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Abstracts

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Guest Editor: Christine A. Zuberbuehler*

Masterfoods Keynote Lecture Series:

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Timothy J. Bartness: **Brain-adipose crosstalk**

Linda M. Bartoshuk: **Do you taste what I taste? Implications of sensory measurement for health**

Andrew J. Hill: **The psychology of food cravings**

The role of CD36 in the perception and utilization of dietary fatty acids: A molecular basis for dietary fat preference.
N. Abumrad. *Washington University, St. Louis, MO 63110, USA*

We previously identified the membrane protein CD36 as a receptor for dietary fatty acids and documented its physiological importance in facilitating uptake and utilization of fatty acids by muscle, heart and adipose tissues. More recent work indicates that CD36 is important for both secretion and clearance of intestinal lipoproteins. CD36-deficient mice have defects in clearance of both fatty acids and triglycerides and exhibit hyperlipidemia, both in the postprandial and fasting states. Similar data suggests that this may apply to humans where CD36 deficiency or polymorphisms of the CD36 gene are relatively common, possibly increasing the risk of diet-induced diabetes. In addition to facilitating and contributing to the regulation of fatty acid uptake/utilization, there is evidence that CD36 together with the PPAR nuclear transcription factors is a component of the cellular fatty acid-sensing machinery that responds to changes in fatty acid flux in a tissue-specific manner. An exciting new development was the recent identification of CD36 as a tongue taste receptor for fatty acids. These studies were conducted in rodents. However, based on the evolutionary conserved structure of CD36 and its documented function as a fatty acid receptor in humans, the new finding are likely to be applicable to humans. This could have great nutritional relevance in that it would provide a molecular basis for our preference for dietary fat.

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Inconsistent pairing of sweet taste and energy does not affect rats' food intake. K. Ackroff, A. Sclafani. *Brooklyn College of CUNY, Brooklyn, NY 11210, USA*

Recent work has suggested that rats exposed to sweet solutions that are sometimes caloric (10% sugar) and sometimes noncaloric (0.3% saccharin) subsequently exhibit disruptions in their regulation of energy intake. However, rats' ability to distinguish between sugar and saccharin suggests that cues other than sweetness may be involved. The present study controlled oral and post-oral experience to provide consistent or inconsistent pairing of sweet taste and energy content. Rats were trained to drink a flavored 0.3% saccharin solution (e.g., grape) paired with concurrent intragastric infusions of equal volume. For the Consistent group, the flavor was paired with 20% sucrose, and on other days they were offered water paired with water infusions. The Inconsistent group always drank the flavor, paired on some days with intragastric sucrose and on other days with water. During the 12-day training period, chow was available ad libitum. For testing, the rats were adapted to 4-h daily chow access with oral water paired with water infusion. Substituting the familiar sweet flavor + sucrose infusion for water + water did not alter fluid or chow intakes, and substituting an unfamiliar sweet flavor (e.g., cherry) + water infusion elevated chow intakes; there were no group differences. Further tests with the flavor offered prior to chow, and with a novel sweet diet preload, also found no difference in the feeding responses of these two treatment groups, suggesting that noncaloric sweeteners may not lead to disordered anticipation of caloric consequences. Supported by NIH DK31135.

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Intracerebroventricular administration of either C89b, a stimulator of carnitinepalmitoyl-transferase-1 (CPT-1s), or cerulenin, an inhibitor of fatty acid synthase (FASi), reduces food intake and body weight in mice. S. Aja, J.M. Mcfadden, A. Aplasca, E. Plummer, J. Hyun, S.M. Medghalchi, A. Vadlamudi, J.N. Thupari, C.A. Townsend, F.P. Kuhajda, T.H. Moran, G.V. Ronnett. *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA*

Brain administration of the FASi/CPT-1s C75 reduces food intake and body weight in rodents. To determine whether either FASi or CPT-1s drive these changes, we administered compounds that alter FAS and/or CPT-1 activity to male C57BL/6 mice via lateral cerebroventricular cannulas. C75 reduced food intake rapidly (30 min) and similarly at all doses (1–56 nmol). Hypophagia remained significant for day 1 and body weight losses lasted at least 4 days. The FASi cerulenin (100–560 nmol) reduced food intake dose dependently at 2 h. Cerulenin at 560 nmol remained anorexigenic for day 1 and mice lost weight. This dose led to rebound hyperphagia and regain of preinjection body weight by day 3. To test whether CPT-1s is important for C75's feeding and bodyweight effects, we used the CPT-1 inhibitor etomoxir to interfere with CPT-1s. Etomoxir itself (32–320 nmol) did not affect day 1 feeding. However, etomoxir at 320 nmol attenuated the hypophagia produced by C75 at 32 nmol, indicating that CPT-1 stimulation is important for C75's effects. Finally, the novel and selective CPT-1s C89b (32–320 nmol) reduced food intake dose dependently at 4 h. Hypophagia lasted for 3 days, and day 1 body weight losses persisted for at least 6 days. These data are the first to show that central CPT-1s reduces food intake and body weight. Together, these results suggest that the feeding inhibitory and body weight effects of intracerebroventicular C75 reflect a sum of FASi and CPT-1 s. Supported by DK068054 and DK064000. FASgen, Inc. provided C75 and C89b.

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The pan opiate antagonist, LY255582, reduces reward-based food intake. J.T. Alexander-Chacko, A.E. Sahr, M.A. Statnick, D.K. Sindelar. *Endocrine Research, Eli Lilly and Company, Indianapolis, IN 46285, USA*

Numerous reports have implicated the endogenous opiate system in the hedonistic aspects of food intake. These experiments were conducted to determine the involvement of the opiate system in the acquisition and maintenance of reward-related eating behavior and the effect on the brain dopaminergic system. Lean, male Sprague-Dawley rats were exposed to a highly palatable diet (HP, 40% fat) at the same time each day for 1 h over 4 days. In all Experiments, LY255582 was sc dosed at 0.1, 0.3, 1.0 and 3.0 mg/kg. In experiment 1, rats were allowed 3 days access to HP with vehicle dosing and on day 4, dosed with vehicle or LY255582. All rats showed an increase in HP intake from days 1–3. At all doses, LY255582 produced a significant reduction in HP intake by ~50% relative to controls, suggesting that a single dose is sufficient to produce a decrease in HP intake, once acquired. In Experiment 2, to try to prevent the increase in HP intake, rats were dosed with vehicle or LY255582 on all 4 days of HP exposure. Repeated administration of LY255582 abolished HP diet intake for all days. In rats with microdialysis probes in the nucleus accumbens shell, dopamine levels increased in response to the HP diet and 0.3 mg/kg LY255582 prevented this rise. These results suggest that an opiate antagonist can reduce acquired HP diet intake and prevent its acquisition. These data also suggest that stimulation of the mesolimbic dopaminergic system by the HP diet can be decreased by an opiate antagonist.

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Validation of a hand-held electronic appetite rating system. E. Almiron-Roig, R. Virgili, S. Pinaud, A. Erkner, H. Green. *Nestlé Research Centre, CH-1000 Lausanne, Switzerland*

Satiation and satiety are subjective feelings that can be translated into quantitative measurements using visual analogue scales (VAS). A variety of satiety ratings exist, with the most widely used scales being those from Hill and Blundell (1986). Paper-based VAS are sensitive and reliable but can be time-consuming and involve error-prone steps such as the measurement and transfer of data. Portable methods have been developed in the past but these are either not commercially available anymore or somehow difficult to carry around under free-living conditions. In this study we present the validation of a new, portable electronic appetite rating system based on a hand-held computer (Dell, Pocket PC 5.0) with a built-in alarm and automatic data capture and storage. Between 20–30 subjects (males and females) came to the lab to have either a high- or low-energy breakfast on 4 separate occasions, following a repeated cross-over design. After breakfast subjects moved to their usual work space and rated appetite, satiety and preference for the meal at 30 min intervals for 2.5 h. Ratings on paper VAS were compared to ratings from the Pocket PC.

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Neurochemical characterization of activated neurones of the rat brain by scheduled feeding regimen. T. Appl, M. Schindler. *Department of Metabolic Diseases, Boehringer-Ingelheim Pharma GmbH & Co KG, D-88397 Biberach, Germany*

Comparison of central activation patterns induced by physiological or pharmacological stimulation could be used to identify mechanism of actions in feeding studies. In order to examine activation patterns within the rat brain by a physiological, orexigenic stimulus, we used a scheduled feeding paradigm as experimental background. Male rats ($n = 9$) were trained to feed for 3 h/daily for 9 days. On the last day of the experiment, animals (FD, $n = 3$) received no food during the 3 h period or chow ad libitum (FR, $n = 3$). Animals were perfused and brain sections taken. Activated neurones within the rat brain were assessed by mapping of protein expression for the neuronal-activation marker and immediate early gene product c-FOS (c-FOS-IR). Immunoreactivity was subjected to further software-supported quantitative analysis in selected brain regions. A clear difference in the expression pattern of c-FOS-IR was observed in the nucleus accumbens, several hypothalamic, thalamic and amygdaloid nuclei and in the nucleus of the solitary tract. A subsequent neurochemical characterization of c-FOS-IR in FD rats within selected hypothalamic regions showed strong colocalisation with Orexin A, but no co-staining for melanin concentrating hormone (MCH) immunoreactivity in the lateral hypothalamic area. In the arcuate nucleus, c-FOS was not co-localized with adrenocorticotrophin hormone immunoreactivity. In the tuberomammillary nucleus, activated neurones in brains of both animal groups show strong colocalization with Glutamate decarboxylase (GAD67). This work provides a first description of c-FOS activation patterns in a scheduled feeding paradigm. This may ultimately help to understand patterns of neuronal activation within feeding circuitries in the rat brain.

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High-fat feeding (HFF) produces early onset adiposity in serotonin (5-HT) 2C receptor (R) mutant (M) mice. L. Asarian[#], N. Geary, W. Langhans. *Institute of Animal Sciences, ETH Zurich, CH-8603 Schwerzenbach, Switzerland*

Tecott and colleagues reported that 5-HT2CR-M mice at the age 2–3 months are hyperphagic and hyperactive and of similar weight and adiposity as wild-type (WT) littermates. By 9 months of age, M mice increase the efficiency of muscular work, which, with continued hyperphagia, causes obesity. Here, we investigated the effect of HFF (60% energy) in 2 months old M and WT mice that were either fed ad lib or weight matched to the chow controls of each genotype. Insulin-sensitivity tests were conducted 0, 1, 3 and 5 weeks later. At 5 week, fat and liver weights and plasma cytokine levels were measured. Ad lib HFF M mice had higher energy intakes and body weights than WT HFF mice. The development of insulin resistance was similarly exacerbated in ad lib-fed and weight-matched HFF mice vs. chow mice, and at 5 week this was greater in M than WT mice. 5-HT2CR-M HFF mice had higher liver weights than HFF-WT or chow-fed mice. Plasma cytokine levels of TNF-α, IL-6 and MCP-1 were not detectably affected by either diet or genotype. These data suggest (1) that defects in 5-HT signaling via the 2CR can lead to early onset obesity in addition to the previously reported 'middle-aged' onset obesity in mice, (2) that the 5-HT2CR should be considered a target for development of therapies for HF-induced obesity, and (3) that the effect of HFF on development of insulin resistance is independent of hyperphagia and weight gain for at least 5 week of HFF.

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Underweight compared with normal-weight rats release more dopamine in the nucleus accumbens shell when bingeing daily on sugar. N.M. Avena[#], P. Rada, B.G. Hoebel. *Department of Psychology, Princeton University, Princeton, NJ 08540, USA*

Underweight animals have low basal dopamine (DA) levels in the nucleus accumbens (NAc) shell and more readily self-administer drugs of abuse. Such animals also have a blunted DA release in response to eating, which may perpetuate binge eating. Since rats bingeing on sugar each day show behavioral signs of dependence and repeatedly release DA in response to tasting sugar, the present study tested whether such rats release more DA when they are underweight. Rats were maintained on a diet of 8-h access to chow with a 10% sucrose solution also available for the first 2 h, for 21 days. Microdialysis performed on day 21, at normal body weight, revealed an increase in extracellular DA to 130% of baseline in response to drinking sucrose. After day 21, the rats were food and sucrose restricted so that by day 28 they were at 85% body weight. Microdialysis revealed that rats released more DA when drinking sugar at 85% body weight (180% of baseline). A control group was tested in the same manner but tasted sugar only on day 1, 21 and 28. At normal body weight, control animals had a non-significant rise in DA when tasting sucrose. On day 28, at 85% body weight, there was a small increase (120%) in DA release; however, this was much lower than the 180% increase observed with the rats with daily sugar access. These findings suggest that sugar-dependent, underweight rats may have a heightened dopaminergic response to sugar that may lead to binge eating and contribute to their dependency.

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A potential new indicator of weight gain: Autonomic nervous system activity (ANSA). E. Aysin[a], K. Nonogaki[b], M. Lowe[c]. [a]*Ansar Group Inc., Philadelphia, PA 19107, USA.* [b]*Center of Excellence, Division of Molecular Metabolism and Diabetes, Tohoku University Graduate School of Medicine, Japan.* [c]*Department of Psychology Drexel University, Philadelphia, PA 19102, USA*

A relatively new and promising predictor of susceptibility to weight gain is sympathetic and parasympathetic nervous system activity (SNSA, PSNA) and their interactions. Autonomic nervous system (ANS) dysfunction may have an effect on energy expenditure and contribute to the development of obesity. Twenty-three 18–19-year-old subjects, who were non-diabetic and not on medications, were studied. Sixteen subjects had normal weight (body mass index (BMI) 18.5–25 kg/m^2). Seven were overweight ($25 < BMI < 29.9\,kg/m^2$). SNSA and PSNA were measured using a non-invasive ANS monitor which allows monitoring of ANS using non-stationary spectral analysis (ANX3.0 Ansar, Inc.) of heart rate and respiratory signals. We found a significant correlation between SNSA and both BMI and leptin ($P < 0.05$). Overweight subjects had significantly lower E/I ratio (the mean of the longest R–R interval in expiration divided by the shortest in inspiration during deep breathing at 6 breaths/min) and valsalva PNSA than normal subjects ($P < 0.05$). Cardiac SNSA was higher in the subjects with higher BMI. Higher SNSA may be a regulatory response to burn fat and minimize weight gain. Leptin is an indicator for obesity. We found significant correlation between plasma leptin and cardiac SNSA. ANS changes with weight gain. ANSA may serve as a good indicator for weight gain. Early identification of ANS dysfunction may prove to be an important aid in the identification of those prone to weight gain and thus to the prevention of obesity.

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OLETF rats have increased motivation to obtain sucrose pellets on a progressive-ratio schedule that is not mediated by Y1 receptors in the dorsomedial hypothalamus (DMH). A.V. Azzara, X. Li, G.J. Schwartz. *Albert Einstein College of Medicine, Bronx, NY 10461, USA*

The Otsuka-Long-Evans-Tokushima Fatty (OLETF) rat is obese and hyperphagic. Additionally, OLETF animals show increased sensitivity to sweet tastes. This phenotype is typically attributed to the lack of CCK-1 receptors in these rats. However, recent work has demonstrated that, in addition to lacking CCK-1 receptors, OLETF rats also have elevated neuropeptide Y (NPY) in the DMH. The relative contribution of this increased NPY to the OLETF hyperphagic phenotype is not known. NPY has been proposed to increase food intake through a specific increase in the appetitive phase of food intake. We hypothesized that elevated DMH NPY in the OLETF animals might contribute to their hyperphagia by increasing their appetitive behavior. To test this hypothesis, we compared OLETF rats and LETO controls on a PR2 bar-pressing schedule, responding for 45 mg sucrose pellets. OLETF rats displays increased operant responding, emitting more pokes and reaching higher breakpoints than did LETO rats. When food deprived to 85% of baseline body weight, both groups increased responding, however the OLETF rats always responded more than did the LETO rats. To determine if this increased responding was due to DMH NPY acting at DMH Y1 receptor sites, we administered the selective Y1 antagonist 1229U91 bilaterally in the DMH. 1229U91 failed to reduce operant responding in either group, demonstrating that DMH Y1 receptors do not mediate appetitive responding for food. These data suggest that DMH NPY acts outside the DMH to promote appetitive responding for food in OLETF rats. Supported by DK065790.

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Stimulation of food intake by mu opioid agonists is blocked by NPY antagonists. M.J. Barnes, D. Braymer, G.A. Bray. *Pennington Biomedical Research Center, Dietary Obesity Laboratory, Baton Rouge, LA 70808, USA*

Mu opioid agonists increase food intake and fat preference when animals have a choice between high- and low-fat diets. In previous studies using histological analysis, we showed that mu opioid receptors were expressed on NPY neurons in the hypothalamus. This suggeted that stimulation of mu opioid receptor might increase the release of NPY, and that the effects of mu agonists might be blocked by blocking NPY receptors. Here, we demonstrated that intracerebroventricular (ICV) injection of DAMGO, a selective mu opioid receptor agonist, increased the gene expression of NPY. To examine the blockade of NPY Y1 receptors, male Long-Evans rats were implanted with ICV cannulas. On the experimental day, animals were injected with saline/saline, saline/DAMGO, saline/BIBP (NPY Y1 antagonist), or BIBP/DAMGO. ICV injection of saline/saline and saline/BIBP had no effect on food intake. Saline/DAMGO significantly increased food intake and this effect was blocked when the NPY Y1 antagonist (BIBP) was administered prior to DAMGO. Taken together, these results suggest that mu opioid receptors increase food intake by increasing the release of NPY. Supported by NIH DK32089 and DK064584.

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Inhibitory effects of LPS on hypothalamic nuclei involved in the control of food intake. C. Becskei[a,#], N. Hernadfalvy[b], D. Arsenijevic[b], T.A. Lutz[a], W. Langhans[b], T. Riediger[a]. [a]*Institute of Veterinary Physiology, University of Zurich, CH-8057 Zurich, Switzerland.* [b]*Institute of Animal Sciences, ETH Zurich, CH-8603 Schwerzenbach, Switzerland*

The hypothalamic arcuate nucleus (ARC) and the lateral hypothalamic area (LHA) represent key structures in the central control of food intake. Both brain areas express c-Fos, a marker of neuronal activation, in 14 h food-deprived mice. Refeeding with chow reverses this activation to levels observed in ad libitum-fed mice. The Gram-negative bacterial cell wall component lipopolysaccharide (LPS) is widely used to model the clinical features of bacterial infection, in particular the anorexia. This study investigated whether an anorectic dose of LPS inhibits ARC and LHA neuronal activity similarly to refeeding. Furthermore, we studied whether LPS modulates the activity of orexin-A positive (OX+) LHA neurons. Food-deprived (14 h) BALB/c mice were injected with LPS (40 μg/mouse sc) or vehicle. Mice were sacrificed 4 or 6 h later and brain sections were processed for c-Fos and orexin-A immunoreactivity. Four hours after injection, LPS reduced the number of c-Fos positive cells in the ARC and in the rostral region of the LHA, which only contains orexin-A negative cells (OX−), but had no effect on c-Fos in LHA OX+ neurons. Six hours after injection, LPS reduced c-Fos expression in the rostral area of the LHA (OX− cells) and in the LHA OX+ neurons, but not in the ARC. The results show that LPS and feeding-related stimuli affect the same neural structures (ARC and LHA) and neurochemical mechanisms and suggest that these effects of LPS contribute to its anorectic properties. The inhibitory effect of LPS on OX+ neurons might also be involved in LPS-induced inactivity.

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Intake suppression following intracerebroventricular and intrahippocampal CCK-8. M. Behl, E.K. Walls, J. Mak, T.L. Davidson. *The Ingestive Behavior Research Center, Purdue University, West Lafayette, IN 49707, USA*

The hippocampus is populated with receptors for cholecystokinin (CCK), a gut-brain hormone implicated in meal termination. Rats lacking hippocampal CCK-A receptors show (a) excessive food intake and body weight gain and (b) impaired hippocampal-dependent learning and memory. A number of studies show that interference with hippocampal functioning impairs the extinction of food rewarded responses and the suppression of eating. It may be that both extinction and inhibition of food intake depend on hippocampal CCK receptor function. To investigate this possibility, we examined the effects on food intake of infusing the CCK receptor agonist CCK-octapeptide (CCK-8) or saline bilaterally into the dorsal and ventral segments of the hippocampus (250 pmol/0.3 μl/side), respectively. These sites for cannulae implantation were chosen based on our earlier findings that infusion of protein synthesis inhibitors at these specific loci interfered with extinction of food-rewarded appetitive responding. In addition, food intake was measured in a third group of rats after third intracerebroventricular (i3vt) infusion of CCK-8 at a volume and dose that was the same as that used for intrahippocampal infusions. CCK-8 reduced food intake relative to saline following i3vt infusions, but not following infusion at the dorsal or ventral hippocampal sites. A second experiment investigated the possibility that while neither the dorsal nor ventral hippocampal segments are directly sensitive to intake suppression by CCK-8, detection of CCK-8 at one or both of these sites augments meal termination by peripheral CCK-8.

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Development of neuropeptide Y overexpression in the dorsomedial hypothalamus in OLETF rats lacking cholecystokinin (CCK) A receptors. S Bi[a], J. Hyun[a], M. Schroeder[b], O. Zagoory-Sharon[b], A. Weller[b], T.H. Moran[a]. [a]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.* [b]*Psychology Department and Gonda Brain Research Center, Bar Ilan University, Israel*

Adult Otsuka Long-Evans Tokushima Fatty (OLETF) rats lacking CCK-A receptors are hyperphagic and obese. Pair feeding OLETF rats to the intake of LETO controls normalized their body weight, and arcuate neuropeptide Y (NPY) and proopiomelanocortin (POMC) gene expression. In contrast, pair feeding resulted in NPY overexpression in the dorsomedial hypothalamus (DMH) of OLETF rats. Since neonatal OLETF rats are also hyperphagic in independent ingestion tests and gain more weight than LETO controls, we assessed when during development alterations in hypothalamic gene expression might be evident. In LETO rats, DMH NPY beginning from low levels on postnatal day 6, expression was 4-fold increased on day 15, and back to low levels on day 65. Compared with LETO controls, OLETF rats had a 7-fold increase in DMH NPY expression on day 15. Levels returned to those of LETO rats on day 37. In contrast to the patterns of DMH NPY expression, developmental patterns of arcuate NPY expression did not differ between OLETF and LETO rats. In LETO rats, arcuate POMC expression showed a gradual developmental increase from low levels on day 6. There was a similar developmental progression in OLETF rats but levels were significantly elevated beginning on day 23. Together, these data are consistent with an etiological role for altered DMH NPY signaling in the hyperphagia and obesity of OLETF rats. Supported by DK57609 and US–Israel Binational Science Foundation. OLETF and LETO rats were a gift of Otsuka Pharmaceutical, Japan.

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Dopamine and norepinephrine reuptake inhibition both contribute to bupropion-induced hypophagia in obese mice. S.K. Billes, M.A. Cowley. *Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR 97006, USA*

Bupropion is an antidepressant that causes mild but significant and sustained weight loss in clinical trials with obese patients. Bupropion inhibits the reuptake of the monoamines, dopamine and norepinephrine. Both dopamine and norepinephrine are important neurotransmitters in brain systems regulating energy balance but the individual contributions of each monoamine to bupropion-induced weight loss are unclear. Because obesity is associated with changes in monoamine turnover and receptor expression, the efficacy of dopamine and norepinephrine reuptake inhibitors at reducing food intake and body weight in obese animals requires further investigation. To identify the therapeutic potential of monoamine reuptake inhibitors in the treatment of obesity, we assessed the effects of bupropion, GBR 12783, and nisoxetine in lean and diet-induced obese (DIO) mice. Administration of a dual monoamine reuptake inhibitor (bupropion), a selective dopamine reuptake inhibitor (GBR 12783), and a selective norepinephrine reuptake inhibitor (nisoxetine) reduced food intake and body weight in lean mice. The effects of dopamine and norepinephrine reuptake inhibitors on energy balance were additive. In obese mice, bupropion, GBR 12783 and nisoxetine were equally or slightly more effective at reducing acute food intake. Furthermore, the additive effects of dopamine and norepinephrine reuptake inhibitors on food intake were preserved in obese mice. This data provides the first evidence that inhibiting monoamine reuptake reduces energy intake in obese mice and supports further investigation into the therapeutic efficacy of monoamine reuptake inhibitors in treating obesity.

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Dieting, junk food, and stress alter food reward in rat models of binge-eating. M. Boggiano, P.C. Chandler, C.E. Pritchett, M.L. Smith. *Department of Psychology, University of Alabama at Birmingham, Birmingham, AL 35294, USA*

Sated rats with a history of caloric-restriction (HCR) and intermittent access to palatable "junk" food (IPF), double their PF-intake when stressed. If stressed while hungry, HCR rats eat more than non-stressed hungry HCR rats ($P<0.01$), suggesting they binge-eat for reward. Indeed, opioids block and exaggerate the binge, respectively, at doses without effect in controls. PF naturally releases opioids and may explain why a bite of PF triggers a chow-binge but only in HCR rats. Protracted access to IPF or daily PF decreased bone-mass density and HCR alone disrupted the association between accumbens dopamine and serotonin turnover ($P<0.001$). IPF + HCR reduced prefrontal DA and serotonin levels. These and other physiological changes (e.g., insulin/glucose, CORT/ACTH, bone-mass) and behavioral-indices of depression, are consistent with comorbid symptoms of binge-eating disorders. Lastly, some rats naturally eat as much food when hungry as when sated but only when PF is available. When stressed, they eat less chow (vs. PF-undereaters that eat less PF not less chow), and if forced to eat a nutritive high-fat diet, only half of each group become obese. Clearly, food reward is altered in these rat models of binge-eating. Clues to treating binge-eating in humans are implicated but also, as we continue uncovering the specific substrates underlying changes in food reward, more targeted treatments for obese non-binge vs. obese-binge vs. non-obese binge-eaters should be forthcoming.

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Examination of caseinomacropeptide (CMP) as a bioactive compound in whey inducing satiety. B. Burton-Freeman. *University of California, Davis, CA 95616, USA*

Whey protein has been reported as more satiating than other protein types. We hypothesized that the satiety effects of whey are a function of caseinomacropeptide (CMP) content, a stimulator of cholecystokinin (CCK). In a within-subjects design, 10 men and 10 women consumed 1 of 4 preload shakes (300 ml, 235 kcal), ~1 week apart. Preload shakes (PS) differed by protein source and content: (PS-A) whey protein isolate; (PS-B) whey protein-minus CMP; (PS-C) low protein control; (PS-D) CMP isolate (1 g). PS protein energy was 46%, 44%, 2% and 3%, respectively, and fat energy, 4–5%. Sensory qualities were matched. Subjective satiety, insulin, glucose and CCK were measured for 60 min at 15 min intervals after PS consumption, at which time a test meal was provided. Measures of subjective satiety (e.g. hunger, fullness, etc.) indicated a significant PS effect ($P<0.001$) and gender × PS interaction ($P<0.01$). Women were more sensitive to the PS protein manipulations than men, scoring PS-A and PS-B as more satiating than PS-C or PS-D. Available data from 8 of 20 subjects indicates higher insulin for PS-A and PS-B compared to PS-C and PS-D ($P<0.001$) and no effect on test meal energy intake; although alterations in macronutrient intake may reflect influences on food selection at subsequent meals. From the data available, the satiety effect of whey is not a function of CMP at the doses tested. However, complete analyses are expected to reveal important details for describing CMP- and whey-associated satiety in young adult men and women.

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Cyclic estradiol treatment modulates the effects of ghrelin on food intake and meal patterns in female rats. P.C. Butera, A.J. Fura, S. Nodzo. *Niagara University, Department of Psychology, Lewiston, NY 14109, USA*

Ghrelin is a peptide hormone synthesized principally in the stomach that binds to the growth hormone secretagogue receptor in the brain. Ghrelin is also an important signal for the regulation of food intake and energy balance, and ghrelin treatment increases food intake and body weight in male rodents. Recent findings indicate that ghrelin production and its effects on behavior and metabolism are influenced by ovarian hormones, suggesting that ghrelin/estrogen interactions may underlie the effects of estradiol on feeding. This experiment examined the ability of estradiol to modulate the orexigenic effects of ghrelin in ovariectomized rats. Three weeks after surgery, animals ($n=17$) were treated with estradiol benzoate (5.0 μg) or the oil vehicle for 2 days. Animals then received an ip injection of ghrelin (6 or 12 nmol) or saline 1 h before dark onset, and food intake and meal patterns were measured during the 12-h nocturnal period. The ANOVA revealed significant main effects of EB and ghrelin, as ghrelin (12 nmol dose) increased food intake by 16% in the oil group and 8% in the EB group. The results also showed that ghrelin (both doses) increased meal number, but not meal size, in oil-treated but not EB-treated rats. As expected, EB decreased meal size and increased meal number during control tests. These data indicate that estradiol can modulate the effects of ghrelin on feeding behavior, and suggest that the inhibitory effects of estradiol on food intake may involve an attenuation of orexigenic signals like ghrelin.

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Sex and strain differences impact learning and motivation in DR and DIO rats. J.B. Chambers, J.U. Heiman, D.J. Clegg, S.C. Benoit. *University of Cincinnati, Department of Psychiatry, Cincinnati, OH 45237, USA*

Diet resistant (DR) and diet-induced obese (DIO) rats have been extensively used as animal models in studies of energy balance and obesity. However, there are relatively few reports detailing other behavioral characteristics of these animals. Our previous data demonstrated impaired operant responding for sucrose in DIO, relative to DR rats. Further, DIO rats maintained on high-energy diet for 4 weeks exhibited reduced performance in progressive ratio schedules and attenuated spatial cognition. In the current studies, we assessed motivation (via PR response schedules) and spatial cognition (via spontaneous alternation tasks) in outbred DR/DIO rats and inbred female DR/DIO strains. Results demonstrate that outbred male DIO rats have significantly impaired performance in behavioral assays of learning and memory compared to outbred DR rats. No significant difference was observed in homecage sucrose intake between outbred DR and DIO rats, consistent with our earlier findings from inbred rats. Consistent with our earlier data, female DIO rats exhibit significantly reduced spontaneous alternation compared to female DR rats. However, we also observed a significant effect of estrus phase on spontaneous alternation performance in the female inbred rats. Collectively, these results suggest that (1) Regardless of DR/DIO strain differences, estrus cycle significantly impacts female rats' performance of learning and motivation tasks, (2) DIO rats are more susceptible to the deleterious effects of dietary fats on CNS processes, and this effect is independent of sex, and (3) Both inbred and outbred DIO rats exhibit reduced motivation compared to DR rats.

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Low doses of peptide YY(3-36) (PYY) inhibit food intake without producing malaise in rats. P.K. Chelikani, A.C. Haver, R.D. Reidelberger. *VA Nebraska Western Iowa Health Care System and Creighton University, Omaha, NE 68105, USA*

PYY is postulated to act as a hormonal signal from gut to brain to produce satiety. A meal produces a 2–3 h increase in plasma immunoreactive PYY in humans and rats. We previously reported that a 3 h IV infusion of PYY dose-dependently inhibits food intake in rats (ED50 = 15 pmol/kg/min), and that 1 h IV infusions of PYY at 30 pmol/kg/min every other hour for 10 d produce a sustained reduction in daily food intake (~20%) and adiposity (35%). Whether PYY reduces food intake by producing satiety or malaise remains controversial. Here, we used a conditioned taste preference paradigm to address this issue. Four independent experiments determined whether a 2 h IV infusion of PYY at 2, 4, 8, and 15 pmol/kg/min produces a conditioned taste preference or aversion in rats. During an 8-d conditioning period, food-deprived rats ($n = 13$–16) received IV infusion of vehicle and PYY on alternating days, each paired with the consumption of a different flavored saccharin solution. On the next 2 d both flavored solutions were simultaneously offered and preferences were determined. During conditioning, PYY at 2, 4, 8 and 15 pmol/kg/min inhibited intake of the paired saccharin solution by approximately 10%, 30%, 30%, and 40%, respectively. Subsequent preferences for the solutions paired with these PYY doses were 50%, 55%, 34%, and 29%, respectively. Thus, low anorexic doses of PYY (2 and 4 pmol/kg/min) appear to inhibit food intake without producing malaise, which is similar to that reported for PYY in humans, and the prototypical satiety peptide CCK-8 in rodents.

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Relative potencies of anorexigenic substances in suppressing food intake in freely feeding rats. P.K. Chelikani, A.C. Haver, R.D. Reidelberger. *VA Nebraska Western Iowa Health Care System and Creighton University, Omaha, NE 68105, USA*

There is a growing consensus that multi-drug therapy aimed at different components of the energy regulatory system will be required to produce a significant reduction in adiposity in obese individuals. An initial step in this process is defining the dose–response effects of anorexigenic compounds known to act upon different components of the food intake regulatory system. We previously reported the dose–response effects of a 3 h IV infusion of CCK-8, amylin-related peptides, PYY(3-36) and GLP-1 at dark onset on food intake in freely feeding rats. In the present study, we used the same experimental model to determine the anorexigenic potencies of cannabinoid receptor antagonist AM251, opioid receptor antagonist naloxone, leptin, and melanocortin receptor agonist MTII. In separate experiments, rats ($n = 13$–16) with jugular vein catheters received a 3 h IV infusion of leptin (30–200 pmol/kg/min), MTII (50–250 pmol/kg/min), AM251 (300–10,000 pmol/kg/min) or naloxone (1000–30,000 pmol/kg/min). The potencies (ED 50 pmol/kg/min) and maximal inhibition (%) of leptin, MTII, AM251, and naloxone in reducing food intake during the 3 h infusion period were: 50 (27%), 150 (29%), 2700 (98%) and 5300 (52%), respectively. Together with our previous data, the rank order of potencies [ED 50 s in pmol/kg/min] of the various anorexigenic substances are: salmon calcitonin [1], amylin [6], PYY(3-36) [15], CCK-8 [18], GLP-1 [23], calcitonin-gene-related peptide [26], adrenomedullin [35], leptin [50], MTII [150], AM251 [2700], and naloxone [5300]. It remains to be determined whether chronic administration of these anorexigenic substances either alone or in combination can produce a sustained reduction in food intake and adiposity in obese rodents.

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Sustainable customs of food intake and physical activity that induce loss of weight. C. Chesneau[a], L. Thibault[a], S.H. Baek[b,c], D.A. Booth[b]. [a]*School of Dietetics and Human Nutrition, McGill University, Ste. Anne de Bellevue, Que., H9X 3V9, Canada.* [b]*Food Quality & Nutritional Psychology, University of Birmingham, UK.* [c]*College of Medicine, Dongguk University, Gyeongju, South Korea*

The rapid rise in obesity is partly attributable to neglect of research into effects on body weight of specific patterns of eating and exercise, and their support from the local environment of food, transport and leisure. Self-described habits validated in England were translated into French and adjusted to customs in Montreal. Healthy-weight Francophone volunteers recorded their weight once a week and then recalled the timings of the last occasion and the time before at which they had eaten or moved in each particular way. The pair of timings for a custom gave that volunteer's exact frequency per week over that calendar period. Across the 14 respondents completing the study, correlations were calculated between change in frequency of each custom and change in weight over intervals of 2–5 weeks, during which time the effects on weight of a change in frequency of a specific custom come to asymptote because lean mass and so BMR changes as well as fat mass. Some behavior did not change in frequency in enough people for consistent correlations to be observed. However, other customs showed correlations between changes in frequency and in weight that were consistently positive or negative across the different intervals. Lagged correlations can support effects of behavior on weight, rather than weight change provoking behavior change. We conclude that, if the weight-lowering direction of change in each specific local pattern of behavior were implemented in succession, a substantial loss in weight would accumulate over the months that the new frequencies continued.

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Increased anxiety-like behavior during the post-stress period in mice exposed to repeated restraint. C. Chotiwat, R.B.S Harris. *Department of Foods and Nutrition, University of Georgia, Athens, GA 30602, USA*

Mice exposed to repeated restraint (2 h of restraint for 3 consecutive days) lose weight and do not return to the weight of non-stressed controls after restraint ends. These mice also exhibit an exaggerated endocrine response to mild stressors in the post-stress period. To determine if other aspects of the stress response were altered mice were repeatedly restrained then evaluated for anxiety-like behavior in various behavioral tests. Restrained mice exposed to the defensive withdrawal apparatus and the marble burying test 6 and 17 days, respectively, after restraint displayed no increase in anxiety-like behavior. Twelve days after the end of restraint half of the control and the restrained mice were subjected to the mild stress of an intraperitoneal injection of saline before placement in an elevated plus maze (EPM). Restrained mice that were not subjected to mild stress showed the same level of anxiety as the control mice exposed to mild stress. Placement in a light–dark box 20 days after restraint also resulted in an increase in anxiety-like behavior in restrained mice when compared with controls. Although baseline corticosterone concentrations were similar, restrained mice released more corticosterone than non-restrained controls exposed to defensive withdrawal or EPM apparatus. These results suggest that repeated restraint induces an exaggeration of both endocrine and behavioral responses to subsequent mild stressors. This post-stress hypersensitivity to mild stress may contribute to the sustained reduction in the body weight of restrained animals. Supported by NIH Grant MH06828101.

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Infants do request food at the hunger glycemic level, but adults do not any more. M. Ciampolini. *Firenze Università, Meyer Hospital, I-50132 Firenze, Italy*

We trained mothers to interpret their 2-year toddlers' food cues appropriately by pairing measurements of blood glucose concentrations with the child's food requests. Furthermore, they adjusted meal-size and content to near the subsequent attainment of hunger-producing level to next mealtime, and reported 7 d-food-diary before and after 50 days training. A total of 40 infants exhibited 94.0 ± 6.4 mg/dl glycemic pre-prandial average (all over 85.4 mg/dl) before training, decreased to 77.6 ± 7.5 mg/dl and reduced energy intake from 1003 ± 276 kcal/d to 747 ± 233 kcal/d (−25.6%). Instead of measuring glycemia, energy expenditure (TEE) was characterized by the doubly labeled water method and indirect calorimetry (SMR) in two further infant groups of same age, 10 in one and 14 in the other before and after training mothers. Daily energy intake decreased from 928 ± 212 to 684 ± 117 kcal (−26%) and from 941 ± 244 to 673 ± 172 kcal (−28%) in the two groups of toddlers, respectively. TEE fell from 80.1 ± 6.9 kcal per kg body weight per day to 67.8 ± 10.0 kcalkg^{-1} d^{-1} and SMR from 59.1 ± 8.0 kcalkg-1 d^{-1} to 49.3 ± 9.4 kcalkg^{-1} d^{-1}. Thus energy expenditure fell approximately 16% in both groups. The similar decreases in energy intake support the view that mothers and their infants can be trained to interpret and give, respectively, food cues appropriately. Without pairing sensation with measurement, most adults were instead unable to consistently recognize the hunger glycemic level (76.6 ± 3.7 mg/dl) in the Groningen and Cincinnati abstracts.

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Ghrelin antagonist is efficacious in lean but not obese rodents. D.J. Clegg, S.C. Benoit, L. Brown, R. Bush, O. Reizes. *Department of Psychiatry, University of Cincinnati and Metabolism Biology, Procter & Gamble Pharm. Inc., Cincinnati, OH 45243, USA*

Appetite suppression by blocking gut signals to the brain is considered an attractive pharmaceutical application for the treatment of obesity. One peptide great interest is the hormone ghrelin. Ghrelin is released from the stomach and increases meal size in humans. The ghrelin receptor is an attractive obesity target for pharmaceutical intervention. We studied the effects of a ghrelin antagonist (GhAnt) in lean and high-fat diet-induced obese rats. The GhAnt bound to the receptor with an apparent Ki of 140 nM and showed receptor selectivity. Third ventricle injection of the GhAnt into lean rats inhibited ghrelin-induced food intake. To assess specificity, we evaluated whether the antagonist could inhibit NPY-induced food intake, a signaling pathway believed to be downstream of the ghrelin receptor. We determined that the GhAnt did not inhibit NPY-induced hyperphagia. When the antagonist was evaluated in single or multiple day injections into the third ventricle of DIO rats, we observed no reduction in food intake or body weight. In contrast, the antagonist reduced food intake and body weight in lean rats in a dose–response fashion. We next food restricted the rats for a period of 2 weeks to increase circulating ghrelin and performed third ventricle injections of the antagonist. Despite restriction-induced increases in plasma ghrelin in the DIO rats, we found no effect of the antagonist at inhibiting food intake. Thus, ghrelin antagonism does not appear to be a reliable method of weight reduction in rat models of dietary-induced obesity.

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Pre-surgical taste experience attenuates the partial loss of behavioral responsiveness to quinine after gustatory deafferentation of the tongue. M.C. Clinton, M. Garcea, A.C. Spector. *Department of Psychology & Center for Taste & Smell, University of Florida, Gainesville, FL 32610, USA*

To extend prior findings, we examined whether pre-surgical experience with quinine would thwart the blunted lick avoidance of this bitter-tasting ligand seen in rats following certain gustatory nerve transections. Rats received either SHAM surgery or transections of the chorda tympani nerve (CTx), the glossopharyngeal nerve (GLx), or both nerves (DBLx). Thirsty rats were trained to lick fluid in a lickometer. They were then tested in a brief-access taste test for three consecutive daily 40-min sessions pre-surgically and post-surgically. Roughly half of the rats in each group received water pre-surgically (PreW) and the others received quinine (PreQ; water, 0.003–3.0 mM; delivered in randomized blocks of 5-s trials with interposing water rinses). All rats were tested with quinine post-surgically. Rats in the PreQ-GLx and PreQ-DBLx groups displayed significantly more post-surgical avoidance of quinine than their PreW counterparts. The PreQ group did not display significantly more post-surgical avoidance than the PreW group in rats receiving SHAM or CTX, but there was a trend for this in the latter surgical condition. Another group that had the gustatory branches of the seventh and ninth cranial nerves transected displayed no concentration-dependent avoidance of quinine post-surgically despite receiving pre-surgical experience with the taste stimulus. Through what seems to emulate a conditioning process, quinine-stimulated signals in the glossopharyngeal nerve pre-surgically, can apparently enhance the effectiveness of quinine-stimulated signals generated in other gustatory nerves post-surgically, compensating for the partial loss of taste input after nerve transection to maintain some degree of behavioral responsiveness to the compound in this task.

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Different histories of optional fat access affect subsequent binge-type eating. R.L. Corwin, D.S. Johnson, F.H.E. Wojnicki. *Penn State University, Nutritional Sciences Department, University Park, PA 16802, USA*

The effects of three levels of restriction to an optional source of dietary fat (vegetable shortening) on subsequent binge-type eating were assessed. Five groups of ten male Sprague-Dawley rats were used. Chow and water were continuously available throughout. Moderate restriction phase: M: 1 h shortening access on Mon, Weds, Fri (MWF). M ate ad libitum during the 1 h access period. MP (M-clamped): 1 h MWF access to 2 g shortening. D: 1 h daily ad libitum shortening access. DP (D-clamped): 1 h daily access to 2 g shortening. 1 h shortening intakes were $M > D > DP = MP$ ($P < 0.05$). After 5 weeks of moderate restriction, M and MP were maintained on the MWF ad libitum 1 h shortening access protocol, while D and DP were maintained on the Daily ad libitum 1 h shortening access protocol. Significantly different 1 h shortening intakes were $M > MP > D$, $M > DP$ ($P < 0.05$). C had no shortening throughout this phase. No restriction phase: M, MP, D, DP: continuous (24/7) shortening access. C had no shortening. Significantly different shortening intakes on day 1: $M > D$, $M > DP$ ($P < 0.05$). After 5 week all groups were maintained on ad libitum 1 h protocols (M, MP, C: MWF; D, DP: daily). Significantly different 1 h intakes were $C > M > D$, $C > MP$, $C > DP$ ($P < 0.05$). Complete restriction phase: no shortening. After 5 week, all groups were returned to their respective ad libitum 1 h protocols (M, MP, C: MWF; D, DP: Daily). One hour intakes were $M = MP = C > D = DP$ ($P < 0.05$). *Summary*: (1) moderate (clamped) restriction protected against subsequent bingeing, (2) no restriction (continuous shortening access) attenuated subsequent bingeing, (3) complete restriction (no shortening) restored subsequent bingeing.

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Antagonism of hindbrain NMDA receptors containing NR2B and/or NR2A subunits increases the size of a sucrose meal.
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Administration of either a non-competitive (MK-801), or a competitive (D-AP5) NMDAR antagonist, directly into the dorsal vagal complex (DVC) delays satiation and increases meal size. This suggests that NMDAR in the DVC participate in the control of food intake. However, NMDAR are heteromers made up of distinct, but different ion channel subunits (NR1A-H; NR2A-D and NR3). Different combinations of subunits are expressed in different NMDAR subpopulations, and efficacy of specific receptor antagonists is affected by the subunit composition of the receptor heteromers. Ifenprodil, a non-competitive, and D-CPPene, a competitive NMDAR antagonist reportedly exhibit selectivity for NR2A and NR2B subunits. In this study, we employed ifenprodil and D-CPPene to assess the role of hindbrain NR2A and/or NR2B subunits in food intake control. We measured deprivation-induced intake of 15% sucrose solution following fourth ventricular (4 V) injection of either saline or various doses of ifenprodil or D-CPPene. Ifenprodil (0.5, 1.0, 1.5, 3.0 μg/3 μl) did not increase 60-min sucrose intake at any dose (16.2 ± 0.4 ml, saline; 14.7 ± 0.8, 13.7 ± 1.0, 15.7 ± 0.9, and 12.5 ± 1.2, ifenprodil doses, respectively). However, D-CPPene (100 ng/3 μl), significantly increased 60-min sucrose intake (19.1 ± 1.2 ml vs. 15.7 ± 0.6 ml). It is not yet clear why one antagonist increased intake and the other did not. It is possible that D-CPPene was more effective in penetrating the DVC than ifenprodil. Our current interpretation is that hindbrain NMDAR participating in control of food intake contain NR2A/B subunits. Use of other subunit selective NMDAR antagonist may be productive tools for investigating glutamatergic control of meal size. Supported by DK-52849, NS-20561.

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Estrogen decreases the latency to begin water intake in ovariectomized rats given a hypertonic NaCl infusion.
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Our previous work in rats suggests that estrogen does not affect water intake stimulated by a systemic salt load; however, the dose or route of administration may have precluded detecting more subtle effects of estrogen on osmotically stimulated water intake. Accordingly, we examined the effect of estrogen treatment on water intake by ovariectomized (OVX) rats in response to a slow intravenous infusion of hypertonic NaCl. Adult female rats were OVX and allowed 7–10 days to recover before being implanted with chronic, indwelling femoral venous catheters. After another 24-h recovery, OVX rats were treated with estradiol benzoate (EB; 10 μg/0.1 ml oil, sc; $n = 9$) or the oil vehicle (OIL; 0.1 ml, sc; $n = 9$) on two consecutive days. During these days, rats also were adapted to test procedures, including the connection of catheters to tubing attached to infusion pumps and the presentation of water in graduated drinking tubes. Forty-eight hours after the second injection, rats were infused with 2 M NaCl (35 μl/min, iv) for 60 min. We recorded the latency to begin drinking and measured water intake at 15, 30, and 60 min during the infusion and 30 min after the infusion. EB-treated rats began to consume water after 13.9 min of NaCl infusion, whereas OIL-treated rats took significantly longer (35.0 min) to begin drinking. Interestingly, however, there were no differences in water intake at any time point. These results suggest that estrogen increases the sensitivity to an osmotic load in regard to water intake, as also has been reported for osmotically stimulated vasopressin release.

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Leptin does not regulate the size of white fat transplants. J. Davenport, R.B.S. Harris. *Department of Foods and Nutrition, University of Georgia, Athens, GA 30605, USA*

Lipectomy and fat transplant studies allow examination of the regulation of body fat content by directly adjusting the amount of white fat present without modifying the size of adipocytes in endogenous fat depots. Leptin has been hypothesized to be a negative feedback signal in the regulation of energy balance and control of body fat mass. In a previous study we found that mice that were leptin deficient or that did not express leptin receptors accurately compensated for removal of fat by lipectomy. Another study demonstrated that wild-type mice compensate for increased body fat achieved by transplant. Therefore, we determined whether db/db mice deficient either in the long-form leptin receptor (C57BL/6J db^{Lepr}/db^{Lepr}) or in all membrane-bound leptin receptors (C57BL/6J db^{3J}/db^{3J}) would respond to an increase in body fat produced by fat transplant. When female db/db mice received homologous inguinal fat transplants or males received epididymal transplants the large pieces (1.5–2.0 g) of tissue remained viable but reduced in size by 20–50% over 84 days and there was little evidence of a compensatory reduction in endogenous body fat of recipient mice. In a second study fat from wild-type mice was transplanted into db/db littermates. The small fat transplants (0.3–0.6 g) increased in weight approximately three-fold over 84 days. Again there was no compensation by endogenous fat depots. Because wild-type fat expresses leptin receptors and db/db mice are hyperleptinemic, these results demonstrate that leptin does not act directly on white fat to reduce body fat mass. Supported by NIH Grant DK053903.

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Food viscosity as a determinant of caloric compensation and utilization. T.L. Davidson[a,b], E.K. Walls[a,c], A. Ferguson[b], J. Mak[b], S.E. Swithers[a,b]. [a]*The Ingestive Behavior Research Center.* [b]*Department of Psychological Sciences.* [c]*Department of Biological Sciences, Purdue University, West Lafayette, IN 49707, USA*

Our recent research with rats confirms earlier findings with humans that calories consumed in low viscosity form produce weaker compensation (i.e., smaller reduction in subsequent caloric intake) than calories in consumed in higher-viscosity form. In rats, intake of low-viscosity foods was also associated with increased weight gain and body adiposity. Here, we report the effects of consuming equicaloric high- and low-viscosity substances on rats' core body temperature, a physiological parameter related to energy regulation. Rats were implanted with small radiofrequency transmitters to monitor continuously core body temperature and gross behavioral activity. These measures were assessed during a 1 h period in which rats consumed 10 g of chocolate Ensure Plus®. For one group, 3.0% guar was added to produce a high-viscosity (pudding-like) supplement. For another group 3.0% water was added to produce a equicaloric, but low-viscosity (milk-like) supplement. Consumption of low-viscosity Ensure produced a significantly smaller increment in body temperature than did high-viscosity Ensure. This pattern was also obtained when gelatin (without guar) was consumed by rats in high- and low-viscosity forms. Furthermore, the magnitude of this effect did not dissipate following repeated exposures to either the high- or low-viscosity supplements. In fact, repeated exposure to high-viscosity Ensure further weakened the ability of low-viscosity Ensure to increase body temperature. Viscosity level did not appear to be correlated with level of general behavioral activity. These data may help elucidate a role for food viscosity in energy and body weight regulation.

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Syndecan-3 modulates the rewarding properties of sucrose. J.F. Davis, O. Reizes, D.J. Clegg, S.C. Benoit. *Obesity Research Center, Department of Psychiatry, University of Cincinnati, Cincinnati, OH 45217, USA*

The hypothalamic melanocortin system is a critical regulator of ingestive behavior and energy balance. Recent data suggests that CNS syndecan-3, a neuronal specific heperan-sulfate proteoglycan, modulates signaling at the melanocortin-4 receptor. Mice with targeted deletion of the syndecan-3 gene (syn-3 -/-) are lean and resistant to dietary-induced obesity. However, the potential roles of reward or hedonics in the ingestive behavior of syn-3 -/- mice have not been examined. In these studies, we assessed the degree to which sucrose would condition a place preference in wild-type and syn-3 -/- mice. During the conditioning phase, syn-3 -/- mice consumed significantly fewer sucrose pellets than wild-type controls. Paradoxically however, syn-3 -/- animals required fewer conditioning trials and exhibited a significantly stronger place preference than controls. After four conditioning session's syn-3 -/- animals displayed a significant place preference whereas their wild-type counterparts did not. These data are consistent with the hypothesis that syndecan-3 facilitates the effects of endogenous AgRP. They also suggest that syndecan-3 may have multiple roles in regulating different kinds of ingestive behavior, including reward or hedonic properties of palatable foods.

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Decreased detection of gastric volume in young and old OLETF rats. B.C. De Jonghe[a], A. Hajnal[b], M. Covasa[a]. [a]*Department of Nutritional Sciences, Pennsylvania State University, University Park, PA 16802, USA.* [b]*Department of Neural and Behavioral Sciences, College of Medicine, Hershey, PA 17033, USA*

We have previously shown that CCK-1r-deficient Otsuka Long-Evans Tokushima (OLETF) rats do not display altered gastric emptying rates of both solid and liquid loads relative to control, Long-Evans Tokushima Otsuka (LETO) rats. The present study assessed whether or not OLETF rats showed deficient feeding or vagal responsiveness to volumetric gastric distension alone, independent of caloric effects of gastric loads. We performed experiments in two age groups (12 and 29 weeks) of OLETF and LETO rats in order to address possible alterations in gastric function as a result of increased body weight and blood glucose abnormalities in OLETF rats. To evaluate feeding responses to gastric distension, rats were sham-fed sucrose with concomitant gastric distension via balloon inflations of either 5 ml or 10 ml 0.9% saline, for 20 min. In both age groups, OLETF rats showed increased sham intake ($P > 0.05$) relative to LETO controls at both inflation volumes. To examine vagal response to gastric distension, Fos immunoreactivity was quantified in the dorsal vagal complex of OLETF and LETO rats subjected to an 8 ml gastric inflation for 90 min. OLETF rats showed an overall decrease in Fos expression specific to the nucleus of the solitary tract compared to LETO rats (110 ± 8.5 vs. 143 ± 9.8 Fos-li immunopositive nuclei; $P > 0.05$, for OLETF and LETO rats, respectively). These findings collectively demonstrate that OLETF rats exhibit decreased responsiveness to gastric distension, which may contribute to increased meal size in these animals. Supported by DK065709.

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Flavor preference conditioning by intraduodenal nutrients is unaffected in OLETF rats. B.C. De Jonghe[a], A. Hajnal[b], M. Covasa[a]. [a]*Department of Nutritional Sciences, Pennsylvania State University, University Park, PA 16802, USA.* [b]*Department of Neural and Behavioral Sciences, College of Medicine, Hershey, PA 17033, USA*

We have recently shown that CCK-1r deficient Otsuka Long-Evans Tokushima (OLETF) rats fail to integrate post-absorptive and orosensory effects of palatable sugars in a conditioning setting compared to Long-Evans Tokushima Otsuka (LETO) control rats. Previous pharmacological work by others using the CCK-1r antagonist devazepide showed the drug to have no effect in the expression of conditioned preference of intraduodenal (ID) nutrient infusion. To examine if OLETF rats exhibit an altered response to nutrient reinforcement relative to LETO, we tested the potency of ID polycose as unconditioned stimulus (US) in a conditioned flavor preference design. Briefly, rats ($n = 7$ per strain) were trained to associate ingestion of a clamped 7 ml volume of either cherry or grape-flavored saccharin solutions (conditioned stimulus, CS) with a 7 ml ID infusion of 8% polycose (US+) or 0.9% saline (CS−) during alternate one-bottle sessions, over 8 days. Conditioned flavor preference was assessed via 30 min two-bottle choice tests, where rats were allowed unlimited access to both CS+ and CS− solutions, in the absence of ID infusion. Results showed that OLETF and LETO rats did not differ in conditioned flavor preference for polycose ($73.3 \pm 2.5\%$ vs. $71.2 \pm 3.5\%$ for OLETF and LETO rats, respectively). This finding using the CCK-1r deficient rat support and extend previous data showing no effect by acute CCK-1r antagonism in normal rats, and confirms that CCK-1 receptors are not directly involved in the expression of conditioned flavor preference to post-absorptive stimuli. Supported by DK065709.

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Enhanced need-free sodium intake in the water deprivation–water repletion model. L.A. De Luca Jr, D.T.B. Pereira, A.S. Leite, J.V. Menani. *Department of Physiology & Pathology, School of Dentistry, 14801-903 Araraquara, Sao Paulo, Brazil*

Recurrent periods of water deprivation are common in animals and humans. A simple protocol to access preference intake for sodium in water-deprived rats has been developed in our laboratory. Daily sodium intake is enhanced in the classic hypovolemic models of sodium appetite. Therefore, we tested whether (1) the same type of enhancement occurs in male adult Holtzman (HTZ), Wistar-Kyoto (WKY) or spontaneously hypertensive (SHR) rats that were deprived of water every other week for 24–36 hours, for 3–4 weeks; (2) the enhancement is specific for sodium in HTZ ($n = 6$–10/group). Water was returned for 2 h (water repletion) after each period of water deprivation. Hypertonic (0.3 M) NaCl or palatable mineral solutions (to HTZ) and food were returned 2 and 4 h after the animal regained access to water. Daily 0.3 M NaCl, but not water, intake was enhanced after the third water deprivation in HTZ, but not WKY or SHR, in spite of similar urine sodium and volume loss or fall in plasma volume during water deprivation. In HTZ, enhanced daily fluid intake occurred to 0.15 M NaCl, but not water, 0.15 M $NaHCO_3$, 0.01 M KCl and 0.05 M $CaCl_2$. Thus, the enhancement of daily need-free intake seems strain and mineral specific.

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Searching for neurofunctional markers of the regulation of eating behavior in humans. A. DelParigi[a,b]. [a]*Pfizer Global Research and Development, Groton, CT 06340, USA.* [b]*The John B. Pierce Laboratory, New Haven, CT, USA*

Common forms of human obesity are predominantly caused by overeating, an abnormal behavior whose neurobiology is not completely understood. We used positron emission tomography (PET) and 15O-water (radiotracer) to measure changes in regional cerebral blood flow (rCBF, a marker of neural activity) in response to the sensory experience of a meal and to the consumption of the same meal to satiety. We studied 21 lean (L), 23 obese (O), and 11 post-obese (PO) subjects, a population that is highly predisposed to obesity. In response to the sensory experience of food, O were distinguished from L by greater rCBF increases mainly in the insular region. Similarly to O, PO exhibited greater rCBF increases in the middle insula as compared to L. In response to satiety, O were distinguished from L by greater rCBF increases in the prefrontal cortex, and by greater decreases in the insula, hippocampus and orbitofrontal cortex. Similarly to O, PO exhibited greater rCBF decreases in the hippocampus as compared to L. Furthermore, in response to satiety, restrained eaters (PO) were distinguished from non-restrained eaters (O and L) by greater rCBF increases in the dorsal prefrontal cortex. In conclusion, sensory experience of food and meal consumption in O elicit abnormal responses in a distributed network of brain areas, including limbic/paralimbic and prefrontal regions. A predisposition to obesity may involve brain responses related to sensory and learning/memory processing. Cortical areas involved in the intentional control of behavior are particularly activated in PO and may represent a neurofunctional marker of successful weight loss maintenance.

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Long-term effects of consumption of yoghurt with a novel fat emulsion (Olibra®) in relation to body-weight management. K. Diepvens[a,#], S. Soenen[a], J. Steijns[b], M. Arnold[c], M.S. Westerterp-Plantenga[a]. [a]*Maastricht University, Maastricht, The Netherlands.* [b]*Campina Innovation, The Netherlands.* [c]*Institute of Animal Sciences, ETH Zurich, CH-8603 Schwerzenbach, Switzerland*

We assessed weight maintenance after weight loss by consumption of yoghurt with a novel fat emulsion (Olibra®) including effects on body composition, resting energy expenditure (REE), hunger feelings and satiety hormones. A total of 96 overweight women (age: 18–58 yr, BMI 25–32 kg/m^2) participated in a randomized, placebo-controlled, double-blind, parallel design. A 6-week weight loss period (2.1 MJ/d) was followed by 18 weeks weight maintenance with test (Olibra®) or placebo yoghurt. In weeks 1, 7 and 25, a satiety test took place with questionnaires and determination of satiety hormones. In weeks 2, 8 and 26, REE, body weight and body composition was measured. During weight maintenance after significant body weight reduction, there was no significant increase in body weight in the test group (1.1 ± 3.4 kg); the placebo group did gain weight (3.0 ± 3.1 kg, $P < 0.001$). Compared to the placebo group, the test group increased in fat-free mass (FFM) and decreased in fat mass (FM) ($P < 0.05$), was less hungry 4 h after yoghurt consumption in week 25 ($P < 0.05$) and showed increased Glucagon Like Peptide-1 values 180 min after yoghurt consumption (week 25 vs. week 1, $P < 0.05$). Measured REE was significantly higher than predicted REE ($P < 0.05$) in week 26 for the test but not for the placebo group. Consumption of Olibra® yoghurt improved weight maintenance compared to placebo which can be explained by the relatively higher REE as a function of FFM, relatively higher increase in FFM and decrease in FM and the relatively lower increase in hunger.

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Improvement in the insulin sensitivity index with weight loss in rodents fed a 40% fat diet. J. Dill, J. Alexander-Chacko, B. Hughes, N. Newton, D.K. Sindelar. *Endocrine Research, Eli Lilly and Company, Indianapolis, IN 46285, USA*

Obese individuals with type 2 diabetes can improve their insulin sensitivity with moderate weight loss. We investigated the correlation of body weight and fat mass loss with the measurement of the insulin-sensitivity index (ISI) using an OGTT in age-matched normal rats fed a chow diet (12% fat) and diet-induced obese (DIO) rats fed a high-fat (HF) diet (40% fat) for 3 months. The ISI of the DIO rats (14% fat mass) was significantly less than the normal rats (8% fat mass) (15 vs. 48, respectively), indicating insulin resistance in the DIO rats. Weight loss was induced in DIO rats by calorie restriction (CR) ranging from 10% to 60% of normal daily intake and diet change from HF diet to low-fat chow over a 2-week period. In the CR study, cumulative body weight change was significantly reduced in all groups compared to controls (-21.8 to -69.7 g) at the end of 2 weeks. All restricted groups had significant fat mass loss (-11.3 g to -40.7 g) compared to the control group over the same time. The 60% CR group had a statistically higher (improved) ISI compared to controls (39.3 vs. 15.1, respectively). Likewise, rats switched to chow had significantly decreased body weight and fat mass (-14.9 and -32 g, respectively) with a significant improvement in the ISI over the HF-fed rats (38.8 vs. 21.5, respectively). In conclusion, a HF diet lowers ISI while decreased weight and fat mass brought about through caloric restriction or decreased dietary fat significantly improved ISI.

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Adaptations of oxytocin neurons during pregnancy: Role in regulating food intake? A.J.Douglas. *Centre for Integrative Physiology, The University of Edinburgh, Edinburgh EH8 9XD, UK*

Pregnancy is a natural state of hyperphagia in rodents, body weight increases and is attributable not only to the growth of the intra-uterine contents and mammary gland development, but also to increased maternal body fat. Adverse consequences of food deprivation in early pregnancy include extended gestation and low birth weight. Oxytocin is a neuropeptide that is released and acts both peripherally and in the brain. Peripherally oxytocin drives uterine contraction at birth and centrally it mediates a variety of behaviors, including maternal behavior and feeding. We have shown that oxytocin neurons adapt during mid-late pregnancy, facilitating their role for parturition and lactation. The adaptation involves strong restraint of both central oxytocin neuron activity and peripheral secretion which is mediated particularly by endogenous opioids and sex steroids. Additionally, central and peripheral oxytocin responses to stress and to osmotic stimuli are attenuated, indicating a global inhibition of their responses to stimuli. Since central oxytocin is inhibitory to feeding behavior, we have investigated whether the lack of central oxytocin action contributes to enhanced feeding behavior in mid-pregnancy. Preliminary data indicate that oxytocin inhibition of food intake in pregnancy may be lost, since central administration of oxytocin antagonist does not increase food intake in pregnant rats as it does in virgin rats. Thus, altered central oxytocin mechanisms, in response to and/or in addition to other concurrent hormone changes, may modulate hunger and satiety signals in pregnancy. Supported by the BBSRC and The Wellcome Trust.

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The role of melanin-concentrating hormone in alcohol drinking in mice. E.A. Duncan[#], S.C. Woods. *Department of Psychiatry, University of Cincinnati, Cincinnati, OH 45237, USA*

Melanin-concentrating hormone (MCH) augments alcohol intake in rats when administered into the brain. Therefore, we tested the hypothesis that endogenous MCH signaling would also enhance alcohol intake. Male MCH receptor 1 deficient (KO) and wildtype (WT) C57BL/6J mice had free access to water, chow and ethanol. Consistent with previous reports, KO mice were hyperphagic (167.1 ± 4.3) compared to WT mice (144.3 ± 2.4 g/kg/24 h, $P < 0.001$). In contrast to our hypothesis, KO mice consumed more 10% ethanol (11.5 ± 1.0) than WT mice (6.3 ± 1.5 g/kg/24 h), $P < 0.05$. It is possible that the increase in alcohol intake reflects a general effect of genotype on energy intake, however, KO mice drank less than WT mice of a solution equal in calories and palatability to 10% ethanol (KO $= 3.1 \pm 3.2$, WT $= 11.0 \pm 3.0$ g/kg/24 h sucrose (17.75%)/quinine (1.3 mM), $P = 0.09$). To control for a possible species effect, MCH (5 μg) was administered into the third-cerebral ventricle of a separate cohort of WT mice. Similar to what occurs with rats, MCH increased 1-hr alcohol (MCH $= 0.9 \pm 0.2$, vehicle $= 0.4 \pm 0.1$ g/kg, $P < 0.05$), and chow intake (MCH $= 14.7 \pm 3.1$, vehicle $= 6.6 \pm 3.4$ g/kg, $P < 0.05$). Therefore, either genetically reducing, or pharmacologically increasing, MCH signaling leads to enhanced alcohol consumption. Further studies are needed to understand the mechanisms underlying the effect of MCH on alcohol intake.

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Ibotenic acid lesions of the anterior piriform cortex do not increase high-protein nor amino acid imbalanced diet intake in rats. R. Faipoux[a], O. Rampin[a], N. Darcel[b], S. Gougis[a], D. Gietzen[c], D. Tome[a], G. Fromentin[a]. [a]*INRA UMR914 PNCA, INA-PG, F-75231 Paris, France.* [b]*INRA NOPA, F-78352 Jouy-en-Josas, France.* [c]*University of California, Davis, CA, USA*

Introduction: High protein- or imbalanced amino acid diets are known to reduce food intake. The brain areas involved in this regulation are unknown. We hypothesized that the anterior piriform cortex (APC) plays this role. *Methods*: A total of 34 male rats were included in either a control ($n = 8$), sham ($n = 4$) or a lesioned group ($n = 22$). APC was lesioned bilaterally using ibotenic acid (6 μg) injected at one of two different sites: A–P 2.4 mm; $L \pm 4.0$ mm; D −6.5 mm ($n = 13$) and A–P 3.0 mm; $L \pm 3.1$ mm; D -6.3 mm ($n = 9$) relative to bregma. Rats were then submitted to a P14 diet for at least 10 days, followed by a threonine devoid diet (Thr-Dev) for 5 days, then by a Thr-Dev corrected for threonine (Cor-diet) for 3 days and finally by a P55 diet for 3 days. Each period was preceded by 2 days of P14 diet in order to determine the basal level of energy intake. APC lesions were verified post-mortem using conventional histological methods. *Results*: Neither transition from P14 to Thr-Dev nor transition from P14 to Cor nor transition from P14 to P55 was altered by APC lesion. Moreover, relative to non-lesioned rats, APC lesioned rats did not increase food intake when given Thr-Dev or P55. Lesions were correctly placed. *Conclusion*: The ibotinic acid sensitive neurons in the APC are not critical for the detection of high protein- or imbalanced amino acid diets.

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Ghrelin induces Fos expression in the nucleus of the solitary tract, but not the arcuate nucleus, after fourth ventricular delivery. L.F. Faulconbridge[a], K.H. Rood[a], H.J. Grill[a], J.M. Kaplan[a], D. Daniels[b]. [a]*Departments of Psychology, University of Pennsylvania, PA 19104, USA.* [b]*Departments of Psychology, University at Buffalo, SUNY, Buffalo, NY, USA*

Ghrelin is a 28-amino acid peptide that increases food intake when injected into either the forebrain or hindbrain ventricles. Brain areas activated by ghrelin after forebrain delivery have been examined using Fos immunohistochemistry and include the arcuate nucleus (ARC) and the nucleus of the solitary tract (NTS). Hyperphagia after forebrain application of ghrelin is blocked by Neuropeptide Y (NPY) receptor antagonists. Recent evidence suggests that NPY also mediates the hyperphagia following fourth-ventricle application of ghrelin [Faulconbridge et al., 2005], but little is known about the pattern of neural activation upon this route of delivery. As such, we examined Fos expression in the ARC and NTS after injecting ghrelin into the fourth ventricle. Ghrelin treatment increased levels of Fos expression in the NTS at the level of the area postrema ($P = 0.03$) but failed to induce Fos expression in the ARC. To investigate the phenotype of the activated cells in the NTS, we used double-labeling for Fos and tyrosine hydroxylase (TH) which is expressed by most NPY neurons in the NTS. Twenty-two per cent of the TH cells were also Fos-immunoreactive in ghrelin-treated animals compared to 13% in vehicle-treated animals, but this result did not achieve statistical significance. These data support the NTS as a target of ghrelin action. We were unable to provide evidence consistent with a primary role for brainstem TH neurons in the mediation of ghrelin hyperphagia. Supported by NIH DK-21397, DK-42284, and DK-73800.

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Circumventricular organs as integrators of circulating signals controlling fluid and food intake. A.V. Ferguson. *Department of Physiology, Queen's University, Kingston, Ont., Canada K7L 3N6*

The absence of a normal blood brain barrier in the circumventricular organs (CVOs) of the brain positions these structures as the only regions of the brain able to directly sense to constituents of the normal circulation. The sensory CVOs, in particular the subfornical organ (SFO) and area postrema (AP) are well established as playing major roles in sensing and integrating essential information regarding body fluid status through efferent connections to hypothalamic and medullary autonomic control centers. Recent work suggests that these two CVOs may play similar roles in sensing a number of important satiety signals associated with the integrated control of metabolism and food intake. Electrophysiological evidence demonstrating the ability of these CVO neurons to sense a variety of these signals including angiotensin II, Na^+, glucose, PYY, ghrelin, adiponectin and amylin makes a persuasive case for essential roles for CVO neurons in the integration of information from these satiety signals. Such data also suggest potentially important roles for these structures not only in the control of fluid balance, but also in the control of feeding and metabolism. Supported by CIHR, NIH, and HSFO.

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Fos expression in the paraventricular nucleus (PVN) after intragastric hyperosmotic NaCl in rats without a rise in plasma osmolality: Gut osmotic clamp. D.A. Fitts, D.J. Femiano, D.K. Zierath, A.V. Savos, J.M. Ho, J.E. Bassett. *Department of Psychology, University of Washington, Seattle, WA 98195, USA*

Studies of gut osmoreceptors require an osmotic challenge to the gut that does not produce a rise in plasma osmotic pressure. Previous studies of Fos expression in the brain after gut loading either employed tiny doses of hyperosmotic saline that did not greatly affect plasma osmolality, or else counteracted the osmotic impact of a robust saline infusion into the hepato-portal vein with an iv infusion of water. However, hepato-portal infusions could bypass important sensors in the lining of the gut. We gave a robust stimulus by gavage (1200 mOsm/kg NaCl) and used variable rates of iv water infusion to counteract the impact of the absorbed sodium on the plasma osmolality (gut osmotic clamp). The hyperosmotic stimulus by itself (with isotonic iv infusion) caused ~6 mOsm/kg rise of plasma osmolality that peaked at 10–20 min ($n = 5$), but the osmolality of clamped rats ($n = 9$) did not differ significantly from that of rats receiving an isotonic gavage and isotonic iv infusion ($n = 7$) at 0, 10, 20, 30, 45, 60, 75 or 90 min. The gut osmotic clamp eliminated the Fos-ir response to the hyperosmotic load in sensory circumventricular organs that are sensitive to plasma osmolality, but the response was merely blunted in the lateral magnocellular region of the PVN and was not reduced at all in the ventromedial parvocellular region of the PVN. This method allows a study of all potential gut osmosensory elements after a robust osmotic stimulus that does not affect plasma osmolality.

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Are models of polydrug abuse useful for understanding food combinations? R. Foltin. *NY State Psychiatric Institute, Division of Substance Abuse, New York, NY 10032, USA*

Polydrug abuse involves the simultaneous or sequential self-administration of drugs from several pharmacological classes by the same individuals. Patterns of polydrug use are most likely related to some change in subjective effects that the user perceives to be unique to the combination. Self-administration of two drugs in close temporal proximity may (a) increase a desired effect common to one or both drugs, (b) decrease an undesired effect common to one or both drugs, (c) increase the duration of desired drug effects, (d) decrease the duration of undesired drug effects, or (e) produce an effect not available with either drug singly. Finally, one drug may be used to alleviate behavioral changes related to repeated heavy or binge use of another drug. One of the better known drug combinations is the use of cocaine in combination, or close temporal proximity to heroin, i.e., "speedball." The initial portion of the talk will present a procedure for studying cocaine–morphine interactions in humans, and the second portion of the talk will discuss how models of drug interactions may be used to help understand the effects of food combinations. Supported by USA NIDA Grants DA-08105 and DA-06234.

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Prewired synaptic plasticity in central dopamine systems of obesity-prone rats and mice. L. Frank, L. Stiles, G. Behr, E.N. Pothos. *Department of Pharmacology and Experimental Therapeutics and Program in Neuroscience, Tufts University School of Medicine, Boston, MA 02111, USA*

We have previously shown that dietary obesity depresses basal and challenged dopamine release in the nucleus accumbens. We now present evidence that in inbred obesity-prone adult female rats, the mean electrically evoked dopamine signal in coronal slices of the nucleus accumbens shell, medial prefrontal cortex and dorsal striatum is significantly lower by at least 50% than in obesity-resistant rats with identical diet history (laboratory chow). In additional experiments with ob/ob (leptin-deficient) mice we found that there is a significant 10-fold decrease in the evoked accumbens dopamine signal of the ob/ob genotype. The effect is maintained in the presence of the DAT-specific inhibitor nomifensine (3 μM for 30 min), suggesting that leptin deficiency attenuates stimulated dopamine release per se without accelerating dopamine reuptake. Findings demonstrate that changes in evoked central dopamine release are present in adult obesity prone animals even if they are not exposed to high-energy diets. The depression of central dopamine is, therefore, prewired in obesity-prone animals. This finding is valid for all three dopaminergic projections of the midbrain. We currently investigate how early in development this difference occurs and whether changes in diet history and/or leptin treatment can reverse the prewired dopamine depression. Support by DK065872 and a Smith Family New Investigator Award administered by the Medical Foundation.

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Macronutrient composition, food intake and body composition in the rat. G. Fromentin, C. Gaudichon, D. Azzout-Marniche, D. Tome. *UMR INRA 914, Nutrition Physiology and Feeding Behavior, Institut National Agronomique Paris-Grignon, F-75231 Paris cedex 05, France*

Rat represents a useful model for studying the effects of different macronutrient combinations on energy homeostasis and adiposity. (1) Increasing the protein content per se in the diet usually reduces energy intake and fat deposition either in a context of a low- or high-fat diet. (2) Lowering carbohydrates content of the diet enhances gluconeogenesis and decrease de novo fatty acid synthesis pathways. This is also associated to an improvement of glucose homeostasis. (3) The carbohydrate to fat ratio rather than the fat content per se in the diet influences the development of adiposity. In this context, a high-fat diet would lead to overfeeding and obesity when the diet is also rich in carbohydrate that favours insulin secretion, lipogenesis and fat deposition, whereas in the absence of carbohydrate, a lower insulin response to feeding would favour lipid oxidation rather than deposition. *Conclusion*: The different macronutrient combinations can influence energy intake and fat storage by three pathways in the rat: decreased energy intake (protein-induced satiety), reduced de novo fatty acid synthesis from glucose, and increased fatty acid oxidation (reduced insulin effect). Additional data are required on the consequences of different fatty acid composition in a context of low-carbohydrate diets.

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Hypothalamic acetyl CoA carboxylase in arcuate nucleus is a mediator of AMP kinase actions in the control of food intake. S. Gao#, S. Aja, K.P. Kinzig, K.L.K. Tamashiro, K.A. Scott, W.W. Smith, Y. Tu, G.V. Ronnett, E.E. Ladenheim, T.H. Moran. *Departments of Biological Chemistry, Psychiatry/Behavioral Sciences and Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Hypothalamic AMP kinase (AMPK) has been demonstrated to play a critical role in hormonal and nutrient-derived anorexigenic and orexigenic signaling. We demonstrate that acetyl CoA carboxylase (ACC), the rate limiting enzyme of the de novo fatty acid synthetic pathway, is a mediator in the signaling cascade of AMPK in its hypothalamic actions. Fasting inactivates ACC in the arcuate nucleus along with activation of AMPK, whereas refeeding stimulates arcuate ACC concomitant with decreasing the activity of AMPK. AICAR, a well-known activator of AMPK, increases food intake and inhibits ACC in both the arcuate and paraventricular nucleus (PVN). Compound C, a selective inhibitor of AMPK, inhibits feeding and activates hypothalamic ACC. Central administration of leptin activates ACC in both arcuate nucleus and PVN through inhibition of AMPK as early as 3 h following injection. Activation of ACC turns out to be required for the anorectic effects of both leptin and Compound C. Infusion of the ACC inhibitor, TOFA, to rats completely blocked the feeding inhibition induced by central leptin. Pretreatment of mice with intracerebroventricular injection of TOFA prevented the hypophagia produced by Compound C. TOFA also prevented the leptin induced decreases in arcuate NPY. The molecular responses to leptin were further verified with an in vitro neuronal cell model. Together these data suggest that hypothalamic activity in the de novo fatty acid synthetic pathway provides signals for controlling food intake. Supported by DK19302, DK70707, and DK068054.

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Vagal and non-vagal contributions to the control of eating by fat metabolism. N. Geary, K. Brandt, M. Leonhardt, M. Arnold, W. Langhans. *Institute of Animal Sciences, ETH Zurich, CH-8603 Schwerzenbach, Switzerland*

Although acute changes in fat metabolism clearly affect eating, questions remain concerning the particular metabolic parameters involved as well as their site(s) and mechanism(s) of action. Under many conditions, inhibition of fatty acid oxidation (FAO) in the liver appears to produce a vagal afferent signal that stimulates eating. Conversely, eating is inhibited both by hepatic portal infusions of fatty acids and by mobilizing endogenous fat stores with systemic β3-adrenergic receptor (β3-AR) agonist treatment. Fasting also increases mobilization of endogenous fat stores and FAO. Here, we tested whether β3-AR agonist- and fasting-induced FAO affect eating via vagal afferent mechanisms using rats with selective subdiaphragmatic vagal deafferentation (SDA) or sham surgery. First, the β3-AR agonist CL 316,243 (0.01, 0.1, and 1.0 mg/kg, IP) inhibited eating similarly in sham and SDA rats, whereas the eating-stimulatory effect of the FAO inhibitor mercaptoacetate (MA) was completely abolished in SDA rats. Second, MA inhibited, rather than stimulated, eating in fasted rats, despite their increased basal FAO. Furthermore, the eating-inhibitory effect of MA in fasted rats was not blocked by SDA, although MA's eating-stimulatory effect in ad libitum-fed rats again was. These data indicate that, whereas decreased FAO stimulates eating via an abdominal vagal afferent mechanism, abdominal vagal afferents are not necessary for the inhibitions of eating after β3-AR agonist treatment or after MA treatment in fasting rats. Supported by NIH DK 060735 (WL, NG).

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Asymmetric lesions of the gustatory thalamocortical loop selectively disrupt morphine-induced contrast, while sparing LiCl-induced conditioned taste aversion (CTA) learning. R.I. Geddes#, L. Han, A. Baldwin, P.S. Grigson. *Department of Neural and Behavioural Sciences, Penn State College of Medicine, Hershey, PA 17033, USA*

Bilateral lesions of the gustatory cortex, like those of the gustatory thalamus [Grigson et al., 2000], selectively disrupt avoidance of a taste cue when paired with a reinforcing drug of abuse, but not when paired with the aversive agent, LiCl [Geddes et al., 2004]. One interpretation of these data is that the taste thalamus, once thought critical, is involved only as a conduit to the gustatory cortex. However, given the strong reciprocal connection between the taste thalamus and cortex, it remains possible that drug-induced devaluation of natural rewards is mediated not by the thalamus or the cortex, per se, but by communication between the two structures. The present study used ibotenic acid-induced asymmetric thalamocortical (THCx) lesions to test this hypothesis. Nine rats received electrophysiologically guided unilateral lesions of the VPMpc and contralateral lesions of the insular cortex (THCx). Three control (Cntl) rats received ipsilateral lesions of the same nuclei. In Experiment 1, water-deprived Cntl and THCx rats were given 5 min access to saccharin paired with morphine or saline injections over a number of trials. In Experiment 2, the same rats were used to evaluate the role of the thalamocortical loop in LiCl-induced CTA. We found that asymmetric lesions of the thalamocortical loop (THCx) selectively disrupted morphine-induced contrast $F(8,64) = 3.32$, $P < 0.05$, while fully sparing LiCl-induced CTA, $F(5,40) = 1.36$, $P > 0.05$. As such, the results of this disconnection study confirm that drug-induced devaluation of a natural reward requires communication between the gustatory thalamus and cortex.

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Fasting ghrelin concentrations did not change 2 and 5 months following Rouen-Y-Gastric Bypass (RYGB) and demonstrated normal postmeal decline. A. Geliebter, M.E. Gluck, M. Takahashi, F.X. Pi-Sunyer, L. Flancbaum. *Obesity Research Center, St. Luke's-Roosevelt Hospital, Columbia University, New York, NY 10025, USA*

The finding that plasma ghrelin concentrations decrease post-RYGB has become controversial. Initially, Cummings et al., [2002], reported extremely low ghrelin levels post-RYGB, and the absence of a post-meal decline. However, those post-RYGB patients were compared cross-sectionally to non-surgical subjects. We prospectively studied patients pre and 2 and 5 months post surgery. There were 16 severely obese, BMI = $48 \pm 9\,kg/m^2$, % body fat (BOD-POD) = 54 ± 6, age = 34 ± 8 years, but otherwise healthy pre-menopausal women. Total ghrelin (Phoenix) was measured prior to and post (−10, 0, 15, 30, 60 min) fixed complete liquid meal of Glytrol, 250 ml, 1 kcal/ml, at 2 pm following an overnight 18 h fast. Nine patients had measurements at 2 months, and seven at 5 months. There were no significant changes from pre- to post-2 or 5 months in fasting levels at 0 min of ghrelin (507, 435, 484 mg/ml) or in area under the curve (16 922, 13 998, 17 121 mg min/ml). Ghrelin also showed a significant ($P < 0.05$) post-meal % decline (−13%,−28%,−27%) at pre- and post-2 and 5 months, which did not differ. There was no change in fasting ghrelin or AUC ghrelin post-RYGB, and the decline in ghrelin post-meal was preserved. It is still possible that RYGB may have prevented the expected weight-loss induced increase in fasting ghrelin. Supported by NIH DK 61519 to AG.

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Mk-801 blocks acquisition of conditioned flavor-taste preferences. G.J. Golden, T.A. Houpt. *Department of Biological Science, Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

Conditioned flavor–taste preference (CFTP) learning is a form of associative learning in which animals will consume more of a flavor (e.g. Kool-Aid) previously mixed with a highly preferred tastant (e.g. fructose) over one previously mixed with a less preferred tastant (e.g. saccharin). Here, the role of the NMDA glutamate–glycine receptor (NR) in CFTP was examined using MK-801, a non-competitive antagonist. Food-restricted rats were injected with MK-801 (100 μg/kg) or vehicle 30 min prior to 2 h, 1-bottle access to Kool-Aid (grape or cherry) mixed with either 8% fructose (CS+/F) or 0.2% saccharin (CS−/S). Conditioning was repeated for 12 days, alternating between CS+/F and CS−/S days; flavors were counter-balanced across groups. Every 4 days, CFTP expression was measured in a 2 h, 2-bottle preference test between the flavors in 0.2% saccharin (CS+/S vs. CS−/S). Vehicle-injected rats showed a significant preference for CS+/S over CS-/S within 4–8 conditioning days. In MK-801-treated rats, however, CS+/S intake was not different from CS−/S intake even after 12 conditioning days. Follow-up experiments demonstrated that MK-801 did not induce a conditioned taste aversion, did not mediate state-dependent learning, and did not affect expression of a previously acquired CFTP. Because MK-801 prior to conditioning completely blocked CFTP, neurotransmission at the NR is necessary for CFTP learning. Furthermore, treatment with D-cycloserine (an agonist at the NR glycine site), enhances CFTP, suggesting that endogenous levels of glycine or D-serine at the NR may constrain CFTP learning. Future studies employing site-specific injections or c-Fos will localize the critical site of NR activity. Supported by NIDCD03198.

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Hormonal induction of central leptin resistance during pregnancy. D.R. Grattan, R.A. Augustine, S.R. Ladyman. *Department of Anatomy and Structural Biology, University of Otago, Dunedin 9001, New Zealand*

Despite elevated plasma leptin, food intake is increased during pregnancy. We have demonstrated that intracerebroventricular (i.c.v.) leptin is unable to suppress food intake in pregnant rats, as it does in non-pregnant animals. Hence, central leptin resistance develops during pregnancy. These changes are physiologically appropriate, providing increased energy reserves to help meet the high metabolic demands of fetal development and lactation. To characterise this central leptin resistance, we have measured levels of leptin receptor (Ob-Rb) mRNA in the hypothalamus, and examined leptin-induced phosphorylation of STAT3 (pSTAT3) in specific regions of the hypothalamus. In addition, to investigate the mechanism underlying pregnancy-induced leptin resistance, we have investigated effects of hormone treatments on hypothalamic responses to leptin in a pseudopregnant rat model. We observed a significant reduction of Ob-Rb mRNA levels in the ventromedial hypothalamic nucleus (VMH) during pregnancy, with no changes detected in other hypothalamic nuclei. Levels of leptin-induced pSTAT3 were specifically suppressed in the VMH and arcuate nucleus of pregnant rats compared to non-pregnant rats. Pseudopregnant rats were hyperphagic but did not become leptin resistant, even when given progesterone implants to extend pseudopregnancy beyond the time that resistance develops during pregnancy. Chronic i.c.v. infusion of ovine prolactin to mimic patterns of placental lactogen secretion characteristic of pregnancy, however, completly blocked the ability of leptin to suppress food intake. These data implicate the VMH as a key hypothalamic site involved in hormone-induced leptin resistance during pregnancy, and suggest that placental lactogen secretion may be mediate the hormone-induced loss of response to leptin.

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Downregulation of hypothalamic insulin receptor expression and signaling by lentivirus mediated gene transfer. C.A. Grillo[a], K.L. Tamashiro[b], G.G. Piroli[a], J.T. Gass[a], S.P. Wilson[a], R.R. Sakai[b], L.P. Reagan[a]. [a]*Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine, Columbia, SC 29208, USA.* [b]*Department of Psychiatry, University of Cincinnati Medical Center, Cincinnati, OH 45237, USA*

Regulation of feeding behavior and energy balance are among the central effects of insulin. Intracereboventricular administration of insulin decreases food intake and body weight, whereas antisense oligodeoxynucleotide downregulation of insulin receptors (IRs) produces hyperphagia. To further examine the role of IRs in the central actions of insulin, we designed an IR antisense lentiviral vector (LV-IRAS) and injected this vector into the third ventricle to selectively decrease IR expression in the rat hypothalamus. Three weeks after LV-IRAS administration, the expression of IRs in the hypothalamus was significantly decreased, whereas no changes were observed in hippocampal IR levels. LV-IRAS administration decreased insulin stimulated phosphorylation of hypothalamic IRs and translocation of the insulin sensitive glucose transporter GLUT4 in the hypothalamus; no changes in IR signaling were observed in the hippocampus of LV-IRAS-treated rats. Lentivirus mediated downregulation of IR expression and signaling increased cumulative body weight gain in the LV-IRAS-treated rats beginning 11 days after virus administration. Additionally, carcass analyses revealed a significant increase in fat mass in rats treated with the LV-IRAS, increases that were selective for the subcutaneous compartment. Conversely, lean muscle mass was not modulated in LV-IRAS-treated rats compared to rats treated with control virus. Collectively, these data demonstrate that virus-mediated gene transfer is an effective tool to decrease the expression and signaling of central IRs in a region specific manner and provide further support for regulation of body composition, especially in terms of fat mass, by hypothalamic IRs.

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Central metabolic adaptations during lactation. K.L. Grove, X.Q. Xiao, M.S. Smith. *Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR 97006, USA*

Lactation is a metabolically challenged state that is met by a dramatic adaptation in the neurocircuitry that controls appetite. Furthermore, there are changes in peripheral metabolic systems to adjust substrate availability and utilization, sparing necessary components for milk production. The major driving force to increase food intake appears to be through an increase in orexigenic peptides in the arcuate nucleus (ARH) and a suppression of the anorexigenic peptides. Furthermore, there is an induction of neuropeptide Y (NPY) in the dorsomedial hypothalamic nucleus (DMH) that is important for maintaining the hyperphagia associated with lactation. Recently, we demonstrated that microinjection of a melanocortin agonist into the DMH inhibits the activation of DMH-NPY neurons as well as suppresses food intake, suggesting that the induction of NPY in the DMH during lactation is dependent on the suppression of POMC neurons. To profile other metabolic adaptations that occur during lactation, we performed microarray analysis of skeletal muscle and ARH. During lactation, muscle switches its glycolytic pathway to primarily make lactate for use as a fuel source. This increased lactate should suppress food intake; however, during lactation the lactate transporter (MCT2) is decreased in the ARH. This decrease in MCT2 would protect ARH neurons against the anorexigenic effects of high circulating lactate. These metabolic changes during lactation make it an interesting and useful model to study the natural adaptations associated with energy drains, as well as identifying abnormalities in energy sensing that may lead to obesity. Supported by NIH Grants HD-14643, RR00163 and DK60685.

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Repeated exposure to capsaicin increases sucrose drinking and gene expression of sweet taste receptors in rats. X.F. Gu[a], V. Ryu[a], J.G. Kim[a], S. Lee[b], J.H. Lee[a], J.W. Jahng[a]. [a]*Department of Oral and Maxillofacial Surgery, Dental research institute, Seoul National University, College of Dentistry, Seoul 110-744, Republic of Korea.* [b]*Department of Pharmacology, Wonkwang University School of Medicine, Iksan 570-749, Republic of Korea*

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is the principle substance responsible for hot and pungent taste of capsicum fruits. Many Asian people generally have been agreed with its appetite-stimulating effect. In this study, a functional mechanism of capsaicin in taste perception was investigated. Rats received 1 ml of 0.02% capsaicin solution in their oral cavity daily for 4 days with ad libitum access to water and chow. Daily sucrose drinking was examined with two-bottle drinking test (water and 2% sucrose) during the experimental period. Body weight and food intake did not differ between the experimental groups. Capsaicin rats drank more water only for the first day of test, compared to the vehicle group. Sucrose consumption of capsaicin rats increased compared with the vehicle group after third exposure to capsaicin. After the behavioral session, tongue tissues were dissected, and mRNA expression levels of T1R2, T1R3, NPY, nNOS and c-Fos genes in circumvallate and foliate papillae were examined by quantitative real-time RT-PCR assays. T1R2, T1R3, and nNOS expressions were increased, NPY decreased, in both tongue regions by capsaicin treatment. c-Fos expression was decreased in circumvallate, increased in foliate, papillae by capsaicin. These results suggest that repeated exposure to capsaicin may increase taste sensitivity to sweet taste, via modulating gene expressions in the taste receptor cells. These preliminary works give some insight into the molecular mechanisms of capsaicin on taste perception. Supported by KISTEP (JWJ).

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Increased operant performance for palatable sucrose solutions in obese OLETF rats. A. Hajnal[a], R.C. Twining[a], N.K. Acharya[a], P.S. Grigson[a], M. Covasa[b], C.S. Freet[a]. [a]*Department of Neural and Behavioral Sciences, Pennsylvania State University, College of Medicine, Hershey, PA 17033.* [b]*Department of Nutritional Sciences, Pennsylvania State University, University Park, PA 16802, USA*

Otsuka-Long-Evans-Tokushima-Fatty (OLETF) rats lack functional CCK-1 receptors, are hyperphagic, and gradually develop obesity and diabetes during their life span. Recently, we have reported a greater preference for both real-, and sham-fed sucrose, and increased lick responses to various sweet tastants in OLETF compared to lean controls (LETO). The perceived reinforcing value of sucrose, however, has not been directly addressed in this strain. Thus, the present study examined the performance of non-deprived, prediabetic OLETF rats (14–18 weeks of age) using fixed-ratio (FR) and progressive-ratio (PR) schedules of reinforcement. Compared to age-matched LETO rats, OLETF rats showed significantly higher consummatory responses (licking) during continuous reinforcement ratio training to both concentrations of sucrose tested (0.3 and 1.0 M: 1984.7 ± 400.9 vs. 1000.8 ± 98.5 and 1531 ± 220.1 vs. 809.3 ± 115.3, respectively; P's < 0.05). Furthermore, OLETF rats emitted more licks on the "active" empty spout on an FR-10 schedule (385.8 ± 56.3 vs. 217.3 ± 29.5; $P > 0.01$) and completed higher ratio requirements on the PR schedule ("breakpoint": 15 ± 1.5 vs. 9.2 ± 1.3) to gain access to 0.3M sucrose (10 s). These findings provide the first direct evidence for increased reward value of sucrose in OLETF rats, and further support the notion that, in addition to peripheral deficits controlling meal-size, disregulation in the reward system, including dopamine may contribute to overconsumption in this strain. Supported by NIH Grant DK065709, and the contributors by DA09815, DA16512.

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Spontaneous physical activity, energy expenditure, and meal structure during the development and maintenance of diet induced obesity. G. Hansen[a], A.N. Madsen[a], B.E. Levin[b], R.V. Sørensen[a], N. Vrang[a], P.J. Larsen[a], M. Tang-Christensen[a]. [a]*Rheoscience A/S, Rødovre, DK-2200 Copenhagen, Denmark.* [b]*VA, Department of Neuroscience, Orange County, NJ, USA*

A global rise in the prevalence of obesity is developing. As the increasing sedentary lifestyle is believed to be a major contributor to the rising prevalence of obesity we speculated that a lower level of spontaneous physical activity (SPA), the single-most variable component of energy expenditure, would be associated with the propensity to develop obesity in diet-induced obese (DIO) and diet-resistant rats (DR). Selectively bred DIO ($n = 34$) and DR rats ($n = 40$) were weaned at 4 weeks of age and randomized into chow (12.6 E% fat) and high-fat (31.8 E% fat) diet groups. Food intake, body-weight and locomotor activity were examined at 12, 22, and 34 weeks of age using a computerized system for food, water and activity measurements. Resting energy expenditure was measured when the rats were 8 and 38 weeks old. Only HE-fed DIO rats developed marked obesity despite consuming a similar amount of calories/gram body-weight as HE-fed DR rats. Interestingly, spontaneous locomotor activity was higher in DIO-HE before, during and after development of DIO. No significant differences between DIO and DR rats regardless of diet were seen with respect to the resting energy expenditure. Several possible explanations for the development of obesity in the DIO-rat are therefore possible. While the development of obesity is not associated with differences in SPA, increased metabolic efficiency could be an explanation, as body-weight gain/calorie intake tended to be higher in HE-fed DIO rats, despite comparable levels of resting heat-production and relative proportion of fat oxidation DIO-HE vs. DR-HE.

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Effect of dietary fatty acid composition on the development of obesity and its reversal in rats. N. Hariri, B. Azadi, L. Thibault. *School of Dietetics and Human Nutrition, McGill University, Ste. Anne de Bellevue, QC, H9X 3V9, Canada*

Dietary fats with different degrees of saturation were shown to affect feeding and body weight. A study investigated the effect of canola-oil and lard-rich diets in rats. Over 26 days, lard- and canola-fed rats had similar body weight gain, food and energy intake and Lee Obesity index. Both groups displayed higher-energy intake and body weight gain than at baseline (chow feeding). Another study examined canola- and butter-rich diets. Over 50 days, butter rich diet induced significantly higher body weight gain and energy intake than canola and chow (control) feeding. Ad libitum low-fat canola or butter diets were then offered for 28 days. Both dietary groups ate less (g) but had similar energy intake and final body weight to those of controls (ad libitum chow). Low butter feeding induced lower weight gain and energy intake compared to high-fat feeding. Then, food offered was restricted to 60% of the mean intake measured during low-fat feeding. Canola and butter fed rats lost weight to the same magnitude, and had a lower Lee Obesity index than controls. Plasma leptin levels were positively linked to body weight. Total ghrelin measured at the end of the dark phase was significantly higher than at the end of the light period. Therefore, different sources of fatty acids have different effect on inducing obesity but not on reversing it. Forced caloric restriction was found to be the most efficient way for weight loss in obese rats, regardless of dietary fatty acid composition.

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Periprandial changes of the autonomic nervous system related to perceived satiety in humans. L.F. Harthoorn, E. Dransfield. *Wageningen Centre for Food Sciences, Wageningen, 6708 PD, The Netherlands*

Regulation of food intake involves a variety of homeostatic and hedonic components controlled by a system of hunger and satiety signals originating in both peripheral and central pathways. In the present study, the relevance and time course of physiological responses reflecting the status of the autonomic nervous system, specifically the sympathetic—parasympathetic balance, was evaluated in relation to food intake and perceived satiety in humans. Eighteen subjects were exposed individually to a lunch-induced hunger–satiety shift, throughout which sensory ratings, physiological, and biochemical characteristics were obtained at 15 min intervals. Subjects rated, on visual analogues scales (VAS), their feeling of satiety, desire to eat, fullness, and hunger on separate questionnaires. Using non-invasive monitoring, heart rate, heart rate variability and blood pressure, as well as cortisol levels and α-amylase activity in saliva were measured. Across subjects and throughout the hunger-satiety shift, all four sensory ratings correlated with heart rate and salivary α-amylase, and reflected high activity of the sympathetic nervous system during the satiety state. Among men cortisol levels were negatively correlated with age and BMI. Finally, neither oral activities like chewing and swallowing nor orosensory stimulation by food, as tested with modified sham feeding, were found to contribute to any extent to the instant heart rate increase after food consumption. In conclusion, after meal ingestion, specific patterns and critical alterations of physiological characteristics reveal a high sympathetic tone that can be used as an objective determinant of the state of satiety.

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Gastric distension enhances CCK-induced c-Fos expression in the dorsal hindbrain by activating 5-HT3 receptors. M.R. Hayes, M. Covasa. *Department of Nutritional Sciences, College of Health and Human Development, Pennsylvania State University, University Park, PA 16802, USA*

The combination of gastric distension and cholecystokinin (CCK) enhances both suppression of food intake and induction of c-Fos immunoreactivity in the dorsal vagal complex (DVC). Previously, we have shown that serotonin type-3 (5-HT3) receptor mediation of suppression of food intake by CCK requires gastric participation. Therefore, we hypothesized that 5-HT3 receptors mediate CCK-induced c-Fos expression in the dorsal hindbrain through a mechanism that involves gastric distension. To test this hypothesis, we quantified c-Fos immunoreactivity in the DVC of ondansetron (1 mg/kg; 5-HT3 receptor antagonist) and vehicle treated rats following gastric balloon distension (5 cm^3), CCK (1 μg/kg) administration, or CCK combined with gastric distension. Ondansetron significantly attenuated DVC c-Fos expression by CCK. Likewise, ondansetron attenuated c-Fos expression by gastric distension in the DVC, nucleus of the solitary tract (NTS) and area postrema (AP) nuclei, with the most pronounced attenuation occurring at medial and intermedial NTS. When combined, CCK and gastric distension enhanced c-Fos expression in the DVC greater than each treatment alone. Pretreatment with ondansetron attenuated DVC, NTS, and AP enhanced c-Fos expression by CCK + gastric distension particularly within the mid-to-caudal regions of these nuclei. Together with previous data, these results show that gastric distension enhances CCK-induced neuronal activation in the dorsal hindbrain by activating 5-HT3 receptors.

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Optimal liking of fat-sweet mixtures varies with markers of bitter taste and taste anatomy. J.E. Hayes, M.E. Dinehart, V.B. Duffy. *Departments of Nutritional Sciences & Allied Health, University of Connecticut, Storrs, CT 06269, USA*

Previously, we have shown simple markers explain complex food sensations and dietary behaviors. Fischer identified the bitter tastants 6-*n*-propylthiouracil (PROP) and quinine hydrochloride (QHCl) as markers of food preferences. Variation in fungiform papillae (FP) number is a noninvasive proxy for taste and somatosensory innervation on the tongue. While bitterness of PROP and QHCl are correlated across groups of subjects, individual responses can be discordant. Presently, 87 subjects (45 males) used the general Labeled Magnitude Scale to rate the sweetness, creaminess and liking sampled milk products, which varied in fat and added sucrose, as well as the bitterness of PROP and QHCL. Using median splits, high-PROP/low-quinine ($n = 20$) and low-PROP/high-quinine ($n = 17$) groups, along with low ($n = 46$) and high ($n = 42$) FP groups were created. Separate quadratic response surfaces models were fit for each group to find maximal liking. Visual inspection revealed large differences: low FP subjects liked sweeter samples and were uninfluenced by fat level, while high FP were more discriminating, with extreme levels being disliked. Likewise, the high-PROP/low-quinine group disliked extremes while the low-PROP/high-quinine group liked high fat, highly sweetened samples. Given these differences, our previous finding that discordant groups differ in the preference for, and intake of sweet foods [Duffy et al. (2003); Dinehart et al. (2005)] is unsurprising, thus reaffirming, that associations between oral sensation and intake are mediated via preference. Supported by NRICGP/USDA.

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Recall of a recent meal decreases afternoon snack food intake: No effect of manipulation of snack food palatability. S. Higgs, A.C. Williamson. *School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*

Cued recall of a recently eaten meal decreases intake in an afternoon taste test, suggesting that awareness of a recent eating episode may be an important factor influencing appetite. The aim of the present study was to investigate whether the inhibitory effect of remembering a recent meal on subsequent snack intake is dependent upon the palatability of the snack. A total of 14 unrestrained male undergraduate students at the University of Birmingham attended two afternoon tasting sessions in a counterbalanced order. At one session they were asked to recall what they had eaten for their lunch that day (experimental condition), and at the other session they were asked to recall what they had eaten for their lunch the previous day (control condition). Following the recall task, participants were asked to taste and rate the pleasantness of three samples of buttered popcorn with increasing amounts of added salt. A 2 (Cue type: lunch today versus lunch yesterday) × 3 (popcorn type: no salt, low salt and high salt) ANOVA revealed a significant main effect of cue type whereby less popcorn was consumed in the lunch today compared to the lunch yesterday condition. There was also a main effect of popcorn type, whereby more corn was consumed with increasing salt levels (consistent with an effect of salt to increase palatability), but there was no significant interaction between cue type and popcorn type. These data suggest that recall of a recent lunch decreases afternoon intake regardless of snack palatability. Supported by the BBSRC.

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Eating for dopamine: Effects of learning, weight loss, bingeing and purging. B.G. Hoebel, N.M. Avena, M. Bocarsly, P. Rada. *Department of Psychology, Princeton University, Princeton, NJ 08540, USA*

Food reinforcement and the release of release can change together through conditioning. A learned-preferred taste releases dopamine (DA) in the nucleus accumbens (NAc), and a learned-aversive taste lowers it. Rats at 85% body weight have extracellular DA as low as 50% of normal. They release less DA when fed a chow meal, but after a sugar binge, DA increases to 175% of baseline, compared to 122% at normal weight. Underweight rats also self-administer more of abused drugs. The drugs are addictive, but food is not. Drugs and food are different. But, key differences disappear if the food is (a) sweet, (b) taken after food deprivation and (c) the animal adjusts its behavior so as to binge regularly for several weeks. Then the food is like a drug. Why? (1) Bingeing on sugar can release DA without fail, like an addictive drug. (2) If the animals are then put on a sugar-free diet they go into withdrawal, with defensive burrowing and anxiety on an elevated plus maze. (3) After 2 weeks of sugar abstinence, they show enhanced responding for sugar or a sugar-linked cue, indicative of growing motivation for the sugar. They also drink more alcohol than controls. (4) A meal releases ACh that counters DA, but not if the animal's stomach is drained with a fistula. This appears relevant to bulimia. Judging by the DA and ACh responses in the NAc, sweet foods are especially motivating due to learned nutrition, weight loss, periodic bingeing, purging and abstinence. Supported by Grant MH-65024.

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Presystemic stimulation of neurohypophyseal vasopressin secretion while rats eat high-NaCl diet. M.L. Hoffmann, E.M. Stricker. *Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA*

Recent work has shown that dehydrated rats use presystemic, postgastric signals to inhibit thirst and neurohypophyseal vasopressin (VP) secretion. These findings are consistent with the ideas that the inhibition of thirst arises from distension signals from the stomach and small intestine, and that early modulation of VP secretion is mediated by visceral osmo- (or Na+) receptors. The current study focused on the presystemic signals that may stimulate VP secretion in rats. Previous investigations used hyperosmotic NaCl loads administered by gavage to stimulate VP secretion. Instead, in our experiment rats self-administered a salt load by eating high-salt diet (8% NaCl) after a period of overnight food deprivation. Because solid foods generally form a dense chyme in the animals' stomachs, which empties very slowly, little of the ingested NaCl actually empties quickly. Consequently, we increased gastric emptying of the NaCl load by presenting the food in a wet mash formed by combining powdered high-salt diet in a 1:1 ratio with water. The results indicated that plasma VP (pVP) was elevated whether rats ate dry high-salt food or wet mash. When rats consumed dry food, the increase in pVP occurred while plasma sodium (pNa) was rising; thus, stimulation of VP secretion could be attributed to signals from visceral osmoreceptors, from cerebral osmoreceptors, or from both. However, when animals consumed wet mash, pVP increased before systemic pNa was affected. This finding indicates that VP secretion was stimulated by a presystemic signal, presumably from visceral osmoreceptors and related to the hypertonicity of the emptied chyme.

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Activation of IL-1 receptors is not required for the suppression of food intake during the ovarian cycle. M.A. Honors, P.C. Butera. *Niagara University, Department of Psychology, Lewiston, NY 14109, USA*

Previous findings indicate that behavioral and physiological effects of IL-1 are sexually dimorphic, with females showing greater responsiveness than males. One potential cause of this sex difference may stem from neuroendocrine, rather than the classic immune, functions of IL-1, as IL-1 plays a role in the processes that regulate follicular development. The fact that IL-1 has neuroendocrine functions in females may explain why responsiveness to IL-1 is modulated by estrogen. Although IL-1 has a physiological effect in females, it is not known if changes in endogenous IL-1 also produce behavioral effects. This experiment was conducted to determine whether endogenous IL-1 is involved in the changes in food intake and meal patterns that occur during the estrous cycle. Ten female rats were given ip injections of the IL-1 receptor antagonist (IL-1ra) or saline 1 h before dark onset during diestrus and estrus stages of the ovarian cycle. Food intake and meal patterns were recorded during the subsequent nocturnal period. As expected, food intake was reduced during estrus, and this effect of cycle stage on feeding occurred via a decrease in meal size and an increase in meal number. However, IL-1ra treatment did not increase food intake during estrus and had no significant effects on meal size or meal number. These findings do not support a role of endogenous IL-1 in the changes in food intake and meal patterns that occur during the rat estrous cycle. Supported by NIH grant HD40238.

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Cumulative effect of an OX-1 receptor antagonist on food intake, body weight, and body composition in diet-induced obese (DIO) Long–Evans rats. B.L. Hughes, M.J. Dill, L.K. Nisenbaum, D.K. Sindelar. *Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA*

Acute systemic dosing with the selective orexin-1 receptor antagonist SB-334867 (30 mg/kg, i.p.) has been reported to produce a significant loss of body weight and inhibition of food intake over a 24-h period. The present study was designed to determine if chronic dosing of SB-334867 could decrease food intake and body weight/fat mass over 14 days of dosing. Diet-induced obese male (DIO) Long-Evans rats were treated daily with an OX-1 receptor antagonist (SB-334867) for 14 days at doses of 0, 1, 3, and 10 mg/kg i.p. Body weight and food intake were monitored daily. Body composition for each animal was determine [total fat (g) and fat-free (g) mass] prior to and after 14-days of dosing. Over 14-days of dosing, body weight (mean $\pm$ SE) decreased in a dose-dependent manner from 22.3 ± 3.0 (0 mg/kg) to -5.3 ± 4.4 g (10 mg/kg). This change in body weight corresponded with a decrease in cumulative food intake in a dose-dependent manner from 267.9 ± 4.2 for 0 mg/kg to 197.1 ± 9.4 g for 10 mg/kg SB-334867. Fat mass increased in the 0 mg/kg group by 15.46 ± 2.25 g over the course of the experiment while it decreased in a dose-dependent manner to -10.82 ± 2.47 g (10 mg/kg). The fat-free mass did not change in any group. This experiment demonstrates that an orexin-1 antagonist (SB-334867) administered daily over 2 weeks reduces body weight, food intake, and fast mass in diet-induced obese male Long-Evans rats.

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Caffeine consumption history alters the aversive and preference-reinforcing effects of caffeine in rats. E.V. Izbicki, K.P. Myers. *Department of Psychology, Bucknell University, Lewisburg, PA 17837, USA*

For rats and humans, caffeine can have reinforcing and aversive effects that vary with dose and prior consumption history. But there have been inconsistencies between the rat and human literature regarding whether caffeine is reinforcing for caffeine-naive individuals, and how its stimulus properties change (or do not change) with experience. In the present experiments using rats, the reinforcing/aversive effects of caffeine were assayed by conditioned preference/aversion for caffeine-paired flavors. In Experiment 1, caffeine-naive rats were trained in brief daily sessions in which they consumed 15 ml in 30 min. Sessions alternated daily between a distinctly flavored (e.g., grape) palatable solution containing caffeine (0.07–0.25 mg/ml, yielding actual doses of $\sim$4–31 mg/kg bodyweight) and a differently flavored (e.g., cherry) solution without caffeine. In post-conditioning choice tests between the paired and unpaired flavors (no caffeine in either) a clear preference/aversion function for the paired flavor was apparent across the dose range, replicating a prior report [Fedorchak, et al. (2002). Behavioral Neuroscience, 116, 334–346] that caffeine can be reinforcing for caffeine-naive rats. In Experiment 2, extensive habitual caffeine consumption prior to flavor–caffeine pairing significantly altered the preference/aversion function. Acclimated rats did not acquire aversion to a high dose that was aversive for caffeine-naive rats, but reinforcement by a low dose was unaffected. However, in Experiment 3 conditioning was conducted on a schedule intended to maximize negative reinforcing (putatively 'withdrawal-alleviating') effects of caffeine, and demonstrated that a dose that is aversive for caffeine-naive rats can become reinforcing with habitual consumption.

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Conditioned place preferences (CPPs) to high-caloric "snack foods" in rats genetically prone vs. resistant to diet-induced obesity. P. Jarosz, J. Kessler, P.K. Sekhon, D.V. Coscina. *Department of Psychology, College of Liberal Arts and Sciences, and College of Nursing, Wayne State University, Detroit, MI 48202, USA*

Last year we reported that Sprague-Dawley (S-D) rats learn equivalent CPPs to two different high-calorie "snack foods"—Cheetos (C, high in fat) vs. Froot Loops cereal (FL, high in sugar), and that the opioid antagonist, naltrexone (NAL), reversed this learning. Using the same apparatus and training conditions, two S–D sub-strains – one bred for diet-induced obesity (DIO) vs. another bred for diet resistance to obesity (DR) – were studied. Four non-deprived groups of eight adult males, half of each strain, were given 20 min sessions to eat either C or FL in one side of a three-chamber CPP apparatus, vs. Chow on the opposite sides, over alternating days of a 20-day period. Following conditioning, rats were tested during 10 min sessions to determine CPPs. Bodyweights, food intake, and motor activity were measured throughout. During training, both C and FL generated high levels of intake compared to Chow, but DRs ate more than DIOs. Yet during testing, both foods elicited equivalent, strong CPPs in both strains. Subsequent CPP tests under NAL (0, 0.25, 0.50, 1.0, 2.5, and 5.0 mg/kg SC) showed no drug effects in modifying these CPPs as previously found in their parent S–D strain. These results imply that (a) despite different propensities to develop DIO, both sub-strains learn CPPs (i.e., "food cravings") equally well to these "snack foods", but (b) unlike the parent S–D strain, some system(s) other than the endogenous opioid one mediates the expression of this learning. Supported by the NIMH-COR training program (J.K.).

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Rats learn anticipatory hunger with a choice of foods as well as on a single diet. S. Jarvandi[a], D.A. Booth[b], L. Thibault[a]. [a]*School of Dietetics and Human Nutrition, McGill University, Ste-Anne-de-Bellevue, Que., Canada, H9X 3V9.* [b]*School of Psychology, University of Birmingham, UK*

Anticipatory hunger is a learnt increase in intake of food having a flavor or texture that predicts a long fast. This under-researched type of learning was studied in rats trained on a single food ($n = 16$), or a choice between protein-rich and carbohydrate-rich foods ($n = 18$), presented for 1.5 h after 3 h without food at the start of the dark phase. Eight training cycles provided a pseudorandom sequence of 3- and 10-h postprandial fasts with a day on maintenance diet between each training fast. The measure of anticipatory hunger is the difference over one cycle between the intake of test foods having an odor predictive of the longer fast (TL) and intake of food with an odor cuing the rat to the shorter fast (TS). Previous experiments showed that learning to avoid hunger during the longer fast competes with conditioning of preference for the odor before the shorter fast, generating a cubic or quartic contrast. TL minus TS showed a strong cubic trend over 8 cycles. A switch from preference for the short-fast odor at Cycle 2 (mean TL–TS = −0.86 g) to a peak of anticipatory hunger at Cycle 6 (TL–TS = 1.57 g) gave a strong linear trend with positive slope between those cycles. Neither analysis gave an interaction with number of training foods. We conclude that anticipatory hunger is learnt when a choice is given between protein- and carbohydrate-rich diets as well as on a single diet as in previous experiments.

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Effects of corn oil consumption on the discriminative stimulus effects of 22 h food deprivation. D.C. Jewett, J.M. Wiebelhaus, T.W. Hahn, A.T. Dunn, E.J. Mack-Olson, T.A. Schweiner, A.J. Kwilasz, T.R. Smith, M.L. Schneider, M.K. Grace, A.S. Levine. *Food Science and Nutrition, University of Minnesota, St. Paul, MN 55108, USA*

We trained rats to discriminate between 2 and 22 h of acute food deprivation in an operant choice paradigm. Previously, we conducted generalization tests, and found 20 min of laboratory chow consumption decreased the stimulus effects of 22 h of food deprivation. Saccharin (0.032–3.2%) had no effect on the stimuli and larger sucrose concentrations (10–32%) reduced the effects of 22 h food deprivation by about 50%. In the present study, food-deprived rats (22 h) were given access to a 15% corn oil emulsion or 100% corn oil prior to the experimental session (20 min, or 2 h before the session began). Following 20 min or 2 h access to 100% corn oil (mean consumption 4.0 g after 20 min access; 7.5 g following 2 h access) there was approximately a 50% reduction in the discriminative stimulus effects produced by 22 h of food deprivation. A smaller concentration of corn oil (15%) produced a similar magnitude of this effect when the solution was made available for 2 h (mean intake 9.3 g), but not after 20 min (7.7 g). Thus, the effects of corn oil on the discriminative effects of food deprivation resemble the effect of sucrose, but are considerably less effective than laboratory chow. The disparity between sucrose/corn oil and chow may be due to the physical form of the food. Supported by University of Wisconsin—Eau Claire Faculty/Student Research Collaboration grant, NIH and the Department of Veterans Affairs.

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The impact of saturated fat on hippocampal-dependent inhibitory learning processes. S.E. Kanoski, T.L. Davidson. *Department of Psychological Sciences, Ingestive Behavior Research Center, Purdue University, West Lafayette, IN 47907, USA*

Previous research shows that diets high in saturated fat can impair some types of hippocampal-dependent learning processes in rats. Reduced brain-derived neurotrophic factor (BDNF) in the hippocampus has been proposed to underlie such diet-induced learning impairments [Molteni et al. (2002)]. The present research examined whether 90 days exposure to one of two high-fat diets (high-fat mixed with sucrose, high-fat mixed with dextrose) impaired hippocampal-dependent inhibitory learning by rats in a discrimination reversal task, and whether any observed learning impairments were accompanied by reduced BDNF in the hippocampus or prefrontal cortex. The possibility that any observed learning impairments were a result of differences in body weight was controlled for by having a group in each diet condition that was food restricted (maintained at 85% ad lib weight) for the 90 day period prior to training. The results showed that the two high-fat diet groups were impaired in inhibitory learning relative to the control group, and that this effect did not depend on whether the animals were food-restricted. BDNF reductions (in both ventral hippocampus and prefrontal cortex) were observed only in the diet condition that displayed the most memory impairment: the high-fat dextrose, nonrestricted condition. Overall, the present data showed that high-fat diets can impair hippocampal dependent inhibitory learning process, independent of body weight differences. This type of inhibitory learning impairment may have implications for body weight gain in our present environment, where energy regulation depends on the inhibition of appetitive responding in the presence of highly marketed, highly palatable foods.

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Sympathetic denervation of epididymal (EPI) or inguinal fat (ING) pads changes norepinephrine turnover in other intact fat depots. E.W. Kelso, R.B.S. Harris. *Department of Foods and Nutrition, University of Georgia, Athens, GA 30602, USA*

Sympathetic denervation of one fat pad increases the size and decreases norepinephrine (NE) content of neurally intact fat pads in mice and rats. Previously depot NE content was used as a measure of sympathetic activity but the results were inconclusive. This study used norepinephrine turnover (NETO) as a measure of adrenergic activity in white and brown fat pads of NIH Swiss mice in which both EPI or both ING fat pads were sympathetically denervated (DDn) by local injection of 6-hydroxydopamine. Two days after denervation mice in each treatment group (Sham, ING DDn, EPI DDn) were subdivided into three groups. NE concentration of each fat depot at time 0 was measured in one group. The second group was injected twice with alpha-methyl-para-tyrosine (300 mg/kg at time 0, 150 mg/kg at 2 h), an inhibitor of NE synthesis, then tissue NE was measured at 4 h. NETO was calculated from the decline in fat depot NE over 4 h. The third group was sacrificed after 4 weeks for measurement of fat depots weights and NE content. Denervation of ING or EPI pads significantly inhibited NETO in ING, retroperitoneal white fat and intrascapular brown fat. NETO was minimal in EPI fat and was not changed by denervation of EPI or ING fat. There was no effect of denervation on the weights of fat depots 4 weeks after denervation. Thus the loss of neural afferents to one fat depot results in an integrated change in sympathetic activity across multiple white and brown fat depots.

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Responsiveness to preloads in a laboratory study of three types of female dieters: Preliminary report. H.R. Kissileff[a], S. Mcnally[a], R. Gordon[a], H. Lofink[a], M. Torres[a], M. Lowe[b]. [a]*St. Luke's/Roosevelt Hospital, Columbia University, New York, NY10025, USA.* [b]*Drexel University, Philadelphia, PA 19104, USA*

Lowe and colleagues have used a dieting history questionnaire to classify female dieters: restrained dieters (RD: currently dieting, score >15 on Herman and Polivy revised restraint scale (1980), restrained nondieters (RND: same criteria except not currently dieting), and weight suppressors (WS: 12 lb difference between highest and current weight, maintained for 6 months). Previously, these groups have been studied with different paradigms and foods; therefore, the purpose of this study was to compare the effects of a standard preload on these groups with a control group (C) of unrestrained nondieters. On separate, counterbalanced days, subjects ate a 300 kcal coffee cake preload (P) or no preload (NP) followed by a yogurt shake breakfast. C's ($n = 15$) ate significantly less (179.03 g ± 29.5 SED, $t = 6.08$, $P = 0.0001$) after the P (242 g) than NP (421 g). WS's ($n = 7$) ate significantly less (170 g ± 43 SED, $t = 3.93$, $P = 0.0004$) after the P (228 g) than NP (398 g). RD's ($n = 6$) did not reduce intake significantly (37.23 g ± 46.59 SED, $t = 0.80$, $P = 0.43$) after the P (237 g) compared to NP (274 g). RND's ($n = 7$) reduced intake marginally significantly (84 g ± 43 SED, $t = 1.94$, $P = 0.06$) after the P (293 g) compared to NP (377 g). RD's may have eaten less than C's on NP, but the same on P, because RD's are insensitive to, or ignore, hunger signals.

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Modified sham feeding in women with bulimia nervosa and healthy controls. D.A. Klein[a], J.S. Schebendach[a], M.J. Devlin[a], G.P. Smith[b], B.T. Walsh[a]. [a]*Columbia University College of Physicians and Surgeons/NYSPI, New York, NY10032, USA.* [b]*Weill Medical College and New York-Presbyterian Hospital, Westchester Division, White Plains, NY 10605, USA*

Although, it is possible that binge eating in humans is due to increased responsiveness of orosensory excitatory controls of eating, there is no direct evidence for this because food ingested during a test meal stimulates orosensory excitatory and postingestive inhibitory controls. To overcome this problem, we adapted the modified sham feeding technique (MSF) to measure the orosensory excitatory control of intake of a series of sweetened solutions. Previously presented data showed the feasibility of a "sip and spit" procedure in 10 healthy control women using solutions flavored with cherry Kool Aid® and sweetened with one of 5 concentrations of sucrose (0–20%). The current study was designed to extend this technique to artificial sweetener and to women with bulimia nervosa (BN). Seven healthy women and 4 women with BN were randomly presented with cherry Kool Aid® solutions sweetened with one of 5 concentrations of aspartame (equivalent to 0%, 2.5%, 5%, 10%, or 20% sucrose) in a closed opaque container fitted with a straw. They were instructed to sip as much as they wanted of the liquid during 1-min trials and to spit the fluid out into another opaque container. In all subjects, quantity of intake increased with increasing sweetness intensity of the solution. At each concentration, women with BN sipped more solution (149–184%) than controls. These preliminary results support the feasibility of a MSF procedure using artificially sweetened solutions, and the hypothesis that the orosensory stimulation of MSF provokes larger intake in women with BN than controls.

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Re-feeding induces rapid recovery of cardiovascular and metabolic responses after 1 year of caloric restriction in male FBNF1 rats. W.D. Knight, M.M. Messina, A.D. Parsons, J.M. Overton. *Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

Caloric restriction (CR) lowers body weight, metabolism, and cardiovascular parameters. Standard housing temperature ($T_a = 23\,^{\circ}C$) is below the rat zone of thermoneutrality elevating food intake, oxygen consumption, heart rate, and blood pressure. Therefore, we determined the responses to re-feeding after 1-year CR in rats under cold ($T_a = 15\,^{\circ}C$) and thermoneutral (TMN) conditions ($T_a = 30\,^{\circ}C$). At both temperatures, CR rats had lower body weight [TMN(AL:449 ± 6 g, CR:316 ± 2 g); COLD (AL:433 ± 7 g, CR:332 ± 4 g)], heart rate [TMN(AL:265 ± 2 bpm, CR:227 ± 5 bpm); COLD(AL:348 ± 4 bpm, CR:319 ± 4 bpm)], and oxygen consumption [TMN(AL:5.5 ± 0.1 ml/min, CR:4.0 ± 0.0 ml/min); COLD(AL:10.3 ± 0.2 ml/min, CR:7.7 ± 0.1 ml/min)] compared to controls. After 12 months, CR animals were re-fed (RF) inducing hyperphagia [TMN(AL:45 ± 1 kcal/d, CR:33 ± 0 kcal/d, RF:69 ± 5 kcal/d); COLD(AL:74 ± 2 kcal/d, CR:58 ± 0 kcal/d, RF:78 ± 7 kcal/d)]. Four days of re-feeding restored only 24% of both CR-induced weight deficit [TMN(AL: 449 ± 6 g, RF:351 ± 4 g); COLD(AL:433 ± 7 g, RF:352 ± 10 g)] and leptin discrepancy [TMN(AL:15.2 ± 0.6 ng/ml, CR:2.3 ± 0.9 ng/ml, RF: 6.0 ± 0.4 ng/ml); COLD(AL:10.6 ± 0.6 ng/ml, CR:1.8 ± 0.6 ng/ml, RF:6.5 ± 0.2 ng/ml)] compared to controls. Re-feeding immediately restored heart rate while oxygen consumption was only completely restored at TMN. Data indicate that the cardiovascular benefits of long-term CR are immediately reversed by re-feeding. Supported by NIA-AG023837.

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Sex differences in bacterial lipopolysaccharide (LPS)-induced c-Fos expression in the rat brain. B. Kopf, N. Geary, W. Langhans, L. Asarian. *Institute of Animal Sciences, ETH Zurich, CH-8603 Schwerzenbach, Switzerland*

Anorexia is an important component of the initial innate immune response to infection. Because sex differences have been reported in the anorectic response to LPS, we explored whether there are also sex differences in brain neuronal activation (as measured by c-Fos expression) induced by LPS doses that elicit similar degrees of anorexia in males and females. Female rats were ovariectomized and treated with either estradiol (E2, 2 μg every 4 d, SC) or Oil for 8 cycles. Then, on the day modeling estrus, 3 h before dark onset, E2-($n = 10$) or oil-treated ($n = 10$) females received IP injections of either saline (1 ml/kg) or LPS (12.5 μg/kg). Males received either saline (1 ml/kg; $n = 7$) or LPS (100 μg/kg; $n = 7$). Rats were sacrificed 60 min later for c-Fos immunocytochemistry. Saline-induced c-Fos in median raphe was increased in E2- and oil-treated females vs. males and in VMH was increased in only in E2-females. LPS increased c-Fos expression in PVN and median raphe in males but not females. LPS decreased c-Fos expression in VMH of E2-treated females, perhaps related to this area's role in female sexual behavior. The LPS-induced increases in c-Fos expression in males replicate previous findings and implicate these areas in the control of LPS-anorexia. The lack of such effects in females suggests that there are sex differences in the mediation of LPS anorexia, in the relation between brain mechanisms producing anorexia and c-Fos expression, or in other factors that affect c-Fos expression, such as the circadian time used.

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Caloric beverage consumption in children: A behavioral phenotype for obesity? T.V.E. Kral, R.I. Berkowitz, A.J. Stunkard, V.A. Stallings, M.S. Faith. *University of Pennsylvania, School of Medicine, Philadelphia, PA 19104, USA*

Behavioral pathways by which genes promote childhood obesity are poorly understood. Increased consumption of fruit juice and soft drinks is a risk factor for childhood obesity [Ludwig et al. (2001)]. Milk consumption has been related to weight status in adults [Zemel (2005)], but data in children are widely lacking. Familial predisposition to obesity may promote a positive energy balance, in part, through increased consumption of caloric beverages. The present study assessed prospectively whether children born at high-risk ($n = 22$) or low-risk ($n = 27$) for obesity (based on maternal pre-pregnancy body weight) differed in consumption patterns of caloric beverages. Milk, fruit juice and soda intakes were obtained from 3-day weighed food records at child ages 3, 4, 5, and 6 years. A 2(risk status) × 4(age) ANOVA indicated a linear risk group by time interaction for milk, fruit juice and soda intake (across analyses $P < 0.03$). Compared to low-risk children, high-risk children consumed more fruit juice at ages 3 (140 ± 26 vs. 358 ± 52 g, $P < 0.0001$) and 4 (158 ± 30 vs. 263 ± 48 g, $P = 0.05$), and soda at age 6 (30 ± 14 vs. 82 ± 23 g, $P = 0.04$). There was a trend for high-risk children to consume significantly less milk at age 3 compared to low-risk children (150 ± 30 vs. 260 ± 37 g, $P = 0.08$). In conclusion, certain beverage consumption patterns appear to be a behavioral phenotype associated with childhood obesity risk. The contribution of the environment and genetic influences on beverage consumption patterns remains to be determined.

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Expression of c-Fos-LacZ transgene after LiCl administration. B.S. Kwon, T.A. Houpt. *Department of Biological Sciences, Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

Conditioned taste aversion (CTA) occurs after pairing of a novel taste with a toxin (e.g. sucrose with LiCl). c-Fos is expressed, e.g. in the amydala, during CTA acquisition, but other transcription factors contribute to CTA learning. To aid in the identification of c-Fos-positive cells for future transcriptional profiling, we characterized β-galactosidase expression in transgenic mice carrying a c-fos-lacZ fusion gene (a gift from J. Morgan). Mice were injected with LiCl (40 ml/kg, 0.15 M, i.p.) or saline and perfused 1, 3, 6 and 9 h later. Tissue sections were processed for c-Fos immunohistochemistry and X-gal staining in the amygdala. There was a high density of both c-Fos- and X-gal-positive cells in cortex and hippocampus. LiCl increased c-Fos and X-gal staining in the amygdala: c-Fos levels were low in the lateral nucleus (<20 cells/section), but increased rapidly in the central nucleus ($631 \pm 97\%$ at 1 h) and slowly in the basolateral amygdala ($185 \pm 29\%$ at 6 h). Interestingly, although the two genes have a common promoter region and showed similar cortical expression, LacZ expression was significantly lower than c-Fos in the central and basolateral amygdala (45% and 33% of c-Fos, respectively). LiCl-induced LacZ expression confirms that gene transcription contributes to c-Fos expression. Differences in the amplitude of LacZ and c-Fos expession suggest chromosomal or regulatory differences between the transgene and endogenous c-Fos gene in the amygdala vs. cortex. Future studies will examine the expression of other transcription factors during CTA learning using laser capture microdissection of c-Fos-immuno-positive or X-gal-positive neurons in the amygdala. Supported by NIDCD03198.

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Gastrin-releasing peptide and melanocortin-4 receptor mRNA's are co-localized in the rat hypothalamic paraventricular nucleus. E.E. Ladenheim, R.R. Behles, S. Bi, T.H. Moran. *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA*

We previously demonstrated that food deprivation decreased gastrin-releasing peptide (GRP) mRNA expression in the medial parvicellular subdivision of the hypothalamic paraventricular nucleus (PVN) in male Sprague-Dawley rats. Lateral ventricular administration of the melanocortin 3/4 receptor agonist, melanotan II (MTII), prevented the reduction in GRP mRNA levels produced by food deprivation and induced c-fos activation in GRP-containing cells in the PVN. Together, these results suggest that the melanocortin system participates in the regulation of GRP gene expression in the PVN. To investigate whether this effect is through a direct interaction of alpha-melanocyte stimulating hormone on GRP-containing neurons we performed dual label in situ hybridization in the PVN for GRP and melanocortin-4 receptor (MC4-R) mRNA using a biotin-UTP labeled cRNA probe for GRP and a digoxigenin-UTP labeled cRNA probe for MC4-R. In confirmation of previous reports, we found that both GRP and MC4-R mRNA were located in the medial parvicellular subdivision of the PVN. Co-localization of GRP and MC4-R gene expression was also detected in this region, although not all neurons that expressed GRP mRNA also expressed MC4-R mRNA. The finding that GRP-containing neurons co-express MC4-R mRNA suggests that the activity of GRP neurons in the PVN is directly modulated by melanocortin signaling and that reduced melanocortin signaling may contribute to decreased GRP mRNA in the PVN following food deprivation.

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Exaggerated endocrine response to mild stress in rats fed high-fat diet. A. Legendre[#], R.B.S. Harris. *Department of Foods and Nutrition, University of Georgia, Athens, GA 30605, USA*

One of the primary endocrine responses to stress is the release of glucocorticoids due to activation of the hypothalamic–pituitary–adrenal (HPA) axis. It has been suggested that high-fat (HF) diet exaggerates this stress response. In an initial experiment, where rats were fed HF diet for 4 days, we found that HF-fed rats were hyperresponsive to the mild stress of tailbleeding but not to the more severe stress of restraint. A second experiment confirmed these results when rats fed HF diet for 4 days showed an exaggerated corticosterone release in response to an i.p. injection of saline and movement to a novel cage, compared to LF-fed rats. Experiment 3 tested the same parameters as Experiment 2 but interchanged the diets. This allowed us to differentiate between the effects of the dietary fat and those of being offered a new diet. Additionally this experiment determined whether the hyperresponsiveness to mild stress in HF-fed rats was sustained during a prolonged exposure to diet. The results confirmed that HF diet, not novelty, exaggerated the endocrine stress response after 9 days on diet but that the effect was no longer present after 23 days on the diet. The hyperresponsiveness of the HPA axis in HF-fed rats is similar to that observed in animals that have been exposed to a significant chronic or acute stress, suggesting that HF diet may initially be perceived as a stressor. Supported by NIH Grant MH 06828101.

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Dietary fat stimulates enkephalin and dynorphin in the paraventricular nucleus: Role of circulating lipids. S.F. Leibowitz, O. Karatayev, R. Ahsan, V. Gaysinskaya, G.-Q. Chang. *Rockefeller University, New York, NY 10021, USA*

Hypothalamic injections of opioid peptides, enkephalin (ENK) and dynorphin (DYN), stimulate feeding behavior and preferentially increase ingestion of a fat-rich diet. Another peptide, galanin (GAL), with similar effects on feeding is itself found to be stimulated by consumption of a high-fat diet. The present study tested different diets and variable periods of high-fat vs. low-fat diet consumption, to determine whether the endogenous opioids respond in a similar manner as GAL. The results demonstrated that ingestion of a high-fat diet increases gene expression and peptide levels of both ENK and DYN, with the strongest and most consistent effect seen in the paraventricular nucleus (PVN). In this nucleus, ENK and DYN are increased by 50–100% after 1 week, 1 day, 60 min and even 15 min of high-fat diet consumption. While showing some effect in the perifornical hypothalamus, these peptides are considerably less responsive in the arcuate nucleus. This effect of dietary fat on PVN opioids is observed with diets equal in caloric density and palatability and without a change in caloric intake, body weight, fat pad weight, insulin or leptin. The data consistently reveal a strong association between these peptides and a rise in circulating levels of triglycerides, supporting a role for these lipids in the fat-induced stimulation of opioid peptides in the PVN, similar to GAL.

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Twenty-four hours energy expenditure, GLP-1 and satiety during a high protein diet measured in a respiration chamber in lean men. M.P.G.M. Lejeune, N.D. Luscombe-Marsh, M.S. Westerterp-Plantenga. *Maastricht University, Department of Human Biology, 6200 MD Maastricht, The Netherlands*

The mechanism of protein-induced satiety remains unclear. We investigated 24 h energy expenditure, GLP-1 and appetite profile during a high-protein diet in a respiration chamber. Subjects were eight healthy lean males (BMI: $22.8 \pm 1.9\,kg/m^2$, age: 24 ± 4 yr). They were fed at energy balance an appropriate-protein (AP: 10/60/30 en% of protein/carbohydrate/fat) or a high-protein (HP: 30/40/30 en% of protein/carbohydrate/fat) diet in a randomized cross-over design. Twenty-four hour energy expenditure, GLP-1 concentrations and appetite profile were measured. 24 h energy expenditure (10.3 ± 0.7 versus 10.0 ± 0.6 MJ/d; $P < 0.05$) was higher during the HP diet. GLP-1 concentrations after breakfast, lunch and dinner, as well as the area under the curve (42 ± 23 versus 28 ± 16 pmol/L.12 h, $P < 0.005$), were significantly higher in the HP diet condition. No differences were found in hunger and satiety scores between both diet conditions. In the HP diet condition, 24 h energy expenditure was positively related to 24 h protein intake ($P < 0.005$, $r = 0.92$), while this relationship was not significant in the AP diet condition ($P = 0.50$). We conclude that a HP diet as compared to an AP diet when fed at energy balance during 4 days increased 24h energy expenditure and GLP-1 concentrations, and had no effect on appetite profile in lean male subjects.

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Constancy of body weight does not mean physiological regulation. D.A. Levitsky. *Division of Nutritional Sciences and Department of Psychology, Cornell University, Ithaca, NY 14853, USA*

A cogent argument for a set-point feedback system between adiposity and feeding behavior is that body weight of humans remains remarkably constant for long periods of time despite large variations in energy intake and expenditure. Consider a yearly weight gain of 0.5 lb (1750 kcal [0.5×3500 kcal/lb]). In relation to total energy intake (and expenditure) of 2200 kcal a day for a year (803,000 kcal), the energetic error is only 0.22% (1750/803.00). How can such precise regulation of body weight (adiposity) occur without physiological regulation? A computer model will be presented can provide such precision without requiring physiological feedback system. The model makes three reasonable assumptions: (1) daily energy intake is normally distributed, (2) daily energy expenditure is normally distributed, and (3) energy expenditure increases with increasing body weight. The model generates daily body weight curves that illustrate (a) stability of body weight over long periods of time, (2) after short periods of weight gain or loss caused by changes in energy intake, body weight returns to its previous level (set-point?), and (3) small, but consistent increases or decreases in energy intake result in shifts in body weight that appear to be defended. This exercise demonstrates that it is possible to demonstrate stability of body weight without necessitating physiological feedback control from adipose stores to eating behavior.

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Phosphatase blockade in the amygdala enhances both conditioned taste aversion learning and cAMP-mediated cellular activation. D.R. Lockwood, T.A. Houpt. *Department of Biological Science, Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

Serine/threonine phosphatases regulate many substrates implicated in conditioned taste aversion (CTA) learning; CTA is also dependent on spinophilin, a protein phosphatase 1-binding protein. To demonstrate directly that phosphatase activity regulates CTA in a critical brain site, we examined the effects of the PP1/2A antagonist okadaic acid (OA) administered into the amygdala on (1) acquisition of CTA and (2) cAMP induction of c-Fos in vivo. Water-restricted rats ($n = 4-9$/group) with bilateral cannulae directed at the amygdala were injected with OA (100 nM) or vehicle (0.15 M NaCl, 1 μl/hemisphere) 5 min before or after one pairing of saccharin (0.125% for 10 min) and LiCl or NaCl (0.15 M, 3 ml/kg ip). CTA was assessed by 24 h, 2-bottle preference tests. Vehicle-treated rats and rats injected with OA alone showed no CTA. All LiCl-injected rats acquired a CTA (lower saccharin preference vs. controls), but rats injected with OA prior to saccharin–LiCl pairing had a significantly enhanced and persistent CTA compared to all other groups. Additional rats ($n = 6-11$/group) were unilaterally injected (1 μl) in the amygdala with vehicle (0.15 M NaCl), the cAMP analog pCPT-cAMP (24.28 mM), OA (100 nM), or the combination of OA + pCPT-cAMP. One hour later, rats were perfused and the brains processed for c-Fos. Vehicle, pCPT-cAMP alone, and OA alone induced little c-Fos. OA + pCPT-cAMP, however, induced robust c-Fos throughout the amygdala and in projection sites such as the gustatory cortex, hippocampus, and brainstem. Thus, phosphatase activity is a constraint on both CTA learning and cAMP-mediated cellular activation in the amygdala. Supported by NIDCD 06129 & 03198.

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The power of food: A new dimension of appetite and a new scale to measure it. M.R. Lowe. *Department of Psychology, Drexel University, Philadelphia, PA 19102, USA*

Three developments motivated the development of a new measure of the psychological impact of the food environment: evidence that restrained eaters' sensitivity to the food environment is not caused by dieting, massive changes in the nature of food environments in developed countries, and evidence that most intake in such environments is motivated more by hedonic than homeostatic mechanisms. Separate factors of the 18-item Power of Food Scale (PFS) measure the perceived influence of food when it is available in the environment but not physically present (Factor 1), physically present but not tasted (Factor 2), and tasted (Factor 3). In a sample of 563 respondents, the PFS was found to be internally consistent (Cronbach's alpha = 0.93) and temporally stable (4-month test–retest $r = 0.80$). A derivation and confirmation factor analysis confirmed the existence of three stable factors. A group of obese binge eaters scored much higher on the PFS than both obese nonbingers and normal weight individuals ($P's < 0.001$). When both the PFS and RS were regressed on four measures from the Eating Inventory and Dutch Eating Behavior Questionnaire, the PFS was independently related to all four while the RS was independently related to two. The PFS may be useful as an alternative to the Restraint Scale for measuring appetitive responsiveness to the food environment and as an individual difference measure of the rewarding properties of food. Supported by HL073775 and DK066759.

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Processing of sucrose-evoked activity in the parabrachial nucleus is altered in obese OLETF rats. R.F. Lundy Jr[a], M. Covasa[b], A. Hajnal[c]. [a]*Department of Anatomical Sciences and Neurobiology, University of Louisville, USA.* [b]*Department of Nutrition Sciences,* [c]*Department of Neural and Behavioral Sciences, Pennsylvania State University, USA*

Otsuka-Long-Evans-Tokushima-Fatty rats (OLETF) lack functional CCK-1 receptors, are hyperphagic, and gradually develop obesity and diabetes. Recently we have reported a progressive increase in lick rate to various sweet tastants in prediabetic OLETF rats compared to age-matched lean controls (LETO). This study investigated sucrose taste processing in the gustatory parabrachial nucleus using a semi-chronic preparation that allows data collection over several recording sessions (Block 1: 12&13; Block 2: 15–20 weeks of age) representing different stages of glucose tolerance. Forty-four taste neurons were tested and, using cluster analysis, categorized based on response profile to 0.1 M NaCl, 0.01 M citric acid, 0.003 M QHCl, and six sucrose concentrations (0.01, 0.03, 0.1, 0.3, 1.0, and 1.5 M). For NaCl-best cells, the Block 2 response rates to 0.1, 0.3, 1.0, and 1.5 M sucrose, on average, were 24% (±6.8%) *lower* relative to Block 1 sessions in OLETF rats, but 16% (±6%) *higher* in LETO. Sucrose-best cells (S-best), on average, were *more* responsive to these concentrations of sucrose during Block 2 sessions relative to Block 1 sessions both in OLETF (45±11%) and LETO (30±8%) rats. In terms of the across-neuron pattern evoked by sucrose, advancing age in OLETF rats, but not LETO rats, increased the proportion of neural information carried by S-best cells and correspondingly decreased it for NaCl-best cells. This altered population code for sucrose may contribute to increased behavioral sensitivity to sweet in this strain. Supported by Dean's Feasibility Grant (PSU-COM to A.H.) and NIH Grants DK065709 and DC006698.

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Gender differences in GLP-1, satiety and hunger responses in high versus standard protein diets consumed at energy balance. N.D. Luscombe-Marsh[#], M.P.G.M. Lejeune, M.S. Westerterp-Plantenga. *Department Human Biology, University Maastricht, Maastricht, The Netherlands*

Standard (SP) versus high-protein (HP) diets were compared between men and women who differed in body composition. Three groups [Group 1: 8 men, 13.9 ± 2.3% body fat (% BF); Group 2: 8 women, 22.6 ± 0.6% BF; Group 3: 8 women, 31.1 ± 1.6% BF] followed, at energy balance, SP (10% protein) and HP (30% protein) diets. After 4 days on HP vs. SP, men showed greater 24 h-energy expenditure (24 h EE) (10.3 ± 0.7 vs. 10.0 ± 0.6 MJ/d) and smaller GLP-1 AUC (28 ± 16 vs. 42 ± 23 pmol/lx12 h, $P < 0.01$). For women, sleeping metabolic rate (6.4 ± 0.47 vs. 6.12 ± 0.24 MJ/d, $P < 0.05$), diet-induced thermogenesis (0.91 ± 0.25 vs. 0.69 ± 0.24 MJ/d, $P < 0.05$) and satiety were greater (973 ± 178 vs. 765 ± 304 mm, 24 h, $P < 0.01$) on HP, and hunger was reduced (822 ± 304 vs. 1101 ± 256 mm VAS, 24 h, $P < 0.005$). Group 2 compared to Group 1, showed greater satiety on HP ($P = 0.008$). When switched from SP to HP, change in satiety AUC was related to change in GLP-1 AUC for Group 3 ($r = 0.769$, $P = 0.043$). For Group 2, change in hunger was related to change in 24 h EE ($r = 0.79$, $P = 0.019$) and for Group 1 change in hunger was related to changes in EE ($r = 0.79$, $P = 0.019$) and GLP-1 AUC ($r = 0.71$, $P = 0.047$). We conclude for non-obese men and women with different body compositions, there are no apparent differences in the cause of satiety on a HP vs. SP diet.

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Increased preference for standard versus palatable chow during long-term amylin treatment. C. Mack, J. Roan, J. Wilson, J. Reynolds, M. Tryon, C. Vu, D. Parkes, K. Laugero. *In vivo Pharmacology, Amylin Pharmaceuticals Inc., San Diego, CA 92121, USA*

This study tested for possible food preference properties as influenced by the anorectic peptide amylin. Adult male rats (490 g) were treated for 11 weeks with amylin (300 μg/kg/d) or vehicle via subcutaneously implanted osmotic pumps. Animals had access to both low fat chow (6% fat kcal, 54% cornstarch kcal) and palatable chow (58% fat kcal and 26% sucrose kcal). Total consumption (both diets combined) was assessed by a Treatment × Week interaction that revealed decreased intake weeks 1–6 and 8 with amylin treatment (P's < 0.05); consumption was equal to controls weeks 7 and 9–11. Consumption across the 11-week period was reduced with amylin (vehicle = 6315 ± 111 kcal vs. amylin = 5309 ± 202 kcal, $P < 0.05$). As to food preferences, amylin-treated rats consumed a greater number and percentage of total calories from low-fat chow compared to controls throughout the study (main effect for number of low-fat chow calories: vehicle = 271 ± 42 kcal vs. amylin 633 ± 145 kcal, and main effect for percent total calories: vehicle = 4.3 ± 0.6% vs. amylin = 12.2 ± 3.2%, respectively, P's < 0.05). Body weight gain was lower in amylin-treated rats (vehicle = 126 ± 10 g vs. amylin = 50 ± 11 g, $P < 0.05$) and was associated with decreased fat mass and increased energy expenditure (P's < 0.05). These data indicate that decreased caloric intake, with a relative preference for low fat versus palatable chow, and increased energy expenditure contributed to the weight-lowering properties of amylin in rats.

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The anorectic effects of the cannabinoid 1 receptor (CB1R) antagonist Rimonabant persist following gut vagal deafferentation. A.N. Madsen[a], E.H.E.M. Van de Wall[b], A. Azzara[b], B. Schuss[b], P.J. Larsen[a], G.J. Schwartz[b]. [a]*Rheoscience A/S, Glerupvej 2, DK-2650 Rødovre, Denmark.* [b]*Albert Einstein College of Medicine, Departments of Medicine & Neuroscience, Bronx, NY 10461, USA*

The selective CB1R antagonist Rimonabant has been shown to reduce food intake in rodents and humans. Although CB1R binding sites have been identified in both the central and peripheral nervous system, including the afferent vagus nerve, it remains unclear whether gut vagal afferents are required for Rimonabant's feeding inhibitory actions. We examined Rimonabant's anorectic effects (0.3–10 mg/kg) in male C57B6 mice with subdiaphragmatic vagotomy (VGX), and in male Sprague–Dawley rats with selective gut vagal deafferentation (SDA). VGX and surgical control (CON) mice maintained on standard chow received access to a scheduled meal of 16% w/v sucrose solution, and 1 h sucrose intake was measured every 15 min. Rats were maintained on either 45 mg chow pellets or nutritionally complete palatable liquid diet (Ensure), and solid meal pattern or total 24 h intake (Ensure) was assessed daily. In both VGX and CON mice, Rimonabant (i.p.) dose-dependently reduced 1 h sucrose intake at all timepoints. Rimonabant (i.g.) also reduced feeding equivalently in both SDA and sham control rats, for both solid and liquid diets. Rimonabant's anorectic effects were manifested as a reduction in pellet meal size with no change in meal frequency. These findings demonstrate that Rimonabant reduces meal size during both scheduled and spontaneous meals, and that gut vagotomy fails to attenuate its effects in both rats and mice. These data suggest that Rimonabant reduces feeding by modulating the potency of meal-related feedback signals, and that central CB1R are sufficient to mediate its feeding inhibitory effects. Supported by DK47208.

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Naloxone decreases sucrose seeking in rats even after long periods of forced abstinence. M.K. Manaois, A. Fyall, D. Osincup, B. Wells, R. Reese, J.W. Grimm. *Department of Psychology, Western Washington University, Bellingham, WA 98225, USA*

Relapsing disorders, such as seen in eating disorders and drug abuse, are difficult to treat due to the associations addicts make with reward-paired stimuli. In rats, discrete cues previously paired with a rewarding substance can elicit seeking behavior (an animal model of relapse). This behavior increases over a period of forced abstinence and is termed 'incubation of craving' in the literature. The present study investigated the role of opioid receptors in the incubation of sucrose craving. Rats were trained to lever press for sucrose reward 2 h a day for 10 days. Following either 1 or 30 days of forced abstinence, rats were allowed to respond in extinction. Systemic injections of either saline or naloxone (0.01, 0.1, 0.3, 1.0 or 10 mg/kg) were administered prior to cue-induced reinstatement. Relapse was initiated by exposure to the discrete tone-light cue previously paired with sucrose delivery. Responding for the sucrose-paired cue was greater on day 30 vs. day 1 of forced abstinence. Naloxone decreased this relapse behavior to a similar extent at both time points. Locomotor activity was reduced, albeit not significantly. These results suggest a role for opioid receptors in sucrose seeking behavior; however, they do not elucidate the underlying neural basis for the incubation effect.

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Effect of a CB1 receptor antagonist on food motivation and taste preference in mice and rats. C.M. Mathes, N.E. Rowland. *Department of Psychology, University of Florida, Gainesville, FL 32611, USA*

Rimonabant, a cannabinoid CB1 receptor antagonist, decreases food intake possibly by reducing the motivational properties of food. The purpose of the first experiment is to determine in mice whether Rimonabant differentially affects earned compared with free food intake. Adult albino (ICR) male mice were fed 20 mg Noyes pellets either freely in their home cage or contingent on an FR5 lever press per pellet in an operant chamber for 30 min sessions each morning. In the afternoon, both groups were freely presented a balance of pellets to total 3.5 g. When morning intakes were stable, mice were injected in counterbalanced order with Rimonabant (5 mg/kg) or its vehicle (polyethylene glycol PG, 1 ml/kg IP) 30 min before access to the morning access. Mean 30 min intakes of the free group were reduced from 1.76 (PG) to 0.91 g (Rimonabant; −48%); corresponding data in the operant group were 1.57 (PG) and 0.38 g (−76%). Suppression of intake was significantly greater ($P > 0.02$) in the operant compared with the free food condition. The second experiment is designed to determine whether Rimonabant causes a decline in the palatability of sucrose as a rightward shift in the concentration–licking curve. Non-deprived adult Sprague–Dawley rats were injected with Rimonabant (3 mg/kg IP) or vehicle 30 min before testing in a "Davis rig" in which six different concentrations of sucrose are presented in 6 s epochs in random order. Licks at each concentration were measured and shifts in the concentration–lick function will be assessed.

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Influence of chronic social stress on food intake. S.J. Melhorn[a,b,#], K.L.K. Tamashiro[c], M.M.N. Nguyen[a,b], L.Y. Ma[b], R.R. Sakai[b]. [a]*Neuroscience Program, USA.* [b]*Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH 45267.* [c]*Department of Psychiatry, Johns Hopkins University, Baltimore, MD 21205, USA*

Male rats form a dominance hierarchy when housed in a mixed-gender visible burrow system (VBS), a laboratory model of chronic social stress resulting in one dominant (DOM) and three subordinate (SUB) males. Previous studies show that DOM and SUB have characteristics consistent with chronic social stress. Control (CON) males were housed with a single female in conventional cages. In this study we examined body weight (BW), body composition, and food intake parameters after 2 cycles of 14-days of social stress in the VBS followed by 21-days of recovery in individual cages. Food intake during VBS cycles and recoveries were monitored with the AccuDiet ID food intake system. During the 14-day stress period SUB lost significantly more body weight than the DOM males. During a 3-week recovery cycle SUB were hyperphagic compared to DOM and gain significantly more adipose tissue compared to DOM. This effect is more pronounced during a second cycle of VBS and recovery. Total intake, location of intake and time of intake differed between DOM and SUB groups. SUB consumed fewer total grams of food and predominantly ate from the smallest chamber, whereas the DOM consumed more food primarily from the largest/surface chamber. These data suggest that chronic social stress can result in changes in food intake behavior. Alterations in meal patterns and overall food intake may be lead to significant changes in body composition in SUB animals. Supported by DK066596.

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Ovariectomy produces weight gain via different mechanisms in female mice and rats. M.M. Messina, A.R. Chandler, A.K. Mehle, J.M. Overton. *Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

We investigated the mechanisms by which lack of gonadal steroids produce weight gain in females. Mice and rats were fed standard diet and housed in metabolic cages (T_a~23 °C) for continuous measurement of oxygen consumption ($\dot{V}O_2$). Cages were positioned on load-beam platforms for detection of locomotor activity (LA). Animals were either ovariectomized (OVX) or underwent sham surgery. Prior to surgery, there were no differences in weight between groups. After 3 weeks, OVX mice had gained 3.2 ± 0.2 g, while shams maintained their weight. OVX rats also gained more (58.3 ± 5.4 g) than shams (32.5 ± 13.9 g). Both OVX and sham mice ate less during post-surgical days 1–4, but by post-surgical day 5, food intake returned to baseline. In contrast, OVX produced hyperphagia in rats (baseline = 28.6 ± 0.7 g, post-OVX = 33.0 ± 0.7 g). In mice, OVX markedly decreased dark-phase LA (pre-OVX = 943 ± 108, post-OVX = 288 ± 164 m); this was associated with reduced dark-phase $\dot{V}O_2$ (pre-OVX = 35.9 ± 0.2, post-OVX = 34.3 ± 0.3 ml/min/kg$^{0.75}$). In contrast, OVX only modestly reduced dark-phase LA in rats (pre-OVX = 118 ± 8, post-OVX = 102 ± 5 m), while dark-phase $\dot{V}O_2$ was unaffected (pre-OVX = 24.5 ± 0.1; post-OVX = 23.9 ± 0.1 ml/min/kg$^{0.75}$). The results suggest that weight gain induced by OVX is mediated by reduced LA and thermogenesis in mice, while it is primarily mediated by hyperphagia in rats. Supported by NIH HL-56732.

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Antagonism of 4th ventricle corticotropin releasing factor receptors (CRFR) exaggerates the effects of stress on food intake. J.R. Miragaya#, R.B.S. Harris. *Department of Foods and Nutrition, University of Georgia, Athens, GA 30602, USA*

Studies have demonstrated that acute stress inhibits weight gain and food intake in rats. Little is known about the brain nuclei area responsible for the initial response to stress, however, infusion of CRFR agonists into the 3rd or the 4th ventricle inhibits food intake. We investigated the role of CRFR located adjacent to the 4th ventricle in the energetic response to stress. In Experiment 1, alpha helical CRF (αhCRF: 5 μg/2 μl), a non-specific CRFR antagonist, infused in the 4th ventricle exaggerated the weight loss and inhibition of food intake caused by repeated restraint stress (RRS: 3 h of restraint/3 days). Experiment 2 tested the effects of αhCRF on food intake of rats exposed to Mild Stress (MS: 2 ml of saline i.p and moving to a different room for 2 h). αhCRF exaggerated the inhibition of food intake measured at 6 h but not at 2 or 24 h after MS. These results could result from the partial agonist effect of αhCRF, except that the control group did not show a change in food intake. Therefore, we conclude that the brainstem may play a protective role against stress induced hypophagia through a negative feedback mechanism. This feedback acts at a site other than the brainstem and may involve down regulation of CRF agonists or of ligands in a different regulatory system. Supported by NIH Grant MH06828101.

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Body weight and physiological measures during ontogeny in rats following intra-uterine growth retardation (IUGR). A. Mitra#, K. Robertson, N.E. Rowland. *Department of Psychology, University of Florida, Gainesville, FL 32608, USA*

According to the fetal origins of adult disease (FOAD) hypothesis, prenatal stressors have long-term consequences on development and health. In the present experiment, Sprague-Dawley dams were synchronously mated and 33% of the mated rats were placed on a Chow ration of 50% that eaten by the remaining 67% adlib feeding dams. At parturition, litters were culled to 8 and cross-fostered to adlib fed dams. From parturition to weaning (PD22) the dams and litters were fed Chow adlib. On PD 22 males and females for a given litter were separated and placed on either a Chow or a high-fat (2chow: 1shortening) diet. Body weight and food intake were monitored every 5 days from PD 0-92 and PD 22-92, respectively. One male and one female per litter were sacrificed on PD 0, 22, 42 or 92 for blood and organ collection. The IUGR rats weighed ~71% of control at birth, but litter mortality rates did not differ between groups. From PD 0 to PD 92, the deprived pups were consistently lighter than the adlib pups, although the difference was not large and was not statistically significant for males fed the high fat diet. Food intake did not differ at any age between control and IUGR offspring. Plasma levels of leptin and insulin showed significant differences with age and diet, but no differences between control and IUGR offspring. Thus, despite a substantial pre-natal malnutrition resulting in IUGR, rats fostered to ad lib mothers exhibited only slightly lower growth curves and few physiological effects.

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Direct regulation of food intake and hypothalamic gene expression by amino acids. C.D. Morrison, C.L. White, X. Xi, J. Ye, R.J. Martin. *Pennington Biomedical Research Center, Baton Rouge, LA 70808, USA*

Nutritional signals act in the brain to regulate feeding behavior and metabolism, and it is increasingly evident that these signals include circulating hormones and metabolic fuels. To test whether the brain senses changes in protein availability, male Sprague–Dawley rats were fed diets consisting of 10% (low), 20% (control) or 35% (high) protein. The low protein diet increased daily food intake within 3 days of diet exposure, and also increased expression of hypothalamic *Agrp* at 7 days ($P<0.05$). To determine if amino acids act directly in the brain to regulate feeding, 24 h fasted rats were treated with either vehicle, an amino acid mixture (RPMI 1640 AA mixture), or leucine (1 μg) directly into the 3rd ventricle. The amino acid mixture and leucine suppressed 24 h food intake ($P>0.05$). To define a potential cellular mechanism, the effects of altered amino acid availability on *Agrp* expression, phospho-AMPK and phospho-p70S6 K was determined in a hypothalamic cell line (GT1-7 cells). Reduced amino acid concentration increased *Agrp* expression ($P>0.05$), as did reducing the concentration of only leucine. Acute exposure to elevated amino acid concentrations increased the phosphorylation of p70S6 K and AMPK, and this activation of p70S6 K was blocked by pretreatment with rapamycin, an inhibitor of mTOR signaling. These data suggest that changes in hypothlamic *Agrp* expression may contribute to changes in food intake following exposure to low protein diets, and in addition implicate the AMPK and mTOR signaling pathways as putative mediators of these amino acid-dependent effects.

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Thermic, behavioral withdrawal symptoms provide further evidence of the addictive nature of sugar in the rat. H.M. Murphy, G.R. Nadzam, C.H. Wideman. *Neuroscience Program, John Carroll University, Cleveland, OH 44118, USA*

In rats, sugar has been shown to have behavioral and neural effects similar to those of drugs of abuse. It has been demonstrated that rats, sustained on an intermittent diet of sugar, develop a pattern of copious consumption of sugar. Addiction is a compulsive need for use of a habit-forming substance, characterized by tolerance and by physical and psychological withdrawal symptoms following the discontinuance of the substance. In the present study, rats were implanted with biotelemetry transmitters that monitored body temperature throughout the 24 h circadian cycle. Animals were divided into experimental and control groups. During weeks 2 and 4 of the study, the experimental group was intermittently presented with a 25% glucose solution. Following the removal of the glucose solution in week 3, experimental rats showed a significant drop in body temperature compared to control animals. A decrease in body temperature is one of the most reliable and consistent indices of withdrawal from drugs of addiction (e.g., morphine) in the rat. In addition to the thermic response observed, altered behavioral responses consistent with withdrawal were shown in experimental animals during the third week. These behaviors included body shakes and teeth chattering, as well as gripping the top grate of the cage with front paws and gnawing on the bars on top of the cage. Similar behavior has been noted in rats during withdrawal from addictive substances. The thermic and behavioral withdrawal responses observed in the present study provide further evidence of the addictive nature of sugar in rats.

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A test of the hedonic and anticipatory hypotheses of nutrient-conditioned flavor preferences. K.P. Myers, S.P. Bradley. *Department of Psychology, Bucknell Univesity, Lewisburg, PA 17837, USA*

Rats learn to prefer flavors followed by postingestive nutrient stimulation. This type of learning ('nutrient-conditioned preference') produces robust effects on flavor selection and intake. But the motivational mechanisms mediating the preference are not well understood. One hypothesis ('hedonic') is that a flavor associated with postingestive nutrient effects increases in palatability. Another hypothesis ('anticipatory') is that the flavor does not become more palatable, but is selected and consumed instrumentally, based on anticipation of beneficial nutrient effects. Evidence for the hedonic hypothesis using taste reactivity has been mixed. The present experiments used a second-order conditioning protocol designed to distinguish between these two possibilities. In brief daily sessions, rats were trained with a flavor (CS+, e.g., cherry) paired with intragastric (IG) maltodextrin infusion, producing strong flavor-nutrient conditioning. Then, in a second-order conditioning phase, a second flavor (CS2+, e.g., coconut) was mixed with the CS+, but consumption of the mixture was paired with IG water. Additional control conditions were included for comparison. The hedonic hypothesis would predict that if the CS+ has increased in palatability, preference for CS2+ should increase via flavor–flavor conditioning. The anticipatory hypothesis would predict that preference for CS2+ should decrease, as it becomes a cue for absence of anticipated nutrient. One experiment using CS+ that was initially palatable (saccharin-sweetened) produced a pattern of results consistent with the hedonic hypothesis. A second experiment using initially unpalatable CS flavors produced results inconsistent with the hedonic hypothesis. This is further evidence that mechanisms of nutrient conditioned preference differ depending on initial stimulus quality.

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Cns μ-opioid stimulation increases intake of high-fat but not high-sucrose diet depending on diet preference in a "binge" model of feeding. A.M. Naleid[a], M. Chimukangara[b], M.K. Grace[b], A.S. Levine[b]. [a]*Department of Psychiatry and Behavioral Science, University of Washington, Seattle, WA 98108, USA.* [b]*Department of Food Science and Nutrition, University of Minnesota, St. Paul, MN 55108, USA*

Previous work from this lab indicates that when rats are given a choice between a high-fat and a high-sucrose diet, opioid blockade with naltrexone (NTX) in a reward-related site (central amygdala) inhibits intake of the preferred diet only, whereas NTX injected into a homeostasis-related site, such as the hypothalamic paraventricular nucleus (PVN), inhibits intake of both diets. However, other work suggests that opioids increase intake of fat specifically when injected into reward/motivation sites, such as the nucleus accumbens shell (AcbSh). We hypothesized that the μ-opioid agonist, DAMGO (0, 0.3, 1, and 3 nmol), injected into the AcbSh would enhance intake of animals' preferred diet, while DAMGO injection into the PVN would enhance intake of both diets. We used a "binge" model with chow-maintained rats given three hours' access to both diets three days a week. We found a significant effect of dose ($P = 0.0002$), and a dose × preference interaction ($P = 0.004$), but no site × dose interaction ($P = 0.40$), with DAMGO dose-dependently increasing fat intake when injected into both the AcbSh and PVN in fat-preferring animals but having no effect on sucrose-preferring animals. DAMGO did not increase sucrose intake when injected into either site, regardless of preference. These results indicate that μ-opioid stimulation preferentially increases fat intake over sucrose intake, whether injected into PVN or AcbSh, but that fat intake at the AcbSh is only increased in animals that prefer fat to sucrose. Therefore, opioid-modulated food intake is not governed by macronutrient or preference alone, but by an interaction between these two factors, among others.

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Are fatty acid/sugar combinations the dietary equivalent of the drug "speedball"? J.A. Nasser. *New York Obesity Research Center, St. Luke's Hospital, New York, NY 10025, USA*

The combining of fat with simple and complex carbohydrates creates a favorable medium for over-consumption that has been observed both in animals and in humans with and without binge-eating disorders, as well as in those abusing cannabinoids and those recovering from substance dependence. Conversely, high-fat/high-carbohydrate foods are selectively avoided by individuals suffering from anorexia nervosa, and those actively abusing alcohol and cocaine. While many studies have examined mechanisms of perception and reward of fats and carbohydrates as individual stimuli, few studies exist examining perception/reward mechanisms for the fat/carbohydrate combination as a unique sensory entity. We have previously reported that perception of free fatty acids in high-fat/high-CHO foods is related to PROP taster status. The fatty acid components in these foods and their interaction with carbohydrates may provide a basis for a unique sensory entity. We present data demonstrating a positive association of BMI with taste perception and preference for a high-fat/high-CHO food containing free fatty acids. In addition, we present data demonstrating that choice of high-fat/high-CHO food, after a caloric preload, in a food-reinforced operant task is related to BED status.

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Effects of GABA in the nucleus accumbens shell on ingestive behavior after dehydration-anorexia. C.M. Neuner, A.G. Watts. *Neuroscience Graduate Program, University of Southern California, Los Angeles, CA 90089, USA*

We have previously shown that rats displaying anorexia as a result of drinking hypertonic saline demonstrate severe attenuation of feeding bouts induced by overnight fast, injection of 2-deoxy-D-glucose (2-DG), or injection of neuropeptide Y (NPY). It has been reported that application of the $GABA_A$ agonist muscimol to the nucleus accumbens shell (ACBsh) can also stimulate ingestive behavior, inducing immediate-onset bouts specific to food intake. Here, we investigated how dehydration–anorexia affects ingestive behavior following muscimol application to the ACBsh. Ingestive behaviors and motor activity following either muscimol (50 ng) or saline vehicle injections to the ACBsh were monitored during a 30-min behavior test in euhydrated, undeprived rats (EU), rats dehydrated (DE) for 5 days, and pair-fed rats (PF) food restricted to match the intake of the DE animals. Rats dehydrated for 5 days showed a significant attenuation of food intake following muscimol injection, as compared to food intake following muscimol injection in the EU animals. DE animals also showed a significant decrease in feeding duration, though the latency to feed following muscimol was unaffected. Interestingly, while EU animals show little or no drinking behavior following muscimol injections, DE animals drink an average 8 ml of hypertonic saline after muscimol, significantly more than the water consumed by EU animals. As expected, PF animals consumed more chow than when undeprived, however there was no difference in feeding behavior in PF animals receiving muscimol or vehicle. These results suggest that DE-anorexia modulates ACBsh neurons in a way that effectively alters an established behavioral output.

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It smells so good I can almost taste it: Evidence that food and nonfood odors are localized differently within the nasal cavity. K.J. Newhouse[a], B. Green[b,c], D.M. Small[a,b,d,e]. [a] *Yale Interdepartmental Neuroscience Program,* [b]*The John B. Pierce Laboratory,* [c]*Department of Surgery,* [d]*Psychology,* [e]*Psychiatry, Yale University, New Haven, CT 06519, USA*

We investigated whether perceiving an odor as a food or nonfood affects where in the nose it is localized. We hypothesized that experience with an odor as a flavor that emanates from the mouth causes the odor to be localized toward the posterior region of the nasal cavity. We defined odor localization as where in the nasal cavity a subject perceives a sniffed odor to be distributed. Subjects were shown three MRI cross-sections of the head depicting hypothetical distributions of odor within the anterior, mid- or posterior portions of the nasal cavity. They were told that that these images represent possible distributions of an odor in the nose. Subjects sniffed six food and six nonfood odors and selected the distribution that best matched the perception of each. In two separate subjects ($n = 14$ and), Chi-square analyses showed that subjects selected the posterior distribution more frequently for food compared to nonfood odors ($P < 0.02$ and 0.05). These results are consistent with the general proposal that experience influences the neural representation of odors, and specifically that experience with food odors affects their spatial distribution. Interestingly, the effect only occurs if the odors are not identified as foods before perception begins, indicating that verbal information changes the way olfactory signals are processed. Supported by NIH/NIDCD RO3 DC006169.

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Influences of androgens on body weight regulation and food intake during chronic psychosocial stress and recovery. M.M.N. Nguyen[a,b], S.J. Melhorn[a,b], K.L.K. Tamashiro[c], L.Y. Ma[b], R.R. Sakai[b]. [a]*Neuroscience Program, USA.* [b]*Department of Psychiatry, University of Cincinnati Medical Center, Cincinnati, OH 45267, USA.* [c]*Department of Psychiatry, Johns Hopkins University, Baltimore, MD 21205, USA*

The Visible Burrow System (VBS) is a model used to study chronic social stress in colony housed rats. A hierarchy develops among the males resulting in dominant (DOM) and subordinate (SUB) animals. Hierarchy associated changes in body weight, composition, behavior and neuroendocrine measures have been observed. After 14 days of stress, SUB have decreased body weight and testosterone (T) compared to DOM. We propose that the differences in body weight are due to stress-associated changes in circulating T. Also, at the end of VBS housing and during recovery, SUB have elevated CORT levels and decreased T levels compared to CON and DOM putting SUB in the perfect neuroendocrine state to regain lost body weight as adipose tissue. To test this, animals were gonadectomized and implanted with T, 5α-dihydrotestosterone (DHT), or cholesterol (CHOL) silastic implants. Implants maintained constant physiological T and prevented the T decrease observed in SUB. SUB significantly lost more adipose tissue and lean body mass compared to CON, while DOM primarily lost adipose tissue during the VBS. Gonadal intact, T, and DHT implant colonies formed hierarchies, whereas, CHOL colonies did not. Intact, T, and DHT SUB significantly lost more weight than DOM, however T and DHT SUB maintained more lean body mass than intact SUB. These data suggest that T may play a role in stress-induced body weight loss and changes in composition. Supported by DK066596 (RRS).

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Anorexic doses of the amylin analog salmon calcitonin (sCT) support conditioned flavor avoidance in rats. J.V. Nguyen, L. Rinaman. *Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA*

The pancreatic peptide amylin reduces food intake in rats, apparently without producing malaise. We sought to confirm whether the amylin analog sCT also inhibits food intake without supporting conditioned flavor avoidance. Male rats with ad lib chow access were injected i.p. with sCT (0, 1.0, 2.5, or 5.0 μg/kg BW) at the beginning of the dark cycle. sCT at 1.0 μg/kg suppressed food intake by 20–30% compared to vehicle, with the effect lasting for a few hours. sCT at 2.5 μg/kg suppressed food intake by a similar degree, but for a longer time period. sCT at 5.0 μg/kg suppressed food intake by more than 75%, for more than 24 h. In experiments examining the ability of sCT to support conditioned flavor avoidance, separate cohorts of rats were water deprived, then given 30 min access to water containing a novel flavor. After flavor exposure, rats were injected with vehicle or sCT (one dose per cohort). The procedure was repeated a few days later, with rats given access to the alternate novel flavor followed by the alternate i.p. treatment. A final two-bottle choice test was later administered, in which rats had simultaneous 30-min access to vehicle- vs. sCT-paired flavors. Each dose of sCT (1.0, 2.5, and 5.0 μg/kg) supported significant avoidance of drug-paired flavors, with greatest avoidance of flavors paired with the highest sCT dose. We conclude that these anorexigenic doses of sCT also support conditioned flavor avoidance, evidence that malaise contributes to the anorexic effect. Supported by NIH #MH59911.

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Cognitive dietary restraint and disinhibition are associated with higher plasma cortisol concentrations in women. A.G. Nieuwenhuizen, F. Rutters, M. Lejeune, M.S. Westerterp-Plantenga. *Department of Human Biology, NUTRIM, Maastricht, The Netherlands*

Stress has been shown to increase food consumption in women with high levels of dietary restraint, a phenomenon that is associated with increased disinhibition. Also, this increase in food consumption following stress is positively correlated to plasma cortisol responses. Therefore, we aimed to study the relationship between plasma cortisol levels and the levels of dietary restraint and disinhibition in a population of non-obese women. A group of healthy women, ageing 19–24 yr and a BMI between 20–25 kg/m^2, were fed in energy balance (P/C/F: 10/60/30%). On day 16, blood samples were collected throughout the day from 8:00 to 22:00 h for the determination of plasma cortisol. The Three Factor Eating Questionnaire (TFEQ) was used to assess cognitive dietary restraint (F1), disinhibition (F2) and susceptibility to hunger (F3). The results show a strong correlation between the plasma cortisol levels (measured as area under the curve from 8:00 to 22:00 h) and cognitive dietary restraint (F1, correlation coefficient: 0.78), as well as between plasma cortisol levels and disinhibition scores (F2, correlation coefficient: 0.80). This relationship between circulating plasma cortisol levels on the one hand, and the level of cognitive dietary restraint and disinhibition on the other may play a role in the intra-individual differences in the effects of stress on food intake.

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Central neural circuitry subserving thirst and hunger – divergence and commonalities. B.J. Oldfield, J. Kampe, J.H. Hollis. *Department of Physiology, Monash University, Clayton, Australia*

Since the identification of the adipocyte-derived hormone leptin and its receptors, concentrating in the mediobasal hypothalamus, there has been a focus on the arcuate nucleus as the headwaters of central circuits maintaining energy balance. In a directly analogous situation, the osmoreceptors in forebrain circumventricular organs have occupied centrestage in the CNS pathways mediating thirst. In each case the final effector limb of the motivated behaviors to eat or drink have received little attention. In these studies, we have investigated the cortical locus of these behaviors using neurotropic viruses. The premise being that virus injected into appropriate areas of the cortex will be transported to neurons in subcortical structures with the appropriate anatomical locations or neurochemical signature to identify the pathways as either thirst or hunger related. For example, transsynaptic retrograde labeling of osmoresponsive neurons in the dorsal cap of the OVLT would indicate an involvement of cortical thirst centres and infection of arcuate neurons containing leptin receptors and feeding related peptides would be consistent with the injection of a cortical hunger site. These data will help fill gaps in our understanding of the central pathways promoting feeding and drinking.

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Low-dose DOCA stimulates salt appetite in obese Zucker rats: Effect of dose and synergistic action with central angiotensin II. S.T. Omouessi, C. Falconetti, S.N. Thornton. *UHP-INSERM U684, Université Henri Poincaré, F-54505 Nancy, France*

Mineralocorticoids and angiotensin II (AngII) play an important role in the regulation of salt intake. Their synergistic interaction in evoking a sodium appetite in rats has been often demonstrated with high doses of deoxycorticosterone acetate (DOCA). In the present study we used obese Zucker rats which have a very low spontaneous salt intake and examined the synergy response between AngII and the different low doses of DOCA on salt (NaCl 2%) appetite. Obese and control lean Zucker rats on low sodium food were systemically treated with 0.5, 1 and 2 mg/kg/day of DOCA for 3 days, before receiving i.c.v. AngII (10 pmol) on the fourth day. Individual food and fluid intakes and urine outputs were measured daily throughout. Results show that i.c.v. AngII alone increased water but not salt intake, whereas all 3 doses of DOCA by themselves enhanced daily salt intake during the treatment period. Only the 0.5 mg/kg dose was not able to stimulate sodium consumption after i.c.v. AngII. The 1 mg/kg was the threshold dose of DOCA for a synergistic response with AngII, and with 2 mg/kg DOCA the obese rats consumed nearly 2-fold more hypertonic NaCl solution than the controls. The synergistic action of these two hormones increased also daily urine and sodium excretion without changing water intake. These results suggest that in the adult Zucker rat a threshold level of mineralocorticoid is necessary for the salt stimulating action of central AngII. In the obese rat this synergistic effect is enhanced with higher doses of mineralocorticoid.

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11 β hydroxysteroid dehydrogenase-1 and obesity.
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The enzyme 11β hydroxysteroid dehydrogenase-1 (11β HSD-1) is thought to play an integral role in the control of intracellular glucocorticoid concentrations in both liver and mesenteric adipose tissue. It converts the active hormone corticosterone into its inactive metabolite 11 dehydrocorticosterone. It also converts the inactive metabolite back into active hormone. 11β HSD-1 message has been reported to be elevated in adipose tissue of obese humans and rats. Further, hepatic 11β HSD-1 message is reportedly low in obese Zucker rats. The present studies set out to determine both message and protein of this critical enzyme in several different animal models of obesity, including dietary and genetic obesities. Significant experiment-to-experiment variation in the differences in message were observed when comparing either densitometry or RT-PCR methods for estimating message. Obese rats have significantly less hepatic 11β HSD-1 message than do controls under some experimental conditions and significantly more message under others. The suppression in message was most evident in livers taken from obese Zucker rats using RT-PCR. However, the suppression of message was not consistently observed in dietary obesity models. Variation in the level of saturation of the dietary fat source was without significant effect. A discussion of the role of nutrients that may be involved in the conversion of active hormone to inert metabolites will be presented. These data point out the importance of measuring both message and protein as well as enzyme directionality in developing an understanding of the role of 11β HSD-1 in different models of obesity.

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Structural requirements of the melanocortin 4 receptor for MAP kinase activation.
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The melanocortin type 4 (MC4) receptor has recently been shown to couple to the activation of p44/42 MAPK. Although mutations in the MC4 receptor that are associated with obesity have been investigated for their role in G-protein-coupled receptor (GPCR) signaling leading to cAMP formation, the effect of such mutations on the activation of p44/42 MAPK has not been studied. In the present experiments, mutations were made in residues of the human MC4 receptor known to be critical for GPCR signaling to determine if these mutations would also alter signaling through p44/42 MAPK. These mutant hMC4 receptors, as well as the wild-type human MC4 and melanocortin type 3 (MC3) receptors, were separately transfected into HEK 293 cells, treated with the melanocortin agonist NDP-α-MSH, and subsequently evaluated for the function of their intracellular signaling pathways. Agonist treatment of the wild-type hMC4 and hMC3 receptors both produced an increase in cAMP formation, but only the hMC4 receptor responded with an increase in activated p44/42 MAPK as well. While the D90N mutation in the second transmembrane domain (TM2) and the D298A mutation in the seventh transmembrane domain (TM7) impaired both cAMP formation and activation of p44/42 MAPK, the more conservative D298N mutation retained cAMP formation but abolished activation of p44/42 MAPK. These data identify, for the first time, structural requirements of the MC4 receptor for the activation of p44/42 MAPK, and differential requirements of the MC4 receptor for activation of the cAMP and p44/42 MAPK pathways.

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Three weeks of post-weaning exercise increases plasma interleukin-6 and permanently prevents obesity in obesity-prone rats fed high energy diet.
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We postulated that voluntary wheel running begun in the post-weaning period would have a sustained preventative effect on the development of obesity in rats selectively bred to develop diet-induced obesity (DIO) on a high-energy (HE;31% fat) diet. We previously showed that when 4-week-old DIO rats were fed HE diet and exercised for 6 weeks post-weaning they gained significantly less body weight and adiposity than sedentary (Sed) rats, even 7 weeks after exercise termination (Ex/Sed). Furthermore, rats exercised for 3 weeks (Ex3 weeks) gained 18% less body weight and had 51% less visceral and subcutaneous fat than sedentary rats even 10 weeks after exercise termination. Additionally, both Ex and Ex/Sed rats failed to increase their food intake during and/or after exercise. We postulated that this failure to increase food intake was due to exercise-induced production of the anorectic cytokine, interleukin-6 (IL-6). Thus, we examined light and dark cycle plasma IL-6 levels during the 1st, 3rd, and 6th weeks of exercise. During the 1st week of post-weaning exercise, Ex rats had comparable plasma IL-6 concentrations to Sed rats. However, during the 3rd week, Ex rats had increased plasma IL-6 (108.491 ± 1.3 pg/ml) compared to Sed rats (66.635 ± 0.3 pg/ml; $P = 0.05$). Since this is also the time at which the exercising rats develop a permanent lowering of body weight even after exercise is terminated, these data suggest that IL-6 may serve as a critical muscle-derived mediator of the their altered set-point for regulating energy homeostasis.

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Sympathetic denervation of specific white fat depots modifies size and norepinephrine content of distant intact depots. D.M. Penn, J. White, E.W. Kelso, R.B.S. Harris. *Department of Foods and Nutrition, University of Georgia, Athens, GA 30602, USA*

We previously found that sympathetic denervation of one epididymal (EPI) or retroperitoneal (RP) fat pad increased the size of other neurally intact depots. This study further characterized the interaction between different fat depots by testing the effects of chemical sympathectomy of one or both inguinal (ING) or EPI fat pads of NIH Swiss mice. Pads were denervated by local injection of 6-hydroxydopamine (6OHDA). A time course study demonstrated this method of denervation was effective as fat pad NE content was reduced by 60% at 24 h with partial recovery by 4 weeks, but NE content was still reduced by 40%. Twenty-eight days after denervation of one ING pad produced a significant increase in the weight of the intact contralateral ING pad, the mesenteric, EPI, and perirenal white fat depots. NE content was significantly decreased in the contralateral ING pad and in intrascapular brown adipose tissue (IBAT). When both ING pads were denervated only IBAT weight increased. In a second study one or both EPI pads were sympathetically denervated. There was no change in size of any intact pads, but NE content decreased in intact contralateral EPI pads, RP and IBAT. These results suggest that there is neural communication between individual white and brown fat depots. How the change in afferent activity is sensed or responded to is unclear, but this neural network may facilitate whole-body response to changes in individual fat depots. Supported by NIH Grant DK053903.

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The effect of peripheral leptin infusions on energy balance in chronically maintained decerebrate rats. J. Power[a], E.W. Kelso[a], T.J. Bartness[b], H.J. Grill[c], R.B.S. Harris[a]. [a]*Department of Foods and Nutrition, University of Georgia; Athens, GA 30602, USA.* [b]*Department of Biology, Georgia State University, GA, USA.* [c]*Department of Psychology, University of Pennsylvania, PA 19104, USA*

The contribution of the caudal brainstem to the response to 13-day peripheral leptin infusions (60 μg/day) was tested using chronically maintained decerebrate (CD) and intact Control rats. Complete transection of the neuroaxis at the mesodiencephalic juncture was achieved in a two-stage surgery. At the second surgery a miniosmotic pump delivering leptin or PBS was placed intraperitoneally in CD and Control rats. Controls ate ad libitum or were tubefed 75%, 100% or 125% intake. CD rats were fed 100% or 75% intake. Energy expenditure (EE) measured by indirect calorimetry was the same in ad libitum and 125%-fed Controls and declined proportionately with lower intakes. Expenditure of 100% CD rats was 73% that of ad libitum Controls and decreased further in 75%-fed CD rats. Respiratory quotient was the same in ad libitum and 75%-fed Controls and increased in all other groups. All CD rats had increased carcass fat and reduced lean mass but a normal body temperature. Serum insulin and glucose were normal but adiponectin was elevated. Leptin reduced body fat in ad libitum-fed and 100%-fed Controls but had no effect on 75%- or 125%-fed controls or on EE of the intact rats. In contrast, leptin inhibited EE but increased carcass fat of 100%-fed CD rats. These results suggest that peripherally infused leptin acts, possibly at the caudal brainstem, to inhibit thermogenesis. This response normally is opposed by afferent signals from more rostral brain areas and is prevented when energy intake is limited. Supported by NIDDK DK053903 and SCRO DK21397.

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Cholecystokinin-8 activates the myenteric plexus of the rat directly. S.J. Raboin[a], S. Gulley[a], S.C. Henley[a], W.-C. Chan[a], A.R. Esdaile[a], S.K. Sharma[a], C.N. Sullivan[a], C.A. Jackson[a], L.H. Billups[a], T.H. Moran[b], J.R. Reeve Jr[c], G.M. Green[d], A.I. Sayegh[a]. [a]*Gastroenterology Laboratory, Department of Biomedical Sciences, College of Veterinary Medicine, Tuskegee University, Tuskegee, AL 36088, USA.* [b]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.* [c]*David Geffen UCLA School of Medicine, CURE: Digestive Diseases Research Center, Los Angeles, CA 90073, USA.* [d]*Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78284, USA*

The pathway that the hormone/peptide cholecystokinin (CCK-8) utilizes to stimulate myenteric neurons of the gut is unknown. In a series of experiments, we utilized immunohistochemical detection of the nuclear protooncogene c-fos product Fos, as a high-resolution metabolic marker for polysynaptic neuronal activation in the dorsal vagal complex (DVC) and myenteric plexus. First, CCK-8 increased DVC and myenteric Fos-like immunoreactivity (Fos-LI) in a dose-response manner. Second, vagotomy and capsaicin treatment attenuated DVC but not myenteric Fos-LI by CCK-8. Third, sympathectomy, by daily injection of guanethidine sulfate, attenuated myenteric but not DVC Fos-LI in response to CCK-8. Fourth, CCK-8 failed to increase Fos-LI in spinal cord segments T3-L2, which represent synapses of visceral afferents supplying the gut. Collectively, these results demonstrate that CCK-8 activates the myenteric plexus of the gastrointestinal tract independent of parasympathetic (vagal and small sensory nerve fibers), sympathetic (celiac and cranial and caudal mesenteric ganglia) and spinal visceral afferent activity (T3-L2). This pattern of results is consistent with direct activation of myenteric neurons by CCK. Supported by Grants NIH S06/GM08091-31, The Birmingham Racing Commission and Pfizer Student Fund.

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Effects of sham intoxication on cognitive functioning and performance. B. Raudenbush, J. Smith, T. Cessna, K. Mccombs, R. Yahn. *Department of Psychology, Wheeling Jesuit University, Wheeling, WV 26003, USA*

Past research indicates that alcohol consumption influences human performance, particularly in terms of aggression, cognition, and emotion. However, little research has been performed regarding whether sham intoxication produces similar effects. The present study examined the effects of sham intoxication on cognitive performance. Experimenters utilized the IMPACT© software program to ascertain whether sham intoxication affects neurocognitive functions such as memory, brain processing, speed, and reaction time. In the control session, participants completed questionnaires assessing aggression, personality, and beverage preferences. In the experimental condition, participants consumed [48] ounces of non-alcoholic beer. During both conditions, experimenters recorded participant's physiological measurements (heart rate, oxygen saturation, and blood pressure). Participants also completed questionnaires related to mood and perceived workload during both conditions. The control and experimental sessions were separated by at least 24 h. Results indicated that participants performed significantly worse on the visual memory task during the experimental condition and exhibited increased impulsivity. They also indicated an increase in physical demand, anger, confusion, and fatigue and a decrease in frustration in the experimental condition. These results further support the impact of sham intoxication, and general placebo effects, on cognitive functioning.

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Effects of sham intoxication: Impact on mood, pain perception and threshold, level of aggression, and physiology. B. Raudenbush, I. Wilson, P. Zoladz. *Department of Psychology, Wheeling Jesuit University, Wheeling, WV 26003, USA*

Past research concerning the effects of perceived intoxication on human behavior has been limited. However, it has been found that perceived intoxication significantly undermines psychomotor skills. The present study was designed to assess the effects of perceived intoxication on pain tolerance, mood, and workload. Thirty-one participants (21 male, 10 female) completed two within factor testing sessions. In the control session, participants completed questionnaires assessing aggression, personality, and beverage preferences. In the experimental condition, participants consumed 48 ounces of non-alcoholic beer, while experimenters intermittently recorded their physiological measurements (heart rate, oxygen saturation, and blood pressure). Subsequently, in both conditions, participants completed a questionnaire assessing mood, a cold pressor task, and a questionnaire examining perceived workload. Two-within ANOVAs revealed that participants' pain ratings in the experimental condition were significantly lower than those in the control condition. Additionally, participants in the experimental condition held their hand in the 3 °C water for a significantly greater amount of time. Regarding perceived workload, the participants reported significantly less physical demand and significantly greater self-evaluated performance in the experimental condition. When examining the physiological changes over time with one-within ANOVAs, there was a significant decrease in pulse and a significant increase in oxygen saturation, systolic blood pressure, and diastolic blood pressure from pre-intoxication to post-intoxication. Implications of the present study are particularly salient in regards to minimizing pain through professional suggestibility.

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The reinforcing value of food: Implications for obesity treatment. H.A. Raynor. *Department of Psychiatry & Human Behavior, Brown University/The Miriam Hospital, Providence, RI 02903, USA*

Food is a powerful reinforcer and understanding factors that influence food's reinforcing value (RV) may improve obesity treatment. Basic studies using a behavioral economics paradigm find that high-fat foods (HFFs) are more reinforcing than low-fat foods (LFFs); non-obese individuals earn more points for HFFs than LFFs (61 points vs. 39 points; $P<0.05$) with equal reinforcement schedules. Acute food deprivation increases RV of food; normal-weight, unrestrained females work harder for food points when deprived than non-deprived (49 points vs. 38 points; $P<0.05$). Moreover, obese individuals find food highly reinforcing; obese females work to earn more food points than non-obese females (28 points vs. 16 points; $P<0.05$). If HFFs are highly reinforcing and deprivation increases RV of food, adherence to a hypocaloric, low-fat diet used in obesity treatment may be difficult. This diet may (1) increase RV of food; and (2) enhance the already elevated RV of HFFs. Furthermore, those obese individuals who find food highly reinforcing may have less weight loss with a traditional diet during obesity interventions. Preliminary findings of a 6-month behavioral weight loss trial in females following a traditional diet found no increase in RV of HFFs and LFFs in participants showing weight loss. Nonetheless, individual baseline differences in RV of HFFs may predict successful weight loss when a traditional weight loss diet is prescribed; there was a trend for baseline RV of HFFs to be lower in participants who lost weight as compared to those who did not (5.8 vs. 6.6).

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Mice with high levels of central ghrelin expression and increased plasma ghrelin have impaired glucose tolerance. J.A. Reed, S.J. Benoit, T. Vahl, E.K. Orr, D. D'Alessio, M. Tschoep, R.J. Seeley. *Obesity Research Center, Genome Research Institute, University of Cincinnati, OH 45237, USA*

Numerous studies suggest that the gut-brain peptide ghrelin is a physiologic regulator of energy balance. However, gene-targeted disruption of ghrelin in mice showed minimal alteration of energy homeostasis, including food intake (FI) or body weight (BW). Furthermore, transgenic mice with peripheral overexpression of ghrelin are not hyperphagic and have normal BW. To determine whether ghrelin action in the brain is important for energy balance, we generated mice with neuron-specific enolase (NSE) promoter sequences to direct expression of mouse ghrelin cDNA in the CNS. Ghrelin mRNA was increased 50-fold in brain tissues in the NSE-Ghrelin (Tg) mice. Despite our attempt to restrict expression to the CNS, active plasma ghrelin was increased approximately 5-fold in one line (TgL43). Ghrelin mRNA levels in TgL43 stomach and duodenum were similar to wild types but were increased in liver. FI was slightly greater in female TgL43 mice, while TgL43 males ate slightly less than controls. By 26 weeks of age, TgL43 mice weighed significantly less than sex-matched controls, with decreased fat mass accounting for the differences in total BW. TgL43 mice had no changes in energy expenditure, but increased activity levels. Despite their lesser adiposity, TgL43 mice had impaired glucose tolerance with plasma glycemia of 125% (males) and 160% (females) that of controls ($P<0.05$). It is unclear how central ghrelin overexpression caused elevations of plasma ghrelin and altered glucose homeostasis is not yet clear, but will provide important insight into the function of ghrelin in normal metabolism.

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Action of circulating amylin to decrease food intake in rats. R.D. Reidelberger, A.C. Haver. *VA Nebraska Western Iowa Health Care System and Creighton University, Omaha, NE 68105, USA*

Amylin is a 37-amino acid peptide that is co-secreted with insulin from the pancreas in response to a meal. If amylin acts as an essential blood-borne signal to produce satiety, then immunoneutralization of circulating amylin should increase food intake. Because of its large size (~150 kD), immunoglobulin when injected IV does not readily pass through capillary walls. Thus, IV injection of an antiserum that neutralizes amylin would preferentially block an endocrine mechanism of amylin action, and have no effect on paracrine or neurocrine mechanisms. In the present study non-food-deprived rats ($n = 13$–14) with jugular vein catheters received at dark onset IV injection of amylin antiserum, non-immune serum, or saline (1 ml each), 15 min before (i) a 3-h IV infusion of amylin (2.5 pmol/kg/min), (ii) a 2-h intragastric infusion of an anorexic dose of polycose (3 kcal/h), or (iii) vehicle administration. Food intake for 17 h after dark onset was determined from continuous computer recordings of changes in food bowl weight. IV infusion of amylin inhibited 3-h food intake by 32%. Pretreatment with amylin antiserum attenuated this response by 63%, whereas control serum was without effect. Intragastric polycose infusion inhibited 3-h food intake by 31%, and amylin antiserum attenuated this response by 89%. Under identical circumstances, a 3-h IV infusion of the amylin receptor antagonist AC187 (2 nmol/kg/min) attenuated polycose-induced anorexia by 61%. These results support the hypothesis that amylin acts as an essential hormonal signal from the pancreas to the brain to inhibit food intake.

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Patterns of infusion of anorexigenic substances that reduce daily food intake and adiposity in freely feeding rats. R.D. Reidelberger, A.C. Haver, P.K. Chelikani. *VA Nebraska Western Iowa Health Care System and Creighton University, Omaha, NE 68105, USA*

Chronic administration of anorexigenic substances to experimental animals usually produces a transient reduction in food intake and body weight. We recently reported that 1-h IV infusions of PYY(3–36) (30 pmol/kg/min) every other hour for 10 d produce a sustained reduction in daily food intake (~20%) and adiposity (35%) in rats. Here we examined the effects of different patterns of IV infusion of leptin and CCK-8 on daily food intake and adiposity in rats tethered via infusion swivels to computer-controlled pumps. Leptin study: Rats ($n = 16$) received two 3-h IV infusions of leptin (60 pmol/kg/min) or vehicle at onset of the light and dark periods for 10 d. Leptin produced a sustained decrease in daily food intake (~30%) and reduced adiposity (53%). CCK-8 study: six different dosing strategies were tested over 12 d: two 3-h infusions (25 pmol/kg/min) during hours 0–3 and 6–9 of the dark period for 3 d, 1-h infusions (25 pmol/kg/min) every other hour for 2 d, 3-h infusions (25 pmol/kg/min) every 5 h for 1 d, 3-h infusions (50 pmol/kg/min) every 5 h for 2 d, 3-h infusions (50 pmol/kg/min) every 4 h for 2 d, and 3-h infusions (75 pmol/kg/min) every 4 h for 2 d. Each dosing strategy produced a transient 1–2 d reduction in daily food intake. We conclude that (i) pattern of administration is critical in demonstrating that leptin and PYY can produce a sustained reduction in food intake and adiposity, and (ii) daily food intake is relatively refractory to CCK-8 administration.

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Hypoglycemia-induced hunger is not associated with increases in plasma ghrelin in humans. M.R. Rickels, R. Mueller, K.L. Teff. *Monell Chemical Senses Center and the Division of Diabetes, Endocrinology and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA*

Ghrelin, postulated as an orexigenic hormone, increases prior to meal ingestion and is correlated with feelings of hunger in humans. To investigate the relationship between hunger and ghrelin during insulin-induced hypoglycemia, we conducted hypoglycemic and euglycemic, hyperinsulinemic clamps in healthy control subjects ($n = 8$, BMI $= 24.5 \pm 1.0\,kg/m^2$, age $= 41 \pm 3$ yr). Subjects filled out symptom questionnaires including hunger-related questions every 15 min during the clamp procedure. The stepped hyperinsulinemic hypoglycemic clamp achieved 45-min plasma glucose plateaus of 80, 65, 55, and 45 mg/dl at 90-min intervals. Plasma ghrelin progressively decreased over the 6 h period relative to baseline but ghrelin levels were not different during the hypoglycemic (827.8 ± 255.2 pg/ml mean over 6 h) and euglycemic (815.0 ± 258.1 pg/nl)conditions. Significant increases in hunger (13.7 ± 3.3, hypo vs. 6.4 ± 1.2, euglycemic clamp; $P > 0.0001$ at 360 min) were evident during the last 45 min when plasma glucose levels were below 50 mg/dl vs. maintained at 90 mg/dl. These data suggest that increases in hunger during insulin-induced hypoglycemia are not associated with increases in ghrelin. The lack of increase in ghrelin may be due to the elevated plasma insulin levels and suggests that low plasma insulin may be required for the reported association between ghrelin and hunger. The mechanisms mediating hunger during insulin-mediated hypoglycemia may not be identical to those prior to meal initiation.

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Estradiol treatment increases Pet-1 and serotonin transporter (5HTT) gene expression in the ovariectomized rat. H.M. Rivera, D.R. Lockwood, B.S. Kwon, T.A. Houpt, L.A. Eckel. *Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

We have shown that estradiol interacts with the serotonin (5-HT) system to decrease food intake in female rats, as evidenced by increased anorexic effect of fenfluramine in estradiol-treated rats. To determine if estradiol alters serotonergic gene expression in the dorsal raphe nucleus (DRN), which might lead to altered serotonergic tone, we examined the effects of estradiol benzoate (EB) on the mRNA expression of the 5-HT transporter (5HTT) and Pet-1, a transcription factor required for expression of 5-HT genes such as tryptophan hydroxylase (TPH) and 5HTT. Ovariectomized rats ($n = 3-6$/group) received s.c. injections of either 0, 2, or 10 μg EB in sesame oil on two consecutive days. Two days later, when EB-treated rats showed significant decreases in food intake and body weight relative to controls, the rats were perfused, brains were removed, and coronal sections were cut through the DRN. 5HTT and Pet-1 gene expression was assessed by in situ hybridization on free-floating sections using ^{35}S-labeled cDNA probes. Both 2 and 10 μg EB significantly increased 5HTT mRNA levels (to $271 \pm 38\%$ and $226 \pm 20\%$ of oil-treated rats, respectively), and Pet-1 mRNA levels (to $304 \pm 54\%$ and $276 \pm 38\%$ of oil-treated rats, respectively). These preliminary results demonstrate that at a time when food intake and body weight are decreased by estradiol, both Pet-1 and 5HTT expression are increased in the DRN. Thus, an increase in other Pet-1-regulated genes (TPH in particular) may contribute to increased serotonergic tone and anorexia in estradiol-treated rats. Supported by MH-63932 and DC-00044-10.

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nNOS expression increases during water deprivation and decreases shortly after water reconsumption in the rat PVN. V. Ryu, X.F. Gu, J.G. Kim, J.S. Lee, J.-H. Lee, J.W. Jahng. *Department of Oral and Maxillofacial Surgery, Dental Research Institute, Seoul National University, College of Dentistry, Seoul, 110-744, Korea*

We previously reported that plasma corticosterone may mediate feeding-related changes in nNOS expression in the paraventricular nucleus (PVN), and CREB phosphorylation may take a role in this regulatory pathway. On the contrary to food deprivation decreases the PVN-nNOS, water deprivation has been reported to increase NADPH-diaphorase staining, histological marker for nNOS activity in the brain, in the PVN. This study was conducted to define the regulatory mechanism of nNOS expression in the PVN by water deprivation. Male Sprague–Dawley rats were water deprived, but not food deprived, for 48 h, and then sacrificed 1 h after water return. Controls had ad libitum access to water and chow. NNOS-immunoreactive neurons were significantly increased in the PVN of water-deprived rats, compared to the ad libitum controls. Number of nNOS-ir neurons returned to the control level by 1 h of water consumption. Number of NADPH-d stained cells in the PVN was also increased by water deprivation, and returned to its control level by 1 h of water consumption. pCREB-ir was colocalized with NADPH-d in the PVN neurons in all water conditions. Plasma levels of corticosterone tended to be elevated in the water-deprived group compared with the control, without statistical significance. Corticosterone levels in the water deprived group were not changed by 1 h of water consumption. These results suggest that nNOS expression in the PVN changes by water condition, and pCREB may take a role in this change. Additionally, plasma corticosterone may not be involved in hydration-related changes of nNOS expression in the PVN. Supported by KISTEP (JWJ).

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Chronic social stress affects body weight and composition. R.R. Sakai. *Department of Psychiatry, University of Cincinnati, Cincinnati, OH 45237, USA*

A dominance hierarchy develops among the male rats within a few days of group housing with dominant (DOM) and subordinate (SUB) animals displaying physiological, endocrine and neurochemical changes associated with social status. Rats are housed for 1 or 2 cycles of 14-day VBS housing separated by a 21-day recovery in individual cages. SUB lose more weight than control (CON) and DOM during both VBS periods. When allowed to recover outside the VBS, both DOM and SUB regain lost weight. SUB are hyperphagic on chow through both recovery periods. Body composition analysis indicated that weight loss in DOM is attributable to loss of adipose tissue while weight loss in SUB is attributable to loss of lean as well as adipose tissue. When the social stress was removed, SUB re-gained weight primarily as adipose tissue during the recovery period and this is exacerbated by repeated exposures to social stress. In addition, SUB preferentially deposited fat in visceral rather than subcutaneous body stores. SUB are also hyperinsulinemic and hyperleptinemic compared to DOM and CON after VBS stress and recovery, suggesting that they may develop conditions contributing to the "metabolic syndrome." The data suggest that neurochemical and peripheral endocrine changes associated with chronic social stress influence systems involved in food intake and body weight regulation and may result in metabolic disorders over long-term, repeated exposures. Supported by DK066596 (RRS).

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Effects of cannabinoid antagonists on intake of different foods. J.D. Salamone, P.J. McLaughlin, K. Sink, C. Brown. *Department of Psychology, University of Connecticut, Storrs, CT 06269, USA*

Antagonism or inverse agonism at CB1 cannabinoid receptors can suppress food intake and food-reinforced behavior, and it has been suggested that drugs that interfere with CB1 transmission could be used as appetite suppressants. In the present studies, a number of CB1 antagonists/inverse agonists were tested on procedures that involve intake of food with different nutrient contents (high fat, high carbohydrate, standard lab chow). Interference with CB1 transmission impaired the intake of all three types of food. When the data were transformed to correct for different baseline rates of consumption, CB1 antagonists/inverse agonists generally exerted equivalent effects on intake of all three food types. The mechanisms through which interference with CB1 transmission can suppress food intake remain unclear, and some evidence indicates that these drugs can produce food avoidance and aversion. Continuing research on the suppression of feeding produced by CB1 antagonists or inverse agonists could contribute to our understanding of the neural mechanisms that regulate food intake.

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Sex differences in the behavioral response to melanin-concentrating hormone. J. Santollo, L.A. Eckel. *Program in Neuroscience, Florida State University, Tallahassee, FL 32306, USA*

While some evidence suggests that the orexigenic effect of MCH is sexually dimorphic, little is known about its effects on water intake, meal patterns, or locomotor activity in either sex. Here, these behaviors were monitored in male and female rats following lateral ventricular infusions of 0, 1, and 5 μg MCH, administered at dark onset. While both doses of MCH increased 4 h food intake in males, only the 5 μg dose of MCH increased food intake for 2 h in females. The increase in food intake following 5 μg MCH, relative to that following vehicle, was also greater in males, than in females (3.0 ± 0.9 g vs. 1.3 ± 0.4 g, respectively, $P < 0.05$). Because the orexigenic effect of MCH was associated with concomitant increases in water intake in males, but not females, MCH appears to induce a prandial increase in water intake that is limited to males. Meal pattern analyses revealed that MCH's orexigenic effect is mediated by an increase in meal size, not meal number, through the first 4h following drug treatment. Again, the magnitude of this effect was greater in males, than females (increase in first dark meal size, relative to vehicle: 1.8 ± 0.6 g vs. 1.0 ± 0.3 g, respectively, $P < 0.05$). Finally, MCH failed to influence running wheel activity in either sex. We conclude that the MCH's effects on food and water intake are sexually dimorphic and that MCH increases food intake by affecting the controls of meal size. Supported by NIH Joint Neuroscience Predoctoral Training Grant and MH63787.

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Effects of different gustatory nuclei lesions on conditioned taste aversion learning in rats. G. Scalera, A. Bigiani. *Department of Biomedical Science, Section of Physiology, University of Modena & Reggio Emilia, I-41100 MODENA, ITALY*

When a taste conditional stimulus (CS+) is paired with an unconditional stimulus (UCS), subsequently that taste is avoided. If modifications in the processing of gustatory information are responsible for the response reversals to the CS+, then lesions of central gustatory nuclei would be expected to disrupt a conditioned taste aversion (CTA). It has been found that either lesions of nucleus of solitary tract (NST), parabrachial nucleus (PBN), and the gustatory thalamic nucleus (VPMpc) interfere with CTA in different ways and to varying degrees. Rats with electrolytic lesions of the NST showed impairment of gustatory preference and aversion, but they could learn CTA; rats with neurotoxic lesions of PBN showed impairment of CTA; rats with neurotoxic lesions of the VPMpc exhibited no significant difference in the CTA learning. Only PBN lesions disrupted CTA acquisition, whereas animals with either NST or VPMpc lesions acquired CTA. PBN represents the first location integrating taste and visceral afferent information. Both sensory systems enter the brain through the NST, but they may not interact at this level. In the forebrain, the two systems may interact, and their cortical and limbic representations appear to be redundant. These results show that within the central gustatory system there is a qualitative difference between the functions of the NST, PBN, and VPMpc. Medullary and pontine but not thalamic gustatory nuclei seem involved in mediating discriminative responses to taste and are necessary for the organization of those complex responses that require taste afferent information to guide the animal's aversive conditioning behavior.

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Pair-feeding studies in young CCK_1 spontaneous knockout rats. M. Schroeder[a], O. Zagoory-Sharon[a], T.H. Moran[b], S. Bi[b], A. Weller[a]. [a]*Psychology Department and Gonda Brain Research Center, Bar Ilan University, Ramat-Gan, IL-52900, Israel.* [b]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA*

The OLETF rat has been extensively studied as a model of hyperphagia, obesity and diabetes mellitus. Male and female OLETF rats are about 30% heavier than their LETO controls by 20 weeks of age. Previous studies in our lab demonstrated that OLETF pups are heavier already from the first postnatal day (PND1). The purpose of this study is to better understand early dietary influences on the development of obesity. We examined the influence of early, short term and chronic food restriction, starting from the day of weaning, on obesity, fat pads hypertrophy and hyperplasia, and leptin and oxytocin levels, in 22–90-days-old male and female OLETF rats. Pups were separated from the dam on PND22 and weighed every fifth day. The first group of males and females was fed from weaning to PND90 according to the amount of food consumed by LETO controls. Tissues were collected on PND38, 65 and 90. In the second group, pups were pair fed from weaning until their weight was normalized (approx. day 30) and for two further weeks (until around PND45) and were then returned to ad libitum food access. Tissues were collected on PND90. OLETF males and females under chronic food-restriction showed normalized (to LETO levels) hormonal and fat levels. Permitting free feeding after restriction allowed OLETF females to regain all the weight and fat. In contrast, OLETF males showed increased weight gain, fat mass and hormone levels, but these remained significantly lower than in freely fed OLETF rats. Supported by US–Israel Binational Science Foundation.

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Flavor conditioning by oral and post-oral actions of sucrose and sucralose in mice. A. Sclafani[a], J.I. Glendinning[b]. [a]*Brooklyn College of CUNY, Brooklyn, NY 11210, USA.* [b]*Barnard College, New York, NY 10027, USA*

Sweet taste receptor proteins (T1R2, T1R3) are located not only in the mouth but also in the gastrointestinal tract of rodents. This suggests that rodents may have a sweet "gut" as well as a sweet "tooth." To examine this possibility, we compared flavor conditioning by orally consumed and intragastrically infused sucrose and sucralose (a noncaloric sweetener). C57BL/6J mice were trained (22 h/day) to consume a flavored solution (CS+, e.g., grape-saccharin) paired with IG infusions of either 16% sucrose or 1.6% sucralose. A different flavored solution (CS−) was paired with IG water on other days; chow was available ad libitum. In a two-choice test, the sucrose-trained mice preferred the CS+ to the CS− by 93%, while the sucralose-trained rats showed a mild CS+ avoidance (36%). Yet, when given oral choice tests with 8% sucrose vs. 0.8% sucralose (the net sweetener concentrations in the IG study) the rats initially preferred sucralose to sucrose and preferred both sweeteners to water (>90%). New mice were trained with CS+ flavors added to 8% sucrose or 0.8% sucralose solutions and CS− flavors in water. Both groups preferred the CS+ to CS− when the flavors were presented in water although the CS+ preference was greater in sucrose-trained mice. These data suggest that the T1R sweet taste receptors in the mouth but not those in the gut mediate flavor preferences. The function of T1R receptors in the gut remains to be identified. Supported by NIH DK31135.

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Exendin-4 reduces food intake in non-human primates through changes in meal size. K.A. Scott, T.H. Moran. *Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Baltimore, MD 21205, USA*

Exendin-4 (Ex-4), a long acting GLP-1 receptor agonist, has been shown to reduce food intake and suppress gastric emptying in rodents and humans. In this study, we investigated the effects of peripheral administration of Ex-4 on food intake and meal patterns in adult rhesus macaques. Rhesus macaques ($n = 4$) that had been trained to lever-press for food pellets were injected intramuscularly (IM) 15 min prior to the start of their 6 h daily feeding period. Ex-4 was given at doses of 0.10, 0.32, 1.0 and 3.0 μg/kg. Ex-4 suppressed food intake in a dose-dependent manner, with the 3.0 μg/kg dose completely preventing feeding during the 6 h period, and the dose of 0.10 μg/kg suppressing intake by 17%. Doses of 0.32, 1.0 and 3.0 μg/kg caused significant reductions in cumulative intake at all 6 timepoints ($P < 0.005$). The dose of 0.1 μg/kg caused a significant decrease in cumulative intake at the 2, 3, 4 and 6 h timepoints ($P < 0.05$). Ex-4 inhibited food intake through a specific effect on meal size. Meal number for doses of 0.10, 0.32 and 1.0 μg/kg was not statistically different from saline. Meal size was significantly reduced in a dose-dependent manner with significant reductions at the 0.32 and 1.0 μg/kg doses ($P < 0.05$). Day 2 and 3 intakes returned to baseline levels with no compensation for Ex-4 induced feeding suppression. These results demonstrate that activation of GLP-1 pathways has potent effects on the controls of meal size and overall food intake in a non-human primate model. Supported by DK19302.

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The leptin driven melanocortin pathway in the regulation of body fat and glucose homeostasis is sexually dimorphic. H. Shi, A.D. Strader, J.B. Chambers, J.E. Sorrell, D.J. Clegg, S.C. Woods, R.J. Seeley. *University of Cincinnati, Cincinnati, OH 45237, USA*

The leptin-driven melanocortin pathway is implicated in the regulation of body fat and glucose metabolism via actions to activate proopiomelanocorticotropin (POMC) neurons of the arcuate nucleus. We previously found that females are more sensitive to central leptin signaling. We hypothesized that sex-specific actions of leptin depend on leptin's interactions with POMC neurons in the arcuate nucleus. In the current study, we used the Cre/loxP mice that lack leptin receptors on POMC neurons to test whether leptin-POMC signaling is sexually dimorphic for both the designation of body fat distribution and glucose homeostasis on chow and high-fat (HF) diets. Both male and female POMC-Cre mice gained more fat on either diet compared with their flox counterparts. Male POMC-cre mice added fat to both visceral and subcutaneous depots whereas female POMC-cre mice accumulated over 60% as visceral fat on chow or HF diet. Male flox and POMC-Cre mice had comparable difference in fat distributions on chow and HF diets. Female POMC-Cre mice however, had greater percentage of subcutaneous fat than female flox mice on chow, but not after HF-diet exposure. Therefore, lack of functional leptin signaling on POMC neurons affected female but not male fat distribution by shifting fat accumulation to the visceral compartment. Paradoxically, regardless of visceral fat gain in female mice, female POMC-Cre mice remained as glucose tolerant as their female controls whereas male POMC-Cre mice developed glucose intolerance. These data indicate that leptin's action on POMC neurons is sexually dimorphic to influence both body fat distribution and glucose tolerance.

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The serotonergic agonist, GR46611 decreases the acquisition but not the expression of learned jaw movements for sucrose reward in a pavlovian paradigm in rabbits. K.J. Simansky, D.M. Nicklous, C. Paul, A.G. Romano. *Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102, USA*

Rabbits will learn jaw movements (JMRs) in response to tones that are associated with the oral delivery of sucrose via a buccal catheter. We tested whether the serotonin (5-HT) agonist, GR46611, which reduces chow intake by stimulating 5-HT1B receptors, would alter acquisition or expression of JMRs. Male Dutch belted rabbits were given rations of their daily chow intake, with remnants of food removed 3 h before sessions. They were conditioned for 4 days (30 trials/30 min daily) using a 5-s, 1 kHz tone as the conditioned stimulus, an unconditioned stimulus of 40% sucrose (1 ml/1 s) and a CS-US interval of 4 s. GR46611 (1 μmol/kg, $n = 6$) or vehicle ($n = 6$) were administered systemically (sc) 30 min before the sessions. Controls made 27.7 ± 0.7 to 29.0 ± 0.4 criterion responses (R's) on days 1–4 and GR46611 modestly reduced responding (21.8 ± 3.3–25.2 ± 1.1). GR46611 dramatically reduced acquisition of learned responses, with controls making 18.7 ± 4.0 CR's on day 4 but drug-treated rabbits only 8.8 ± 1.8 CR's. Virtually identical data were obtained in a session when 6 extinction trials were included. However, GR46611 did not reduce either R's or CR's in rabbits that had already learned JMR's under vehicle. Thus, stimulating 5-HT1 (presumably 5-HT1B) receptors altered acquisition of new learned responses for sucrose reward, but not the expression established conditioned ingestive responses. The relative importance of altered reward value and associational processes in this dissociation remains to be evaluated. Supported by DK58669 to KJS.

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The VTA modulates feeding behavior induced by cannabinoid receptor antagonists in both wild-type and Agouti mice. P. Sinnayah, L. Tonelli-Lemos, A.J. Eusterbrock, K.L. Grove, M.A. Cowley. *Oregon National Research Primate Center, Oregon Health & Science University, Beaverton, OR 97006, USA*

Cannabinoids, the active components of marijuana stimulate appetite and cannabinoid receptor (CB1-R) antagonists have been shown to reduce food intake in both humans and animals. The melanocortin pathways are thought to play a pivotal role in regulating appetite and energy balance. Agouti yellow (A^y) mice have disrupted melanocortin signaling due to overexpression of an endogenous MC-R antagonist. Our group has shown that CB1-R antagonists are equally effective at inhibiting food intake in A^y and wildtype (WT) mice, indicating that cannabinoid effects are not mediated by the melanocortin system. In the present study, we further investigated the loci of action of CB1-R antagonists by direct injections into the ventral tegmental area (VTA). Male A^y(B6.Cg-A^y/J) and WT C57BL/6J mice were age and weight-matched, were randomly assigned to treatment groups, and were implanted with guide cannulae into the VTA. Mice were fasted overnight prior to treatment and given ad libitum access to food immediately after intra-VTA injection with AM251 or saline vehicle. Food intake was recorded for 24 h and normalized to wild-type saline control. Intra-VTA AM251 (1 μg in 1 μl) similarly decreased food intake in both WT and A^y mice. Using c-Fos labeling was found in regions such as the BST, LH, DMH and VMH. Thus, the reward system may regulate long-term energy balance, and is sufficient to mediate the effects of cannabinoids on energy balance. This provides a mechanistic rationale for the treatment of addiction disorders with cannabinoid antagonists. Supported by DK 62202 and RR 0163.

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Brain representation of food reward in normal weight humans. D. Small. *Department of Surgery and Psychology, Yale University and The John B. Pierce Laboratory, New Haven, CT 06519, USA*

Flavor is a multisensory perception dependent upon input from three distinct sensory modalities; taste, retronasal olfaction, and oral somatosensation. The sight and aroma of food are also powerful sensory cues that impact flavor and guide feeding behaviors. The affective value of each of these sensory components constitutes one facet of food reward. Homeostatic mechanisms that contribute to hunger and satiety form a second determinant of food reward and may interact with the affective value of sensory stimuli. Food reward can also be considered as having an anticipatory and consummatory phase, each with distinct neural substrates [Berridge, 1996]. The goal of this talk will be to provide a brief summary of the brain correlates of these facets of food reward in normal weight healthy humans.

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Oral exposure and sensory-specific satiety. A.J.P.G. Smeets[a,b], M.S. Westerterp-Plantenga[a,b]. [a]*Maastricht University, Department of Human Biology, 6200 MD, Maastricht, The Netherlands.* [b]*Wageningen Centre for Food Sciences (WCFS), 6700 AN, Wageningen, The Netherlands*

Satiety has been shown after oral exposure to food that was chewed but not eaten (Modified Sham Feeding (MSF)). The aim of the study was to explore the role of sensory specific satiety (SSS) in satiety development with MSF. The subjects were studied on three test days and they received, in random order, water, MSF, or a meal. At the start and the end of each course of the lunch condition subjects evaluated appetite sensations, taste perception and pleasantness of taste using Visual Analogue Scales (VAS). SSS was present when eating soup and when eating salad. SSS also occurred with MSF of salad. When eating the soup no significant changes in appetite ratings occurred. When the salad was eaten we observed an increase in satiety ($P<0.01$) and a decrease in hunger ($P<0.01$) and desire to eat ($P<0.01$). Chewing the salad resulted only in a decrease in desire to eat ($P<0.01$). The taste perception did not change when the salad was eaten. During MSF of the salad taste perception changed, i.e. creaminess and intensity increased ($P<0.05$ and 0.02, respectively). In this experiment merely chewing a salad produced SSS. A decrease in perceived creaminess of the MSF salad might have contributed to a decrease in pleasantness of taste indirectly through a decrease in desire to eat.

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Microstructural analyses of food, water, sucrose and salt intake. J.C. Smith, K.S. Curtis. *Department of Psychology, Florida State University, Tallahassee, FL 32306, USA*

In our laboratory, we emphasize "how" a laboratory rat ingests food and fluids as well as "how much". To make these observations, we modified a standard plastic "shoebox" cage such that feeding and drinking stations are equipped with electronic sensors, allowing us to record when eating and drinking bouts occur, with 6-s resolution. Associated software allows analysis of the patterns of eating and drinking over time periods up to 24-h. We have used this apparatus to measure food and water intake by rats maintained on high salt diets or undergoing a variety of food and liquid deprivation schedules. We also have examined salt and water intake by rats that have had a salt appetite induced by various experimental methods. Together, these studies have revealed in detail striking and reliable patterns of intake. More specifically, the juxtaposition between eating solid food and drinking water and between consuming salt and drinking water suggests that interrelated signals influence ingestive behaviors. Our behavioral studies also show a profound influence of taste, especially sweet taste, on the patterns of ingestion. With regular chow, water, and sucrose solutions available, rats consumed large volumes of sucrose but virtually no water (presumably obtaining sufficient water from the sucrose solutions). Interestingly, one molar sucrose availability disrupted the typical prandial drinking. The interval between a feeding bout and a subsequent fluid bout increased from <5 min when water was consumed to >70-min when sucrose was consumed. Thus, patterns of ingestion also may be affected by gustatory signals.

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D1 and D2 dopamine antagonists have differential effects in repetitive brief-access tests with sucrose. G.P. Smith[a], J.C. Smith[b]. [a]*Weill Medical College, New York, NY 10605, USA.* [b]*Florida State University, Tallahassee, FL 32306, USA*

Central dopaminergic mechanisms are important for the orosensory stimulation of intake by sucrose in a variety of test situations [for review, see G.P. Smith, 1995, 2004]. The effect of dopaminergic antagonists on the orexic effect of orosensory sucrose in brief-access tests, however, is not known. To investigate this, we tested non-deprived, male, Sprague Dawley rats ($n = 10$; 200–225 g) in a taste-testing apparatus [J.C. Smith et al., 1992] that allowed for automated presentation of 5 sipper tubes containing 0.5 M sucrose. Each tube was presented for 30 s and the intertrial interval was 30 s. SCH23390, an antagonist of D1 receptors, raclopride, an antagonist of D2 receptors, or vehicle were administered IP 15 min before the presentation of the first bottle of sucrose. The doses of both antagonists were individualized for each rat to produce ~50% decrease of total licks in preliminary experiments. SCH23390 increased the latency to the first lick significantly, but raclopride had no effect on this latency. Both antagonists decreased the total number of licks significantly and equivalently, but the patterns of their inhibitory effects were different. There was a significant interaction between trial number and raclopride—raclopride produced its largest decrease of licks in the fourth trial. This interaction did not occur with SCH23390. The results demonstrate that D1 and D2 dopaminergic receptor mechanisms are important for the orexic effect of orosensory sucrose in brief-access tests. Their inhibitory effects, however, were different—SCH23390 decreased appetitive and consumatory behavior, while raclopride decreased only consumatory behavior.

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Intestinal denervation eliminates the rapid inhibitory signal associated with distention of the stomach and small intestine when dehydrated rats drink water. C.A. Smith, E.M. Stricker. *Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA*

In recent studies, a close relation between fluid intake and distension of the stomach and small intestine was observed when dehydrated rats drank water or NaCl solution, thus suggesting that gastrointestinal fill provides a signal inhibiting fluid consumption [Hoffmann et al., (2006). American Journal of Physiology, in press]. In ongoing experiments, we are investigating the effect of intestinal denervation on the early inhibition of fluid intake when dehydrated rats drink water or 0.15 M NaCl. Intestinal denervations were performed by transecting and resuturing the proximal and distal small intestine and removing nerve fibers from the descending mesenteric artery. Animals were allowed to recover for 4 weeks before being placed on a water-deprivation schedule. In non-terminal tests, rats were given access to water (but not food) after overnight water-deprivation, and intakes were measured at 5, 10, 15, 30, and 60 min. Control rats slowed their intake after the first 6–8 min in response to a rapid inhibitory signal from GI fill. In contrast, intestinally denervated rats consumed far more fluid than control rats did in the first 10 min and throughout a 1-h test. In fact, fluid intake was inhibited only after plasma osmolality had decreased to normal levels. These results suggest that fluid ingestion is not constrained by a rapid inhibitory signal associated with distention of the stomach and small intestine in intestinally denervated rats. Current studies are also investigating the effect of intestinal denervation on rapid inhibition of vasopressin secretion, which is likely to involve a visceral osmoreceptor.

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Poor energy intake compensation of any type of liquid preload. S. Soenen, M.S. Westerterp-Plantenga. *Department of Human Biology, Maastricht University, 6200 MD Maastricht, The Netherlands*

The objective was to examine if there is a compensation in energy intake of a meal (cruesli + yoghurt 10.1 kJ/g) preceded by a difference in liquid preload; 1.5 MJ/800 ml sucrose, fructose/glucose (55%/45%), milk, light 0 MJ, in 20 men and 20 women (BMI 22.4 ± 2.1 kg/m^2). It appeared that visual analogue scales of appetite scores differed significantly at 50 minutes ($P<0.05$), therefore it was decided to serve the meal at 50 min after preload during the second series of experiments. Compared to light: sucrose, fructose and milk showed significantly lower energy intake ($P<0.05$), higher GLP-1 ($P<0.001$), and lower ghrelin ($P<0.05$) after preload consumption, although total energy intake (preload + meal) was significantly higher ($P<0.001$). No effects were present between sucrose and fructose. Energy intake compensation of sucrose or fructose preload compared to light was 44%, thus passive overconsumption was 56%. Energy intake compensation for milk was 28%, thus passive overconsumption was 72%, not significantly different from sucrose or fructose. Therefore poor compensation may be due to passive overconsumption of liquids and does not only hold for soft-drink consumption. Hunger scores were not different between the 4 conditions after ingestion of the meal. We conclude that poor compensation of energy intake of a liquid preload is independent of its type.

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Control of thirst and salt appetite in rats by pre-systemic stimuli. E.M. Stricker. *Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA*

Pre-systemic signals have been recently shown to reduce vasopressin secretion when dehydrated rats drank water. Ongoing studies are investigating whether pre-systemic signals also inhibit thirst and salt appetite in rats. In one experiment, dehydrated rats were found to consume the same volume in an initial drinking bout whether water or dilute NaCl solution was available. This inhibition appears to derive from signals related to the cumulative volume of ingested fluid in the stomach and small intestine. These and other findings collectively suggest that drinking in rats is inhibited by pre-systemic signals related to gastrointestinal fill and to the concentration of gastric fluid emptying into the small intestine, regardless of whether thirst or salt appetite motivates fluid consumption. In other studies, after surgical removal of all salivary secretions, rats increased their consumption of water while eating dry laboratory chow, and they consumed even more water while eating powdered high-salt food. The Na^+ concentration of systemic plasma in these animals was not elevated during or immediately after the meal, which suggests that cerebral osmoreceptors were not involved in mediating the increased water intake. A pre-systemic osmoregulatory signal likely provided the additional stimulus for thirst because the Na^+ and water contents of their gastric chyme computed to a solution approximating 150 mM NaCl. Thus, in addition to the established systemic signals that can inhibit or stimulate fluid ingestion by rats, these recent experiments suggest that pre-systemic signals can have the same effects.

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Structural organization of the essential circuit underlying mammalian ingestive behavior. L.W. Swanson. *University of Southern California, Los Angeles, CA 90089, USA*

The review will begin with an overview of anatomically defined axonal connections between the dorsal vagal complex and the hypothalamic paraventricular nucleus, which appears to play an important role in the expression of eating and drinking behaviors. This is followed by a consideration of other sources of sensory, behavioral state, and cognitive inputs to the paraventricular nucleus, and by a review of the three major projections of the paraventricular nucleus—to the posterior pituitary, median eminence, and brainstem/spinal cord. Finally, recent evidence suggesting the existence of a more extensive behavior control column in the medial hypothalamus and midbrain will be discussed. This behavior control column appears to be essential for the expression of ingestive, defensive, and reproductive behaviors, and for the exploratory/foraging behavior common to all of them.

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Influence of prenatal stress and high-fat diet on offspring. K.L.K. Tamashiro, K.A. Scott, J. Hyun, T.H. Moran. *Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD 21205, USA*

The intrauterine environment can have profound effects on the development and health of offspring. Alteration in maternal nutritional status and prenatal stress has long-term consequences on offspring development and behavior. However, the mechanisms responsible for these changes are unclear. Pregnant female Sprague-Dawley rats were maintained on standard chow (CHOW) or 60% high fat (HF) diet throughout gestation and lactation. Half of each group (STRESS) were exposed to a novel variable stress paradigm during the third week of gestation while control dams (CON) were left undisturbed. One male pup was randomly selected from each litter for each postnatal test. Body weight and independent ingestion of milk were measured in male offspring once per week after birth. At 4 weeks of age all groups were challenged with an oral glucose tolerance test (OGTT). Birth weights were not different among groups. HF diet resulted in offspring that had greater weight gain and increased adiposity at weaning compared to CHOW offspring and these differences were enhanced by prenatal stress. Milk intake was elevated in both CHOW- and HF-STRESS groups compared to CON. CHOW- and HF-STRESS groups had lower basal glucose levels than CON. However, CHOW- and HF-STRESS offspring had higher glucose area under the curve during the OGTT compared to CON. These data suggest that higher body weight and adiposity induced by HF diet during pregnancy and lactation may occur, in part, via increased perinatal milk intake. Prenatal stress can further enhance these effects. Supported by DK-19302 (THM) and MH-15330 (KLKT).

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The road to obesity: How stress drives us there. S.L. Teegarden, D.E. Pankevich, K.M. Carlin, T.L. Bale. *Department of Animal Biology, University of Pennsylvania, Philadelphia, PA 19104, USA*

Despite direr health consequences, behavioral compliance remains a fundamental impedance in obesity treatment. There are critical sex differences in obesity development, with females having much higher rates than males. Similarly, females show a much greater sensitivity to stress compared to males. As stress has been shown to be a driving force influencing overeating, elucidating the underlying neurobiology of these sex differences in stress pathways related to caloric consumption and motivation toward over-consumption may provide novel therapeutic directions by which more effective obesity treatments are designed. Our studies have examined how stress sensitivity increases the drive for preferred high fat food utilizing a mouse model of increased stress sensitivity (CRF receptor-2-deficient mice) and examining sex differences in these paradigms. Results from these studies have found increased motivation of females compared to males to obtain access to a preferred diet. Females show a decreased latency to locate and consume buried high fat food pellets compared to males. In a limited access exposure, females selectively elevate their daily intake of high fat food, but not high-carbohydrate foods, while males show no dietary differences. During withdrawal from chronic high-fat diet exposure, mice show an elevated stress state and increased risk for dietary reinstatement. These data reveal potent sex differences in the reinforcing properties of high-fat diets that may be related to differences in stress sensitivity and the increased predisposition for obesity development.

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Food-cue reactivity predicts overweight and larger food portion sizes in humans. A.C. Tetley[a], J.M. Brunstrom[b]. [a]*Department of Human Sciences, Loughborough University, Loughborough, LE11 3TU, UK.* [b]*Department of Experimental Psychology, University of Bristol, Bristol, BS8 1TN, UK*

In humans, exposure to the sight and smell of food (a food cue) is found to elicit a learned appetite for that food. However, very few studies have explored individual differences in this 'food-cue reactivity.' In this study, 117 female participants (mean age = 20.9 years) were exposed to the sight and smell of pizza for three minutes. Before and after exposure four measures of cue reactivity were taken; change in desire to eat, change in craving, change in ideal portion size, and change in tolerable portion size. After this period, the participants provided measures of their everyday dietary behavior (normal everyday portion size, dietary restraint, and dietary disinhibition). Our results indicate that following cue exposure, overweight participants ($n = 25$) experienced a greater increase in their 'ideal' portion of pizza and a greater willingness to tolerate portions served in a larger size. Individuals who were especially reactive also reported consuming larger everyday portion sizes and were more likely to engage in disinhibited eating. Taken together, these data confirm that food-cue exposure can increase the amount of food that a person is likely to consume. Moreover, they indicate that highly reactive individuals are at risk of becoming overweight because their reactivity promotes the consumption of larger portion sizes, both inside and outside the laboratory.

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Hindbrain estradiol implants inhibit feeding and increase NTS c-Fos immunoreactivity in female rats. S. Thammacharoen[a,#], T.A. Lutz[a], N. Geary[b], L. Asarian[b]. [a]*Institute of Veterinary Physiology, Vetsuisse Faculty University of Zurich, CH-8057 Zurich, Switzerland.* [b]*Institute of Animal Sciences, ETH Zurich, CH-8603 Schwerzenbach, Switzerland*

Estradiol (E_2) reduces food intake and body weight in female rats. The site(s) and mechanism(s) mediating these effects remain uncertain. To test whether direct caudal brainstem administration of E_2 is sufficient to inhibit food intake, ovariectomized Long–Evans rats received both brainstem (C) and subcutaneous (SC) implants of either a low-dose E_2 (0.2 μg) in cholesterol (CHOL) or CHOL alone. Rats in C-E_2 group received brainstem E_2 and SC CHOL. Rats in P-E_2 group received brainstem CHOL and SC E_2, and the CON group received brainstem and SC CHOL. Food intake was significantly lower in C-E_2 rats than in P-E_2 or CON rats 2 days post-implantation. Because cholecystokinin (CCK) is part of the mechanism of E_2's inhibitory effect on food intake, we used the same paradigm to investigate the effects of hindbrain E_2 administration on CCK-induced neuronal activation as measured by c-Fos expression. CCK-induced c-Fos expression in the C-E_2 rats was significantly higher than P-E_2 or CON rats in caudal and subpostremal NTS. Neither P-E_2 nor C-E_2 significantly increased c-Fos in the PVN, Arc, or VMN. The effect of C-E_2 on CCK-induced c-Fos expression was not due to a peripheral effect of E_2 because we did not see an increase in plasma E_2 following C-E_2 or CON administration, but, as previously we detected physiological pro-estrus plasma E_2 levels following 2 μg of P-E_2 treatment. We conclude that the inhibitory effect of C-E_2 on feeding is partly due to E_2 acting in the caudal brainstem to increase the CCK-induced neuronal activation.

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Genetic controls of voluntary calcium and sodium consumption: Quantitative trait loci determined from C57BL/6J x PWK/PhJ segregating hybrid mice. M.G. Tordoff, L.K. Alarcón, F. Ollinger, M.P. Lawler, D.M. Pilchak, A.A. Bachmanov, D.R. Reed. *Monell Chemical Senses Center, Philadelphia, PA 19104, USA*

We aim to discover the genetic basis of mineral appetite using quantitative trait locus (QTL) analysis. We measured 96-h two-bottle test mineral salt preferences of 481 C57BL/6J x PWK/PhJ F2 hybrid mice. DNA from the mice was used in a genome scan with ~10 cM.between markers. Interval mapping revealed several QTLs. For NaCl, NH_4Cl and KCl preference, the largest QTL was on chromosome 5 (LOD = 8.41, at ~38 cM) in a region with no obvious candidate genes. There were no QTLs associated with components of the rennin–angiotensin-aldosterone system, which argues that different genes control "need-free" and "need-related" sodium intake. Interval mapping revealed two QTLs common to $CaCl_2$, CaLa and $MgCl_2$ preference. One had a peak close to Casr, an extracellular calcium receptor. This supports hypotheses that calcium consumption is governed by circulating calcium concentrations. The other had a peak close to Tas1r3, a sweet receptor. Work using B6.129 Tas1r3 congenic mice confirmed that the sweet receptor was involved in the response to calcium: Mice with the B6 form of Tas1r3 introgressed onto the 129 background drank significantly less $CaCl_2$, CaLa, and $MgCl_2$ (but more saccharin) than did wild-type 129 littermates. This suggests that the interaction of calcium with the sweet receptor is positively hedonic in some strains of mice. Perhaps PWK/PhJ mice like calcium because they perceive it as sweet. Supported by NIH DK46791 and CIDR/NO1-HG-65403.

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Diversity in dietary obesity in inbred mice. M.G. Tordoff, Q. Zhang, D.R. Reed. *Monell Chemical Senses Center, Philadelphia, PA 19104, USA*

Feeding animals an energy-dense diet often causes them to become obese but some get fatter than others. This diversity in dietary obesity occurs even among individuals from the same inbred strain. Because inbred strains are presumed to be genetically identical and are usually reared under rigorously controlled, nearly identical environmental conditions, the reason for the diverse dietary obesity is unknown. One hypothesis is that the presumption of genetic identity is wrong, and that undetected genetic variation either from residual heterozygosity or acquired mutations and the resulting genetic drift accounts for the diversity of the dietary response. We tested this hypothesis by comparing the dietary obesity of offspring of male C57BL/6J mice that were either susceptible or resistant to dietary obesity. Contrary to the hypothesis, offspring from obesity-susceptible male mice were slightly lighter and slightly less fat than were those born to obesity-resistant fathers. These data suggest that the diverse pattern of weight gain found among C57BL/6J mice in response to diet is not accounted for by permissive or pre-disposing genetic variation inherited from the father, or by epigenetic modification of the paternal genome of a type that would favor fat accumulation.

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The herbivorous rodent *Neotoma albigula* regulates toxin intake through decreasing meal size. A.-M. Torregrossa[a,#], A.V. Azzara[b], M.D. Dearing[a]. [a]*Department of Biology, University of Utah, Salt Lake City, UT 84112, USA.* [b]*Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461, USA*

Generalist herbivores are predicted to regulate intake of plant toxins by adjusting meal size or number of meals. We investigated the spontaneous feeding behavior of a herbivorous rodent (*Neotoma albigula*) on diets with increasing concentrations (0–90%) of fresh juniper (*Juniperus monosperma*). Juniper comprises a portion of the natural diet of *N. albigula* and at least 2% of juniper's dry weight consists of terpenes, a class of plant toxins. We found that animals increased total food intake and therefore toxin intake across increasing concentrations of juniper until the 90% concentration. At 90% they decreased total intake ($P = 0.02$) and meal size ($P < 0.01$) compared to the preceding concentration of 60%. The total amount of toxin consumed at 90% was not significantly different than that consumed at 60% ($P = 0.30$). Likewise the amount of toxin consumed in an average meal did not differ between 60% and 90% juniper ($P = 0.44$). However, the data suggest a trend toward an increase in meal number between 60% and 90% juniper ($P = 0.06$). These data provide evidence that at high concentrations of plant toxins, *N. albigula* regulates toxin intake primarily by decreasing meal size. Supported by NSF IBN 236402.

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Critical role of dopamine D1 receptors in nucleus accumbens shell in flavor preference conditioning by intragastric glucose infusion. K. Touzani[a], R.J. Bodnar[b], A. Sclafani[a]. [a]*Brooklyn College of CUNY, Brooklyn, NY 11210, USA.* [b]*Queens College of CUNY, Flushing, NY 11367, USA*

The present study investigated the role of dopamine transmission in the nucleus accumbens (NAc) in flavor preference conditioning by the post-oral consequences of carbohydrates. Male rats were fitted with bilateral cannulae in the NAc shell and a chronic gastric catheter. In Experiment 1 they were trained with one flavor (CS+) paired with intragastric (IG) infusions of 8% glucose and a different flavor (CS−) paired with IG water infusions (30 min/day). CS flavor preference was then evaluated in 2-bottle tests conducted 10 min after administration of 0, 6, 12 or 24 nmol/0.5 μl of the dopamine D1 antagonist, SCH23390 into the NAc shell. SCH23390 produced dose-related reductions in CS+ intake but did not block the CS+ preference, with the exception of the highest dose which totally suppressed intake. In Experiment 2, new rats were injected daily in the NAc shell with either saline or 6 nmol/0.5 μl SCH23390 prior to training sessions with CS+/glucose and CS-/water. CS intakes of the saline controls were matched to those of the drug rats. In a subsequent 2-bottle test the control rats but not the drug rats significantly preferred the CS+ to CS−. These results demonstrate that D1 receptors in the NAc shell are critically involved in the acquisition, but not the expression, of flavor preferences conditioned by post-oral glucose. Supported by: NIH DK071761.

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Appetitive and motivational effects of agouti-related peptide (AgRP) on responding for fat and carbohydrate. A.L. Tracy[a,#], J.F. Davis[a], J.U. Heiman[a], D.J. Clegg[a], T.L. Davidson[b], S.C. Benoit[a]. [a]*Department of Psychiatry/Obesity Research Center, University of Cincinnati, Cincinnati, OH 45237, USA.* [b]*Department of Psychological Sciences/Ingestive Behavior Research Center, Purdue University, West Lafayette, IN 47907, USA*

Agouti-related peptide (AgRP) is an antagonist of the melanocortin-4 receptor that robustly increases food intake when administered icv to rats. Previous studies have demonstrated that AgRP selectively increases intake of high-fat, but not low-fat, diet when presented in a simultaneous choice test [Hagan et al., 2001]. Here, we further explore the effect of AgRP on fat and carbohydrate selection using two separate conditioning techniques. Experiment 1 assessed the effects of AgRP on anticipatory responses to cues paired with the consumption of fat and carbohydrate. Animals were trained to associate one cue (light) with the presentation of sucrose and a second cue (tone) with the presentation of peanut oil. Responses to these cues were then measured subsequent to i3vt AgRP or saline administration. Consistent with intake data, AgRP increased responding for the fat-paired cue, but not the carbohydrate-paired cue. Tests were conducted in extinction, indicating an AgRP-induced increase in fat-specific appetitive behaviors even in the absence of orosensory or postingestive feedback. In Experiment 2, animals were trained to bar press for peanut oil or sucrose and the effect of AgRP on their willingness to work to obtain these reinforcers was assessed using a progressive ratio schedule. The number of responses for peanut oil and sucrose was measured after administration of i3vt AgRP or saline. Collectively, these results suggest that the melanocortin system may play a significant role in regulating not only overall food intake, but food selection as well, with AgRP preferentially enhancing behaviors directed toward obtaining and consuming fat calories.

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What do we understand about the brain mechanisms underpinning the eating disorders. J. Treasure, S. Brooks, H.C. Freidrich, R. Uher, I. Campbell. *Institute of Psychiatry, King's College University of London, London SE1, UK*

Although images of food are subjectively aversive to all people with eating disorders the restrictive (AN) and bulimic (BN) subtypes have marked contrasts in eating behavior. Neurophysiological and scanning studies in these patient groups may inform research into the central mechanisms of eating behavior. In a fasting paradigm in normals women had greater subjective response to food cues after fasting and more activation in the insula [Uher et al. 2006]. Women with both AN and BN have activation of the orbito frontal cortex and the anterior cingulate in response to images of food [Uher et al. 2003;Uher et al. 2004]. BN is distinct from AN as there is no dorsolateral frontal activation to food cues. Also BN have an appetitive response—with startle inhibition to food. Women with AN in contrast have an aversive response with startle potentiation in AN. The activation of the orbitofrontal cortex and anterior cingulate remains even following full physical and psychological recovery. However, in such cases there is additional activation in the apical frontal area. These findings suggest that there are alterations in reward sensitivity to food in AN and BN. The craving for food seen in bulimia nervosa may be associated with a failure of activation of the dorsolateral frontal cortex. Indeed preliminary studies activating this area with TMS was associated with a reduction in craving [Uher et al. 2005].

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Peripheral ghrelin reverses the anorectic effect of lipopolysaccharide (LPS) on food intake in mice. E.H.E.M. Van de Wall, S. Hong, A.V. Azzara, G.J. Schwartz. *Division of Endocrinology, AECOM of Yeshiva University, Bronx, NY 10461, USA*

Peripheral and central administration of ghrelin potently stimulates food intake and promotes adiposity. LPS, a major component of the outer membrane of Gram-negative bacteria, has been used to model sepsis, stimulate cytokine release and produce an acute phase response, characterized by behavioral depression and anorexia. LPS decreases fasting ghrelin levels to acute postprandial levels, supporting the suggestion that this reduction may contribute to LPS's anorectic actions. Therefore, we investigated whether exogenous peripheral ghrelin administration would reverse LPS's effects on food intake. Male C57B6 mice (Jackson labs, 25–30 g) were individually housed on a 12:12 light–dark cycle, and ad libitum food intake of standard chow 20 mg pellets was continuously monitored. Animals received either LPS or saline vehicle (50 μg/kg/0.1 ml, i.p.) at 10:00 h followed 3 h later by ghrelin (3.2. nmol/0.1 ml/animal, i.p) or saline vehicle. Ghrelin alone potently increased food intake by selectively increasing meal size without affecting meal frequency, whereas LPS alone significantly reduced both meal size and meal frequency. Ghrelin completely reversed LPS's feeding inhibitory effects to the level of vehicle injected controls. These data suggest that LPS's anorectic effect may occur by modulating the potency of ghrelin signaling. Because neither peripheral ghrelin nor LPS requires intact gut vagal afferents for their respective feeding modulatory effects, the present data suggest that ghrelin reversal of LPS anorexia is the result of a central integration of LPS inhibitory and ghrelin excitatory influences on feeding. Supported by DK47208.

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Degree of leptin resistance is a function of body weight in rats maintained on a high-fat diet. J.R. Vasselli, J.O. Moreno, J.A. Johnson, V. Garel, P.J. Currie. *Columbia University, New York, NY 10027, USA*

Background: Leptin resistance is defined as decreased responsiveness to the feeding-inhibitory and body weight-reducing effects of the hormone. Although leptin resistance accompanies rapid body weight (BW) gain, degree of leptin resistance as a function of maintained BW has not been investigated. Groups of 12-week-old male Sprague–Dawley rats were fed either chow (CH, $n = 6$) or a moderately high fat (45% kcal as fat) diet (HF, $n = 12$) for 7 months. For testing, groups were injected with 1.0 mg/kg rrLeptin i.p. and food intake (FI) was measured 4, 8 and 24 h later. BW was measured pre- and 24 h post-injection. *Results*: Both CH and HF groups showed reductions of 8 and 24 h FI ($P < 0.01$) vs. saline injections. However, only CH showed a reduction of BW (−5.0 g, $P < 0.01$). The HF group was subdivided into lower BW (LBW-HF, $n = 7$, 808.1 ± 39.6 g) and higher BW (HBW-HF, $n = 5$, 1008.6 ± 60.6 g) sub-groups. FI at 8 and 24 h was reduced for LBW-HF only ($P < 0.01$), while nonsignificant BW effects were seen in the sub-groups. A regression analysis ($n = 18$) of BW gain as a function of pre-test BW yielded a strong positive correlation ($r = 0.7616$, $P < 0.0002$), indicating that the lower the pre-test BW, the more likely weight loss was in response to leptin. *Conclusions*: Different BW thresholds exist for loss of response to the feeding-inhibitory vs. body weight reducing effects of injected leptin. Further, responsiveness to the weight-reducing effects of leptin is an inverse function of greater BW (presumably body fat) at weight maintenance.

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Short-term food intake in MC4RKO mice after CCK and bombesin administration. C.H. Vaughan[a], C. Haskell-Luevano[b], A. Andreasen[b], N.E. Rowland[a]. [a]*Department of Psychology, University of Florida, Gainesville, FL 32611, USA.* [b]*Department of Medicinal Chemistry, University of Florida, Gainesville, FL 32611, USA*

We investigated whether either heterozygous (HET) or homozygous (knockout, KO) disruption of the melanocortin type 4 receptor (MC4R) gene alters satiety responsiveness of mice to exogenous administration of cholecystokinin (CCK) and bombesin (BBS). Fan et al (2004) reported that administration of CCK-8 (3 nmol/kg) reduced intake of a solid test food in wild type (WT) but not in KO mice. Our major aim was to examine this finding with a liquid diet and examine another satiety-related peptide, BBS. WT, HET and MC4RKO mice were first adapted the palatable liquid diet, Ensure (1.1 kcal/g), so that they would consume it promptly when presented. In the main part of the experiment, the mice were food deprived for 12 h, and then given an intraperitoneal injection of peptide or vehicle. Five minutes after the injection, mice were given access to Ensure in their home cage and intake was measured volumetrically after 30 min. Mice were tested repeatedly at 2-3 day intervals with CCK-8 (2, 6, or 18 μg/kg) and BBS (2, 4 or 8 μg/kg) with vehicle injection days intervening between drug days. Contrary to the results of Fan et al, we found that the HET and KO mice suppressed intake more than WT to both CCK and BBS administration. The meal size after vehicle did not differ between the three genotypes (1.76 ml). This experiment suggests that diminished responsiveness to gut satiety hormones cannot explain hyperphagia in MC4RKO mice. All mice were generated from Millenium Pharmaceuticals' original stock.

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Determinants of overweight in a Dutch children cohort. N. Vogels, D.L.A. Posthumus, E.C.M. Mariman, F.G. Bouwman, P. Rump, G. Hornstra, M.S. Westerterp-Plantenga. *University of Maastricht, Maastricht, 6200 MD, The Netherlands*

Of a Dutch cohort of 105 children, anthropometrical measurements were determined from birth till 7 yr. At 12 yr, anthropometrical measurements were executed again, as well as body composition, leptin concentration, 3 polymorphisms, the three factor eating questionnaire (TFEQ), and physical activity. In addition, parental BMI and TFEQ scores were determined. We investigated the effect of early development, parental and genetic variables on overweight at 12y, as well as the behavioral causes or consequences. Children's mean BMI at 12 yr was $19.0 \pm 2.6\,kg/m^2$ and 15.2% were classified as overweight. From the first year of life, BMI tracked significantly with BMI-12 yr ($r = 0.24$, $P < 0.05$). Linear regression analyses showed that a large body weight increase during the first year of life, a high BMI of the father and high restraint scores of the mother were significant predictors for overweight at 12 yr ($r = 0.55$, $P < 0.05$). No genetic relationship was observed. In addition, overweight was positively associated with dietary restraint (TFEQ) of the child and percent fat mass was negatively associated with the child's activity score ($r = 0.51$, $P < 0.05$). Even in this homogenous cohort of normal weight to moderately overweight children, tracking of BMI during childhood took place from the first year of life. Overweight at 12 yr was predicted by early rapid body weight increase and parental influences. Overweight during childhood may be maintained or even promoted by a high dietary restraint score and low physical activity.

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Daily physical activity and activity-counts as a function of body weight in a Dutch children cohort. N. Vogels, K.R. Westerterp, D.L.A. Posthumus, F. Rutters, M.S. Westerterp-Plantenga. *University of Maastricht, Maastricht, 6200 MD, The Netherlands*

Daily physical activities at home, and activities performed according to the same instructed protocol, were measured with tri-axial accelerometers (Tracmor-4) in lean and overweight children. *Methods*: 14 overweight children (59.8 ± 9.5 kg) and 15 lean matched controls (47.2 ± 8.7 kg) wore the Tracmor-4 for 1 week in the daily living environment. In addition, a sports afternoon was organized where all children (matched for age height and gender) performed the same activities. Physical activity was estimated using a modified Baecke questionnaire. Body composition, dietary restraint (three factor eating questionnaire) and snack intake during the sports afternoon were determined. Total mean Tracmor counts/day were significantly lower for the overweight children than for the lean (46.1 ± 6.9 vs. 54.4 ± 11.2 kcounts/day, $P = 0.02$), while reported activities (Baecke score) were similar. When performing exactly the same activities, there was no difference in mean Tracmor counts between the two groups (36.3 ± 6.9 vs. 34.7 ± 6.6 kCounts, $P = 0.6$). Compared to the lean, overweight children had a lower snack intake (1.8 ± 1.2 MJ vs. 2.7 ± 0.9 MJ, $P < 0.05$), tended to score higher on dietary restraint (6.7 ± 3.9 vs. 4.3 ± 3.0, $P = 0.07$) and scored significantly higher on disinhibition (3.4 ± 1.2 vs. 2.6 ± 0.9, $P < 0.05$). As compared to lean children, overweight children moved less without being aware of it; yet performed the same movements per activity. Afternoon snack intake was lower in the overweight children, coincided with dietary restraint.

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Common brain mechanisms in addiction and obesity. N.D. Volkow, G-J. Wang, J.S. Fowler. *National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA*

Food intake is regulated by multiple factors that include metabolic and nutritional needs as well as the reinforcing properties of food. Similarly, obesity likely results from the complex interplay of these factors as well as genetic, developmental, and environmental factors. The reinforcing component of food is particularly relevant since it motivates food consumption. The reinforcing effects of food are mediated in part by its ability to increase dopamine in brain reward and motivation circuits, and imaging studies in humans have shown that the increases in dopamine induced by the display of food are associated with the desire and the motivation to consume the food. Since the reinforcing effects of drugs of abuse are also mediated by their ability to increase dopamine in the same circuits as food, why does food not produce addiction? This likely reflects the fact that the increases in DA induced by food when compared with those of drugs of abuse are smaller, of shorter duration, and habituate with repeated administration. Despite these differences, in some obese individuals the loss of control and compulsive food taking behavior share characteristics with the compulsive drug intake observed in drug-addicted subjects. Imaging technology has been used to investigate in these obese individuals both the brain DA system as well as regional brain metabolism, and to compare it with the changes seen in drug addicted individuals. Findings from these studies are increasing our understanding of the brain mechanisms common to both disorders and have important implications for targeted treatment development.

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Temporal association of decreased food intake and cellular coupling of receptors to G-proteins after irreversible inhibition of mu opioid receptors (MORs) in the parabrachial nucleus (PBN). H.G. Ward#, K.J. Simansky. *Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102, USA*

Using [35S]GTPγS autoradiography, we demonstrated previously that a single, bilateral microinfusion of the irreversible MOR antagonist, β-funaltrexamine (β-FNA; 8.0 nmol/0.5 μl) into the lateral PBN prevented MOR agonist stimulated G-protein coupling in the region. This decreased coupling correlated with reduced intake of standard but not palatable chow intake for at least 1 week. We analyzed the time course for these cellular and ingestive phenomena. β-FNA ($n = 20$) or saline ($n = 19$), were infused once into the lateral PBN of rats and daily intakes of Ensure® (4 h test) and standard chow (20 h) were measured until there was no difference in food intake between saline- and β-FNA-treated rats. β-FNA persistently decreased consumption of chow by approximately 23% for 19 days. β-FNA decreased consumption of Ensure® for only the first 2 days after infusion; water intakes did not change. β-FNA decreased body weights for 16 days. Subgroups of rats were sacrificed 2, 8, 16, or 20 days after infusion to autoradiographically quantify long-term regional loss of MOR G-protein coupling. On day 2, the MOR agonist DAMGO doubled receptor coupling in controls in most of the regions measured. β-FNA prevented coupling in the lateral central and external lateral subregions and greatly decreased coupling in medial subregions. The magnitude of receptor inhibition lessened and then normalized over the 3-week time course. These studies provide further evidence for a physiological relationship between MOR cellular function in the PBN and eating. Further, they direct new analyses of the critical subregions involved in this function. Supported by NIDDK067648 to KJS.

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Interactions between the telencephalon and hypothalamus during anorexia. A.G. Watts, C. Neuner, D. Salter, R.H. Thompson. *Neuroscience Research Institute, University of Southern California, Los Angeles, CA 90089, USA*

When rats drink hypertonic saline for 3–5 days they develop a robust anorexia (DE-anorexia) that is reversed when animals are again allowed access to water. The relative simplicity of these behaviors provide a good model for exploring the functional organization of neural networks underlying adaptive feeding behaviors. To this end, we have recently demonstrated that a significantly reduced sensitivity to NPY of the hypothalamic paraventricular nucleus (and to a lesser extent, the lateral hypothalamic area) is a signature of DE-anorexia. To investigate whether telencephalic regions might also be functional loci for the development of DE-anorexia, we have now examined the responses of the nucleus accumbens to muscimol injections during DE-anorexia. These studies show that the feeding responses to muscimol delivered to the nucleus accumbens are also significantly attenuated during DE-anorexia. Collectively, these data point to the involvement of an extended neural network in this adaptive ingestive behavior. Behavioral and neuroanatomical results will be discussed in the context of the structure of telencephalic and hypothalamic networks responsible for generating DE-anorexia.

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Augmentation of cocaine hyperlocomotion by chronic administration of ghrelin in the rat. P.J. Wellman, C. Hollas, S. Clifford, A. Elliott. *Cellular and Behavioral Neuroscience Division, Department of Psychology, Texas A&M University, College Station, TX 77843, USA*

The neural basis through which food restriction (FR) enhances the hyperlocomotor and reinforcing actions of drugs such as cocaine or amphetamine remains unknown. Plasma levels of the gut peptide ghrelin are elevated by food deprivation whereas administration of ghrelin elicits eating. More importantly, systemic injections of ghrelin (5 nmol/rat) augment the locomotor stimulating effects of cocaine [Wellman et al., (2005). *Regulatory Peptides*, 125, 151–154]. In the present study, we examined the capacity of chronic ghrelin administration (0, 5 or 10 nmol/rat, IP: once per day for seven days) to alter the hyperlocomotor effects of cocaine (0, 7.5, or 15 mg/kg, IP) administered on day 8. ANOVA of total distance traveled scores (15 min pre- and 45 min post-cocaine) revealed significant effects ($P < 0.03$) of cocaine administration, as well as an interaction between ghrelin pretreatment and cocaine administration. The present study suggests that daily administration of ghrelin is sufficient to augment the hyperlocomotor effects of cocaine and is consistent with the notion that ghrelin may mediate the impact of FR on psychostimulant reactivity. Portions of this project were supported by NIDA 1R21DA017230-01A2 to PJW.

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The effect of amylin on energy expenditure. P.Y. Wielinga#, B. Alder, T.A. Lutz. *Institute of Veterinary Physiology, University of Zurich, CH-8057 Zurich, Switzerland*

Amylin is a pancreatic hormone which is co-secreted with insulin from B-cells. The acute food intake inhibitory effect of amylin is well documented. It has also been reported that chronic peripheral delivery of amylin or repeated administration of amylin's agonist salmon calcitonin (sCT) reduce feeding and body weight gain. Furthermore, amylin deficient mice increase their body weight faster than the control mice but their 24 h food intake does not differ. Because only very little is known about the effect of amylin on energy expenditure, we investigated whether amylin and sCT increase energy expenditure by using indirect calorimetry. Single injection of amylin (5 μg/kg, ip) at dark onset significantly reduced food intake until 2 h after injection. There was no effect of amylin on energy expenditure or activity. However, when the same dose was administered in the middle of the light phase without access to food, amylin tended to increase energy expenditure until 90 min after injection. sCT (1 μg/kg, ip) administered under the same conditions significantly increased energy expenditure until 3 h after injection, without changes in physical activity. These results suggest that, besides an effect of amylin on food intake, energy expenditure may also be influenced by amylin. Furthermore, these data are in line with the finding that sCT acts longer and more potently than amylin due to the irreversible binding of sCT to the amylin receptor. Ongoing studies focus on the effect of chronic administration of amylin and sCT on energy expenditure and body temperature.

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Leptin enhances and fasting inhibits the anorexic response to Exendin-4 in the rat. D.L. Williams#, D.G. Baskin, M.W. Schwartz. *VA Medical Center and Department of Medicine, University of Washington, Seattle, WA 98104, USA*

One mechanism whereby leptin reduces food intake is by enhancing satiety responses to gastrointestinal signals produced during food consumption. Glucagon-like peptide-1 (GLP-1), secreted by the intestine in response to nutrients in the gut, is one such putative satiety signal. We hypothesized that leptin enhances sensitivity to the anorexic effects of the GLP-1 receptor agonist Exendin-4 (Ex4). Male Wistar rats received IP injections of leptin (0.5 mg/kg) or saline 60 min before Ex4 (1 μg/kg) or saline, and subsequent dark-phase food intake was measured. Saline/Ex4 administration reduced food intake by 30% relative to the saline/saline group during the first 4 h after injections. Although this low-dose leptin did not affect feeding when delivered prior to saline, leptin pre-treatment significantly enhanced the anorexic response to Ex4, reducing intake by 60%. Neither leptin nor Ex4 alone affected overnight food intake, but the leptin/Ex4 group's intake was significantly reduced. We next investigated whether food deprivation, which reduces endogenous leptin levels, attenuates the anorexic response to Ex4. Rats were either fed ad libitum or fasted overnight before IP injection of saline or Ex4 (0.1 or 0.33 μg). Food was returned to all rats after injections, and subsequent intake was monitored. Ex4 significantly reduced intake in fed rats, but prior fasting completely prevented this anorexic response. Our observations support a model in which the satiety response to GLP-1 signaling is regulated by changes in plasma leptin levels, and that reduced sensitivity to GLP-1 may contribute to fasting-induced homeostatic responses favoring the recovery of lost weight.

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Prolactin, leptin and the hyperphagia of lactation. B. Woodside, L. Naef, C. Frate. *Center for Studies in Behavioral Neurobiology, Concordia University, Montreal, Que., Canada H4B1R6*

Lactation in rats is accompanied by a reduction in fat stores and circulating leptin levels, as well as a pronounced hyperphagia. Using the galactophore transection procedure we eliminated the energetic costs of lactation by preventing milk delivery, while maintaining suckling. We observed dramatic increases in both plasma leptin and insulin levels as well as increased adiposity in galactophore-cut (GC) females compared not only to lactating females, but also to nonlactating rats. In spite of the increased levels of circulating leptin, GC females were hyperphagic compared to cycling females. When prolactin levels were suppressed by administration of the D2-like agonist bromocryptine, GC females showed a decrease in food intake and a fall in leptin levels with no significant reduction in fat pad weight. Prolactin replacement in bromocryptine-treated rats, either by chronic infusion into the lateral ventricle or by subcutaneous injection, restored food intake. Chronic infusion of prolactin into the lateral ventricle also increased food intake in nonlactating rats. Moreover, prolactin-treated rats failed to show a decrease in food intake or body weight in response to central leptin administration when tested either after a 24 h fast, or during free feeding, although vehicle-infused rats showed a robust response in both conditions. Together these data suggest that prolactin promotes hyperphagia in both lactating and nonlactating rats, and that one mechanism through which this effect is achieved is by the induction of a state of central leptin resistance. Supported by NSERC #7538.

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Ad libitum sucrose or saccharin for 1 h reverses fasting-induced increase in plasma corticosterone. S.B. Yoo[a], V. Ryu[b], J.W. Chang[a], J.W. Jahng[b]. [a]*Department of Neurosurgery, BK 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, 120-752, Republic of Korea.* [b]*Department of Oral and Maxillofacial Surgery, Dental Research Institute, Seoul National University, College of Dentistry, Seoul, 110-744, Republic of Korea*

Oropharyngeal-esophageal and gastric cues contribute to meal-induced neuronal activation, referred by c-fos expression, in the paraventricular nucleus (PVN) and the nucleus tractus of solitarius (NTS). Gastric distension plays an important physiological role in promoting satiety to food ingestion. This study was conducted to determine if fasting induced increase of plasma corticosterone is restored by stimulation of oral-pharyngeal, esophageal, and gastric cue, depending on calorie or taste. Male Sprague-Dawley rats (300–350 g) were installed with gastric fistula 7–10 days before the experiment. Rats underwent 48 h of food deprivation, and then received ad libitum access to 8% sucrose or 0.2% sodium saccharin for 1 h with gastric fistula open (sham refeeding) or closed (real refeeding). Rats were perfused with 4% paraformaldehyde, and brains were processed for c-Fos immunohistochemistry. Cardiac bloods were collected for plasma corticosterone assay. Real refeeding, but not sham, after food deprivation, regardless caloric or non-caloric, appeared to activate the PVN neurons. NTS neurons were activated by 1 h of sucrose, but not by saccharin, perception after food deprivation. Sham sucrose appeared to generate stronger signals to induce c-Fos in the NTS, compared to real sucrose. Refeeding with sucrose or saccharin, regardless real or sham, reversed fasting-induced increase in plasma corticosterone level. These results suggest that neuronal activations in the PVN and NTS by oropharyngeal-esophageal and gastric cues following refeeding may not be related with plasma corticosterone levels. Supported by KISTEP (JWJ).

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Effects of hormone replacement on binge-type eating in ovariectomized female rats. Z. Yu, F.H.E. Wojnicki, R.L. Corwin. *Penn State University, Nutritional Sciences Department, University Park, PA 16802, USA*

Binge eating is more common in females than in males. This study investigated the effects of female hormones in a rat model of binge-type eating. Six groups of ovariectomized Sprague-Dawley rats were used ($n = 13$/group). All rats had continuous access to chow and water throughout the 6-week study. Three groups were injected every fourth day with estradiol (2 μg/100 μl oil) and progesterone (500 μg/100 μl oil) and three groups were injected with oil vehicle. The following protocols were used: (1) control oil (CO) and hormone (CH): no shortening access; (2) low-restriction oil (LO) and hormone (LH): 1-h shortening everyday; (3) high-restriction (binge) oil (HO) and hormone (HH): 1-h shortening on Monday, Wednesday, and Friday. (1) Oil rats consumed significantly more energy than hormone rats during the 1-h shortening period ($P < 0.0001$) and overall ($P < 0.0001$). (2) High-restriction rats consumed significantly more energy than control and low-restriction rats during the 1-h shortening period ($P < 0.0001$). (3) HO compensated for the increased shortening consumption by decreasing intake of chow in week 1. In contrast, compensation was delayed in HH until week 3. (4) For cumulative energy intake, HH, LH > CH ($P < 0.05$), and LO > CO, HO ($P < 0.05$). (5) Daily energy intake demonstrated a 4-day pattern in CH and LH, but not in HH. (6) For final body weight, HH, LH > CH ($P < 0.05$), but no differences in oil rats. These results suggest that female hormones may inhibit compensatory intake under binge-type conditions, which increases energy intake and body weight relative to chow controls receiving the same hormones.

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Robust operant responding by rats for an ethanol-polycose gel.
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We have described high levels of ethanol self-administration using 1 h/day free access to an ethanol–Polycose gel without the need for food or fluid restriction and now examine the motivational characteristics of this behavior. Nine adult female Sprague–Dawley rats were tested for daily 30 min sessions in operant chambers with an alcoholic gel (10% w/w ethanol. 10% w/w Polycose®, 0.25% gelatin) as the reinforcer (0.28 g in 10 s), delivered from a syringe. Initially, a fixed ratio (FR) 1 lever press cost was imposed and within a few days daily intake stabilized at 1.3 ± 0.05 g/kg ethanol. The ratio was slowly increased to FR30. At this highest FR, intake was substantial (0.7 ± 0.05 g/kg), but less than at lower FRs. The rats then were shifted to a progressive ratio (PR) schedule (initial cost 5, step size 5 presses) with breakpoint (BP) defined by the last completed ratio within the timed session. The BP with ethanol gel was 34.5 ± 1.3 and this did not differ from the BP with 10% Polycose gel without ethanol (36.2 ± 1.8). Higher BPs were found with a PR10: 51.8 ± 3.1 & 52.2 ± 3.8 for gels with or without ethanol, respectively. To assess whether forced exposure to ethanol affects self-administration, these rats were injected i.p. on four occasions with 3 g/kg ethanol. Their subsequent BP (58.6 ± 4.8) was unaffected. This study shows that Sprague-Dawley rats are motivated to consume pharmacologically relevant (0.5–1.3 g/kg) doses of ethanol from a 10% ethanol-Polycose gel with no food or fluid restriction. Supported by PHS Grant AA014708 to JP&NR.

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