hour post-injection in the PVT ($n = 8$; $p = .03$) but not after injection in VTA. There was also a significant site dependency of the ambulatory response in the PVT at 0–1 h ($n = 8$, .004) and 0–2 h ($n = 8$, .03) post-injection. Significant site dependency of the feeding response ($n = 8$; $p = .04$) was also observed in the 0–1 h time interval. There was no effect of OxA in PVT on food intake, yet there was an insignificant increase in 1–2 h food intake after orexin injection into the VTA. These data suggest that feeding and activity response to OxA varies by brain site, and suggests the PVT as an important mediator of OxA-induced SPA.

doi:10.1016/j.appet.2010.04.052

Gastric emptying and sodium intake by dehydrated rats after serotonergic blockade in the lateral parabrachial nucleus

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Serotonergic blockade with methysergide (METHY) in the lateral parabrachial nucleus (LPBN) enhances hypertonic NaCl intake in dehydrated rats. This blockade might increase gastric emptying rate of hypertonic NaCl, thereby reducing inhibitory signals for NaCl intake. Water and 0.3 M NaCl intake was tested in rats treated with bilateral injections of METHY (4 μg/0.2 μl) or vehicle (VEH) into the LPBN combined with previous (45 min before) sc injection of furosemide (FURO, 10 mg/rat) or iv infusion of 2 M NaCl (1.5 ml/10 min). METHY induced 0.3 M NaCl intake in FURO-treated rats (14.6 ± 1.6 ml/2 h; VEH: 4.0 ± 0.6 ml/2 h; $n = 24$) or hyperosmotic rats (14.1 ± 3.3 ml/2 h; VEH: 1.7 ± 0.5 ml/2 h; $n = 11$). Five days later, rats were dehydrated again by sc FURO plus overnight sodium restriction (late-hypovolemia) or iv NaCl 2 M. Then, 15 min after METHY or VEH into the LPBN, they received a fixed amount (3 ml) of 0.3 M NaCl either to drink (late-hypovolemic rats) or by gavage (cell-dehydrated rats). The stomachs were removed 10 min after the initial access to 0.3 M NaCl for determination of their total liquid content. METHY did not alter stomach liquid content in cell-dehydrated (2.9 ± 0.2 g, $n = 6$; VEH: 3.2 ± 0.2 g, $n = 5$), but reduced it in sodium depleted rats (2.1 ± 0.1 g, $n = 6$; vs. VEH: 2.5±0.3 g, $n = 7$). The results suggest that alterations in gastric empting of hypertonic NaCl are not essential for the effect of METHY on 0.3 M NaCl intake.

Support: CNPq, FAPESP.
doi:10.1016/j.appet.2010.04.053

SeXX and adipose tissue

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Disruption of estrogen (E2) signaling by estrogen receptor (ER)-α ablation yields an obese, glucose intolerant phenotype. These findings support a role for E2 and ERα in preventing obesity; however, the molecular mechanisms and tissue specific sites conferring ERα activity are unknown. ERα is expressed in multiple tissues, and here we have developed a novel mouse model with which we can directly study the effects of ERα in adipocytes. To this end we have employed the $ER\alpha^{lox/lox}$ mouse crossed to a mouse that expresses CRE recombinase under the control of the adiponectin promoter. Adiponectin expression is highly restricted to adipocytes and is not present in macrophages or in other components of the stromal vascular fraction of adipose tissue. Preliminary analyses of these mice demonstrate that female $ER\alpha^{lox/lox}$/Adipo-CRE mice differ in body weight but not food intake when compared to their $ER\alpha^{lox/lox}$ littermate controls. However, the $ER\alpha^{lox/lox}$/Adipo-CRE mice show an increased triglyceride deposition in their visceral adipose depots and enlarged visceral adipocytes. Moreover, both male and female $ER\alpha^{lox/lox}$/Adipo-CRE mice have impaired glucose tolerance when compared to $ER\alpha^{lox/lox}$ littermates. Additionally, male $ER\alpha^{lox/lox}$/Adipo-CRE mice have decreased pyruvate tolerance, suggesting that this glucose intolerance is the result of liver insulin resistance. In conclusion, our data demonstrate that adipocyte ERα is crucial in mediating adipocyte and systemic metabolic homeostasis.

doi:10.1016/j.appet.2010.04.054

Optogenetic control of arousal and brain reward

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The hypothalamus is a federation of nuclei with diverse functions in the regulation of homeostasis and behavior. The complex and heterogeneous nature of hypothalamic nuclei makes it difficult to assign causal relationships between activity of defined cell groups and complex behavior. We have recently targeted the light activated cation channel, channel rhodopsin 2 (ChR2) to different hypothalamic cell groups that promote arousal. We have demonstrated that optogenetic stimulation of neurons producing hypocretins (also known as orexins) increases the probability of sleep to wake transitions. However, mild homeostatic sleep pressure prevents these optogenetic-induced transitions. We have also demonstrated that low frequency activity noradrenergic neurons in the locus coeruleus, which receive direct synaptic input from hypocretin neurons, is sufficient to drive sleep to wake transitions. In sum, optogenetics can establish causal relationships between the activity of genetically defined cell groups and sleep-to-wake transitions with an unprecedented millisecond temporal resolution.

doi:10.1016/j.appet.2010.04.055

Programmed impairment of hypothalamic neural stem cell proliferation and differentiation. Mechanism of adult obesity in low birth weight (LBW) offspring

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LBW offspring exhibit reduced hypothalamic neural satiety pathways and dysregulated signaling leading to programmed hyperphagia and adult obesity. Hypothalamic appetite circuits develop during early life, under the influence of neurotrophic hormones (leptin, insulin). Notably, LBW newborns have reduced plasma leptin and insulin levels. As neurons and glia arise from neuronal precursor cells (NPC), we postulated that a programmed impairment of NSCs may contribute to reduced hypothalamic neural pathway development in LBW offspring. Control dams received ad libitum food, whereas study dams were 50% food-restricted from pregnancy day 10–21 to produce LBW newborns. At day 1 of age, hypothalamic NPCs were cultured as neurospheres (NS) and treated with leptin (10, 20, 40 ng/ml) or insulin (10, 20, 40 μg/ml). Cell proliferation and differentiation into neurons or astrocytes was analyzed. LBW NS had markedly reduced basal (50–60%) and leptin/insulin stimulated *proliferation* as compared to Controls. Further, LBW NS had reduced *basal differentiation* to both neuronal (22%) and astrocyte (42%) cell lines. In response to leptin, LBW NS exhibited significantly reduced differentiation to both neurons (34%) and astrocytes (29%). In contrast to leptin, insulin induced NS differentiation only to neurons, with a marked impairment evident in LBW as compared to Controls. Thus, programmed dysfunctional hypothalamic NPCs likely contribute to reduced anorexigenic neural pathways in LBW offspring, and to the resulting hyperphagia and obesity.

doi:10.1016/j.appet.2010.04.056

Maternal obesity and programmed offspring hyperphagia

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In parallel with the population-wide obesity epidemic, there has been a marked increase in mean maternal body weight and increased incidence of obesity during pregnancy. Although mean newborn weight has not changed, the potential exists for programming of offspring orexigenic regulation as a result of the altered pregnancy and lactation nutrient environment. We determined whether exposure to maternal obesity and high fat (HF) diet causes offspring hyperphagia. Weanling female rats were fed a HF (60% k/cal) or Control (10% k/cal) diet. At 11 weeks of age, rats were mated and continued on their respective diets during pregnancy and lactation. Newborns were nursed by the same dam and weaned to normal fat diet. Though HF males had similar body weights as the Controls (7.4 ± 0.2 g vs. 7.3 ± 0.1 g), they had significantly increased body weight (73 ± 3 g vs. 56 ± 2 g) by the end of nursing period (3 weeks). Following weaning, HF males showed rapid weight gain in conjunction with significantly increased food intake. Thus, maternal obesity and HF diet during pregnancy and nursing periods predisposes offspring to programmed hyperphagia and adult obesity.

doi:10.1016/j.appet.2010.04.057

Maternal obesity and increased risk of offspring metabolic syndrome

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Exposure to either under- or over-nutrition in early life increases the risk of adult obesity. Offspring born to mothers with a high body mass index show increased adipose tissue mass, and obesity and diabetes risk in later life. As the prevalence of obesity among pregnant women continues to rise, increasing number of children are exposed to an 'obese intrauterine environment' during development. We determined whether exposure to maternal obesity increases the risk of obesity in the offspring. Weanling female rats were fed a high fat (HF: 60% k/cal) or Control (10% k/cal) diet. At 11 weeks of age, rats were mated and continued on their respective diets during pregnancy and lactation. Newborns were nursed by the same dam. At 1 day of age, HF males had similar body weights as the Controls (7.4 ± 0.2 g vs. 7.3 ± 0.1 g) with notably decreased plasma leptin levels (2.1 ± 0.5 ng/ml vs. 4.9 ± 0.9 ng/ml, $p < 0.01$). At 3 weeks of age, HF males exhibited accelerated growth, resulting in significantly increased body weight (73 ± 3 g vs. 56 ± 2 g) and body fat ($12.6 \pm 1.2\%$ vs. $6.4 \pm 1.0\%$) with decreased lean body mass ($85.5 \pm 1.3\%$ vs. $91.6 \pm 1.0\%$). Further, blood glucose (131 ± 6 mg/dl vs. 96 ± 7 mg/dl) and plasma leptin (3.9 ± 0.5 ng/ml vs. 1.3 ± 0.2 ng/ml) and triglycerides (103 ± 12 mg/dl vs. 68 ± 8 mg/dl) levels were significantly elevated. Despite no differences in body weights at birth, offspring of obese dams when nursed by obese dams, showed marked increased body weight, adiposity and metabolic abnormalities. These findings suggest that maternal obesity during critical period of development may increase the susceptibility of the offspring to obesity.

doi:10.1016/j.appet.2010.04.058

The influence of eating and taste detection on food reinforcement

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The reinforcing value of food plays a role in energy intake. The purpose of this study was to determine how food intake and taste detection thresholds affect food reinforcement in adults. During one visit, taste detection thresholds were measured. On the next two visits, participants completed a computer based food reinforcement task to earn points toward portions of a highly liked snack food. During one visit, participants were instructed that the 100 kcal portion of food had to be eaten immediately after it was earned. On the other visit, participants earned as much food as they wanted and were instructed to wait until the end of the experiment to consume it. The order of these conditions was counterbalanced. There was a main effect of condition on food reinforcement, with reduced food reinforcement when eating occurred during the experiment. There was also an interaction between condition and BMI with overweight participants showing larger difference between the conditions when compared to lean participants. For taste detection thresholds, there were main effects of quinine and sucrose detection on food reinforcement, with higher detection thresholds associated with greater food reinforcement. There were also interactions between detection thresholds and BMI, with overweight individuals with high detection thresholds showing the highest level of food reinforcement for both quinine and sucrose. When taken together, these data suggest that feedback from acute food intake as well as taste detection can play a role in the reinforcing value of food.

doi:10.1016/j.appet.2010.04.059

Interaction between food deprivation and access to food period on eating behavior

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The purpose of the present study was to explore the interaction between food deprivation and access to food period on intake pattern in rats. Regarding that both variables are present in any episode of food intake, it is necessary to explore their effect on magnitude intake. A factorial design 2×2, food deprivation (ascending and descending order) and access to food period (short and long) was implemented using 24 rats. Groups of three subjects were exposed to a different combination of both variables. Before and after all experimental conditions rats had free access to food and water. Every experimental condition was implemented during 15 days while a 12-h light–dark cycle was maintained. Mean food consumed were 13.87 (SD = 1.94) for short ascending; 14.88 (SD = 1.78) for short descending; 12.1 (SD = 3.26) for long ascending; and 11.78 (SD = 3.97) for long descending. Food deprivation and access to food period interaction was significant for total intake ($F = 4.70$, $p < .05$). Post hoc test using Tukey HSD indicated that short descending group consumed more food than any other group. These findings support the idea that the interaction of both variables modulates the intake pattern and evidence the necessity to include both variables in future studies about eating behavior. Supported by PROMEP 103.5/09/3912.

doi:10.1016/j.appet.2010.04.060

Fat intake stimulates endocannabinoid mobilization in the small intestine through a cephalic mechanism

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We have shown that dietary oleic acid is converted into the satiety factor, oleoylethanolamide (OEA) by the absorptive epithelium of the small intestine. OEA shares several biosynthetic and degradative steps with the endocannabinoid (eCB) anandamide (AEA), which participates in controlling energy balance through both central and peripheral mechanisms. We asked, therefore, whether fat intake might influence AEA mobilization in the small intestine. Separate groups of 18-h food-deprived Sprague-Dawley rats were sham-fed (30 min) liquid Ensure (15 ml), a sucrose solution (8% w/v; 15 ml), or a fat emulsion (25% v/v; 10 ml). Ensure increased the levels of both common eCBs, AEA [from 3.0 ± 0.2 ($n = 7$) to 4.9 ± 0.6 ($n = 8$) pmol/g tissue; $p < 0.05$] and 2-arachidonoyl glycerol (2-AG; from 14.0 ± 0.7 to 22.6 ± 1.8 nmol/g tissue; $p < 0.01$) in the jejunum. Sucrose failed to modify jejunal AEA [from 3.7 ± 0.7 ($n = 5$) to 3.2 ± 0.6 ($n = 5$)] or 2-AG (from 16.2 ± 1.6 to 18.0 ± 1.7). In contrast to sucrose, fat intake robustly increased jejunal AEA [from 9.9 ± 1.3 ($n = 5$) to 20.3 ± 4.2 ($n = 5$); $p < 0.05$] and 2-AG [from 16.4 ± 1.3 ($n = 5$) to 33.4 ± 6.1 ($n = 5$); $p < 0.05$]. The results suggest that a cephalic mechanism engaged by fat ingestion stimulates eCB mobilization in the small intestine. The physiological significance of this response is under investigation.

doi:10.1016/j.appet.2010.04.061

Central leptin fails to enhance CCK-induced conditioned taste aversion

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Previous studies have shown that leptin (LEP) pre-treatment enhances cholecystokinin (CCK)-induced anorexia. One potential explanation for this effect is that leptin enhances the aversive characteristics of CCK, rather than increasing the satiating properties of CCK. To address this possibility, we examined whether LEP enhances CCK's ability to induce a conditioned taste aversion (CTA). Rats were given daily 20-min access to water while otherwise water-deprived. On the training day, rats received 20-min access to 0.5% saccharin paired with one of the following conditions: 3rd-icv vehicle (VEH) + IP VEH; 3rd-icv LEP (5 μg) + IP VEH; 3rd-icv VEH + IP CCK (100 μg/kg); 3rd-icv LEP + IP CCK; or IP LiCl. The acquisition of CTA was tested the next day, when rats received ad lib access to both saccharin and water. Over the next 24 h, the VEH/VEH group showed a preference for saccharin (88% of total fluid intake), while the LiCl group showed a strong aversion to saccharin (21%). The LEP/VEH group preferred saccharin (86%), as expected. The VEH/CCK group showed a mild, but significant aversion to saccharin (62%), and LEP pretreatment did not enhance this effect of CCK (LEP/CCK group: 65%). There was considerable variability in saccharin intake within each CCK-treated group (range from 25 to 93% of total intake), but LEP did not affect this distribution. Based on these data, we conclude that LEP does not enhance CCK-induced anorexia by increasing the aversive properties of CCK.

doi:10.1016/j.appet.2010.04.062

The kappa receptor agonist salvinorin A suppresses phasic dopamine signaling and motivation for food reward

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Kappa opioid receptors (KORs), expressed on dopamine (DA) terminals in the nucleus accumbens (NAc), act to decrease extracellular DA over minutes. Brief, subsecond changes in DA (phasic) are critical for reinforcement but their modulation by KORs remains unknown. Here, we used fast scan cyclic voltammetry (FSCV) to measure the temporal effects of the KOR agonist salvinorin A (salvA) on phasic increases in NAc DA evoked by stimulation of the ventral tegmental area (VTA). SalvA decreased evoked DA release in the NAc core ($37.27 \pm 2.4\%$ of baseline, 15 min post-injection; $p < 0.001$) and shell ($51.67 \pm 8.3\%$ of baseline, 15 min post-injection; $p < 0.01$). However, suppression of phasic DA release in the core was greatly prolonged relative to that in the shell. SalvA has previously been shown to induce a dysphoric state. Here, in parallel to FSCV studies, we determined the effects of salvA on motivation to work for sucrose reward on both progressive and fixed ratio 5 schedules of reinforcement. SalvA potently reduced breakpoint in the progressive ratio and the time course of salvA effects on responding closely resembled those on phasic DA in the nucleus accumbens core. These acute effects of salvA are contrasted with prolonged effects observed 24 h post-salvA treatment. Collectively, these studies provide strong evidence for KOR regulation of affective and motivational processing through suppression of phasic DA signaling in the NAc.

doi:10.1016/j.appet.2010.04.063

The Power of Food and Disinhibition Scales prospectively predict the emergence of loss of control over eating in young women prone to weight gain

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The Power of Food Scale (PFS) is a measure of preoccupation with food when not energy deprived. We examined it as a prospective predictor of the emergence of subjective or objective binge eating (Loss of Control over Eating, or LCE) in a sample of normal weight college women ($N = 294$) who were prone to weight gain. LCE was assessed with items from the Eating Disorders Examination. Using logistic regression the PFS predicted, among participants who did not report any LCE at baseline ($N = 239$), the emergence of LCE at 6-month ($p = 0.023$) and 12-month ($p = 0.004$) follow-ups. Results did not change when BMI at baseline was entered as a covariate. The PFS "Food Available" and "Food Present" factors, but not the "Food Tasted" factor, accounted for this prediction. This is consistent with research suggesting that obesity is related to increased reward responses to the anticipation of eating but not to consumption of food. Those who did exhibit LCE at baseline ($N = 55$) were also examined, but PFS scores did not prospectively predict change in frequency of LCE at follow-up assessments. Additionally, the Disinhibition scale from the TFEQ was tested as a predictor. Though it also predicted emergence of LCE at 6- and 12-month follow-ups, the strength of the prediction was reversed relative to the PFS (at 6 months, $p < 0.001$; at 12 months, $p = 0.043$). These results suggest that measures of food preoccupation and disinhibitory eating may provide warning signs of those vulnerable to developing problems with LCE.

doi:10.1016/j.appet.2010.04.064

Differential mechanisms underlying food-entrainment versus chocolate-entrainment

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Animals have the capacity to estimate time, which allows them anticipating the coming feeding opportunity preparing digestive functions for the expected meal. In the laboratory restricted feeding schedules induce anticipatory activity (FAA) and impose daily oscillations of c-Fos and clock proteins in brain structures and peripheral oscillators. We have proposed that the fasting/feeding cycle drives a network of brain oscillators in interaction with our organs. The metabolic state of scarcity leads to an increased motivational state associated with FAA. In order to differentiate the contribution of metabolic cycles from the motivational state to induce FAA, we compared the influence of daily access to food or chocolate on Fos and PER1 cycles in hypothalamic and corticolimbic structures. Rats were exposed to daily restricted food access or 5 g of chocolate in the middle of the day. Both restricted food (RF) and daily chocolate delivery produced FAA, however RF induced FAA of higher intensity and duration. RFS entrained mainly hypothalamic structures while chocolate induced rhythmicity in corticolimbic structures. This pattern persisted for up to 8 days after interruption of both entraining protocols. RF induced fast shifts of daily rhythmicity in brain structures while chocolate required 8 days to build up the daily pattern. Present data evidence different oscillatory systems in the brain driven differentially by metabolic stimuli or by motivation and reward. Granted by CONACyT 43950-M and 82462.
doi:10.1016/j.appet.2010.04.065

Improvements in weight, mood and cardiovascular disease risk factors in obese individuals with clinical depression

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Obese individuals with clinical depression are at high risk for incident cardiovascular disease (CVD), but are routinely screened out of weight loss trials due to concern that weight reduction will lead to adverse psychiatric outcomes. These concerns, however, are not based on empirical evidence. No treatments exist for obese individuals with clinical depression. This ongoing prospective study was designed to test whether obese, depressed individuals can lose clinically significant amounts of weight, and show improvements in mood and CVD risk factors. Twelve obese patients diagnosed with clinical depression who had at least 1 additional risk factor for CVD (mean age = 45.5 yr, BMI = 34.6 kg/m^2; Framingham risk score 4.2%) participated in a 16-week lifestyle modification program combined with group cognitive behavioral therapy for depression. Changes in weight and mood (as measured by the Beck Depression Inventory-II, BDI-II) were assessed weekly. Changes in CVD risk factors will be assessed (via Framingham Risk scores) at week 16. Baseline BDI-II scores were 29.9 ± 10.4, indicating severe depression. At week 8, patients lost $6.1 \pm 2.2\%$ of initial weight ($p < 0.001$), and reported a mean decline of 6.7 ± 9.1 points on the BDI-II ($p < 0.001$; i.e., an improvement in mood). Decrease in BDI-II score was not correlated with percent weight loss at 8 weeks ($r = 0.3$). These data show that obese, depressed individuals can lose clinically significant amounts of weight and show improvements in their symptoms of depression.
doi:10.1016/j.appet.2010.04.066

Effects of acute energy restriction on gastrointestinal motor, hormone, and energy intake responses to duodenal lipid in obese men

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Previous patterns of energy intake influence gastrointestinal function and appetite, probably reflecting changes in small intestinal nutrient-mediated feedback. As a group, the obese consume more fat and may be less sensitive to its GI and appetite-suppressant effects than lean individuals. We hypothesised that in obese individuals, the effects of duodenal fat on GI motor and hormone function and energy intake would be enhanced by a short period on a very-low calorie diet (VLCD). 8 obese men (50 ± 1 yr; BMI 34 ± 1 kg/m^2) were studied twice, immediately before (V1), and after (V2), a 4-day VLCD (70% energy restriction). On both days, motility (pressure waves) in the antrum, pylorus and duodenum, and plasma CCK, PYY and ghrelin were measured during a 120-min duodenal fat infusion (2.86 kcal/min). Immediately afterwards, energy intake from a cold-buffet-style lunch was assessed. During V2, the total number (V1: 1078 ± 17, V2: 1402 ± 20) and mean amplitude (mmHg; V1: 39 ± 3, V2: 51 ± 5) of pyloric pressure waves were greater, while numbers of antral (V1: 694 ± 29, V2: 212 ± 11) and duodenal (V1: 2989 ± 91, V2: 1910 ± 66) pressure waves were less, compared with V1 (all $P < 0.05$). Moreover, baseline ghrelin (pg/ml; V1: 138 ± 22, V2: 175 ± 25; $P < 0.05$), but not PYY (pg/ml; V1: 251 ± 28, V2: 229 ± 31), was higher, and the stimulation of PYY (conc at $t = 120$ min (pg/ml); V1: 571 ± 32, V2: 679 ± 43), and suppression of ghrelin (conc at $t = 120$ min (pg/ml); V1: 107 ± 21; V2: 109 ± 17), in response to lipid were greater (both $P < 0.05$), with no difference in CCK; and energy intake (kJ; V1: 4378 ± 691, V2: 3634 ± 701) was less (all $P < 0.05$), compared with V1. Our data suggest that in obese males, the effects of small intestinal lipid on GI motility and hormone responses and appetite are enhanced after a 4-day VLCD.
doi:10.1016/j.appet.2010.04.067

The role of MAPK signaling in a model of endogenous angiotensin II-induced water and sodium appetite

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This study tested the hypothesis that parallel downstream signaling limbs of the angiotensin II (AngII) type 1 receptor (AT1R) differentially mediate water and sodium ingestion in a model that elevates endogenous AngII. The AT1R is coupled with two intracellular signaling pathways: inositol trisphophate production and phosphorylation of mitogen-activated protein kinase (MAPK; specifically p42 and p44). The role of divergent signaling to induce water and sodium intake separately was suggested by studies that centrally administered AngII to rats. Treatment with the diuretic furosemide and a low dose of the angiotensin converting enzyme inhibitor captopril, which blocks peripheral but not central AngII production, has been shown to induce a rapid onset of water and sodium intake mediated by central AT1R. We treated male rats ($n = 17$/group) with furosemide and captopril and measured water and saline (1.5%) intake. In addition, animals were treated intracerebroventricularly with vehicle, an AT1R antagonist (irbesartan, 200 ng/μl), or a blocker of MAPK phosphorylation (U0126, 1 Mm). Consistent with previous studies, the AT1R antagonist reduced both water and salt intake from 8.0 ± 0.7 to 4.4 ± 0.6 ml (55%) and 6.3 ± 0.8 to 3.1 ± 0.7 ml (49%), respectively. Treatment with the inhibitor of MAPK phosphorylation reduced sodium intake to a similar extent (60% baseline). The U0126 treatment also reduced water

intake (70% baseline; all $p < 0.05$). These results suggest a role for MAPK in furosemide/captopril-induced water and sodium intake. Supported by HL091314.
doi:10.1016/j.appet.2010.04.068

Nucleus accumbens circuits in appetitive and consummatory behavior

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Reversible inactivation of subregions of the nucleus accumbens (NA) produces robust feeding behavior while electrical stimulation of NA interrupts locomotion and feeding. In addition, NA microinjection of opioid agonists promotes consumption of preferred tastants. Single unit recordings from NA neurons in awake behaving rodents has demonstrated subpopulations of neurons that encode sucrose palatability and preference and others that encode learned sensory cues that predict sucrose availability. A larger proportion of NA neurons show inhibitions beginning just prior to the initiation of approach to and/or consumption of sucrose. The temporal pattern of their firing indicates that the inhibitions permit approach and consumption of sucrose. The NA receives input from prefrontal cortex, amygdala, and a dense dopaminergic projection from the midbrain. All three regions (and dopamine action in NA) are required for responding to learned cues predicting sucrose availability. In addition, reversible inactivations of the ventral medial prefrontal cortex or the shell of the nucleus accumbens disinhibit appetitive behaviors. Our results indicate that parallel circuits in the NA exert either inhibitory or facilitatory influences on appetitive and consummatory behaviors.
doi:10.1016/j.appet.2010.04.069

Chronic stress, body weight, and cardiovascular function

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Chronic stress is associated with dysregulation of energy homeostasis, but the link is not currently known. In the laboratory, periods of chronic stress reduce weight gain. We hypothesized that these reductions in weight are an additional homeostatic challenge that contributes to the chronic stress syndrome. The current study examined cardiovascular responsivity following exposure to prolonged intermittent stress. We used radio-telemetry to monitor activity, mean arterial pressure (MAP), and heart rate (HR) in freely moving, conscious rats. Three groups of animals were tested: chronic variable stress (CVS), weight-matched (WM), and non-handled controls. Using this design, we can distinguish between effects due to stress and effects due to body weight. WM, but not CVS, markedly reduced basal MAP and HR. Although an acute stress challenge elicited similar peak HR, WM expedited the recovery to basal HR. The data suggest that CVS prevents the weight-induced attenuation of cardiovascular stress reactivity. We next hypothesized that CVS exaggerates plasma metabolic hormones, driving sympathetic activity. However, CVS blunted glucose, leptin, and insulin responses below WM levels. Overall, our data suggest that the impact of CVS is not solely due to body weight and that the passive restriction of food intake attenuates cardiovascular responses, an effect that is reversed by chronic stress.
doi:10.1016/j.appet.2010.04.070

The effect of body dissatisfaction and gender on dietary restraint

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The aim of this research was to evaluate the effect of body dissatisfaction and gender on dietary restraint. The sample included 252 university students (56.75% women and 43.25% men) with a mean age of 20.47 years (SD = 2.89). Participants completed the Eating Attitudes Test (EAT) and Body Shape Questionnaire (BSQ); weight status was measured using a calibrated scale and portable stadiometer. According to BSQ the rates of Body Dissatisfaction (BD) were 14% for women and 10% for men; the Body Mass Index indicated that 40% of women with BD were normal-weight and 5% were underweight, while 54% of men with BD were normal-weight. The ANOVA analysis revealed that satisfaction/dissatisfaction and gender (women and men) interaction had a significant effect on dietary restraint subscale of EAT ($F = 14.94$, $p < .001$). Post hoc test using Least Significant Differences indicated that women with BD scored significantly higher on eating restraint subscale of EAT than the other groups. Additionally, a higher percentage of women with BD indicated that have been missed one of three daily meals than those who were satisfied with their body ($p < .05$). Findings from the present study evidence an important effect of gender and body dissatisfaction on dietary restraint, specifically women with BD were high likely to report dietary restraint behaviors. Supported by PROMEP/103.5/09/3912.
doi:10.1016/j.appet.2010.04.071

Effects of obesogenic intrauterine environment on brain reward systems in the offspring

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There is increasing evidence that the prenatal environment plays a critical role in the development of obesity in the offspring of obese mothers. Using a selectively inbred rat model of obesity predisposition, we have shown decreased basal and stimulated dopamine release in the obesity-prone (OP) rats compared to the obesity-resistant (OR) rats as early as postnatal day 1. Development of this system, which codes for food reward, begins in the prenatal environment. We now consider whether the intrauterine environment associated with predisposition to obesity affects the development and phenotype of the brain dopamine systems in the offspring. We completely alter the prenatal environment in a controlled fashion via oviduct transplantation of the same number of embryos from an OP mother into an OR dame (OP/OR offspring) and vice versa (OR/OP offspring) on embryonic day 1. Effects on electrically stimulated dopamine release are measured in acute coronal slices by carbon fiber amperometry. We have found that 15-week-old female OR/OP and OP/OP offspring have significantly lower evoked dopamine release from the nucleus accumbens shell than the OR/OR and OP/OR offspring ($112.1 \pm 13.0 \times 10^6$ and $125.1 \pm 23.2 \times 10^6$ molecules v. $209.6 \pm 26.1 \times 10^6$ and $240.4 \pm 26.4 \times 10^6$ molecules, respectively; $p < 0.01$). The results indicate that the prenatal environment of an obesity-prone mother can at least partially determine central dopamine signaling in the offspring. Supported by DA023760, DK065872, P30 NS047243.
doi:10.1016/j.appet.2010.04.072

Sex differences following Roux-en-Y gastric bypass (RYGB)

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While it is established that ovarian hormones have a striking influence on food intake, energy expenditure, and glucose homeostasis, it is unknown if these differences persist following Roux-en-y gastric bypass (RYGB). We placed male and female C57/BL6 mice on a high fat diet for 90 days to increase their body weight. Once their body weight stabilized on the high fat, the mice received either the RGYB surgery, a sham surgery where the mice were exposed to all of the same manipulations but were left intact, and a final control group that were weight matched to the sham surgeries, or pair-fed to the sham surgeries, to determine if there is a sexual dimorphism in metabolic improvement following bariatric surgery. We found both females and males have a significant amount of weight loss following RYGB compared to all control groups, with females losing more weight and having a more rapid surgical recovery following the RYGB procedure. Additionally, while males showed recidivism toward their pre-operative body weight, females maintained their lower body weight. The mice were placed in a metabolic chamber, and both male and female RYGB mice had improved energy expenditure, and this improvement was greatest in the females. Additionally, following an oral glucose tolerance test, both male and female RYGB mice have significant improvements in glycemia, however the females have nearly completely normalized response to the oral glucose challenge. Our data suggest that estrogen provides a mediating role in weight loss and overall metabolic function following RYGB.

doi:10.1016/j.appet.2010.04.073

The effects of obesity on cognition in adult Sprague–Dawley rats

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When exposed to diet-induced obesity rats exhibit impairments in cognition when compared to age matched controls. This has been illustrated through dietary maintenance on chow high in sucrose as well as chow with a high fat content. This study used a repeated acquisition water maze task to test the hypothesis that obesity which has not been diet-induced will result in deficits in spatial memory and learning. Two groups of 10 adult male Sprague–Dawley rats were utilized in this study. Both groups were obtained from the same supplier on the same date and were kept under the same conditions while fed ad libitum however weights differed significantly between these groups ($P < 0.05$) with a difference of 136 g between mean weights at the initiation of cognitive testing. Testing occurred at 12 months of age and all animals received 10 days of testing in an open field water maze. Each rat received 4 daily trials during which they were placed in the water ($23 \pm 1\,^{\circ}C$) and allowed to use extramaze cues to locate a hidden platform and latency to platform acquisition was recorded. For the purposes of data analysis the last daily trial was discarded to remove any possible effects of exhaustion. ANOVA examining the mean times obtained from the first three daily trials revealed a significant difference between groups $F(1,18) = 4.51$, $P = 0.05$. Thus, in these animals obesity resulted in impaired learning.

doi:10.1016/j.appet.2010.04.074

HB-EGF regulates energy balance and fat storage

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Fat tissue grows continuously throughout life, which has to be accompanied by vasculature development. Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is expressed in fat tissue, initiates vascular gene expression, and induces vasculature growth. There is a direct correlation between obese mice and HB-EGF gene expression in fat tissue. We hypothesized that HB-EGF plays important roles in fat accruement during obesity development. Specifically, mice with higher levels of HB-EGF are obesity-prone whereas mice with lower levels of HB-EGF are obesity-resistant. HB-EGF over-expressing (OE) and knockout (KO) transgenic mice and a high-fat diet-induced obesity model were used to test this hypothesis. Body weights, calories consumed, and body composition of individual mice were measured. VO_2 and VCO_2 were measured using an indirect colorimeter to reflect energy expenditure, and respiratory quotient (RQ; VCO_2:VO_2) was calculated to indicate source of fuel that mice use. Although HFD-fed OE mice ate slightly more calories, female OE mice had significantly less body fat percentage than wild-type controls due to increased VO_2 per gram of lean mass, suggesting that OE mice were hypermetabolic with increased energy expenditure. HFD-fed KO mice ate less calories compared to wild-type and heterozygous mice. Interestingly, HFD-fed female KO mice had a higher percentage of body fat and exhibited a greater respiratory quotient in dark phase, indicating that KO females selectively used carbohydrate rather than fat as an energy substrate to facilitate fat storage. These findings suggest that HB-EGF regulates energy balance and fat utilization.

doi:10.1016/j.appet.2010.04.075

Ovariectomy and estradiol treatment affect subcutaneous more than intra-abdominal adipose tissue in rats

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Overeating is thought to contribute to aging-associated increases in adipose tissue (AT) in women, and loss of estrogens is thought to cause a shift in AT deposition from the subcutaneous (S) to the intra-abdominal (IA) compartments during reproductive senescence. To model these processes, intact and ovariectomized (OVX) rats were offered either chow ad libitum (Ch $n = 5$, Ch-OVX $n = 8$) or 3 daily rations of Ensure Plus (En $n = 8$, En-OVX $n = 8$) in amounts that led to total (T) AT gain similar to Ch-OVX rats. AT was measured weekly by CT. After 30 d, TAT gains were 12 ± 1, 10 ± 2, and 13 ± 3 g in Ch-OVX, En, and En-OVX rats, all more than Ch (5 ± 2 g, Ps < 0.05). TAT gains were predominately SAT (Ch-OVX 7 ± 1, En 5 ± 1, En-OVX 9 ± 2 vs. Ch 2 ± 1 g, Ps < 0.05). Only Ch-OVX rats, however, gained body weight (Ch-OVX 67 ± 6 vs. Ch 38 ± 4, En 26 ± 2, En-OVX 35 ± 2 g, Ps < 0.05). We then shifted En-fed rats to chow ad libitum and treated OVX rats with estradiol (E2, 2 μg/4 d SC) for 25 d. During this recovery phase, Ch and Ch-OVX/E2 rats tended to gain SAT (3 ± 2, 2 ± 1 g), whereas formerly En-fed rats lost SAT (En-1 ± 1, En-OVX-3 ± 2 vs CH, Ps < 0.05 vs Ch). Neither IAAT nor TAT change differed across groups. Thus, loss (i.e., OVX) and reinstatement of E2 affected SAT, not IAAT. Further work is needed to understand why our data do not parallel regional AT changes in peri-menopausal women measured by CT (Lovejoy et al., *IJO* 32:949, 2008) or in OVX and E2-treated rats measured by a different method (Clegg et al., *Diabetes* 55:978, 2006). Support: Swiss National Fund Grant 3100-122567.

doi:10.1016/j.appet.2010.04.076

Time course of estradiol effects related to body fluid balance in rats

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Estrogens influence behaviors and physiological systems, such as those involved in body fluid balance, in species including rats. Ovariectomized (OVX) rats typically are tested 48 h after treatment with estradiol benzoate (EB); thus, it has been assumed that observed changes are attributable to genomic actions of EB. Our goal was to evaluate the time course of EB effects on behavior and physiology related to fluid balance. Two groups of OVX rats were tested on a 4-day schedule: rats treated with EB or oil vehicle (OIL) on day1 and then tested on day2, and rats treated with EB or OIL on day1 and day2, and tested on day4. Rats were weighed daily during testing. Water intake was monitored after injection with isoproterenol (ISOP), a β-adrenergic agonist which stimulates drinking by activating the renin-angiotensin system. After behavioral testing, rats were sacrificed to collect blood and uteri. Uterine weight in EB-treated rats was greater than that in OIL-treated rats, and the differences were comparable on day2 and day4. EB effects to attenuate water intake stimulated by ISOP also were comparable on day2 and day4. In contrast, body weight increased in OIL-treated rats and decreased in EB-treated rats, but the difference did not occur until day4. Plasma protein concentration was elevated by EB, but only on day2. Finally, neither hematocrit nor plasma Na^+ concentration was affected by EB. Thus, EB effects occur at different rates, with effects on the drinking response to ISOP occurring more rapidly than previously reported. These observations suggest selective EB actions with diverse mechanisms.

doi:10.1016/j.appet.2010.04.077

Flavor cues and nicotine self-administration

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We have examined whether a flavor cue can serve as a better or equally salient secondary reinforcer compared with a light cue in a nicotine self-administration (NSA) protocol. Sprague–Dawley rats were first trained to lever-press for food, then underwent intraoral (IO) and/or intravenous (IV) catheter implantations. Rats were divided into two groups. All were studied in NSA (1-s infusions of 0.017 mg free base nicotine contingent on lever pressing) paired with either a traditional light cue or with a 1-s simultaneous IO infusion of a flavor (cherry flavored Kool-Aid in a 0.1% saccharin solution). We also examined the rate of responding for IO Kool-Aid alone or in the presence of noncontingent nicotine. Flavor preferences for the nicotine paired flavor were examined after these studies and after an experiment in which nicotine was given noncontingently in the presence of ad libitum Kool-Aid in a 23 h access protocol. Rats that received simultaneous infusions of the flavor were unable to maintain responding at an equal rate to those who acquired the behavior when infusions were paired with the light cue, despite lever pressing for the flavor alone. Rats did not press for the flavor in the presence of noncontingent nicotine, and showed an avoidance for the nicotine paired flavor. These results indicate that the Kool-Aid was unable to serve as a reinforcer in these studies and did not potentiate NSA. Rats run in a 23 h protocol however, showed a flavor preference for the nicotine paired-flavor, indicating that duration of exposure to both the flavor and nicotine is important.

doi:10.1016/j.appet.2010.04.078

Measuring food reward and the transfer effect of sensory specific satiety

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Sensory specific satiety (SSS) is the decrease in reward for an eaten food in comparison to other uneaten foods. Foods that share sensory characteristics with the eaten food also decline in pleasantness relative to foods that do not share these. The strength of this transfer effect for different tastes, however, is unclear. It has been proposed that SSS represents a decrease in both liking and wanting components of reward. Objective of our study was twofold: (1) to compare several measures of liking and wanting of food, (2) thereby investigating the transfer effect of SSS for sweet and savory taste to other foods. We used a cross-over design, consisting of 3 methods. Sixty-one healthy, unrestrained subjects (19M/42F), with a mean age of 22 ± 3 y and a mean BMI of 21.7 ± 1.5 kg/m^2 were served either a sweet or savory preload (rice meal). Afterwards, liking and wanting for 16 snack products, varying in taste (sweet/savory) and fat (high/low), were assessed. Method 1 assessed ad libitum intake, method 2 working for access, and method 3 explicit and implicit responses to photographic food stimuli. In all methods, a transfer effect of SSS was evident. After eating a preload with a certain taste, liking and wanting for snacks with a congruent taste was less than for snacks with an incongruent taste. This transfer effect was not equipotent for sweet and savory. It appears that savory taste has a stronger modulating effect on subsequent food choice than sweet.

doi:10.1016/j.appet.2010.04.079

The effect of protein content and taste on satiety and food choice

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It is argued that protein intake is tightly regulated by the human body. As savory food products are generally high in protein levels while sweet products are high in carbohydrates, a link between taste and macronutrient content in the control of intake is plausible. Objective of our study was to determine the effect of protein content and taste of a meal on satiety and subsequent food choice. We used a cross-over design with 4 conditions. Sixty healthy, unrestrained subjects (23M/37F) with a mean age of 21 ± 2 y and a mean BMI of 21.5 ± 1.6 kg/m^2 were offered 1 of 4 isocaloric preloads (rice meal) for lunch: 2 were high in protein (30 en% derived from protein) and 2 were low in protein (7 en%). Both had a sweet and savory version. Thirty minutes after preload consumption, subjects were offered an ad libitum buffet, consisting of 16 snack products of 4 different food categories: high-protein sweet, high-protein savory, low-protein sweet, low-protein savory. Our main outcome measure was the difference in intake (g) of the 4 food categories at the ad libitum buffet between the 4 conditions. Preliminary results indicate no effect of protein content on ad libitum intake (g); high-protein sweet preload 216 ± 121 g, high-protein savory preload 214 ± 135 g, low-protein sweet preload 203 ± 122 g, low-protein savory preload 219 ± 112 g. Choice of snack products differed after the 4 preloads, whereby taste appeared to exert the strongest influence.

doi:10.1016/j.appet.2010.04.080

Repeated gastric distension alters food intake and neuroendocrine profiles in rats

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Bulimia nervosa (BN) is an eating disorder characterized by a pattern of uncontrolled ingestion (binging) and expulsion (purging) of food. Bulimics have increased gastric capacity, delayed gastric emptying, blunted post-meal ghrelin and insulin responses, disproportionately low leptin levels, resistance to α-melanocyte stimulating hormone, and increased neuropeptide Y (NPY) expression. Binge eating induces gastric distension and the stimulation of gastric mechanoreceptors to a greater degree than experienced by non-binging individuals. To test the effects of repeated gastric distension (RGD) without nutrient absorption on the neuroendocrine factors involved in energy homeostasis, a permanent intra-gastric balloon was implanted in rats, and inflated daily for 4 weeks. Though body weights and daily food intakes remained equivalent in RGD and control rats, a significant delay in the onset of feeding was present during the first and second, but not the third and fourth weeks of inflations. Leptin levels were decreased after RGD ($p < 0.05$); insulin and ghrelin were unaffected. Expression of proopiomelanocortin was unaffected by RGD. Fasting arcuate NPY levels in RGD rats were suppressed significantly more than control animals following food intake (control and RGD decreases from baseline were 184.95% and 257.42%, respectively). NPY expression in the nucleus of the solitary tract followed a similar pattern. These data suggest a role for RGD in multiple factors associated with BN.

doi:10.1016/j.appet.2010.04.081

Leptin—TRH interactions in the Solitary Nucleus. An in vitro calcium imaging study

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Thyrotropin releasing hormone [TRH] is at the center of endocrine and autonomic thermoregulation and thermogenesis is gated by leptin. We observed that leptin injected into the fourth ventricle increases the potency of TRH to increase brown adipose tissue [BAT] temperature. This effect is order specific; leptin applied **before** TRH produced a much larger increase in BAT than when leptin is applied **after** TRH. This synergy suggests that leptin "gates" TRH transduction [e.g., PLC-mediated ER calcium release which, in turn, triggers changes in membrane excitability]. Rapid leptin signaling depends on the activation of a PI3kinase. Studies in culture systems suggest that PIP3 [product of PI3kinase] potently upregulates PLC. We recently showed that NST neurons possess both LepRb and TRHR1 receptors, making these cells likely loci for leptin-TRH interactions [Hermann et al., 2006, 2009; Rogers et al. 2009]. In vitro calcium imaging of the medullary slice was used to test the hypothesis that leptin modulates TRH transduction in NST neurons. Calcium green 1AM [calcium indicator] was injected into the NST; medullary slices containing the NST were harvested and transferred to the recording chamber of a confocal microscope. Slices were subjected to TRH alone, leptin alone, leptin followed by TRH or leptin plus wortmannin [PI3Kinase inhibitor] followed by TRH. The results show that while leptin alone did not produce an increase in NST neuronal calcium, leptin pretreatment significantly increased the NST activation caused by TRH. The combination of wortmannin with leptin blocks the interaction with TRH.

doi:10.1016/j.appet.2010.04.082

Effects of portion size and social modeling on food intake of young women

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People eat more or less when their eating companions eat more or less. Moreover, they eat more when being served a larger portion compared to a smaller portion. The current study was conducted to examine the potential influences of both types of situational norms on young women's intake. The experiment involved a 3 (confederate's eating condition: low-intake, normal-intake, large-intake) by 2 (portion size condition: small vs. large) factorial design. One hundred females participated. Participants' intake was observed during a 20-min break. The total quantity of food consumed (in g) was used as our dependent variable. An ANOVA was used to examine the main and interactive effects of the modeling and portion size conditions. Results show a significant interaction between modeling condition and portion size condition on participants' intake. Closer inspection revealed a modeling effect in the normal-portion size conditions, but not in the small-portion size conditions. Our results suggest that if women are served a portion of food that is too small to serve as a complete meal, they eat regardless of what their eating companion is eating. However, if they are served a normal portion of food, then their intake is subject to social modeling processes.

doi:10.1016/j.appet.2010.04.083

Sex and photoperiod regulate central and peripheral endocannabinoid signaling

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Siberian hamsters (*Phodopus sungorus*) adapt to seasonal changes in environment with marked changes in body mass, primarily in the form of adiposity. Winter-like conditions (e.g., short days) are sufficient to decrease body mass by ~30%, with corresponding changes in food intake. The neuroendocrine mechanisms responsible for these changes are not well understood, and homeostatic orexigenic/anorectic peptides provide little explanation. We investigated the potential role of endocannabinoids, known modulators of appetite and metabolic profiles, as mediators of seasonal changes in energy balance. Specifically, we housed hamsters in long or short days for 0, 3, or 9 weeks ($n = 6$ per group) and measured endocannabinoid levels in the hypothalamus, liver, and retroperitoneal white adipose tissue (RWAT). Levels of the endocannabinoid 2-AG were significantly elevated in RWAT of short-day animals by week 9. No photoperiodic changes were seen in the hypothalamus or liver, however sex differences were found in the liver (M > F) and RWAT (F > M). Ongoing analyses will determine whether photorefractory hamsters (i.e., short-day-housed hamsters reverting back to long-day phenotype) demonstrate a return of 2-AG RWAT levels comparable to those seen in long days. Brainstem endocannabinoid levels will also be examined as previous work has demonstrated effects of photoperiod on cannabinoid receptor (CB_1) levels in brainstem nuclei. Together these findings will shed light on mechanisms that defend dynamic states of energy balance and provide important implications for those that contribute to human states of obesity and leanness.

doi:10.1016/j.appet.2010.04.084

Changes in expected satiation after repeated consumption of a low- or high-energy-dense soup

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Expectations of a food's satiating capacity may play a role in decisions on portion size. We assume that these expectations may be modified over time by learned associations between food properties and post-ingestive effects, and investigated whether repeated consumption to low- (LED) or high-energy-dense (HED) soup modifies 'expected satiation' and consequent intake. In a parallel intervention, healthy adults (20 ± 2 y; BMI: 21.3 ± 1.6 kg/m^2) were offered either a novel-flavoured LED (50 kcal/100 g) ($n = 32$) or a HED (154 kcal/100 g) ($n = 32$) soup. Soups were served in a fixed amount on 4 consecutive days (day 1–4). Participants completed a measure of expected satiation at baseline and 2 and 4 days after repeated consumption. On day 5, the soups were offered ad libitum, and intake was measured. Expected satiation was higher for HED (346 ± 54 kcal) than for LED soup (314 ± 70 kcal) on day 1 ($p = 0.003$). Expected satiation did not change after repeated consumption for LED soup ($p = 0.39$) or HED soup ($p = 0.21$). We observed no differences in ad libitum intake between LED (461 ± 213 g) and HED soup (391 ± 164 g) ($p = 0.14$). Expectations on day 1 seem to rely on the soup's sensory attributes, but we did not observe changes in expected satiation in response to repeated consumption of LED or HED soup. Further analyses will be conducted.

doi:10.1016/j.appet.2010.04.085

Insulin sensitivity and glucose tolerance are altered by maintenance on a ketogenic diet

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The effects of consuming low-carbohydrate, ketogenic diets (KD) for weight loss or management of Type II Diabetes remain controversial. In these studies we assessed if long-term lack of dietary carbohydrates would affect responsivity to glucose, insulin, and dietary carbohydrates in a test meal. Rats were maintained on chow (CH) or KD. Caloric intake after peripheral insulin, and insulin and glucose levels following glucose or insulin tolerance tests were assessed. Glucose and insulin responses to a low- or high-carbohydrate test meal were measured. Additionally, rats maintained on KD were returned to a CH diet, and insulin sensitivity and glucose tolerance were evaluated in order to determine post-KD effects. Maintenance on KD resulted in decreased sensitivity to peripheral insulin and impaired glucose tolerance (insulin AUC for glucose tolerance test, CH: 4.9 ± 1.4, KD: 6.8 ± 0.6, $p < 0.05$). Furthermore, consumption of a high-carbohydrate meal in rats that habitually consumed KD induced significantly greater insulin and glucose levels for an extended period of time, as compared to chow-fed controls (insulin AUC for meal test, CH: 2.9 ± 0.4, KD: 6.3 ± 0.9, $p < 0.01$; glucose AUC for meal test, CH: 335.6 ± 10.1, KD: 385.4 ± 14.9, $p < 0.01$). Finally, returning to a chow diet rapidly reversed the effects of KD on insulin sensitivity and glucose tolerance. These data suggest that maintenance on KD negatively affects glucose homeostasis, an effect that is rapidly reversed upon cessation of the diet.

doi:10.1016/j.appet.2010.04.086

Gastric distension, but not luminal glutamate or denatonium, activates vagal afferent fibers in the rat

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Evidence indicates that gastric vagal afferent pathways detect volume distension and play little role in nutritional signaling to control food intake. However, more recent reports on the presence of taste receptors in the stomach and stimulation of vagal afferent fibers by gastric nutrients challenge this view. To further elucidate these possible pathways, we conducted electrophysiological studies of gastric vagal afferent signaling in the rat using umami and bitter taste stimuli, glutamate (150 mM) and denatonium (10 mM). We investigated three variables: (1) an interaction of these stimuli with volume distension by controlling the flow of fluid exiting the stomach, (2) the recording site on the abdominal vagus to potentially sample different fiber types, and (3) the amount of time recorded after stimulus infusion (5–30 min). There was no evidence that gastric infusion of glutamate or denatonium, compared to saline, activates vagal afferent fibers. Conversely, vagal afferents displayed a large acute response to gastric volume distension. The current results suggest that gastric vagal afferent fibers are not sensitive to these umami and bitter compounds but are responsive to volume distension. These results could have implications for understanding the controls of food intake since these data, and other reports, find little involvement of gastric nutrient detection in nerve signaling to the brain.

doi:10.1016/j.appet.2010.04.087

Why don't rats and mice vomit? A behavioral and anatomical investigation

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Laboratory rats and mice are known to lack a vomiting response and the dimensions of the abdominal esophagus might be an important constraint (Andrews, 1995, *Physiol. Zool.*). However, a broad evaluation of Rodentia is lacking. Here we determined the behavioral responses and esophageal and diaphragm anatomy from 4 of the 5 Suborders. We used prototypical emetic agents, apomorphine (s.c.), veratrine (s.c.), and copper sulfate (i.g.), which are thought to produce emesis by action on the area postrema, nodose ganglia, and vagal afferent fibers, respectively. None of the rodents, including nutria (*Myocastor coypus*), beavers (*Castor canadensis*), mountain beavers (*Aplodontia rufa*), voles (*Microtus townsendii*), guinea pigs, and laboratory rats and mice vomited. In rodents, ~72% of the diaphragm area was muscle compared to 100% in emetic control species (musk shrews and cats). The abdominal esophagus was also relatively long and narrow in rodents (esophageal circumference/length ≤ 0.7, rodents, vs. ≥ 0.8 in emetic species). These data indicate, (1) a lack of vomiting is a common feature in rodents, and (2) rodents might have anatomical constraints on their ability to vomit.

doi:10.1016/j.appet.2010.04.088

Pre-exposure to intragastric or intraduodenal denatonium reduces its reinforcing efficacy

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Rats are reported to show weaker preference for a flavor paired with intragastric (IG) infusions of denatonium benzoate (DB), a bitter unconditioned stimulus (US). To further assess learning about such gastrointestinal "taste" signals, our experiment investigated whether prior exposure to DB (US pre-exposure) through IG or intraduodenal (ID) infusions reduces the ability of the compound to reinforce flavor conditioning. Food-deprived rats ($n = 31$) were assigned to four groups, two fitted with IG catheters and two with ID catheters. During 6 daily US pre-exposure sessions, two groups (one IG and one ID) were infused with DB and two groups were infused with H_2O. Then, all groups were trained over 6 daily sessions to drink one flavor (CS+) with yoked IG or ID infusions of DB (3 sessions) and consume another flavor (CS−) with IG or ID infusions of H_2O (3 sessions). Post-training two bottle choice tests showed that (a) across all groups, CS+ intake (M = 6.7 ml, SEM = 0.4) was less than CS-intake (M = 8.8 ml, SEM = 0.4) ($p < .01$) and (b) overall rats pre-exposed to IG/ID DB consumed more of both CSs (M = 8.5 ml, SEM = 0.3) than rats pre-exposed to H_2O (M = 7.0 ml, SEM = 0.3) ($p < .01$). The findings confirm that an IG or ID DB "taste" conditions a negative flavor preference and suggest that pre-exposure to IG/ID DB reduces its subsequent reinforcing power. This pre-exposure design may be used to study the sensory and reinforcing properties of other IG or ID stimuli (NIH HD052112).

doi:10.1016/j.appet.2010.04.089

Maintenance on a high-fat diet impairs the anorexic response to glucagon-like peptide 1 receptor activation

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Previous data suggests that the adiposity signal leptin reduces food intake in part by enhancing sensitivity to short-term signals that promote meal termination, including glucagon-like peptide 1 (GLP-1). We hypothesized that high-fat diet-induced obesity, which causes resistance to leptin, would impair GLP-1's ability to reduce food intake. To test this hypothesis, we examined Long-Evans rats' food intake after intraperitoneal injection of saline or exendin-4 (Ex-4), a potent, degradation resistant GLP-1 receptor agonist, first while the rats were maintained on standard rat chow and then after maintenance on high-fat (60%) diet. During the chow maintenance phase, Ex-4 significantly reduced food intake relative to saline. By contrast, Ex-4 was ineffective when administered during the third and fourth weeks on high-fat diet, regardless of whether the test food was high-fat diet or standard chow. The rats were then switched back to standard chow maintenance diet, which resulted in significant weight loss. After 3 weeks on the chow diet, Ex-4 was again able to significantly reduce food intake relative to saline. These data indicate that high-fat diet-induced obesity reduces sensitivity to GLP-1 receptor activation, and this effect may contribute to overconsumption of high-fat foods. This research was supported by NIH-NIDDK 4R00DK078779-03.

doi:10.1016/j.appet.2010.04.091

Automatic detection of cancer chemotherapy-induced vomiting in musk shrews

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Vomiting and anorexia are common side effects of cancer chemotherapy. In animal studies, long-term food intake is easily measured by manual recording, but the detection of vomiting usually requires direct observation. Here we report a method to automatically detect emetic events in musk shrews (a mouse-sized animal with a rapid emetic sequence, up to ∼8 Hz of retching for ∼1 s for each event). As a proof of concept, we injected 10 shrews with the chemotherapy agent cisplatin using an emetic threshold dose (20 mg/kg, i.p.) and videotaped their behavior for 2 h. Emesis was scored independently by two observers and these results were compared to those generated by a computer algorithm. Half the shrews developed vomiting and the second half served as non-vomiting controls. The body contour in each video frame was normalized to a parameterized shape template, and projected to a feature space maximizing the shape variations in the consecutive frames during retching. The emesis events were detected when there were three consecutive retches. This method detected 91% of the emetic episodes. This approach should open a new vista into chemotherapy research to permit long-term tracking of emesis in small animal models and facilitate the development of new antiemetic therapies for cancer patients.

doi:10.1016/j.appet.2010.04.090

Neonatal maternal separation may increase dopaminergic activity responding to food consumption in the hippocampus and striatum of the offspring during fasting/refeeding cycles later in life

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Male SD pups were separated from dam for 3 h daily during PND 2-14 (MS) or left undisturbed (NH). Half of NH and MS pups were deprived from food every other day, otherwise had free access to food from PND 28 (NH/RF or MS/RF). NH/C or MS/C had free access to chow throughout the experimental period. Rats were sacrificed at two months of age, at the end of either fasting or refeeding day. Hippocampus and ventral striatum were collected for HPLC analysis of DA and its metabolites DOPAC and HVA. After the last refeeding, the hippocampal and striatal DA contents increased significantly in MS/RF, compared to NH/C or MS/C. DOPAC/DA ratio increased in the hippocampus, but decreased in the striatum, of MS/RF compared to NH/C. HVA/DA ratio decreased both in the hippocampus and striatum of MS/RF, compared to MS/C. DA contents and DOPAC/DA ratio of NH/RF did not differ from NH/C in both brain regions, but HVA/DA ratio was lower, after the last refeeding. Before the last refeeding, DA contents and its metabolic rates in the brain regions of MS/RF did not significantly differ from the rest groups, except a lower HVA/DA ratio in the hippocampus compared to NH/C. Results reveal that fasting/refeeding cycles may sensitize DAergic activities responding to food consumption in the hippocampus and ventral striatum of MS rats, via increasing DA neurotransmission and decreasing its degradation at pre-/post-synaptic levels. Supported by 21st Century Frontier Research Program (2009K001269).

doi:10.1016/j.appet.2010.04.092

An analysis of licking microstructure in diet-induced obese mice

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Nutrition labels were designed to promote healthy eating. A previous study in our laboratory found that energy intake during a buffet lunch was decreased when the foods were displayed with standard nutrition labels. The purpose of this study was to compare the effects of standard labels to a more simplified labeling technique based on the Traffic Light Diet, which rates the nutritional value of food with green, yellow, or red colors (eat as much as desired, moderately, or sparingly, respectively). Participants were 18–50 year old, male and female, lean and obese subjects. A buffet lunch was provided with each labeling condition (no labels (NL), standard labels (SL), or traffic light labels (TL)) presented in a randomized, crossover design. Foods were weighed before and after each visit to determine energy intake. There was a main effect of labeling condition on energy intake from low energy density (LED) and green foods; with intakes of both being higher in the TL condition relative to NL condition. Obese participants had higher intakes of high energy density (HED) foods in all labeling conditions, but intake of green foods was significantly increased in obese participants in the TL condition compared with lean participants. Total energy consumption was not greatly reduced in the TL or SL conditions, but food choices were improved. Promoting consumers to eat more healthfully may be viewed as progress toward a healthier nation. Thus, TL labels may be a quick and effective visual tool for all consumers to better assess their food choices.

doi:10.1016/j.appet.2010.04.093

Body sodium challenges and anxiety behaviors in OVX rats

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Stress, whether environmental or physiological, can increase anxiety. These studies were performed to evaluate the effect of specific physiological stressors—disturbances of body fluid balance—on anxiety in ovariectomized (OVX) female rats. Rats were tested on the Elevated Plus Maze (EPM) before, and in response to, three different challenges to body fluid balance. First, rats were given access to isotonic saline (ISO) in addition to regular chow and water for two weeks and then tested on the EPM. Next, they were then given subcutaneous (SC) injections of hypertonic saline (HS) or the saline control injection and then tested on the EPM. Finally, rats were placed on a Na^+ deficient diet for 10 days and then tested on the EPM. Access to ISO for 2 weeks did not reliably alter the amount of time rats spent on the open arms of the EPM, nor did injection of HS affect this behavioral indication of anxiety. Similarly, the number of times rats crossed the center of the EPM, an indication of activity and exploratory behaviors, was not altered by ISO or injection of HS. In contrast, maintenance on a Na^+ deficient diet reduced the amount of time OVX rats spent on the open arms of the EPM, indicating increased anxiety, and also reduced the number of times rats crossed the center of the EPM, indicating decreased activity and exploratory behaviors. These observations that Na^+ deficiency, but not Na^+ excess, decrease both time spent in the open arms of the EPM and the number of center crossings suggest stressor-specific effects on behavioral manifestations of anxiety in OVX rats.

doi:10.1016/j.appet.2010.04.094

Hippocampal leptin signaling reduces food intake and body weight and influences appetitive spatial memory

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The increase in obesity prevalence highlights the need for a more comprehensive understanding of the neural systems controlling food intake; one that extends beyond food intake driven by metabolic need and considers that driven by higher-order cognitive factors. The hippocampus, long considered important for learning and memory, has recently been linked with the higher-order controls of energy regulation. Here we focus on the neurohormonal processes mediating the hippocampal controls of feeding behavior by examining the role of leptin signaling in the hippocampus in food consumption and procurement in rats. First, food intake and body weight were examined following bilateral leptin delivery to either the dorsal or ventral region of the hippocampus. Our results show that 0.1, 0.2, and 0.4 μg leptin delivered to the ventral hippocampus suppressed 24 h food intake and body weight, whereas only the 0.4 μg dose produced intake suppressive effects following dorsal hippocampal delivery. Second, the effects of intrahippocampal leptin on memory for the spatial location of food were examined using an appetitive 4-arm maze paradigm. Interestingly, dorsal hippocampal leptin (0.4 μg) administered immediately after training improved memory consolidation, whereas ventral hippocampal leptin delivery impaired memory consolidation. Collectively, our results support a role for hippocampal leptin signaling in feeding-related behaviors, including food procurement and the inhibition of food intake. Supported by DK21397.

doi:10.1016/j.appet.2010.04.095

Translational research in anorexia and bulimia nervosa

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Anorexia nervosa (AN) and bulimia nervosa (BN) have puzzling symptoms that are unique to the disorder, such as extremes of eating (restricting, bingeing/purging), relentless drive to lose weight, body image distortions, and denial of illness. We have little understanding of how such symptoms are encoded in the brain. Animal models have not been developed displaying these unique symptoms. The symptoms that can be displayed by animals have been – e.g., "bingeing" on sugar, wheel running to starvation, etc. Thus, studies in humans are essential. In the past, understanding of how behavior is coded in the brain was limited by our inability to interrogate the brain in living humans. However, much recent progress has been made due to advances in brain imaging and basic science. There are no centers in the brain that are responsible for a diagnosis of anorexia nervosa. Rather, components of behavior are coded in the molecular structure of neural circuits. The brain is the organ that modulates our internal milieu and interacts with the external environment to meet our needs. Substantial advances have been made in understanding how the brain is organized to meet these needs. For example, imaging studies suggest that temperament and personality traits that create a vulnerability for developing AN may be related to alterations of neural circuits that regulate appetitive behaviors, reward, inhibition, uncertainty and anticipation, and interoceptive awareness. This knowledge may aid in the development of specific and effective treatments.

doi:10.1016/j.appet.2010.04.096

Systemic BrdU induces conditioned flavor aversions and c-Fos

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Bromodeoxyuridine (BrdU) is a thymidine analog that can be incorporated into the DNA of proliferating cells. Systemic BrdU is often used in studies of adult neurogenesis and olfactory learning. However, BrdU can also have toxic effects that might confound learning. To determine if BrdU is aversive at common doses, we examined conditioned flavor aversion (CFA) and c-Fos induction in the NTS after acute BrdU injection. Water-restricted rats ($n = 6$/group) received 10 min access to 0.05% Kool-Aid flavor (grape or cherry counterbalanced, CS+) mixed with 0.05% saccharin, followed by ip injection of vehicle, BrdU (50 or 200 mg/kg), or LiCl (76 mg/kg) as a positive control. The next day, rats began 24 h, 2-bottle preference tests of grape vs cherry Kool-Aid for 14 days. Both vehicle and low-dose BrdU groups showed 45–57% preference for the CS+. Both high-dose BrdU and LiCl groups showed a strong CFA with 5–7% preferences for the CS+ across all 14 days. A similar strong CFA was found after 48-h access to Kool-Aid mixed with 8% glucose was paired with 4 injections of BrdU (100 mg/kg) given every 12 h, demonstrating that BrdU interfered with conditioned flavor-nutrient preference learning. To determine if BrdU's aversive effects were correlated with activation of the visceral neuraxis, rats ($n = 4$/group) were injected with vehicle or 200 mg/kg BrdU, perfused 1 or 3 h later, and the brainstem processed for c-Fos. In the NTS, BrdU induced significantly more c-Fos than vehicle at both 1 and 3 h. We conclude the BrdU has aversive effects, perhaps secondary to GI toxicity that can confound olfactory learning.

doi:10.1016/j.appet.2010.04.097

Food neophobia in young adults. Genetic architecture and relation to personality, BMI, and pleasantness and use frequency of foods

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Food neophobia has been studied extensively in children, but its causal origins and relationship to eating behavior in adults are not well understood. We studied the genetic and environmental effects on variation in food neophobia (measured by the Food Neophobia Scale) and explored associations between food neophobia and personality, BMI, and pleasantness and use frequency of selected foods in young adult twins ($N = 1175$, aged 20–25 years, 54.7% women). In women, additive genetic effects (heritability) accounted for 61% (95%CI: 49–71%) of variation in food neophobia, whereas in men, shared environmental effects explaining 45% (95%CI: 31–56%) of the variation were observed; the remaining variation was accounted for by nonshared environmental effects. Food neophobia correlated negatively with the personality trait Openness ($r \sim 0.35$), and in women with BMI ($r = 0.15$). In addition, food neophobia was negatively correlated with pleasantness and use frequency of vegetables and fish, and with average pleasantness of foods. Thus, genetic and environmental factors contribute to food neophobia differently in women and men and food neophobia is associated with personality and eating behavior. Specifically, food neophobia is related to the quality of diet and, to a lesser extent to energy intake displayed by BMI.

doi:10.1016/j.appet.2010.04.098

Current concepts of gastrointestinal (GI) fat sensing focusing on all aspects from luminal, absorptive and postabsorptive in animal models

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Dietary fat is made up mostly of triacylglycerol (TG). TG is first digested in the stomach by acid lipase to form diacylglycerol (DG) and fatty acids (FA). The DG and FA formed promote the emulsification of fat in the gastric lumen in preparation for the subsequent digestion of TG to form 2-monoacylglycerol (2-MG) and FA. The 2-MG and FA are re-esterified in the enterocytes to form TG to be packaged into chylomicron (CM) for export into the body via the lymphatic system. The sensing of luminal FA has been demonstrated and discussed by Rick Mattes in this symposium. Suffice to say that FA in the intestinal lumen is a potent stimulus for the secretion of CCK and the incretins (GIP and GLP-1). However, it should be pointed out that while there is clear *in vitro* data showing direct effects of FA on the enteroendocrine cells, the relationship in the *in vivo* situation is less clear. In terms of intracellular sensing, we and others have shown that this is probably tide to the formation and secretion of CMs. For instance, apo AIV (a potent satiety factor) is stimulated by fat absorption and it is directly linked to the formation and secretion of CMs. Consequently, only the absorption of FA consisting of 14 carbons or more result in the stimulation of apo AIV production. Furthermore, the inhibition of CM formation by Pluronic L-81 also inhibits the lipid induced apo AIV production. Lastly, CMs are transported almost exclusively in lymph and we have data (unpublished) showing that the secretion of CMs may activate the mucosal mast cells, resulting in the discharge of various molecules and agents by these cells.

doi:10.1016/j.appet.2010.04.099

Taste cells of the gut and endocrine cells of the tongue

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Gustducin, T1r3 and other taste proteins are present in gut endocrine L cells that express glucagon-like peptide 1 (GLP-1). In gut, gustducin and T1r3 are critical to L cell release of GLP-1. We recently found that endocrine cells in pancreas also express taste proteins. *Methods:* RT-PCR, in situ hybridization and immunohistochemistry were used to examine expression of taste proteins in endocrine cells of gut and pancreas. Similar techniques were used to identify GLP-1 and gut hormones in taste cells. ELISA was used to monitor in vivo release of GLP-1 from taste cells into the bloodstream. Hormone release from pancreatic islets in culture and taste papillae explants was examined for responses to tastants. *Results:* Gustducin and T1r3 are expressed in pancreatic islets. Noncaloric sweeteners enhanced glucose-dependent insulin release from islets in culture. Taste cells express GLP-1 and other gut hormones. In wild-type mice application of glucose to the tongue induced a rapid elevation of blood GLP-1. Stimulation of taste cell explants with glucose led to release of GLP-1 into the medium. Glucose stimulation of gustducin-null mice did not lead to significant release of GLP-1 from taste cells in vivo or circumvallate explants ex vivo. *Conclusions:* (1) Insulin release from pancreatic islets ex vivo is modulated by taste signalling proteins; (2) the cephalic phase of circulating GLP-1 depends in part on direct release of GLP-1 from gustducin-expressing taste cells into the bloodstream. Supported by NIH grants DC007399 and DK073248 to BM and DC03055 and DC03155 to RFM.

doi:10.1016/j.appet.2010.04.100

Effects of breakfast consumption on satiety and energy intake in 8–10-year-old children

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Cross-sectional data indicate an inverse relationship between breakfast consumption and adiposity in children. It has been suggested that skipping breakfast may adversely affect appetite which could lead to overeating later in the day. The aim of this study was to test the effects of eating versus skipping breakfast on children's ratings of appetite and energy intake at subsequent meals. Twenty-one children (15 girls, 6 boys), ages 8–10 years, with a BMI-for-age < 95th percentile, were served a compulsory breakfast or no breakfast and lunch, consumed *ad libitum*, once a week for two weeks. On each test day, parents completed food records that captured children's food and beverage intake for the remainder of the day. There was no significant main effect of breakfast condition on the amount of calories children consumed at lunch ($P = 0.36$) or throughout the remainder of the day ($P = 0.85$). There was a significant main effect of breakfast condition ($P = 0.04$) on daily energy intake indicating that on the day when subjects did not eat breakfast, they consumed 362 fewer calories over the course of the day than when they did eat breakfast. On the day when no breakfast was served, subjects indicated to be significantly hungrier, less full, and could consume more food before lunch than on the day when they did eat breakfast ($P < 0.001$). In this study, skipping breakfast affected children's appetite ratings, but not their energy intake at subsequent meals. The dissonance between children's subjective ratings of prospective consumption and their actual intake should be further examined.

doi:10.1016/j.appet.2010.04.101

Voluntary running wheel exercise increases fosB expression in the dorsal medial portion of the ventromedial hypothalamic nucleus

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Physical exercise protects against obesity and metabolic dysregulation. Previously, we found that voluntary running wheel (VRW) exercise induces weight loss without a compensatory increase in food intake in chow-fed mice and prevents diet-induced obesity. We have now determined the effect of 6-week exposure to VRW exercise and/or a high-fat diet on activation of CNS neurons. Chronic neuronal activation can be measured by the accumulation of the nuclear factor ΔfosB. The hypothalamus contains several areas, such as the arcuate (ARC), ventromedial (VMH), and paraventricular (PVN) nuclei. These centers receive and integrate signals of energy state, and modify behavior and metabolism to maintain body weight and energy homeostasis. We hypothesized that VRW can affect energy homeostasis by altering hypothalamic neural activation. FosB-positive neurons were counted via immunohistochemistry in areas known to regulate energy balance. As previously described, VRW increased fosB expression in the core of the nucleus accumbens in chow-fed mice. Within the hypothalamus, VRW exercise significantly increased the number of fosB-positive cells in the dorsal medial portion of the VMH (dmVMH) in mice fed either chow or high-fat diet. However, high-fat diet decreased chronic activation of fosB in the dmVMH of sedentary mice. Exposure to VRW or high-fat diet did not alter the number of fosB positive cells in the ARC or PVN. These data suggest that the beneficial effects of exercise might involve the activation of circuits in the VMH to regulate energy homeostasis.

doi:10.1016/j.appet.2010.04.102

LiCl induces activation of MAP kinase and c-Fos expression in the amygdala. Intracellular signaling in conditioned taste aversion learning

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A high dose of lithium chloride (LiCl) increases c-Fos expression in the central amygdala (CeA). LiCl-induced chemoreceptive stimulation is indirectly relayed to the amygdala from the area postrema and nucleus of the solitary tract via the release of transmitters such as glutamate and glucagon-like peptide-1 (GLP-1). However, the intracellular pathway that leads to c-Fos expression following LiCl administration is little known. In the present study, we investigated if the intracellular signaling cascade including mitogen-activated protein (MAP) kinase, perhaps downstream of NMDA and GLP-1 receptors, affects LiCl-induced c-Fos expression. We examined the time course of phosphorylation of MAP kinase by immunohistochemistry following LiCl. Rats were sacrificed 10, 30, 60 and 180 min after LiCl (0.15 M, 12 ml/kg, ip) or saline injections. LiCl highly increased the numbers of phospho-MAP kinase at 10, 30 and 60 min in the CeA compared with saline, which preceded peak c-Fos induction at 60 min. To determine if MAP kinase has a functional role in LiCl-induced conditioned taste aversion (CTA), rats were injected with the MAP kinase kinase inhibitor SL327 (1 μg/0.5 μl/side) or vehicle during the pairing of saccharin and LiCl. All rats acquired a CTA, but SL327-treated rats extinguished much faster than vehicle-treated rats during 2-bottle tests. Thus, MAP kinase activation following LiCl may be upstream of c-Fos induction, and MAP kinase is a necessary intracellular signal for CTA acquisition. Support: NIDCD03198.

doi:10.1016/j.appet.2010.04.103

The importance of choice for the obesogenic properties of a high-fat high-sugar diet

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Rats with free access to a diet consisting of chow, saturated fat and liquid sugar (HFHS diet) overeat persistently, become obese and are insulin resistant. We determined whether a choice element is important for the observed hyperphagia on a HFHS diet. We subjected rats to either a choice HFHS (cHFHS), a non-choice HFHS (ncHFHS) or a chow diet. For the cHFHS diet the animals had free access to separate badges of chow, saturated fat and liquid sugar. The ncHFHS diet was custom made using the same ingredients as used for the cHFHS diet. For the composition of the ncHFHS diet, we used the same percentages for fat, sugar and chow as consumed previously by rats on a cHFHS diet (la Fleur et al., 2007, 2010). Rats on a cHFHS and on a ncHFHS diet consumed equal amounts of calories over the first two days, which was significantly higher as compared to rats on chow. This was followed by a steady decline in caloric intake towards pre-diet levels in rats on a ncHFHS diet, whereas rats on a cHFHS diet remained hyperphagic. Hyperphagia on the cHFHS diet was due to more meals/day, whereas on the ncHFHS diet hyperphagia was due to larger meals which were compensated for by decreased meal numbers after day 2. A leptin sensitivity test (1 mg/kg, ip), performed in week 3, revealed that rats on a cHFHS diet were leptin resistant, whereas rats on a ncHFHS or on a chow diet were not. We conclude that choice is indeed important for the hyperphagic response (characterized by increased meal frequency) on a cHFHS diet.

doi:10.1016/j.appet.2010.04.104

Effect of diabetes on the reduction of food intake by cholecystokinin-8 and 33

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Type II diabetes is manifested by increased glucose levels. We hypothesized that this increase will inhibit cholecystokinin (CCK), a gut/brain peptide secreted from the duodenum that increases insulin secretion and inhibits food intake, from evoking satiety as measured by meal size, intermeal interval (IMI) and satiety ratio. The current work investigated this hypothesis by utilizing two groups of rats ($n=8$ rats each) injected with streptozotocin (60 mg/kg) to induce diabetes or a citrate buffer solution control. Following recovery, the rats were deprived of food but not water overnight. The next morning, rats were given CCK-8, 33 (1, 3, 5 nmol/kg) or saline vehicle and the intake of a 10% sucrose test diet was measured and behaviorally analyzed for 120 min to determine meal size, IMI and satiety ratio. We found that CCK-8 and CCK-33 reduced meal size and increased satiety ratio in control rats more than in diabetic rats, and CCK-8 was more effective than CCK-33. However, there was no effect by both peptides on the IMI. Devazepide, a CCK_1 receptor antagonist, but not L365, 260, a CCK_2 receptor antagonist, blocked the reduction of food intake by CCK. In conclusion, reduction of food intake by CCK in diabetic rats speaks against our hypothesis. Elevated glucose and insulin levels may not inhibit CCK from reducing food intake. In diabetic rats, reduction of food intake by CCK is not glucose-dependent. Type II diabetes and reduction of food intake by CCK may have different pathways.

doi:10.1016/j.appet.2010.04.105

Altered meal patterns in $CCK_1R-/-$ mice. Role of ghrelin receptors expressed on vagal afferents and activation of arcuate neurons

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CCK and ghrelin interact at the level of the vagal afferent pathway; ghrelin suppresses afferent activity and expression of anorexigenic peptides and receptors. We hypothesized that the ghrelin receptor (Growth Hormone Secretagogue Receptor-1a; GHSR1a) contributes to altered feeding behavior via the vagal CCK_1R pathway. Expression of immunoreactive GHSR1a protein was significantly increased in nodose neurons of $CCK_1R-/-$ compared to WT mice ($p<0.05$). $CCK_1R-/-$ mice ate larger, longer meals compared to WTs, particularly when ingesting a high fat diet; this was reversed by administration of GHSR1a antagonist D-(Lys3)-GHRP-6 (2.8 μg/kg) ($p<0.05$). After a short fast, $CCK_1R-/-$ mice initiated feeding earlier than WT mice ($p<0.05$), an effect also reversed by D-(Lys3)-GHRP-6 ($p<0.05$). Peripheral administration of ghrelin (40 μg/kg, ip) had no effect on the number of fos-immunopositive (IP) neurons in the dorsal vagal complex of either strain. The baseline number of fos-IP neurons was significantly higher in the ventromedial arcuate nucleus (ARC) of $CCK_1R-/-$ compared to WT mice. Ghrelin administration increased fos-IP ARC neurons of WT but not $CCK_1R-/-$ mice; D-(Lys3)-GHRP-6 decreased fos-IP levels in $CCK_1R-/-$ to a level not significantly different from that in WT mice. The data suggest that absence of CCK_1R augments initial meal events and neuronal activity in the ventromedial ARC, effects dependent on GHSR1a. $CCK_1R-/-$ mice may have augmented orexigenic signaling to drive first meal events mediated by an increase in vagal GHSR1a expression and increased activity in ARC neurons.

doi:10.1016/j.appet.2010.04.106

Exploring the relationship between experimentally manipulated attentional bias for food cues and food intake

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Two recent studies have reported that obese/overweight individuals show an attentional bias towards food cues, suggesting that increased responsiveness to the salience of cues might increase overeating (Castellano et al., 2009, IJO:33; Nijs et al., 2009, e-pub Appetite). Here we attempt to establish a link between attentional bias to food cues and food intake using an attentional retraining paradigm that has previously been shown to alter intake of and approach for alcohol in social drinkers (Field & Eastman, 2005, Psychopharm:183). Volunteers ($N=51$) were trained to either attend to or avoid food stimuli using a modified visual probe task. The avoid group were instructed to find a visual probe displayed in the same on-screen location as pictures of neutral objects (e.g. stationery), whilst the attend group had to find the probe in the same location as picture of food. A measure of attentional bias before and after training was taken using a standard visual probe task, as well as mood, appetite ratings, and levels of restraint, external and emotional eating. Food intake (chocolate and mini-cookies) was measured in a disguised taste test at the end of the study. Both the attend and avoid groups displayed a slight, but non-significant, attentional bias to food stimuli at baseline. Attentional retraining increased the attentional bias for food cues in the attend condition and decreased bias for food cues in the avoid group (time x condition interaction $F(1,49)=23.06$, $P<0.01$). Training increased self-reported hunger and desire to eat in both groups ($P<0.05$). During the taste test, the attend group consumed more food than the avoid group, however this difference was significant only when levels of restraint were controlled for ($F(1,48)=6.52$, $P<0.05$) found to be significant. This study demonstrates attentional retraining can alter food intake, however these findings also suggest that factors such as dietary restraint may mediate the relationship between attention and food consumption.

doi:10.1016/j.appet.2010.04.107

Galanin knockout and overexpressing mice show disturbances in fat and ethanol intake

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There is growing evidence suggesting that the orexigenic peptide, galanin (GAL), in the hypothalamus has a role in promoting the consumption of ethanol as well as a fat-rich diet. The present study further examined this possibility in GAL knockout (GALKO) and GAL-overexpressing (GALOE) mice trained to voluntarily drink increasing concentrations of ethanol. The GALKO mice compared to wild-type (WT) exhibited a: (1) 35–45% decrease in 15% ethanol intake and preference, which was stronger in females than males; (2) 48% decrease in acute intake of a fat-rich diet, again stronger in females; and (3) gender-specific changes in lateral hypothalamic peptides (orexin and melanin-concentrating hormone) that stimulate ethanol and food intake, which were markedly decreased in females but increased in males. In the GALOE vs WT mice, the results revealed the opposite effects, with the GALOE mice showing a: (1) 35–40% increase in ethanol intake and ethanol preference at the highest (15%) ethanol concentration; (2) significantly larger, 60–75% increase in ethanol intake and ethanol preference after a day of food deprivation; and (3) 55% increase in consumption of a fat-rich diet during a 2 h test period, in both male and female GALOE mice. These results provide strong support for a physiological role of GAL in stimulating the consumption of ethanol, as well as a high-fat diet. The stronger effect in female mice may reflect the functional relationship of GAL to reproductive hormones in the stimulation of consummatory behavior.

doi:10.1016/j.appet.2010.04.108

Lateral hypothalamic leptin receptor neurons regulate energy balance and the mesolimbic dopamine system

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The anorectic hormone leptin signals via neurons expressing the leptin receptor (LepRb) to regulate energy balance and obesity. One aspect of leptin action that remains poorly understood is how leptin regulates motivated behaviors such as intake of palatable food and locomotor activity, which can promote weight gain. Leptin action and motivated behavior may intersect via the lateral hypothalamic area (LHA), which contains neurons that project to the ventral tegmental area (VTA) and other components of the mesolimbic dopamine (DA) system to control hedonic intake and activity. We discovered a large population of GABAergic LHA LepRb neurons that are distinct from previously described LHA neurons. LHA LepRb neurons project onto other LHA neurons and to the VTA, suggesting a pathway by which leptin may regulate the mesolimbic DA system. Indeed, leptin action via LHA LepRb neurons reduces food intake and body weight concomitant with increased VTA DA synthesis and nucleus accumbens (NAc) DA content. Furthermore, there are at least 2 subpopulations of LHA LepRb neurons that differ in transmitter content. Using novel mouse models, we have begun to parse the connectivity and physiology of LHA LepRb neurons. Disruption of leptin action on these circuits alters motivated behaviors and promotes obesity.

doi:10.1016/j.appet.2010.04.109

An intact dorsomedial hypothalamic nucleus is necessary for short day melatonin signal-induced responses in Siberian hamsters

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Siberian hamsters are useful in determining mechanisms underlying obesity reversal because they naturally reverse their extreme adiposity when transferred from long 'summer-like' (LDs) to short, 'winter-like' days (SDs). These daylength changes are coded into melatonin (MEL) signals by the pineal gland resulting in stimulation of MEL receptors (MEL_{1a}-Rs), some of which are located on central sympathetic nervous system (SNS) outflow neurons to white adipose tissue (WAT) including neurons in the dorsomedial nucleus of the hypothalamus (DMH), an area recently shown to be sufficient to induce SD responses. SD MEL signals induce gonadal regression and decrease body fat mass and food intake, thereby reversing the LD obesity. Here, we tested the necessity of the DMH to respond to SD MEL signals. We created SD-like, long duration MEL signals in sham-operated or DMH-lesioned (DMHx) hamsters by delivering subcutaneous MEL injections 3 h before the beginning of the dark phase, thereby lengthening the LD to SD-like MEL signals. We found that DMHx blocked SD-like testicular regression and body fat decreases but did not affect food intake. This non-responsiveness to SD-like MEL signals was not due to lesion-induced inappropriate nocturnal MEL secretion suggesting DMH involvement in downstream mechanisms regulating both SD WAT and reproductive responses. Therefore, the DMH can be added to the suprachiasmatic nucleus as a site necessary for SD responses in this species.

doi:10.1016/j.appet.2010.04.110

French adults aged 20–39 y have low dietary restraint and disinhibition levels according to their Three-Factor Eating Questionnaire average scores

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The Three-Factor Eating Questionnaire (TFEQ) of Stunkard and Messick (1985) is commonly used to evaluate eating behaviours in human food studies. The aims of our study were to characterize the food behaviour of French young adults and to analyse the association between the 3 TFEQ variables and gender, BMI and socio-demographic data in this population. Online TFEQ questionnaire was sent on a nationally representative sample of 1000 French people aged 20–39 y. The average scores were 6.30 ± 0.13 (sem) for dietary restraint, 6.03 ± 0.10 for disinhibition and 4.98 ± 0.13 for hunger. Compared to the limit commonly used in human food studies, French adults are characterized by low restraint and low disinhibition levels. There is a significant gender effect on both restraint and disinhibition scores. Age, restraint, disinhibition significantly predicted BMI for men, whereas for women BMI was significantly predicted by disinhibition and education level. BMI increased with higher restraint and disinhibition scores, the latter is the factor most strongly associated to BMI. The highest restrained and disinhibited subjects are mainly women with high education level and an average BMI of $25.09 \pm 0.64\,kg/m^2$. Our results questioned the limit commonly used to define restrained and unrestrained population and their interpretation.

doi:10.1016/j.appet.2010.04.111

What can rodents teach us about perinatal influences on feeding and body weight regulation?

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Both the pre- and postnatal environments affect food intake, body weight and fat gain during childhood and adult life. In rodents, maternal obesity, undernutrition, hyperinsulinemia and diabetes during various phases of gestation and/or lactation can promote offspring obesity, particularly in genetically predisposed individuals. Many of these perturbations of the maternal environment produce their effects by altering the development of neural pathways involved in the regulation of energy homeostasis. Hormones such as insulin and leptin, whose plasma levels generally reflect carcass adiposity, act as catabolic signals once central feeding pathways have matured. However, prior to this, they are critical factors involved in the birth, migration, process outgrowth and survival of neural pathways involved in energy homeostasis regulation. Since both hormones are secreted in maternal milk and can be absorbed by the neonate, maternal milk content and the amount of milk ingested can have a major impact on the development of these pathways and subsequent development of, or protection from obesity in offspring. As in humans, where two-thirds of obesity is inherited, the impact of these perinatal factors in rodents on later food intake, body weight gain and obesity are highly dependent upon the genetic background of the affected individual. Thus, although there are caveats, rodent models can provide important clues for identifying factors in the perinatal environment that might prevent humans from becoming obese.

doi:10.1016/j.appet.2010.04.112

Watching TV food commercials increases food consumption of snacks, but not meals

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Watching food commercials on television has been shown to cause an increase in food consumption. Almost all of the published work has used consumption of snacks as the dependent variable and children as subjects. We tested the generalizabilty of the finding by examining the effect of watching three, 14 min, TV commercials involving, (a) food, (b) cars, or (c) people eating, in young adults just prior to being served lunch. Fifteen males and 21 females, ages 8 to 57 volunteered for a study. Lunch was served from a buffet table and food intake was measured. No effect of watching any of the commercials on the amount consumed was observed. A very similar study using 19 females and 7 males was then performed but instead of consuming a meal, snacks were placed in front of the participants as they watched the commercials. Watching the food advertisements significantly increased intake by about 25% ($p = 0.04$). The results indicate that watching food advertisements increases snacking behavior in young adults and does not affect spontaneous eating of a meal when served after watching the advertisements.

doi:10.1016/j.appet.2010.04.113

Experience with activity based anorexia affects conditioned taste aversion in rats

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Activity based anorexia (ABA) is a model of anorexia nervosa (AN). In this model, rats reduce food intake and lose weight dramatically as a result of enhanced running wheel (RW) activity during conditions of restricted food access. The aim of this study was to investigate whether ABA alters food reward. We compared the acquisition and extinction of a conditioned taste aversion (CTA) in naive (ad lib with no access to RW), ABA, and pair-fed to ABA (with access to a locked RW) in female Sprague–Dawley rats. The CTA conditioning was conducted after the ABA and pair-fed rats had recovered to pre-ABA body weights. There was no difference in the rate of a CTA acquisition to 0.3 M sucrose paired with low dose LiCl (0.009 M and 0.018 M at 1.33 ml/100 g of body weight, i.p.). However, ABA rats suppressed sucrose intake more than the controls. After 10 conditioning trials, 67% ABA rats completely avoided the sucrose while 43% naive and 20% pair-fed rats showed the same degree of aversion. When extinction was assessed by 1-bottle tests, the ABA rats tended to extinguish more slowly. The results of 2 bottle tests (sucrose and water simultaneously) confirmed that the ABA rats recovered their reference for sucrose more slowly than the pair-fed ($p < 0.007$) and naive ($p = 0.06$) controls. These data suggest that experience with AN-like symptoms could cause a devaluation of food reward thereby affecting the strength of CTA learning and retention. Supported by NIH grant DK19302.

doi:10.1016/j.appet.2010.04.114

Imaging glucose-induced gut-to-brain signalling pathways in humans. Role of the CCK_1 receptor

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Glucose inhibits neuronal activity in the hypothalamus, measured as a decrease in Blood Oxygenation Level-Dependent (BOLD) signal using magnetic resonance imaging (phMRI). However, the signalling pathway by which glucose exerts this effect is unclear. This study determined the effects of glucose on BOLD signal over the whole brain, and whether the effects of glucose on CNS activity are mediated by the CCK_1 receptor. The CNS responses to intragastrically administered 1 M glucose or 0.9% saline were studied in 12 healthy subjects on 3 occasions in a blinded, randomised fashion using phMRI. Blood glucose levels and subjective appetite perceptions were also assessed. The experiment was conducted with and without the CCK_1 receptor antagonist dexloxiglumide (600 mg orally). We identified that glucose modulated BOLD signal in the same brainstem and hypothalamic areas that we had previously demonstrated in response to lipid. However, in contrast to our previous results with lipid, glucose decreased, rather than increased, BOLD signal, suggesting neuronal inhibition. This effect of glucose was blocked by pre-treatment with dexloxiglumide. There was no effect of treatment on appetite perceptions. Blood glucose levels were higher, and equivalent, during glucose and glucose + dexloxiglumide conditions when compared with saline ($P < 0.05$). We have identified that glucose activates a CCK-mediated gut-brain activation matrix. Changes in BOLD signal appeared independent of changes in blood glucose concentrations.

doi:10.1016/j.appet.2010.04.115

Effects of fat on appetite and energy intake in humans

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There is a strong positive relationship between the intake of dietary fat with total energy intake and body weight. Dietary fat contributes to overeating hence recommendations for reduced dietary fat intake as a first line treatment for obesity. However, the sensing of dietary fat, and particularly of free fatty acids, by receptors in the tongue and intestine induces potent effects on gastrointestinal motility and gut peptide secretion that favour suppression of hunger and energy intake. In humans, oral hyposensitivity to fatty acids has been associated with higher energy intake and body mass index suggesting that impairment of fat taste sensing mechanisms may contribute to overeating and obesity. Furthermore, while in humans small intestinal triglycerides modulate gastrointestinal motility, stimulate gastrointestinal hormone release, including cholecystokinin (CCK) and peptide YY (PYY) and suppress subsequent energy intake; recent data from our lab indicate that these effects of fat are attenuated in individuals with reduced oral sensitivity to fat, and following consumption of a high-fat diet. This presentation will focus on emerging aspects of fat sensing in both the tongue, and the intestine, and the physiological mechanisms induced by dietary fat which may mediate dietary fat preference, satiation and satiety. A particular focus will be on the translational aspects of this research for the treatment of obesity.

doi:10.1016/j.appet.2010.04.116

Preference for sucralose is associated with the number of fungiform papillae in rats

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Rats vary in their preference for sucralose. While sucralose preferers prefer sucralose over water across a range of sucralose concentrations, sucralose avoiders prefer water over concentrations of sucralose >0.1 g/L. Previously, we demonstrated that this preferer/avoider profile is influenced by individual differences in sensitivity to a bitter taste quality of sucralose. Because sex and strain can influence responsiveness to bitter/bittersweet compounds, our goal was to determine whether sucralose preference is influenced by sex or strain. Further data in humans suggests that increased sensitivity to bitterness is positively correlated with the number of fungiform papillae on the tongue. Thus, our second goal was to determine whether the number of fungiform papillae differ in sucralose preferers/avoiders. Male and female rats were given access to ascending concentrations of sucralose (0.0001–2.0 g/L) and water in two-bottle, 24-h preference tests. Neither the proportion of preferrers/avoiders nor the preference curves differed as a function of sex. The same experiment was conducted in male Long-Evans (LE) and Sprague–Dawley (SD) rats. LE preferrers, were more accepting of sucralose at all concentrations, relative to SD preferrers. No strain differences were detected among LE/SD avoiders. Examination of the tongues of a subset of LE rats revealed that sucralose avoiders had more fungiform papillae than sucralose preferrers ($p < 0.05$). We conclude that individual differences in the number of fungiform papillae predict sucralose avoidance/preference profiles in rats.

doi:10.1016/j.appet.2010.04.117

Food availability and control of binge eating

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Probably the binge eating control is related to physiological, psychological and social factors. Nevertheless, an element of high importance is food availability. The objective of the present study was evaluating the effects of food availability control on the occurrence of binge eating behavior. Fifty albino rats (4-month-old at the beginning of the experiment) were divided in three groups. Groups 1 and 2 were deprived of food for a period of 72 h, and then returned to free food access according to one of the two procedures. The first procedure involved a return to the average of food intake registered during the baseline for 60 days, immediately return to free access. The second procedure involved return to free food access. Group 3 was exposed to free access all experiment. Water was freely available during the experiment. In second procedure, binge eating and excessive drinking were observed. In the first procedure binge eating and drinking were controlled by limiting food access. These results suggest that restriction of food availability could be a useful procedure to prevent eating disorders.

doi:10.1016/j.appet.2010.04.118

Nucleus accumbens neurons encode the enhanced palatability of hypertonic saline following sodium depletion

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The nucleus accumbens (NAc) differentially encodes the hedonic valence of taste stimuli. Appetitive tastes evoke phasic decreases in firing rate whereas aversive tastes evoke phasic increases. Here, we used sodium (Na^+) depletion to ask whether NAc neurons can track changes in palatability of hypertonic saline (NaCl) due to a change in Na^+ balance. Extracellular single-unit recordings were made in the rat to measure the activity of individual NAc neurons during brief (4 s, 200 μL) intra-oral infusions of 0.45 M NaCl under different conditions (Na^+ replete, deplete and re-replete). After each session, rats were given access to 0.45 M NaCl and distilled water in their home cages. Daily intakes were used to measure preference for NaCl. We hypothesized that the taste of NaCl would shift from unpalatable to palatable under the deplete condition, which would be encoded as a shift from overall increasing NAc activity to decreasing. In the NAc shell, recordings revealed that the shift from an increasing to a decreasing population response was due to an increase in the proportion of phasic decreases under the deplete condition rather than a change in the magnitude of individual neural responses. Thus, the NAc shell tracks enhanced palatability of a single taste stimulus by decreasing its activity. The role of these phasic decreases may be to disinhibit downstream areas such as the ventral pallidum in order to produce behavior.

doi:10.1016/j.appet.2010.04.119

Weight suppression is a robust predictor of key features of bulimia nervosa

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Weight suppression (WS) is the difference between one's current weight and highest ever body weight. Individuals with bulimia nervosa (BN) show elevated WS; recently there has been an upsurge in research on the role of WS in BN. Findings from our and other groups indicate that level of WS in BN (1) is related to more frequent binge eating and purging, (2) predicts weight gain over periods ranging from a few months to 5 years, (3) predicts poorer response to treatment in a clinical population receiving cognitive-behavioral therapy and a longer time period until remission from the disorder is achieved in a naturalistic, longitudinal study of BN, and (4) over a period of 10 years, predicts onset of BN-spectrum problems in those initially without them and, in those with a BN-spectrum problem, predicts a reduced probability of improvement 10 years later. Many covariates (e.g., current BMI, highest ever BMI, dieting frequency, subscales of the Eating Disorders Examination) have been tested but none have accounted for the predictive power of WS. These findings suggest that WS in BN may create a "biobehavioral bind" wherein greater WS induces more binge eating and weight gain, resulting in redoubled efforts at weight loss, thereby increasing WS and perpetuating a vicious cycle. Current approaches for treating BN do not take WS into consideration but perhaps should begin to do so.

doi:10.1016/j.appet.2010.04.120

Compensatory behavioral responses to combined challenges to sodium and fluid balance

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Dietary sodium deprivation is a well-known stimulus for sodium appetite in rats, while water deprivation is a well-known stimulus for thirst. The goal of this study was to examine the combined effect of these competing challenges to body fluid balance on compensatory behavioral responses by male rats. Rats were placed on a sodium deficient (NaD) diet and, after 10 days, were water deprived overnight. Three additional groups were used for comparison: rats maintained on the NaD diet but not water deprived, rats maintained on regular sodium diet and then water deprived, and rats maintained on regular sodium diet but not water deprived. On the test day, intakes of 0.5 M NaCl and water were measured for 7 h. As expected, rats maintained on the regular sodium diet and then water deprived consumed a large amount of water and very little salt. Rats maintained on the NaD diet but not water deprived consumed both salt and water in typical amounts and in the typical pattern. In contrast, rats maintained on the NaD diet and then water deprived consumed nearly twice as much water, but only half as much sodium. These results show that competing challenges to body fluid and sodium balance affect compensatory behavioral responses by rats and suggest that, in the face of combined sodium deficiency and water deprivation, the stimulus for thirst may be more salient.

doi:10.1016/j.appet.2010.04.121

The effects of realistic and preferred doses of red pepper on energy intake and expenditure

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Previous studies suggest consumption of red pepper promotes negative energy balance. However, the dose of red pepper provided in these studies generally exceeded the amount preferred by the population (e.g., 10 g/meal). The objective of this study was to evaluate the effects of realistic and preferred doses of red pepper served at a single meal in healthy, lean individuals. Twenty-five men and women (aged 23.0 ± 0.5 years, BMI 22.6 ± 0.3 kg/m^2, 13 spicy food users and 12 non-users) participated in a randomized crossover trial during which they consumed a standardized quantity (1 g); their preferred quantity (regular spicy foods users 1.8 ± 0.3 g/meal, non-users 0.3 ± 0.1 g/meal); or no red pepper. Diet-induced thermogenesis and post-meal energy intake were measured. Energy expenditure was increased in the 2.5 h following a red pepper-containing meal after a high-carbohydrate diet lead-in ($P < 0.05$). Energy intake was decreased following a red pepper-containing meal in non-users ($P < 0.05$), but not in users. This implies that individuals may become desensitized to the effects of red pepper with long-term spicy food intake ($P > 0.05$). Energy expenditure was similar following ingestion of red pepper in oral and capsule form ($P > 0.05$). This suggests that the effects of red pepper are metabolic rather than sensory.

doi:10.1016/j.appet.2010.04.122

Acute effects of high- and low-energy density preloads on upper gut function, thermogenesis and energy intake in obese men

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The acute effects of a subtle increase in energy density on gastric emptying (GE), gut hormones (glucagon-like peptide-1 (GLP-1), insulin), thermogenesis (DIT), and appetite, and the relationship with energy intake (EI), remains unclear. 16 obese men (BMI: 32 ± 1 kg/m^2) were studied on 3 separate occasions. GE, plasma GLP-1 and insulin concentrations, DIT, appetite and EI were measured in response to 670 g preloads; (i) high-energy dense, high-fat (HEDHF; 999 kcal, 1.5 kcal/g), (ii) low-energy dense, high-fat (LEDHF; 777 kcal, 1.1 kcal/g), and (iii) low-energy dense, high-protein (LEDHP; 777 kcal, 1.1 kcal/g). EI was quantified 180 min after preload ingestion. GE was slower with HEDHF compared with LEDHF and LEDHP (GE T50 (min); HEDHF: 158 ± 8; LEDHF: 147 ± 8, and LEDHP: 130 ± 8; $P < 0.05$). Plasma GLP-1 ($n = 8$) was higher with HEDHF at $t = 150$ min and $t = 180$ min compared with both LED preloads ($P < 0.05$), with no difference between LED preloads. Plasma insulin ($n = 6$) was higher with LEDHP at $t = 15$ min compared with LEDHF and HEDHF, and with LEDHP at $t = 75$ min and $t = 180$ min compared with LEDHF ($P < 0.05$). DIT was lowest with HEDHF ($10.5 \pm 0.7\%$) compared with LEDHP ($18.1 \pm 1.2\%$) and LEDHF ($14.9 \pm 1.1\%$) ($P < 0.001$), with no difference between the LED preloads. DIT was not related to GE. Fullness scores were highest after LEDHF compared with HEDHF and LEDHP ($P < 0.05$). EI at the buffet (kcal; HEDHF: 1111 ± 71; LEDHF 1135 ± 90; LEDHP 1125 ± 67) and total EI (buffet + preload) (kcal; HEDHF: 2059 ± 72; LEDHF 1875 ± 91; LEDHP 1866 ± 68) did not differ between preloads. In conclusion, while HEDHF resulted in modulation of GE, GLP-1 and DIT, suggestive of greater appetite suppression, EI at the next meal was not suppressed. This may have led to a tendency for passive over consumption and indicate a temporary "uncoupling" of gut satiety factors and EI regulation after even a subtle increase in energy density.

doi:10.1016/j.appet.2010.04.123

Comparative effects of fat, protein and carbohydrate, and increasing protein loads, on appetite and energy intake in lean and obese men

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Protein is regarded as the most satiating macronutrient, but concerns exist regarding the high amounts of protein frequently used in such studies, i.e. ~1.8–2.3 g/kg. We evaluated the acute effects of (i) high-fat, high-protein and high-carbohydrate meals, and (ii) meals containing increasing amounts of protein, on appetite and subsequent energy intake, and (iii) compared these responses between lean and obese individuals. 16 healthy (BMI 24 ± 0.4 kg/m^2) and 14 obese (BMI 33 ± 0.5 kg/m^2) men were studied on four occasions in response to isocaloric (~3000 kJ) meals that were (i) high in fat ('HF', 65% energy from fat), (ii) high in protein ('HP', 55% protein, 1.2–1.6 g/kg), (iii) high in carbohydrate ('HC', 70% CHO; and also low in protein 'LP', 0.2 g/kg) or (iv) adequate-protein ('AP', 0.7–0.9 g/kg). Hunger and fullness were measured for 180 min, after which energy intake (EI) was quantified. In the lean, EI was reduced by HF compared with HC/LP, and by HP compared with HC/LP and AP (kJ; HF: 4042 ± 363, HP: 3724 ± 394, HC/LP: 4372 ± 333, AP: 4429 ± 396; $P < 0.05$). In the obese, EI was reduced by HP compared with HF and HC/LP, and by AP compared with HC/LP (kJ; HF: 5107 ± 372, HP: 4429 ± 389, HC/LP: 5444 ± 369, AP: 4871 ± 341; $P < 0.05$). In the lean, but not obese, EI after HF was $12 \pm 6\%$ lower than after AP ($P < 0.05$), and there were relationships between EI with hunger ($r = 0.70$, $P < 0.001$) and fullness ($r = -0.50$, $P < 0.001$) at $t = 180$ min. In conclusion, obese subjects appear less sensitive to the satiating effects of fat, while sensitivity to even adequate protein loads is retained. Studies are required to investigate whether the acute appetite-suppressant effect of protein is maintained in the longer term.

doi:10.1016/j.appet.2010.04.124

Metabolic consequences of chronic social defeat stress

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Several psychiatric disorders are associated with an increase in mortality from cardiovascular disease. While the precise mechanism for this association has not yet been established, patients with psychiatric illness frequent develop obesity and dyslipidemia. In order to study the interaction of stress and metabolic dysregulation, we utilized chronic social defeat stress (CSDS), a mouse model of chronic stress with features of post-traumatic stress disorder and major depression. Following exposure to CSDS, mice were given access to either regular chow or a western style diet high in fat and cholesterol and comprehensive metabolic and behavioral testing was then conducted. Mice subjected to CSDS and then fed a high-fat diet for 30 days display a combination of both severe behavioral and metabolic disturbances. Stressed mice have a complex metabolic phenotype including hyperphagia, redistribution of body fat, insulin resistance, and elevated non-HDL cholesterol compared to control mice. Furthermore, mice subjected to CSDS display reduced serum leptin levels and central leptin resistance. Transcriptional profiling of peripheral tissues also revealed a significant effect of chronic stress on the activity of many transcription factors involved in glucose and lipid metabolism including LXR, SREBP1c, and ChREBP. We present CSDS as a model of social stress induced metabolic dysregulation and propose that social stress alters food intake and body weight regulation by altering leptin and melanocortin signaling. While these responses may improve behavioral deficits, they contribute to significant and long-lasting metabolic abnormalities.

doi:10.1016/j.appet.2010.04.125

Roux-en-Y gastric bypass reduces bone mineral density independent of body weight in rats

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Roux-en-Y gastric bypass (RYGB) surgery is an effective anti-obesity therapy. A major concern after RYGB is increased bone turnover that may result in reduced bone strength. Here, we examined the specific effect of RYGB on bone structure in rats, independent of RYGBs effect on body weight (BW). Male Wistar rats (BW 490 g) underwent RYGB ($n = 8$) or sham operation. Sham rats were fed ad lib ($n = 8$) or BW-matched ($n = 8$) to RYGB. Bone parameters were assessed by microcomputer tomography in vertebral bones (L1; LaTheta LCT100, Aloka), femur and tibia (XCT960A, Stratec). Rats were fed standard chow; feces were analyzed for calcium (Ca) and phosphate (P). After surgery, RYGB rats lost about 20% of their initial BW which remained stable thereafter (d60: 411 ± 8 g vs. 565 ± 7 g ad lib, $P < 0.0001$). Total bone mineral density (BMD), trabecular and cortical BMD in L1 was reduced by 40–45% compared to both sham ad lib and BW-matched rats. Cortical bone thickness was unaffected. Fecal Ca and P content did not differ between RYGB and sham ad lib. Similar reduction in BMD but not in cortical thickness or bone length was observed in femur and tibia at the time of sacrifice (d150 after RYGB). Our observations suggest that RYGB surgery has a profound effect on bone mineral density which may predispose to bone fractures. The effect is specific and independent of reduced BW. The underlying mechanisms require further study; reduced Ca and P availability do not seem to be involved.

doi:10.1016/j.appet.2010.04.126

Development of food preferences in early childhood

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At the beginning of life, major transitions occur in feeding mode within a very few years, with the human infant switching from cord feeding to milk feeding, going through complementary food introduction to ultimately eating foods from the family table, which is generally achieved well before the second birthday. This rapid adaptation poses two general questions. First, what are the consequences of these early feeding experiences on further preference for specific foods and on further temperament related to feeding? Second, which factors favour the transition from one feeding mode to the next, and the acceptance of foods during each stage? Regarding the first question, longitudinal studies highlighted the fact that food preference and variety of the food repertoire are formed early in life, probably before the age of three years and could track at least until the beginning of adulthood. This underlines the importance of understanding the key drivers of food acceptance during the first years of life. To analyse the role of factors influencing transitions between feeding modes, one can consider the impact of milk-related feeding experience on food acceptance at weaning. More specifically, the impact of breast-feeding can be analysed in terms of taste and flavour exposures: both types of exposure could impact taste and food acceptance at weaning. Besides the role of milk feeding experience, the impact of weaning food tastes on their acceptance was recently studied and this revealed that most infants easily accepted the weaning foods they were offered, but their acceptance was higher for foods containing some salt, compared to bland or slightly bitter alternatives. Furthermore, a recent study on the role of salt on food intake showed that in toddlers adding or suppressing salt does not impact similarly upon vegetable or green bean intake. This variety of feeding experiences at the beginning of life occur within the family context, and further data add to the understanding of the role of the parental environment by revealing an association between the children's food selectivity and neophobia at the age of 2 years, parental education style and feeding strategies. Altogether, these recent findings enhance our understanding of how early eating habits develop as a result of feeding experience under the control of parents.

doi:10.1016/j.appet.2010.04.127

Countering the biological drive to regain weight with exercise

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Weight loss is accompanied by a number of metabolic adaptations that coordinately promote rapid, energetically efficient weight regain. These adaptations affect energy balance, nutrient metabolism, lipid storage, and peripheral signals of energy status. These changes in energy homeostasis do not appear to dissipate with time after weight has been lost. We have used a preclinical paradigm of weight regain after weight loss to study these metabolic adaptations to weight loss and the strategies that may counter them. Not surprisingly, regular exercise has emerged as one of the most potent strategies, having a broad range of effects

on energy homeostasis that may facilitate weight maintenance. The most apparent of these effects is the reduced drive to eat in excess of the suppressed energy requirements. Exercise also alters the metabolism and storage of ingested nutrients and likely alters peripheral signals of energy status that would impact energy balance regulation. Our recent studies suggest that the beneficial effects of exercise, both on energy balance and on peripheral nutrient metabolism, may be dependent upon the composition of the diet. If these observations are translated to the human condition, the effects of exercise on food intake and other aspects of energy homeostasis may make it easier for someone to stay on a weight maintenance diet and may reduce the extent of regain with occasional excursions off their diet. The impact of exercise on the biological drive to regain lost weight may explain why it is so critical for successful long term weight maintenance.
doi:10.1016/j.appet.2010.04.128

Effect of chronic consumption of glucose on feeding behavior in albino rats

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Few studies have investigated the effect of drinking different sugar-sweetened beverages on feeding behavior. Evidence has demonstrated that heavy consumption of sweetened products has been associated with high body weight and other disorders like addictive behaviors to carbohydrates. Present study investigated the effect of chronic consumption of glucose sweetened beverages on feeding behavior and body weight. Twenty-four albino rats (3-month-old at the beginning of the experiment) were randomly assigned in two groups ($n = 12$/group) to consume 7% glucose solution (one bottle condition) or the same glucose solution and additional bottle with water (two bottle condition) for 16 weeks. All rats received ad libitum standard laboratory chow. Group in two bottle condition (glucose solution and water) consumed significantly more glucose solution than group in one bottle condition (only glucose solution) ($P < 0.05$). Food consumption decreases in all subjects in glucose condition. Body weight did not show significative changes. Additionally, rats showed an increasing of activity. These results suggest that chronic consumption of glucose beverages affect feeding behavior but no modifies body weight in albino rats. The role of procedure, glucose solution and activity over feeding behavior and body weight is discussed. Supported by CONACYT 101314.
doi:10.1016/j.appet.2010.04.129

Portion size affects how much students consume in an eating occasion

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Portion sizes have increased in multiple eating places, including restaurants and grocery stores. Various studies reported the relation between eating behavior and portion sizes. The objective of this work was to investigate the effect of varying portion sizes on food consumption in college students. Participants were divided into six groups: (1) four women, (2) four men, (3) two women and two men, (4) four women, (5) four men, and, (6) two women and two men. Groups were exposed to free access on traditional food in occident of Mexico called empanada (a kind of pie stuffed with ham, cheese and jalapeños). In first session Groups 1, 2 and 3 received a one large size portion of empanada (500 g) and in second session received ten short size empanadas (50 g each one) equivalent in taste and texture to one large size portion. Groups 4, 5 and 6 received first the ten short size empanadas and then one large size portion. Men consumed significantly more food when offered the largest portion compared with smallest portions. Results of women did not show significantly differences between both conditions. Mixed groups (3, 6) consumed 20% more food compared with participants of the other groups. When we asked to participants in which condition they have eaten more food, men answered correctly whereas answers of women did not coincide with their food consumption. These findings suggest that portion size and social behavior affects how much college students consume in an eating occasion.
doi:10.1016/j.appet.2010.04.130

Roux-en-Y gastric bypass in rats increases sucrose licking depending on deprivation state and trial taking in brief access tests

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Humans report eating fewer sugary foods after Roux-en-Y gastric bypass (RYGB). Here we used brief access tests to assess immediate licking responses to small samples of sucrose solution in rats after RYGB or SHAM surgery ($n = 7$). Ten to twenty days post-surgery, the body mass of rats given RYGB had dropped 15% compared to their presurgical mass, while those in the SHAM group gained 5%. Both pre- and post-surgery, rats were tested in a lickometer while ~23-h food-deprived in 30-min sessions and given access to water and 6 sucrose concentrations (0.01–1 M) in 10-s trials. Rats were retested while nondeprived and also after systemic modulation of glucagon-like peptide-1 (GLP-1), which increases after RYGB, via i.p. injection of antagonist exendin-3 (9-39) (30 μg/kg), agonist exendin-4 (1 μg/kg), or vehicle (PBS 1 ml/kg). When food-deprived or after peptides, no differences were seen in sucrose licking relative to water, but when nondeprived, RYGB rats licked sucrose more than SHAM rats. Thus in contrast to expectations, we found no evidence for decreased sucrose responsiveness after either RYGB or GLP-1 modulation. In all post-surgical conditions, RYGB rats took 2–4× more trials than SHAM rats. Collectively, RYGB increases appetitive behavior (trial initiation) and, in some conditions, enhances concentration-dependent licking in brief access taste tests with sucrose.
doi:10.1016/j.appet.2010.04.131

Is there a taste component to dietary fat?

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Dietary fats play critical roles in health and disease so an early signaling system for their detection may hold selective advantages. Minimal evidence supporting the primacy of a taste quality includes: (A) it is ecologically valid; (B) has a defined class of effective stimuli that initiate responses; (C) is transduced by a specialized mechanisms; (D) initiates a signal in the periphery that is conveyed centrally by one or more gustatory nerves; (E) is perceptible and unique; and (F) evokes a functional physiological and/or behavioral response. Data are emerging on each point. With respect to ecological validity, the textural properties of fats appear to be orexigenic and encourage consumption of beneficial fatty acids whereas the olfactory and taste cues are anorexigenic and discourage consumption of unwholesome rancid foods. Although not definitively established, only non-esterified fatty acids are effective taste stimuli and can promote depolarization of taste receptor cells. An array of free fatty acid receptors have been proposed including delayed rectifying potassium channels, CD36, GPCR 40, 41, 43, 120. Several have been localized to taste receptor cells. In rodent models, transection of the chorda tympani or glossopharyngeal nerves impairs fat detection and sectioning both nerves leads to greater disruption of fat sensing. Although the lexicon for fat taste is not easily defined, the sensations it evokes do not reflect combinations of other putative taste quality primaries. Oral exposure to fat elicits pancreatic exocrine and endocrine responses as well as mobilization of intestinal fat stores. Current data support, but do not prove fat has a taste.

doi:10.1016/j.appet.2010.04.132

Vagal afferents activate astrocytes in the NST. Evidence for a tripartite synapse

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Recent studies indicate that NST astrocytes can detect chemical signals and use this information to modulate autonomic reflex control. Further studies of NST astrocyte signaling mechanisms revealed the possibility that chemosensory astrocytes could serve not only to modulate vago-vagal reflex mechanisms but could themselves be the subject of modulation by visceral afferents in the vagus. We examined this possibility using live cell calcium imaging in in vitro medullary brain slices. The NST of urethane anesthetized rats was injected with a mixture of calcium green 1AM [calcium reporter dye] and SR101 [astrocytic vital stain]. Horizontal medullary slices were harvested and transferred to the recording chamber of a confocal microscope. Astrocytes [and neurons] responded to vagal afferent electrical stimulation with a sharp elevation in intracellular calcium time-locked to the stimulation pulse. Application of various glutamatergic antagonists suggested that the vagal-astrocyte stimulation effect was mediated by AMPA receptors; supported by subsequent application of glutamate receptor specific agonists and immunohistochemical analysis. Astrocytes in the NST are capable of chemosensory signaling that modulates vago-vagal reflex-mediated autonomic functions. Apparently these same astrocytes are also subject to regulation by vagal afferent input. These data support the existence of a complex "tripartite" interaction between vagal afferents, second-order NST neurons and interspersed astrocytes that regulate the sensitivity of brainstem chemosensory processes.

doi:10.1016/j.appet.2010.04.133

Direct and indirect activation of the paraventricular nucleus of the hypothalamus and the nucleus of the solitary tract by urocortin I

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Urocortin I (UcnI) reduces food intake, increases blood glucose, and stimulates Fos expression in brain structures such as the paraventricular nucleus of the hypothalamus (PVN) and the nucleus of the solitary tract (NTS). Previous studies indicate that these effects occur with a similar magnitude regardless of whether UcnI is injected into the lateral ventricle (LV) or fourth ventricle (4V); however, it remains unclear which brain areas mediate these responses and which are activated directly by ventricular application of UcnI. To address these open questions, we have begun comparing the effects of UcnI after application to the LV, 4V, NTS or PVN. We confirmed earlier findings related to feeding, glucose, and Fos expression after ventricular administration of UcnI, but found that Fos expression in the PVN was more sensitive to LV injections of UcnI than it was to 4V injections. We also replicated earlier studies by finding that UcnI administered directly to the PVN decreased food intake. Contrary to our prediction based on earlier work using decerebrate rats, injection of UcnI into the NTS did not increase blood glucose. Current studies are measuring Fos expression in the hindbrain and forebrain after application of UcnI to the PVN or NTS. Taken together, our preliminary studies suggest that the PVN is involved in the behavioral response to UcnI and can be activated both directly and indirectly, and that UcnI in the NTS fails to recruit pathways required for at least one of the physiological effects of UcnI.

doi:10.1016/j.appet.2010.04.134

Comparing the effects of prefrontal cortical opioids and monoamines on feeding behavior and associated motor activity

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We compared the behavioral effects of manipulating medial prefrontal cortex (mPFC) opioid receptors versus dopamine (DA), serotonin (5HT), and norepinephrine (NE) receptors. The mu-opioid agonist DAMGO dramatically increased food intake, producing motoric activation and abrupt termination of behavioral sequences. To explore pharmacological specificity within the opioid system, we tested intra-mPFC infusions of the agonists DPDPE (delta) and LPK-26 (kappa); neither altered food intake. To compare these effects to those seen with monoamine manipulations, separate groups of rats received bilateral mPFC infusions of agonists and antagonists for dopamine, serotonin, and norepinephrine receptors. Blockade of D2 receptors or 5HT2A receptors produced a slight increase in food intake and a slight decrease in motor activity. Manipulating D1, 5HT1A, α- and β-adrenergic receptors was without effect. We then explored the anatomical specificity of the DAMGO effect by infusing DAMGO into primary motor cortex (M1) and ventral orbital PFC (voPFC). Infusion of DAMGO into M1 failed to influence food intake, while a small increase in food intake was observed in voPFC. Together, these results argue for a pharmacologically and anatomically specific role of mPFC mu-opioid neurotransmission in augmenting food intake and motor output, while manipulations of other opioid or monoamine receptors were far less robust. These results demonstrate the heterogeneity of neuropharmacological control of feeding by systems in the mPFC.

doi:10.1016/j.appet.2010.04.135

Effect of ileal interposition on reduction of food intake by cholecystokinin-8 and -33 in rats

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Short term control of food intake is regulated by upper and lower gastrointestinal peptides, e.g., CCK (upper gut) and GLP-1 (lower gut). We hypothesized that ileal interposition, a surgery that increases GLP-1 secretion, affects the ability of CCK-8 and -33 to reduce food intake in rats. Two groups of rats underwent ileal interposition ($n = 8$) or sham surgery ($n = 7$) and received CCK-8, CCK-33 (1, 3, 5 nmol/kg) or saline i.p., followed by measuring the intake of a 10% sucrose during a 120-min test. CCK-8 and -33 reduced meal size and increased the satiety ratio in both groups with an enhanced effect in the sham rats. CCK-8 shortened the intermeal interval but CCK-33 prolonged it. Devazepide, a CCK_1 receptor antagonist blocked these effects. Rats with Ileal interposition showed more body weight reduction compared to the sham group. In conclusion, no additive satiety effect was noted by interposition surgery on CCK. These finding suggest that the release of ileal peptides may require activation by different components of the chyme or at different time periods of meal consumption compared to satiety peptides from the upper gut.

doi:10.1016/j.appet.2010.04.136

Influence of the ovarian cycle on binge eating evoked in female rats by stress and food restrictions

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Dieting and stress are key determinants of binge eating (BE). In the model adopted by our group [Cifani et al. (2009), Psychopharmacology, 204, 113–125] BE for highly palatable food (HPF) is evoked in female rats by the combination of cyclic food restrictions and stress. Since variability in the occurrence of BE was observed, taking into account the inverse association between plasma estradiol levels and feeding [Geary & Asarian (1999), Physiol. Behav., 141–147] or BE [Klump et al. (2008), Psychol. Med., 38, 1749–1757; Lester et al. (2003), Psychol. Med., 33, 51–60], we investigated whether the variability may be related to the ovarian cycle. Female Sprague-Dawley rats were divided into 2 groups: NR + NS rats were normally fed and not stressed on the test day (d 25); R + S rats were exposed to three 8-day cycles (4d 66% of the usual chow intake + 4d food ad libitum) of yo-yo dieting and then stressed. Stress was induced by preventing access to HPF for 15 min, while rats were able to see and smell it. Following examination of vaginal smears on the test day, statistical analysis revealed that HPF intake was significantly lower during the estrous phase both in NR + NS and R + S rats. HPF intake of R + S rats was significantly higher than that of NR + NS rats during proestrous, metaestrous and diestrous, but during estrous there was no difference in HPF intake between the two groups. Present findings show that BE in our model does not occur during the estrous phase and that the variability of the results can be almost completely abolished if female rats in estrous are not included in the statistical evaluation.

doi:10.1016/j.appet.2010.04.137

Effects of nociceptin/orphanin FQ (N/OFQ) in a model of binge eating in female rats

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Stress is a determinant of binge eating. N/OFQ is a functional antagonist of CRF, the main stress mediator. The present study evaluated the effect of N/OFQ in rats in which binge eating for highly palatable food (HPF) was evoked by combining stress and repeated food restrictions. Female Sprague-Dawley rats were submitted to three 8-day cycles of food restriction/refeeding (4d 66% of the usual chow intake; 4d food ad libitum) and to acute stress on d25. Stress was induced by preventing access to HPF for 15 min, while rats were able to see and smell it. Four groups of rats were used: NR + NS rats were normally fed and not stressed on the test day (d25); NR + S rats were similarly fed but were stressed on d25; R + NS rats were exposed to 3 cycles of yo-yo dieting but not stressed; R + S rats were exposed to 3 cycles of yo-yo dieting and then stressed on d25. N/OFQ was given by ICV injection. Only R + S rats exhibited binge eating; their HPF intake at 15 min was about 50% above that of NR + NS rats. N/OFQ, 0.125–0.25 nmol/rat, slightly attenuated it; 0.5 nmol/rat significantly reduced it, while no reduction was observed at 1 nmol/rat. The last dose did not modify HPF intake in NR + NS or NR + S rats, but significantly increased it in R+NS rats. Also NPY, 0.2–0.4 μg/rat, was inactive in NR + NS rats, but elicited hyperphagia following food restriction. Thus, N/OFQ slightly reduces binge eating at low doses. However, repeated food restrictions sensitize rats to its hyperphagic effect, preventing its anti-binge effect at higher doses. Interestingly, repeated food restrictions enhanced the hyperphagic response to both N/OFQ and NPY.

doi:10.1016/j.appet.2010.04.138

Ghrelin reduces salt intake under some natriorexigenic conditions

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Recent studies suggest that ghrelin plays a role in fluid balance in addition to its well-established effect on food intake. Previous work in our lab demonstrated that rats treated with ghrelin drank less water than controls after injection of hypertonic saline or angiotensin II (AngII) and another lab reported a similar effect of ghrelin after water deprivation or injection of polyethylene glycol (PEG). Although the effect of ghrelin on water intake has been evaluated under a variety of circumstances, its effect on salt intake has not been tested. Accordingly, we measured water and salt intakes after injection of ghrelin in rats receiving icv AngII or rats exposed to a water deprivation-partial rehydration (WD-PR) paradigm. Although our preliminary studies using AngII suggested the possibility of a more selective effect of ghrelin on saline intake than on water intake, a more complete set of studies using a two-bottle approach found that ghrelin treatment decreased AngII-induced water intake without affecting concomitant 1.8% NaCl intake. When we used the WD-PR paradigm to stimulate saline intake, ghrelin reliably decreased intake of 1.8% NaCl. Preliminary data from ongoing studies in the lab suggest that ghrelin reduces saline intake after PEG treatment without affecting water intake. Thus, it appears that ghrelin attenuates salt intake in some, but not all, natriorexigenic conditions. Understanding the physiological basis for these differences and determining the mechanism of action involved merit further investigation.

doi:10.1016/j.appet.2010.04.139

Proestrus rats have reduced inflammation and ER stress in the liver after 72 h on a high fat diet

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There is evidence that obesity is characterized by chronic activation of inflammatory pathways. The protective effects of ovarian hormones may be a result of the anti-inflammatory effects of estradiol and progesterone in the muscle and adipose tissue. In the present study we sought to determine if this effect is present when a high-fat (HF) diet is first introduced. Age-matched male and female Long-Evans rats (3-month-old) were given a HF or a low-fat (LF) diet for 72 h ($n = 89$). Females were phased daily and started on the HF diet on the day of estrus so that 72 h later they would be in proestrus at sacrifice. The liver was extracted and processed using quantitative PCR of IL-6, SOCS3, TNFα , and XBP1. Females on the HF diet had lower SOCS3 and TNFα expression than their LF controls. However, in males there was no difference in inflammatory gene expression between diet groups. Endoplasmic reticulum (ER) stress, measured by higher expression of XBP1, was reduced in females on the HF diet compared the LF controls. However a sex difference in ER stress did exist. Males in both diet groups had higher XBP1 expression than their female counterparts. These data provide support for the protective role of ovarian hormones in inflammatory diseases.
doi:10.1016/j.appet.2010.04.140

Sex differences in diet-induced obesity and central leptin sensitivity in middle-aged rats

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As humans and animals age, many get fatter and develop insulin and leptin resistance, making them more susceptible to the metabolic syndrome. In the current study we sought to determine whether the sex differences in central leptin sensitivity found in young rats disappears with age and if age increases susceptibility to diet-induced obesity. Middle-aged male and female rats (8–9 months old) were maintained on either a low-fat (LF) diet or high-fat (HF) diet for 5 weeks and given weekly intra-third-cerebral ventricle (i3vt) injections of leptin (1.5, 3.5, 5.0 and 7.5 μg). Females on the LF diet given i3vt leptin had a dose-dependent decrease in FI and BW. In contrast, males on the LF diet were leptin resistant. Females on the HF diet responded to leptin at a higher dose, starting at 5.0 μg, while males on the HF diet were leptin resistant. These data indicate that a sex difference in central leptin remains in middle-aged rats, however since age-matched males were significantly heavier than the females, it remains to be determined whether the higher BW played a role. During the study females given the HF diet gained 20% in BW compared to their LF diet controls, while males on the HF diet gained 10% in BW compared to their LF diet controls. These results suggest that aged rats of both sexes are susceptible to diet-induced obesity and that middle-aged female rats remain sensitive to central leptin.
doi:10.1016/j.appet.2010.04.141

The hunting of the snark. Interpretive issues in neurobiological analysis of food-entrained circadian rhythms

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When food is freely available, feeding behavior in mammals is controlled by a circadian clock (the suprachiasmatic nucleus) entrained by daily light–dark cycles. When food is temporally restricted, food seeking behavior comes under control of a separate circadian mechanism entrained to mealtime. The physical location, inputs, outputs and molecular basis of this food-entrainable mechanism have proven difficult to establish and remain contentious, but as this symposium will show, progress has been made. I will discuss interpretive issues in evaluating the effects of lesions and gene manipulations on food-entrained rhythms in rats and mice, with a special focus on the role of the dorsomedial hypothalamus and known circadian clock genes.
doi:10.1016/j.appet.2010.04.142

Butorphanol effects on feeding and neuropeptide Y gene expression in the rat

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Butorphanol ([BT] an opioid receptor agonist) is different from other opioid agonists in that a single dose of BT can elicit up to 12 g of chow intake in a satiated rat whereas most opioid agonists induce a mild feeding response (2–3 g). Here, we first examined whether the effectiveness of BT to elicit feeding was affected by dose, time of day, and method of infusion and possible tachyphylaxis following administration. Secondly, we examined whether BT administration influenced hypothalamic NPY gene expression and peptide levels. A single dose administration of BT (4 or 16 mg/kg) significantly increased food intake at 2, 4 and 6 h after administration. However following repeated injections of BT at 4 mg/kg, the cumulative long-term intake of BT-treated rats did not differ from that of controls, indicating that the animals compensate for the increased feeding following BT injection by decreased feeding at a later time. An ascending dose schedule of repeated BT injections resulted in additional feeding. NPY gene expression in the ARC was influenced by feeding status but not by BT. The amount of food consumed and the level of NPY mRNA were inversely correlated. This is consistent with NPYs role in normal feeding. We conclude that the feeding produced by BT is sensitive to dose and dosing paradigm. Further, its mechanism of action does not appear to be mediated by NPY pathways. This work was supported by the VAMC, NIH DK42698, NIDA DA03999 and NIDCR T32DE007288.
doi:10.1016/j.appet.2010.04.143

What can we learn from animal models of eating disorders?

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Eating disorders are behavioral disorders of unknown pathophysiology. However, their characteristic behaviors are well documented. In anorexia nervosa, underweight individuals greatly limit their intake, often exercise excessively and have distortions of body image and fear of fatness. Bulimia nervosa and binge eating disorder are similar in that individuals consume excessive amounts of food in individual eating bouts but differ in their compensatory behaviors and body weight outcomes. Animal models can be used to mimic the ingestive and physical activity behavioral patterns of eating disorders. For instance, running wheel access with a restricted period of food access results in rats voluntarily decreasing their food intake and losing body weight. In contrast a feeding schedule with periods of food deprivation followed by scheduled access to a high calorie highly palatable fat/sugar mixture results in binge like behavior in which most of a normal day's caloric intake is consumed in a short period. In each case, aspects of the behaviors are self-sustaining and repeatedly engaging in these behaviors results in changes in neural systems that may facilitate their continuation. Thus, rather than providing insights into the pathophysiology of eating disorders, behavioral animal models can identify the physiological and neural changes that sustain these disorders and emphasize the need to interrupt the behaviors as an important aspect of treatment.

doi:10.1016/j.appet.2010.04.144

Increased orexin (OX) and melanin-concentrating hormone (MCH) expression in the perifornical lateral hypothalamus (PFLH) of rats prone to overconsuming a fat-rich diet

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Initial access to a high-fat (HF) diet provides measures of intake and weight gain during the first 5 days that are strong predictors of long-term eating patterns. Sprague–Dawley rats ($n = 24$) were subgrouped based on their intake of a HF relative to chow diet, with control rats consuming <5% and HF overconsumers (HFC) ingesting 10–35% more of the HF diet. This study examined the expression of the orexigenic peptides, OX and MCH, in the PFLH of these subpopulations. After 5 days on the HF diet, the HFC rats compared to controls exhibited a significant increase ($P < 0.05$) in OX and MCH mRNA, as revealed by quantitative real-time PCR (qRT-PCR). An anatomical analysis using *in situ* hybridization (ISH) additionally revealed a region-specific increase ($P < 0.05$) in OX mRNA in the PF, but not LH. To determine if these disturbances in PFLH OX and MCH mRNA are an inherent characteristic of the HFC rats that are still evident in the absence of the HF diet, we next measured peptide mRNA using qRT-PCR or ISH in subgroups of animals ($n = 24$/group) 2 weeks after being switched to a chow diet. The HFC rats on chow still showed an increase ($P < 0.05$) in OX and MCH mRNA levels. In additional tests prior to HF diet exposure, the activity level of these rats was found to be strongly, positively correlated with their initial HF diet intake ($r = +0.71$, $p < 0.05$). Together, these studies show that the increased consummatory behavior of HFC rats that show a preference for dietary fat is related to a possible baseline increase in OX and MCH peptide along with enhanced activity levels.

doi:10.1016/j.appet.2010.04.145

Olanzepine-induced adiposity in female rats

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Weight gain is not only a common problem for most Americans, but with the use of many antipsychotic drugs it is a prominent side-effect. Olanzapine is an atypical antipsychotic drug that has been reported to increase appetite, with subsequent changes in body weight, in female rats. In the present study, olanzapine was placed in a "treat" (condensed milk) to ensure complete consumption of the daily dose of the drug at a specified time, which simulates a human taking the drug on a typical once-a-day schedule. Twelve male and female Long Evans rats were assigned to either a control or experimental group and were subjected to a 3-week habituation period, in which they all received a condensed milk "treat". Following habituation, six experimental rats, in their respective genders, received olanzapine dissolved in ethanol in the condensed milk, while the control rats received only ethanol in the milk. The drug period lasted for 3 weeks. The only difference between experimental and control animals in food consumption occurred during the first week of drug administration where experimental female animals consumed more food than control animals. Of particular significance was the difference in adiposity between genders, with male rats having less fat than female rats and female rats, receiving olanzapine, developing more adiposity than female rats not exposed to the drug. Differences in drug pharmacokinetics, as well as modulatory effects of some hormones, may explain the gender-related observations induced by olanzapine. Drug-related metabolic influences may have produced within gender differences in female rats.

doi:10.1016/j.appet.2010.04.146

The meal as medicine. Anti-obesity effects of soy in rat model of menopause

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Estrogen deficiency may be responsible for the gain in body weight and visceral fat experienced by postmenopausal women because, in rodent models of menopause, estradiol administration counteracts these effects. Soy contains phytoestrogens such as isoflavone, which have a chemical structure similar to estradiol; it may thus be a natural alternative to reduce menopausal symptoms. We tested whether phytoestrogens have anti-obesity effects, similar to estradiol, by monitoring daily food intake and body weight of female Long-Evans rats that were either bilaterally ovariectomized (OVX; $n = 16$) or sham operated (SHAM; $n = 15$) and fed either phytoestrogen-free control diet (AIN-76A – CTRL) or phytoestrogen-rich (AIN-76A + 1000 mg/kg soy isoflavone – SOY) diets. SOY diet significantly reduced body weight compared to CTRL diet in both OVX (345 ± 3 g vs. 381 ± 2 g) and SHAM (272 ± 2 g vs. 304 ± 10 g) animals. To determine the cause of the change in body weight, intact rats ($n = 16$) fed either the CTRL or SOY diet had their food intake, activity, oxygen consumption and carbon dioxide production measured for four days. We found no differences between the groups in food intake or respiratory exchange rate; however, relative to rats fed CTRL diet, rats fed SOY diet had significantly higher heat production (8.2 ± 0.2 kcal/h/kg vs. 7.4 ± 0.1 kcal/h/kg) and activity ($70{,}921 \pm 3067$ vs. $57{,}993 \pm 4082$ beam breaks per day). These findings suggest that soy isoflavones inhibit obesity-related symptoms of menopause by increasing physical activity and energy expenditure.

doi:10.1016/j.appet.2010.04.147

Rats learn stronger preferences for flavors occurring late in a high-fat meal

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Rats learn to prefer flavors that are paired with the postingestive effects of macronutrients. It has been suggested that flavors routinely consumed late in a meal (desserts) may become more strongly preferred because they are most closely associated with delayed postingestive effects of the entire meal. To the contrary, we have previously found that rats learn similar preference for flavors occurring both early and late in a carbohydrate (glucose) meal, indicating that relevant postingestive events are rapidly detected. The present study investigated learning about early and late flavors when the calorie source is fat. Rats ($n = 16$) with gastric catheters repeatedly experienced two types of training sessions: in (+) meals, they consumed non-caloric cue flavors paired with intragastric (IG) infusion of high-fat solution (heavy cream diluted in water, 0.5 kcal/g); in (−) meals flavors were accompanied by IG water infusion. In each type of session, one flavor (E) always occurred in the Early half (8 min) and another flavor (L) in the Late half of the meal. Thus each rat was trained with four flavors: E+ and L+, E− and L−. Subsequent two-bottle choice tests were conducted to assess whether rats learned flavor preferences based on flavor-nutrient associations. Rats preferred the L+ but not E+ flavor, supporting the idea that flavors occurring late in the meal become most strongly associated with delayed postingestive effects of fat. Unexpectedly, the preference for L+ was even stronger when rats were tested shortly after chow feeding than when they were tested food deprived.

doi:10.1016/j.appet.2010.04.148

Visceral NTS projections to nucleus intermedius

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The medullary reticular formation is involved in coordinating and modulating basic survival behaviors such as breathing and the oromotor phase of ingestion. Recent evidence implicates the reticular area adjacent to the hypoglossal motor nucleus (mXII), the intermedius nucleus of the medulla (ImN), as a potential region for integrating multiple afferent sensory signals (Edwards et al., 2009). Moreover, previous retrograde tracing studies demonstrate that ImN neurons send axons to mXII, consistent with a role in oromotor function. Using anterograde fluorescent tracers we demonstrate that the ImN receives afferent projections from both the rostral and caudal nucleus of the solitary tract (rNTS, cNTS). To further study the inputs and outputs of the ImN, we injected mXII with a retrograde tracer in neonatal rat pups prior to patch clamp recordings in a slice preparation. Traced ImN neurons displayed time-locked inhibitory and excitatory post-synaptic currents (IPSCs, EPSCs) in response to electrical stimulation of the cNTS. In some ImN neurons, there was also an increase in driven miniature EPSCs or IPSCs following short trains of stimulation. Pharmacologic antagonism of ionotropic glutamate receptors blocked only some EPSCs indicating multiple excitatory phenotypes. Together, these results suggest that the ImN may act as a substrate for convergence of gustatory signals from the rNST and visceral signals from the neurochemically diverse cNST. These data are consistent with the hypothesis that the ImN integrates multiple afferent signals through complex synaptic mechanisms to coordinate diverse oromotor behaviors.

Supported by NIH DC000416 and DC000417.
doi:10.1016/j.appet.2010.04.149

Loss of affect for foods in patients with anorexia nervosa

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High sugar and/or fat foods tend to cause release of dopamine and promote consumption of food. Over activity of the dopamine reward circuitry has been found in recovered anorexia nervosa (AN) patients. If AN patients restrict food intake because "pleasant" stimuli provoke excessive dopamine release and anxiety, AN patients might be coaxed into eating substantial amounts of foods that control subjects find unpalatable or disgusting. This possibility was tested in a brief exposure taste test in which eight control women and eight ILLRAN tasted 28-g servings of foods prejudged by the experimenters as palatable "PAL" or unpalatable "UNP", (eight of each type), eating as much or as little as they liked and giving a rating of each on a 9-point scale of liking. PAL foods included string cheese and chocolate pudding and UNP foods included gelatinized bread and elemental amino acids. Patients ate slightly more (3.3 ± 5, $F = 3.3$, $P = 0.1$) total grams of UNP foods (11.9 ± 11.5) than PAL foods (8.6 ± 6.7) and rated both types of foods as marginally palatable (5.0 = PAL and 3.0 = UNP). Controls ate less UNP food (21.1 ± 14.6) than PAL (34.3 ± 21.2) and the difference was significant ($F = 6.8$, $P = 0.035$). The between group PAL-UNP food intake difference was highly significant ($F = 9.4$, $P = 0.008$) Controls rated the PAL ($M = 7.6 \pm 1.5$) food significantly more liked by 4.5 ± 0.4, ($P < 0.001$) than the unpalatable ($M = 3.0 \pm 2.3$). The prediction that AN patients will eat more UNP than PAL food is promising and suggests that making high energy foods unpalatable might be an effective strategy to induce AN patients to eat.

doi:10.1016/j.appet.2010.04.150

Development of food preferences in early childhood

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At the beginning of life, major transitions occur in feeding mode within very few years, with the human infant switching from cord feeding in utero to milk feeding, going through weaning and complementary food introduction to ultimately eating foods from the family table, which is generally achieved before his/her second birthday. This poses two general questions. First, one might search to understand the factors which favour the transitions from one feeding mode to the next, or which favour food acceptance at a certain stage. Second, one might like to understand the consequences of these early feeding experiences on preference for specific foods and on food temperament. The first question will be discussed in particular by analysing the role of milk-related feeding experience on food acceptance of weaning. Certain individual factors will also be considered such as the impact of taste acceptance on acceptance of weaning foods. More generally, the role of taste on food intake will be discussed. The second question will be addressed based on results from longitudinal studies underlying the impact of exposure to a variety of foods on further food acceptance, and also considering the role of parental feeding practices on children's feeding temperament, including selectivity and neophobia.

doi:10.1016/j.appet.2010.04.151

Inhibition of sweet taste responses by AM251, an antagonist of endocannabinoid receptors in *db*/*db* mice

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Our recent studies demonstrated that the taste organ is a peripheral target for both leptin, an anorexic mediator and endocannabinoids (anandamide:AEA and 2-arachidonoyl glycerol:2-AG), orexigenic mediators. In mice, administration of leptin leads to reduction of sweet taste responses of taste nerve and cells via activation of leptin receptors. Oppose to the action of leptin, administration of AEA or 2-AG enhances behavioral, taste nerve and taste cell responses to sweet taste. This enhancing effect of cannabinoids was not evident in mice genetically lacking CB1 receptors [Yoshida et al. (2010), PNAS]. These data indicate that exogeneously applied endocannabinoids enhance sweet taste via activation of CB1 receptors. However, it remains unclear that circulating endocannabinoids could actually affect sweet taste responses independently of the sweet taste modulation system by leptin. To address this issue, we examined potential effects of AM251, an antagonist for CB1 receptor, on taste nerve responses of leptin receptor-deficient *db*/*db* mice with increased endocannabinoid levels in the hypothalamus and enhanced sweet taste responses. The results showed that responses of the chorda tympani nerve to sweet compounds, but not to other taste compounds, were significantly reduced after administration of AM251. This suggests a possibility that endocannabinoids may tonically activate CB1 receptors to maintain the enhanced sweet taste responses in *db*/*db* mice.

doi:10.1016/j.appet.2010.04.152

Lesions of the thalamic trigeminal taste area dissociate natural from drug reward

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The devaluation of natural reward is a common feature among addicts. This study investigated the effects of bilateral ibotenic acid lesions to the thalamic trigeminal taste area (TTA) on the association of natural and drug reward. Based on preliminary findings from a sham feeding study, we hypothesized that these lesions would disrupt the association of a drug reward with a taste cue under real-feeding conditions. Experiment 1 employed an anticipatory contrast paradigm where rats avoid intake of a palatable taste cue (CS) when it is followed by access to a more rewarding sucrose solution. Results indicate that the lesions did not affect suppression of the intake of the saccharin cue in this paradigm (Saccharin-Sucrose, 205 ± 42 licks; Saccharin-Saccharin, 414 ± 46 licks). Experiment 2 used a similar paradigm with a palatable Polycose cue paired with a drug of abuse, morphine. Results indicate that the lesion completely blocked morphine-induced suppression of intake of the Polycose cue (Morphine, 6.9 ± 1.9 ml; Vehicle, 8.6 ± 1.5 ml). Experiment 3 tested whether subjects with TTA lesions could develop a conditioned taste aversion to a NaCl cue paired with LiCl-induced malaise. Results found that both control (LiCl, 4.0 ± 1.7 ml; Vehicle, 12.7 ± 1.1 ml) and lesion subjects (LiCl, 2.8 ± 1.5 ml; Vehicle, 8.6 ± 0.7 ml) suppressed NaCl intake when paired with LiCl. These results demonstrate separate circuits for the comparison of disparate natural rewards and for the comparison of a natural reward with a drug of abuse.

doi:10.1016/j.appet.2010.04.154

Family drug use predicts snack consumption of college students

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Several questionnaire and taste test studies suggest that drug and food consumption are related. Drug dependent patients report higher preference and consumption of sweet and "junk" foods. The purpose of the present study was to examine actual food intake in relation to reported drug use. 46 college students (31 women and 15 men) were given a selection of foods (cookies, cheese, potato chips, chocolates, carrots, orange slices) to eat as an afternoon snack in the laboratory. VAS measures of hunger and fullness were taken as well as ratings of pleasantness and desire to eat for each food. They were also asked to report on their own and family drug use on the Core Alcohol and Drug Survey and measures of height and weight were made. Participants were categorized by their own drug use as well as family history of drug use. MANCOVA revealed that participants who reported a family history of drug use ($n = 18$) ate more food than those who did not ($n = 28$), $F(1,41) = 9.86$, $P = 0.003$ (in particular, chips, cookies and carrots). Time since last meal and the number of different drugs tried by the student were significant covariants but BMI, hunger, and age of first drug use were not. The different number of drugs tried was a strong predictor of total amount of food eaten, $r(39) = 0.404$, $P = 0.011$ (and specifically, oranges and cookies). No differences in hunger, pleasantness and desire to eat ratings by family history were detected. Our findings suggest that variety seeking in drugs is associated with higher food consumption in the laboratory and that family history of drug use should be considered in studies of food and drug consumption.

doi:10.1016/j.appet.2010.04.153

Effects of the μ-opioid receptor inverse agonist GSK1521498 on eating behaviour in overweight and obese subjects

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GSK1521498 is a μ-opioid receptor ligand under development for the treatment of obesity. In this study we examine the effects of GSK1521498 on eating behaviour using a hedonic taste preference test and an ad libitum food intake paradigm in obese and overweight volunteers. The study adopted a double-blind placebo controlled cross-over design (GSK1521498 (25 mg), placebo) in 20 otherwise healthy overweight/obese males (BMI 25–35 kg/m^2). GSK1521498 significantly reduced hedonic ratings of sugar and fat at all levels of fat and sugar content, the highest levels of fat and the highest levels of sugar. GSK1521498 also reduced snack food intake by 27% for all categories of fat and sugar and by 39% for the high fat/high sugar category. These findings are consistent with the literature implicating μ-opioid receptors in hedonic and consummatory aspects of eating behaviour. They also provide encouraging evidence that GSK1521498 can selectively reduce caloric intake attributable to foods with high fat and/or high sucrose concentrations and may provide a viable treatment option for obesity.

doi:10.1016/j.appet.2010.04.155

Relationship between obsessive and compulsive binge-eating behaviour and dimensions of impulsivity in an overweight and obese population

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Behavioural and personality traits such as binge eating and impulsivity have been linked to obesity. This study set out to assess the relationship between binge-eating behaviour and impulsivity and their relationship to BMI in overweight/obese participants. 188 (133M/55F) healthy overweight/obese participants (BMI > 25 kg/m^2). All completed: BES, Y-BOCS-BE, BIS-11. Spearman's correlations indicated that all three sub-scales of BIS-11 were significantly, but weakly, correlated with total score of the BES (r = 0.20–0.29, all P's < 0.01). All sub-scales of the BIS-11 were weakly correlated with total score and the sub-scales of Y-BOCS-BE (r = 0.20–0.37, all P's < 0.01). Y-BOCS-BE and BES total scores exhibit a high correlation (r = 0.71, P < 0.0001). BMI was moderately correlated with BES total score (r = 0.41, P < 0.0001). BMI was also weakly correlated with total score and sub-scales of Y-BOCS-BE (r = 0.19–0.28, all P's < 0.01). Obese participants scored significantly higher on the BES when compared to overweight participants (P < 0.0001). The current investigation indicates a link between obsessive and compulsive binge-eating behaviour and dimensions of impulsivity in a local community sample of overweight and obese participants. These results indicate that specific eating behaviours and psychological traits may provide important therapeutic targets in the development of novel centrally acting anti-obesity drugs.

doi:10.1016/j.appet.2010.04.156

Functional reciprocity in nutrient-satiety peptide interactions. Sugar intake and oxytocin

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Mice deficient for anorexigenic oxytocin (OT) eat more sugar, which suggests that OT may be a satiety mediator specific for sucrose. We sought to corroborate these findings by defining the role of OT in sugar-specific satiety in wild-type rodents. We also hypothesized that overconsumption of sucrose upon extended exposure to this nutrient is facilitated by sugar's inhibitory effect on activation of hypothalamic OT neurons. We found that OT mRNA is upregulated in animals fed short-term (48 h) with sucrose compared to those given fat or standard chow. OT antagonist, L368,899, increases intake of 10% sucrose presented alone or alongside fat. We also detected a higher % of Fos-positive OT neurons upon termination of calorie-matched intake of sugar than fat in non-naïve animals unaccustomed to regular sugar/fat consumption. Interestingly, when sucrose meals were given chronically (21d) vs. short-term (1d), % of Fos+ OT cells following the intake of the same amount of food was lower in animals regularly receiving sugar. Extended sucrose exposure also reduced % of Fos+ OT neurons in response to subsequent bland chow intake. We conclude that OT exerts specific control over sugar intake. However, continuous exposure to sugar-based reward dampens feeding-related activity of the OT system. The reduction in satiety signaling precipitated by regular sugar intake may lead to generalized overeating.

doi:10.1016/j.appet.2010.04.157

Hindbrain glucagon-like peptide-1 receptors (GLP-1R) mediate the eating-inhibitory effect of hepatic portal vein (HPV) GLP-1 infusions

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Intrameal, HPV GLP-1 infusions selectively reduced ongoing meal size [Rüttimann et al. (2009), Endocrinology 150, 1174] and increased the number of c-Fos expressing cells in the area postrema and nucleus of the solitary tract under comparable conditions [Baumgartner et al. (submitted), J. Neuroendocrinol.). This suggests that hindbrain GLP-1R are involved in the eating-inhibitory effect of circulating GLP-1. Here we examined this possibility by testing the effect of intra-fourth ventricular (IC4V) injections of the GLP-1R antagonist exendin 9-39 (Ex-9) on the eating-inhibitory effect of HPV GLP-1 infusions. Adult male rats (n = 8) received IC4V Ex-9 (10 μg) or vehicle (Veh) injections 2–1 h before dark onset and intrameal GLP-1 (1 nmol/kg) or Veh infusions by remote control during the first spontaneous nocturnal meal. As previously, intrameal HPV GLP-1 infusion reduced (P < 0.05) meal size vs. Veh (Veh/Veh: 4.5 ± 0.8 g, Veh/GLP-1: 2.7 ± 0.9 g; mean ± SEM). IC4V injection of Ex-9 alone did not significantly affect meal size (Ex9/Veh: 4.0 ± 0.9 g), but blocked the eating-inhibitory effect of HPV GLP-1 (Ex-9/GLP-1: 3.7 ± 0.9 g vs. Veh/GLP-1: 2.7 ± 0.9 g, [Veh/Veh]–[Veh/GLP-1] vs. [Ex9/Veh]–[Ex9/GLP1], P < 0.05). Subsequent eating was not affected by any treatment. These data indicate that hindbrain GLP-1R are involved in the eating-inhibitory effect of HPV GLP-1, but that activation of these receptors is not necessary for the control of spontaneous meal size under the present conditions.

doi:10.1016/j.appet.2010.04.158

Hindbrain orexin A treatment increases meal size and attenuates amylin-induced anorexia

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The neuropeptide orexin-A (ORXA) increases food intake when injected into the cerebral ventricles. Most research has focused on orexin receptors in the forebrain, however, orexin neurons project to the caudal brainstem and 4th-ventricular (4th-icv) injection of ORXA increases food intake. To further investigate the effects of hindbrain ORXA on ingestion, we performed a dose-response analysis in rats consuming standard chow (n = 7–9). When injected 4th-icv shortly before dark onset, 0.05 and 0.1 nmol ORXA significantly increased the size of the first meal relative to vehicle (by 29 and 51%, respectively), but the effect of 1 nmol (28%) was not significant. The lower doses did not affect the interval between the first and second meals, but 1 nmol significantly reduced the inter-meal interval by 50%. These data support the suggestion that hindbrain ORXA may increase intake by limiting satiation at lower doses and satiety at higher doses. Because an intact Area Postrema is required for both ORXA and amylin to affect food intake, we asked whether 4th-icv ORXA (0.05 nmol) impairs the ability of IP amylin (5 μg/kg) to reduce intake (n = 8). Amylin significantly reduced intake during the first meal of the dark cycle (vehicle/vehicle mean 6.0 ± 0.79 g; vehicle/amylin mean 3.41 ± 2.7 g), and this effect was completely blocked by 4th-icv ORXA pre-treatment (ORXA/vehicle mean 7.3 ± 0.4 g; icv ORXA/amylin mean 7.2 ± 1.6 g). Based on these data, we suggest that hindbrain ORXA increases intake in part by reducing the ability of rats to respond to amylin during a meal.

doi:10.1016/j.appet.2010.04.159

GI glucose enhances "mere" exposure in humans

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Humans often dislike, reject, or are reluctant to try unfamiliar foods. This is called food neophobia. The best-documented method for reducing food neophobia is to give people repeated experience with the food, or "mere exposure". The word, "mere" usually implies that the process does not involve associative learning. But, although this strategy is very well documented we still do not understand how it works. It has been shown that animals can learn to prefer flavors that have been paired with calories supplied to the stomach. Given the existence of gut glucose receptors and a variety of metabolic sequelae, we asked whether we might get a stronger exposure effect for beverages that are accompanied by glucose calories as compared with beverages that are accompanied by no calories (cellulose). This would be an associative mechanism for "mere exposure". Glucose and cellulose were delivered by gelatin capsules consumed 10 min prior to the exposure session. There was no sweet taste. The stimuli were 4 unfamiliar, disliked, unsweetened iced teas. Participants got 20, 10, 5, or 0 exposures to the teas in a single session counterbalanced across teas. At end of the session, they rated liking for each tea. The glucose capsule group had significantly higher liking ratings for the teas than did the cellulose group ($F(1,94) = 9.5$ ($P = 0.003$)). Our conclusion is that in humans, post ingestional glucose enhances the exposure effect in the absence of sweet taste. We believe that our technique for providing nutrients to the gut will become a useful tool.

doi:10.1016/j.appet.2010.04.160

Forebrain circuits and control of feeding by learned cues

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Appetite and eating are not only driven by energy needs, but also by extrinsic factors unrelated to energy balance. Environmental signals such as learned cues can override homeostatic signals to stimulate eating in sated states, or inhibit eating in states of hunger. Such influences are important, as environmental rather than genetic/metabolic factors are believed to underlie the increased susceptibility to overeating and the rise in obesity in the developed world. Similarly, environmental and social factors critically interact with the genetic/biological background to contribute to the onset and maintenance of anorexia nervosa. Nevertheless, how learning enables environmental cues to control feeding, and the underlying brain mechanisms are poorly understood. We developed two rodent models to study how environmental cues are integrated with homeostatic signals within functional forebrain networks, and how these networks are modulated by experience. In one model, a cue previously paired with food when an animal was hungry induces eating in sated rats. In the other model, food-deprived rats inhibit feeding when presented with a cue that signals danger, such as a tone previously paired with footshocks. Evidence will be presented that the forebrain network formed by the amygdala, lateral hypothalamus and medial prefrontal cortex mediates cue-driven feeding, while a parallel amygdalar circuitry mediates suppression of eating by the aversive cue. Findings from these animal models will be informative for understanding aspects of motivational control of appetite and eating in humans, including maladaptive mechanisms that contribute to overeating and anorexia.

doi:10.1016/j.appet.2010.04.162

Salt intake sensitization and gene expression of the hypothalamic renin–angiotensin system

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Sodium intake occurs either as a spontaneous or an induced behavior, which is increased by repeated episodes of water deprivation followed by partial rehydration (WD-PR). In this work, we investigated changes in the hypothalamic RAS mRNA in rats that had a history of WD-PR. Adult male Holtzman rats ($n = 6$–12/group) had water and 0.3 M NaCl measured daily. The animals were submitted to 1 or 3 episodes of WD-PR, with 7-day interval among the three episodes. The animals were sacrificed at the end of the 1st or 3rd WD-PR (dehydrated) or four days after none, 1st, or 3rd WD-PR (hydrated). The hypothalamus was dissected and expression level of mRNA for components of the RAS was determined by qRT-PCR. Dehydrated animals increased their hypothalamic mRNA encoding of angiotensinogen, aminopeptidase N, ANG II receptor type-1-associated protein, ANG receptor like-1 or apelin receptor by 43%, 60%, 36%, and 159%, respectively, in the 3rd versus the 1st WD-PR. There was not any difference in the hypothalamic gene expression of RAS among hydrated animals. The 0.3 M NaCl intake was enhanced in the 3rd compared to the 1st sodium appetite test in a separate group. These data suggest that enhancement in the induced sodium intake is associated with alterations in gene expression related to RAS in the hypothalamus. Therefore, hypothalamic ANG II and apelin may play a role in the long-term changes of sodium appetite. Research supported by FAPESP and CNPq.

doi:10.1016/j.appet.2010.04.161

Early life overfeeding alters palatable food intake in response to tail pinch stress in adulthood

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Palatable food is related to obesity, but little is known about how neonatal overfeeding impacts its consumption in adulthood. We aimed at verifying feeding behavior in this model under different situations. Rat litters were standardized to 4 (reduced litter – RL) or 8 pups (control – CL) at postnatal day 1. Weaning was done at day 21, and all tests were conducted after day 60 of life. Prior to testing, rats were habituated to the sweet pellets. Chow consumption was measured at baseline, in response to 24 h fasting, in the presence of palatable food, during social isolation and after 1 min tail pinch stress. Locomotion was assessed in an automated box. RL rats were heavier than CL and had increased abdominal fat. Locomotor activity was not different in regard to total distance, but RL rats spent more time in the center, an indicative of less anxiety ($P = 0.036$). No difference was found in chow ($P = 0.085$) or sweet food intake at baseline ($P = 0.65$). RL rats also did not eat more in the presence of sweet ($P = 0.085$), in response to fasting ($P = 0.36$) or social isolation ($P = 0.085$), but had higher intake in response to tail pinch stress (test × group interaction, $P = 0.006$). Exposure to overfeeding during the neonatal period decreases anxiety, induces obesity and programs the feeding behavior persistently, in such a way that the animals eat more palatable food in response to an acute stressor related to accumbal dopamine.

doi:10.1016/j.appet.2010.04.163

Amylin induces ERK 1/2 phosphorylation in structures of the AP/NTS-LPB-Ce-BSTL axis

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Peripheral amylin inhibits food intake via activation of the area postrema (AP). The extracellular-signal regulated kinase 1 and 2 (ERK) cascade mediates cholecystokinin anorexia via the nucleus of the solitary tract (NTS). Amylin induces ERK phosphorylation (pERK) in osteoclasts, so it might also activate this cascade in AP neurons. Further, previous studies had shown that a high number of amylin activated neurons in the AP are noradrenergic as they express dopamine-beta-hydroxylase (DBH). Hence, we investigated in immunohistochemical experiments whether amylin activates the ERK cascade in the AP and downstream, in synaptically activated areas. Furthermore, we phenotyped the pERK-positive AP-neurons using DBH as a marker for noradrenergic neurons. To evaluate the time-course of amylin-induced pERK, we injected 24 h fasted rats with saline or amylin (5 or 20 μg/kg, SC) and perfused the animals 10, 15, 20 or 30 min later. Brain sections containing the AP, NTS, lateral parabrachial nucleus (LPB), central nucleus of amygdala (Ce) and lateral bed nucleus of stria terminalis (BSTL) were stained for pERK. The peak of ERK phosphorylation in the AP occurred between 10 and 15 min after amylin treatment; 22% of pERK-positive neurons in the AP were noradrenergic. The other analyzed areas also showed amylin-induced pERK. These results show that amylin stimulates pERK in the AP-BSTL axis and that a subpopulation of amylin-responsive AP neurons are noradrenergic. These findings suggest a potential role of pERK signaling in amylin's anorectic effect.

doi:10.1016/j.appet.2010.04.164

Centrally administered QRFP-26 increases high fat intake in female rats

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QRFP is strongly conserved across vertebrates and is a member of the RFamide-related peptides, with the motif Arg-Phe-NH_2 at the C-terminal end. In rodents, QRFP is expressed in localized regions of the mediobasal hypothalamus which are abundant in neurotransmitters, neuropeptides and receptors systems that are important for food intake regulation and reproductive behaviors. Our previous experiments have reported an increase in the intake of a high fat diet (HFD), but not a low fat diet (LFD) in male rats following central administration of QRFP-26. The current experiments were conducted to investigate the effects of centrally administered QRFP-26 on the intake of a HFD (60% kcal from fat) in female rats and to determine if hypothalamic QRFP mRNA levels were affected by estrous cycle. In Experiment 1, randomly cycling female rats were administered varying doses of QRFP-26 (0.3 nM, 0.5 nM, 1.0 nM) via lateral ventricle cannula. All doses of QRFP-26 administered increased the intake of the HFD, but not LFD (10% kcal from fat) in female rats. In Experiment 2, estrous cycle was monitored daily and brains were removed during diestrous, proestrous, or estrous. Real-time PCR was used to determine the levels of prepro-QRFP mRNA in specific regions of the hypothalamus (paraventricular nucleus, lateral hypothalamus, and ventromedial/arcuate nucleus (VMH/ARC)). The level of prepro-QRFP mRNA in the VMH/ARC was affected by estrous cycle, and was increased during proestrous. These data suggest that QRFP-26 plays a role in both feeding behavior, specifically high fat feeding, and reproductive status in female rats.

doi:10.1016/j.appet.2010.04.165

CD36 receptor expression on the tongue is differentially affected by high fat diet in obesity-prone and obesity-resistant rats

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There are individuals that are susceptible to becoming obese when consuming a high-fat diet (HFD), while others are resistant to becoming obese when consuming a HFD. The detection of dietary fat in the mouth plays an important role in the consumption of dietary fat. Therefore, individual differences in the detection of dietary fat by the mouth are probable. The current experiment was conducted to determine differences in the expression of the fatty acid receptor, CD36, on the tongues of obesity-prone (Osborne-Mendel; OM) and obesity-resistant (S5B) rats fed a HFD. OM and S5B rats were fed either a standard chow diet, a HFD or a low fat diet (LFD) for 1 day, 3 days or 14 days. CD36 receptor mRNA expression was measured by real-time PCR from the circumvallate papillae of the tongue, which has been shown to have the highest concentration of CD36 receptor mRNA on the tongue. CD36 receptor mRNA levels did not differ between OM and S5B rats fed a chow diet. In S5B rats, CD36 receptor mRNA levels on the circumvallate papillae were increased within 1d of access to the HFD, however, this effect was transient and was diminished by 3d. Unlike S5B rats, OM rats did not exhibit an initial increase in CD36 receptor mRNA levels on the circumvallate papillae following 1d access to the HFD. The consumption of a HFD increased CD36 receptor mRNA levels on the circumvallate papillae of OM rats at 3d and 14d. These data suggest that HFD affects CD36 receptor mRNA expression in a time and strain dependent manner and may play a role in the detection of HFD by the mouth.

doi:10.1016/j.appet.2010.04.166

Differential effects of high-energy diets on sensitivity to dopamine receptor antagonists in reducing intake of sucrose and fructose in rats

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To investigate how high energy diets influence the reward system's responsiveness to palatable carbohydrates (CHOs), Sprague–Dawley male rats were fed high fat low CHO (60 and 20%kcal, 4.1 kcal/g, VHF; $n = 11$) or moderate fat high CHO (32 and 51%kcal, 4.6 kcal/g, HFHC; $n = 11$) or chow (3.3 kcal/g, $n = 8$) for 24 weeks. 2-h one-bottle intake of isocaloric 0.3 M sucrose and 0.4 M fructose was tested following i.p. administration of equimolar doses (0, 50, 200, 400, 600 nmol/kg) of dopamine D1 (SCH23390; SCH) or D2 (Raclopride; RAC) receptor antagonists. Whereas both antagonists reduced CHO intake dose-dependently, the effects varied with respect to the diets and test solutions. SCH suppressed intake of sucrose equally in all diet groups. For fructose, SCH only reduced intake at higher concentrations, with VHF rats being more sensitive (40% vs. 20–25% reduction at 200 nmol/kg, $p > 0.001$). Except at the highest dose, RAC produced significant effects for sucrose only in VHF rats (200 nmol/kg: 61%, $p > 0.01$; 400 nmol/kg: 57%, $p > 0.01$). In contrast, for fructose the HFHC rats showed the largest suppression of intake to RAC (200 nmol/kg: 49%, $p > 0.01$; 400 nmol: 45%, $p > 0.001$; 600 nmol: 44%, $p > 0.001$), while VHF rats were insensitive to all but 600 nmol/kg. These findings show that dietary fat and CHOs coupled with chronic high energy intake may alter dopamine signaling, and that ingestion of fructose and sucrose may recruit different mechanisms of reward.

doi:10.1016/j.appet.2010.04.167

Gestational stress and high-fat diet effects on maternal behavior, milk composition, pup ingestive behavior and hypothalamic gene expression

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Offspring of prenatally stressed or high-fat diet fed dams have increased body weight and adiposity and are predisposed to diet-induced obesity in adulthood. In this study we characterized the effects of these treatments on maternal behavior, milk composition, pups independent ingestion and hypothalamic neuropeptide expression. Pregnant female rats fed standard chow or high-fat (60%) diet were subjected to a variable stress paradigm in the 3rd week of gestation (CH-STRESS, HF-Stress) or left undisturbed (CH-CON, HF-CON). STRESS dams show less maternal licking and grooming during postnatal week 1 while HF dams show increased arched-back nursing and licking and grooming in week 2. Milk from HF-fed dams had greater fat content than that of CH-fed dams at PND 21. Offspring of both CH-STRESS and HF-STRESS dams had increased milk uptake in an independent ingestion test at PND 3 but showed no difference by PND 10. Pups from HF-fed dams have increased PVN CRH and decreased arcuate NPY expression at PND 21. Pups from STRESS dams had decreased DMH NPY expression on PND 21. Taken together these data suggest that maternal diet and stress alters maternal behavior, and offspring neuropeptide expression in ways that may contribute to increased susceptibility to diet-induced obesity in offspring. Supported by NIH Grants HD055030, DK077623.

doi:10.1016/j.appet.2010.04.168

Nitric oxide contributes to LPS-induced anorexia

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Nitric oxide (NO) is a pro-inflammatory neuromodulator which is produced in the arcuate nucleus (ARC) by inducible nitric oxide synthase (iNOS) in response to the endotoxin lipopolysaccharide (LPS). NO inhibits ghrelin-excited ARC neurons pointing to a possible involvement of NO in disease-related anorexia. We therefore evaluated whether the specific iNOS inhibitor 1400W counteracts the anorectic effect of LPS in rats. In addition we investigated whether LPS-induced anorexia is associated with STAT3 phosphorylation in the ARC. In part of the rats, LPS tolerance was induced by repeated LPS treatment. Rats that received a peripheral 1400W injection (10 mg/kg sc) showed a lower LPS-mediated suppression of food intake than untreated controls. 1400W treatment also attenuated LPS-induced adipsia and it increased physical activity. LPS-induced anorexia was paralleled by a STAT3 phosphorylation in the ARC starting 2–4 h after LPS treatment. LPS did not suppress feeding in rats that were repeatedly (3×) injected with LPS. The loss of LPS-induced anorexia was associated with a blunted pSTAT3 response in the ARC in these rats. This study provides evidence that NO contributes to disease-related anorexia and associated sickness symptoms. A pharmacological blockade of NO formation might be a therapeutically useful approach to prevent disease-related anorexia. STAT signalling might be part of in the pro-inflammatory cascade suppressing food intake. Although STAT is involved in the transcriptional regulation of iNOS expression, the functional link between pSTAT3/NO formation in the ARC and the inhibition of feeding remains to be confirmed.

doi:10.1016/j.appet.2010.04.170

Effects of glycine-extended and serine^{13}-phosphorylated forms of peptide YY on food intake in rats

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Peptide YY (3-36) [PYY(3-36)] is significantly more potent than PYY(1-36) in decreasing food intake in rats and humans. Other Glycine-extended and Ser^{13}-phosphorylated PYY forms have been detected or predicted based upon known cellular processes of PYY synthesis and modification. We previously showed that 3-h IV infusion of PYY(3-36) at dark onset decreased feeding in rats with free access to food with an estimated mean effective dose of 15 pmol/kg/min, while PYY(1-36) was an order of magnitude less potent than PYY(3-36). Here we compared the effects of 3-h IV infusions of PYY(1-36), PYY(3-36), PYY(1-36)-Gly, PYY(3-36)-Gly, Ser^{13}PO$_3$-PYY(1-36), Ser^{13}PO$_3$-PYY(3-36), Ser^{13}PO$_3$-PYY(1-36)-Gly, and Ser^{13}PO$_3$-PYY(3-36)-Gly on food intake in rats under the same experimental conditions. PYY(3-36) and Ser^{13}PO$_3$-PYY(3-36) similarly inhibited food intake at 50 pmol/kg/min, while PYY(3-36), but not Ser^{13}PO$_3$-PYY(3-36), inhibited food intake at 15 pmol/kg/min. PYY(1-36)-Gly, PYY(3-36)-Gly, Ser^{13}PO$_3$-PYY(3-36)-Gly, and Ser^{13}PO$_3$-PYY(1-36)-Gly had no effect on food intake at doses of 50 or 150 pmol/kg/min. Taken together, these results indicate that (i) PYY(3-36) is an order of magnitude more potent than PYY(1-36), (ii) Gly-extended forms of PYY are significantly less potent than non-extended forms, and (iii) Ser^{13}-phosphorylation of PYY(3-36) decreases its anorexigenic potency. Thus, PYY(3-36) appears to be the most potent PYY form for reducing food intake in rats. Supported by NIH DK073152 and Medical Research Service of Department of Veterans Affairs.

doi:10.1016/j.appet.2010.04.169

Examining food memories. Relationships between experienced and remembered enjoyment

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Food choice is often dependent on remembered enjoyment of food so there is a need to examine how we construct memories of past eating experiences. Previous research has suggested that the peak, trough, beginning and end of an experience may be important in shaping affective memory. The present study examined the relationship between online rated experience and remembered enjoyment of a meal. Forty participants (26 female, 14 male; 18–33 years old) ate a standardised 5-item lunch. Piloting ensured the amount of time taken to eat each food item was similar across the 5 items. Each participant ate the foods in the same order and after eating a food item (Quiche, carrot sticks, potato chips, pastry and pretzels) they rated how enjoyable the item was (online measure of enjoyment). Participants returned 2 h later and rated their overall enjoyment of the meal. Averaged online rating for the 5 items, the rating of the last item, first item, trough (lowest item rating) and peak (highest item rating) were entered into regression analysis as potential predictors of remembered meal enjoyment. Analysis revealed that participant's rating of the most enjoyable food item (peak) was the only significant predictor of overall remembered enjoyment. Including the 4 additional predictors in the regression model resulted in no significant increase in explained variance. These data suggest that remembered enjoyment of a multi-item meal is largely dependent on experienced enjoyment during the best part of the meal. Hence meals that contain at least one highly liked item are likely to be remembered positively.

doi:10.1016/j.appet.2010.04.171

Does increasing the variety of vegetables served at a meal influence vegetable intake?

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Previous research has shown that increasing the variety of available foods leads to increased intake; yet few studies have determined whether increased variety can be used strategically to promote intake of low-energy-dense foods such as vegetables. The present study tested whether the number of vegetables served at a meal influences vegetable consumption and energy intake. Once a week for 4 weeks, 66 adults (34 women; 32 men) were served a meal consisting of 600 g pasta (energy density 1.57 kcal/g) and 600 g cooked vegetables (mean ED 0.52 kcal/g) using a counterbalanced design. At 3 meals the pasta was served with a single vegetable (broccoli, carrots, or snap peas) and at the other meal 200 g each of the 3 vegetables was served. The results showed that subjects ate significantly more vegetables when served the variety than when served any single type (mean 49 ± 9 g; $p = 0.038$). The increase in vegetable intake remained significant when the variety condition was compared to each subject's preferred vegetable (mean 23 ± 7 g; $p = 0.002$). Men consumed significantly less energy at the meal when broccoli or carrots were served than when peas or a variety of vegetables were served (mean 80 ± 17 kcal; $p < 0.04$), but meal energy intake in women did not vary significantly across conditions. The weight status of the participants did not significantly influence the effect of variety on intake. The results of this study suggest that increasing the variety of low-energy-dense vegetables served at a meal can be used as a strategy to increase vegetable intake. Support: DK059853.

doi:10.1016/j.appet.2010.04.172

Does the timing of consumption of a low-energy-dense food influence meal energy intake?

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Previous studies showed that consuming a low-energy-dense food as a first course reduced meal energy intake. In the present study we hypothesized that this effect depends on the interval before the test meal, and that satiety mechanisms are engaged to a greater extent by consuming the food at the start of a meal rather than with the main course. Once a week for 5 weeks, 45 women were served a meal of pasta, which was consumed as desired, and a low-energy-dense salad (300 g; 100 kcal). At two meals the salad was served 20 min before the main course; one time subjects were instructed to consume the salad in full and once to consume it as desired. At two other meals the salad was served along with the main course; again, one was consumed in full and one was consumed as desired. At one meal no salad was served. The results showed that subjects ate more of the discretionary salad when it was served as a first course (217 ± 10 g) than when it was served with the main course (180 ± 11 g; $p = 0.0007$). Meal energy intake, however, did not differ significantly when the salad was served as a first course compared to when it was served with the main course, for either the discretionary salad (511 ± 22 versus 510 ± 28 kcal) or the compulsory salad (477 ± 26 versus 476 ± 23 kcal). Compared to having no salad, consuming the compulsory salad resulted in a mean decrease in meal energy intake of 58 ± 19 kcal ($p < 0.015$). These results show that the effect of a low-energy-dense food on meal energy intake was not influenced by the timing of consumption. Supported by DK039177.

doi:10.1016/j.appet.2010.04.173

Sweet and polycose taste preferences of FHH-Chr n^{BN} consomic rats

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Each strain comprising the FHH-Chr n^{BN} consomic set has a chromosome from the Brown Norway (BN) rat strain introgressed onto a Fawn Hooded Hypertensive (FHH) rat strain background. Thus, a difference between a consomic strain and the FHH strain reveals the chromosomal location of a gene or genes responsible for trait variation. In this study, we exploited the FHH-Chr n^{BN} strain set to identify the chromosomes responsible for variation in taste preferences. Groups of 5–15 adult male rats from the FHH, BN, and each of 22 consomic strains (Chr 1–20, X and Y) received a series of 4-day two-bottle tests with a choice between water and several taste solutions, including 1 mM saccharin, 32 mM sucrose and 1% Polycose. Saccharin consumption was influenced by genes on Chr 4, 10, 11, 16 and 17; sucrose consumption was influenced by genes on Chr 5, 11, 16, 17, and Y; Polycose consumption was influenced by genes on Chr 6 and 7. The chromosomes influencing the response to both sweeteners (Chr 11, 16, and 17) do not harbor genes implicated in sweet taste transduction in the mouse, including *Tas1r2* and *Tas1r3* (on Chr 5), *Gnat3* (gustducin; on Chr 4), *Trpm5* (on Chr 1) or *Plcb2* (on Chr 3). The responses to sweeteners and to Polycose involved different chromosomes, which supports the notion of a distinct mechanism governing Polycose intake. This is the first study to identify the chromosomal contribution to sweet and Polycose consumption in the rat. Supported by NIH RO1 DC-10149. The rats were provided by a Seed Grant Program sponsored by Physiogenix Inc.

doi:10.1016/j.appet.2010.04.174

Body weight regulation. "Why is it so hard to keep weight off?

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Following experimental underfeeding or overfeeding, humans rectify body fat spontaneously thus suggesting that energy homeostatic systems are sensitive to signals relevant to both short-term (e.g., glucose) and long-term (e.g., leptin) energy status. We have examined responses to sustained weight loss of 10% or more while regulating such potentially confounding factors as diet composition, weight stability, and physical activity. Reduced weight maintenance in lean or obese individuals is associated with sustained decreases in energy expenditure below those predicted by changes in body composition, and reflects autonomic (decreased sympathetic and increased parasympathetic nervous system tone), neuroendocrine (decreased circulating concentrations of bioactive thyroid hormones and leptin), metabolic (increased skeletal muscle work efficiency), and behavioral (delayed satiety, increased food-related neuronal activity in brain areas involved in the emotional and cognitive responses to food, and decreased activity in areas involved in restraint) changes which conspire to restore energy stores to pre-weight loss levels[1,2] and many of which are reversed by administration of "replacement doses" of the adipocyte-derived hormone leptin. These observations are informed by – and consistent with – studies of leptin and weight loss physiology in animals and support the hypothesis that the weight-reduced state is "perceived" by leptin-sensitive CNS pathways as one of relative leptin deficiency resulting in predicable coordinate changes in energy homeostasis that oppose the maintenance of a reduced body weight. Research relating to this abstract was funded by the National Institutes of Health (grants DK 64473, DK 26687, and UL1 RR024156). A-100 leptin and metreleptin were generously provided by Amgen, Inc., Thousand Oaks, CA and by Amylin Pharmaceuticals Inc., San Diego, CA.

doi:10.1016/j.appet.2010.04.175

Role of social influence in childhood obesity

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There is emerging evidence that youth's social network may be uniquely relevant and influential to eating behavior and choice of activities. Individuals are influenced by the eating and activity norms set by those around them and friendship and peer relationships can either maintain obesigenic behaviors or reinforce healthier eating and activity habits. This oral presentation, consisting of descriptions of laboratory and field studies, summarizes the research on the effects of social influence on the control of intake (food consumption), food selection (with an emphasis on food choices and preferences) and choices of sedentary and physically active leisure activities. Drawing from these findings and from the work of others we contend that decreasing sedentary behavior and increasing active leisure activities may require the social structure of meaningful relationships with friends, as friendship may help to promote or "socialize" active lifestyles. Attempts to substitute physical activity for sedentary behavior may not be effective if problematic peer relationships persist, in part because sedentary activities are more reinforcing, easily accessible, easily performed alone and less threatening for socially isolated youths. Conceivably, the involvement of children's social ecology in prevention efforts is a promising approach to set the stage for health trajectories.

doi:10.1016/j.appet.2010.04.176

Estradiol decreases the orexigenic strength of the melanin concentrating hormone (MCH) system through indirect changes in MCH and MCH receptor (MCHR1) protein expression

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Previously, we demonstrated that MCH-induced feeding is decreased by the rise in estradiol secretion in cycling rats and by estradiol treatment in ovariectomized (OVX) rats. Because estradiol binds to nuclear estrogen receptors (ERs) that are capable of influencing gene expression, we hypothesized that estradiol suppresses MCH signaling by decreasing MCH and/or MCHR1 expression. In support of this hypothesis, both endogenous and exogenous estradiol reduced hypothalamic MCH and MCHR1 protein expression (assessed via immunocytochemistry (ICC) and western blot) in cycling and OVX rats, respectively (*P*s < 0.05). In a second experiment, we determined whether these actions of estradiol occur at the level of the MCH/MCHR1 gene. Estradiol (10 nM) was directly applied to a neuronal, hypothalamic, cell line (N-42) that expresses ERs, MCH and MCHR1. We found, however, that estradiol failed to decrease either MCH or MCHR1 gene expression *in vitro*. This finding was further supported by a subsequent experiment involving *in vivo* ICC in which we determined that while MCH and ERα are both expressed in the lateral hypothalamus (LH) and zona incerta, they are not co-localized within the same neurons. In a final experiment, we determined that microinfusions of 2.5 μg estradiol directly into the LH failed to decrease MCH's orexigenic effect in OVX rats. Taken together, these studies demonstrate that estradiol decreases MCH signaling by decreasing MCH and MCHR1 protein expression via an indirect mechanism residing outside of the LH.

doi:10.1016/j.appet.2010.04.177

Pilot intervention promoting responsive feeding, the division of feeding responsibility, and healthy dietary choices during infancy

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Parents' feeding practices play a critical role in the development of children's food preferences and dietary intake. This research examined the effect of a behavioral intervention designed to teach parents about responsive feeding, division of feeding responsibility, and making healthy dietary choices. Mother–infant dyads ($n = 110$) intending to breastfeed were randomized to receive an intervention that taught parents about the timing and methods for the introduction of solids and how to overcome food neophobia, using repeated exposure to improve liking and acceptance of unfamiliar foods such as vegetables. Parents reported when complementary foods were introduced. Infant feeding video-taped data were collected at age 1. Results revealed that only 17% of the intervention group introduced solids before 4 months of age compared with 34% of the control subjects ($p = 0.06$). More babies in the intervention group (42%) did not consume desserts or sweets in the past week compared to the control. Within the intervention group, infants showed significantly greater consumption of green beans ($p < 0.001$), peas ($p < 0.05$), and squash ($p < 0.05$) from the first to last day of exposure. At 1 year, only 10% of infants in the intervention group rejected an unfamiliar food at age 1 year compared to 25% of the control group ($p < 0.05$). These findings indicate that this behavioral intervention successfully trained parents to delay the introduction of solids and increased infant acceptance of vegetables and novel foods.

doi:10.1016/j.appet.2010.04.178

Personality as a risk factor for developing obesity and insulin resistance

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We investigated the interactions between personality and diet as risk factors for developing insulin resistance and hypothesized that rats characterized by a passive coping style are more susceptible for developing insulin resistance and visceral obesity than proactive coping rats. This hypothesis was tested by comparing insulin and glucose responses to an intravenous glucose tolerance test (IVGTT) and body fat distribution in passive and proactive personalities from two different rat strains (Roman High and Low Avoidance rats and Wild Type Groningen rats). We found that the most extremely passive individuals are characterized by elevated insulin levels during a IVGTT, even on chow. Moderate passive individuals display normal insulin responses under chow conditions, but develop insulin resistance on a palatable medium fat (45%) diet. Carcass analysis revealed that passive individuals are also characterized by increased epididymal fat deposition. Proactive individuals are remarkably resistant to insulin resistance and visceral obesity, even when overfeeding on a medium fat diet. We conclude that a passive personality is prone to develop insulin resistance and visceral obesity on a palatable fat diet and that a proactive personality might be protected against the development of diet-induced insulin resistance. In our most recent studies we investigated, both in rats and humans, whether personality may also serve as an important factor determining the success of life style intervention programs and found that in particular passive individuals may benefit from these programs.

doi:10.1016/j.appet.2010.04.179

Diacylglycerol acyltransferase-1 (DGAT-1) inhibition reduces food intake and blunts postprandial increases in circulating fat metabolites in high fat diet (HFD)-fed rats

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DGAT-1 catalyzes the final step in triglyceride (TG) synthesis. DGAT1-deficient mice show increased energy expenditure and resistance to diet-induced obesity, but the role of DGAT1 in the control of eating has not been systematically studied. We have investigated the effects of a DGAT1-inhibitor (DGAT1-I) on eating, circulating metabolites and gastric emptying in rats adapted to an 8 h feeding-16 h deprivation schedule. Intragastric (IG) infusions of DGAT1-I (3 and 9 mg/kg BW) reduced food intake (18% and 21%, respectively, 8 h postinfusion) in HFD-fed, but not in chow-fed rats. IG DGAT1-I infusion (9 mg/kg) prior to a 5 g HFD meal offered at the onset of the 8 h feeding period blunted the increases in circulating TG, glycerol and free fatty acid levels and increased β-hydroxybutyrate levels compared to vehicle, suggesting a metabolic shift from TG synthesis to fatty acid oxidation. Under similar conditions, DGAT1-I inhibited gastric emptying of a 2 g HFD test meal containing 1% (w/w) paracetamol as indicated by the postprandial appearance of paracetamol in the plasma. Also, DGAT1-I inhibited eating both in rats after subdiaphragmatic vagal deafferentation or sham surgery, indicating that vagal afferent signaling is not the major mechanism for the eating-inhibitory effect of IG DGAT1-I. Thus, pharmacological inhibition of DGAT1 acutely inhibits eating in rats, but the mechanism of this effect remains to be identified.

doi:10.1016/j.appet.2010.04.180

Long term obesity moderation in OLETF rats by post-weaning time-specific food restriction

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OLETF rats are a model of early onset hyperphagia-induced obesity. OLETF males show earlier "turning-points" of increased obesity than females (around postnatal day [PND] 48 and 90, respectively). We attempted to bias their obesity tendency towards a more "lean" and healthy adulthood. OLETF males and females underwent food restriction (pair-feeding to LETO intake levels) from weaning (PND 22) until PND 90 (chronic group), or from weaning (PND 22) until PND 45 (early group). Additional females were pair-fed between PND 45-70 (late group). The long-term influence of these manipulations on body weight, intake, adiposity and selected hormonal levels was examined. The results suggest that: (a) OLETF rats (both sexes) are normalized by chronic food restriction, with sex-differences in peripheral adaptations regarding adipocyte morphology; (b) the early manipulation successfully reduced body weight and intake in both sexes, but achieved significant long term reduction in adiposity only in males; and (c) selective food restriction around adolescence in the females did not produce any beneficial effects and even induced long lasting hyperphagia (beyond regular OLETF levels) and significant reduction in lean body mass as reflected by low creatinine levels. The findings suggest a time frame when interventions can potentially moderate the males' obesity. However, females strongly adhere to their genotype and present resistance to adiposity loss through peripheral adaptations in adipose tissue allowing them to retain high adiposity levels even when food restricted.

doi:10.1016/j.appet.2010.04.181

An environmental cue to eat slowly reduces food consumption

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Simple environmental cues that indicate how much food has been eaten during a meal have been shown to reduce food intake. The purpose of this study was to examine the effect of bite-rate feedback, an environmental cue that indicates eating speed, on the amount of food consumed during a breakfast meal. Thirty university students participated in a repeated-measures laboratory experiment with four conditions: Orientation, Baseline, Feedback, and Feedback with Target. In the two feedback conditions, real-time bite-rate was displayed on a computer monitor as a simple step-graph, with time on the *x*-axis and bites on the *y*-axis. Bite size was held constant across all meals. In the Feedback with Target condition, the participant was given a bite-rate target 50% slower than their baseline rate. A repeated measures ANOVA revealed a significant difference in the total grams of food consumed between the four conditions, $F(3,87) = 2.75$, $p < 0.05$, $\eta^2 = 0.09$. Least significant difference (LSD) post hoc tests indicated that the Feedback with Target condition ($M = 113.59$ g, $SE = 10.25$ g) resulted in significantly fewer grams of food consumed than the Feedback condition ($M = 135.94$ g, $SE = 11.67$ g; $t(29) = -3.54$, $p = 0.001$). The results suggest that our bite-rate feedback method paired with a slow target bite-rate can reduce food consumption. However, bite-rate feedback alone may not be an adequate environmental cue for changing eating behavior.

doi:10.1016/j.appet.2010.04.182

Techniques associated with assisted reproductive technologies alter growth and glucose metabolism of mice

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It is estimated that ~3% of births worldwide have occurred through assisted reproductive technologies (ART). Although the majority of these children appear healthy, data suggest increased rates of imprinting disorders, and a susceptibility to metabolic disturbances. Previous data show that mice exposed as embryos to *in vitro* culture and embryo transfer weigh more than control mice in adulthood. In this study we determined whether manipulations commonly used in ART affect growth and glucose metabolism of mice. At birth, male and female mice generated through *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) weighed more than naturally bred mice (STOCK), although this difference disappeared shortly after birth. At 8 weeks of age, IVF males and females exhibited increases in basal and/or glucose-stimulated plasma insulin, despite similar body weights and body composition. At 9 weeks of age, male and female IVF and ICSI mice weighed more than STOCK mice, and this persisted throughout the 24 week study. At 20 weeks of age, male and female ART mice exhibited modest elevations in plasma insulin levels in response to a glucose challenge. Male and female IVF mice had significantly more adiposity and higher plasma leptin levels compared to STOCK mice at 24 weeks of age. These data suggest that *in vitro* manipulation of embryos results in alterations in plasma insulin and glucose handling which precede weight gain and may promote obesity in adulthood.

doi:10.1016/j.appet.2010.04.183

Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men

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In humans, both taste perception and feedback from the gastrointestinal (GI) tract contribute to energy intake regulation. GI responses to nutrients may be reduced in the obese, potentially contributing to increased energy intake. It is not known whether individuals who are less sensitive to the presence of fat in the small intestinal lumen also exhibit reduced sensitivity to fat in the oral cavity. We hypothesised that obese subjects would be less sensitive to both oral and small intestinal fat than lean subjects, reflected by a reduced ability to taste fat and lower GI motor, hormone and appetite responses to intraduodenal oleic acid ("C18:1") in the obese. 9 obese (age 40 ± 4 years, BMI 32.4 ± 0.9 kg/m^2) and 10 lean (age 36 ± 5 years, BMI 23.8 ± 0.5 kg/m^2) males were studied on 3 occasions in single-blind, randomized order. On 2 visits, pyloric pressures and plasma CCK were measured during a 90-min intraduodenal infusion of saline ("C") or C18:1 (rate: 0.78 kcal/min), after which energy intake was quantified at a buffet lunch. On visit 3, taste sensitivity to C18:1 was evaluated. In lean subjects, pyloric stimulation was greater in response to C18:1 compared with C (number/90 min; C: 8.8 ± 1.8, C18:1: 37.7 ± 5.2) and also compared with C18:1 and C in the obese (all $P < 0.05$), with no difference between C18:1 and C in the obese. C18:1 stimulated plasma CCK in both lean and obese subjects compared with C ($P < 0.001$), with mean concentrations higher in the lean compared with the obese. C18:1 suppressed energy intake compared with C in lean subjects (C: 5174 ± 403, C18:1: 4640 ± 415 kJ; $P < 0.05$), but not in the obese (C: 5864 ± 566, C18:1: 5410 ± 549 kJ). Taste thresholds for C18:1 were lower in lean subjects compared with the obese (lean: 3.8 ± 1.2 mM, obese: 9.6 ± 0.8; $P < 0.05$). Taste thresholds were related directly to BMI ($r = 0.7$, $P < 0.05$). In addition, pyloric pressures were inversely related to oral taste thresholds ($r = -0.46$, $P < 0.05$). In conclusion, the ability to detect fats both orally and within the GI tract is compromised in obese males, and the oral and GI responses to fat are related. Further research is warranted to evaluate underlying mechanisms and whether a high-fat/high-energy intake is cause or effect to our observations.

doi:10.1016/j.appet.2010.04.184

Attentional and approach biases for food cues in normal weight, overweight, and obese individuals

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Few studies have examined eating behavior using the incentive-habit theory of addiction. The current study examined the relationship between eating behavior, incentive learning theory, and incentive-habit theory. A sample of undergraduate students completed two computer tasks. A matrix task was used to assess the participants' ability to attend to food-related pictorial cues, and a stimulus-response compatibility task measured the participants' tendency to approach food-related pictorial cues. Participants were also asked to complete a demographic questionnaire and the Eating Disorder Inventory (EDI). Height and weight for each participant was also measured for body mass index (BMI) calculations. Results evaluated comparisons between the EDI, BMI, and reaction times for each of the computer tasks. A general discussion considers the two competing theories as possible explanations for the increase of obesity in the United States.

doi:10.1016/j.appet.2010.04.185

Oscillators entrained by food and the emergence of anticipatory timing behaviors

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The suprachiasmatic nucleus (SCN) is the master circadian clock in the brain, and photic input to the SCN is important in setting phase of the brain clock. However, even at the time that the SCN was first discovered, lesion studies revealed that in nocturnal rodents, daytime restriction of food and water could set the circadian phase of responses such as plasma corticoids and body temperature, and that these rhythms persisted in SCN-lesioned animals under conditions of restricted food access. Phase setting responses to regularly recurring restricted daily feeding include both driven (phase set by external stimuli) and circadian/anticipated (phase set by internal timing mechanisms) behaviors. Relevant in the present context is evidence that the control of the behavioral and physiological responses that constitute food anticipatory activities (FAAs) is not dependent on the SCN. To understand the nature of the underlying timing mechanisms and metabolic processes involved in timing physiology and behavior, we explore the controlling signals. Our focus is on delineating daily behavioral and metabolic activities and their adjustment to the external and internal environment of the body. We review evidence that multiple cues derived from feeding/fasting normally determine the timing of sleep/wake cycles and the activities associated with these states. We suggest that numerous sources of temporal information, including hormonal cues such as corticoids, insulin and ghrelin, as well as conditioned learned responses play a role in food anticipation. Importantly, under ad libitum feeding conditions, SCN dependent circadian and non-SCN dependent temporal signals *both* contribute to modulate daily activities. The driven component may entail either oscillatory or interval-type hourglass timers. Experimental food restriction allow separation of these two components. In the absence or dysfunction of the circadian component (e.g. in SCN-lesioned or in various clock mutant animals) the driven component is enhanced. In the absence driven components (e.g. ghrelin receptor knockout or diabetic animals), the SCN-derived circadian component is enhanced. Multiple temporal signals interact to modulate daily activity rhythms. The sources of temporal information used to time behavioral and physiological responses differ among individuals, with strain and with genetic background. Sensitivity to internal and external signals varies over circadian time, time since the previous meal, time to the next meal or duration of food deprivation as well as the light–dark cycle. All of these cues are integrated in sites throughout the body and in circuits modulating physiology and behavior. At the level of the cell these changes affect metabolic processes with implications for underlying timing mechanisms. At the level of the whole organism such changes in internal and external signals are interpreted as "hunger", and activity levels and behaviors are adjusted accordingly.

doi:10.1016/j.appet.2010.04.186

Hindbrain BDNF activity reduces food intake through modulation of energy status signaling

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Brain derived neurotrophic factor (BDNF) is an essential component of the CNS circuitry controlling energy balance. BDNF activation of its high affinity receptor tropomyosin-related kinase receptor type B (TrkB) is hypothesized to play a role in the downstream mediation of the intake inhibitory effects of anorectic

signals processed within the dorsal vagal complex (DVC). However, the satiating signals engaging BDNF and the meal pattern profile following TrkB activation within the DVC remain unknown. We find that TrkB fusion protein (TrkB-Fc; 0.5 or 5.0 μg, icv), which enhances endogenous BDNF activity, reproduces the intake inhibition observed with exogenous 4th icv BDNF (0.1, 0.2, 0.5, 1.0 or 2.0 μg). Meal pattern analysis reveals that TrkB-Fc and BDNF-induced suppression in food intake occurs through reductions in meal number, with no alteration in meal size. Current experiments are evaluating whether pretreatment with K252a (TrkB antagonist, 10 μg, 4th icv) alters the intake inhibitory effects of 4th icv leptin (5 μg). The collective results suggest that unlike the prototypical within-meal satiation signals that act within the DVC, endogenous DVC BDNF activity may modulate basal energy status by inhibiting overall daily caloric intake through suppression in meal number. Supported by DK21397.
doi:10.1016/j.appet.2010.04.187

Thrifty genes and drifty genes. The evolutionary context of the obesity epidemic

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Obesity and diabetes are conditions that lead to profound negative health consequences. Yet it has also been shown that they also have a strong genetic component. A fundamental puzzle therefore is to understand how natural selection could have favoured the evolution of such disadvantageous traits. A solution to this problem was suggested over 50 years ago by the Amercian geneticist James Neel. He suggested that in our evolutionary history we would have often faced periods of food shortage. This would have favoured genes that efficiently deposit fat stores (called 'thrifty' genes) enabling people to deposit fat in periods between such food shortage and thus survive the periods without food. In modern society these genes promote fat deposition in preparation for a food shortage period that never comes—and the result is widespread obesity. A major issue with this idea is that such selection over the time scales involved would predict we should all have inherited the thrifty genes and hence we should all be obese. Yet even in western societies obesity (BMI > 30) is still less than 30% of most populations. A resolution to this problem is to suggest that there has been intense selection only since the dawn of agriculture about 15,000 years ago, during agricultural famines. The reality of famines however suggests that the mortality rates and fecundity effects are insufficient to have caused such intense selective pressure. An alternative model based on factors regulating energy balance in small rodents is that the genes favouring fat deposition have been drifting for the past 2 million years as a result of release from predation risk that accompanied the development of social behaviour, fire and weapons with the appearance of Homo erectus: the 'drifty gene' hypothesis. A direct test between these ideas is possible by interrogating the human genome to look for signatures of strong recent selection in genes that predispose to obesity. The thifty gene idea predicts such signatures of selection while the drifty gene hypothesis does not.
doi:10.1016/j.appet.2010.04.188

Mice with brown fat transplantation partially resist to diet-induced obesity and glucose intolerance

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When energy intake is greater than energy expenditure, extra calories are primarily stored in white fat and leads to obesity. In contrast, brown fat is an energy-burning type of fat that counteracts obesity. We hypothesized that increasing amount of brown fat would have beneficial effects on energy homeostasis. Six groups of male C57BL/6 mice were matched for weight, body fat, fasting glucose, and areas under glucose curves during intraperitoneal glucose tolerance tests (ipGTT). Interscapular brown adipose tissue (IBAT) from 2 donor groups was added into subcutaneous regions of 2 recipient groups; 2 groups were sham-operated. After surgeries, a group of sham mice and recipients were switched to a high-fat diet (HFD-sham, HFD-BAT), and the others were maintained on chow. Both HFD groups consumed more calories and gained more adiposity than the chow groups. Caloric intake was not different between transplanted and sham groups within the same diet. HFD-BAT mice had lower body fat than HFD-sham mice with increased oxygen consumption and lowered respiratory quotient, suggesting that HFD-BAT mice exhibited greater energy expenditure and tended to use fat as fuel source. HFD-BAT mice had better glucose tolerance compared to HFD-sham mice. Both transplanted and endogenous IBAT of HFD-BAT mice had significantly higher mRNA levels of UCP1 and PGC-1α (genes related to thermogenesis) than the IBAT of HFD-sham mice; thus the brown fat of HFD-BAT mice was more thermogenic. In summary, mice with brown fat transplantation exhibited a partial resistance to HFD-induced obesity and glucose intolerance due to increased energy expenditure.
doi:10.1016/j.appet.2010.04.189

Paradigm and concentration affect salt appetite impairments after parabrachial lesions in rats

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Previous studies have demonstrated that bilateral lesions of the gustatory (medial) zone of the parabrachial nucleus (PBN) in the pons, induced by local injections of ibotenic acid, eliminate the salt appetite induced in rats by treatment with the diuretic drug, furosemide. The present studies re-examined the effects of lesions of the gustatory PBN on NaCl intake by rats using multiple models of salt appetite. The absence of a conditioned taste aversion, an established consequence of medial PBN lesions, was used as an initial screen with which to assess the effectiveness of the lesions. Rats with PBN lesions did not drink either 0.3 M or 0.5 M NaCl in response to daily treatment with desoxycorticosterone acetate. In contrast, rats with PBN lesions did increase their intakes of water and 0.3 M NaCl in response to hypovolemia induced by subcutaneous injection of 30% polyethylene glycol (PEG) solution. However, most rats with PBN lesions did not drink 0.5 M NaCl after PEG treatment. These and other findings indicate that lesions of the gustatory PBN in rats may eliminate salt appetite depending on which model is used and which concentration of NaCl solution is available. Supported by research grants DC05435 and DA12473.
doi:10.1016/j.appet.2010.04.190

Maternal high fat diet during gestation or suckling differentially affects offspring obesity

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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 prenatal or postnatal exposure to maternal HF diet is more critical to offspring's obesity. Female Sprague Dawley rats arrived on gestation day 2 were divided randomly to receive chow (CH) or HF diet. Dams were maintained on their respective diets until weaning at PND21. 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. CH–HF and HF–HF pups gained more body weight by PND7. This persisted until weaning. Pups cross-fostered to HF dams had more subcutaneous and visceral adiposity and higher plasma leptin concentration than CH–CH group on PND21. CH–CH and HF–CH pups did not differ on these variables. Female CH–HF and HF–HF pups had impaired glucose tolerance at weaning. In adulthood, male offspring from CH–HF and HF–HF groups still gained more body weight than CH–CH controls. Female offspring's body weight was indistinguishable among the four groups. Peripheral leptin injection suppressed food intake of only CH–CH males at 9 weeks. Taken together, these data suggest that postnatal HF exposure during suckling may be more critical in offspring's metabolic programming than prenatal HF exposure.

Supported by NIH grants DK077623, HD055030.
doi:10.1016/j.appet.2010.04.191

Feeding responses to gastric nutrient loads in diet-induced obese and resistant rats

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Deficits in satiation signals are strongly suspected to contribute to, and accompany, the obese state. When fed a high-fat (HF), high-energy (HE) diet, a subset of the outbred Sprague–Dawley population becomes obese (DIO) while another is resistant (DR) to subsequent obesity. Prior work in DIO rats has shown these rats consume more calories per day than DR rats with an increase in meal size rather than number. Little is known about the contribution of peripheral satiation signals to DIO's hyperphagia and weight gain. We have recently shown that chow-fed DIO rats have an enhanced responsiveness to the satiation signal, CCK. In order to further dissect if DIO and DR rats have differential feeding responses to other satiation signals, we examined the effects of gastrointestinal nutrients loads (50% glucose and 20% intralipid) on subsequent food intake. Gastric loads of glucose (5 ml; 10 kcal) or intralipid (5 ml; 10 kcal) at the onset of the dark cycle resulted in suppression of HF/HE diet intake compared to baseline saline controls in both DIO and DR groups. Furthermore, we found that total daily food intake of DIO rats was significantly higher than DR rats. Together, these preliminary findings suggest that changes in gastrointestinal feedback to nutrient loads do not seem to contribute to DIO rats' hyperphagia on a HF/HE diet and subsequent weight gain.

doi:10.1016/j.appet.2010.04.192

Altered intestinal, but preserved oral sensitivity to nutritive sweet solutions in C57BL/6J germ-free mice

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A role for the gut microflora in obesity has recently emerged. Specifically, when placed on an energy dense western diet, germ-free (GF) C57BL/6J (B6) mice are resistant to weight gain and obesity relative to normal B6 mice. Furthermore, inoculation of GF mice with microbiota results in increased energy harvest from the diet and subsequent increase of body fat and insulin resistance. Some studies suggest that GF rats consumed more food and that conventionalized mice have increased expression of nutrient responsive receptors in the ileum and colon. Whether this results in altered taste and intestinal sensitivity to nutritive stimuli is largely unknown. Therefore, our current study examined both oral and intestinal sensitivity to a range of nutrient (sucrose) and non-nutrient (saccharin) sweet solutions in GF B6 mice compared to normal B6 mice by measuring acceptance and preference using two-bottle tests over 48-h. We found that GF mice consumed more of the high (8 and 16%) sucrose solutions compared to normal mice, leading to a significant increased energy intake. No significant differences in intake of low sucrose or any tested saccharin concentrations were found between GF and normal mice. Although GF mice preferred high concentrations of sucrose more than normal mice, there were no significant differences between groups. Similarly, bodyweight, food and water intake were not different between GF and normal mice. These results suggest that GF mice may have decreased intestinal sensitivity to nutritive sweet solutions while taste sensitivity remains unaltered.

doi:10.1016/j.appet.2010.04.193

Short-term administration of the atypical antipsychotic olanzapine induces insulin resistance in healthy subjects, independent of weight gain or psychiatric disease

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The atypical antipsychotics are associated with an increased incidence of diabetes and cardiovascular disease. The mechanisms underlying these metabolic defects are not understood, although it has been speculated that the initiating pathophysiology is weight gain, secondary to centrally mediated increases in appetite. Our objective was to determine if olanzapine administration impaired post-prandial responses to the physiologically relevant stimulus of a meal, independent of weight gain or psychiatric disease. Nine healthy male subjects (BMI = 69.8 + 2.6) were admitted into the CTRC for 12-days. Activity was maintained for each subject at a level matched to their free living levels. Using a within-subject design, a 600 kcal mixed nutrient meal challenge was given prior to and following 9-days of olanzapine administration. Stable isotopes were utilized to determine glucose appearance, glucose disposal and endogenous glucose production. Weight remained stable for the 12-days. (69.8 ± 2.6, pre: 70.1 ± 2.9, post-olanzapine). No significant differences in food intake were found. Olanzapine induced significant increases in post-prandial glucose (area under the curve: pre, 4436 ± 3993 vs. post, 6705 ± 1903, $P < 0.03$), insulin (6883 ± 4400 vs. 13431 ± 6651, $P < 0.002$) and triglyceride (1962 ± 3995 vs. 4200 ± 3938, $P < 0.01$) levels as well as significant decreases in glucose disposal ($P < 0.01$) and free fatty acids

($P < 0.001$) relative to pre-treatment responses. These data demonstrate that short-term administration of olanzapine to normal subjects induces a profound state of insulin resistance, with impairments in post-prandial glucose and lipid metabolism, independent of weight gain or psychiatric disease. The metabolic dysregulation likely contributes to the increased incidence of metabolic disease in patients treated with this and similar medications.
doi:10.1016/j.appet.2010.04.194

Inhibition of the sweet taste receptor with lactisole attenuates post-prandial glucose levels and increases glucagon-like peptide levels in normal weight men

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The G-protein coupled receptors, T1R2 and T1R3 which form the sweet taste receptor (STR) and gustducin, the G protein involved in taste signal transduction are expressed in the small intestine of humans and animals. The taste signaling elements are also co-expressed in the intestinal L-cells which secrete the hormone, glucagon-like peptide (GLP). Stimulation of the STR upregulates the intestinal sodium-glucose transporter (SGLT1), promoting glucose absorption and elicits the release of GLP. There are few studies examining the functional role of the STR in human glucose metabolism. Our objective was to determine if inhibition of the STR by lactisole, a sweet taste receptor inhibitor could alter glucose metabolism in humans. We used a within subject design with each subject participating in three experimental conditions involving ingestion of a 350 ml solution: (1) lactisole alone (0.85 mM); (2) glucose (50 g; 0.79 M) and (3) glucose and lactisole. Seven normal weight ((BMI = 67.8 ± 2.8) men participated and completed the study. Subjects arrived fasted and an intravenous catheter was placed in a hand vein to allow for arterialized venous blood draw. Blood samples were taken from −30 to 180 min post-ingestion. We found that the lactisole solution had no significant effect on any blood variable measured. In contrast, when lactisole was added to the glucose solution, a significant decrease in post-prandial glucose area under the curve (14687.29 ± 9184.461 mg/dl/180 min) was observed compared to glucose alone (16367.5 ± 8757.680, $P < 0.02$). Significant increases in plasma GLP levels following ingestion of the glucose and lactisole solution compared to glucose alone were also found. The effects on post-prandial glucose and GLP occurred independent of significant changes in insulin. The decrease in post-prandial glucose levels may be a consequence of decreased glucose absorption due to inhibition of SGLT1by lactisole or secondary to an increase in GLP-mediated glucose disposal.
doi:10.1016/j.appet.2010.04.195

Circadian and age-associated differences in feeding and spontaneous physical activity contribute to reduced adiposity in obesity resistant rats

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We hypothesized that circadian and age-associated differences in feeding and spontaneous physical activity (SPA) would contribute to less fat mass and food intake, and greater SPA in obesity resistant (OR) rats. We determined circadian patterns of food intake and SPA in OR and Sprague–Dawley (SD) rats throughout 18 months of observation. Body composition, 24 h SPA and food intake at 4 h intervals over 24 h were measured at 6, 12 and 18 months of age. OR rats had significantly less body weight and fat mass at all times ($p < 0.0001$ all comparisons). 6-month old OR rats had significantly less food intake during the 4 h period before, after the onset of, and during the dark cycle ($p < 0.03$ all comparisons). 12-month old OR rats had significantly greater food intake during the 4 h period before light and dark onset, while SD rats had significantly greater food intake during the first and second 4 h period after dark onset ($p < 0.04$ all comparisons). There were no group differences in feeding at 18 months. Circadian differences in feeding resulted in less 24 h food intake in OR rats at 6 ($p = 0.045$), 12 ($p = 0.056$) and 18 months ($p = 0.604$). OR rats had significantly greater SPA during the 4 h period before and after dark onset, the light cycle and 24 h period at 6, 12 and 18 mo and during the dark cycle at 6 months ($p < 0.02$ all comparisons). These data suggest that circadian differences in SPA persist with age while circadian differences in feeding are less consistent across age and together contribute to adiposity differences observed.
doi:10.1016/j.appet.2010.04.196

Anti-ghrelin Spiegelmer NOX-B11-2 inhibits ingestive behavior in the Siberian hamster

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Ghrelin is a gut–brain peptide that is released from the stomach as a signal indicating hunger. Circulating ghrelin concentrations increase in direct proportion to the length of time since the last meal. Peripheral ghrelin injection increases ingestive behaviors. Spiegelmer NOX-B11-2 (SPM) reduces the effects of ghrelin, as it is an L-oligonucleotide that specifically binds to ghrelin and inhibits peptide-receptor interaction. Previously, this SPM has been shown to inhibit ghrelin-induced neural activation, as assessed by cFos-immunoreactivity, in the arcuate nucleus, and food intake in rats. Therefore, we asked: Does pretreatment with SPM prevent the ghrelin induced increases in food foraging, hoarding, and intake? Siberian hamsters were housed in a wheel running-based foraging system with a simulated burrow to examine the effect of peripheral injections of SPM (18 mg/kg body mass) 4 h prior to ghrelin administration (30 μg/kg body mass) at light offset. Food intake and hoarding were assessed 1-, 2-, 4-, and 24 h and for the next 8 days. Exogenous ghrelin increased food hoarding above saline at all time points, an effect prevented by SPM at 1-, 2-, 4-, and 24 h. Food intake was increased by 50–100% by ghrelin at 1-, 2-, 4-, and 24 h after injection compared with saline, an effect that was inhibited by SPM at 1- and 24 h. Food intake was not increased over saline at any subsequent time point. Therefore, SPM inhibits ghrelin-induced increases in ingestive behaviors of food hoarding and intake. Funded by NIH R01 DK 78358 and SPM gift from NOXXON Pharma AG.
doi:10.1016/j.appet.2010.04.197

Behavioral factors associated with weight loss maintenance. Lessons learned from the National Weight Control Registry (NWCR)

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By studying over 6000 individuals who have maintained a weight loss of at least 30 lb, the NWCR has demonstrated that long-term maintenance of a substantial ($\geq$ 30 lb) weight loss is feasible. The registry shows that successful weight loss maintainers reliably exhibit key behavioral characteristics that are associated with successful weight maintenance, including very high levels of physical activity, self-monitoring of body weight and food intake, and consumption of a diet that is low in calories and fat. Other factors associated with weight maintenance include infrequent fast-food consumption, high levels of dietary consistency, low levels of TV viewing and regular breakfast consumption. Recently, advanced statistical techniques have been used to accurately model weight trajectories and behavioral predictors of successful weight for up to 10 years, starting with the initial weight loss. NWCR investigators have also used neuroimaging techniques to show that weight loss maintainers exhibit heightened cognitive inhibition and control when confronted with food stimuli. These and other findings suggest that the NWCR is useful for identifying behavioral characteristics and strategies that may be used to facilitate weight loss maintenance following a substantial weight loss.

doi:10.1016/j.appet.2010.04.198

Isoproterenol inhibits salt apetite in rats

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Isoproterenol (ISOP) is a mixed β1, β2 adrenergic receptor agonist that reduces blood pressure, releases renin and stimulates water drinking upon systemic administration. However, in light of the endocrine and hemodynamic effects caused by ISOP, it is remarkably ineffective in eliciting salt appetite. We investigated if ISOP treatment actually inhibits sodium intake. In one test, rats were depleted of sodium by sc administration of the diuretic, furosemide (10 mg/kg bw) and overnight access to sodium deficient diet with only water to drink. The next morning, the rats received vehicle (n = 7) or ISOP (n = 7, 30 μg/kg sc) just before burettes of water and 0.3 M NaCl were placed on the cages. The groups drank equivalent amounts of water, but ISOP-treated rats drank only half as much salt solution (7.1 ± 1.4 ml vs. 3.3 ± 0.8 ml). In a second test, rats received daily injections of deoxycorticosterone acetate (DOCA, 5 mg/kg bw) to stimulate salt appetite. Saline solution (0.3 M NaCl) was provided for 2 h/day. On the fourth day, the rats received vehicle (n = 7) or ISOP (n = 7, 30 μg/kg, sc) just before access to the saline solution. Again, the groups drank equivalent amounts of water but rats given ISOP drank less than half as much saline solution (9.0 ± 1.1 vs. 4.1 ± 1.1). We conclude that ISOP treatment produces signals, possibly arising from mechano- and chemosensitive receptors in the cardiac ventricles, that inhibit salt appetite. This work was supported by AG-025465 to RLT and HL-14388, DK-066086, and MH-080241 to AKJ.

doi:10.1016/j.appet.2010.04.199

Synphilin-1 interacts with AMPK and ATP

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Synphilin-1 is a cytoplasmic protein enriched in brain neurons with unclear function. We recently generated a human synphilin-1 transgenic mouse model that displays some key features of obesity and diabetes including increased food intake, body weight and body fat, hyperinsulinemia, hyperleptinemia and glucose insensitivity. 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. AMPK is a central neuronal energy sensor that plays a major role in maintaining energy homeostasis. Activation of AMPK in hypothalamic sites can play a role in reducing food intake. Interestingly, synphilin-1 also reduced the inhibitory effect of insulin on AMPK phosphorylation compared with the effect in vector only control cells. Increase in the AMP/ATP ratio can activate AMPK. We found that synphilin-1 binds to ATP using ATP binding assays. Currently we are investigating whether synphilin-1 binding with ATP regulates AMPK activation. These studies may provide a novel insight into the molecular mechanisms underlying synphilin-1-induced hyperphagia and obesity and will increase our knowledge of the biological functions of synphilin-1.

doi:10.1016/j.appet.2010.04.200

Expression of CRF2 receptor is decreased in the lateral septum and ventromedial hypothalamus in the rat model of sucrose binge eating

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Episodes of binge eating frequently involve highly palatable food and often are followed by imposing of restricted regimens or dieting that by itself represents a risk of relapse. The advancements in treatment strategies for binge eating require vigorous investigations of the neurological mechanisms of eating disorders in animal models. Our rat model of sucrose binge eating was developed by using chronic intermittent access to palatable sucrose combined with food restriction (4-days-per-week access to chow and sucrose restricted to 2 h per day, and following 3-days-per-week maintained on unrestricted chow; SIR rats). This regimen led to a development of sucrose overeating when these rats regained the access to sucrose. These sucrose-binge-eating rats were compared to animals submitted to intermittent access to sucrose without food restriction (4-days-per-week ad libitum access to sucrose in addition to chow, and following 3-days-per-week exclusive feeding of chow; SIA rats) and to rats continuously fed chow and sucrose (SA rats) or chow (CA groups). The rats maintained on intermittent sucrose regimens but not on continuous feeding, demonstrated attenuated anorectic response to 1-h weekly sessions of restraint stress. Also the SIA and SIR rats were characterized by excessive sucrose-licking activity and attenuated stress-induced induction of expression of c-fos mRNA in the lateral septum (LS). The LS also showed decreased levels of expression of corticotropin-releasing factor type 2 receptor (CRF2-R) in rats maintained on intermittent sucrose. Combination of intermittent access to sucrose with food restriction decreased the expression of CRF2-R not only in the LS, but also in the ventromedial hypothalamus. Therefore, simultaneous alterations in the expression of CRF2-R in the ventromedial hypothalamus and lateral septum in sucrose overeating rats may contribute to the development of sucrose binge eating.

doi:10.1016/j.appet.2010.04.201

The amplitude of differences measured in vivo between respiratory and food quotients is different in spontaneously leaner and non-obese fattier rats and suggests differences in the processes controlling body fat storage

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Individuals are known to present large differences of sensitivity to body fat accumulation, in particular when challenged by a high fat (HF) high calorie diet. To shed light on the underlying processes, we measured during 4 consecutive days total energy expenditure (TEE) and feeding behavior in 12 rats while fed their usual low fat (LF) diet (2 days), then during the first 2 days of transition to a HF diet. Transition to the HF diet increased caloric intake similarly in all rats while TEE was not increased. Accordingly, differences between rats' RQ values and the quotient of oxidation of the food (food quotient (FQ)) showed an increase in the difference between RQs and FQ (d-RQ) under HF feeding. Further analysis of individual d-RQ and adiposity values showed that, in particular during HF feeding, a tight correlation ($R^2 > 0.9$) existed between adiposity and d-RQ in 7 rats but was weaker and had a lower slope in the 5 other rats. Analysis of the data according to these two groups showed that EE adjusted to lean body mass was larger, and body weight and body adiposity was lower in the 7 rats with a high d-RQ relative to body adiposity. These results suggest that the mechanisms involved in fat deposition are not the same in leaner and fattier (but non-obese) rats. The higher d-RQ and TEE values suggest that, in the leaner rats, de novo lipogenesis relative to direct fat deposition may be larger.

doi:10.1016/j.appet.2010.04.202

Concentration-dependent licking to glucose, maltose and maltotriose but not Polycose in a brief-access test is blunted in both *T1r2* and *T1r3* null mice

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The T1R2 and T1R3 proteins are expressed in taste receptor cells and form a heterodimer binding with compounds humans describe as sweet. Both *T1r2* knock-out (KO) and *T1r3* KO mice unconditionally lick Polycose in a concentration-dependent manner similar to wild-type (WT) controls. Because Polycose contains glucose polymers of varying lengths, here we tested *T1r2* KO and *T1r3* KO mice and their WT littermate controls in three 25-min brief-access taste tests (5-s trials) to six concentrations of glucose, maltose (2 glucose units), maltotriose (3 glucose units) and Polycose to address what the optimal stimulus is for the postulated polysaccharide taste receptor. Both KO groups displayed reduced licking to glucose. Both KO groups showed blunted responses to maltose and maltotriose but in the third session, some KO mice showed some degree of concentration-dependent licking, likely attributable to learning. In contrast, KO mice displayed concentration-dependent licking to Polycose, evident in the first session, similar to that of WT. These results are consistent with findings in the literature implicating the T1R2+3 heterodimer as the principal taste receptor for "sweet" ligands and suggesting that there may be a novel receptor(s) that mediates polysaccharide taste. The optimal ligand for this receptor likely possesses more than 3 glucose moieties. These findings also provide support for postingestive cues to potentially influence responding in a brief access taste test. Supported by NIH R01-DC004574.

doi:10.1016/j.appet.2010.04.204

Bout analysis of the natural variation in sucralose preference

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Rats show variability in their preference for the artificial sweetener sucralose over water. To explore this variability we categorized rats by comparing intakes of increasing concentrations of sucralose and water via 2-bottle, 24-h preference tests. Rats preferring sucralose to water at all concentrations (0.0001–2.0 g/L) were classified as preferers ($n = 6$); rats displaying avoidance at the highest concentrations ($\geq$0.25 g/L) were classified as avoiders ($n = 10$). Group differences in sucralose intakes were maximal at 2.0 g/L sucralose. In order to examine group differences in licking behavior at this concentration, rats were given a single bottle containing 2.0 g/L sucralose for 3 days. Avoiders drank less sucralose than preferers (day 3: 52 g vs. 39 g, respectively, $p < 0.001$). Lick analysis revealed that this decrease was due to a decrease in bout size ($p = 0.004$), not bout number. Rats were then given access to 2 g/L sucralose and water in a 2-bottle, 24-h preference test. Avoiders failed to consume sufficient sucralose to conduct a bout analysis. However, a preference test of 0.1 g/L sucralose and water resulted in both groups consuming some sucralose. Preferers drank more sucralose than avoiders (53 g vs. 22 g, respectively, $p = 0.005$) and under these conditions the avoiders' reductions in intake were due to decreases in both bout size and number ($p < 0.05$). These data suggest that the preference categorization is robust under single bottle conditions and that avoiders drink smaller bouts than preferers, which is consistent with a reduction in palatability.

doi:10.1016/j.appet.2010.04.203

AT_1 receptor-mediated G protein signaling may not be required for angiotensin II-induced behavioral desensitization

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Angiotensin II (AngII) plays a key role in body fluid homeostasis and central injection of AngII stimulates water and saline intakes. An interesting component of the AngII system is an observable, short-term reduction in the effect of AngII after repeated exposure to the peptide. This tachyphylaxis may be an important aspect of a coordinated physiological response to AngII. Although much about the behavioral aspects of this reduced response remains unknown, earlier work in our lab demonstrated that 3 icv injections of a large dose of AngII (300 ng) decreased water intake stimulated by a 4th injection of AngII (100 ng). To test if AT_1 receptor-mediated G protein activation is required for this observed response, we used an AngII analog, Sar^1,Ile^4,Ile^8-AngII (SII), which stimulates the AT_1 receptor without G protein activation. When rats were given repeated injections of SII (30 μg), they drank less water in response to a test injection of AngII (100 ng, 20 min after SII) than rats given repeated injections of vehicle. In a separate experiment, we gave an injection of SII 20 min before AngII and failed to detect an effect of SII on AngII-induced water intake. These results suggest that the SII-induced desensitization was not simply an antagonistic effect of SII on the test injection of AngII. Although additional studies are needed to determine the mechanism through which AngII and SII decrease responses to subsequent AngII administration, the present results suggest that the mechanism does not require G protein activation. Supported by DK073800 and HL091911.

doi:10.1016/j.appet.2010.04.205

Differential growth patterns and formula intakes among healthy formula-fed infants

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Rapid growth during infancy is a predictor of later obesity risk. Thus, interventions aimed at preventing obesity should begin during infancy when children are fed predominantly milk-based diets. Because of the striking differences among infant formulas (e.g. protein hydrolysate formula [PHF] and cows milk-based formula [CMF]) we hypothesized that infants fed PHF would consume less formula and, consequently, show slower rates of growth across infancy. Infants whose mothers had decided to formula feed were randomized to feed either PHF ($n = 24$) or CMF ($n = 32$) across 0.5–7.5 months of age. Infants were weighed and measured monthly, then videotaped feeding their assigned formula under naturalistic conditions. Although no group differences existed at study entry, PHF infants had significantly lower weight-for-age *z*-scores across ages 2.5–7.5 months and less change in weight-for-age *z*-scores across ages 1.5–7.5 months compared to CMF infants. Throughout the study, infants fed PHF consumed less formula to satiation than infants fed CMF. That there were no differences in infant acceptance or maternal rating of infant enjoyment suggests that lower intakes of PHF cannot be attributed to rejection of PHF. In conclusion, infants fed PHF satiated faster than infants fed CMF and the ensuing decreased intakes resulted in more normative growth trajectories. Whether the enhanced satiating effect of PHF is attributable to its higher protein content, amino acid distribution, or some other metabolic effect is an important area for future research. Supported by NIH Grant R01HD37119.

doi:10.1016/j.appet.2010.04.206

The importance of eating behavior in eating disorders

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The commonly recognized eating disorders, Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder, are defined by abnormalities of eating behavior. Yet, until recent years, surprisingly little attention has been paid to characterizing these abnormalities objectively and assessing their clinical implications. While the most striking, and not surprising, behavioral abnormality of Anorexia Nervosa is reduced caloric intake, recent studies document more subtle alterations in food choice that may play an important role in the maintenance of the disorder and may be a useful target for clinical interventions. Laboratory studies of individuals with Bulimia Nervosa and Binge Eating Disorder have documented major disturbances in eating behavior, but also raised questions about how incorporate this information into an improved understanding of the syndromes and their pathophysiology. This presentation will briefly review information about disturbances of eating behavior in eating disorders and their implications. Anorexia Nervosa will be a major focus, and, if time permits, some perspectives on Bulimia Nervosa and Binge Eating Disorder will be offered.

doi:10.1016/j.appet.2010.04.207

Effects of three types of dietary fiber on food intake in a real life setting

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The diverse physical properties of dietary fiber types may differently affect satiety and food intake. The aim of this study was to determine the effect of three types of isolated dietary fiber on food intake and feelings of satiety in healthy subjects in a real life setting. In a cinema setting, six test foods were randomly offered to 121 healthy, non-restrained subjects (BMI 18–25 kg/m^2). Test foods were cookies in which flour was replaced by cellulose (5%), guar gum (2.5% and 1.25%) or alginate (5% and 2.5%). The control cookie did not contain added fiber. On six test days and after a fixed preload, foods were offered in a surplus, and consumed until pleasantly satisfied. Changes in feelings of hunger, fullness, appetite and prospective food intake did not differ between the six test foods. Mean intake (±se) of the test food with 5% alginate (147.8 ± 8.5 g) was lower ($p < 0.001$) than mean intake of the control food (177.0 ± 8.5 g). Intakes of test foods with 5% cellulose, 2.5% and 1.25% guar gum, and 2.5% alginate did not differ from control. A dose-response effect of alginate (0% > 2.5% > 5%) was found ($p < 0.05$). Compared to control, foods with 5% cellulose, 2.5% guar gum and 5% alginate were liked less ($p < 0.01$). Correcting the results for liking scores did not change the findings. Addition of an alginate isolate, a dietary fiber with gelling properties, to food products reduced ad libitum food intake. Effects of bulking and viscous fibers on food intake were not found.

doi:10.1016/j.appet.2010.04.208

Mechanisms involved in reduction of diet-induced obesity by captopril in C57BL/6J mice

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Obesity, the excess accumulation of adipose tissue, is a major health problem faced by Western societies. Evidence suggests that angiotensin II (ANG II) may play an important role in the accumulation of adipose tissue. Captopril, a drug that prevents formation of ANG II, has been shown to reduce body fat in both mice and rats. In the present study, C57 mice were fed a high fat diet (w/w 21% fat) for 3 or 28 days. The mice were allowed access to water (control, CON), water with captopril (0.05 mg/ml) added (captopril, CAP), or water, but with food restricted the amount eaten by the CAP group (pair fed, PF). Metabolic rate (MR; indirect calorimetry), body composition (DEXA) and plasma adiponectin were determined. The results demonstrated that despite an early reduction in food intake, CAP animals maintained MR at the level of CON animals at 3 days, while PF animals had reduced MR. CAP animals had higher plasma adiponectin, and this increased adiponectin occurred prior to any observed body weight or body fat reduction. By 28 days, CAP animals weighed less than both CON and PF animals, PF also weighed less than CON. CAP and PF animals had lower MRs than CON, even though CAP animals had higher plasma adiponectin. Thus, the rapid reduction in body weight caused by CAP may be explained by an adiponectin-induced increase in oxidation that maintains MR in the face of decreased food intake. Adiponectin, however, does not appear to maintain MR after body weight loss has occurred in CAP-treated animals.

doi:10.1016/j.appet.2010.04.209

Exercise vs. enriched environment. Effects on obesity in male and female OLETF rats

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OLETF rats lack CCK_1 receptors and are a model of early onset hyperphagia-induced obesity. They show pre-obese characteristics from birth, becoming gradually obese towards adolescence. We evaluated the post-weaning environment's contribution to their obese phenotype by (1) providing obese and lean (LETO) strain males and females with running wheels for 3 weeks postweaning. (2) Chronic group housing with large cages and toy—an enriched environment (EE). Body weight (BW), voluntary intake, adiposity, leptin, insulin, corticosterone and adiponectin levels were among the parameters examined at adulthood. The results suggest a significant contribution of the rearing conditions to the OLETF males' hyperphagia and obesity. Intake was reduced similarly after RW and EE (around 15%), while BW reduction was around 8% and 1.5%, respectively. RW OLETF males reduced 32% retroperitoneal and inguinal fat and 39% visceral fat, while after EE the reduction was 21% and 13% respectively. Accordingly, leptin levels were reduced 33% after RW vs. 18% after EE. In contrast, OLETF females adhered to their genotype, presenting strong resistance to adiposity loss after both manipulations, with no evident beneficial responses. Male LETO responded to exercise by reducing intake and adiposity levels while females increased intake, BW and muscle mass. Enriched environment had no effect on LETO physiology. Overall, the moderation in adiposity observed after EE and RW in the OLETF males suggests that standard, impoverished conditions may exacerbate the hyperphagia and obesity of the males, worsening their phenotype.

doi:10.1016/j.appet.2010.04.210

Psychosocial influence on diet preference and caloric intake in female monkeys

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Social dominance status in macaque monkeys functions to control aggression and access to resources. Because subordination is imposed through non-contact aggression, the continual harassment of subordinate females by more dominant animals emerges as a potent psychosocial stressor, resulting in periodic hypercortisolemia, less frequent targets of affiliative behavior, and increased anxiety behaviors, associated with changes in monoamine activity in limbic-hypothalamic regions. Social status differences are also evident in appetite and energy regulation. When fed a low fat high fiber diet, subordinates eat less, reflected in fewer and smaller meals, have lower body weight, less total body fat, and a hypometabolic condition. However, estimates of energy expenditure, assessed from activity patterns, do not show a social status difference. In contrast, when given a choice between this low caloric diet (LCD) and diet high in fat and sugar, subordinates consume significantly more calories, largely from the high caloric diet (HCD). While dominant females also prefer the HCD, they nonetheless show caloric restriction, consuming similar calories regardless of diet availability. Although stress hormone responsivity is not affected, the increased consumption of the HCD is anxiolytic in subordinate females whereas the removal of the HCD is anxiogenic in all females. The model provides the opportunity to examine the neurobiological mechanisms for understanding the comorbidity of anxiety and emotional feeding in females. Supported by NIH HD46501, F32-MH073525, RR00165 and NFS IBN 9876754.

doi:10.1016/j.appet.2010.04.211

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 inactivating mutations in the leptin signaling cascade that are associated with pediatric-onset obesity and present some of the translational studies that have attempted treatment directed at correcting the observed defects.

doi:10.1016/j.appet.2010.04.212

Anti-angiotensin type 1 receptor siRNA delivered into rat hypothalamus. A traceable reagent that reduces angiotensin binding, signal transduction and thirst

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Angiotensin II (AngII) is involved in the control of water and salt intake. Traditional approaches to study the cellular mechanisms that underlie these behaviors have relied on receptor ligands and other inhibitors injected into rat hypothalamus. These reagents have limitations: the extent of their diffusion in the brain is unknown and specific inhibitors are not available for many potential targets. Thus, we injected siRNA into rat brain targeting the AngII type 1 receptor (AT1R) as a platform to optimize procedures for other effective siRNA-mediated selective protein knockdown. First, we used an in vitro model (WB cells) to evaluate various AT1R siRNA sequence candidates. One siRNA candidate diminished AT1R levels by 90% and blocked any AngII-induced cell signaling compared to cells pretreated with luciferase (non-silencing) siRNA. With the efficacy of an AT1R siRNA validated in WB cells, we began using this siRNA in vivo. Preliminary results have shown that rats treated with a single icv injection of AT1R siRNA substantially reduced their drinking responses to subsequent AngII injections compared to non-silencing siRNA at 22 h and 46 h. Furthermore, preliminary radioligand binding assays of the hypothalami of siRNA-treated rats demonstrated that AT1R siRNA diminished AT1R binding activity compared to the non-silencing siRNA. Experiments using biotin-tagged siRNAs are now planned to determine the extent of the affected areas by these reagents. Supported by NHLBI HL091314.

doi:10.1016/j.appet.2010.04.213

Hindbrain leptin and GLP-1 receptor signaling interact in food intake control

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Physiological control of feeding involves endogenous leptin receptor (LepR) and glucagon-like-peptide-1 receptor (GLP-1R) activation in the NTS. Both hindbrain GLP-1Rs and LepRs mediate the intake inhibitory effects of gastrointestinal satiation signaling. Here, using a variety of strategies, we evaluate whether the intake inhibitory effects of hindbrain LepR and GLP-1R signaling interact to control food intake. We examined whether there is an endogenous role for hindbrain GLP-1R signaling in the long-term regulation of energy balance, as established for hindbrain LepR (Hayes et al., 2010), through chronic 4th icv osmotic pump delivery of the GLP-1R antagonist, Exendin-(9-39) (Ex-9; 20 μg/day). Chronic blockade of hindbrain GLP-1R increased daily weight gain and chow intake following ingestion of a preload. Second, to determine the nature of the interaction between hindbrain LepR and GLP-1R signaling in food intake control, we evaluated intake following 4th icv delivery of leptin (6.0 μg) and the GLP-1R agonist Exendin-4 (0.3 μg) at effective doses. Combined 4th icv delivery of leptin and Exendin-4 enhance 24 h food intake inhibition in an additive fashion. Third, we determined whether intake inhibition following hindbrain leptin delivery is mediated in part through endogenous hindbrain GLP-1R signaling. Blockade of hindbrain GLP-1R by 4th icv Ex-9 (10 μg) reversed the 1 h- and 3 h-intake inhibitory effects of 4th icv leptin (10 μg). Conclusion: Current data demonstrate that hindbrain GLP-1R and LepR signaling interact in the control of food intake. Support: DK21397 and DK077484.
doi:10.1016/j.appet.2010.04.214

Viral-mediated expression of CCK 1 receptors in the dorsomedial hypothalamus affects meal size and glucose levels in OLETF rats

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Our previous data have suggested that the absence of CCK 1 receptors (CCK1R) in the dorsomedial hypothalamus (DMH) contributes to the hyperphagia and obesity of OLETF rats. To directly investigate such a role, we have generated an adeno-associated viral vector (AAV) expressing CCK1R (AAVCCK1R) and examined whether the targeted replacement of CCK1R in the DMH affects the metabolic phenotype of OLETF rats. We found that OLETF rats receiving DMH injections of control vectors (AAVGFP) had increased food intake and body weight compared to lean LETO controls receiving DMH injections of AAVGFP. Although daily food intake did not differ between OLETF AAVCCK1R and OLETF AAVGFP rats, meal pattern analysis revealed an effect of DMH AAVCCK1R replacement on meal size. While OLETF AAVGFP rats ate a significantly large meal compared to LETO AAVGFP rats, DMH CCK1R replacement normalized this increase. At sacrifice, although body weight and fat mass were not affected in OLETF AAVCCK1R rats, plasma glucose levels were significantly reduced compared to OLETF AAVGFP rats. We further found that DMH administration of CCK enhanced glucose tolerance in lean rats. Together, these data support a role for DMH CCK1R in the control of meal size and suggest a novel role in glucose homeostasis. Supported by NIH DK057609 and DK074269.
doi:10.1016/j.appet.2010.04.215

The taste of starch. Studies of T1R3 and TRPM5 knockout mice

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Recent studies indicate that rodents have separate taste receptors for sugar and starch-derived polysaccharides (Polycose). Rodents also appear to "taste" pure starch but little is known about the sensory mechanism involved. This study investigated starch preference in knockout (KO) mice missing the T1R3 sweet taste receptor or the TRPM5 ion channel required for taste signaling and wild-type controls (WT, C57BL/6J; $n = 10$/group). Two-bottle choice tests (48-h) were conducted with 0.5–32% cornstarch (suspended in 0.3% xanthan gum) versus gum vehicle. T1R3 KO and WT mice preferred starch to vehicle at 1% and 2%, respectively, and displayed similar increases in starch intake as concentration increased. In contrast, TRPM5 KO mice failed to prefer starch at any concentration. When the test series was repeated, T1R3 KO and WT mice strongly preferred 0.5–32% starch while the TRPM5 KO mice were again indifferent as a group although 4 mice preferred starch. With further testing, all TRPM5 KO mice developed a strong starch preference, which is attributed to a learned response to post-oral reinforcement. These data indicate that the unlearned preference for starch depends on TRPM5 taste signaling but not the T1R3 taste receptor.
doi:10.1016/j.appet.2010.04.216