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Abstract

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Post-oral infusion sites that support glucose-conditioned flavor preferences in rats

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Rats learn to prefer a flavored solution (CS+) paired with a gastrointestinal glucose infusion over an alternate flavor (CS−) paired with a non-caloric infusion. Prior work implicates a post-gastric site of glucose action, which is the focus of this study. In Exp. 1, male rats (8–10/group) were infused in the duodenum (ID), mid-jejunum (IJ), or distal ileum (II) with 8% glucose or water as they drank saccharin-sweetened CS+ and CS− solutions, respectively, in one-bottle 30-min sessions. Two-bottle tests (no infusions) were followed by a second train-test cycle. By the second test, the ID and IJ groups preferred the CS+ (69%, 67%) to the CS− but the II group did not (48%). In Exp. 2, rats (10/group) drank CS solutions in one-bottle, 30-min sessions and were given 2-h ID or hepatic-portal vein (HP) infusions. The CS+ and CS− were paired with 10 ml infusions of 10% glucose and 0.9% saline, respectively. Following 8 training sessions, the ID group preferred the CS+ (67%) to the CS− but the HP group did not (47%) in a two-bottle test. The similar CS+ preferences displayed by ID and IJ, but not II groups implicate the jejunum as a critical site for glucose-conditioned preferences. A preabsorptive glucose action is indicated by the CS+ preference displayed by ID but not HP rats in Exp. 2. Our data were obtained with non-nutritive CS solutions. HP glucose infusions are reported to condition preferences for a flavored food that itself has pre- and postabsorptive actions. Thus, there may be multiple sites for glucose conditioning with the upper or mid-intestines being the first site of action.
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A possible role for central α_2-adrenoceptors on the inhibition of sodium appetite by endotoxin

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Results from systemic injections of yohimbine, an α_2-adrenoceptor antagonist, suggest that this receptor mediates the inhibition of sodium appetite by lipopolysaccharide (LPS). The objective of the present study was to investigate the effects of a central injection of RX-821002, an α_2-adrenoceptor antagonist, on LPS-induced inhibition of sodium appetite. Male Holtzman rats ($n = 6$–7/group) with stainless steel cannula implanted into the cerebral lateral ventricle (LV) received furosemide (10 mg/rat) and access to both water and sodium deficient food for 24 h. After this period, LPS 026:B6 from *E. coli* (2 mg/kg b.w.) or saline was injected intraperitoneally (ip) 120 min before rat access to 0.3 M NaCl and water. RX-821002 (80 or 160 nmol/1 μl) or saline was injected icv 15 min before the injection of LPS. Arterial pressure and heart rate were recorded in another group of sodium-depleted rats. LPS reduced 0.3 M NaCl intake (1.4 ± 1.3 vs. saline: 13.5 ± 1.6 ml/5 h, $p < 0.05$). RX-821002 icv (160 nmol/1 μl) abolished the inhibitory effect of LPS on 0.3 M NaCl intake (11.1 ± 1.6, $p < 0.05$), while RX-821002 (80 nmol/1 μl) did not affect the inhibitory effect of LPS on 0.3 M NaCl intake. LPS ip and RX-821002 (160 nmol/1 μl) icv, alone or combined, produced no effect on MAP and HR. RX-821002 (160 nmol/1 μl) injected ip did not affect the inhibitory effect of LPS on 0.3 M NaCl intake. The inhibition of sodium appetite by LPS depends on the activation of central α_2-adrenoceptors.
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Anxiolytic response after palatable diet consumption but not food restriction in rats

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Anxiety disorders have been implicated in both obesity and eating disorders such as anorexia nervosa, but the causal relationship is not fully understood. The aim of the present experiment was to investigate the effects of subchronic food restriction and diet-induced obesity on anxiety-like behavior in male rats. All rats were screened in the elevated plus-maze and either subjected to food restriction or provided access to a high-fat diet, a high-sugar diet, or both. After a period of 10 days, the rats were again evaluated for anxiety-like behavior (open field test; OF). The food restricted animals had increased overall activity in the OF but there were no anxiolytic effects (increased time spent in the centre). A regression model explained 49.4% of the variance in activity in the OF; both the level of food restriction ($p = 0.001$) and the pretest novelty-induced activity ($p < 0.001$) contributed significantly. In the diet-induced obesity experiment, both pretest anxiety-like behavior and consumption of the high-fat diet ($p = 0.005$) contributed to the variance in time spent in the centre of the OF. In conclusion, we here show an anxiolytic effect of a high-fat diet, whereas food restriction affected general activity but not anxiety-like behavior.

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Moxonidine into the lateral parabrachial nucleus enhances sodium balance in cell dehydrated rats

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Activation of α_2-adrenergic receptors in the lateral parabrachial nucleus (LPBN) by bilateral injections of moxonidine (α_2-adrenergic/imidazoline receptor agonist) induces a strong 0.3 M NaCl intake in rats submitted to intracellular dehydration induced by a 2 ml gavage of 2 M NaCl (Na^+ load). However, natriuresis is reduced in response to moxonidine under similar conditions, but with no access to sodium for ingestion. Therefore, the objective of the present study was to determine sodium balance (ingestion minus renal excretion in the same animals) in rats treated with moxonidine into the LPBN. Male Holtzman rats ($n = 8$) with stainless steel cannulas implanted into the LPBN were submitted to a Na^+ load and placed in metabolic cages without food, water or sodium. Moxonidine (0.5 nmol/0.2 μl) or vehicle was injected into the LPBN 45 min after Na^+ load and 15 min later rats had access to water and 0.3 M NaCl and urine collection started. Moxonidine increased NaCl intake (7.5 ± 1.7 vs. veh: 0.5 ± 0.2 mEq/2 h) and natriuresis (5.2 ± 1.4 vs. veh: 1.6 ± 0.3 mEq/2 h), but the increased sodium output was smaller than sodium intake, thus resulting in a positive sodium balance (2.3 ± 1.4 vs. veh: -1.2 ± 0.4 mEq/2 h). Therefore, the results suggest that moxonidine into the LPBN activates behavioral and renal mechanisms that facilitate sodium retention and body fluid volume expansion. Supported by FAPESP, CNPq, FAPEMIG.

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Interactions between central nucleus of the amygdala and lateral parabrachial nucleus in the control of sodium intake

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The lateral parabrachial nucleus (LPBN) and the central nucleus of the amygdala (CeA) are important areas for the control of sodium appetite. In the present study we investigated the effects of bilateral lesions of the CeA on the facilitation of 0.3 M NaCl intake produced by the blockade of serotonergic mechanisms or activation of α_2-adrenoceptors in the LPBN, with bilateral injections of methysergide or moxonidine, respectively. Male Holtzman rats ($n = 6$–10) with bilateral sham or electrolytic lesions of the CeA (2 mA, 10 s) and stainless steel cannulas implanted bilaterally in the LPBN were used. In sham rats treated with furosemide (10 mg/kg) combined with captopril (5 mg/kg) s.c., bilateral injections of moxonidine (0.5 nmol/0.2 μl) or methysergide (4 μg/0.2 μl) into the LPBN increased 0.3 M NaCl intake (31.5 ± 4.2 and 18.3 ± 3.1 ml/2 h, respectively, vs. veh: 8.3 ± 1.1 ml/2 h). Lesions of the CeA (5–18 days) abolished the increase in 0.3 M NaCl produced by injections of moxonidine (12.9 ± 3.3 ml/2 h) or methysergide (11.7 ± 2.8 ml/2 h) into the LPBN. The present results show that the increase in 0.3 M NaCl intake produced by serotonergic blockade or α_2-adrenergic activation in the LPBN depends on the integrity of the CeA, suggesting that facilitatory mechanisms present in the CeA are essential for the increase of hypertonic NaCl intake produced by the blockade of the LPBN inhibitory mechanisms. Supported by FAPESP, CNPq.

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Mercaptoacetate (MA) increases intestinal vagal afferent activity

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The current hypothesis is that MA stimulates eating after peripheral injection mainly by inhibiting hepatic fatty acid oxidation (FAO), thus activating a vagal afferent signal from the liver. While recent data question this hypothesis, the loss of MA's hyperphagic effect after subdiaphragmatic vagal deafferentation still indicates that MA acts in the abdomen to stimulate eating. We therefore tested whether MA affects vagal afferent signaling from the proximal small intestine. Celiac branch fascicles were isolated and fiber bundles were peeled off and placed on a tungsten hook electrode. Spontaneously active fibers were screened for serotonin (5HT) sensitivity by injecting 2.5 μg/30 μl 5HT into the superior mesenteric artery (SMA). Neural activity was amplified, filtered (300–1000 Hz) and stored for later spike discrimination and frequency analysis (Cambridge Electronic Design, Cambridge; MA). Baseline activity was recorded from 5–10 min prior to 5–10 min after SMA 5HT injection. Then, isotonic MA (200 μmol, pH 7.3) was infused (100 μl/min × 5 min) into the SMA and vagal afferent activity was recorded for 30 min. In 11 units from 4 rats, MA transiently increased 5HT-sensitive single unit vagal afferent activity at both 5 min ($93 \pm 48\%$, mean ± SE) and 10 min ($178 \pm 79\%$) (both P's < 0.05) after infusion onset. SMA dye infusion pictures suggest that the responsive units originated in the proximal jejunum. These findings indicate that MA affects vagal afferent signaling from the small intestine. This is consistent with the hypothesis that intestinal or enterocyte FAO generates a vagally mediated signal that affects eating.

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Selective RNAi knock-down of estrogen receptor-α (ER-α) neurons in the nucleus tractus solitarii (NTS) eliminates estradiol's (E2) inhibitory effect on food intake in ovariectomized (OVX) rats

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Eating is inhibited by E2 in many animal species and in women. We demonstrated that ER-α neurons in the NTS just caudal to the AP (cNTS) are sufficient for this effect, in part by increasing the satiating action of CCK. Here we used RNAi technology to determine whether these NTS ER-α neurons are also necessary for this effect. OVX rats were injected with adeno-associated viral vectors expressing small hairpin RNA silencing either luciferase (LUC) or ER-α (ERV). The vectors were infused bilaterally into the cNTS. Rats were then treated once every 4 d with either 2 μg E2 or oil SC. Spontaneous eating and body weight were recorded, and the effect of the CCK1-receptor antagonist Devazepide (1 mg/kg) was tested. Finally, rats were injected with CCK (4 μg/kg, IP), perfused 90 min later, and their cNTS examined for ER-α and c-Fos expression. Data from ERV rats lacking detectable ER-α were used. E2 produced cyclic and tonic decreases in meal size and reduced weight in LUC rats, but not in ERV rats. Devazepide increased meal size in E2-treated LUC rats, but not in ERV rats. CCK increased c-Fos expression in the cNTS in E2-treated LUC rats, but not ERV rats. These data indicate that a subpopulation of ER-α-expressing neurons in the cNTS is necessary for the normal contribution of E2 to CCK satiation, spontaneous eating patterns, and body weight regulation in female rats.

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Evidence that LPS elicits anorexia via PGE2 signaling in the midbrain raphe

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Anorexia is an element of the complex initial immune response to peripheral bacterial infections, or acute phase response (APR). How peripheral immune events are relayed to the CNS and produce anorexia remains poorly understood. Activation of inducible cyclooxygenase-2 (COX-2) in blood–brain barrier endothelial cells and subsequent release of prostaglandin E2 (PGE2) is one candidate mechanism. Here we further tested the effects of PGE2 and of the COX-2 antagonist NS-398 on the anorectic effect of the gram negative-bacterial toxin LPS in rats. Because of the prominent role of serotonin (5HT) in LPS anorexia, we focused on the midbrain raphe (dorsal and median raphe nuclei), the source of major 5HT projections to the forebrain. IP NS-398 1 h before IP LPS (100 μg/kg) completely eliminated LPS anorexia and reduced or eliminated LPS-induced c-Fos expression measured 90 min after LPS in the midbrain raphe, the NTS and several forebrain areas involved the control of normal eating or other aspects of the APR. These data indicate that PGE2 is necessary for LPS anorexia and much of the initial LPS-induced neural activation. Injection of PGE2 into the midbrain raphe was sufficient to reduce food intake, and injection of NS-398 into the midbrain raphe significantly reduced LPS anorexia, indicating that PGE2 signaling in the midbrain raphe nuclei is necessary for LPS anorexia. These data support an important role for the midbrain raphe in APR-anorexia. Whether the same neural circuits also contribute to the control of normal eating deserves attention.

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Diet and TNF-α differentially regulate the insulin receptor and its transporter at the blood–brain barrier

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High fat diet (HFD)-induced elevation in circulating lipids elicits a progressive sequence of events leading to insulin resistance, in part, by an over-activation of the immune system and consequent increases in TNF-α in tissues and plasma. Our hypothesis was that the up-regulation of TNF-α elicited by HFD-feeding decreases the permeability of the BBB to insulin and, consequently, decreases the insulin transport to the brain, resulting in central insulin resistance. Male mice (70 WT and 70 TNF-α KO) were maintained on HFD (60% kcal from lard) or chow (CH) for 3 months after which their brains were perfused with [^{125}I] human insulin for 1–5 min. Individual brain regions were dissected and weighed. Brain region/perfusate ratios were: (perfusate vol/g tissue) × (radioactivity in brain tissue/radioactivity in a given vol of perfusate). For the whole brain, KO mice had increased receptor binding of insulin to the endothelial cells (Vi), whether or not they were fed HFD or CH. There were no differences in the whole brain transport of insulin across the BBB (Ki) between genotypes or diets. In the hypothalamus, there was no genotype or diet difference in Ki or Vi, whereas in the thalamus, KO CH mice had significantly better insulin transport than all other groups, but no differences in insulin binding. These preliminary results suggest that diet and TNF-α regulate BBB insulin receptor binding and insulin transport differentially among brain regions.

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Operant acquisition of food compared between C57BL/6 and DBA/2 mice

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Demand functions describe the relationship between the consumption of a commodity and its mean or unit price. In the present study, we study food demand in two strains of mice (C57BL/6 and DBA/2) that differ on several behavioral dimensions, but have not been studied extensively for differences in feeding. Mice worked for food pellets in a continuous access closed economy in which total intake and meal patterns could be measured. A series of fixed (FR), variable (VR), and progressive (PR) ratio schedules of cost per pellet were imposed. Under all schedules, DBA/2 mice consumed significantly more food than C57BL/6, a difference that was not attributable to disparity in body weight or weight gain. The higher intake of DBA/2 mice was due exclusively to larger meal size compared with C57BL/6, with no strain difference in meal frequency. Thus, DBA/2 mice were motivated to sustain a higher daily food intake and meal size than C57BL/6 under the range of demand costs employed in the present work.

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Food demand of MC4-R and MC3-R knockout, and double knockout mice under fixed ratio costs for food

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Homozygous deletion of MC4-R ($Mc4r^{-/-}$) results in an obese phenotype including hyperphagia, showing that this receptor has a role in limiting food intake and stimulation of energy expenditure. In contrast, while $Mc3r^{-/-}$ mice also have increased body fat, they have decreased lean mass, their body weight is normal, and they eat less that wild type controls. Previous studies from our lab reported that $Mc4r^{-/-}$ mice did not maintain hyperphagia and lost weight when procurement of food was contingent upon a lever press operant with a fixed ratio schedule. However, under a progressive ratio schedule $Mc4r^{-/-}$ mice maintained weight gain and stayed hyperphagic. The present study aims to examine the effects of a wide range of consummatory costs on demand in a closed economy in $Mc4r^{-/-}$, $Mc3r^{-/-}$, and mice with deletion of both these receptors (double knock out) and their wild type litter mates. Mice of these 4 genotypes were exposed an incrementing series of fixed ratios for 20 mg food pellets (FR2, FR5, FR10, FR25, FR50, nose poke response) as the main experimental procedure, with 4 days at each schedule. Mice lived in operant chambers for 23 h each day. At low costs, double knock out mice were more hyperphagic than any of the genotypes, followed by the $Mc4r^{-/-}$ mice. $Mc3r^{-/-}$ and wild type mice ate similar amounts. However, under the highest cost schedules, double knock out and $Mc4r^{-/-}$ mice decreased their intake sharply, and consumed less than the wild type and $Mc3r^{-/-}$ mice. Thus, the phenotypic expression of its deficiency was shown to be affected by the economic structure of the environment.

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Intermittent 'binges' of sweetened-fat intake sensitize feeding responses induced by GABA receptor stimulation in the nucleus accumbens shell

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We explored whether exposure to intense bouts of palatable feeding would produce plastic changes in nucleus accumbens (Acb) shell GABA systems. Ad libitum-maintained rats were given 30 min access to either sweetened fat, or standard chow, in behavior-observation cages for five days. They were then challenged with intra-Acb shell injections of saline or a threshold dose of muscimol (10 ng), and offered chow. There were no differences between the chow- vs. fat-exposed groups following the saline challenge. In contrast, muscimol-induced chow intake was markedly increased in the fat-exposed rats. Next, we investigated whether repeated stimulation of μ-opioid receptors would also produce sensitization to intra-Acb shell muscimol. Ad libitum-maintained rats were given four daily intra-Acb shell infusions of either saline, or the μ-receptor-selective peptide, DAMGO (2.5 μg), and immediately placed into testing cages for 2 h with access to chow. This procedure resulted in robust DAMGO-induced hyperphagia and a sensitization of DAMGO-induced feeding. Rats then received intra-Acb shell challenge injections of saline or muscimol (10 ng). As before, a sensitization of muscimol-induced hyperphagia was observed. These findings suggest that sweetened-fat exposure and repeated μ-opioid receptor stimulation produce similar plastic changes in Acb shell GABA systems that are manifested as augmented feeding responses.

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Estradiol metabolite stimulates binge eating

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A major conundrum of binge eating is that women are significantly more likely to suffer from binge-related disorders, even though estradiol decreases food intake. 2-hydroxyestradiol (2OHE2), a metabolite of estradiol, may account for the apparent contradiction. Studies have shown a link between binge eating and dopamine (DA). Since 2OHE2 and DA are degraded by the same enzyme, catechol-O-methyltransferase (COMT), 2OHE2 can competitively inhibit COMT, thereby theoretically increasing DA availability. We hypothesized that 2OHE2 would stimulate intake of an optional source of dietary fat in binge rats but not in controls. For this preliminary study, 32 non-food-deprived male Sprague–Dawley rats were separated into either a daily control (D) group (those that received an optional source of dietary fat for one hour every day) or a bingeing (INT) group (those that received the fat intermittently, i.e. one hour on Mon, Weds, Fri). After a 7-wk period of binge induction, rats were injected with 2OHE2 (0.001, 0.003, or 0.01 mg/kg intraperitoneally) or vehicle 10 min prior to the 1-h fat access. All rats got all dosages as assigned using a Latin square. The INT group showed a significantly higher 1-h fat intake after 0.003 mg/kg 2OHE2 (compared to vehicle; $p < 0.01$). There were no statistically significant effects of 2OHE2 in the D group. These data suggest a biological mechanism that may, in part, account for the increased risk of binge-related eating disorders in females. Supported by MH67943 (RLWC).
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Sodium and water intake by rats treated with low protein diet

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Angiotensin II plays an important role in the maintenance of blood pressure in rats raised in a deficient protein diet (DPD). Because ANG II is also involved in the control of water and sodium intake, we investigated water and 0.3 M NaCl intake induced by different protocols in DPD rats. After weaning, male Fisher rats ($n = 9$/group) had free access to water and DPD (6% of protein) or normal protein diet (NPD, 15% of protein). At the 36th day of DPD or NPD, rats had access to 0.3 M NaCl. After a period of adaptation, water and NaCl intake tests started. Results were expressed as ml/100 g of body weight. Water intake induced by 24 h of water deprivation, sc injection of furosemide + captopril and 24 h of sodium depletion was slightly reduced in DPD rats (3 ± 0.2; 2.7 ± 0.3; 0.7 ± 0.2; ml/2 h) compared to NPD rats (4 ± 0.2: 3.5 ± 0.3; 2.1 ± 0.6; ml/2 h, respectively). However, 0.3 M NaCl intake induced by the same protocols increased in DPD rats (3.5 ± 0.5; 2.7 ± 0.3; 6.6 ± 0.8 ml/2 h) compared to NPD rats (1 ± 0.1; 1.5 ± 0.2; 5.4 ± 0.7 ml/2 h, respectively). Water intake induced by intragastric 2 M NaCl load was not different. The results show that low protein diet malnourished rats have an increased ingestion of hypertonic NaCl and a reduced intake of water, except water intake induced by intragastric 2 M NaCl. Perhaps changes in renal excretion or plasma ANG II levels might be the cause of these effects, but further studies are necessary to verify these possibilities.

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Preference for a high fat diet, but not hyperphagia following activation of mu opioid receptors is blocked in AgRP knockout mice

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Activation of mu opioid receptors (MOR) makes animals hyperphagic and selectively increases their preference for a high fat diet independent of their dietary preference. The orexigenic peptide Agouti Related Peptide (AgRP) also produces hyperphagia and selectively increases fat preference. Using AgRP knockout mice (Dr. George Argyropoulos' laboratory) we tested the hypothesis that the effect of MOR on feeding behavior will be attenuated in the absence of the orexigenic peptide AgRP. Our data demonstrated in a dose response experiment that the MOR agonist DAMGO increased food intake in wild-type and AgRP KO mice, but only increased fat preference in the wild-type animals. At both 1 and 6 h after injection, the middle dose of DAMGO (0.25 μg) significantly increased the percentage of high fat diet eaten by the wild-type animals, but did not significantly change the percentage of high fat diet eaten by the AgRP KO mice. The highest dose of DAMGO reduced food intake in the control and AgRP KO mice, probably due to somnolence. These data demonstrate that the increase of fat preference after stimulation of MOR is attenuated in the absence of AgRP, but the increase in food intake (i.e., hyperphagia) is not. This study was supported by National Institute of Health, NIDDK, grant number DK R34-32089 to GB and DK62156 to GA.
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Dietary ω-3 polyunsaturated fatty acids (PUFA) eliminate thirst deficits associated with aging

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During the European heatwave of 2003 more than 40,000 people died; the majority were over 65. This was primarily attributed to failure to maintain adequate hydration. Senescent animals have a reduced sensation of thirst when challenged by stimuli that typically induce thirst in adults. Aging results in up-regulation of ω-6 PUFA derived prostaglandins (which inhibit thirst following dehydration) in the midbrain; increasing tissue ω-3 PUFA reduces production of ω-6 PUFA derived prostaglandins. Therefore, we examined the effect of dietary ω-3 PUFA on thirst in aging. Adult (4-month) and aged (22-month) male Brown Norway rats were maintained for 6 months on an ω-3 PUFA deficient diet or ω-3 PUFA supplemented diet. Between 2 and 6 months on the diet animals were subjected to a battery of thirst stimuli including injection of hypertonic saline, injection of angiotensin II, 24-h water deprivation and acute thermal dehydration. Aged animals had an impaired thirst response to dehydration compared with adult animals following hyper-osmotic and dehydration stimuli. Thirst responses were restored by dietary ω-3 PUFA supplementation. Supplementation did not alter thirst responses in adult animals. Diet had no effect on urine output, plasma vasopressin or atrial natriuretic peptide. These results provide the first evidence that ω-3 PUFA supplementation restores thirst in aging. This may lead to clinical trials of ω-3 PUFA supplementation in elderly populations.
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Continuous or binge access to sweet-fat food reduces mu-opioid receptor mRNA expression in the nucleus of the solitary tract in female rats

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Dietary conditions alter endogenous opioids. The aim was to investigate how repeated palatable food (i.e., sweet-fat; 90% vegetable shortening/10% sucrose) access and/or acute calorie restriction altered mu-opioid gene expression in the nucleus of the solitary tract (NTS) as measured by in situ hybridization. Five groups of adult Sprague–Dawley females rats ($n = 6$ to 8) were used in this 6-week study. The first group, BINGE, received repeated days of intermittent 33% calorie restriction followed by re-feeding with standard chow and 2 h optional access to sweet-fat 2 h into the dark cycle. The second group, CHOW-RESTRICTED, had an identical pattern of restriction with chow re-feeding only. The third group, SCHEDULED, had ad lib chow and received the sweet-fat at the same time and frequency as the BINGE. The fourth group, CONTINUOUS, had ad lib chow and sweet-fat without calorie restriction or scheduling. Another group, NAIVE controls, had ad lib chow only. Although the CONTINUOUS consumed more daily calories, the BINGE consumed more total calories during 2 h re-feeding period ($p < 0.001$). After the 6 weeks, the CONTINUOUS had greater body and fat pad weights ($p < 0.001$ for both). In the NTS, mu-opioid mRNA was reduced by ~30% in the BINGE and ~40% in the CONTINUOUS ($p < 0.05$ for both, from NAIVE). These results suggest that long-term or repeated bouts of overconsuming palatable foods alter hindbrain opioid systems contributing to the perpetuation of eating pathologies. Supported by DK19302 and DK078484.
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Oral sensory and cephalic hormonal responses to fat and non-fat liquids in bulimia nervosa

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Sensory evaluation of food involves endogenous opioids. Bulimics typically limit their food choices to low fat "safe foods" and intermittently lose control and binge on high fat "risk foods". We sought to determine whether the oral sensory effects of a fat versus a non-fat liquid food (half and half) resulted in different subjective and hormonal responses in bulimic ($n = 10$) compared with healthy women ($n = 11$) and whether any differences were opioid mediated. Naltrexone (50 mg PO) or placebo was administered 1 h before, and blood sampling began 30 min prior to, and 29 min after, a 3-min modified sham-feeding trial. Following an overnight fast, three morning trials (Fat-Naltrexone, Fat-Placebo, and Non-Fat Placebo) were administered in a random double-blind fashion separated by 3–7 days. Overall, there were no differences between Fat-Placebo and Non-Fat Placebo trials. HUNGER ratings were higher for bulimics at baseline and only bulimics demonstrated a significant reduction after sham feeding ($P < 0.001$). Bulimics also had higher FATTINESS taste ratings and were more FEARFUL OF SWALLOWING ($P < 0.005$, $P < 0.01$). Total ghrelin levels were ~40% higher in bulimics ($P < 0.001$); however, ghrelin, insulin, and glucose were not altered by the modified sham-feeding. Elevations in blood glucose in both groups were observed with naltrexone ($P < 0.05$). These data suggest bulimics have different sensory responses to a tastant that are not explained by opioid blockade, hormonal responses, or fat content.

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High-fat diet offsets the long-lasting effects of a four-week running wheel access on food intake and body weight in OLETF rats

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We have previously demonstrated that running wheel activity prevents hyperphagia and obesity in Otsuka Long-Evans Tokushima Fatty (OLETF) Rats. A period of exercise beginning at eight weeks of age produces long-lasting effects on food intake and body weight in OLETF rats. To determine whether diet modulates these long-lasting effects, we examined the effects of high-fat diet on food intake and body weight in OLETF rats that had prior access to running wheels for four weeks. We found that four weeks of running wheel access significantly decreased food intake and body weight of OLETF rats. Four-week exercise also produced long-lasting effects on food intake and body weight in OLETF rats fed a regular chow diet. When wheels were relocked, OLETF rats stabilized at lower levels of food intake and body weight than sedentary OLETF rats. High-fat diet access offset these effects. When OLETF rats were switched to a high fat diet following wheel relocking, they significantly increased their food intake and body weight. Overall, their food intake and body weight reached levels similar to those of sedentary OLETF rats fed a high-fat diet. In situ hybridization determination revealed a regulatory deficit in neuropeptide Y gene expression in the dorsomedial hypothalamus in OLETF rats. Together, these results demonstrate that high-fat diet modulates the long-lasting effects of exercise on food intake and body weight in OLETF rats.
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Neurotoxic lesioning of oxytocin-sensing hindbrain neurons attenuates the satiety response to CCK-8

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Increasing evidence suggests that paraventricular (PVN) oxytocin (OXY) neurons that project to the nucleus tractus solitarius (NTS) enhance the satiety response to cholecystokinin (CCK-8). To test this hypothesis, we measured the 30-min feeding response to CCK-8 (0.96 nmol/kg) or saline following bilateral NTS administration (0.5 μL) of an OXY-conjugated saporin toxin (OXY-Sap, which destroys neurons expressing OXY receptors) or an equimolar mock peptide conjugated to saporin (BLANK-Sap) at doses of 0.008, 0.017, and 0.03 μg. CCK-8 reduced food intake by 54 and 45% following BLANK-Sap treatment at 0.017 and 0.03 μg, respectively, but inhibited food intake by only 29% following OXY-Sap treatment at 0.017 μg ($P < 0.05$). Treatment with OXY-Sap at 0.03 μg completely blocked the effect of CCK-8 to reduce food intake, whereas treatment with OXY-Sap at 0.008 μg was ineffective at altering CCK-8-induced satiety. These findings suggest that the satiety response to CCK-8 is dependent on OXY release in the NTS. Similarly, whereas ICV administration of an OXY receptor antagonist stimulated 4-h food intake in BLANK-Sap treated rats by 77% ($P < 0.05$), it was ineffective following OXY-Sap treatment at 0.017 μg. Thus, tonic inhibition of food intake mediated by OXY involves actions on NTS neurons. OXY-Sap produced a 42% reduction of OXY receptor mRNA compared to BLANK-Sap as measured by RT-PCR of NTS obtained by laser capture microdissection (0.03 μg; $P < 0.05$). These findings suggest that OXY-sensing hindbrain neurons are critical determinants of the response to meal-related satiety signals such as CCK.
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Personality as a risk factor for insulin resistance and hypertension

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The personality of an individual may be an important risk factor for the development of weight gain, insulin resistance and hypertension. In this study we have taken advantage of two different rat strains, one that demonstrates a proactive coping style and the other exhibiting a reactive coping style. We find that reactive rats are more prone to develop adiposity, insulin resistance and hypertension. There are several lines of evidence for this. First, indirect calorimetry reveals that reactive rats have a lower resting energy expenditure. Second, reactive rats are more susceptible for diet-induced obesity because they consume more of a highly palatable medium fat diet than their proactive counterparts (there are no differences in body weight on a chow diet). Third, carcass analysis reveals that reactive rats have a higher percentage of visceral adiposity. Fourth, baseline insulin levels are elevated in reactive rats; in response to a continuous intravenous glucose infusion, reactive rats show increase insulin levels at both peak and plateau. Finally, telemetry measurements reveal that resting blood pressure is elevated in reactive compared to proactive rats. Taken together, these data indicate that reactive rats are more prone to develop adiposity, insulin resistance and hypertension. On the other hand they are more likely to response well to a life style intervention program, i.e., we found that particularly reactive rats voluntarily increase their daily activity when given the opportunity to run, and in this situation, plasma insulin levels and resting blood pressure are normalized.
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Effects of chocolate consumption on pain perception and pain tolerance

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Recent research indicates participants who held a sucrose-sweetened water solution in their mouths were able to keep their hand submerged during a cold-pressor test for significantly longer durations than a control group. The current study, a one-way repeated measures design, used 30 participants to compare pain tolerance with type of chocolate consumption, with the chocolate varying in level of sweetness. Each participant participated in four randomized conditions (milk chocolate, dark chocolate, carob, and control). Demographics, physiological measures (blood pressure and pulse), pain ratings, chocolate sweetness ratings, mood, task load, and chocolate consumption data were collected. Analyses show a main effect for diastolic blood pressure, with posttest readings significantly lower for each of the three consumption conditions than that of the control condition. Additionally, a significant effect was found for chocolate (sweetness) type, such that milk chocolate consumption (the highest sweetness content) led to lower pain ratings than control, and pain ratings in the control condition were lower than those in the carob condition. Implications for such research include seeking ways to use sweetened chocolate as an adjunct to pharmaceuticals for pain management techniques.
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Acute stress decreases food reward related brain activity

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Stress results in eating in the absence of hunger, likely due to changed food reward signaling. Our hypothesis: stress decreases central food reward signaling. To determine the effect of acute stress on food choice reward related brain activity, fasted women ($n = 10$, BMI = 21.5 ± 2.2 kg/m^2, Age = 24 ± 4 years) came 2× to randomly complete either the rest or stress (math test) condition. Per session, 2 fMRI scans were made, wherein subjects chose a meal (food images). The food's rewarding value (liking & wanting), food characteristics (crispiness, FullnessOfTaste etc.), energy intake, plasma cortisol and VAS hunger & satiety were measured. Fasted state was confirmed by low satiety/high hunger (10.0 ± 10.3, 79.4 ± 15.3 m VAS). All conditions: Meal 1 energy intake (3 ± 1 MJ) and liking were equal, and food wanting was lower at meal 2 ($\Delta = -.3$ items/category, $p < .01$). At rest: Meal 1 decreased hunger, increased satiety (-41.5, 50.6 mm VAS, $p < .01$), and energy intake and putamen activity was lower at meal 2 (-1.1 MJ/AUC = $-.9$%BOLD s, $p < .05$). The math-test led to stress (cortisol ΔAUC = $+2.2 \times 10^4$ nmol min/l, $p < .05$). Under stress: Satiety was lower after meal 1 (-8.0 mm VAS, $p < .01$), Meal 2 energy intake was similar to meal 1, crispiness and FullnessOfTaste were chosen more and brain activity was lower in relevant areas: putamen, amygdala and hippocampus (AUC = -1.0, -4.7, -2.5%BOLD s, $p < .05$). Our data suggest lower reward signaling and reward sensitivity under stress.

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Evidence for multiple inhibitory feeding signals in dehydration anorexia

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Dehydrated (DE)-anorexic rats reliably begin eating within minutes of drinking water. Given the rapidity of this effect, we hypothesize that drinking water produces disinhibitory signals that release stimulatory networks to promote feeding. To investigate these inhibitory signals, we compared the ingestive behaviors of DE rats after the return of free access to water to the behavior exhibited by pair-fed (PF) rats after the return of free access to food. While both groups exhibit similar neuropeptidergic and hormonal profiles that are consistent with negative energy balance and usually promote feeding, DE rats exhibit hyperosmolality and voluntarily restrict food intake. We hypothesize that the rapid release (disinhibition) of stimulatory networks following the return of water is a distinct process that is dissociable from the slower suppression of inhibitory signals that impact central feeding networks. The components of feeding and drinking that constitute meal microstructure were analyzed for both groups in the minutes and days following the return of water or food. We found that DE but not PF rats maintain deficits in feeding behavior for some time, suggesting that some suppression of feeding networks persists in DE rats following water consumption. Our results show that although drinking water quickly disinhibits stimulatory feeding networks in DE rats, complete removal of all inhibitory signals requires additional time. Thus, hyperosmolality generates multiple inhibitory signals to inhibit feeding that are differentially disengaged and suppressed over time upon the return to euhydration.

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Effects of hunger and experience on portion size estimation by men

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This study explores how hunger and experience influence portion size perception. Underestimation of food portion sizes, particularly in energy dense foods is associated with energy overconsumption; however its underlying mechanisms are poorly understood. Research suggests that postingestive consequences of food consumption may create links between foods and their ability to evoke fullness (Perceived Satiation, PS). Whether such links alter portion size perception is unclear. Twenty-seven men were tested in a 2×2 design on their estimate of portion sizes after an overnight fast (hungry) or after breakfast (full); and prompted or not with a PS cue ("how full would you be after consuming this amount of food") before estimating portions. Foods included candy, cake, fruit, cereals, chips and caloric drinks. Estimates were compared with ADA, FDA, BDA and FSA portion standards. Portion size estimates for all foods/drinks were significantly smaller under hungry than under full conditions ($p < 0.01$). The PS cue had no effect. Error of estimates increased with increasing ED ($r = 0.42$, $p < 0.05$). Except for the banana, estimates were significantly smaller than actual amounts displayed, irrespective of appetite status ($p < 0.001$). This study confirms that hunger, a physiological cue, alters perception of food amounts. Higher ED foods and caloric beverages were worse estimated than other foods, in agreement with their reported obesity-inducing nature. There were large discrepancies between subjects' perceptions of a portion and recommendations from governments/health professionals.

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Proestrus rats on a high-fat diet have less central inflammation than male rats

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There is evidence that obesity is characterized by chronic activation of inflammatory pathways. The neuroprotective effects of ovarian hormones may be a result of the anti-inflammatory effects of estrogen and progesterone in adipose and cardiovascular tissue. In the present study we sought to extend these findings to the CNS. Three-month-old male and female Long-Evans rats (age matched) were given a HF or a low-fat (LF) diet for 72 h ($n = 22$) and sacrificed. Females were phased daily and started on the HF diet on the day of estrus so that 72 h later they would be in proestrus which is the peak of estradiol and progesterone. The medial basal hypothalamus was extracted and processed to determine if females were protected from HF-diet induced increased expression of inflammatory markers. Real-time quantitative PCR was performed for IL-6, SOCS3 and TNFα. Males on the HF diet had increased hypothalamic expression of IL-6 and SOCS3 when compared to the LF diet while TNFα mRNA was unchanged. In contrast, females on the HF diet had reduced hypothalamic expression of IL-6 when compared to the LF diet while mRNA for SOCS3 and TNFα were unchanged. These data provide evidence that estradiol, previously demonstrated to be anti-inflammatory, may protect females from the metabolic syndrome or the diseases associated with obesity because exposure to a HF diet results in less CNS inflammation.

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Effects of perceived volume on 'expected satiation' and self-selected meal size

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Satiation appears to be determined by the volume of food that is consumed rather than by its energy or macronutrient content. In this study we sought to determine whether this effect of volume is reflected in decisions about portion size, before a meal begins. Participants ($N = 60$) were shown 9 different foods and were asked to self select 'ideal' portion sizes for lunch. They then used a 'method of adjustment' to provide estimates of perceived volume and 'expected satiation.' In 7 of the test foods we found a significant difference between judgments based on volume and those based on satiation. This indicates that expected satiation is not governed solely by perceived volume. We also considered the extent to which self-selected portion size is predicted by expected satiation and perceived volume. Expected satiation was associated with self-selected portion sizes ($r = -.61$), and this was the case even after controlling for perceived volume ($r = -.38$). By contrast, after controlling for expected satiation, perceived volume was a poor predictor of portion selection ($r = -.002$). Together these findings indicate that decisions about portion size are associated with expected satiation and that this relationship is not mediated solely by perceived volume. This mismatch between the effects of volume in actual and expected satiation merits further scrutiny, and it highlights the importance of understanding portion-size decisions and their role in determining energy intake.

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Rapid gastric emptying when hypovolemic rats drink water and saline

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Injection of 30% polyethylene glycol (PEG) solution (5 ml, sc) produces hypovolemia in rats, with plasma volume losses increasing progressively to ~40% after 12 h and asymptoting at that level for an additional 12 h or so. Appropriate to their needs, PEG-treated rats are known to develop thirst and salt appetite. In a recent report [Smith et al., Am. J. Physiol. 292 (2007) R2089–R2099], we found that rats consumed water, 0.15 M NaCl, or 0.30 M NaCl when they were given either fluid alone to drink in a 1-bottle test 16 h after PEG treatment, but gastric emptying of the ingested fluid differed significantly among the three groups; it was much more rapid when they drank 0.15 M NaCl than when they drank water or 0.30 M NaCl. In the present experiment, rats were given both water and 0.30 M NaCl to drink in a 2-bottle test 16 h after PEG treatment. The rats drank the two fluids alternately in a lengthy initial drinking episode, concocting a fluid mixture of 0.10–0.15 M NaCl. During this episode, gastric emptying of ingested volume and Na^+ was relatively slow in the first few minutes but then it increased markedly to rates that were as high as when they drank 0.15 M NaCl alone. In other words, the hypovolemic rats drank water and saline in relative amounts that were appropriate to restore their plasma volume deficits, and they soon emptied the ingested fluid mixture at a very high rate and thereby hastened fluid absorption into the circulation and plasma volume restoration.

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Is Disinhibition a moderator or mediator of exercise-induced weight loss?

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TFEQ Disinhibition is a dynamic trait which reflects an individual's tendency to eat opportunistically. High levels of Disinhibition are associated with a dysregulated eating pattern, weight gain, obesity and less success with weight management. The role of Disinhibition in weight loss was examined in a supervised exercise program. 58 overweight and obese men and women completed 12 weeks of exercise, expending 500 kcal, 5 d/week. Following 12 weeks of exercise, a significant amount of body weight and body fat was lost. In a regression analysis, controlling for baseline fat mass, a more successful weight loss was predicted by a higher baseline Disinhibition score. Baseline Restraint and Hunger did not predict weight loss. More specifically, a higher baseline Internal Disinhibition (from the subscales) was found to be a significant predictor of more success at weight loss, body fat loss and reduction in waist circumference. Over the 12 weeks, a reduction in Disinhibition was found to predict an increased weight loss, and reduction in waist circumference. However, an increase in Restraint was associated with an increased weight loss and reduced waist circumference. A decrease in Internal Disinhibition also predicted higher success at weight loss and fat mass loss. In contrast to previous evidence, these findings suggest that weight loss induced by exercise is highly beneficial to those individuals with a high level of Disinhibition. Disinhibition may be a moderator and mediator of exercise-induced weight loss when exercise is mandatory and supervised.

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First hours food intake after stress is marker for anti-stress activities

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Restraint stress (RS) and forced swimming stress (FSS) are classical stressors used in animal experimentation to test the efficiency of anxiolytic drugs. Both stressors cause a significant reduction in food intake. The aim of this study was to determine whether food intake measured after RS and FSS is a suitable parameter for testing anti-stress agents. Males Wistar rats were exposed to 3 h of RS ($n = 16$) or 10 min of FSS ($n = 16$) for 3 consecutive days. In each group, 8 rats were administrated 1 mg/kg diazepam before stress. For each stressor, a group of 8 control rats was included. On the first 2 days of stress, food intake was recorded and compared with baseline. On the third day, corticosterone (CORT) level was measured immediately after stress. RS and FSS significantly inhibited food intake only over the first 3-h period after stress. This inhibition was twice more important after RS than after FSS. Daily food intake was significantly reduced after RS but not after FSS compared to baseline. Diazepam injections suppressed or reduced food intake inhibition caused by FSS and RS, respectively. Compared to control rats, plasma CORT level was increased after RS and FSS. This increase was reduced in rats treated with diazepam. Diazepam has an anti-stress effect during RS and FSS considering CORT level and it also reduces the initial inhibition of food intake in both RS and FSS. Altogether, these data provide evidence that food intake during the first 3 h after stress exposure is a good parameter to test anti-stress activities.

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Intake of fructose and sucrose solutions as a function of concentration

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There have been few direct comparisons of fructose (F) and sucrose (S) intake to determine differences in drinking patterns across concentrations. Adult male rats in S and F groups ($n = 8$/group) were housed in "hotel" cages which monitored rats' access to powdered chow (3.6 kcal/g) and licking at each of 2 drinking bottles in 6-s bins. Each week, rats were given access to water, a single concentration of sugar (S or F) and chow for 5 days, followed by a 2-day break with chow and water only. Rats were tested with S (0–1 M) or F (0–2 M) solutions in ascending order. Sugar intake was significantly greater than baseline water intake at or above 0.03 M S or 0.06 M F. Intake as a function of concentration peaked at 0.25 M S (136 ± 15 g/d) and 0.5 M F (138 ± 12 g/d). When expressed as caloric density, the intake curves for S and F were not different, with a peak at 0.34 kcal/g. While S and F intake was similar, there was a significant effect of sugar on chow intake and lick rate. Sucrose rats decreased chow intake as S increased above 0.03 M (0.04 kcal/g). Fructose rats did not significantly decrease chow intake compared to baseline and ate significantly more chow than S rats when drinking 0.08 kcal/g solutions and above. Thus, cumulative caloric intake was much greater in F rats (3607 ± 63 kcal) than S rats (2025 ± 107 kcal, $p < 0.05$). Also, S rats showed an orderly increase in mean lick rate with concentration from 2.5 licks/s to 5 licks/s. The lick rate of F rats remained constant at ~3.5 licks/s. Thus F and S elicit markedly different patterns of ingestion and caloric intake.

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Context-dependent expectation of palatable food activates the orexin system

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Stimuli previously associated with palatable food intake induce overfeeding in rodents. The hypothalamic neuropeptide orexin participates in cue induced neuronal activation for both food and drug reinforcers. In this study, we assessed the hypothesis that context dependent expectation of palatable food activates the orexin system. To accomplish this, we conditioned 8 male long-evans rats to expect chocolate in a novel environment. Another 8 rats, serving as controls, were only exposed to the novel environment and received chocolate at random times in their home cages. After 10 days of conditioning, we assessed cue induced neuronal activation in orexin neurons as well as target substrates of the orexin system. Results demonstrate that expectation of chocolate activates both orexin neurons and its target regions. Specifically, a greater number of cells expressing orexin-A colocalized with c-Fos expression in animals conditioned to expect chocolate when compared to non-conditioned controls. Moreover, conditioned rats displayed higher levels of c-Fos immunoreactivity in the medial prefrontal cortex, paraventricular thalamus and ventral tegmental area, all of which are implicated as target regions for orexin signaling. This is consistent with previous reports and we are investigating the colocalization of c-Fos with orexin-1 receptor expression in these target regions. These data suggest that context-dependent expectation of a palatable food activates the orexin system which may play an important role in promoting non-homeostatic feeding behavior.

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Pre-exposure to environmental cues predictive of food availability elicits HPA axis activation and increases operant responding for food

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The present study evaluated the effect of rimonabant, fluoxetine, sibutramine and topiramate on food cue-induced increased motivation for food under operant self-administration conditions. For 5 days female Wistar rats were trained to self-administer standard 45 mg food pellets in a 30-min daily session under FR1 schedule of reinforcement. Rats were then trained to FR3 schedule and finally divided into two groups. The first group was subjected to standard 30 min FR3 self-administration session. The second group was exposed to 5 presentations of levers and light for 10 s each (every 3 min, in 15 min), previously associated to food delivery. After this pre-session, a normal 30-min session started. Pre-exposure to environmental cues associated to food delivery increased responding for food when the session started. Corticosterone and ACTH plasma levels, measured after the 15 min pre-exposure were significantly increased. Rimonabant, sibutramine and fluoxetine significantly reduced food intake in both animals pre-exposed and in those not pre-exposed to food associated-cues. Topiramate selectively reduced feeding only in pre-exposed rats. The present findings support the idea that food-associated cues play an important role in the motivation to food intake. They also suggest that topiramate may control the increased motivation for food induced by food related cues.

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Reversal of high-fat diet-induced leptin resistance by dietary fructose

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Leptin, which is thought to be a feedback signal in the regulation of energy balance, inhibits food intake, increases energy expenditure and selectively reduces body fat mass in lean animals. Recently it has been suggested that increased consumption of fructose has contributed to the increased incidence of overweight and obesity in Westernized societies. We have reported development of leptin resistance in rats fed low-fat diets containing 60% kcal fructose, but the high-fructose fed rats were already thin before leptin was administered. The objective of this study was to test leptin responsiveness in rats fed a high fructose, high fat diet and to determine whether leptin resistance was a monosaccharide-specific or a fructose-specific effect. Male Sprague Dawley rats were offered one of six diets; 30% kcal fat, 50% glucose (HFHG), 30% kcal fat, 40% fructose, 10% glucose (HFHFr), 30% kcal fat, 15% fructose, 10% glucose (HFLFr), 10% kcal fat, 50% glucose (LFHG), 10% kcal fat, 40% fructose, 10% glucose (LFHFr), 10% kcal fat, 15% fructose, 10% glucose (LFLFr) for 10 days. Rats within each dietary treatment were infused for 12 days with either PBS or 40 μg leptin/day from an intraperitoneal miniosmotic pump. Leptin inhibited 12-day food intake only in rats fed the HFHG diet. In contrast, leptin decreased body fat by 12% in all low-fat fed rats and in HFHFr-fed rats, but not HFHG or HFLFr rats. These results show that low peripheral doses of leptin can reduce body fat independent of a change in energy intake. In high-fat fed rats, feeding fructose up to 40% kcal has the ability to prevent leptin resistance.

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Bingeing is not necessary for the reinforcing efficacy of dietary fat to be enhanced by intermittent access

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Intermittent access to an optional source of dietary fat promotes binge-type consumption of the optional fat in non-food-deprived rats. The present investigation was designed to determine if intermittent access also would enhance the reinforcing efficacy of the optional fat. Non-food-deprived male Sprague–Dawley rats, age 60 days at the start of the study, were maintained on feeding protocols in which 1-h access to a bowl of vegetable shortening (fat) was provided either daily (D group, $n = 15$), or intermittently, i.e. on Mon, Weds, Fri. each week (INT group, $n = 15$). After 5 weeks on these protocols, shortening intake of the INT group significantly exceeded that of the D group. At this time, the rats were trained to press a lever for a shortening reinforcer (0.1 g) in operant chambers. Rats were then tested under progressive ratio 1 (PR1) and PR3 schedules of shortening reinforcement. Responding was significantly greater in the INT than in the D group under the PR1, but not the PR3, schedule. Furthermore, in subsets of INT and D rats in which home cage shortening intakes were matched ($n = 8$ per group), INT responding remained significantly greater than D. These results indicate that intermittent access to a palatable fatty food can increase the reinforcing efficacy of that food, even among individuals who do not binge. Supported by MH67943 (RLWC).
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Ghrelin inhibits visceral afferent activation of catecholamine neurons in the solitary tract nucleus (NTS)

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The solitary tract nucleus (NTS) of the brainstem is the primary site through which visceral afferents carrying information from the gastrointestinal system enters the brain. The A_2/C_2 group of catecholamine (CA) neurons lie within the NTS and have been proposed to be critical for both the satiety effects of CCK and the orexigenic effects of ghrelin. Previously, we have shown that 90% of NTS-CA neurons are directly activated by incoming visceral afferents, with 50% also activated by CCK, supporting the hypothesis that they lie in a satiety pathway. To determine whether ghrelin also regulates these neurons we identified CA neurons using transgenic mice expressing enhanced green fluorescent protein under the control of the tyrosine hydroxylase promoter (TH-EGFP). We then recorded their synaptic responses to activation of visceral afferents in the solitary tract (ST-EPSCs) in horizontal slices using patch clamp techniques. 100 nM ghrelin reduced the ST-EPSC amplitude in 5/9 NTS-CA neurons tested, with the average inhibition being $41 \pm 9\%$ (ACSF had no significant effect). Ghrelin also significantly inhibited the frequency of spontaneous glutamate inputs (sEPSCs) in 6/12 NTS-CA neurons by an average of $43 \pm 1\%$. Furthermore, CCK increased the frequency of sEPSC in 4/6 ghrelin-sensitive NTS-CA neurons. These data suggest that ghrelin inhibits afferent activation of primarily CCK-sensitive NTS-CA neurons. Inhibition of this critical satiety reflex is a potential mechanism by which ghrelin could increase food intake. Supported by NIH grant DK063040.
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CB1 receptor antagonism alters the anxiogenic and feeding-stimulant effects of ghrelin

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We have recently reported that paraventricular nucleus (PVN) injections of ghrelin stimulate eating, alter energy metabolism, and elicit anxiety-like behaviors in the rat. Other work has shown that ghrelin gene expression in the stomach is altered by tail pinch stress and that CRH antagonism attenuates the anxiogenic action by reversing the suppression of time spent in the open arm of the elevated plus maze. With respect to eating behavior, the CB1 receptor antagonist SR141716 is reported to block the orexigenic effects of PVN ghrelin. Given that both ghrelin and the endocannabinoids are implicated in eating and anxiety, the present study examined whether the CB1 receptor antagonist, AM251, would alter the anxiogenic and orexigenic effects of ghrelin administered into the PVN. Rats ($n = 12$/group) were treated with vehicle, ghrelin (200 pmol) or AM251 (0.75–3 mg/kg IP) paired with vehicle or ghrelin and then placed in an elevated plus maze for 10 min. Each test was performed as a single trial per animal. Ghrelin significantly decreased the number of entries and time spent in the open arms of the plus maze. When rats were pretreated with AM251, the effect of ghrelin was potentiated. In separate testing ($n = 10$/group), PVN injections of the ghrelin significantly increased food intake over 2 h. This effect was blocked by AM251. These findings are consistent with the argument that the anxiogenic and orexigenic effects of ghrelin are mediated, at least in part, via endocannabinoid signaling.
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Alterations of energy expenditure following central administration of insulin detemir in rats

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Insulin detemir (Levemir®) is a newer insulin analog that, unlike other long-acting forms of insulin such as NPH, significantly inhibits weight gain in diabetic patients. As the mechanism for this effect remains unknown, the present study investigated the effects of insulin detemir on energy expenditure (EE) and respiratory quotient (RQ) when centrally administered. The effects of insulin detemir were compared to those of regular insulin (Humulin R), the form of insulin present in NPH. Male S–D rats ($n = 6$) were given ascending doses of detemir or regular insulin into the 3rd ventricle in a volume of 1.0 μl of aCSF. Specifically 0, 1.0, and 2.0 mU/rat of insulin detemir were microinjected at midday and effects compared with equimolar doses of 0, 4, and 8 mU/rat of regular insulin. Following dosing, the rats were placed in metabolic chambers and O2 consumption and CO2 production were measured at 24-h intervals for 3 days. Both forms of insulin increased EE and decreased RQ over 24–48 h post-injection ($p < 0.01$), but detemir had a greater effects on EE and RQ at 24–48 h ($p < 0.05$), and in contrast to regular insulin its effects were dose-dependent for both EE and RQ at 24 h ($p < 0.05$). Both insulins decreased BW over the 3-day period ($p < 0.01$), but the effect of detemir on BW was greater at 48–72 h ($p < 0.05$). Our data show that centrally administered insulin detemir produces more robust alterations in EE and RQ than regular insulin, and suggest that detemir may have longer residency and/or more potent signaling effects in the hypothalamus.
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Food intake, body mass and gut peptide responses to intrajejunal infusions of a fatty acid, protein or glucose

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Gastric bypass is one of the most successful weight loss strategies and is known to alter gut peptide levels. Although the mechanism is unclear, a key component may be greater delivery of undigested nutrients to the jejunum of the intestine. To test whether particular nutrients are more effective at producing decreases in food intake, body mass and induce changes in gut peptide levels, intrajejunal infusions of linoleic acid (LA), glucose (Glu) or casein (Cas) were made in male Sprague–Dawley rats. Equal kcal content of these nutrients or vehicle was infused into the jejunum at lights out for 7 h for 5 days. Continuous food intake and daily body mass were measured. After the infusion on day 8, rats were sacrificed and plasma collected. Intrajejunal infusions of LA and Glu, but not Cas, suppressed food intake in excess of the caloric load of infusate with no compensatory increase in food intake after the infusion period. The body mass of LA and Glu rats was also lower than controls across the infusion days. Plasma leptin was decreased and GLP-1 was increased in both the LA and Glu rats compared with controls, with no significant change in the Cas-treated animals. PYY and ghrelin were differentially expressed across the groups. These results suggest that intrajejunal infusions of LA and Glu may decrease food intake and body mass via alterations in signaling of leptin and GLP-1. These data provide insight into the mechanisms that may contribute to the effectiveness of gastric bypass surgery. Supported by DK19302.
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Divergent regulation of water and saline intake

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The regulation of water and saline intake has been the focus of intense study by behavioral neuroscientists. In most cases, hormonal cues associated with hypovolemia, such as angiotensin II (AngII), stimulate both water and salt intake. Our laboratory is particularly interested in opportunities to explore the differential regulation of these ingestive behaviors. Manipulations of intracellular signaling pathways have been especially informative. Specifically, we have found that MAP kinase inhibitors attenuate saline intake, but not water intake, after central injection of AngII. We also have observed suppression of AngII-induced water intake after concomitant treatment with ghrelin. When both water and saline are available, however, the effect is supplanted by marked reduction in saline intake, without an observable effect on water intake. Additional experiments show that pretreatment with AngII desensitizes subsequent responses to AngII. Experiments in our laboratory suggest that this phenomenon is also specific to water intake, without affecting saline intake. Further experiments raise the possibility that these effects relate to specific intracellular signaling pathways. Taken together, these approaches may reveal interesting divergent mechanisms regulating water and saline intake, especially as stimulated by AngII. Support provided by NIH award DK073800.
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Inhibition of midbrain leptin receptor expression augments sucrose reinforced behavior and mesolimbic dopamine in the rat

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Due to the overlapping neurobiology of food and drug reward, obesity is viewed by some as an addictive behavior. A hallmark of the addictive process is the ability of reinforcing stimuli to alter reward-seeking behavior and this is evident in obese humans and animals. The hormone leptin is positively correlated with body mass in humans and animals and recent work suggests that leptin can alter mesolimbic dopamine function and drug reinforcement in animals. We hypothesized that leptin signaling directly within the ventral tegmental area (VTA) modulates responding for palatable food and mesolimbic function. To test this, we used a lentiviral construct expressing shRNA targeting rat leptin receptor to reduce leptin receptor expression in the VTA. Intra-VTA injection of this virus resulted in a significant reduction of leptin receptor gene expression. Additionally, consumption of a high fat diet also reduced VTA expression of leptin receptor. Further, inhibition of leptin receptor expression increased responding for a palatable food under a progressive ratio schedule of reinforcement. Finally, shRNA-mediated inhibition of leptin receptor expression rescued dopamine levels in the nucleus accumbens of rats maintained on a high fat diet. Collectively these data suggest that leptin can negatively regulate responding for palatable foods and dopamine neurochemistry by acting on mesolimbic neurons.
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FOS expression during sodium appetite

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Earlier FOS studies during Na-appetite used 0.15 M NaCl as a stimulus and found few differences between the deplete and replete states particularly when compared with parallel data from rats sham-ingesting sucrose. The differences observed for sucrose, however, appeared only at a high concentration, 0.6 M. Thus, we repeated our original Na-appetite experiment using stronger NaCl, 0.3 M. Thirty-three rats were used but to date the data from only 16 have been analyzed, so these results are preliminary. The rats had gastric fistulas and sham-fed for 60 min in the AM over 2 weeks. On alternate mornings they had access to either distilled water (w) or 0.3 M NaCl (n). Because experience influences Na-appetite, each rat had 2 test trials separated by a week. The afternoon before each trial, the rats were injected with either furosemide (F, 10 mg/kg, sc) or saline (S). The 6 groups were counterbalanced as follows – SnSn, FnFn, FnSn, SnFn, FwFw, SwSw. Thirty min after the end of their second test trial, the rats were sacrificed with an overdose of pentobarbital (150 mg/kg ip), perfused, and their brains stained immunohistochemically for FOS. Regardless of their prior experience, the rats that sham drank NaCl in the final trial had more FOS labeled neurons in the lateral hypothalamus and nucleus accumbens than those that drank water ($p < 0.01$). A similar trend occurred in the bed nucleus of the stria terminalis but it failed to reach significance. In the central nucleus of the amygdala and the ventral tegmental area FOS expression did not differentiate between stimulus, motivation, or experience. Supported by NIH DC05435, DC008937.
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The control of intake in free-living humans. Facts, theories, and simulations

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Ideas regarding the mechanisms that control food intake have focused on physiological and genetic variables that include negative feedback loops with intake. Evidence, however, suggests that these models although informative, are incomplete. They cannot account for the rapid rise in obesity rates, the lack of detectable compensatory control in natural environments, and the presence of powerful environmental factors that do not have negative feedback loops. Alternatively, the general model of intake regulation postulates that intake is influenced by sets of both environmental and physiological factors. Data and behavioral genetic analysis will be presented on a number of environmental, psychological, dietary, and social variables that have large impacts on the intake of free-living humans in their everyday environments. Recent evidence of built-environment influences on activity and intake will also be presented. A computer simulation of the general model of intake regulation demonstrates that the model predicts different maintained levels of intake and body weight depending upon the external environment and that change in the environment can produce new sustained levels. Since most of these environmental, psychological, dietary, and social factors have changed in value over the last several years in synchrony with the rise in societal obesity rates, it is suggested that some or all of these changes may be responsible for the current epidemic of obesity. It is also suggested that eating is influenced by a myriad of physiological and non-physiological factors and that total intake results from the integral of their influences.

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Opposing actions of ACE inhibition. Central vs. peripheral effects on energy balance

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To evaluate the role of the renin angiotensin system (RAS) in energy balance, we determined the effect of diet-induced obesity on RAS activity in the plasma, adipose tissue and brain of male Long Evans rats. We then assessed energy balance and glucose tolerance in rats given an angiotensin converting enzyme (ACE) inhibitor systemically (captopril [CAP]; ~40 mg/kg/day) and/or into the lateral cerebral ventricle (icv; 10 μg). When administered systemically, CAP, which does not cross the blood–brain barrier, inhibits angiotensin II (ANGII) formation in the periphery but augments central ANGII due to increased circulating ANGI that enters the brain coupled with active central ACE. Rats given systemic captopril ate less food despite increased arcuate nucleus NPY mRNA and gained significantly less weight than both *ad libitum*- and pair-fed controls. The reduction of weight was mainly attributable to reduced adipose mass. Systemic captopril-treated rats also had improved glucose tolerance compared to *ad libitum*-fed controls. Conversely, acute icv CAP administration resulted in a dose-dependent increase in food intake during basal conditions and a reversal of systemic CAP-induced decreased food intake. These results suggest that inhibition of ACE in the periphery protects against the development of diet-induced obesity, while brain ACE inhibition has the opposite effect. Moreover, these data suggest that an important mechanism of systemic CAP-induced weight loss involves an increase in brain ANGII.

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Water deprivation-induced sodium appetite

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Restricted access to water has important implications for human and animal health and increases salt preference in both species. Data from the literature and our laboratory show that water restriction is a valid method to produce sodium appetite in the rat because it induces the typical hedonic shift towards hypertonic NaCl intake and selective ingestion of sodium solutions. The use of a protocol that allows to distinguish sodium appetite from thirst in a water-deprived rat, the water deprivation-partial rehydration (WD-PR) protocol, is extending the importance of angiotensin II as a hormone of sodium appetite and providing new information about brain gene expression in response to dehydration, both in normotensive and hypertensive strains.

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Postprandial responses in hunger and satiety are associated with a genetic variant in the *FTO* gene

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The common rs9939609 SNP in FTO is associated with adiposity, possibly by affecting satiety responsiveness. The current study aims to determine whether postprandial responses in hunger and satiety are associated with rs9939609, taking variation in other relevant candidate genes into account. Sixty-two women and 41 men (age 31 ± 14 years; BMI 25.0 ± 3.1 kg/m^2) were genotyped for five SNPs in *FTO*, *DNMT1*, *DNMT3B*, *LEP* and *LEPR*. Subjects subsequently received fixed meals provided in energy balance. Hunger and satiety were determined pre- and postprandially using visual analogue scales. A general association test shows a significant association between postprandial responses in hunger and satiety with rs9939609 ($P < 0.05$). Subjects with low postprandial responses in hunger and satiety are overrepresented among carriers of the minor A allele in rs9939609 (*FTO*) (dominant and additive mode of inheritance, respectively, $P < 0.05$). Multifactor dimensionality reduction shows that subjects with a low postprandial response in hunger are overrepresented among carriers of the A, C and G allele in rs9939609 (*FTO*), rs992472 (*DNMT3B*) and rs1137101 (*LEPR*), respectively ($n = 39$), compared with subjects homozygous for at least one protective allele ($P < 0.0001$). Our results confirm a role for FTO in responsiveness to hunger and satiety cues in adults in an experimental setting. The epistatic interaction involving SNPs in *FTO*, *DNTM3B* and *LEPR* for the postprandial response in hunger suggests that DNA methylation, an epigenetic process, affects appetite.

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"Permanent" dysregulation of central leptin signaling responses to peripheral leptin in programmed obese IUGR offspring

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Maternal food restriction results in IUGR newborns with reduced body fat and plasma leptin levels. IUGR develop hyperphagia and hyperleptinemia with adult obesity. Leptin mediates central (arcuate nucleus, ARC) anorexigenic responses via ObRb receptor, activating JAK-STAT3 pathway, with signaling inhibition by SOCS3. We previously showed altered ARC leptin signaling in 1-day-old IUGR. We studied if dysregulated central leptin signaling persists in IUGR adults. From pregnancy day 10 to 21, dams received ad libitum food (Control) or were 50% food-restricted (IUGR). Pups were nursed by controls and weaned to ad libitum diet. At age 12 weeks, male offspring received saline or leptin (1 μg/g, i.p.). ARC was dissected at 15, 30 and 45 min and protein expression of ObRb, STAT3, pSTAT3 and SOCS3 was analyzed. Leptin and saline treated IUGR and Controls are compared. Adult IUGR had increased *basal* levels of ObRb, STAT3 and the inhibitor SOCS3 than Controls, suggesting an inhibition of leptin signaling. In response to peripheral leptin, Controls showed increased ObRb (2-fold), pSTAT3 (2-fold) and SOCS3 (5-fold) at 30 min. In contrast, IUGR males showed marked delay and dysfunction in ARC leptin signaling responses. Despite increased ObRb (5-fold) at 45 min, pSTAT3 decreased markedly (0.5-fold), in conjunction with a further increased SOCS3 (3-fold). IUGR adults show enhanced basal and stimulated SOCS3 inhibition of central leptin signaling which contributes to offspring hyperphagia and programmed obesity.
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Systemic leptin antagonist inhibits hypothalamic leptin signal transduction in newborn rat pups

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Leptin mediates central anorexigenic signaling responses via ObRb receptor, activating JAK-STAT3 pathway with signaling inhibition by SOCS3. Maternal food restriction results in growth restricted newborns that develop hyperphagia and hyperleptinemia prior to adult obesity. Thus, inhibition of increased leptin mediated effects early in life may alter the sensitivity of the JAK-STAT3 signaling and prevent obesity. We studied the effects of recombinant rat pegylated leptin antagonist (L39A/D40A/F41A) on hypothalamic leptin signaling. 1-day-old males received either saline; leptin (10 μg/g, s.c.); pegylated leptin antagonist (PEG-MLA, 20 μg/g, s.c.); or leptin plus PEG-MLA. Hypothalamus was dissected at 30, 45 and 60 min. ObRb, STAT3, pSTAT3 and SOCS3 protein expression was analyzed. All treatments are compared to saline. Leptin treatment upregulated JAK-STAT3 signal molecules at 30 min. In contrast, leptin plus PEG-MLA showed no change in any of the signal molecules except for pSTAT3 which was downregulated at 45 and 60 min (0.5-fold). PEG-MLA treatment showed similar changes as PEG-MLA with leptin. Thus, systemically administered PEG-MLA effectively blocks leptin signal induction of hypothalamic JAK-STAT by impairing binding of leptin to its ObRb receptor. Leptin-specific antagonists may provide understanding of mechanisms contributing to programmed or diet induced obesity, and a potential therapeutic intervention strategy.
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Hypothalamic neuronal progenitor cells. Divergent effect of leptin and insulin on growth and differentiation

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Growth restricted (IUGR) newborns have reduced anorexigenic responses that may contribute to hyperphagia and obesity. Anorexigenic hormones, leptin and insulin, are prenatal neurotrophic factors that impact brain growth and development. We hypothesized that reduced leptin and insulin levels, as seen in IUGR newborns, may contribute to reduced anorexigenic neural pathway development and altered appetite regulation. Rat embryonic (E20) hypothalamic neuronal progenitor cells (NPC) were cultured in differentiating medium. NPC were treated with leptin (0, 10, 20, 40 ng/ml) or insulin (0, 10, 20, 40 μg/ml) every 48 h for 8 days. The effect on cell proliferation rate and differentiation, and protein expression of neuronal markers during development (early, DCX; β-tubulin3; late, NeuN) and astrocyte marker (GFAP) were determined. Leptin and insulin induced dose-dependent increases in cell proliferation (leptin, 30%; insulin, 50%) and expression of DCX and β-tubulin3, both of which are associated with microtubules and essential for neuronal migration, differentiation and stability. However, leptin and insulin had divergent effects on differentiation—leptin increased NeuN (3.6-fold) but not GFAP expression whereas, insulin increased GFAP (2-fold) but not NeuN expression. Thus, leptin and insulin enhance neuronal growth, with selective effects on neuronal/glial differentiation. Reduced insulin and leptin levels in IUGR fetuses may lead to reduced neuronal pathway development with subsequent impact on appetite regulation.
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The effect of stress on food preferences

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It has been shown that some stress circumstances produce not only a food intake increase but also an increase of unhealthy food. However, these facts have not been demonstrated clearly. In this study the objective was to determine the stress effects on food choice (grapes vs chocolate) under a stress condition. In this research, 138 undergraduate students were randomly divided into two groups: stress and no-stress. Subjects received either 10 unsolvable or 10 solvable four-letter anagrams. Subjects were also given a questionnaire asking them to rate how stressed they were, how healthy they thought each of the two foods were and how much they liked each of the two foods. The stress group reported being significantly more stressed (M = 3.0, SD = 2.5) than the no-stress group (M = 2.1, SD = 2.0). The no-stress group consumed more grapes and chocolate than stress group. Groups did not differ in their ratings of the healthiness neither how much they liked the two foods. The finding of food consumption suggests considering other variables such as food availability. Given that no-stress group completed the task before stressed group, the first one had more time for eating. Complementary, stressed subjects were focused on solving task, an incompatible response with eating. These findings suggest that new approaches are needed in order to improve our knowledge of stress and its relations with food intake.
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Selective co-expression of insulin receptor substrate 2 (IRS-2) in specific hindbrain monoamine cell groups

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Insulin receptor substrate 2 (IRS-2), a receptor protein that mediates cellular actions of insulin, is implicated in energy homeostasis and is present in brain areas crucial for feeding and metabolism. IRS-2 is known to be expressed in catecholamine neurons of the A2 cell group (Pardini et al., 2006), but other monoaminergic cell groups have not been examined. Here we examined IRS-2 co-expression in brainstem norepinephrine, epinephrine and serotonin cell groups using dopamine beta hydroxylase (DBH), phenethanolamine n-methyl transferase (PNMT) and trypophan hydroxylase (TryH) antibodies, respectively, to label these phenotypes for immunohistochemical detection. We found that IRS-2 was co-expressed in both catecholamine and serotonin neurons, but was limited to particular cell groups or subgroups. In cell group A2, IRS-2 was co-expressed exclusively in the compact small-diameter DBH-immunoreactive cell bodies in the dosomedial NTS, but not in the large A2 cells within the commissural and medial subnuclei. IRS-2 and DBH were extensively co-expressed in groups A5, A6 and A7. In striking contrast, IRS-2 was co-expressed only rarely in C2 neurons and was not co-expressed in cell groups A1, C1 or C3. IRS-2 was strongly expressed in raphe pallidus, obscurus and magnus (B1, B2 and B3), where it was frequently, but not exclusively, co-expressed with TryH. IRS-2 was not co-expressed with TryH in other serotonin cell groups. Results suggest that the central effects of insulin are mediated in part by its selective action on particular catecholamine and serotonin neurons.

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Microarray analysis of gene expression in Neuropeptide Y expressing neurons of the Dorsomedial nucleus of the Hypothalamus

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The Dorsomedial nucleus of the Hypothalamus (DMH) is important for the regulation of food intake and body weight. The DMH contains neurons expressing Neuropeptide Y (NPY) during specific physiological conditions of hyperphagia and obesity. In contrast to NPY neurons in the Arcuate nucleus of the Hypothalamus (ARH), the role and chemical phenotype of DMH-NPY neurons has yet to be characterized. This study compares the gene expression profiles of DMH and ARH-NPY neurons by microarray, to understand the role of DMH-NPY neurons in energy homeostasis. DMH and ARH sections were microdissected from NPY-GFP mice at postnatal day 16 and GFP neurons were sorted with Fluorescent Activated Cell Sorting. RNA was extracted and labeled target cDNA was prepared for microarray analysis. Statistical analysis was performed to identify genes that are differentially expressed in the DMH-NPY samples compared to the ARH. The key findings from this study were as follows: (1) Several receptor systems that are expressed on ARH-NPY neurons, including leptin receptor and NPY-Y5 receptor, were undetectable on DMH-NPY neurons. (2) DMH-NPY neurons showed differential expression of several transcription factors that are involved in energy homeostasis. (3) DMH-NPY neurons did not express GABAergic markers, suggesting that they may not be GABAergic. These findings strongly suggest that DMH-NPY neurons could play a distinct role and are differentially regulated from ARH-NPY neurons through different afferent inputs and transcriptional regulators.

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The effect of food preferences, food intake, and taster status on body weight in children with autism

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The purpose of the study was to identify differences in food preferences, food intake and BMI status between young children diagnosed with autism and a control population. Feeding problems in autistic children throughout infancy and childhood are common, and the frequency rates for autism spectrum disorder range from 3.8 to 60 per 10,000 children, with rates of diagnosis increasing annually. The prevalence of childhood obesity or overweight has increased for children ages 2–5, from 5% (1976–1980) to 12.4% (2003–2006). The influence of food preferences and taster status on body weight in young children (ages 3–5) is not well understood, and even less has been uncovered about the autistic population. In study 1, we examined the relationship between food preference, food intake as measured by a 7-day diary, and Body Mass Index (BMI) in 3–5 year old children ($n = 32$; 15 participants were diagnosed with autism and 17 were normal). In study 2, we examined the relationship between parent taster status, parent food preferences (mothers, $n = 32$) and children's taster status and food preferences. Differences between the autistic and normal population on the food preference measure were found for a number of food items.

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The impact of binge eating on anxiety-like behavior in the rat

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Rats given daily limited access to palatable food exhibit increased anxiety when food deprived. It is unclear if this is due to the acute deprivation from the palatable food, or chronic binge-eating. To clarify this issue we used the Corwin model of binge-eating. We hypothesized that binge-eating experience, and not merely the deprivation from a scheduled palatable meal, would elevate anxiety. Male Long-Evans rats received sweetened vegetable shortening (SVS) for 1 h daily (7D group), once every 3 days (3D group), or never (naïve group) for 30 days. By the fourth week, the 3D group were eating significantly more total calories on the days they received the SVS (total 24-h calorie intake: 3D = 152.8 ± 13.9 kcal, 7D = 122.4 ± 3.4 kcal and naïve = 119.5 ± 8.3 kcal, $p < 0.05$) relative to the other groups. On the non-SVS days the 3D group ate less than the other groups (total 24-h calorie intake: 3D = 90.1 ± 8.0 kcal, 7D = 117.7 ± 8.6 kcal and naïve = 115.2 ± 6.3 kcal, $p < 0.05$). After the binge protocol, anxiety-like behavior was measured in an elevated plus maze (EPM) following a 24-h food deprivation. Rats in the 3D group spent less time in the open arms of the EPM compared to rats in the 7D group (percent time in the open arms: 3D = 9.0 ± 3.5% and 7D = 24.0 ± 3.9%, $p < 0.05$), but did not differ from the naïve group (15.5 ± 3.5%). These findings suggest that binge-eating may elevate anxiety, while deprivation from a palatable meal does not.

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Hindbrain catecholamine neurons contribute to the growth hormone but not the feeding response to ghrelin

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Ghrelin is a peptide that is released peripherally in association with food deprivation and that stimulates food intake (FI) and growth hormone (GH) secretion. Y. Date et al. (2002) have claimed that these responses to ghrelin are conveyed to the brain by the vagus nerve, which in turn activates hypothalamically projecting catecholamine (CA) neurons in the dorsal vagal complex that stimulate FI (Date et al., 2006). The latter assertion was based on the loss of ghrelin-induced FI in rats injected into the arcuate (ARC) with anti-dopamine beta hydroxylase (DBH) conjugated to saporin (DSAP), which retrogradely destroys DBH-containing CA neurons. We previously showed that DSAP microinjection either into the hypothalamic paraventricular nucleus (PVH) or ARC abolished glucoprivic feeding. Since glucoprivation alters both FI and GH secretion, we reasoned that CA neurons sensitive to glucoprivation may contribute to these responses to ghrelin. We injected DSAP or unconjugated saporin (SAP) bilaterally into the PVH of Sprague-Dawley rats. Feeding responses to s.c. 2-deoxyglucose (2DG) and i.p. ghrelin were conducted 3 wks later. Thus, we measured GH at 0, 20, 40, and 60 min after 4th ventricular aCSF or ghrelin. DSAP abolished 2DG-induced FI, as expected, but did not alter ghrelin-induced FI, indicating that these two responses are not controlled by the same CA neurons. Our results challenge the conclusion that ghrelin-induced FI is CA-mediated. In contrast, ghrelin-induced GH secretion was significantly prolonged in DSAP-treated rats, indicating that CA neurons inhibit ghrelin-induced GH secretion.

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Food reinforcement and obesity

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Increased motivation to eat and a reduced motivation to be active are important determinants of positive energy balance and obesity. This paper reviews research on individual differences in food reinforcement in obese and lean adults and children, and reviews behavioral factors that are associated with food reinforcement, including food deprivation and food variety. Dopamine genotypes that have been related to food reinforcement are reviewed, focusing primarily on the dopamine D2 receptor genotype. Finally, implications of individual differences in food reinforcement for treatment of obesity are presented.

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Stimulus specificity of habituation of motivated responding for food

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Motivated responding for food reliably decreases with repeated presentations, and increases after presentation of a new food, consistent with habituation theory. There is no research designed to test the stimulus specificity of foods that produce recovery of motivated responding. We assessed whether foods that differed in texture and appearance from the habituating food would result in recovery of habituated responding, and whether sensitization, or an increase in responding prior to habituation, was related to the rate of habituation or recovery of responding. Overweight and lean children ($n = 64$) worked for access to servings of elbow macaroni and cheese until they habituated, when they were provided either more elbow macaroni and cheese, spiral macaroni and cheese, or chicken nuggets. Recovery of responding increased when children were provided chicken nuggets or spiral macaroni and cheese in comparison to being provided more elbow macaroni and cheese ($p < 0.015$) along with greater amount of food ($p = 0.0002$) and energy intake ($p < 0.0001$). Children who sensitized showed slower habituation ($p < 0.025$) and consumed more food ($p = 0.015$) and more energy ($p = 0.015$) than those who did not sensitize, but did not differ in recovery of responding to the chicken nuggets or spiral macaroni and cheese. Results suggest that small variations in characteristics of foods may lead to recovery of responding and increased intake after children have habituated. Also, sensitization is reliably associated with slower habituation and greater energy intake.

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Food reinforcement and energy intake in obese and nonobese adults

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Eating is a highly reinforcing activity and individual differences in the reinforcing efficacy of food may influence excess energy intake and positive energy balance. Research has shown that obese adults and children are more motivated to work for palatable, favorite foods than leaner peers. In addition, those high in food reinforcement consume more food in an ad libitum eating task than those who do not find food as reinforcing. This study assessed the influence of individual differences in food reinforcement and obesity on energy intake. Overweight and lean adults ($n = 106$) were studied. During the first session participants completed an ad libitum snack eating task where they were presented with six different snack foods to taste and rate. During the second session, participants were asked to complete a food reinforcement task for access to portions of their favorite snack food. Food reinforcement, BMI, age, sex, education, hunger and dietary measures were assessed as determinants of energy intake using a multiple regression model. Results showed main effects of food reinforcement ($p < 0.01$), BMI ($p = 0.01$), sex ($p < 0.01$), age ($p < 0.01$) and hunger ($p = 0.03$) on energy intake. There were no significant interactions between any of the predictors and energy consumption. In addition, there was a significant correlation between food reinforcement and BMI ($p < 0.01$). The results show that obese individuals and those high in food reinforcement will consume more food in an ad libitum eating session than those nonobese individuals and those lower in food reinforcement. These results support earlier research and provide support for the importance of studying food reinforcement as a contributor to obesity.

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Stimulus specificity of habituation of motivated responding for food

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Motivated responding for food reliably decreases with repeated presentations, and increases after presentation of a new food, consistent with habituation theory. There is no research designed to test the stimulus specificity of foods that produce recovery of motivated responding. We assessed whether foods that differed in texture and appearance from the habituating food would result in recovery of habituated responding, and whether sensitization, or an increase in responding prior to habituation, was related to the rate of habituation or recovery of responding. Overweight and lean children ($n = 64$) worked for access to servings of elbow macaroni and cheese until they habituated, when they were provided either more elbow macaroni and cheese, spiral macaroni and cheese, or chicken nuggets. Recovery of responding increased when children were provided chicken nuggets or spiral macaroni and cheese in comparison to being provided more elbow macaroni and cheese ($p < 0.015$) along with greater amount of food ($p = 0.0002$) and energy intake ($p < 0.0001$). Children who sensitized showed slower habituation ($p < 0.025$) and consumed more food ($p = 0.015$) and more energy ($p = 0.015$) than those who did not sensitize, but did not differ in recovery of responding to the chicken nuggets or spiral macaroni and cheese. Results suggest that small variations in characteristics of foods may lead to recovery of responding and increased intake after children have habituated. Also, sensitization is reliably associated with slower habituation and greater energy intake.

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Interaction between serotonin and cannabinoids in the paraventricular hypothalamus in the regulation of food intake

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Serotonergic transmission in the paraventricular nucleus of the hypothalamus (PVN) produces suppression of food intake (FI). Additionally, it is well known that CB1 receptors (CB1R) are expressed at the PVN and their activation increases food consumption. PVN receives serotonergic innervation from dorsal raphe nucleus, where neurons co-express tryptophan hydroxylase type 2 and CB1R mRNA. Accordingly, it is possible that stimulation of FI induced by cannabinoids is related to an action on serotonergic terminals at the PVN via presynaptic CB1R. The present study was aimed to test the hypothesis that serotonergic transmission in the PVN is involved in the cannabinoid-induced hyperphagia. Microdialysis and FI experiments were conducted in food-restricted rats ($n = 56$), firstly evaluating the effects of systemic administration of ACEA (CB1R agonist, 0.5 mg/kg) on the fluoxetine-induced accumulation of serotonin (5-HT) in the PVN, and then assessing the effects of intra-PVN administration of ACEA (0.25 μg) on FI in rats pre-treated with 5-HT (2 μg). The increase of extracellular 5-HT concentration in the PVN induced by fluoxetine (5 mM) was significantly decreased by ACEA; furthermore, the intra-PVN pre-treatment with 5-HT prevented the increase of FI induced by ACEA. The present results suggest a functional interaction between the endocannabinoid and the serotonergic systems in the PVN in the regulation of food intake.

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Behavioral and metabolic effects of peripherally administered Olanzapine and Topiramate in male and female rats

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In humans the anti-psychotic Olanzapine (OLZ) has aversive side effects: it increases body weight and the risk of developing type II diabetes. The anti-convulsant Topiramate (TPM) has the opposite effects on metabolism: it decreases body weight and improves insulin sensitivity. TPM might be given together with OLZ to counteract the side effects of OLZ. To study the mechanisms by which OLZ and TPM influence metabolism, we developed a rat model in which the drugs are administered intragastrically twice a day during the active phase. TPM treatment led to a small reduction in body weight and fat mass and a marked improvement of the glucose/insulin profile during an intragastric glucose tolerance test. Food intake was reduced only at the first days of treatment, water intake was continuously increased. In OLZ and OLZ + TPM treated animals food intake was reduced leading to a strong decrease in body weight. Water intake was reduced in OLZ treated but not in OLZ + TPM treated animals. In both OLZ and OLZ + TPM treated animals the reduction in body weight was not followed by a change in glucose and insulin levels. This was rather unexpected since weight reduction normally improves glucose and insulin profiles. We conclude that TPM treatment leads to weight loss and an improved glucose/insulin response and reduced visceral fat in both humans and rat. With respect to OLZ, there are clear species differences in the feeding response but the negative metabolics effects of OLZ occur are more or less similar in rats and humans.

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Estrogen and hindbrain activation in response to sodium loss in rats

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Estrogen alters water and sodium intake in rats induced by injection of the natriuretic/diuretic drug, Furosemide (Furo). The present study was conducted to determine whether estrogen affects Furo-induced activation in the area postrema (AP) and the nucleus of the solitary tract (NTS), hindbrain nuclei that detect circulating and neural signals of sodium loss, respectively. Female rats were ovariectomized (OVX), treated with estradiol benzonate (EB) or OIL on 2 consecutive days, and 24 h later were injected with Furo or 0.15 M NaCl. After 18 h with water but no food, rats were anesthetized and perfused with paraformaldehyde. Uteri were removed to assess size and weight. Brains were removed and cut into 40u sections; standard immunocytochemical methods were used to label the fos protein (Calbiochem AB5; rabbit anti-c-fos) in the AP and NTS. Uterine weight and circumference were significantly greater in EB-treated rats than in OIL-treated rats, an indication of the effectiveness of EB treatment. Furo had comparable effects on plasma osmolality and volume in the two groups. In the caudal NTS, Furo increased fos labeling slightly in both groups. In the middle NTS (mNTS), Furo increased fos labeling in EB-treated rats, but not in OIL-treated rats. Neither Furo nor EB affected fos labeling in the AP. Thus, estrogen effects on neural activation in the hindbrain after Furo are selective to the mNTS. Moreover, estrogen effects on Furo-induced water and sodium intake by OVX rats may be related to increased activation in the mNTS in response to sodium and/or volume loss.

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Improvements in weight, mood and CVD risk factors in depressed, obese patients treated by lifestyle modification

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Depression and obesity are independent risk factors for the development of cardiovascular disease (CVD). Moderate weight loss improves risk factors for CVD, yet depressed individuals are routinely screened out of weight loss trials due to concern that weight reduction will exacerbate depression. This study examined this issue. Patients ($n = 49$) with binge eating disorder (BED) (mean age = 47.3 yrs, BMI = 43.9 kg/m^2) received a 6-month behavioral weight loss program. Changes in weight, mood (Beck Depression Inventory-II, BDI-II), and CVD risk factors were assessed at 2 and 6 months. Mean BDI-II scores in the depressed ($n = 24$) and non-depressed groups ($n = 25$) were 23.8 ± 10.0 and 7.5 ± 4.2 ($p < 0.001$) at baseline. At 6 months, depressed participants lost $8.2 \pm 8.3\%$ of initial weight, compared with $11.3 \pm 7.8\%$ for non-depressed individuals ($p = 0.19$), and reported significantly greater reductions on the BDI-II at this time than non-depressed individuals ($-13.5 \pm 9.6\%$ vs. $-1.6 \pm 4.9\%$, $p < 0.001$). There was a trend towards higher triglyceride levels in the depressed group at baseline ($p = 0.06$), and they showed greater reductions in triglycerides at 6 months ($-18.2 \pm 17.6\%$ vs. $-6.7 \pm 23.7\%$, $p < 0.05$) than non-depressed individuals. Collapsing across the two groups, significant reductions were also observed in glucose, insulin, HDL cholesterol or CRP levels (with no significant differences between groups). These data indicate that depressed, obese individuals can achieve clinically significant weight losses that are associated with significant improvements in mood and CVD risk factors.

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*Taq*IA A1 polymorphism associated with attenuated nigrothalamocortical response during food consumption

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The A1 allele (A+) of the *Taq*IA restriction fragment length polymorphism is associated with impaired dopaminergic (DA) functioning, namely decreased DA D2 receptor (DRD2) density and binding. Although not unambiguously linked, this polymorphism is associated with addiction (AD), obesity, and personality traits such as impulsivity. Recently, *Taq*IA has been identified as part of a novel ANKK1 regulatory gene, located down stream from DRD2. Here, we used fMRI to determine whether subjects (Ss) with (A+: A1/A1, A1/A2; $n = 13$) and without (A−: A2/A2; $n = 13$) the *Taq*IA A+ show differential neural response to the ingestion of food. Our aim was to isolate differences specific to the *Taq*IA polymorphism, independent of body mass index (BMI) and AD; therefore, groups were matched for BMI, eating style, age, gender, race and ethnicity, and had no history of psychiatric illness or AD. Ss underwent an fMRI scan while passively consuming milkshake (mlk) and tasteless (t) solutions. Using a region of interest approach, comparison of mlk–t showed decreased midbrain (substantia nigra, including the ventral tegmental area), medial dorsal thalamus, medial orbital frontal cortex and, at a lower threshold, caudate response in A+ compared to A−. No differences were observed in stimuli perceived pleasantness or intensity, nor willingness to work for food. These data indicate there are fundamental differences in the neurophysiology of reward among A+ and A− individuals, specific to nigrothalamocortical DA pathway. Supported by RO3 DA022292-01 and a donation to DMS.

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Central urocortin 2 anorexia is attenuated by high fat diet access and obesity risk genotype in female rats

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Corticotropin-releasing factor type 2 (CRF_2) receptor agonists reduce food intake. We tested the hypothesis that third ventricle infusion of urocortin 2 (Ucn 2, 0.1–3 μg), a CRF_2 agonist, retains anorectic activity in a genetic model of obesity risk, despite high-fat (HF) diet history. Female, diet-induced obesity prone (DIO) and resistant (DR) rats ($N = 122$) were provided ad lib access to chow or HF diet or binge-like access to HF (1 h/day, 3 days/week), with chow otherwise provided. Food intake and body composition were measured for 3 weeks. Ad lib HF-fed DIOs showed greater baseline 1 h and daily caloric intake and gained 2.5× more weight and fat mass by the 3rd week than HF-fed DRs. During binge-like access to HF, DIO and DR binge rats equally overate relative to ad lib-fed animals. However, binge-fed DIOs ate more chow in the other 23 h than DRs, yielding greater total daily intake. Despite eating more during the "binge" hour, total daily intake, weight and fat content of "binge" groups did not differ from chow-fed rats by the 3rd week. ICV Ucn 2 reduced chow intake with less potency in DIOs than in DRs. However, Ucn 2 did not reduce HF diet intake in either genotype under ad lib or binge access conditions. Thus, the central anorectic activity of Ucn 2 was attenuated by HF diet and by obesity risk genotype. Supported by DK07118 and a Hungarian Eotvos Fellowship.

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Increased sample size efficiency in small *N* animal research

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Sequential Stopping Rules (SSRs) are up to 30% more efficient in terms of the use of subjects than the Fixed Stopping Rule (FSR) that is employed in almost all experimental research using null hypothesis tests. The existing SSRs were validated for large experiments (e.g., social or cognitive psychology) where subjects are plentiful and there are few ethical issues with adding additional subjects (e.g., smallest $N = 16$). I have used Monte Carlo techniques to optimize SSRs for small-sample research where subjects may be expensive or heavily instrumented, or there may be ethical issues with using large sample sizes, such as in some invasive experiments with animals in the study of the mechanisms of metabolism or ingestive behavior. Using 100,000 simulated experiments per run, I modeled small-sample *t*-tests using SSRs with 8 effect sizes, 6 different added sample sizes per sequential test, 4 levels of alpha, and 17 low and 7 high criteria for stopping the testing sequence. The simulations validate the use of SSRs with small sample *t*-tests and allow small-sample researchers to enjoy the benefits of increased efficiency (as high as 30% fewer animals) with the same power and alpha as FSR tests. Small modifications from the existing large sample SSR techniques are required. SSR techniques are simple to use, and they allow researchers to conduct initial or pilot tests of hypotheses with small *N* and then to add more animals if results appear promising, without inflating alpha. Many researchers already use a similar strategy, but they use it in a way that unintentionally inflates alpha from .05 to .13 or more.

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Effects of sham intoxication on physical performance using the Nintendo Wii Fit

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Past research has shown sham intoxication leads to an increase in pain tolerance, anger, confusion and fatigue. In addition, cognitive performance is significantly affected. The present study examined the effects of sham intoxication on balance via the Wii Fit video game for the Nintendo Wii console. Thirty participants underwent two conditions. In the experimental condition, participants consumed four, twelve-ounce, non-alcoholic beers. They then played a series of four balance games on the Wii Fit, including Ski Slalom, Soccer Heading, Tight Rope Walk, and Table Tilt. In the control condition, participants filled out the Big 5 Personality and Trait Aggression surveys prior to playing the Wii Fit balance games. Paired sample *t*-tests were used to analyze performance scores. Results showed significance between the sham alcohol and control Tight Rope times, between the sham alcohol and control Table Tilt points, and sham alcohol and control Table Tilt level reached. There was a trend between the sham alcohol and control Soccer Heading points and between the sham alcohol and control Ski Slalom time. In all cases, performance diminished in the sham alcohol condition when compared to the control condition. These results indicate perceived intoxication effects on balance are not entirely physiological, as they seem to depend on individual expectations of intoxication.
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Flavor preference conditioning in children and young adults

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Conditioned flavor preference learning has been studied extensively using the laboratory rat as an animal model. However, observations of the same associative processes are relatively scarce in humans, especially in children. The few studies that have investigated flavor preference conditioning in children have failed to account for important variables such as hunger levels, consumption, and individual differences in preferences for sweet tastes. The present study used a within-subjects conditioning procedure to measure flavor-taste and flavor-calorie associations in a sample of children between the ages of 5–12 years ($n = 29$), and a sample of young adults ($n = 24$). After determining their level of sweet preference, participants were trained using a simultaneous conditioning procedure in which they drank 5 mL of three flavored herbal teas that were either mixed with a sweet-tasting nutritive reinforcer (CS++), a sweet-tasting nonnutritive reinforcer (CS+), or presented alone (CS−) over 42 training trials in total. Preliminary results indicated that adults who preferred concentrations of sugar solutions greater than 10% acquired a flavor-calorie association. However, children failed to acquire a conditioned preference for either of the reinforced flavor cues, regardless of their preferred concentration of sucrose. It is possible that children failed to acquire conditioned flavor preferences because the flavors of the teas were unfamiliar and particularly unpleasant or because of the difficulty of the conditioning task.
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Functional evidence of hindbrain mechanism for aldosterone-induced sodium appetite

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In the present study we investigated the effects of chronic infusion of aldosterone into the fourth ventricle (4 V) or into the lateral ventricle (LV) on sodium appetite. Male Wistar rats (280–350 g) with guide cannulas implanted into the 4 V or LV were used. Vehicle (1% ethanol-saline; $n = 5$) or aldosterone (1, 10 or 100 ng/h into the 4 V; $n = 5$/dose, and 10 or 100 ng/h into the LV; $n = 4$/dose) was infused during 6 days. Regular chow, water and hypertonic saline (HS, 0.3 M NaCl) were provided ad libitum during the protocol. Aldosterone (10 and 100 ng/h) induced a robust dose-dependent daily HS intake (up to 46 ± 15 and 130 ± 6 mL/24 h, respectively, vs. vehicle: 1.2 ± 0.6 mL/24 h, $p < 0.001$) that returned to baseline levels few hours after stopping the infusion of aldosterone. However, the same doses of aldosterone infused into the LV failed to induce HS intake (3.2 ± 3.2 and 1.8 ± 1.2 mL/24 h, respectively, $p > 0.5$). These data reinforce the central action of aldosterone to induce sodium appetite and beyond previous neuroanatomical studies, this is the first functional evidence for a preferential site within the hindbrain for aldosterone to induce sodium appetite. Supported by FAPESP, CNPq, CAPES.
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The role of perfectionism on eating behaviors among women with eating disorder

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The aim of this study was to assess the relation between perfectionism and eating behaviors among women with eating disorders. The sample comprised 67 women diagnosed with eating disorders with a mean age of 17.33 years (SD = 3.87). They were asked to complete Eating Attitudes Test (EAT), Bulimia Test (BULIT) and Multidimensional Perfectionism Scale (MPS) in a single session. According to MPS score, the participants were distributed into two groups: high perfectionism (HP, 52.2%) and low perfectionism (LP, 47.8%). The results showed that concern over mistakes of MPS was positively associated with restrictive diet ($r = .49$, $p < .01$), food preoccupation ($r = .62$, $p < .001$) of the EAT, binge eating and compensatory behaviors ($r = .35$ and .38, respectively, $p < .05$) of the BULIT among HP women. In the case of LP women concern over mistakes of MPS only correlated with food preoccupation ($r = .47$, $p < .01$). A higher percentage of HP women reported that they have control over the amount of food that they consume (31.7%), eat uncontrollably once a day or more (21.9%) and have been on a diet more than four times in the past year (71.9%) in comparison with LP women (17.1%, 14.3% and 48.5%, respectively). These findings support the idea that an important portion of people with eating disorders shows perfectionist traits, and in these cases, it correlates with specific eating behaviors.
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Maternal high-fat diet increases adiposity and glucose intolerance in adult offspring of obesity-resistant (DR) rats

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The present study tested the hypothesis that early exposure to high-fat diet (HF) increases adult obesity risk even in genetically resistant animals. Female diet-induced obesity prone (DIO) and resistant (DR) rats were fed HF or low-fat (LF) diet for 6 weeks before mating and then through weaning. Most DIO females fed HF did not yield litters. Female offspring from other groups (DIO/LF, DR/LF, DR/HF) were weaned onto chow and studied as adults. Adult DR/LF, DR/HF, and DIO/LF offspring showed similar chow intake, yet DR/HF weighed more and were fattier than DR/LF offspring. DIO/LF rats were heaviest and fattiest. Fasting blood glucose (BGL), leptin and insulin levels were highest in DIO/LF rats, but DR/HF offspring also showed higher fasting leptin levels than DR/LF rats. During an oral glucose tolerance test, DR/HF rats showed a slower decline in BGL and higher insulin than DR/LF rats. Rats were then fed purified HF or LF diet for 4 weeks; groups did not differ in normalized energy intake or lean mass gain. When fed either diet, DIO/LF rats gained more fat mass than DR rats. DR/HF rats became fattier when fed the HF diet, unlike HF-fed DR/LF rats, which resisted fat gain. Adult HF diet exposure also increased fasting BGL in DR/HF, but not DR/LF, offspring, with similar trends for leptin and insulin. Thus, an early HF diet environment may increase risk for adult obesity and glucose intolerance despite genetic resistance and may impair reproduction in genetically-prone individuals.

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Sympathetic system controls feeding-induced mobilization of NAPE and OEA in the small intestine

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N-acylphosphatidylethanolamine (NAPE) and oleoylethanolamide (OEA) are produced by the upper small intestine in response to food intake and have been proposed to serve as satiety hormones through local (OEA) and systemic (NAPE) actions. Previous studies have shown that intestinal NAPE and OEA levels decrease during fasting and rebound after re-feeding. However, the sensory neural control of this response remains unknown. To investigate the role of autonomic afferents in the intestinal production of NAPE and OEA, we examined whether pharmacological or surgical blockade of sympathetic activity affects feeding-induced intestinal production of these molecules. The results show that feeding-induced OEA mobilization in the small intestine is blocked by β adrenergic antagonist, specifically by β2-selective adrenoceptor antagonist, but is not affected by β1, β3 or α adrenoceptor antagonists. The effect of β2 adrenoceptor antagonist on feeding-induced OEA mobilization is accompanied by reduction of OEA precursor NAPE and decreased activity of the OEA-synthesizing enzyme NAPE-specific phospholipase D (NAPE-PLD). Furthermore, the feeding-induced production of NAPE and OEA in the small intestine is completely abolished in rats in which the splanchnic nerves had been transected by removing the celiac-superior mesenteric ganglion. The results suggest that sympathetic activity facilitates the biosynthesis of NAPE and OEA induced by food intake in the small intestine.

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Downstream signaling mechanisms of arcuate nucleus malonyl-CoA in the hypothalamic control of energy balance

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Malonyl-CoA in the hypothalamic arcuate nucleus (Arc) has recently emerged as a mediator in the control of food intake and energy balance. The downstream signaling of Arc malonyl-CoA is largely unknown, although carnitine palmitoyltransferase-1 liver-isoform (CPT-1A) is proposed as a target. To clarify such a role for CPT-1A, we activated the CPT-1A in the Arc by stereotaxic injection of an adenovirus expressing CPT-1A into the Arc of rats. Activation of Arc CPT-1 produced anorectic actions, which was evident from day 3 through day 9 following the virus injection. The AMPK signaling in the Arc was not affected by the altered activity of CPT-1. The increased activity of CPT-1 reduced the levels of long-chain acyl-CoA's (LCFA-CoA's), CPT-1 substrates, and increased the malonyl-CoA level in the Arc. LCFA-CoA's are allosteric inhibitors of acetyl-CoA carboxylase (ACC) that produces malonyl-CoA. Thus, the observed increase of malonyl-CoA level may be accounted for by the de-inhibition of ACC following decreased LCFA-CoA's, which is in line with our finding that intra-hypothalamic delivery of palmitate rapidly stimulated feeding and lowered the malonyl-CoA level. In the Arc, LCFA-CoA's were increased with a decrease of malonyl-CoA by fasting and LCFA-CoA's were reduced with an increase of malonyl-CoA by refeeding. Our data suggest that target(s) other than CPT-1A and long-chain acyl-CoA's exist in mediating Arc malonyl-CoA control of food intake and energy balance.

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Glucose-conditioned preferences in taste-impaired TRPM5 knockout mice

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Knockout (KO) mice missing the TRPM5 taste signaling protein are indifferent to dilute sugar solutions (0.5–4%) but prefer concentrated solutions (8–32%) in 24-h tests. This preference has been attributed to the post-oral actions of the sugar. This study investigated oral and post-oral influences on glucose preference in KO mice. Food and/or water deprived KO mice, unlike C57BL/6J wild-type (WT) mice, were indifferent to 8% glucose (vs. water) in 60-s two-bottle tests. Yet, like WT mice, they consumed more glucose than water in 1-bottle, 30-min tests. KO mice, like WT mice, also consumed more glucose than water in 24-h tests and strongly preferred (95%) glucose in subsequent 24-h two-bottle tests. This 24-h preference may represent a learned association between TRPM5-independent orosensory (texture, odor, taste) and viscerosensory sugar stimuli. Since TRPM5 and other taste signaling elements are found in intestinal cells, we next determined if KO mice show a normal post-oral conditioning response to sugar. Water-deprived KO and WT mice were trained 1 h/day to drink flavored water (grape, cherry) paired with intragastric infusions of 16% glucose or water. After 6 one-bottle training sessions, KO, like WT mice, significantly preferred the glucose-paired flavor. Yet, when given 1-h oral glucose vs. water tests, the KO mice were indifferent to the sugar. Thus, KO mice have a substantial sweet taste deficit but an intact post-oral flavor conditioning response to glucose.

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Novel insight into ghrelin secretion in rats. New RAPID method for blood processing

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Ghrelin circulates in acylated (A-Ghr) and desacylated (D-Ghr) forms. A-Ghr stimulates food intake while D-Ghr may modulate A-Ghr's action. Studies describe total ghrelin (T-Ghr) and A-Ghr and ratio of T/A ghrelin in the systemic circulation varying from 1:10 up to 1:50, probably due to not-optimized blood sampling as A-Ghr is rapidly degraded. *Aim:* To assess changes in T-Ghr and A-Ghr serum levels by RIA under different metabolic conditions in rats using a novel method maximizing A-Ghr recovery. *Methods:* Blood was withdrawn at 8AM from ad libitum fed and 24-h fasted conscious rats ($n = 5$/group) with jugular vein catheter. EDTA-blood was processed using the RAPID method (Refrigerated temperatures, Acidic pH, Protease inhibitors, Isotopic recovery standards, Dilution). *Results:* T-Ghr levels increased 2.8-fold after fasting compared to fed rats ($p < 0.001$). A-Ghr levels were also 3-fold higher after fasting ($p < 0.001$). The T/A ghrelin ratio remained 1:5 under both metabolic conditions. A standard blood sampling method (EDTA-blood) resulted in a significant increase in T-Ghr and A-Ghr after fasting, however the ratio was 1:41 and differed from ad libitum feeding (1:19). The standard method resulted in a > 80% A-Ghr loss compared to the RAPID method. *Conclusions:* Fasting increases T-Ghr and A-Ghr levels without influencing the ratio compared to fed rats assessed by the RAPID method that prevents A-Ghr degradation. The low T/A-Ghr ratio and high A-Ghr levels with RAPID compared to standard method points to key importance of proper blood processing before A-Ghr measurement to avoid false estimates.

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Gastric emptying of hexose sugars in healthy humans. Effects of osmolality and molecular structure

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It has been suggested that hexose sugars signal to the brain to slow gastric emptying (GE) via osmoreceptor stimulation in the small intestine; however, equi-osmolar glucose and fructose appear to empty differently, and large inter-individual differences in the responses to sugars are apparent. Therefore, we aimed to (i) examine the effects of hexose type as well as osmolality, on GE and (ii) determine whether GE responses were consistent within individuals.

23 healthy lean adults were studied to evaluate effects of 250, 500 and 1000 mOsmol solutions of glucose, galactose, fructose, and its poorly absorbed analogue, tagatose, using water, NaCl and lactulose as volumetric, and osmotic, controls. GE was assessed using a ^{13}C-acetate breath test. 3 subjects subsequently underwent 32 studies to evaluate intra-individual reproducibility.

At 250 mOsmol, a sugar-specific effect was apparent: tagatose slowed GE ($P < 0.05$) compared with water, glucose and fructose. Fructose ($P < 0.05$), but not glucose and galactose, slowed GE but with substantial inter-individual differences in responsiveness. As the osmolality increased, GE of all hexoses was more potently slowed ($P < 0.001$), and the differences between them were abolished. 500 mOsmol solutions of lactulose and saline did not, whereas equi-osmolar solutions of glucose, fructose and tagatose did, slow GE when compared with water ($P < 0.05$). While inter-individual differences existed in the response to 250 mOsmol solutions of fructose, the response within an individual was consistent. While all hexose sugars slow GE at higher osmolarities, tagatose, and in some subjects, fructose, slowed GE more potently than glucose or galactose at lower osmolality indicating that hexose-specific effects must operate on gut-to-brain signalling.

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Chronic sucrose intake reduces satiety-related activity in hypothalamic oxytocin neurons

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Oxytocin (OT) is one of many peptides thought to play a role in satiety. In light of the inhibitory effect of opioids on the activation of OT neurons, and the hypothesized role of opioids in mediating palatability, we measured whether long-term consumption of a sweet vs. a non-sweet diet would alter OT activity in a manner similar to that of opioids. Male rats were adapted to a food restriction regimen (2 h/day). Half the rats were given a sucrose-based diet for 20 days, while the other half was given a cornstarch-based diet ($n = 14$ per diet group). On the 21st day, half the rats in each group were given the opposite diet, and all diets were removed after 45 min. They were deeply anesthetized and perfused 60 min later. Double immunohistochemical staining (c-Fos and OT) was performed on coronal sections. The percentage of c-Fos positive OT cells in the PVN was significantly reduced in rats fed the sucrose-based diet, regardless of whether they received the sucrose or the cornstarch diet on day 21 ($35.2 \pm 3.5\%$ for starch diet vs. $20.8 \pm 2.7\%$ for sucrose diet, $p < 0.01$). A similar pattern was observed in the supraoptic nucleus. This suggests that sucrose intake reduced activity in the OT system, and that the effect is not an acute effect of sucrose intake. The findings indicate that the consumption of sugar, in addition to providing taste reward, may also decrease activity in pathways that act as satiety systems. Decreased activity of satiety signals, therefore, could lead to overconsumption of foods other than sugar. Supported by NIH DA 021280.

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CD36 deletion is associated with decreased OEA production in the mouse small intestine

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Oleoylethanolamide (OEA) is a lipid-derived satiety factor produced by small intestinal enterocytes in response to fat ingestion. We previously showed that the fatty-acid transport protein CD36 plays a key role in mediating small-intestinal OEA biosynthesis following intra-duodenal fat infusion. Here we examined the impact of CD36 deletion on normal OEA production and feeding behavior in mice. Food intake (FI) was continuously analyzed in adult male CD36-null mice and wild-type C57BL/6J mice (WT) under free-feeding conditions for 12 consecutive days using an automated system. In a separate experiment, OEA levels were measured by LC/MS in a panel of tissues obtained from WT and CD36-null mice sacrificed during the dark or the light phase. OEA levels were lower in jejunum of CD36-null mice. No such difference was observed in other tissues, including duodenum, liver, fat and brain. No change was observed in the uptake of saturated or unsaturated fatty acids in duodenum and jejunum of null mice, compared to WT. Total FI was higher in CD36-null mice. This effect was observed mainly during the light phase and was associated with higher meal frequency and meal size and lower postmeal interval and satiety ratio. No genotype differences were found in plasma cholesterol, triacylglycerols, glucose, β-hydroxybutyrate, leptin, adiponectin or insulin. These results support the hypothesis that CD36 contributes importantly to OEA production in the small intestine. The findings further suggest that CD36-null mice may have impaired satiety, which might be partly due to a decreased OEA signaling.

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Sucrose is more potent to prevent habituation of accumbens dopamine release than corn oil

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It has been proposed that different nutrients and access conditions may differentially affect the food reward system and in turn influence meal size and food choices. To test this, we measured dopamine (DA) release in the nucleus accumbens (NAcc) using chronic microdialysis in Sprague–Dawley male rats ($n = 32$) following an 8-week dietary regimen. Rats received either continuous (7 days a week) or intermittent access (limited to 2 consecutive days each week) to a palatable sucrose solution (27%) or isocaloric corn oil emulsion (12%). Water and regular lab chow were available ad libitum. Rats consumed 2–4 times more sucrose than oil. On access days, corn oil intake gradually decreased to ~50% over the 8-week period, whereas sucrose intake sharply increased by ~50%. Sucrose groups overall consumed significantly more energy from the treats and less from chow compared with the corn oil groups. Upon testing, both meals stimulated DA release in the shell and the core of the NAcc (135–160% relative to baseline), except corn oil in the continuous access group which had no effect on DA. These findings suggest that sucrose compared with dietary fat is more potent in sustained stimulation of the reward system especially when access is unrestricted. A similar effect may contribute to chronic overeating of sweet meals, and may diminish compensation to dietary fat intake when it is presented in combination with sucrose. This research is supported by salesforce.com Foundation and by NIH grants DK065709, DC00240, DK079182.
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Altered taste functions following ROUX-EN-Y gastric bypass surgery

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Although gastric bypass surgery (GBS) mechanically restricts food intake and results in malabsorption, it also appears to reduce appetite and the appeal of savory meals. However, it is unclear why the motivational system fails to drive patients to compensate for this massive weight loss with increased food intake and preference for palatable, calorie-dense foods—the normal homeostatic response. To investigate this paradox, our laboratory examined the effects of GBS on taste and food reward functions. We observed that following GBS, genetic obese and high energy/high fat diet-induced obese rats exhibit a reduced two bottle preference and a decreased lick-response to high concentrations of sucrose compared to sham-operated controls. Semi-chronic single neuron recording in the second central gustatory relay, the pontine parabrachial nuclei (PBN) reveal that GBS alleviates neural deficits in sweet coding independent of the etiology of obesity. Recent data from patients and rats suggest increased glucagon-like peptide-1 (GLP-1) signaling as a potential mechanism for altered orosensory sensitivity to sweet after GBS. Information concerning the underlying neural substrates of the beneficial effects of GBS on long-term weight maintenance could assist in the development of effective non-surgical approaches to obesity treatment. This research is supported by NIH grant DK080899, the PA Tobacco Settlement Fund and the PennState Institute for Diabetes and Obesity.
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A protein and fibre enriched dairy product consumed at breakfast reduces subjective appetite over the morning

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The aim of the study was to assess the effect of a dairy product, consumed within a light breakfast, on the evolution of appetite feelings over the morning. A randomized, cross-over (2 periods) study was conducted in 60 women (age: 27.0 ± 6.2 years; BMI: $23.7 \pm 1.5\ kg/m^2$) who were regular breakfast cereal and dairy consumers. Subjects were trained to the protocol in a specific experimental session. The two study breakfasts were composed of either the test or the control product with a fruit salad and a hot drink. The control product consisted of milk with cereals. The test product consisted of a protein and fibre enriched yogurt with cereals. Study products (170 g, 126 kcal) and breakfasts (495 g, 230 kcal) were isoweight and isoenergetic. Appetite ratings (hunger, desire to eat, prospective consumption, gastric fullness) were collected on Visual Analogue Scales every 30 min over 4 h following breakfast. In comparison with the control breakfast, the calculated composite appetite score was significantly reduced over 4 h after the beginning of the test breakfast ($p < 0.001$). This significant reduction in the appetite score was corroborated by the significant effects on all measured appetite feelings, i.e. reduction of hunger, desire to eat and prospective consumption; increase in fullness feelings (all $p < 0.001$). In conclusion, the protein and fibre dairy product consumed within a light breakfast reduced subjective appetite over the morning. Such product could be helpful for appetite and weight management, although further studies must address its effect on energy balance in chronic conditions.
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A training session to rate appetite feelings increases the robustness of methodology

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The use of Visual Analogue Scale is a recognised methodology to measure appetite feelings. However, subject's appetite assessment practice over several experimental sessions is rarely addressed. We previously observed in cross-over (2 periods, 2 products) appetite study designs, a significant quantitative interaction product by period on the appetite score (a score calculated from VAS of hunger, fullness, desire to eat and prospective consumption). Indeed, the difference between the test and the control products increased by 7.5 mm at period 2 ($p < 0.05$). Our hypothesis to explain this interaction is that on the first experimental visit, subjects narrowed their ratings to the middle of VAS, whereas they used the whole width of the scale at the next visit, whatever the product consumed. This suggests the presence of a training effect on the use of VAS ratings. Therefore, to check this hypothesis and to prevent the training effect on the product evaluation visits, w e introduced in the present study a training session conducted under the same conditions as in the evaluation visits, but with the subject's usual breakfast instead of the test or control breakfasts. The usual breakfast mean energy was slightly higher than evaluation breakfasts. In comparison with the evaluation visits, the appetite score of training visit was 10 mm lower ($p < 0.001$) at baseline, and 7 mm higher right after breakfast consumption ($p < 0.05$), despite having consumed slightly more energy. The slope observed over 4h00 was smaller. Furthermore, no product by period interaction between experimental periods was observed (1 mm difference, $p = 0.8$). In conclusion, with the introduction of a training session, we demonstrated that there was a training effect on use of VAS and we successfully eliminated the product by period interaction. This design, which reduced the heterogeneity of the product effects between periods, is thus increasing the robustness of the overall product effect.
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Dietary carbohydrate interacts with dietary fat to influence leptin responsiveness in rats

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Previously we showed that a 60% kcal fructose, and 10% kcal fat diet induces leptin resistance in rats. All rats fed the 60% kcal fructose diet were thinner than those fed a diet with 17% fructose and 10% fat (LFruc/LF), therefore, we tested leptin responsiveness in rats fed either a 40% kcal fructose and 30% kcal fat (MFruc/HF) or the LFruc/LF diet. An i.p. injection of 2.0 mg/kg leptin inhibited food intake and weight gain of both MFruc/HF and LFruc/LF rats after days 7, 14, and 21 on diet. On day 36, leptin inhibited 14-h energy intake only in LFruc/LF fed rats. To determine whether changes in leptin responsiveness were due to fructose specifically or increased dietary monosaccharide, a second study tested leptin responsiveness in rats fed a 50% kcal glucose and 30% kcal fat diet (HGluc/HF), MFruc/HF or LFruc/HF diet. After 10.5 weeks, i.p. injections of 2.0 mg/kg leptin inhibited 14 h weight gain and food intake in MFruc/HF and HGluc/HF groups but not LFruc/HF rats. These data suggest that dietary fat and carbohydrate have independent effects on leptin responsiveness and monosaccharides may reverse dietary fat-induced leptin resistance. Supported by NIH grant DK053903.
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Endogenous leptin signaling in the NTS is required for energy balance regulation

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Nucleus tractus solitarius (NTS) neurons express leptin receptors (LepR) and intra-NTS delivery of leptin, at hindbrain (4th) ventricle subthreshold doses, reduces food intake and body weight. Here we examine the functional contribution of endogenous leptin signaling in NTS neurons to energy balance control and report that chronic knockdown of NTS LepR [via adenoassociated (AAV)-short hairpin RNA (shRNA) targeting LepR (ObRb) mRNA (LepRKD)] resulted in significant increase in daily body weight gain in rats maintained on high fat diet (60% kcal from fat) compared to rats receiving AAV-shRNA without mRNA target (shCtrl; negative control). Increase in body weight was accompanied by an increase in total body fat mass. There was no alteration in daily energy expenditure between the two groups; rather, the increase in body weight resulted from increased daily caloric intake and reduced sensitivity to vagally mediated satiation signaling. Prior to NTS AAV-shRNA injections, baseline intakes of 15% sucrose following vehicle IP injection were identical, as were the intake suppressive effect of IP cholecystokinin (CCK; 3 μg/kg). Four weeks following NTS AAV-shRNA delivery, NTS-LepRKD rats: (1) consumed significantly more sucrose under vehicle conditions and (2) showed reduced sensitivity to the intake suppressive effects of CCK (no significant suppression of sucrose intake) compared to shCtrl rats. These findings provide direct support for a role of endogenous leptin signaling in the NTS in the control of food intake and energy balance regulation. DK21397 and DK077484.
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Food intake and body image satisfaction

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Environmental factors such as exposure to photos of slim models and recent food intake can alter body image. It is not clear if this dissatisfaction is a result of food intake or of beliefs about the negative attributes of high-calorie foods. To examine this question, body image satisfaction was determined before and after young women ate snack foods considered "healthy" or "unhealthy". Normal-weight women were told they were participating in a study examining the effects of snack food on cognition. Participants completed questionnaires including the 3-factor eating questionnaire, the restraint scale, the body image states scale (BISS), a body size estimation scale, and the profile of mood scale (POMS). Participants were assigned to 1 of 3 conditions: control (no food); "healthy" food (banana), or "unhealthy" food (donut). The two foods contained a similar number of calories. After eating, participants completed cognitive tasks. Participants were then given another set of questionnaires which they were told were to get more information on their lifestyle. The BISS, figure estimation scale, and POMS were included to assess if there was a change in body image or mood after food intake. Consumption of a donut, but not a banana decreased body image satisfaction and increased the estimation of body size. Depression scores decreased from before to after food intake in all conditions. Vigor scores decreased across time in controls, and tension scores decreased in women who had eaten the donut or banana. These results indicate that intake of a food believed to be "unhealthy" can negatively influence body image.
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Observation of eating increases sensory-hedonic evaluation of the observed food

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Eating with familiar diners increases intake although the mechanisms responsible are unclear. Observation of eating may enhance sensory-hedonic evaluation of foods. This is consistent with theories of embodied simulation, which suggest that observation of actions activates the same neural structures involved in our own experiences. We investigated whether viewing a silent video of an actor eating a cookie would increase sensory-hedonic evaluation of a cookie compared with a condition in which the actor was talking (to control for similar motor movements). 43 female students (mean age 19, mean BMI 22) were tested individually at one session. Both videos lasted for 1 min (with a 1 min break) and began with a shot of a cookie to control for cue reactivity. The same female actor maintained a neutral facial expression throughout. Video order was counterbalanced. After each video, participants tasted and rated a cookie using 100 mm line rating scales that assessed liking, strength of taste and sweetness. Participants who guessed the purpose of the experiment when questioned at the end were excluded ($N = 7$). 2-Way repeated-measures ANOVA revealed a significant effect of condition (eating, talking) but no effect rating type (liking, strength, sweetness) and no significant interaction. All ratings were significantly higher in the eating than the talking condition. There was no effect of condition order and no interactions with order. The data suggest that social facilitation of eating may be related to increases in sensory-hedonic evaluation of foods by eating observation.
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Plasma levels of 'adiposity signals' do not reflect adiposity in rats compensating for under- or over-weight

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Leptin and insulin are proposed to signal adiposity and play crucial roles in the regulation of energy balance, yet little is known about their responses after manipulations of body weight (BW). Here we measured leptin and insulin levels and fat pad mass in male LE rats recovering from forced underweight (UW) or overweight (OW). UW were restricted to 60% of baseline food intake until BW was 75% of ad lib-fed, normal weight (NW) rats, and OW were overfed (up to 190 kcal/d) by gastric infusions until BW was 125% of NW. Manipulations were then stopped. Rats were equipped with jugular vein catheters for recurring blood sampling. Basal plasma leptin and insulin were assayed by radioimmunoassay. Fat pad mass was periodically estimated by computerized tomography. At 75% of NW BW, UW had only 35% of NW fat pad mass and reduced leptin and insulin levels. At 125% of NW BW, OW had 380% of NW fat pad mass and increased hormone levels. During recovery these variables all moved towards NW levels, but at different rates. UW leptin and insulin levels did not differ significantly (ns) from NW on d 4, whereas fat pad mass was still 75% of NW on d 30. OW leptin levels were ns versus NW from d 17 on, whereas fat pad mass was still 145% of NW on d 40. OW insulin levels were ns versus NW on d 1–5, and less than NW from d 8 on. These data are inconsistent with the hypotheses that plasma leptin and insulin reflect adiposity and suggest that changes in these hormone levels under our conditions reflect energy balance flux rather than state, i.e., adiposity per se.

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Intra-abdominal and subcutaneous fat pad measurements by computerized tomography in rats and mice

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Computerized tomography (CT) scanners for in vivo imaging of laboratory rodents have recently become available. One, the LaTheta scanner (LCT-100, Aloka, Tokyo, Japan), includes software for automated determination of intra-abdominal (IA) and subcutaneous (SC) fat. To establish the accuracy and sensitivity of this system, we performed cross-sectional scans in male Long Evans rats (200–550 g) and C57Bl6 mice (12–35 g) and used the manufacturer's software or post-mortem dissection to quantify IA and SC fat. Scanned total and dissected IA or SC fat pads were linearly correlated in rats ($r = 0.99/r = 0.99$, $n = 6$) and mice ($r = 0.97/r = 0.97$, $n = 11$). Whole body fat pad mass was not a linear function of body weight. Dissected fat pad samples of 0.5–3 g for rats and 10–100 mg for mice were placed IA or SC in other rodents that were scanned before and after. Percent recoveries (mean ± SD) of the smallest samples in rats were 100.9 ± 0.5% for IA and 106.0 ± 5.4% for SC; recoveries in mice were 97.5 ± 2.7% for IA and 103.3 ± 13.8% for SC. Scans of IA and SC fat between lumbar vertebrae 1 and 6 (L1–L6) were well correlated with whole body IA ($\rho = 0.99$, $n = 19$) and SC fat ($\rho = 0.99$, $n = 19$) in rats and with whole body IA fat ($\rho = 0.96$, $n = 29$), but less so with SC fat ($\rho = 0.67$, $n = 29$) in mice. In conclusion, CT can accurately and sensitively measure IA and SC fat in rats and mice over a wide range of BW, making it a valuable tool for experimental analyses of rodent obesity models.

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Endocannabinoids regulate energy balance in Siberian hamsters

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Siberian hamsters undergo marked seasonal changes in body mass and food intake, and this natural fluctuation serves as an important model for understanding human states of obesity and leanness. Transfer of animals to short, winter-like photoperiods (SD) results in ~30% loss in body mass, and this decrement is regained upon return to long summer-like photoperiods (LD). The neuroendocrine mechanisms responsible for seasonal changes in adiposity are not well understood; gene expression profiles of "classic" regulatory peptides cannot fully explain these effects. The endocannabinoid (EC) system affects appetite and energy balance, and empirical data support the involvement of hypothalamic CB1 receptors in cannabinoid-induced feeding. To determine whether ECs are involved in mediating seasonal changes in energy balance in Siberian hamsters, we examined EC signaling across photoperiods. Specifically, we transferred animals from LD to SD and compared levels of central CB1 receptors to those of LD controls at 0, 2, 6, and 12 weeks ($n = 5$ per group). Effects of CB1 stimulation or blockade on food intake and body mass were also examined in SD- and LD-acclimated animals by administering daily i.p. injections of a CB1 agonist (ACEA) or antagonist (SR141716) for five days ($n = 7$ per group). Immunocytochemical analysis revealed CB1 staining in several CNS regions including the hypothalamus; ongoing analyses will determine seasonal and sex differences in CB1 labeling. Blockade of CB1 reduced food intake in LD and SD hamsters. Collectively, these findings suggest that ECs affect energy balance and may regulate photoperiodic changes in adiposity.

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Plasma endocrine profiles during and following maintenance on a ketogenic diet

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Low-carbohydrate, high-fat ketogenic diets have been popularized for weight loss in recent years. We have previously demonstrated that maintenance on a ketogenic diet (KD) affects multiple neuroendocrine systems involved in energy homeostasis. The present experiments explored the development of these changes over time and the endocrine effects of returning to a chow diet (CH) following 8 weeks of KD consumption. Eighty-eight male Long Evans rats were maintained on KD or CH 8 weeks, after which KD rats were placed on CH for 8 additional weeks. Samples were collected following 1, 4, and 8 weeks of KD feeding, and 1, 4, and 8 weeks after the switch to CH (9, 12, and 16 total weeks). Following 1 week on KD, leptin was significantly increased as compared to CH (CH: 2.6 ± 0.3 ng/mL, KD: 3.8 ± 0.4 ng/mL, $p < 0.05$), as was insulin (CH: 1.4 ± 0.1 ng/mL, KD: 2.5 ± 0.1 ng/mL, $p < 0.05$). At 8 weeks, increased leptin (CH: 7.8 ± 1.3, KD: 14.9 ± 2.2 ng/mL, $p < 0.01$) and decreased insulin (CH: 2.2 ± 0.3 ng/mL, KD: 1.4 ± 0.2 ng/mL, $p < 0.05$) were present in KD rats. The switch to CH in KD rats produced a significant increase in caloric intake at week 16, as compared to CH (CH: 77.3 ± 4.3 kcal, KD: 92.3 ± 3.9 kcal, $p < 0.05$), and significantly increased ghrelin 1 week after the dietary switch and increased insulin 8 weeks after the switch. Collectively, these data demonstrate that maintenance on KD followed by a return to chow results in hyperphagia and enduring endocrine effects.

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Green tea catechin plus caffeine supplementation to a high protein diet has no additional effect on body weight maintenance after weight loss

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Background: Green tea (epigallocatechin gallate (EGCG) + caffeine), and protein each have been shown to improve body weight maintenance (WM) after weight loss. Therefore we investigated the effect of an EGCG–caffeine mixture added to a high-protein diet, on WM after body-weight loss in moderately obese subjects. *Design:* A randomized placebo-controlled double blind parallel trial in 80 overweight and moderately obese subjects, (age: 44 ± 2 (SD) years; BMI: 29.6 ± 2.0 kg/m^2) matched for gender, age, BMI, height, body-mass and with a habitually low caffeine intake. A very low energy diet intervention during 4 weeks was followed by 3 months WM; during the WM period the subjects received a green tea–caffeine mixture (270 mg EGCG + 150 mg caffeine/day), or placebo, both in addition to an adequate protein diet (AP: 50–60 g protein/day) vs. a high protein diet (HP: 100–120 g protein/day). *Results:* Subjects lost 7.0 kg ± 1.6, or 8.2% ± 2.0 body-weight ($p < 0.001$). During the WM phase, WM, resting energy expenditure (REE), fat free mass (FFM) were relatively increased, in both the HP groups and in the AP + EGCG–caffeine mixture group ($p < 0.05$), while respiratory quotient (RQ) and body-fat (FM) were reduced, all compared to the AP + placebo group. Satiety was only increased in both HP groups ($p < 0.05$). The EGCG-caffeine mixture was only effective in the AP diet. *Conclusion:* EGCG–caffeine mixture, as well as a HP diet improved WM independently, through thermogenesis, fat oxidation, sparing FFM, and for the HP diet through satiety; a possible synergistic effect failed to appear.
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Effects of green tea on weight loss and weight maintenance. A meta-analysis

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Introduction: Different outcomes of the effect of green tea on weight loss (WL) and weight maintenance (WM) have been reported in studies with subjects differing in ethnicity and habitual caffeine intake. By conducting a meta-analysis the question whether or not green tea plays a role in body weight regulation can be elucidated. *Methods:* Studies about WL and WM after green tea supplementation (GT) were identified through PubMed and based on the references from retrieved articles. Out of the 49 studies initially identified, a total of 11 articles fitted the inclusion criteria and provided useful information for the meta-analysis. Effect-sizes (mean weight change in treatment versus control group) were computed and aggregated based on a random-effects model. The influence of several moderators on the effect-sizes was examined. *Results:* Catechins significantly decreased body-weight and significantly maintained body-weight after a period of WL ($\mu = -1.31$; $p < .001$). Inhibition of this effect by high habitual caffeine intake (>300 mg/d) failed to reach significance ($\mu = -0.27$ for high and $\mu = -1.60$ for low habitual caffeine intake; $p = .09$). Also the seemingly smaller effect of catechins in Caucasian ($\mu = -0.82$) subjects compared to Asians ($\mu = -1.51$; $p = .37$) did not reach significance. Interaction of ethnicity and caffeine intake was a significant moderator ($p = .04$). *Conclusions:* Catechins or an epigallocatechin gallate (EGCG)-caffeine mixture have a positive effect on WL and on WM. The results suggest that habitual caffeine intake and ethnicity may be moderators, as they may influence the effect of catechins.
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Blockade of abdominal visceral NMDA receptors increases food intake

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Previously we reported that intraperitoneal injection of NMDA-type glutamate receptor antagonists, MK-801 or DCPPene, increase food intake. Furthermore, injection of either antagonist into the fourth ventricle or nucleus of the solitary tract also increases food intake at doses one-tenth to one-hundredth the effective peripheral doses. Finally, increased food intake in response to hindbrain NMDA receptor antagonist injection appears to depend on intact central of vagal afferent terminals. Collectively, these results suggest that hindbrain NMDA receptors participate in the control of food intake. However, recent reports suggest that NMDA receptors expressed on peripheral vagal afferent endings participate in gastrointestinal vagal afferent signaling. In order to test the hypothesis that these peripheral vagal afferent receptors are involved in control of food intake we infused MK-801 (12 ng, 25 ng or 100 ng/30 min) either via the jugular vein, (intravenous) or via aortic catheters with tips positioned adjacent to the aortic–celiac orifice (near celiac). MK-801 (100 ng) significantly increased food intake when infused via the near-celiac route, but not when infused intravenously. Near celiac infusion of 25 ng MK-801 produced a trend to increased intake, while the 12 ng infusion failed to increase intake by either the near celiac or intravenous route. These results are consistent with participation of abdominal visceral NMDA receptor in control of food intake.
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Dietary free glutamate as a moderator of gastric emptying, and its effect on fullness for liquid, semi-liquid and solid meals in humans

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Dietary free glutamate activates taste receptors and elicits a umami taste. It also activates the vagus nerve in the stomach, enhances gastric juice secretion and enrichment of glutamate promotes gastric emptying (GE) of a high-protein liquid diet [Am. J. Clin. Nutr. 89(1):431–5, 2009]. However, its effect on GE and postprandial sensations after regular meals in our daily lives remains unknown. In this study, we examined the effect of free glutamate enrichment (0.5% w/v) on the GE rate measured by ^{13}C breath test and postprandial subjective fullness after corn soup (liquid), rice gruel (semi-liquid meal) and an egg sandwich (solid meal) in humans. Ten or 11 healthy males were included in each crossover tests. Free glutamate significantly increased the lag phase (T_{lag}) for liquid and semi-liquid meals (each 60.6 ± 6.8/53.2 ± 7.2 min, 48.5 ± 17.8/44.0 ± 19.3 min, glutamate +/−, mean ± S.E., $P < 0.05$), suggesting that glutamate delays the early phase in GE. Glutamate increased the half emptying time (181 ± 63/150 ± 52 min, glutamate +/−, mean ± S.E., $P < 0.01$) for solid meal without affecting the T_{lag}. Free glutamate increased fullness after the liquid meal ($P < 0.05$). These data indicate that free glutamate moderates GE of all types of meals tested and it enhances fullness. Taken together with previous report, these data suggest that dietary free glutamate modulates GE depending on ingredients or nutritional factors of food ingested and its effect might be relevant to satiety.
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Exploring expected satiety for common foods with a novel psychophysical methodology

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Expected satiety is an important determinant of self-selected portion size, which in turn is a good predictor of amount eaten. Expected satiety is also highly related to familiarity: more familiar foods are expected to confer more satiety. We hypothesized that familiarity with eating a food to fullness may be the critical factor which informs expected satiety. A Method of Constant Stimuli (MOCS)-based procedure measured expected satiety for 7 common foods. Judgments were made as to which of a pair of foods would confer more satiety if eaten. The portion size of one food was held constant whilst the other varied. All foods were paired together. Two of the foods were then eaten to self-reported satiety (at least 500 kcal). Following this the MOCS task was completed again. This procedure was repeated 3 times within 2 weeks. The MOCS task alone was completed 3 more times over the following month. 56 participants (mean age 24) took part. A significant increase in expected satiety for the less familiar food (a candy) emerged for those participants who ate it, but no significant increase in expected satiety emerged for the more familiar food (chocolate). A significant correlation between magnitude of change in expected satiety for the candy (before/after eating) and baseline level of familiarity with eating it to fullness was also seen. Thus it appears that eating an unfamiliar food to satiety causes a persistent change in expectations associated with that food. This finding sheds new light on expected satiety, an aspect of dietary learning which has significant implications for intake/weight management.

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Instrumental learning reinforced by hunger in rats

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Learning processes play a major role in controlling intake of food. Studies were conducted to investigate anticipatory learning in laboratory rats, using training on two lengths of fasting (short: 2–3 h, long: 8–10 h) to test their ability to predict the postingestive effects of a particular food from its sensory characteristics. We demonstrated that an animal can anticipate the duration of subsequent food deprivation from predictive sensory qualities of a food, and hence increase the amount eaten of that cueing food. Anticipatory eating is learnt when a choice is given between protein- and carbohydrate-rich foods and on a single balanced test food. The learnt extra intake of food is instrumental to preventing the return of hunger, removal of which negative reinforcement extinguishes the response. Learning of anticipatory eating competes with classical conditioning of sensory preference. Conditioning of preference is likely to be stronger with the shorter than with the longer length of fasting. Therefore, the difference between intakes before the long and the short fast at each trial is the summed result of these two mechanisms of acquired increase in intake. Depletion-avoidance increases for as long as has been tested, with interruptions of rapid self-extinction and re-learning. This self-extinction contributes to the homeostatic character of this learning. High-fat maintenance diet attenuates the learning of anticipatory eating. The findings provided robust evidence that eating in rats can be controlled by instrumental learning reinforced by hunger.

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Body–brain signaling and mechanisms for central synthesis of salt appetite

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In many mammals a salt appetite is generated in response to a body sodium deficit. Unlike the classic sensory systems (vision, taste, etc.), there is no single dedicated receptor or sensory organ for detecting a sodium deficiency. The seeking and ingestion of salty solutions associated with salt appetite relies on the central nervous system receiving hormonal and afferent neural signals derived from the periphery. In effect, the generation of salt appetite is the result of the integration of systemically generated information and a central synthesis by the brain to create this motivational state. This presentation will discuss the (1) varied sources and nature of systemic hormonal and neural signals that are used to inform the central nervous system of a sodium deficiency, (2) portals of entry to the brain of these stimuli, and (3) key brain structures where these types of information from multiple sources are processed to generate a hunger for salt. This work was supported by NIH grants HL-14388 and DK-066086.
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Ghrelin alters the appetitive and consummatory response to learned cues associated with food

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The obesity epidemic may be partially mediated by exposure to food-paired cues that are capable of initiating intake under conditions of satiety. The mechanism is unclear, but may involve ghrelin, an orexigenic peptide that alters responses to conditioned place stimuli and neural responses to food images in non-homeostatic feeding nuclei. We tested whether a ghrelin antagonist alters the influence of food-paired cues on performance of instrumental responses that earn food and the consumption of food itself using tests of Pavlovian-to-instrumental transfer (PIT) and potentiated feeding (PF), respectively. When food restricted, rats received Pavlovian training where an auditory cue was paired with sucrose delivery, as well as separate lever training for sucrose. Following training and 7d ad lib access to food, rats were then injected with either a ghrelin antagonist or saline prior to testing. Half the rats were tested for PF feeding, whereby we assessed the ability of the sucrose-paired cue to elevate feeding relative to baseline. The remaining rats were tested for PIT in which the capacity of the cue to augment lever pressing was assessed in the absence of sucrose. While saline-treated rats showed both PF and PIT, the preliminary results suggest that the ghrelin antagonist disrupted these effects. Fos also was differentially expressed based on drug condition and experimental test. These results suggest a role for ghrelin in cue-associated food intake and procurement under sated conditions. NIH DK19302; MH53667; MH60179.
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Estrogen effects on neural activation in circumventricular organs in response to hyperomolality

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Previous studies from our laboratory showed that ovariectomized (OVX) rats treated with estradiol benzoate (EB) had a shorter latency to begin drinking water when given a slow hypertonic saline (HS) infusion compared to control OVX rats. The decreased latency was not due to HS differentially affecting plasma osmolality or volume, suggesting that differences in latency could be due to differences in the ability of the central nervous system to detect hyperosmolality. Circumventricular organs (CVOs) are CNS structures with an incomplete blood-brain barrier and therefore, are able to detect changes in plasma osmolality. Moreover, CVOs are critically important in mediating central activation by and responses to osmotic challenges. Accordingly, we used fos-immunoreactivity as a marker for neural activation to determine whether there were differences in neural activation in EB-treated and control OVX rats in response to hyperosmolality. We found no differences in activation in forebrain CVOs between EB and control OVX rats after HS infusion. These findings suggest that the behavioral effects after EB treatment are not attributable to EB-mediated alterations in the detection of osmotic stimuli by forebrain CVOs. Interestingly, HS-induced neural activation in the hindbrain CVO, the area postrema (AP), was attenuated in EB-treated rats. One possible explanation for this observation could be that estrogen increases AP sensitivity to hyperosmolality; thus, less activation is required to stimulate drinking behavior in response to a salt load.

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Oral sensory stimulation with alcohol lowers serum free fatty acids in women

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Background: Preingestive or cephalic phase responses, triggered by sensory stimulation of nutrients, influence the organism's digestive and endocrine responses and substrate mobilization. *Objective:* To determine whether oral alcohol exposure provokes cephalic phase responses in normal-weight and overweight women. *Design:* In a semi-randomized, open label, crossover trial, eleven normal-weight (BMI 19–25 kg/m^2) and eleven overweight (BMI 27–35 kg/m^2) postmenopausal women sham-fed, after an overnight fast under three separate conditions four weeks apart, 41 g cake (750 kJ), 25 cL white wine (750 kJ; ~26 g alcohol) or 25 cL water. Venous blood was drawn prior to and for 30 min after two 3-min episodes of modified sham feeding (MSF). Blood samples were analyzed for free fatty acid (FFA), triglyceride, glucose, pancreatic polypeptide (PP), insulin and alcohol concentrations. *Results:* Area under the curves (AUC) of FFA concentrations differed significantly ($P < 0.001$) between the three treatments but not between BMI categories ($P > 0.05$). After sham feeding white wine, mean FFA concentrations dropped to a minimum of $77 \pm 3\%$ of baseline concentrations at $t = 12 \pm 2$ min after baseline and returned to baseline at $t = 30$ min, whereas mean FFA concentrations after MSF with cake and water gradually increased. AUC of triglycerides, glucose, PP and insulin concentrations did not differ between the three treatments ($P > 0.05$). *Conclusions:* Oral sensory stimulation with alcohol elicits a cephalic phase response by decreasing free fatty acid concentrations. This effect is independent of BMI.

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Postprandial peripheral N-acylethanolamides are associated with free fatty acids but not with sensations of appetite and well-being in young normal-weight women

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Introduction: Mounting evidence suggests a role of the endocannabinoid system in appetite regulation and rewarding value of food intake. However, to what extend plasma endocannabinoids (EC) and related N-acylethanolamides are involved in the regulation of appetite and well-being is unknown. *Objective:* To explore whether a meal with or without alcohol affects peripheral EC and related compounds and whether these compounds are related to subjective sensations of appetite and well-being. *Design:* Twenty-four young normal-weight women consumed a standardized meal (kJ) with beer or alcohol-free beer in a randomized, crossover study. Sensations of appetite and well-being and venous blood samples for glucose, insulin, free fatty acids (FFA) arachidonoylglycerol (2-AG) and the N-acylethanolamides anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) were sampled before and frequently after a meal. *Results:* Postprandial sensations of appetite and plasma N-acylethanolamides but not 2-AG concentrations decreased after both meals whereas glucose and insulin levels and sensations of well-being increased (all $P < 0.05$). Beer consumption with the meal dampened glycemia and postprandial decreases in PEA and OEA compared to alcohol-free beer. No correlations were observed between postprandial changes in EC concentrations and sensations of appetite or well-being (all $P > 0.05$). However, postprandial changes in FFA were highly correlated with changes in AEA, PEA and OEA (All $r > 0.85$; $P < 0.01$), independent of alcohol consumption with the meal. *Conclusion:* The strong associations between postprandial changes in several circulating N-acylethanolamides with changes in FFA suggest that peripheral N-acylethanolamides are a mere reflection of FFA levels rather than predictors of appetite and well-being.

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The impact of a western diet on higher-order discrimination learning and blood–brain barrier integrity in rats

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Saturated fats and simple carbohydrates, two of the primary components of a modern western diet, are associated with cognitive impairments in both humans and nonhuman animals. In rats, these dietary components have been shown to disrupt hippocampal-dependent learning and memory; however, little is known about their effects on cognitive processes that do not require an intact hippocampus. We examined the impact of maintenance on a diet high in saturated fat and glucose (high-energy, or HE-diet) compared to a standard chow diet on the ability of rats to solve discrimination tasks which differed with respect to their dependence on the structural integrity of the hippocampus. Our results showed that the HE-diet produced a selective impairment in a hippocampal-dependent feature negative discrimination (A+, X → A−), while preserving performance in feature positive (A−, X → A+) and non-conditional (B+, C−) discrimination learning, two tasks that are not sensitive to hippocampal damage. We then explored the hypothesis that the effects of consuming HE-diets on hippocampal function are linked to increased blood–brain barrier (bbb) permeability. We found that the HE-diet produced an increase in bbb leakage of sodium fluorescein in the hippocampus, but not in the striatum and the prefrontal cortex. These results show that hippocampal function is particularly vulnerable to disruption by HE-diets, and that this disruption may be related to the effects of this type of diet on bbb integrity.

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Mood changes associated with carbohydrate quality (CQ) during weight loss

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Weight loss generally improves mood. High dietary CQ (e.g., ↑ fiber, whole grains; ↓ refined grains (RG)) may also improve mood. We examined mood changes associated with CQ during energy restriction (ER) in a 6-week randomized trial ($n = 33$; aged 39 ± 7 year; BMI 30 ± 4 kg/m^2). Subjects received ∼50% of daily target energy intake with CQ varied by amount of legumes (beans) provided per d, 6 d/wk (low: 1 T, med: 0.5 c, high: ∼2–2.5 c). Self-selected CQ was determined from multiple-pass 24 h dietary recalls. Mood was measured using daily ratings (9-pt scale) and the Profile of Mood States (POMS). Over the 6 weeks, all groups lost weight (1.8–3.8 kg), and total mood disturbance, anger, irritability, and mental fatigue improved ($p \leq 0.05$). From weeks 4–6, the high bean group had ↓ anger and ↑ concentration ($p \leq 0.05$). Among subjects, greater weight loss was associated with ↑ concentration, but also ↑ anxiety and boredom ($r = -0.35$ to -0.49; $p \leq 0.06$). Independent of weight loss, reduction in self-selected RG over weeks 0–3 was associated with improved mood (↓ anxiety, irritability, mental fatigue; ↑ concentration, happiness). From weeks 4–6, CQ associations with mood were mixed. High CQ during ER may help improve some mood states. Funding: Pulse Canada.

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CCK-1R reduces food intake in single meals in women

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This study was done to determine the dose of a CCK1 receptor agonist that would significantly reduce food intake in women of normal weight during instructions to eat to satisfaction and to binge eat. Although IV infusions of CCK reduce food intake in humans, the IV route is impractical therapeutically. However, an orally administered CCK receptor agonist, as used in this study, could prevent overeating at single meals. To test this hypothesis, twenty-three women each ate two macaroni and beef meals (1.2 kcal/g), following a screening meal 20 min after a 500-gram preload of tomato soup. Each participant received both the drug and the placebo on separate days in counterbalanced order. Either the receptor agonist GSK GI181771X or placebo was administered 10 min before the soup, at dose levels of 1 mg for the first four subjects, 2 mg for the next four, and 4 mg for the next eight, with the instruction to eat until satisfied. Seven additional subjects received the 4 mg dose with the instruction to binge eat. There was no difference in food intake between placebo and drug for the two lowest doses, but the food intake after the 4 mg dose was significantly ($p = 0.007$) less by128.19 g (±41.6 SE) after drug than saline, without any adverse side effects in subjects instructed to eat until satisfied. When subjects were instructed to binge eat, intake was significantly less ($p = 0.003$) after drug than saline by156 g (±44.6 SE). These results indicate there is a potential application of a CCK receptor agonist to treat binge eating in patients with eating disorders.

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Role of TTF-1 in the hypothalamic control of hyperphagia induced by streptozotocin

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Thyroid transcription factor-1 (TTF-1) is a member of the NKx family of homeodomain genes and plays an important role in the control of neuroendocrine functions. Recently, we reported that a novel role of TTF-1 in the regulation of feeding behavior in the rat hypothalamus. Blockade of hypothalamic TTF-1 significantly reduced hyperphagia induced by food deprivation. Furthermore, expression of TTF-1 was significantly increased in the hypothalamus from fasted rats [mRNA (3.6-fold increase, $P < 0.01$) and protein (2.2-fold increase, $P < 0.05$)]. To determine whether TTF-1 is involved in diabetic hyperphagia, we investigated expression of TTF-1 in streptozotocin (STZ)-induced diabetic rats. STZ-induced diabetic rats showed hyperphagia and weight loss compared with control rats. Hypothalamic TTF-1 synthesis was significantly increased in the diabetic rats [mRNA (2.4-fold increase, $P < 0.05$) and protein (3.3-fold increase, $P < 0.01$)] as compared with control rats. In addition, blockade of hypothalamic TTF-1 synthesis by intracerebroventricular administration of an antisense TTF-1 oligodeoxynucleotide markedly reduced diabetic hyperphagia (36.7 g/day vs. 25.8 g/day, $P < 0.05$) and changed expression of neuropeptides related to feeding behavior [NPY (1.9-fold decrease, $P < 0.05$), AGRP (1.3-fold decrease, $P < 0.05$) and POMC (1.6-fold increase, $P < 0.05$)]. These data suggest a possible connection between hypothalamic TTF-1 synthesis and diabetic hyperphagia.

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Effects of video game console and snack type on snack consumption during play

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Past research has shown the effects of distraction on food intake. The present study examined the effects of snack type (healthy, unhealthy, and neutral) on snack consumption while playing a variety of video game consoles. Participants wore a device to measure the amount of their movement during the session. For one of the conditions, the participants played the Nintendo Wii boxing game that comes equipped with Wii Sports. For another condition, the participants played the Xbox version of Rocky Legends on exhibition mode. In both gaming conditions, the participant warmed-up for five minutes and then continued to play for the duration of the fifteen-minute session. The third condition was used as a control, and the participants sat in an empty room for the duration of the 15 min. Before and after the video game play or the control session, the participants' physiological measurements were taken. Three different snack types (healthy, unhealthy, neutral) were left in the room. For each participant, 38 grams of pretzels, 160 g of carrots, and 100 g of M&M's were presented. Overall activity level was greatest in the Wii condition, indicating significantly more calories burned, and participants ate less in that condition. Although both the Wii and Xbox conditions showed less snack consumption in general, participants ate more healthy snacks in the Wii condition.

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Acute surges of blood glucose affect pontine taste processing differentially in lean and obese rats

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Recently, we have demonstrated altered taste processing in the brainstem of obese rats. To investigate potential underlying mechanisms, we compared the effects of acute changes in blood glucose levels (BGL) on gustatory activity in the pontine parabrachial nuclei (PBN) of prediabetic, obese Otsuka Long Evans Tokushima Fatty (OLETF) and age-matched lean LETO rats. We used semi-chronic extracellular single neuron recording while stimulating the tongue with NaCl, citric acid, and sucrose (0.1, 0.3, 1 M). The analysis included taste responses from 47 neurons, before and after peripheral administration of dextrose (1.25 g/5 ml, i.p.), following an overnight fasting. Whereas dextrose overall increased taste responses as a function of concurrent BGL, the magnitude of the effects and the across neuron pattern was significantly different in obese and lean rats. Sodium-best neurons displayed significantly larger responses to NaCl and all concentrations of sucrose but not citric acid in obese compared with lean rats (+72% vs. +25%; +60% vs. +35%; +39% vs. +38%, respectively). In contrast, sucrose-best units in obese rats responded more rigorously only to NaCl (+68% vs. +18%), but showed no change to 1.0 M sucrose (+23% vs. −6%) following dextrose. These findings demonstrate that BGL affect taste processing in the PBN, suggesting a role for across neuron code for sweet taste in the altered sensitivity to this satiety signal in obese rats.

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Effects of increasing the portion size of fruit and vegetable side dishes at a meal on children's intake regulation

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The portion size (PS) of foods has been identified as an important environmental factor to influence children's intake. It remains to be investigated if increasing the PS of healthy foods, such as fruits and vegetables (F&V), can be used to increase children's intake of these foods and displace intake of other, more energy dense foods at a meal. The aim of the present study was to examine the effects of doubling the PS of F&V side dishes on children's food and energy intake at a meal. Forty-three children (22 boys, 21 girls), ages 5–6 years, were served dinner once a week for 2 weeks. Each dinner consisted of pasta with tomato sauce, three F&V side dishes (broccoli, carrots, applesauce), and milk. The PS of the F&V was doubled between experimental conditions while the size of the pasta and the milk remained constant. Doubling the PS of the side dishes resulted in a 43% increase in children's intake of the fruit side dish ($P = 0.001$), but did not affect their intake of the two vegetable side dishes ($P > 0.60$). Further, when the PS of F&V was doubled, children ate significantly less of the pasta ($P = 0.04$). The difference in meal energy intake (19.5 ± 16.3 kcal) and food intake (10.3 ± 16.3 g) between portion size conditions was not significant ($P > 0.24$). Variations in PS can be used to increase children's intake of fruits. More studies are needed to test different strategies to also promote children's intake of vegetables.

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Eating behaviors of children in the context of their family environment

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The finding that "obesity runs in families" suggests that shared genes operate in a particular family environment which may be conducive to overeating and excessive weight gain in children. It is important to identify intermediary behavioral eating traits which promote this increased energy intake and weight gain in children and to determine the extent to which the association between eating traits and excessive weight gain in children may be influenced by genetic factors, environmental factors, or both. The focus of this talk will be to review and discuss data from both short-term experimental and longitudinal studies on eating behaviors of children at various stages in their lives. Amongst others, these data will include behavioral data from a prospective cohort study of children who were born at high or low risk of obesity based upon maternal pre-pregnancy body mass index. Select eating traits will be further examined in the context of children's home environment and their familial predisposition to obesity. Findings from this research may provide important insights as to how modifications to the food environment or food properties can be used strategically to moderate energy intake and promote intake of healthy foods in children, especially those who may be at risk for obesity. The merit of behavior genetics designs which can partition genetic and environmental sources of variability in behavioral traits will be discussed.

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Weight loss is a mediator of cardiovascular and behavioral responses to stress

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This study examined the influence of body weight on the cardiovascular and behavioral responses to acute and chronic stress. Male rats were implanted with telemetry devices to continuously record cardiovascular parameters. Two weeks later testing began and rats were either fed ad libitum (CON), exposed to 7 days of chronic variable stress (CVS) or food restricted to produce the weight loss (WL) that occurs during CVS. One week after the cessation of CVS rats were given a 30 min restraint challenge and mean arterial pressure (MAP) and heart rate (HR) were recorded. Following restraint, the MAP and HR of WL rats recovered to baseline more quickly than that of CVS or CON. To determine the behavioral consequences of this attenuated cardiovascular response, rats were once again exposed to the CON, CVS (14 days) or WL conditions. 24 h after the cessation of CVS all rats were acclimated to a fear-conditioning chamber, given 5 unpredictable shocks and then returned to home cages for recovery and recording of cardiovascular parameters. The next day, rats were re-exposed to the chamber and freezing behavior was scored. Similar to the restraint challenge, the MAP and HR of WL rats recovered to baseline more quickly following shock. Interestingly, the WL rats had significantly less freezing behavior during re-exposure to the chamber when compared to that of CON and CVS groups. One interpretation of these results is that weight loss blunts the cardiovascular response to stress and promotes resiliency to a conditioned aversive stimulus.

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Voluntary exercise and CNS control of energy balance

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The metabolic and health benefits of physical exercise are in part secondary to changes in CNS control of energy balance. These mechanisms are still poorly understood. To study the effect of voluntary PE on energy balance (EB) and body composition, 3-month-old male C57B6J mice fed standard chow were exposed to mobile or blocked running wheels (RWSC & SEDSC). Daily food intake (FI) and running wheel (RW) activity (distance and velocity) were monitored. Body weight (BW) and composition (measured by NMR) were measured at baseline and every 2 weeks. After 6 weeks, BW among groups was similar, but RWSC mice lost significantly greater amount of fat mass compared to SEDSC (-0.77 ± 0.11 vs -0.18 ± 0.27 g in RWSC vs SEDSC, $p < 0.001$). Despite the fat mass loss, RWSC mice had similar daily FI (ANOVA $p > 0.05$). To determine whether voluntary PE prevents diet-induced obesity, a cohort of mice was fed a high fat diet (60%) with or without mobile RWs (RWHF, SEDHF). At 6 weeks, SEDHF gained significantly more fat mass than RWHF (9.39 ± 0.84 vs 2.31 ± 0.67 g in SEDHF vs RWHF, $p < 0.001$). Daily FI was similar in both groups (ANOVA $p > 0.05$). In agreement with previous studies, PE-induced weight loss does not trigger compensatory increase in FI. The lack of hyperphagia with significant fat loss suggests that PE alters CNS regulation of EB leading to the defense of a lower fat mass, regardless of dietary fat content. Thus, the beneficial effects of PE involve modification of CNS circuitries that are still unidentified. Using markers of chronic neuronal activation (ΔFosB) and immunohistochemistry we are currently investigating what CNS circuits are activated by PE in our studies.

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Brain mechanisms of infection-induced anorexia

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Bacterial lipopolysaccharide (LPS) and other microbial substances trigger the organism's acute phase response and cause anorexia. Anorexia during peripheral infections is mediated mainly through increases in circulating pro-inflammatory cytokines, but how this stimulates the brain to inhibit eating is not fully resolved. One emerging mechanism involves the stimulation of COX-2 in blood brain barrier endothelial cells and the subsequent release of prostaglandin-E_2 (PGE_2). Also, several findings indicate that serotonin (5-HT) neurons in the midbrain raphe (dorsal raphe [DR] and median raphe [MnR]) are targets of PGE_2 and that 5-HT projections from the midbrain raphe to the hypothalamus are crucial for LPS anorexia. Thus, (1) LPS increased the number of c-Fos expressing cells in midbrain raphe 5-HT neurons, the hypothalamic PVN and several other sites, (2) IP pretreatment with the specific COX-2 inhibitor NS-398 reduced or eliminated LPS-induced c-Fos in these areas, (3) IP or local DR injection of NS-398 reduced LPS anorexia, (4) midbrain raphe injection of a $5\text{-}HT_{1a}$ autoreceptor agonist or IP injection of the $5\text{-}HT_{2c}$ receptor antagonist SB 242084 reduced LPS anorexia, and (5) SB 242084 reduced LPS-induced c-Fos in the PVN and other sites. 5-HT neurons connect to hypothalamic POMC neurons through $5HT_{2c}$ receptors, and MC4 receptor signaling has also been implicated in the mediation of LPS anorexia. In sum, these data indicate that LPS- and cytokine-induced increases in PGE_2 signaling activate pathways which converge on central neural circuits that control normal eating and suggest a prominent role for 5-HT projections from the midbrain raphe to the hypothalamus.

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Systemic administration of sodium butyrate intensifies LiCl-induced c-Fos and phospho-acetyl-histone H3 in the amygdala

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Chromatin modification such as acetylation and phosphorylation in the transcriptional region is necessary for optimal gene expression, and expression may be increased by inhibiting histone deacetylase activity. A high dose of lithium chloride (LiCl) increases c-Fos expression in the central amygdala (CeA). Continuing our studies on gene expression in the amygdala in conditioned taste aversion (CTA) learning, we investigated if (1) LiCl-induced c-Fos expression in the CeA is correlated with histone acetylation and phospho-acetylation and (2) if sodium butyrate (NaB, a histone deacetylase inhibitor) has effects on LiCl-induced c-Fos expression and CTA learning in rats. LiCl (0.15 M, 12 ml/kg, i.p.) highly increased the levels of acetylation and phospho-acetylation of histone H3 in the CeA. The time courses of these increases corresponded to the LiCl-induced c-Fos time course. Moreover, LiCl-induced c-Fos co-localized with phospho-acetylated histone H3 in a majority of LiCl-induced c-Fos-positive cells in the CeA. NaB (0.3 M, 0.4 g/kg, i.p.) significantly increased the levels of LiCl-induced c-Fos and phospho-acetylated histone H3 in the CeA, however it did not strengthen CTA learning. These results suggest a possible correlation between LiCl-induced c-Fos expression and modification of histone H3, especially phospho-acetylated histone H3, in the CeA.

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Intrameal IP Exendin-9 (Ex-9) infusion blocks the satiating effect of exogenous GLP-1, but alone fails to increase meal size

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Brief, intrameal, hepatic portal vein or IP GLP-1 infusions selectively reduce spontaneous meal size in rats [Rüttimann et al., Endocrinology 150:1174, 2009]. Here we examined the physiological significance of endogenous GLP-1 for meal size by testing the effects of the GLP-1 receptor antagonist Ex-9 on spontaneous eating and on the satiating effect of exogenous GLP-1. Adult male rats ($n = 15$–16) equipped with IP catheters received remotely controlled infusions (2.5 min, 0.2 ml/min) beginning 2 min into the 2nd (Ex-9 alone) or 1st (Ex-9 + GLP-1) nocturnal meal. Infusions of 10 or 30 nmol/kg Ex-9 vs. vehicle (V) did not affect meal size (10 nmol/kg, *V*: 2.5 ± 0.3, Ex-9: 2.0 ± 0.3 g; 30 nmol/kg, *V*: 2.0 ± 0.2, Ex-9: 1.8 ± 0.2 g, mean $\pm$ SE, *P*s > 0.05) and decreased rather than increased meal duration (10 nmol/kg, *V*: 14.9 ± 1.8, Ex-9: 9.5 ± 1.3 min; 30 nmol/kg, *V*: 11.9 ± 2.7, Ex-9: 4.6 ± 0.4 min, *P*s < 0.05). Subsequent meals and cumulative food intake were not affected. Infusions of 30 nmol/kg Ex-9 abolished the satiating effect of 10 nmol/kg GLP-1, but again did not increase meal size by itself (*V*: 2.6 ± 0.2; Ex-9: 2.5 ± 0.2; GLP-1: 2.1 ± 0.2; Ex-9 + GLP-1: 2.8 ± 0.3 g; ΔV/GLP-1 > ΔEx-9/Ex-9 + GLP-1, $P < 0.05$). These data show that a dose of Ex-9 that is sufficient to block the satiating effect of exogenous GLP-1 fails to increase meal size when administered under comparable conditions alone. This questions the physiological relevance of endogenous GLP-1 for the control of meal size under the present conditions.

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Gastric and vagal afferent ghrelin system is altered by high fat (HF) diet in diet-induced obese rats

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The vagal afferent pathway is involved in nutrient sensing and appetite regulation. Chronic HF diet increases expression of ghrelin receptor GHSR1a in rat nodose ganglia (Paulino et al., AJP Endo, 2009). The present study aimed to further characterize changes in the vagal afferent and gastric ghrelin system in response to a HF diet. Sprague–Dawley rats (Harlan, San Diego) were fed 10% low-fat (LF) or 45% HF diets; plasma and tissues (stomach, nodose ganglia) were collected at 8 weeks. mRNA for ghrelin, GOAT (ghrelin O-acyltransferase), GHSR1a and PC1/3 (prohormone convertase 1/3) was measured by Taqman RT-PCR and protein determined using Western blots. Diet-induced obese (DIO) rats ($n = 5$) had increased body weight and energy intake compared to LF ($n = 5$) or diet-resistant rats (DR, $n = 5$) ($p < 0.05$). Fasted and fed plasma insulin and leptin were significantly elevated in DIO compared to LF or DR rats ($p < 0.01$). Plasma ghrelin of DIO rats decreased in the fed state compared to LF or DR rats ($p < 0.05$). Ghrelin, GHSR1a and PC1/3, but not GOAT, mRNA was detected in vagal afferent neurons; ghrelin and PC1/3 expression were significantly lower ($p < 0.05$) in DIO rats compared to DR with an increase in GHSR1a expression. Western blot analysis of gastric mucosa demonstrated a significant decease in PC1/3 ($p < 0.05$) but no significant changes in ghrelin or GHSR1a. Changes in ghrelin signaling in the gut–brain axis in HF feeding may result in hyperphagia and weight gain.

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Intended use of controlling child-feeding practices is related to maternal weight status and planned choice of feeding method

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Breast-feeding promotes a permissive child-feeding style after weaning as both self-reported and observed use of control are lower in mothers who breast-fed and are related to the amount of time breast-feeding continued. Recently we demonstrated that maternal use of controlling strategies begins in early infancy (0–26 weeks) than previously thought. Infant-feeding style depends on feeding method, as breast-feeding mothers were less likely to limit or encourage milk intake compared to those who used formula exclusively. Even a short experience of breast-feeding promoted an infant-led feeding style as mothers who ceased breast-feeding by 7 days postpartum were less controlling than formula users. Here we explore intended use of maternal control and the influence of prenatal weight status. Women in the 2nd or 3rd trimester of their first pregnancy self-reported prenatal height and weight, use of dieting during pregnancy, attitudes and beliefs about infant feeding, and a prospective version of the Child Feeding Questionnaire. Participants were grouped by chosen feeding method: formula from birth ($N = 49$), breast-feed 6 weeks ($N = 44$), breast-feed 26 weeks or longer ($N = 191$). There was significant effect of group on intention to limit [$F(2, 279) = 20.5$, $P < 0.001$] or encourage feeds [$F(2, 279) = 19.6$, $P < 0.001$]. Intention to control was lowest in those who planned to breast-feed for 26 weeks. There was a significant correlation between maternal BMI and intention to limit feeds ($P < 0.05$) but not with encouragement to feed. In addition, dieting during pregnancy was correlated with intention to limit ($P < 0.001$) and encourage feeds ($P < 0.001$). These data suggest that antecedents of maternal overcontrol are present before birth and may influence the extent to which breast-feeding promotes a hands-off feeding style.

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Satiety and glycemic index of potatoes in relation to other carbohydrate-rich test meals

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The potato has been viewed as a high glycemic index (GI) food that may increase appetite and therefore to be avoided while dieting. We investigated the satiety of common carbohydrate-rich side dishes of various GIs. Twelve healthy normal-wt participants (6m, 6f), aged 22–30, consumed 5 test meals (baked potato, mashed potato, pasta, brown rice, and white bread) in randomized order followed 2 h later by an ad libitum lunch. All test meals contained 240 kcal, 50 g of carbohydrate, and were similar in protein, fat, and fiber. Appetite ratings preceded blood draws which took place first at 10 min prior to the test meal, and then at, 0, 15, 30 60, 90 and 120 min. The white bread was used as the GI reference. For appetite ratings, no significant differences were found in "hunger" or "fullness" AUC (area under curve). However, "desire to eat" AUC for baked potato and brown rice were lower than that for pasta ($p = .03$ and $p = .004$). At 120 min, the baked potato was associated with a lower "how much could you eat right now" than brown rice ($p = .04$). The ad libitum lunch energy intake did not differ and was not correlated with "fullness" AUC ($r = -.21$). "Fullness" AUC and GI across test meals were also not significantly correlated. There was also no significant relationship between test meal GI and fullness. Although the potato meals produced somewhat greater satiety, this did not translate into differences in energy intake at a subsequent meal.

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Effects of stress on food choice and intake in the absence of hunger

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Background: Eating behavior can be influenced by the rewarding value of food, i.e. liking and wanting, which in turn can be influenced by stress. It is hypothesized that stress diminishes the reward response. *Objective:* Assess the effects of stress on the rewarding value of food in normal weight dietary unrestrained (NU)/restrained (NR) and visceral overweight (VO) subjects in the absence of hunger. *Methods:* Subjects (13 NU, age = 26 ± 9 year, BMI = 22 ± 2 kg/m^2; 14 NR, age = 25 ± 9 year, BMI = 22 ± 2 kg/m^2; 15 VO, age = 36 ± 12 year, BMI = 28 ± 1 kg/m^2) came to the university twice, fasted, for either a rest or stress condition (randomized). During each test session rewarding value, i.e. liking and wanting, for 72 items divided in 6 categories (bread, filling, drinks, dessert, sweets, and stationery) was measured twice using a computer test, each time followed by a wanted meal. Appetite profile, heart rate, serum cortisol, mood state and level of anxiety were measured. *Results:* High hunger, low satiety (22 ± 20, 64 ± 19 mmVAS) confirmed fasted state. Consumption of 1st meal decreased hunger, increased satiety ($p < 0.0001$), decreased ranking of liking of bread and increased ranking of liking of stationery. Wanting for food decreased from the 1st to 2nd meal in rest in NR and VO and in stress in NR only. Rest vs. stress: was confirmed by heart rate, anxiety and hostility ($p \leq 0.03$); VO showed higher fat and carbohydrate intake during 2nd meal. *Conclusion:* In VO stress prevented a decreased wanting and energy intake in the absence of hunger, in contrast to NR.

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Meal intake of humans is a function of the number of foods offered

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Our previous research demonstrated that reducing the number of foods offered at a buffet table reduces the amount of food consumed. However, by eliminating various foods from a meal changes the nutrient composition of the meal. Thus, the reduction in amount consumed by offering fewer foods may be a function of nutrient composition, not the number of foods offered. The present study attempts to overcome this limitation by offering the same foods but served either as separate foods or prepared as a composite meal. The study was performed on twenty-four Cornell volunteers recruited from summer school undergraduates and the Cornell staff. Two different combinations of foods were offered. The foods of one meal consisted of onions, corn, carrots, peas, and broccoli, the other meal was made from onions, celery, beans, and cauliflower. The meals were served either as separate foods offered from a buffet take, or combined into a stir-fry or a stew. The subjects consumed the meals as lunch once a week for four consecutive weeks. The groups were run on four different days of the week and received the foods in a difference sequence so that each meal was tested on each week. The amount of each food removed from the buffet to their plates as well as the amount of food removed from their plates (by consumption) was weighed by the staff. The results clearly indicated for both combinations of foods, people consumed more food when the foods are served separately then they were served as a composite meal. These data demonstrate that the number of foods served at a meal is a significant determinant of human food consumption.
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Hindbrain AMP kinase and glucoprivic feeding

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A role for hindbrain AMP kinase (AMPK) in glucoprivic feeding was investigated in rats. Systemic 2-deoxy-D-glucose (2DG, 300 mg/kg) injection increased feeding for 4 h. 2DG also increased the phosphorylated (or activated) form of AMPK (pAMPK) in tissue punches from the ventrolateral medulla (VLM) catecholamine cell groups (A1–C1) of established importance for glucoprivic feeding. However, the pAMPK increase was present only at the 45 min time point. Increased pAMPK was not observed in the ventromedial medulla, immediately adjacent to A1–C1m. Involvement of endogenous AMPK in glucoprivic feeding was examined by injecting compound C (an AMPK inhibitor) into 4th ventricle (4 V) just prior to systemic 2DG injection. Compound C reduced 2DG-induced feeding during the first 2 h of the test. We also injected 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR), an activator of endogenous AMPK, into the 4 V. AICAR produced a brief (30 min) enhancement of food intake. These results are consistent with a contribution of AMPK phosphorylation to the glucoprivic feeding response. Because systemic administration of 2DG potentially reduces glucose utilization in all neurons, the fact that there were regional differences in the level of pAMPK in response to the same stimulus is an important finding. Determining whether the AMPK mechanism is crucial for "glucoprivation-related" signal transduction in these hindbrain neurons will require further work.
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Lesions of the gustatory parabrachial nucleus but not the thalamic orosensory area eliminate anticipatory contrast for sucrose and corn oil in sham feeding rats

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An anticipatory contrast effect (ACE) occurs when rats suppress intake of a weak solution (e.g., low sucrose concentration) when it is followed closely in time by access to a strong solution (e.g., high sucrose concentration) relative to intake by control rats that only have access to the weak solution. Experiment 1 tested whether oral stimulation alone was sufficient to allow for the development of an ACE when using disparate concentrations of sucrose or corn oil. Rats were implanted with gastric fistulas for sham feeding. With the fistula open, the rats were then given 3-min access to a weak sucrose (0.06 M) or an oil emulsion (2.5% or 5%), followed immediately by 3-min access to either the same weak concentration or to a strong sucrose (1.0 M) or oil emulsion (25%). There was one such pairing a day for a number of trials. In experiment 1, the rats developed a clear ACE for sucrose and for oil. Experiment 2 investigated the effects of parabrachial (PBN) or thalamic orosensory lesions on the development of sucrose and oil ACEs. Lesions centered on the gustatory PBN, but not those in the orosensory thalamic relay disrupted ACEs for both sucrose and corn oil. Taken together, the results show that an intact PBN is essential for comparing disparate concentrations of both a gustatory stimulus, such as sucrose, and an orosensory stimulus, such as corn oil. Support: NIH DC00240, DK079182, DA017243, PA State Tobacco Settlement Award.
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Role of intestinal "taste" receptors in the regulation of gastric emptying in humans

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Background: Sweet (T1R2/3) and bitter (T2Rs) taste receptors are expressed by gut enteroendocrine cells. In cell line and animal models, sweet and bitter agonists induce secretion of gut peptides (GLP-1/CCK) and slow gastric emptying (GE), but whether these receptors are involved in the regulation of GE in man is unclear. *Aims:* To determine whether, (i) intragastric infusion of "equi-sweet" (Study A) or "equi-bitter" (Study B) solutions slow GE to the same extent, (ii) a hyper-sweet glucose solution will slow GE more potently than glucose alone and (iii) whether phenotypic variation in oral bitter taste sensation (phenylthiocarbamide (PTC) taster status) would influence GE of bitter agonists. *Methods:* 20 (8 Study A, 12 Study B) healthy lean subjects were studied in a single-blind, randomized fashion. Subjects received 500 ml intragastric infusions of: "equi-sweet" solutions of glucose (560 mOsmol), fructose (290 mOsmol), aspartame (200 mg), saccharin (50 mg); a hyper-sweet solution of glucose + saccharin, or water (volumetric control) (*Study A*), or "equi-bitter" solutions of quinine (0.198 mM), naringin (1 mM), or water (*Study B*). GE was evaluated using a ^{13}C-acetate breath test and sweetness and bitterness, and appetite, ratings using visual analogue scales. *Results: Study A*: Glucose, but not fructose, aspartame or saccharin, slowed GE compared with water and aspartame ($P < 0.05$), with no difference between glucose and the hyper-sweet glucose + saccharin solution. *Study B*: Bitter tastants did not slow GE compared with water, and there was no effect of PTC taster status. There was no effect of any treatment on appetite. *Conclusions:* In man, the presence of sweetness and bitterness *per se* in nutrient solutions does not appear to influence upper gut function independently of other characteristics of the nutrient, e.g. hexose composition.
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Glycemic index (GI) and satiety. Is low GI really superior to high GI for producing satiety in women?

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The clinical utility of a low glycemic index (GI) diet for appetite and food intake control and hence, long-term body weight management is controversial. The relationship between GI and satiety may depend on multiple factors. We previously reported that high GI in overweight pre-menopausal women was superior to high fiber low GI when compared on the basis of subject satiety. The aim of the present study was to investigate the mechanisms of this response and to determine if fiber type was a significant factor in the response. In a randomized crossover study, visual analog scales (VAS), cholecystokinin (CCK), glucose and insulin were measured for 3 h at defined time points after overweight pre- and post-menopausal women consumed 1 of 3 meals: (1) a high GI (HGI) meal, (2) a low GI meal containing 80% of fiber from a soluble source (LGI-SF) or 80% fiber from an insoluble source of fiber (LGI-IF). Test meals provided ∼1/3 of daily energy intake and matched on energy from fat, available carbohydrate and protein, respectively. Fiber content of LGI and HGI meals was ∼12 g and 1 g, respectively. The LGI-SF used psyllium husk and the LGI-IF used cellulose as primary fiber sources. Nine of 20 women have completed to date. The HGI and LGI-SF meals produced greater suppression of hunger than the LGI-IF meal ($p < 0.05$), whereas fullness and desire to eat were not influenced differentially by these dietary manipulations. The HGI and LGI-IF meals suppressed prospective consumption more effectively than the LGI-SF meal ($p < 0.05$). The least square means as an estimate of 3 h response suggests a lower plasma glucose response after the LGI-SF meal compared to LG-IF meal ($p < 0.001$), and marginally different from the HGI meal ($p = 0.12$). A low GI diet for optimal satiety and appetite control in overweight women remains to be validated.

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Effect of intraperitoneal and intravenous administration of cholecystokinin-8 and apolipoprotein AIV on intestinal lymphatic CCK-8 and apo AIV concentration

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Cholecystokinin (CCK) and apolipoprotein AIV (apo AIV) are gastrointestinal satiety signals whose synthesis and secretion by the gut are stimulated by fat absorption. Intraperitoneally administered CCK-8 is more potent in suppressing food intake than a similar dose administered intravenously, but the reason for this disparity is unclear. In contrast, both intravenous and intraperitoneally administered apo AIV are equally as potent in inhibiting food intake. When we compared the lymphatic concentration of CCK-8 and apo AIV, we found that neither intraperitoneally nor intravenously administered CCK-8 or apo AIV altered lymphatic flow rate. Interestingly, intraperitoneal administration of CCK-8 produced a significantly higher lymphatic concentration at 15 min than did intravenous administration. Intraperitoneal injection of apo AIV also yielded a higher lymphatic concentration at 30 min than did intravenous administration. Intraperitoneal administration of CCK-8 and apo AIV also resulted in a much longer period of elevated CCK-8 and apo AIV peptide concentration in lymph than intravenous administration. Furthermore, enzymatic activity of dipeptidyl peptidase IV (DPPIV) and aminopeptidase was higher in plasma than in lymph during fasting, and so, satiation peptides such as CCK-8 and apo AIV in the lymph are protected from degradation by the significantly lower DPP-IV and aminopeptidase activity levels in lymph than in plasma. Therefore, the higher potency of intraperitoneally administered CCK-8 as compared to intravenously administered CCK-8 in inhibiting food intake may be explained by both its higher concentration in lymph as well as the prolonged duration of its presence in the lamina propria.

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An examination of the mixed preference/avoidance response to sucralose in male and female rats

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In rats, the artificial sweetener sucralose is either strongly preferred or strongly avoided across a range of sucralose concentrations (.25–4.0 g/L). The mechanism underlying this phenomenon is unknown, but may be related to individual differences in sensitivity to a bitter taste quality of sucralose. Here, we determined whether sucralose avoidance is absolute or whether it may be attenuated at dilute concentrations (<.25 g/L) that are maximally preferred by sucralose preferrers. Because preference for sweets can be influenced by estrogens, we sought to determine the effects of sex on sucralose preference. Female ($n = 10$) and male ($n = 8$) rats were given 24-h, two-bottle preference tests between water and varying concentrations of sucralose (.0001, .001, .01, .25, .50, 1.0, 2.0 g/L) presented in an ascending order. The preference/avoidance profiles were sexually dimorphic in two ways. First, the proportion of sucralose avoiders was greater in females, compared to males (67% vs. 43% respectively). Second, the preference for sucralose concentrations of .25 g/L and higher was greater in males, compared to females (among sucralose preferring rats, males displayed a 46–120% increase in sucralose preference). Regardless of sex, most rats that avoided sucralose at concentrations of .25 g/L and higher did display a preference for sucralose concentrations of .01 g/L and lower. We conclude that preference for sucralose is sexually dimorphic and that the preference curve for sucralose is shifted to the left in sucralose avoiding rats. Supported by DK73936.
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MCH agonism in the nucleus accumbens shell increases the hedonic response to a sweet stimulus in rats

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The brain Melanin-Concentrating Hormone (MCH) system has an important role in the regulation of energy balance. Particularly, MCH neurons projections toward the nucleus accumbens shell (NAcSh) are known to induce food intake. Knowing the long range of functions attributed to the NAcSh in the regulation of reward and pleasure, we assumed that MCH agonism in the NAcSh increases the pleasure associated with food intake. Using protocols of taste reactivity, we assessed the level of pleasure in response to a sweet stimulus (1 ml of 2% sucrose, intraoral) by quantifying facial mimics. These hedonic responses were monitored in Wistar male rats, 15 min after the 2 μl injection of MCH agonist (5 μg) versus vehicle. Each animal received the two different injections, so that it was its own control. Two different experiments were conducted, with the agonist injected in the 3rd ventricle or in the NAcSh. We observed that the MCHR1 agonist injection within the Nacsh induced a clear increase in the hedonic response to the sweet stimuli (12 rats, $p = 0.008$). On the contrary there was no significant increase in this response with an injection in the 3rd ventricle (12 rats). Enkephalin and dynorphin neurons in the NAcSh, which carry MCHR1 receptors, might be involved in this phenomenon. Our results indicate that MCH agonism in the NAcSh is very likely to be involved in food

palatability. This control may explain the effect of MCH on appetite and may constitute an important link between the homeostatic and hedonic regulations of energy balance.
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Cachexia in clinical settings

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The role of nutrition and balanced metabolism in normal growth, development, and health maintenance is well known. Patients affected with either acute or chronic diseases often show disorders of nutrient balance. In some cases, a devastating state of malnutrition known as cachexia arises, brought about by a synergistic combination of a dramatic decrease in appetite and an increase in metabolism of fat and lean body mass. Other common features that are not required for the diagnosis include decreases in voluntary movement, insulin resistance, and anhedonia. This combination is found in a number of disorders including cancer, cystic fibrosis, AIDS, rheumatoid arthritis, renal failure, and Alzheimer's disease. The severity of cachexia in these illnesses is often the primary determining factor in both quality of life, and in eventual mortality. Indeed, body mass retention in AIDS patients has a stronger correlation with survival than any other current measure of the disease. This has led to intense investigation of cachexia and the proposal of numerous hypotheses regarding its etiology. Most authors suggest that cytokines released during inflammation and malignancy act on the central nervous system to alter the release and function of a number of neurotransmitters, thereby altering both appetite and metabolic rate. This talk will discuss the salient features of cachexia in a number of human diseases. Current and future therapies for this condition will be discussed in the context of what is known about its pathophysiology, and ongoing clinical trials will be reviewed.
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Stress does not affect determinants of hedonic value of acceptable foods

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Stress has been shown to affect food choice. Our objective was to assess whether the hedonic value of food and its determinants are affected by stress. Twenty subjects (BMI: 22.3 ± 1.9 kg/m^2, age: 27 ± 9 years) completed visual analog scales (VAS) to describe their appetite profile. In a normal and stress condition 67 acceptable food items, as confirmed beforehand by all subjects, were rated on pleasantness of taste, creaminess, crispiness, fullness of taste, sweetness, sourness, bitterness, and saltiness using VAS. Appetite profile between different visits did not differ. In the normal condition hedonic value appeared to be determined by creaminess, fullness of taste and not by crispiness ($P < 0.0001$; $R^2 = 0.06$), hedonic value was positively correlated with sweetness and saltiness and negatively with bitterness ($P < 0.0001$; $R^2 = 0.1$). Under stress these relationships remained the same ($P < 0.0001$; $R^2 = 0.09$; $R^2 = 0.10$). In conclusion stress does not affect the determinants of hedonic value of acceptable foods. We suggest that stress may alter rather the wanting then the liking of foods.
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Saccharin consumption degrades sweet taste-calorie relations in rats

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Association of a stimulus with an outcome can be "blocked" or prevented if that stimulus is trained in compound with a cue that already predicts the outcome. Some data suggest that sweet taste may predict caloric outcomes even without explicit training (Rescorla, 2008). Thus, consuming sweet taste in compound with a novel flavor could prevent that flavor from becoming associated with calories. Swithers and Davidson (2008) proposed that such sweet taste-calorie associations can be weakened by consuming sweet tasting, but noncaloric substances. This hypothesis predicts that prior experience ingesting sweet, noncaloric substances should degrade the strength of the sweet taste-calorie association, thereby reducing the ability of sweet taste to block subsequent learning that a novel flavor signals calories. We tested this prediction. Male rats were pretrained with plain or saccharin-sweetened water and then given training with novel-flavored (e.g, grape Kool-Aid) glucose (sweet) and novel-flavored (e.g., cherry Kool-Aid) Polycose (nonsweet) solutions. We then tested the rats with each flavor without glucose or Polycose. Only rats pretrained with saccharin consumed significantly more of the flavor that had been trained with the sweet taste compared to the flavor trained with the nonsweet taste. This suggests that pretraining with saccharin reduced the strength of the sweet taste-calorie association, thereby reducing the ability of sweet taste to block learning about novel flavors. NIH DK076078 and HD052112.
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Assessment of the cannabinoid-1 receptor antagonist AM251 as an unconditioned stimulus in taste aversion conditioning and its effects on meal patterns in rats

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The impact of the cannabinoid-1 receptor antagonist AM251 on daily meal structure has not been determined. It is also possible that any effect may be secondary to malaise produced by the drug. We addressed this in a conditioned taste aversion (CTA) paradigm. Rats were given for 15 min either grape or cherry Kool-aid in a 0.2% saccharin solution (CS−) on Days 1, 4, 10, and 16. Rats were given the other flavor (CS+) on days 7, 13, and 19 and injected ($n = 6$/group) with either 0.15 M LiCl or NaCl, or one dose of AM251 (0, 0.1, 0.3, 1, 3 mg/kg). Rats injected with LiCl drank more CS− on Day 16 than CS+ on Day 19 (5.3 ml vs 0.5 ml; $p < 0.01$); rats injected with 3 mg/kg AM251 also drank more CS− than CS+ (17.4 ml vs 13.8 ml; $p = 0.03$). Only rats injected with LiCl drank more CS− than CS+ flavored solution during 15 min and 24 h 2-bottle preference tests on Days 23 and 35 ($p < 0.01$). Since there was little evidence to suggest that AM251 produced robust CTA, we explored the effects of the highest 3 doses on daily meal patterns. Rats ($n = 8$) were housed in cages designed to measure temporal eating patterns. Once a week, rats were injected with a dose of AM251; on the day before and after dosing the rats were injected with vehicle. AM251 reduced chow intake via a decrease in meal size and eating rate at 1 ($p = 0.035$; $p < 0.01$) and 3 mg/kg ($p = 0.021$; $p = 0.04$). These results suggest that AM251 reduces food intake by affecting satiation not through malaise and by processes related to meal termination as opposed to meal initiation.
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Can liking of a healthy food increase with repeated exposure?

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Repeated exposure to foods varying in selected sensory/nutrient properties (e.g., fat, salt, sugar, energy density) alters their appeal, but knowledge of the breadth of such learning is limited. We examined this issue using data from a partial-feeding study in which subjects ($n = 43$; aged 26–49 years; BMI 25–40 kg/m^2) were randomly assigned to low, medium, or high legume (bean) groups as part of a weight-loss intervention. Subjects were not regular bean consumers. At 0 and 6 weeks, subjects tasted and rated multiple-ingredient foods for sensory qualities (appearance, taste, odor, and texture) using a 9-point hedonic scale. The 28-food test battery included a range of flavors and textures and was balanced with respect to foods provided/not provided in the study, and those with/without beans. We hypothesized that liking for bean-containing foods would increase in the medium bean group, but not in the low or high bean groups due to less than optimal and excessive exposure to beans, respectively. Repeated measures ANOVA showed greater increases in the hedonic ratings of provided foods compared to non-provided foods (provided $\Delta = +0.2$–0.3; non-provided $\Delta = +0.1$; $p \leq 0.001$); however, these changes did not depend on whether the foods contained beans or the amount of beans provided during the study. Repeated exposure to specific foods can increase liking for those foods, including foods containing beans. Funding: Pulse Canada PIP; Hatch IND030472.
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Food history and social status affect food intake in monkeys

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Chronic stress can lead to mood disorders that are often comorbid with a number of adverse health effects including changes in appetite. While stress may be associated with anorexia, availability of high caloric diets (HCD) can lead to excess calorie consumption. Using social subordination in female rhesus monkeys as a model of psychosocial stress, we tested the hypothesis that diet choice would influence total calorie intake. Using an automated feeding system that logs calorie consumption, daily calorie intake of a low calorie diet (LCD; 3.22 kcal/g) was significantly less in subordinates compared with dominant females, consistent with status differences in body weight and indices of adiposity. In contrast, when given a choice between the LCD and a HCD (5.64 kcal/g), subordinate females preferred the HCD and ingested significantly more calories per day than dominant animals. Under the choice condition, dominant monkeys also preferred the HCD but consumed a similar number of total calories as in the LCD only condition. When females were again fed only the LCD following the choice condition, subordinates continued to consume more calories than dominant females. Changes in metabolic phenotype and hormone levels were associated with increased calorie intake in subordinates. These data suggest that stress significantly increases consumption of a HCD and that previous exposure to a HCD increases intake of a LCD. The mechanisms accounting for the increased intake of the HCD in subordinates are not known at this time. Supported by HD46501 and RR00165.
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DAMGO-induced stimulation of μ-opioid receptors in the mPFC leads to increases in food intake and a fragmentation of feeding microstructure

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The goal of the present study was to examine the role of the μ-opioid system within the mPFC on food intake and feeding microstructure. In both ad libitum and food restricted rats, bilateral infusions of the μ-agonist DAMGO within the mPFC significantly increased locomotor activity and fecal boli production, suggesting a highly aroused or stress-like state. Intra-mPFC DAMGO infusions also resulted in frequent feeding bouts in both groups, although the duration of these bouts was significantly shortened, as was the duration of rearing and grooming bouts. These changes in feeding microstructure resulted in significant increases in food intake. Interestingly, effects on drinking behavior were also found, with prandial drinking significantly reduced. This fragmentation of behavior was reminiscent of the effects of bicuculline, which disinhibits PFC activity, suggesting a common mechanism between both manipulations. In support of this idea, pre-treatment with the $GABA_A$ agonist, muscimol, attenuated the DAMGO-induced changes in feeding microstructure, further suggesting that the DAMGO effect is mediated by increased PFC activity. Together, these findings suggest a role for μ-opioid receptors within the mPFC on feeding microstructure and food intake. To the best of our knowledge, this is the first report of increased food intake following local μ-opioid receptor stimulation within the prefrontal cortex.
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The anti-dipsogenic effect of ghrelin does not require the neuropeptide Y Y_5 receptor

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Ghrelin attenuates angiotensin II (AngII)-induced water intake, but almost nothing is known about how or where in the brain this effect is mediated. In contrast, much is known about the effect of ghrelin on food intake, including its mediation of hyperphagia through neuropeptide Y (NPY). Because the drinking response to AngII requires forebrain substrates, and the hyperphagic effects of ghrelin in the forebrain depend on the NPY Y_5 receptor, we tested if the attenuation of fluid intake by ghrelin also requires Y_5. To this end, we first replicated previous findings, showing that forebrain administration of a Y_5 antagonist blocked the feeding effect of forebrain-delivered ghrelin. Using this paradigm, we tested the effects of a Y_5 antagonist on both feeding and water intake. Specifically, rats were pretreated with a Y_5 receptor antagonist or vehicle, followed by treatment with ghrelin or vehicle and AngII. Subsequent food and water intakes were measured. As shown previously, ghrelin-treated rats drank less in response to AngII than vehicle-treated controls. Moreover, we found that the anti-dipsogenic effect of ghrelin was present even early in the light cycle when ghrelin did not increase feeding. These initial studies failed, however, to find evidence that Y_5 is required for the anti-dipsogenic effect of ghrelin. Further studies are needed to clarify the specificity of these findings for AngII-induced intake and the potential role of other NPY receptors in the anti-dipsogenic effects of ghrelin.
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Meal induced changes in BOLD fMRI activity in the rodent brain

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Blood Oxygen Level Dependent Functional Magnetic Resonance Imaging (BOLD fMRI) techniques are an important tool for investigating central regulation of hunger and satiety in humans. Our objective is to develop a reproducible rodent model for studying the effect of a mixed-nutrient liquid meal (Ensure) on BOLD fMRI activity in the brain. Adult Sprague–Dawley rats with implanted intragastric (IG) catheters were adapted to 12-h Ensure access on a reverse light schedule. Under anesthesia, the rats received IG infusion of either saline ($n = 4$) or Ensure ($n = 4$; 12 kcal) at 2 ml/min. Brain images were acquired with a 9.4 T magnet using a surface RF coil, and a cluster analysis program (Evident) was used to identify voxel changes within the brain which correlated with the infusion paradigms. Ensure infusion resulted in a transient reduction in MR signal intensity in the Nucleus Tractus Solitarius (NTS), hypothalamus, thalamus, hippocampus, ventral tegmental area (VTA), caudate putamen and higher cortical structures (parietal cortex). Time course analysis indicated that Ensure produced a 6% reduction in MR signal intensity within the hypothalamus, NTS and VTA, and a 4% reduction in signal intensity within the hippocampus and caudate putamen. Saline infusion did not produce a similar response. These results suggest that IG infusion of a mixed nutrient liquid meal produces a transient generalized reduction in BOLD fMRI signal intensity in brain regions that are hypothesized to regulate food consumption.

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Consumer views of hunger and fullness. A qualitative approach

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The objective of this study was to gain a better understanding of the complex ideas of hunger and fullness from consumers through the use of focus groups. We report results of 4 focus group interviews with (1) eight female normal weight dieters, (2) nine female normal weight non-dieters, (3) seven female overweight dieters and non-dieters, and (4) seven male normal weight dieters and non-dieters. Hunger and fullness sensations were described as having both physical and psychological components that were divided into two groups: typical and extreme. Overall, hunger was described as the presence of stomach growls, stomach hunger pains, emptiness, focus on eating, loss of energy, and desire to eat. Fullness was described as a feeling of food in the stomach, stomach stretch, satisfaction, contentment, energized, focused, and lack of the desire to eat. Typical fullness was described with many psychological components while typical hunger was primarily physical in nature. Participants described situations in which sensations of hunger and fullness overlapped, which provided evidence that hunger and fullness are not polar opposites.

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Learned preference for flavors experienced early vs. late in a nutritive meal

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Food preferences are strongly influenced by learned associations between flavors and postingestive consequences. Rats learn to prefer a flavor that has been paired with postingestive effects of carbohydrates. The present experiment investigates this learning when multiple flavors occur in a meal accompanied by carbohydrate, specifically, a flavor experienced in the early half vs late half of the meal. Stronger learning about either the earlier or later flavor may indicate how soon after meal initiation the "reinforcing" postingestive events occur. Rats with intragastric (IG) catheters were accustomed to drinking a sweet but calorically dilute solution in brief daily sessions. They then experienced two types of training sessions in which flavors were added. In (+) sessions, consumption of flavors was accompanied by IG glucose infusion. In (−) sessions consumption of flavors was accompanied by IG water. In both types of sessions, an "early" (E) flavor was provided in the first half (10 min) of the session and a "late" (L) flavor in the second half. Thus, rats were trained with four flavors: E+ and L+ in the (+) sessions, and E− and L− in the (−) sessions. Learned preferences for E+ and L+ were then assessed in two-bottle choice tests between E+ vs E−, L+ vs L−, and E+ vs L+. Rats learned to prefer E+ but not L+, possibly suggesting that the reinforcing postingestive events have fairly rapid onset. However, we also observed an unexpected tendency of rats to suppress consumption of L+ during training, possibly limiting their opportunity to learn about L+.

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Identification of melanocortin receptor subtypes involved in lipolysis in murine 3T3-L1 adipocytes

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The melanocortins have been proposed to play a central role in regulating adipocyte metabolism. The metabolic effects of melanocortin peptides and their receptors have aroused an interest for the system, due to the global epidemics of obesity and type 2 diabetes. Five melanocortin receptors have been identified: melanocortin receptor (MC) 1, MC2, MC3, MC4 and MC5. These belong to the 7-transmembrane G-protein coupled receptor family and are located diversely in humans. Natural occurring melanocortin peptides such as ACTH and a-MSH are generated from proopiomelanocortin (POMC). These peptides as well as the a-MSH analogs MTII, SHU-9119, LY2112688 and beta adrenergic agonist isoproterenol have been found to induce lipolysis in murine 3T3-L1 adipocytes. When MC receptors are stimulated by an agonist, triglyceride is hydrolysed to glycerol and free fatty acids (FFA), after which FFA can be measured as an index of lipolysis. By using receptor specific analogs, MC receptors of lipolytic importance can be identified. Furthermore, MC1-5 mRNA transcript abundance by means of q-PCR in differentiated 3T3-L1 adipocytes, indicate which MC receptors might be exerted during lipolysis. Our data show that only MC1, 2 and 5 are involved in 3T3-L1 lipolysis during stimulation. Furthermore, MC1 and 5 mRNA transcripts are up-regulated in differentiated 3T3-L1 cells compared to non-differentiated 3T3-L1 cells.

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Effect of the melanin concentrating hormone 1 (MCH 1) receptor antagonist SNAP 94847 on food self-administration and relapse to food seeking

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Many studies report an important role of MCH 1 receptors in home-cage food intake. In contrast, the role of these receptors in operant food self-administration or relapse to food-seeking is unknown. In Experiment 1, we trained food-restricted rats (~16 g/day) to lever press for 45 mg high-fat pellets for 14 days (3 h/day, every other day) under a fixed-ratio-1, 20 s timeout reinforcement schedule. We then tested the effect of the MCH 1 receptor antagonist SNAP 94847 (3–30 mg/kg, i.p.) on pellet self-administration. In Experiment 2, we trained rats to self-administer high-fat pellets as in Experiment 1, and after extinction of the food-reinforced responding over 10–17 days, tested the effect of SNAP 94847 on reinstatement of lever responding (the operational measure of food seeking) induced by MCH (20 μg, icv), non-contingent exposure to three pellets (pellet-priming), cues previously associated with pellet delivery (pellet-cue), or the pharmacological stressor yohimbine (2 mg/kg, i.p.). We found that SNAP 94847 attenuated pellet self-administration and MCH-induced reinstatement of lever responding. In contrast, SNAP 94847 had no effect on pellet-priming-, pellet-cue- or yohimbine-induced reinstatement of lever responding. These data indicate an important role of MCH 1 receptors in operant pellet self-administration and MCH-induced reinstatement of food seeking, but not in reinstatement induced by acute exposure to high-fat food, food cues or the stress-like state induced by yohimbine.

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Estrogen and HSD_2 labeling in the nucleus tractus solitarius of rats

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11-β-Hydroxysteroid dehydrogenase type 2 (HSD_2), an enzyme found in neurons of the nucleus tractus solitarius (NTS), has been shown to be influenced by sodium need and salt intake. In female rats, salt intake is stimulated during high estrogen conditions. Therefore, the goal of this study was to determine whether estrogen influenced basal levels of HSD_2 in the NTS of female rats. Adult female Sprague–Dawley rats were bilaterally ovariectomized and allowed to recover before treatment with estradiol benzoate (EB) or the oil vehicle (OIL) on two consecutive days. Rats were perfused 48-h after the second injection; brains were removed, post-fixed overnight, and then cut into 40 μm sections. HSD_2 labeling in the NTS was visualized using standard immunohistochemical methods (primary antibody: rabbit anti-HSD_2, Santa Cruz; secondary antibody: Cy2 goat anti-rabbit IgG, Jackson Immunoresearch). HSD_2 labeled neurons were quantified in the caudal, middle, and rostral regions of the NTS using fluorescence microscopy and NIS Elements software. Overall, there were significantly fewer HSD_2 neurons in the caudal region compared to the middle and rostral regions. However, there were no differences between OIL- and EB-treated rats in the number of HSD_2-labeled neurons in any of the three regions of the NTS. These results show that the number of HSD_2 neurons in the NTS was not affected by the presence of estrogen under basal conditions. Thus, estrogen effects on basal salt intake are not attributable to differences in the number of HSD_2 neurons.

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Ingestion of highly palatable foods modulates c-Fos expression in the nucleus accumbens responding to stress in rats

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It has been reported that ingestion of highly palatable foods attenuates the HPA axis responses to stressors. Not only stressors but also palatable food intake produces strong signals in the nucleus accumbens (NAcb). This study was conducted to examine if ingestion of palatable food modulates the stress-induced neuronal activation in NAcb and/or gene expression of tyrosine hydroxylase (TH), rate limiting enzyme of dopamine biosynthesis, in the ventral tegmental area (VTA). Rats on ad libitum chow diet received daily 1 h access to chocolate cookie for 7 days, and then were placed in restraint cage for 2 h following the last cookie session. Control group received 2 h restraint omitting cookie sessions. Tail bloods were collected at 0, 20, 60 and 120 min time points during the restraint session. All rats were sacrificed immediately after the end of restraint, and the brains were processed for c-Fos immunohistochemistry in NAcb and TH mRNA in situ hybridization in VTA. No stress control rats were processed in parallel. Stress-induced increases of plasma corticosterone and the hypothalamic CRH were blunted in the cookie group. Interestingly, stress-induced Fos expression was not affected in NAcb-core, and even further increased in NAcb-shell, by cookie intake. Results suggest that palatable food intake may increase susceptibility of NAcb neurons to stress, perhaps, in relation with blunted response of the HPA axis. The VTA-TH is under analysis.

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Emotional and external eating are associated with poor sleep quality in college students

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Short sleep duration (SD) has been associated with elevated BMI [Gangwisch et al., *Sleep* 2005;28:1289–1296], disordered eating [Hicks & Rozette, *Percept. Mot. Skills* 1986;62:209–210], emotional stress [Vgontzas et al., *Int. J. Obes.* 2008;32:801–809] and neuroendocrine control of appetite [Cauter et al., *Horm. Res.* 2007;67:2–9]. The possible role of emotional and external eating in the SD–BMI association was tested by examining the relationship between sleep quality, SD, BMI, and scores on the DEBQ in a sample of college students ($N = 240$, 75% female, mean age = 19 years, BMI = 23 kg/m^2, 23% overweight or obese, 84% White). Participants were administered the DEBQ, Sleep Quality Index (SQI), and asked to report height and weight in small groups in a laboratory setting. Based on SQI score, participants were divided into good sleep quality ($n = 31$), occasional sleep difficulty ($n = 177$), and poor sleep quality ($n = 31$) groups. One-way MANOVA revealed that participants with poor sleep quality had higher emotional eating, $F(2, 234) = 3.99$, $p = .02$, and external eating scores, $F(2, 236) = 3.44$, $p = .03$. There was no difference in restraint scores or BMI. A significant correlation was found between SD and BMI, $r(231) = -.15$, $p = .01$. BMI was correlated only with restraint on DEBQ, $r(236) = .14$, $p = .01$. In this sample, emotional and external eating may not mediate the relationship between BMI and SD. However, students who emotionally eat may be setting unhealthy patterns that will affect BMI as they age. A relationship between emotional eating and BMI has been found in samples with higher mean age (van Strien et al., *Addict. Behav.* 1985;10:333–343).

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Effect of Roux-en-Y gastric bypass surgery on brain activation in response to appetitive cues

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Little is known about the effect of Roux-en-Y gastric bypass (RYGB) surgery on brain activation in response to appetitive cues. 5 severely obese women receiving RYGB surgery were scanned, using fMRI, at 1 mo pre- and 1 mo post- surgery. Activation in areas associated with ingestive behavior was examined in response to high-palatability food, low-palatability food, and non-food stimuli following a fixed (250 kcal) meal. Results for pre-surgery > post-surgery analyses at $p < 0.05$: More global brain areas were activated in response to high-palatability foods than to low-palatability foods and non-foods. These response differences were most pronounced in limbic and paralimbic areas, in particular amygdala (processing of predictive reward value of food), ventral prefrontal cortex (emotional processing area which responds to hunger and exposure to food stimuli) and orbitofrontal cortex (reward value and expected reward value of food). Areas in which activity in response to high-palatability food, relative to non-food stimuli, decreased post-surgery were most pronounced in the hippocampal gyrus (emotional control of food intake), inferior frontal gyrus (judging likes or dislikes of foods), precentral gyrus (associated with motor planning and satiation), and anterior cingulate and caudate (expectation of reward). These data suggest that post-surgery pts may be less motivated towards food stimuli, experience greater satiation, and react less emotionally to food cues.

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Metabolic effects of a high fat diet differ between light vs. dark period access

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Shift workers have an increased risk of developing cardiovascular disease and metabolic syndrome. Although previous studies have demonstrated that shift workers exhibit impaired glucose and lipid tolerance after a single nighttime test meal, the mechanisms underlying the relationship between shift work and metabolic risk factors are poorly understood. In this study, we evaluated the feeding and metabolic effects of light vs. dark period restricted access to a high fat diet. Male Sprague-Dawley rats were divided into 3 groups ($n = 6$ per group). Group 1 received ad libitum access to a high fat diet (Research Diets, 60% kcal from fat; AD LIB). Group 2 was given 3 h access to the high fat diet at the beginning of the dark period (DARK) and Group 3 was given 3 h access to the high fat diet at the beginning of the light period (LIGHT). After 12 weeks on this feeding regimen, there was no difference in body weight between AD LIB and DARK rats. In contrast, rats fed during the light period exhibited a 13% decrease in body weight compared to AD LIB rats, as well as decreased food intake. Despite lower food intake and body weight, LIGHT rats had significantly elevated blood glucose levels compared to AD LIB when challenged with an oral glucose tolerance test 15 and 30 min after oral gavage of 2.0 g/kg glucose. These results demonstrate that high fat food consumption at a time when rats are not normally active and feeding may have detrimental effects on metabolism that may be attributed to mismatches between energy consumption and endogenous circadian rhythmicity.

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Japanese consumers' "food selection criteria" dimension

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This research was aimed at understanding the dimensions of food selection by Japanese consumers. In this report the food selection criteria have been extracted using the measures of Steptoe, Pollard, and Wardle (1995) whose reliability has been confirmed in UK with 358 samples. A questionnaire survey about food selection criteria containing 36 items was administered to 156 female college students. The students evaluated each item into 4 levels. Around two months later, the same investigation was conducted once again, with the same target group. The 1st data set was used for the main analysis. The 2nd data set was used to check the reliability of the food selection criteria dimension extracted from the 1st data set. We performed principal component analysis and the following five dimensions were extracted: (1) mood, (2) safety, health, and nutrition, (3) convenience, (4) weight control, and (5) price. In order to verify the reliability of the five dimensions of food selection criteria, the second data set was also used to extract 5 dimensions, as with the first data set. The correlation coefficients between the dimensions of each component were more than 0.600, which clearly indicates correspondence. These five dimensions were not overly abstract and moreover, corresponded well with the dimensions that Steptoe et al. (1995) extracted. Therefore, it seems that these five dimensions are effective for accurately understanding the food selection behavior of Japanese people.

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Subacute endotoxemia temporarily impairs insulin sensitivity and beta-cell function in cats

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Systemic low-grade inflammation is a pathogenic component in chronic disease like obesity and type 2 diabetes mellitus (T2DM). In humans and cats, chronic inflammation is associated with elevated proinflammatory cytokines. Here, we hypothesized that low-grade induced inflammation impairs insulin sensitivity and β-cell function in cats. Ten healthy cats were infused IV with lipopolysaccharide (LPS; 10–1000 ng/kg/h; $n = 5$) or saline ($n = 5$) for 10 days. Body temperature, plasma glucose, insulin and α_1-acid glycoprotein levels were assessed each day. Before and after the infusion, IV glucose tolerance tests (ivGTT) were performed. Tissue specimens were collected. LPS was well tolerated. Body temperature and glucose levels increased during the first 5 days of LPS and then decreased to baseline. Insulin did not differ from controls at any time. β-cell function and insulin sensitivity were decreased in the LPS group on day 1–3. From day 1–10, α_1-acid glycoprotein was increased in the LPS-infused cats. Based on the ivGTT at the end of the infusion, insulin secretion pattern and insulin sensitivity did not differ between groups. LPS-treated cats had more neutrophils in the liver. LPS induced an inflammatory response that lasted throughout the infusion. This was accompanied by reduced insulin sensitivity and β-cell function that were short-lasting. Because body temperature and glucose levels returned to normal, desensitization to LPS may have occurred.

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Evidence for a role of the hindbrain in the satiating effect of hepatic portal vein (HPV) infusions of glucagon-like peptide-1 (GLP)-1 in rats

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We recently showed that remotely controlled intrameal HPV GLP-1 infusions selectively reduce spontaneous meal size in rats (Rüttimann et al., Endocrinology 150:1174, 2009). The brain sites involved in this effect are currently unknown. To address this question we equipped male Sprague–Dawley rats with HPV catheters, delivered GLP-1 or vehicle (*V*) by remote control at dark onset, and assessed their effects on eating and neuronal activation by measuring c-Fos expression in crucial areas of the forebrain and hindbrain. In a within-subjects design ($n = 10$) GLP-1 (1 nmol/kg) reduced the size of a dark-onset meal induced by 3 h of food deprivation compared to *V* (*V*, 4.4 ± 0.6 g; GLP-1, 2.5 ± 0.3 g; $p < 0.05$). Without food access, but under otherwise identical conditions, GLP-1 ($n = 8$, 1 nmol/kg) increased ($p < 0.05$) the number of c-Fos expressing cells compared to *V* ($n = 7$) in the area postrema (cells/section: *V*, 20 ± 2; GLP-1: 96 ± 22) and in the subpostremal nucleus of the solitary tract (V, 93 ± 16; GLP-1: 172 ± 31), but did not significantly affect the number of c-Fos expressing cells in the hypothalamic paraventricular and arcuate nuclei or in the central nucleus of the amygdala. These data suggest a role for the hindbrain rather than the forebrain in the mediation of peripheral GLP-1s satiating effect.

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Intra-accumbens scopolamine decreases food intake without affecting food-seeking behaviors

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The nucleus accumbens (Acb) is a brain region known to play an important role in the modulation of feeding behavior. Recently, Acb acetylcholine has been shown to modulate food intake. The following experiments were designed to further define the feeding effect observed when muscarinic receptors are blocked within the Acb. Three hours following bilateral intra-Acb scopolamine infusion (10 μg/0.5 μl), we observed a decrease in sucrose pellet intake with a significant increase in general motor activity; however, no scopolamine-induced activity was observed when rats were tested in locomotor cages in the absence of food. A second experiment was designed to separate the anticipatory from the consummatory behaviors associated with feeding by placing a wire-mesh screen in front of the sucrose pellets. After 15 min, the screen was removed and rats had ad libitum access to the food for 30 min. Food intake was significantly decreased with a 3 h pretreatment, but anticipatory behaviors were unaltered. Finally, intra-Acb scopolamine failed to decrease operant responding for a food-associated conditioned cue. The current work suggests that intra-Acb scopolamine decreases food intake specifically without altering food-seeking behaviors or the incentive properties of food-associated cues. We are currently conducting studies to determine receptor-mediation and anatomic specificity of the scopolamine effect.

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Altered gene expression in brainstem and forebrain nuclei following taste aversion learning

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A learned taste aversion (CTA) alters taste palatability and is manifest behaviorally by the avoidance of a previously accepted gustatory stimulus following association with visceral malaise. Although the central pathways involved in such learning and its dependence on immediate early gene transcription are reasonably well understood, the modulation of downstream gene expression is not. The present study used oligonucleotide microarrays to identify altered gene expression in the parabrachial nucleus (PBN), central and basolateral nuclei of the amygdala (CeA and BLA) and lateral hypothalamus (LH) following CTA. The control group had two pairings of sucrose intake and intraperitoneal saline injection, while in conditioned animals sucrose intake was paired with LiCl injection. Three days after the second taste/injection pairing, brains were extracted immediately following re-exposure to sucrose. Total RNA from each brain region was isolated then cRNA was hybridized to whole rat genome chips. Out of 28,142 genes present in each region, 251 (PBN), 113 (CeA/BLA), and 103 (LH) showed differential regulation of at least 2-fold and a p value ≤ 0.05. Relative to control animals, CTA altered the expression of various peptides, transcription factors, phosphatases, kinases, receptors and ion channels. Directional change in expression of subsets of genes was confirmed by qRT-PCR. The present data provide a starting point for understanding gene expression specific to gustatory and aversive visceral stimulation, as well as learning dependent modulation of taste palatability.

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Organization of vagal afferent inputs to single neurons in medial solitary tract nucleus. Limited direct afferent convergence with C-/A-fiber segregation

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Various modalities of cranial visceral afferents travel together in the vagal trunk to contact neurons within the NTS and activate a range of homeostatic reflex pathways. Vagal afferents either directly or indirectly contact NTS neurons while the precise relationships remain poorly understood. Brainstems from male Sprague–Dawley rats were removed under deep isoflurane anesthesia and horizontal brainstem slices containing the solitary tract (ST) and medial NTS prepared. Brain slices were maintained in aCSF and whole-cell patch clamp recordings were made under voltage clamp. Electrical shocks to the ST produced fixed latency glutamatergic EPSCs that identified NTS neurons with direct ST afferent innervation. Detailed analysis of stimulus threshold intensity, latency to onset, and EPSC waveform discriminated between unitary or multiple afferent contacts as well as indirect polysynaptic inputs. Across neurons, over half receive only one direct afferent contact (46/85). The remaining neurons received either two (28/85) or three (11/85) direct inputs. A subgroup of NTS neurons was tested with capsaicin. The presence of TrpV1 and sensitivity to capsaicin is evidence of C-fibers. Neurons with multiple inputs were either completely sensitive or resistant to capsaicin exposure; indicating separate C- and A-fiber innervation. The organization of vagal afferent to medial NTS indicates relatively limited direct afferent convergence with segregation of C- and A-fiber information. HL-088894 (JHP), NHMRC-400405(SJM) and HL-041119 (MCA).

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Noradrenergic neurons of the area postrema mediate amylin's anorectic action

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Peripheral amylin inhibits food intake via activation of the area postrema (AP). 59% of amylin-activated AP neurons are noradrenergic (NA), i.e., they express dopamine-beta-hydroxylase (DBH). Here, we wanted to test whether AP NA neurons mediate amylin's anorectic effect. We performed a specific lesion of AP NA neurons using a saporin conjugated to an antibody against DBH (DSAP). IgG-saporin was used in sham controls. After 2–3 weeks necessary for neuronal degeneration, we tested the rats for the effect of amylin (5 or 20 μg/kg BW, s.c.) to reduce food intake. In a terminal experiment, the rats received amylin (20 μg/kg) or saline; brain sections with the AP and nucleus of the solitary tract (NTS) were stained for DBH to assess lesion success and for c-Fos expression to evaluate amylin-induced neuronal activation. DBH staining revealed that 10 DSAP-injected rats had NA lesion equal to or above 50%, defined as successful; 6 had lesions below 50%. Daily food intake and body weight gain did not differ between lesioned and sham groups. Amylin-induced anorexia was observed in sham rats with both amylin doses, while rats with a successful lesion had no significant reduction in eating after either amylin dose. Rats with lesions below 50% only ate less after the higher amylin dose. In contrast to sham-lesioned animals, successfully NA-lesioned rats did not show amylin-induced c-Fos expression in the AP and NTS. These results provide first evidence for a functional role of NA neurons in the AP in the mediation of amylin's anorectic effect.

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The consumption of a portion of cheese as first course of a meal does not impact meal and daily food intake

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The consumption of cheese at the end of a meal (whereas we are no longer hungry) is often described as extra-energy ingested, promoting overweight. However, cheeses present nutritional qualities like a great amount of calcium. We wondered if consuming cheese at first course of meals could permit to benefit from their nutritional qualities while preventing over energy consumption, since in this case energy brought by cheese would be immediately taken into account in first pre-absorptive satiety signals. 37 women (33.8 ± 1.6 years; BMI = 21.0 ± 0.3 kg/m^2) participated to 4 randomised test days corresponding to 3 different portions of cheese and a control day. The 3 cheeses were a portion of 30 g (80 kcal) of camembert cheese, and portions of 30 g (80 kcal) or 75 g (200 kcal) of light pressed cheese. In each test day, the subjects had to consume the cheese at the beginning of lunch and their food intake was measured during the next meals (lunch, collation and dinner). No difference of energy intake was found between control and test days both at lunch and on the whole day. Moreover, neither the composition nor the quantity of cheese affected energy intake since there was no difference between the 3 test days. These results show that consuming a portion of cheese at first course of a meal does not promote over energy consumption and could be a mean to increase intake of diary products without negative effect on weight management.

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No difference in the satiety effect of disguised preloads with the same energy, volume and palatability but containing only proteins, carbohydrates or lipids

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Protein as the macronutrient with the highest satiety effect is still matter of debate because of the diversity of designs employed. The aim of this study was to compare the effect on satiety of different preloads constituted only by protein, fat or carbohydrate in very controlled conditions (iso-palatabilty, -energy, -volumetry). 56 subjects participated to 4 randomised test days, one day per macronutrient and a control day. In each test day, they had to consume the preload entirely and their food intake was measured during the next meals. The volunteers were separated in 2 groups: the first one (T0) consumed the preload immediately before lunch and the second one (T1) 1 h before. Whatever the delay, no difference was found on food intake at lunch between the 3 preloads. In the T1 group, energy intake of preload and lunch was higher after lipid preload than in the control. In the T0 group, the same result was observed with lipids but also with proteins. We did not observe an effect of the delay between preload and test-meal. Our results do not confirm the highest satiety effect of proteins, may be because we used unusual foods as preloads. According to the concept of learned satiety, the results could not be the same if the subjects were previously familiarised to the preloads.

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Effects of intermittent intraperitoneal infusion of exendin-4 and PYY(3–36) on food intake and adiposity in diet-induced obese rats

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Our aim was to determine whether intermittent IP infusion of exendin-4 can produce a sustained reduction in daily food intake, body weight and adiposity in diet-induced obese rats. Rats (641 ± 9 g, 143 ± 5 g fat) with intraperitoneal catheters tethered to infusion swivels and programmable pumps had free access to a 45% fat diet. Food intake was measured by continuous computer recording of changes in food bowl weight. Body fat was measured by quantitative nuclear magnetic resonance. Vehicle-treated rats ($n = 24$) had a stable food intake, body weight and adiposity during the 8-week study. Two, 3-h infusions of exendin-4 (20 pmol/h) at the beginning and end of the dark period each day in a second group of rats ($n = 24$) produced a sustained $19 \pm 1\%$ decrease in daily food intake for 14 days, and a 5% and 18% decrease in body weight and adiposity, respectively. Loss in efficacy of exendin-4 appeared to be due to activation of a homeostatic response to increase food intake when energy reserves declined. Subsequent co-infusion of PYY(3–36) (240 pmol/h) and exendin-4 (20 pmol/h) restored the inhibitory effect of exendin-4 on daily food intake. Together they produced a sustained $22 \pm 1\%$ reduction in daily food intake for 20 days, and a further decrease in body weight and adiposity of 6% and 16%, respectively. Thus, chronic intermittent IP infusion of exendin-4 alone and in combination with PYY(3–36) can produce a relatively prolonged reduction in daily food intake, body weight and adiposity in diet-induced obese rats.

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Amylin deficient mice have decreased fiber density in AP-NTS projections

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The pancreatic hormone amylin decreases food intake via an activation of the area postrema/nucleus of the solitary tract (AP/NTS). We investigated whether amylin might act as a neurotrophic factor during brain development. We implanted crystals of the lipophilic tracer DiI into the AP of postnatal (P10 and P14) amylin knockout mice (IAPP−/−) and their wildtype littermates. P10 IAPP−/−-neonates had a significantly lower average fiber density in the NTS compared to IAPP+/+ mice. There was no gender specific difference although fiber densities tended to be lower in females mice. There seemed to be neuronal remodelling processes between P10 and P14, which were reflected by a decrease in AP-NTS projections during this time period. Plasma amylin levels in neonates (P6–P9) were similar to those of adult mice. The critical time window when amylin affects the maturation of neuronal AP-NTS connections remains to be established. This study provides first evidence for a critical function of amylin as a neurotrophic factor affecting the development of important brainstem pathways involved in the control of food intake. The present findings substantiate the concept that the developing brain is imprinted by and possibly vulnerable to hormonal influences during the perinatal stage. Such processes may have an impact on the risk to develop metabolic diseases (e.g. diabetes mellitus) and obesity later in life.
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The ability of amylin to reduce eating depends on the protein content of the diet

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Numerous lines of evidence indicate that the pancreatic hormone amylin contributes to meal-ending satiation. This action seems to be mediated by direct action of amylin on area postrema (AP) neurons. Here, we investigated the effect of different nutrients on amylin's ability to induce c-Fos expression and to reduce eating. Amylin (5 μg/kg SC) increased c-Fos expression in the AP more strongly in fasted rats and in rats fed a nutrient-deficient non-caloric diet (NCD) than in rats fed chow ad libitum. Supplementation of NCD with protein, but not with glucose or fat, reduced the amylin-mediated AP c-Fos response. Similarly, parenteral injection of an amino acid mixture also significantly attenuated the amylin-induced c-Fos expression in the AP in rats that had no access to food. Feeding studies are in line with these findings in that amylin injection failed to reduce food intake in NCD/protein fed rats, whereas amylin did reduce food intake in animals fed NCD, NCD/glucose or NCD/fat. Amylin's effect to reduce eating was particularly strong in rats fed a low-protein (1%) diet (85% reduction in eating compared to controls versus approx. 50% in normal-protein [22%] diet). To summarize, our studies designed to understand the influence of dietary components on the effectiveness of amylin to reduce eating showed that amylin's effect is particularly strong when the protein content of the diet is low. The exact mechanisms through which protein diets/amino acids reduce amylin's effect to inhibit eating are still unknown.
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Viscerosensory projections from the nucleus of the solitary tract to brain regions involved in feeding and energy homeostasis. Anterograde tracing and immunocytochemical analysis

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The goal of this neuroanatomical study is to provide a more complete characterization of central neural projections arising from the caudal viscerosensory nucleus of the solitary tract (NST) that target brainstem, hypothalamic, and limbic forebrain regions implicated in the control of food intake and body energy homeostasis. Projection pathways have been mapped throughout the rostrocaudal neuraxis of rats after microinjection of the anterograde tracer Phaseolus vulgaris-leucoagglutinin (PhAL) into the caudal NST. In addition, immunocytochemical localization of glucagon-like peptide 1 (GLP-1)-positive fibers and terminals has been used to identify projections of this phenotypically distinct subset of viscerosensory NST neurons. GLP-1 immunolabeling has been combined with localization of lithium chloride-induced neural Fos expression in regions that receive GLP-1 inputs. NST projections that have been mapped via PhAL and GLP-1 immunolabeling have been overlaid onto digitized images of central noradrenergic innervation fields, to provide a more integrated view of projections that arise from the caudal NST vs. those that arise from other brainstem nuclei. Initial studies have been conducted in adult male Sprague–Dawley rats. Continuing work will include examination of potential sex differences within these ascending neural pathways, and the extent to which ascending pathways are modified by early life experience.
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Fos expression in brain of MC4R, MC3R, and double receptor knockout mice in response to CCK, BN or MTII

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Knockout (KO) of the melanocortin (MC) 4 receptor results in hyperphagia and obesity whereas KO of the MC3 receptor does not affect food intake or body weight in mice, but results in higher body fat. We examined induction of Fos in select brain regions in response to administration of cholecystokinin (CCK), bombesin (BN), or the MC agonist, MTII. Mice, genotyped to be homozygous 4RKO, 3RKO, or double KO, and the normal wild types, were used. CCK-8 or BN were injected immediately before 'dessert' feeding tests or, on another occasion, 1 h before the mice were sacrificed and brains harvested for determination of Fos in forebrain (PVN) and hindbrain (AP/NTS) regions. In MTII studies, mice were surgically implanted with a lateral ventricular cannula. A feeding study was conducted after overnight food deprivation and on another occasion, MTII was injected 1 h before sacrifice for Fos determination. The anorectic effect of BN was slightly greater in double KO mice, but overall the anorectic effects of CCK and BN were similar across genotypes. There were no genotype differences in Fos induced in the brain regions examined. MTII had little effect on food intake of double KO mice, but had a partial effect in both 3KO and 4KO relative to wild types. Fos expression to MTII was greatly attenuated in double KO mice, and was partially attenuated in single KO, with some differences between PVN and AP/NTS. The data are consistent with the hypothesis that MC3 and MC4 receptors are functionally additive in regard to MC action in feeding circuits. DK064712.
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The effect of failure to conform to a social norm for appropriate eating on self-perceptions

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The purpose of this study was to examine whether violating a social norm for appropriate eating affects self-perceptions. Females may apply negative stereotypes about large eaters to themselves when they eat excessively and, consequently, evaluate themselves negatively. Ninety females ate until satiated and were told they would later be interacting with a female partner. They learned that their fictitious partner had eaten the same amount as or less than they had eaten, or were given no information. In addition, before completing self-evaluative measures, half were given the opportunity to attribute their eating to hunger as a means of mitigating or excusing the expected negative self-evaluations by those who "overate". A 3 × 2 between-subjects analysis of variance conducted on the self-ratings revealed that participants whose partners had eaten less than they ate felt the least positive about themselves (M = −.25, SD = .70), followed by those who received no information (M = +.04, SD = .63), and then those whose partners had eaten the same amount (M = +.21, SD = .60). Also, those who were given the opportunity to attribute their eating to hunger felt more positive about themselves (M = +.14, SD = .73) than those who were not (M = −.14, SD = .56). To conclude, females evaluated themselves negatively when they violated a social eating norm. Also, excuse-making affected all who were given the opportunity to do so, regardless of whether or not they overate, suggesting that eating may be fraught for all women and excusing their eating leads to more positive self-feelings.

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Stress impacts brain encoding of food

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Stress influences food intake; especially in vulnerable individuals. The neural correlates of this phenomenon are unknown. However, it is clear that stress recruits similar brain areas as those recruited during consumption of a palatable food, and that experiencing stress may lead to neural plastic changes in these regions. Critically, some of these regions, such as the amygdala, also show abnormal responses to food as a function of body mass index and play a role in the initiation of non-homeostatic feeding. We therefore reason that a mechanism by which stress may influence intake is by enhancing amygdala response to food. We are currently testing this using a 3T Trio Siemens magnet to scan overweight women consuming a palatable milkshake while listening to a personal story that recalls a stressful or a relaxing event. The scripts are highly stylized and contain descriptions of the setting, events, emotions, dialogue, and physiological responses from autobiographical stories recounted by participants. SPM 5 and random effects models are used to analyze the data. The pattern emerging from preliminary data is that there is greater amygdala response to milkshake vs. tasteless while listening to stress vs. neutral scripts, particularly for those women who score high on measures of disinhibited and emotional eating. These results accord with a prior study by Bohon et al. and suggest that acute stress enhances brain response to palatable foods in key brain regions known to drive non-homeostatic feeding. We therefore speculate that this is one mechanism by which stress may influence food intake in vulnerable individuals.

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Effects of atypical antipsychotic Olanzapine on feeding behavior and energy metabolism

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The induction of significant weight gain and insulin resistance by atypical antipsychotic drug Olanzapine (OLZ) is a major reason for patients to discontinue their treatment. The mechanism underlying OLZ-induced weight gain has not been fully elucidated. To assess the potential roles of feeding, energy expenditure and locomotor activity in the OLZ effect, we housed female rats in metabolic cages. To mimic oral administration of OLZ in humans, we treated the rats with OLZ via intragastric catheters two times per day, on three consecutive days. Initial doses of 5 mg/kg BW and 2.5 mg/kg BW showed a dramatic decrease of locomotor activity and food intake. Judging the rats' behavior, we assumed these effects were mainly due to a sedating effect of OLZ at this dose. Therefore, we decided to lower the dose to 1 mg/kg BW. At this dose, the rats were not visibly sedated. We measured an increase in meal size, but not meal number. Specifically the first meal in the dark phase 24 h after OLZ treatment almost doubled in size compared to control days. This effect was still present on the day after the last OLZ injection, i.e. when no injection at all was given, but had disappeared another day later. However, there was no acute effect of OLZ on food intake, i.e. the first meal in the dark phase directly following the very first OLZ injection was not affected compared to that on control days. Therefore, OLZ appears to have a delayed rather than acute effect on food intake. Further analysis of the energy expenditure data is warranted.

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Hypothalamus/pituitary/adrenal (HPA) axis functioning in relation to body fat distribution

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Objective: To relate HPA axis functioning and HPA feedback functioning to body fat distribution in normal weight to obese subjects. *Methods*: In 91 men and 102 women (age 18–45 year, BMI 19–35 kg/m^2, waist-to-hip ratio (WHR) 0.6–1.1) we assessed anthropometry, body composition through hydrodensitometry and deuterium dilution method, cortisol variability through measuring 5-h cortisol concentrations, and cortisol feedback functioning through a standardized high intensity test under 4 mg dexamethasone. *Results*: an inverse relationship was observed between 5-h cortisol variability (nmol/ml) and waist circumference (cm) ($r = 0.23$, $p < 0.05$) in men and WHR ($r = 0.32$, $p < 0.01$) in women, indicating impaired HPA-axis function with larger waist circumference. Similarly, an inverse relationship was observed between negative feedback expressed as baseline cortisol concentrations minus post dexamethasone cortisol concentrations (nmol/ml) and waist circumference ($r = 0.43$, $p < 0.001$) in men and WHR ($r = 0.43$, $p < 0.001$) in women. Moreover, an inverse relationship was observed between negative feedback in a challenged condition expressed as percentage increase of cortisol concentrations after standardized high intensity test under 4 mg dexamethasone (%) and waist ($r = 0.21$, $p < 0.10$) in men and WHR ($r = 0.21$, $p < 0.05$) in women. *Conclusion*: Disturbance of HPA axis functioning under basal and challenged conditions was related to visceral fat accumulation.

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Social influence on youth food intake and choice of activities

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An ever-increasing number of children and adolescents are considered overweight and obese. The social environment clearly influences youths' eating behavior and choice of activities. In this presentation we will review a series of studies conducted in our laboratory on the effects of peers and friends on children's eating behavior and choice of activities. This research shows that overweight youth eat more when alone than when in company of peers and also eat more in the presence of overweight peers than in the presence of leaner peers. Additionally, time spent alone is directly associated with sedentary levels of activity. These findings suggest that the presence of peers and friends can be used to promote healthier eating and involvement in physically active leisure activities in overweight youth. By contrast, social isolation resulting from being rejected due to weight status may decrease the reinforcing value of physical activity and increase the value of sedentary activities that can be completed alone such as television watching and snacking.

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Selective ERα antagonist's effect on food intake in ovariectomized and cycling rats

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Estrogens exert many of their behavioral effects by binding to nuclear estrogen receptor (ER) proteins, ERα and ERβ. Recent studies involving ER knockout mice and selective ER agonists suggest that estradiol's anorexigenic effect is mediated via activation of ERα. To further investigate this hypothesis, we examined whether presumptive ERα antagonists could block estradiol's anorexigenic effect. In the first series of experiments, the effects a silent ERα antagonist (MPP) on food intake and uterine weight were monitored in ovariectomized (OVX) rats treated with either a physiological dose of estradiol benzoate (EB) or a selective ERα agonist (PPT). In the next set of experiments, food intake was monitored following acute administration of MPP in ovarian-intact (cycling) female rats. Contrary to our hypothesis, MPP failed to attenuate either EB's or PPT's ability to decrease food intake and increase uterine weight in OVX rats. However, in ovarian-intact rats, a similar regimen of MPP treatment attenuated the phasic decrease in food intake that is associated with estrus. We conclude that MPP may be a useful tool to investigate the behavioral actions of endogenous estradiol, but may have limited utility in studying the behavioral effects of exogenous estradiol in OVX rats.

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Neuroendocrinology of anorexia nervosa

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We reviewed the literature on the effects of food restriction and starvation in humans and suggest that the symptoms of anorexia nervosa are epiphenomena to starvation and the associated disordered eating. Keys and collaborators decreased the food available to mentally and physically healthy men and found that these men developed most of the symptoms of eating disorders, including the psychiatric symptoms, indicating that an eating disorder can be developed without an antecedent mental disorder. Humans have evolved to cope with the challenge of starvation and the neuroendocrine mechanisms that have been under this evolutionary pressure are responses to the externally imposed shortage of food. We will provide examples for this by showing the actions and alterations of Neuropeptide Y, dopamine and norepinephrine in an animal model for anorexia nervosa. Based on the observation in patients in the anorexia clinic in Sweden and experiments with the rat model we developed a theoretic framework for the development of anorexia nervosa suggesting that the brain mechanisms of reward are activated when food intake is reduced and that disordered eating behavior is subsequently maintained by conditioning to the situations in which the disordered eating behavior developed via the neural system for attention. In a method based on this framework, patients are taught how to eat normally, their physical activity is controlled and they are provided with external heat. The method has been proven effective in a randomized controlled trial.

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The varied influences of intestinal 'bitter taste' on ingestive behavior

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Bitter taste receptors are expressed in the intestinal mucosa, but little is known about their roles in detection and ingestive behavior. The present study examined the effects of concurrent intraduodenal (ID) infusions of a bitter stimulus, denatonium benzoate (DB), on the microstructure of licking for water. Rats with ID catheters were trained to take their daily water in 30 min. During control sessions, each lick at a lickometer spout delivered water simultaneously to the spout (4 μL) and ID (2 μL). Probe sessions were identical to control sessions, except that DB instead of H_2O was infused ID during 5–8 min. An ascending DB series (0.01–10 mM) over 12 probe sessions was applied. Even at the lowest concentration (0.01 mM), ID infusions of DB caused more licks per session. This difference was characterized by a faster lick rate, pronounced by more rapid interlick intervals (<250 ms), and further evident in an increase in lick burst size, with no change in burst duration, in DB probe sessions. The DB stimulation effect weakened over the ascending concentration series, suggesting that habituation may have occurred. To test for habituation, rats were given a single offline pairing of oral DB and LiCl. This dishabituation pairing reinstated responding to ID DB. Finally, to determine if the ID DB was aversive, rats were trained to associate a flavor (CS+) with ID 10 mM DB and another flavor with ID water. In a two-bottle test, rats avoided the CS+. The results suggest ID DB has rapid, distinct unconditioned and conditioned effects on ingestive behavior. NIH HD052112 and DK27627.

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Oral and post-oral determinants of sweetener appetite in mice
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The avidity of male C57BL/6J (B6, $n = 59$) mice for the non-caloric sweetener sucralose and caloric sugars was investigated in short- and long-term tests. In an initial 24-h choice test, B6 mice equally preferred 0.8% sucralose and 8% sucrose. Yet after separate 24-h exposures to each sweetener they strongly preferred sucrose. This was attributed to the post-oral effects of sucrose. Sucralose was next compared to the components of sucrose that have strong (glucose) and weak (fructose) post-oral reward effects. New mice preferred 0.8% sucralose to both 8% sugars in 1-min choice tests, suggesting it has a sweeter taste at these concentrations. In 24-h choice tests, other mice preferred sucralose to fructose but glucose to sucralose. The switch from a sucralose preference at 1 min to a glucose preference at 24 h suggests the action of post-oral glucose reward. To probe the rapidity of this post-oral action, new food-deprived mice adapted to lick 0.8% sucralose in 60-min, one-bottle tests were switched to either 8% fructose or glucose. The licking response to fructose was suppressed, relative to sucralose, in the first min and remained so throughout the 60-min test. The licking response to glucose was also suppressed in the first minute but then increased and surpassed the sucralose licking rate by 6 min. These results suggest that glucose has a rapid post-oral action that stimulates ingestion in mice within minutes. The differential response of mice to sucralose, glucose and fructose may be a useful model system to explore oral and post-oral determinants of sweetener appetite.
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Effects of amylin on food intake, weight gain and body composition following exposure to chronic social stress
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Amylin, co-released with insulin in response to meals, slows gastric emptying and reduces food intake. Peripheral administration reduces body weight through adipose loss, while preserving lean mass. In this study we hypothesized that amylin would attenuate the hyperphagia and adipose gain that occurs following chronic social stress. In the visible burrow system (VBS), an ethologically relevant model of social stress, male rats rapidly form a dominance hierarchy, with one male dominant (DOM), and the others subordinate (SUB). Although DOM and SUB rats lose weight in the VBS in comparison to pair-housed control (CON) animals, DOM quickly regain lost weight, whereas SUB maintain a lower body weight throughout VBS housing. Following removal from the VBS, SUB is hyperphagic and regains weight predominantly as adipose tissue. In this study we implanted CON, DOM and SUB rats with either a subcutaneous osmotic minipump which released amylin or a blank pump. CON, DOM and SUB rats gained less weight than their blank implanted counterparts. 24-h food intake of DOM and SUB was reduced in the first days of recovery from the VBS. Although not statistically significant, CON, DOM and SUB treated with amylin tended to have less fat than their blank implanted counterparts 14 day following implantation. These data demonstrate that amylin decreases weight gain, hyperphagia and may alter body composition following social stress. Current studies are investigating the effects of post-VBS amylin treatment on gene expression in hypothalamic and hindbrain regions.
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Effects of the droplet size of intraduodenal fat emulsions on antropyloroduodenal motility, hormone release and appetite in healthy males
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Small intestinal fat modulates gut motility, plasma CCK and PYY release and appetite and energy intake. These effects are dependent on the lipolysis of fat. We hypothesized that increasing the droplet size of a fat emulsion would attenuate these effects. Ten healthy males were studied on four occasions in randomized order. Antropyloroduodenal pressures, plasma triglycerides, CCK and PYY, and appetite were measured during 120-min intraduodenal infusions of fat emulsions comprising 3 droplet sizes: (i) 0.26 μm ("LE-0.26"), (ii) 30 μm ("LE-30") or (iii) 170 μm ("LE-170") and (iv) saline ("control"). Energy intake at a buffet lunch was quantified immediately after the infusions. Increasing the lipid droplet size was associated with diminished suppression of antral and duodenal pressure waves ($r < 0.80$, $P < 0.01$) and stimulation of isolated and basal pyloric pressures ($r > -0.83$, $P < 0.01$), attenuation of the stimulation of plasma triglycerides, CCK and PYY ($r > -0.83$, $P < 0.001$), as well as reductions in the suppression of hunger and energy intake ($r < 0.75$, $P < 0.001$). In conclusion, the acute effects of intraduodenal fat emulsions on gut function and appetite are dependent on the fat droplet size. These observations have implications for the design of functional foods to maximize effects on those gut functions that are involved in the suppression of appetite.
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Estrogen enhances sucrose pellet reinforcement
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Adult female rats are more sensitive to psychostimulant drugs, an effect that appears to be mediated by estrogen. We hypothesized that estrogen enhances reinforcement learning and we predicted that increased estrogen levels would promote operant responding for sucrose. We examined fixed and progressive ratio responding under a variety of hormonal conditions. We first examined reinforcement learning in intact male and female rats across estrous cycle. Females at proestrous phase with highest levels of circulating estradiol earned significantly more sucrose reinfocers and lever-pressed more than did females at other phases and males. Then we tested reinforcement learning in rats that received ovariectomy (OVX) accompanied by estradiol benzoate (2 μg/0.1 ml sc; OVX + E) or oil replacement (0.1 ml sc; OVX + V) every four days. One week after OVX, there was no difference in body weights between OVX + E and OVX + V groups. OVX + E rats earned significantly more sucrose reinfocers than OVX + V rats did. In addition, OVX + E rats had a trend to lever-press more than OVX + V rats ($P = 0.06$) on the first after injection when circulating estradiol reached its peak. Body weighs of OVX + E rats were significantly less than those of OVX + V rats two weeks after OVX, and no difference was observed for sucrose reinforcement between OVX + E and OVX + V rats two, six, or ten weeks after OVX. In summary, our findings suggest that sex differences in food reward are relevant when body weight are matched with evidence implicating circulating estradiol level, at least in part, contributes to the enhanced sensitivity to the reinforcing effects of sucrose in females.
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Enhanced postprandial PYY, GLP-1, amylin, suppression of ghrelin, and restoration of glucose homeostasis in a rat model for Roux-en-Y gastric bypass surgery

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Roux-en-Y gastric bypass (RYGB) surgery is the most effective treatment for obesity and associated diabetes, but the mechanisms involved are poorly understood. We have developed a rat model for RYGB to investigate the potential role of gastrointestinal hormones. Male Sprague–Dawley rats made obese on a high-fat diet were subjected to RYGB ($n=5$) or sham-surgery ($n=5$), and continued on a two-choice (chow/high-fat) diet after surgery. Lean rats never exposed to high-fat ($n=5$) served as additional controls. 3–4 months after surgery, hormonal responses to a test meal (5 ml of Ensure, 1 ml/min, delivered via intra-oral fistulas) were examined by frequent blood sampling through chronic jugular catheters in freely behaving rats and commercially available Multiplex-Luminex assays. Obesity-induced hyperleptinemia and hyperglycemia were completely reversed by RYGB, while the postprandial insulin response was augmented compared with lean rats. Meal-stimulated levels of PYY (AUC: RYGB, 45 ± 10; sham, 9.3 ± 3.9; lean, 8.5 ± 5.4), active GLP-1 (RYGB, 7.2 ± 2.1; sham, 0.9 ± 02), and amylin (RYGB, 4.2 ± 0.4; sham, 2.5 ± 0.6) were significantly increased, while meal-induced suppression of acylated ghrelin (RYGB, $72\pm1\%$; sham, $41\pm5\%$; lean, $47\pm8\%$, all $p<0.05$) was enhanced after RYGB compared to both sham (obese) and lean controls. The model thus confirms and extends reports in RYGB patients and provides a basis for mechanistic studies and specific hypothesis testing.

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Categorization of healthy and unhealthy foods. Reaction times and explicit responses

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People do not have difficulties in classifying healthy and unhealthy foods. We hypothesized, however, that people differ in their response times when classifying foods as healthy or as unhealthy. Response times can be viewed as a measurement of how automatic the association of healthy/unhealthy with a food product is. Healthy (e.g., apple), neutral (e.g., pasta), and unhealthy (e.g., Big Mac) stimuli were presented. Participants ($N=78$) were asked to classify 18 food stimuli, as quickly as possible, as healthy or unhealthy. The computer recorded the responses and the response times. Consumption frequency and likeability of the foods were also measured. Response times differed significantly across food categories and across groups of participants. Participants needed more time to evaluate unhealthy food items compared with healthy food items. It seems easier to classify a healthy food item as healthy than an unhealthy food item as unhealthy. Women were quicker in evaluating healthy and unhealthy food stimuli than men. No gender differences were observed for neutral food items. Results suggest that likeability and consumption frequency are possible factors affecting response times. People who need more time to decide that a food item is unhealthy may be more likely to consume such food. People using stereotypical information about food may have a healthier diet.

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PVN and PBN in prostaglandin induced fever and anorexia

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Fever and anorexia are induced by an immune system challenge. While these responses are adaptive when short lasting, they can be deleterious if prolonged. Therefore it is crucial to understand the signaling elements and neurocircuitry mediating these responses. Prostaglandins (PGE) are a critical signaling element. Despite the presence of PGE receptors (EP-R) in several brain areas, research has focused on the role of preoptic area of the hypothalamus as the site of PGE action, especially for the pyrogenic effect. Little is known about the location of other EP-Rs mediating the anorexic or pyrogenic effects of PGE. Paraventricular (PVN), parabrachial nucleus (PBN) and nucleus tractus solitarius (NTS) neurons express EP-Rs, contribute to neurocircuits underlying both temperature and intake control, and are activated during systemic pathogen infection. Their role in PGE fever and anorexia is unclear and is the subject of our study. Two doses of PGE_2 (0.1 and 0.2 μg) were microinjected into dorsal PVN, lateral PBN and medial NTS; core temperature, heart rate, activity and food intake were measured in freely moving rats. PGE_2 stimulation of either PVN or PBN induced a short latency (<10 min) fever and tachycardia. However, only PVN stimulation produced an anorexic effect. No significant changes in locomotor activity were found for either site. NTS PGE_2 stimulation had no effects on the measured parameters. Our data highlight new targets of action in CNS and, importantly, indicate two independent trigger zones for PGE_2 induced fever. The data underscore a potential anatomical dissociation of pyrogenic and anorexic effects of PGE_2.

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Eating less, while burning more; acute effects of bioactive components during energy restriction

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Adherence to weight-loss diets is difficult and uncomfortable. It is therefore of importance to design weight-loss diets that tackle undesirable physiological responses of the body. The aim was to investigate whether an 80% energy requirement (ER) diet plus bioactive mixture (BM), containing resistant starch, capsaicin, green tea, and dietary protein, reaches the same satiety and thermogenesis level as a 100% ER diet without BM. Sixteen subjects were studied for 2 days in 4 conditions: (1) 100% ER diet plus BM (100%H); (2) 100% ER diet, without BM (100%C); (3) 80% ER diet plus BM (80%H); (4) 80% ER diet, without BM (80%C), while appetite profile and energy expenditure were continuously monitored. Feelings of satiety were significantly higher in condition 80%H (1210 ± 86 mm*24 h) than in condition 100%C (1022 ± 100 mm*24 h, $p<0.02$). Total energy expenditure was significantly higher in condition 80%H (9.14 ± 0.32 MJ/d) than in condition 100%C (8.90 ± 0.29 MJ/d, $p<0.02$). Fat balance in condition 80%H (-20 ± 5 g/d) was significantly different from fat balance in condition 100%C (16 ± 4 g/d, $p<0.001$). Carbohydrate balance was significantly different in condition 80%H (-43 ± 9 g/d) from carbohydrate balance in condition 100%C (25 ± 7 g/d, $p<0.001$). Protein balance was not different between condition 80%H (-1 ± 7 g/d) and condition 100%C (-1 ± 2 g/d). In conclusion, a combination of bioactive components may facilitate adherence to an energy deficit diet by sustaining satiety and energy expenditure.

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Oral anesthesia reveals individual differences in food-related sensory interactions

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Flavor sensation incorporates taste, oral touch, and retronasal olfaction (RO), which merge into a unitary percept localized to the mouth. The mechanisms governing this process are not fully understood, but our data reveal important interactions among food-related cues. Mounting evidence shows that regional oral sensory loss produces compensatory disinhibition at remaining oral loci: Chorda tympani (CT) anesthesia leads to elevated glossopharyngeal sensation; among supertasters of 6-n-propylthiouracil, it also enhances trigeminal (V) sensation. Moreover, oral sensation supports RO: individual differences in it extend to RO, and CT block compromises RO function without affecting orthonasal sensation. Our most recent study suggests that the effects of oral sensory change occur in proportion to genetic taste status, and that affected sensations are differentially susceptible to these effects. In healthy subjects with low taste function, unilateral block of either CT or the lingual nerve (i.e., CT + V) asymmetrically suppressed posterior taste sensation; this may reflect mild disinhibition. Contralateral anterior oral burn remained intact with both nerve blocks, while posterior oral burn was blunted bilaterally; these data confirm that disinhibition at V is linked to high taster status. Finally, both nerve blocks produced similar RO losses, suggesting that taste input surpasses trigeminal input in supporting RO. In sum, the modulation of flavor components by oral sensation varies by modality, taster status, and pathology, leading to broad individual differences in the balance of food-related sensory input.

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Low carbohydrate intake only shows a larger decrease in body weight and fat percentage in the presence of high protein intake

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Introduction: Our objective was to examine if combination of high-protein and low-carb intake (HPLC) compared to high-protein (HPNC) or low-carb (NPLC) or normal-protein normal-carb intake (NPNC) results into a difference in body composition. *Methods*: Body-weight and body composition (deuterium-dilution) of 143 subjects (BM 106.6 ± 20.1 kg FM% 43.9 ± 5.8%) and blood- and urine-parameters were assessed before and after 3 months energy intake reduction of 67%. HPLC consisted of 60/5/35E% protein/carb/fat and resulted in 120 ± 41 g of protein intake (24 h nitrogen), HPNC of 60/35/5E% and 105 ± 30 g, NPLC of 30/5/65E% and 73 ± 21 g, and NPNC of 30/35/35E% and 67 ± 16 g. *Results*: HPLC reduced BM and FM% most. The synergistic effect of HP and LC and the effect of HP in the LC condition was already significant on BM-reduction after 1 month (HPLC vs. NPNC −6.7 ± 2.1 vs. −5.1 ± 1.8, $p < 0.005$; and vs. NPLC −5.8 ± 1.7, $p < 0.05$). The effect of HP was significant after 3 months in the normal- (HPNC vs. NPNC; BM −12.6 ± 4.1 vs. −10.6 ± 4.0, $p < 0.01$ and FM% −5.7 ± 3.3 vs. −3.9 ± 2.5, $p < 0.05$) and low-carb condition (HPLC vs. NPLC; BM −15.3 ± 4.5 vs. −12.2 ± 4.4, $p < 0.01$ and FM% −6.6 ± 2.6 vs. −4.8 ± 3.7, $p < 0.05$). There was no effect of LC in the normal- (NPLC vs. NPNC) or the high-protein (HPLC vs. HPNC) condition. Changes in waist, MDRD, albumin-creatinin-ratio, glucose, insulin, and cholesterol were not different between diets. *Conclusion*: High-protein shows a larger decrease in BM and FM% irrespective of the presence of low-carb, while low-carb only shows a larger decrease in BM and FM% in the presence of high-protein.

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Eating behavior and lifestyle characteristics within a sample of vegetarian and non-vegetarian university students

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Since the 1980s, interest in new-wave vegetarianism has become increasingly popular. The limited research conducted in this area has produced conflicting results, with only some studies showing a clear positive relationship between vegetarianism and eating disordered behavior. These discrepant findings may be due to inconsistent definitions of vegetarianism, small sample sizes, and disparate age-ranges between groups. The current study aimed to address some of these issues in order to better understand the relationship between vegetarianism and eating disordered behavior. Fifty vegetarians (88% female) and 50 non-vegetarians (68% female), matched for age, ethnicity, race, family income and other lifestyle characteristics such as alcohol and cigarette use, completed a battery of questionnaires about their eating behavior. Results suggest that vegetarians were less food neophobic and similar in their restrained eating when compared to non-vegetarians. There were no significant differences between groups on the Eating Attitudes Test, suggesting that vegetarians did not differ from non-vegetarians in their current disordered eating behavior. However, of the seven participants who indicated that they had previously been treated for an eating disorder, five became vegetarians by the age of 14 years. Thus, consistent with prior research, becoming a vegetarian at a young age may serve as a risk factor for later disordered eating. These results add to the existing literature and provide further insight into the complicated connection between vegetarianism and eating behavior.

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Dopamine-related genotypes moderate relation between reward circuitry activation and weight gain. A prospective fMRI study

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The present study tested whether elevated anticipatory food reward is related to elevated weight and future weight gain, and whether genotypes associated with reduced dopamine signaling (DRD2, DRD4) moderated these relations. We used fMRI to measure responses in meso-limbic reward system and associated regions in response to imagined intake of appetizing food, unappetizing foods, or glasses of water in 39 girls (14–18 years; BMI range = 17.3–38.9). Cross-sectional analyses indicated that BMI was positively correlated with activation in the superior frontal gyrus, medial orbitofrontal cortex, putamen, and frontal operculum in response to imagined intake of appetizing food and that these relations were moderated by DRD2 and DRD4 genotype status. Yet prospective analyses indicated that participants who showed a blunted response in the putamen, medial frontal cortex, and frontal operculum in combination with these genotypes showed the greatest weight gain over the 1-year follow-up. These latter results converge with evidence that women who showed reduced dorsal striatum activation in response to food and possessed the DRD2 genotype showed the greatest future weight gain. Results suggest that blunted response of food reward circuitry increases risk for weight gain if coupled with genetic risk for compromised dopamine signaling. Findings also illustrate the importance of prospective fMRI studies, rather than cross-sectional studies.

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Excess dietary salt intake alters the excitability of central neural networks

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Salt intake is regulated by complex humoral, visceral, and neural stimuli to maintain body fluid homeostasis. However, excess dietary salt intake increases the risk for the development of several cardiovascular diseases including salt-sensitive hypertension. In this regard, compelling evidence from clinical studies and experimental models indicates that dietary salt intake acts synergistically to exacerbate the level of hypertension through increases in sympathetic nerve activity (SNA). Therefore, we hypothesized that excess dietary salt enhanced the excitability of sympathetic-regulatory networks. Male Sprague–Dawley rats (200–300 g) were fed standard laboratory chow and given access to water or 0.9% NaCl for 14 days ($ns > 8$). Excitation of sympathetic-regulatory neurons in the rostral ventrolateral medulla (RVLM) with injection of L-glutamate (1 nmol) produced significantly greater increases in renal SNA (123 ± 8 vs $82 \pm 6\%$) and blood pressure (44 ± 3 vs 24 ± 1 mmHg) of rats drinking 0.9% NaCl versus water. Conversely, inhibition of RVLM neurons with GABA (10 nmol) produced significantly greater decreases in blood pressure (-31 ± 3 vs -15 ± 1 mmHg) of rats drinking 0.9% NaCl versus water. Additional experiments demonstrate: (1) lesion of the ventral forebrain lamina terminalis prevents these salt-induced changes, and (2) excess dietary salt does not enhance the excitability of all sympathetic-regulatory networks. Collectively, these findings suggest that excess dietary salt intake may have adverse effects on the excitability of central neural networks to contribute to the pathogenesis of cardiovascular disease.

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Enkephalinergic signaling in the limbic forebrain modulates palatable food intake

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Palatability associated cues potently increase food intake. Opioid signaling has been implicated in modulating palatable food consumption, but neural mechanisms underlying this effect are poorly understood. We investigated the role of the endogenous opioid ligand enkephalin, which is widely expressed in taste and reward circuits, in palatability-driven food intake and taste encoding. Preproenkephalin KO mice did not differ from WT littermates in baseline feeding behavior. However, systemic administration of the opioid antagonist naltrexone (NTX) suppressed sucrose intake in WT mice, but slightly increased intake in the KO. This was true for caloric and noncaloric tastants, indicating that NTX effects were independent of postingestive effects. NTX reduced positive taste reactivity patterns in WT mice, suggesting effects on intake occurred through a palatability based mechanism. We analyzed cfos immunohistochemistry to pinpoint anatomical loci where NTX-induced changes in expression diverged between WTs and KOs. NTX increased cfos expression in the central nucleus of the amygdala (CeA), a direct recipient of brainstem taste inputs, in WT mice but not KO mice. Direct NTX infusion into the CeA decreased intake in WT animals. Finally, we used electrophysiological methods to investigate taste encoding in the amygdala in behaving mice. Preliminary results suggest that NTX acts to attenuate the magnitude of palatable taste-evoked responses in WT but not KO mice. Our results suggest enkephalinergic signaling in the amygdala importantly modulates palatability processing.

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The effects of maternal obesity on anxiety, stress response and food preference of juvenile Japanese macaques

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Alterations in maternal nutrition during development have long-term effects on offspring behavior. Given the current obesity epidemic it is critical to examine the consequences of maternal over nutrition on offspring behavior. The goal of this study was to examine the consequences of maternal obesity and high-fat diet consumption on anxiety like behavior, stress sensitivity and food preference of juvenile nonhuman primates. Offspring from female Japanese macaques consuming either a low-fat (13%) control diet or a high-fat (35%) diet (HFD) were examined. The Human Intruder test and novel object tests were used to assess stress and anxiety responses to a social threat or novel item. These tests were adapted from tests used in children and have been shown to reliably assess individual differences in primate stress response and anxiety. Preference for diets of differing fat and sugar content were also examined. At 4 months of age, offspring from mothers fed a HFD exhibited increased latency to explore novel objects and increased aggression. Also, CSF serotonin was decreased in offspring from HFD fed mothers. Food preference testing revealed that offspring from HFD fed mothers were more likely to consume novel diets and had increased preference for the diet that was high in fat and sugar content as compared to offspring from control diet fed mothers. This data suggests that maternal over nutrition results in heightened anxiety and aggression in juvenile nonhuman primates potentially due to decreased serotonin levels.

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Increased expression of Igf2 and glucose transporters in placenta of mice produced by assisted reproductive techniques (ART)

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ART that allow infertile couples to have children have increased such that 1–3% of all children are now conceived by ART. Although all the long-term consequences are not yet known, children produced by in vitro fertilization (IVF) have a significantly increased incidence of metabolic and cardiovascular deficits. Of concern, mice produced by somatic cell nuclear transfer (SCNT) have adult-onset obesity, hyperleptinemia, hyperinsulinemia and impaired glucose tolerance. Although SCNT is not currently used in humans, SCNT and ART such as IVF and intracytoplasmic sperm injection (ICSI) share some in vitro techniques. Placental hypertrophy in SCNT mice suggests that placental function and in utero nutrient transfer may be altered as a consequence of in vitro manipulation. Expression of Igf2, Glut1 and Glut3 was measured by RT-PCR in E19.5 placentas from female mice impregnated by natural mating (STOCK), IVF, ICSI, and SCNT. IVF, ICSI and SCNT mice all had higher Glut1 expression compared to STOCK ($P < 0.05$). SCNT mice also had greater expression of Igf2 ($P < 0.05$) and Glut3 ($P < 0.05$). These data suggest that in vitro manipulation and culture conditions used in ART may increase offspring susceptibility to metabolic consequences through alterations in placental nutrient transfer to the fetus. NIH grants HD055030, DK072488, DK068273.

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Dose-dependent effects of caffeine on physiology and behavior in adolescents

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Caffeine is the most widely used psychoactive substance in the world, but its effects in children and adolescents remain understudied and poorly understood. The purpose of our study was to assess the extent to which adolescents develop tolerance to the effects of caffeine and to examine the effects of acute (dose) and chronic (group) caffeine on snack food intake and liking and detection of sucrose solutions. In addition, we assessed the relationship between caffeine use and use of other substances. Children, ages 12–17, visited our lab on four occasions, each separated by 1 week. The participants consumed a beverage containing 0 mg, 50 mg, 100 mg, or 200 mg of caffeine (order counterbalanced). They completed a behavioral checklist, had heart rate and blood pressure taken every 10 min for 1 h, completed questionnaires to assess licit and illcit substance use, completed a hand tremor test, a sucrose detection panel, and an ad libitum eating session. We found a dose-dependent increase in blood pressure and decrease in heart rate regardless of usual caffeine consumption. We also found a group, dose, and dose by group interactions on hand tremor. Low caffeine consumers were significantly more likely to report consuming alcohol than high caffeine consumers. Finally, there was a significant interaction of group and dose on perception of sweetness. When taken together, these data suggest that caffeine has a broad range of effects on physiology and behavior in adolescents, but we found little evidence for tolerance.

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Effects of age on DOCA salt appetite in rats

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Old rats, like elderly humans, have diminished thirst and drinking responses to many challenges to fluid homeostasis. In addition, salt appetite in response to sodium depletion is nearly absent in old rats. The present work investigates the effects of aging in a model of salt appetite, i.e., mineralocorticoid-induced salt appetite, that produces a state of sodium excess. We used young (4 mo, $n = 6$), middle-aged (12 mo, $n = 5$) and old (30 mo, $n = 6$) male Brown Norway (BN) rats housed in standard metabolism cages. The rats had ad libitum access to water, 0.3 M NaCl and sodium deficient diet. After 5 days of baseline, they received deoxycorticosterone acetate (DOCA; 5 mg/(kg day), sc) for 6 days. In response to DOCA, old rats drank as much saline solution as young rats (~25 ml/day, peak response), but middle-aged rats drank the most (~75 ml/day). After adjusting intakes for body weight, the order of salt consumption was 12 mo > 4 mo > 30 mo. In addition, old rats had reduced saline preference ratios (saline/total fluid intake) compared to the other groups. There were no obvious age-related differences in fluid excretion or fluid balance. Therefore, the significant effects of age on DOCA salt appetite in BN rats may be due to age-related differences in mineralocorticoid receptor binding, or to central processing of taste signals or fluid balance/volume signals, but not to age-related differences in fluid balance/volume levels per se. This work was supported by AG-025465 to RLT and HL-14388 and DK-066086 to AKJ.

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Multi-day administration of the GLP-1 agonist, exendin-4, reduces food intake and body weight and prevents fasting related alterations in hypothalamic gene expression

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Exendin-4 (Ex-4), a long-lasting GLP-1 receptor agonist, decreases food intake and body mass in humans and other species. Repeated daily administration of Ex-4 in non-human primates continues to suppress feeding across days with no compensatory increase after Ex-4 is stopped. The mechanisms through which Ex-4 act, however, are not yet clear. In this study, we investigated whether the continued effects of Ex-4 and the lack of compensation could be mediated by changes in leptin, ghrelin and hypothalamic gene expression in male Sprague Dawley rats. Rats were given Ex-4 (10 μg/kg) or saline prior to feeding for five consecutive days and were then sacrificed on the 6th day prior to feeding. As expected, Ex-4 administration decreased food intake and body mass over the 5-day period. This decrease in body mass was reflected by a decrease in white adipose tissue and plasma leptin levels, with no change in ghrelin. There were no significant differences in arcuate or dorsalmedial hypothalamic gene expression between Ex-4 treated rats compared to saline rats. Pair-fed control rats, that lost significant weight, had alterations in gene expression. These results demonstrate that multiple day activation of GLP-1 receptors appears to prevent the changes in hypothalamic gene expression due to reduced food intake and this action may explain the lack of compensatory response seen in the prior primate experiments. Supported by NIH DK19302.

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Heterogeneous weight gain by inbred mice fed a high-energy diet. Influence of litter characteristics

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When fed high-energy diet, some C57BL6/J mice gain body weight rapidly but others do not. This is puzzling because the mice have (almost) identical genes and an (almost) identical environment. What causes the variation? To investigate the contribution of early environment, 158 litters of C57BL/6J mice aged 17-wk were fed high-energy "Surweit" diet for 8 wk. Males gained 12.7 ± 0.3 g (range −3.9 to 26.8 g; $n = 327$) and females gained 7.5 ± 0.2 g (range, −2.8 to 22.2 g; $n = 357$). Diet-induced weight gain was weakly but significantly associated with weight before diet access in males ($r = 0.16$) but not females ($r = 0.06$). Surprisingly, litter size did not affect body weight or weight gain. For example, males from litters with 1–4 pups weighed 26.5 ± 0.6 g and gained 12.6 ± 1.2 g ($n = 29$); males from litters with 10–12 pups weighed 26.1 ± 0.3 g and gained 12.3 ± 0.6 g ($n = 40$). Litter sex ratio did not influence body weight; nor was there a difference between mice from single-sex or mixed-sex litters. The mice of a mother's 1st, 2nd or 3rd litter had similar body weights. These mice were significantly heavier than mice from a 4th or later litter (e.g., males from litter 1 = 26.2 ± 0.3 g, $n = 125$; litter 4–6 = 24.7 ± 0.4 g, $n = 38$), but litter number did not affect the response to high-energy diet. In summary, litter characteristics had remarkably little influence on body weight and could not account for the heterogeneous response of C57BL/6J mice to high-energy diet.

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Rodent herbivores fed novel bitter plant compounds regulate meal size

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Mammalian herbivores are faced with plants containing toxic compounds at every meal and safe ingestion of these foods requires the detection and detoxification of these compounds. One mechanism herbivores employ is to adjust meal size in a dose-dependent manner to minimize intake of plant toxins when concentrations vary. We chose to examine the ability of an herbivorous rodent, *Neotoma albigula*, to regulate an ecologically novel toxin by measuring spontaneous feeding behavior of animals fed diets with increasing concentrations (0.5%, 1%, 2% and 4%) of phenolic resin extracted from creosote (*Larrea tridentata*). Diets were presented for three days per concentration and in order of increasing concentration to allow for liver enzyme acclimation. Animals decreased total intake and meal sizes on the 2% and 4% diets compared to lower toxin diets. In a second experiment, we chose to examine the mechanism of meal size regulation by testing the hypothesis that regulation of toxin intake may be CCK-dependent. To test this hypothesis, we administered CCK-8 (0, 0.5 and 1.0 μg/(ml kg)) when animals were fed three concentrations of phenolic resin (0.5%, 2% and 4%). Although CCK produced a dose-dependent reduction in meal size, the reduction was equivalent on all three diets. In summary, although these herbivores can regulate meal size to avoid overdosing on plant toxins, the potency of CCK does not change with diet toxicity.

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Site-specific stimulation of brain melanocortin receptors increases brown adipose tissue (BAT) thermogenesis via sympathetic nervous system (SNS) innervation

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Fat breakdown (lipolysis) occurs via β-adrenoreceptors and then intracellular cascades involving hormone sensitive lipase (HSL) and perilipin A proteins in brown and white adipocytes. White adipose tissue (WAT) lipolysis and interscapular BAT (IBAT) thermogenesis is also affected by melanocortin system activation. There is extensive co-localization of melanocortin 4 receptor (MC4R) mRNA on sympathetic outflow neurons to WAT and IBAT across the neuroaxis. 3rd ventricular MTII (a MC3/4R agonist) significantly increases sympathetic drive to subcutaneous WAT and IBAT, IBAT thermogenesis and phosphorylated HSL and perilipin A (lipolytic markers) in WAT and IBAT. These experiments tested whether microinjections of MTII or cyclo [β-Ala-His-D-Phe-Arg-Trp-Glu]-NH2 (a MC4-R agonist) into the sub zona incerta (subZI), a site of high MC4R mRNA co-localization of SNS outflow neurons to WAT and IBAT, triggered IBAT thermogenesis and/or WAT lipolysis. MTII significantly increased IBAT temperature at 1-h post injection at 0.075 nmol and 4 h post injection at 0.05 nmol.The cyclo compound increased IBAT temperature at 1-, 2-, and 3-h post injection. Neither MTII nor the cyclo compound increased peripheral WAT lipolytic markers (glycerol and free fatty acids serum levels). Tests for phosphorylated HSL and perilipin A levels are ongoing. These results help in defining the chain of events beginning with SNS outflow neurons in brain and ending with the lipolytic changes in the adipocyte *in vivo*. This work was supported by NIH R01-DK35254 and F32-DK82143.

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Differential effects of ghrelin on spatial learning in males and females

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Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor (GHSR) is well-known for its effects on food intake and body weight. Ghrelin has also been demonstrated to enhance performance on multiple learning and memory tasks, while mice with a selective deletion of the ghrelin gene display impaired memory retention. Peripherally administered ghrelin has been shown to enter the hippocampus, bind to GHSR, and increase dendritic branching, while decreased branching was observed in ghrelin-deficient mice (Diano et al., 2006). Here, we demonstrate that selective deletion of the GHSR gene specifically impairs performance in the Morris water maze, a hippocampal-dependent spatial learning task. It is also known that ghrelin's ability to increase food intake is diminished in intact females relative to males and varies with estradiol level (Clegg et al., 2007). Therefore, we also assessed spatial learning in female mice. In contrast to males, GHSR deficiency did not affect performance on this task in females. We further assessed ghrelin supplementation on performance of this hippocampal-dependent task in both male and female mice. Our results extend previous data by demonstrating that the effect of ghrelin to alter hippocampal dendritic morphology extends to behavior on a hippocampal-dependent test of spatial learning and memory. Further, our data indicate that the effect of ghrelin on learning and memory is sex-dependent, and suggest that ghrelin and GHSR may play a role in sex differences in spatial learning.

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Gluconeogenesis and energy expenditure after a high protein, carbohydrate-free diet

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A high protein diet, especially in the absence of carbohydrates, may stimulate gluconeogenesis (GNG) and this process may be responsible for the increased energy expenditure (EE) at such a diet. Here, the objective was to study whether a high protein, carbohydrate-free diet increases GNG and can explain the increase in EE. Ten healthy male subjects (mean ± SEM BMI: 23.0 ± 0.8 kg/m^2, age: 23 ± 1 years) received an iso-energetic high protein, carbohydrate-free (H, 30/0/70En% protein/carbohydrate/fat) or a normal diet (N, 12/55/33En% P/CHO/F) for one and a half day in a randomized, crossover design in a respiration chamber. Endogenous glucose production (EGP) and fractional GNG were measured using infusion of [6,6-$^2H_2$]glucose and ingestion of ^2H_2O; absolute GNG was calculated by multiplying fractional GNG with EGP. Body glycogen stores were lowered at the start of the intervention with an exhaustive glycogen-lowering exercise test. EGP was lower in H than in N (181 ± 9 g/d vs. 226 ± 9 g/d, $p < 0.001$) whereas fractional GNG (0.95 ± 0.04 vs. 0.64 ± 0.03, $p < 0.001$) and absolute GNG (171 ± 10 g/d vs. 145 ± 10 g/d, $p = 0.06$) were higher. The increase in resting metabolic rate (RMR) in H compared with N (8.46 ± 0.23 MJ/d vs. 8.12 ± 0.31 MJ/d, $p < 0.05$) was a function of the increase in GNG ($\Delta RMR = 0.0046^* \Delta GNG - 0.0021$, $r = 0.65$, $R^2 = 0.42$, $p < 0.05$). In conclusion, a major part of the increased energy expenditure at a high-protein, carbohydrate-free diet can be explained by increased gluconeogenesis.

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Desensitization of dipsogenic activity after repeated angiotensin II administration

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Angiotensin II (AngII) is a potent stimulus for water intake, but several reports indicate that repeated injections lead to desensitization of this dipsetic property. Additional studies *in vitro* demonstrate rapid desensitization of the AngII type 1 (AT_1) receptor in cardiomyocytes and vascular smooth muscle. Little is known, however, about the mechanism involved in AngII-induced desensitization. To address this issue, we established a reliable protocol to generate desensitization of AngII-induced water intake. Specifically, we found that three pre-test injections of 300 ng AngII, given 20 min apart, reduced the drinking response to a test injection of 10 or 100 ng AngII. The desensitizing property of the pre-test injections was dependent on the timing and dose of the injections used. To examine the specificity of the response to repeated AngII exposure, we used a two-bottle test in which rats had access to both water and 1.5% NaCl. This experiment demonstrated a surprising specificity of the effect to water, but not saline intake. Ongoing experiments are attempting to elucidate the intracellular signaling mechanisms that give rise to this phenomenon. These experiments utilize a synthetic AngII analog which activates only a subset of AT_1-induced intracellular signaling cascades. Preliminary results suggest that the behavioral desensitization observed after repeated AngII administration may be associated with the selective activation of specific intracellular signaling pathways.

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9-Tetrahydrocannibinol (THC) attenuates weight loss in an activity-based model of anorexia nervosa

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Activity-based anorexia (ABA), an animal model of anorexia nervosa (AN), involving scheduled feeding and voluntary exercise (running wheel activity (RWA)) leads to hypophagia, dramatic body weight loss and ammenhoria. The cannabinoid system is involved in appetite control however its efficacy in preventing the development of ABA is not well known. Here the effect of chronic THC treatment in ABA rats given a standard chow or high fat food on a scheduled feeding regimen was investigated. Firstly, female Sprague-Dawley rats ($N = 15$) were treated with vehicle or THC (2 mg/kg i.p.) daily for 5 days and allowed access to standard laboratory chow for 1.5 h. THC treated animals showed a significant attenuation of ABA while producing only a transient stimulating of feeding. A second cohort of rats ($N = 15$) was treated for 7 days as described above and on this occasion given access to a palatable high fat diet. THC treatment again produced a significant attenuation of ABA with only a transient increase in feeding. THC treated chow fed animals were indistinguishable from vehicle treated animals fed a high fat diet; however, when THC and a high fat diet were combined, a synergistic attenuation of weight loss was observed that was significantly greater than would be attributed to the attenuation of weight loss in vehicle treated high fat fed and THC treated chow fed animals. In both cohorts RWA was not significantly affected by THC treatment. These data establish the efficacy of cannabinoids in attenuating weight loss seen in AN at least as observed in the ABA model.

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Evidence for a novel role for the CB2 receptors in the mediation of energy intake and expenditure

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The endocannabinoid system has long been recognized as an important modulator of energy balance; an effect exerted mainly via the cannabinoid CB1 receptor. The CB2 receptor has primarily been implicated in mediating immune function, however recent evidence has pointed towards an involvement in energy intake. Here we show the effect of sub chronic manipulation of CB2 receptors on energy intake, body weight, and energy expenditure. C56BL/6J mice ($N = 8$) were made diet induced obese (DIO) by maintaining them on a high fat diet for 3 months. The CB2 receptor agonist JWH-015 (5 mg/ml i.p.) or vehicle was injected for 7 days and food intake and body weight measured daily. JWH treated animals showed a significant reduction in body weight that continued despite only a transient reduction in food intake. In order to determine the extent to which the sustained reduction in body weight was due to an impact on energy expenditure, mice were housed in calorimetry cages was acclimatized to the indirect calorimetry cages for 3 days and injected with either vehicle or JWH for two days. Results showed a significant elevation in O_2 consumption coupled with a reduction in respiratory quotient, the latter suggesting increased fat oxidation. In conclusion, these data show the impact of the CB2 receptor system in influencing body weight via a shift in energy expenditure and nutrient partitioning.

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Disruption in satiety signaling in people with schizophrenia taking olanzapine or clozapine

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Weight gain due to second generation antipsychotics, particularly olanzapine (OLAN) and clozapine (CLOZ), is significant and has led to other health problems including diabetes and cardiovascular disease. The mechanism(s) by which these drugs cause weight gain is unknown. The present investigation compared test meal (TM) intake following a nutritive (12 oz Ensure) or nonnutritive (12 oz water) preload in people with schizophrenia who were taking either OLAN ($n = 13$); CLOZ ($n = 12$) or non-weight-gain-producing antipsychotics (NWPAs) ($n = 6$); and healthy controls ($n = 11$). Wheat Thins and Nilla Wafers were used as the test meal. Groups were age- and BMI-matched. As hypothesized, preliminary analyses reveal that OLAN (M = 234.0, SD = 125.0 g) and CLOZ participants (M = 245.6, SD = 206.8 g) tend to consume more TM than the control participants (M = 174.9, SD = 164.g) in the Ensure condition, and in the water condition (olan: M = 316.6, SD = 135.9 g; cloz: M = 330.6, SD = 294.9 g; controls: M = 178.1, SD = 125.5 g). Though not statistically significant, the magnitude of effect was moderate (Cohen's $d = 0.39$) for the Ensure condition and large (Cohen's $d = 0.84$) for the water condition. OLAN participants (M = 56.6, SD = 27.3) rated the flavor of a meal as significantly less important, on a 100 mm visual analogue scale, than CLOZ participants (M = 80.7, SD = 14.1 mm) and control participants (M = 96.6, SD = 8.3 mm), $F(2, 27) = 11.98$, $p < 0.05$ (NWPA data is incomplete at this time). Participants on OLAN rated "how full it makes you feel" as a significantly more important aspect of food than the other groups, $F(3, 41) = 4.71$, $p < 0.05$. TM intake and hunger rating comparisons reveal that OLAN appears to disrupt hunger and satiety signaling. OLAN participants had a greater disconnect between hunger ratings and TM intake and tend to make food choices based on perceived hunger-relieving properties of food rather than flavor. OLAN participants may gain weight due to aberrant satiety signaling causing increased consumption that is maintained throughout the day. In contrast, CLOZ participants tended to consume according to hunger ratings consistent with the theory that weight gain induced by CLOZ may have a metabolic component. This preliminary data helps in understanding metabolic and

weight gain differences associated with antipsychotic treatment. As data collection continues, we will be better able to tease apart the effects of these medications on satiety signaling.
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Gastrin releasing peptide activates the dorsal vagal complex and the submucosal plexus of the jejunum in the rat

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We have shown that gastrin releasing peptide-29 (GRP-29) reduces food intake in rats. Here, we investigate a possible pathway for this reduction by detecting Fos-like immunoreactivity (Fos-LI; a marker for neuronal activation) in the feeding areas of the dorsal vagal complex (DVC) in the hindbrain, and in the enteric (myenteric and submucosal) neurons of the gastrointestinal tract in response to GRP-29. Eighteen male Sprague–Dawley rats were deprived of food but not water overnight. The next morning, the rats received an intraperitoneal (i.p.) injection of GRP-29 (12 μg/kg), cholecystokinin-8 (CCK-8, 5 μg/kg) or saline, and were sacrificed 30, 60, 90 and 120 min post injection to determine maximum Fos expression in the DVC, stomach, duodenum, jejunum and colon. We found that GRP-29 increased Fos-LI in the DVC 30 and 60 min post injection, in the submucosal plexus of the jejunum 30, 60 and 90 min post injection and in the myenteric plexus of the jejunum 60 and 90 min post injection. As reported previously, CCK-8 increased Fos-LI in the DVC and enteric neurons of duodenum and jejunum. In conclusion, GRP may reduce food intake by activating the DVC directly (endocrine route) or through activating enteric neurons of the gut by vagal or sympathetic routes. The lack of activation in the stomach, the main source of peripheral GRP, may indicate that GRP does require the enteric neurons of the stomach to reduce food intake or dose not stimulate c-Fos.
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Sugarcane-derived polyphenols decrease diet-induced obesity

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Polyphenols are plant metabolites characterized by aromatic rings and hydroxy groups. Sugarcane contains a unique mix of antioxidant polyphenols such as hydroxycinnamic and benzoic acids. Our aim was to investigate the effect of sugarcane-derived polyphenols (SDP) on diet-induced obesity. Male C57BL/6J mice were divided into control (CON) or experimental groups, $n = 12$ mice/group. All groups were fed a high fat (21%) diet for 16 weeks; the experimental groups were supplemented with 200 or 400 mg/100 g diet, SDP200 or SDP400. Body weight, food and water intakes, body composition (DEXA); energy expenditure (indirect calorimetry), energy content of faeces (bomb calorimetry); glucose clearance and insulin sensitivity (following glucose load) were determined. The results indicated that relative to CON, food intake was decreased and fluid intakes were increased during the experimental period. Body weight was decreased by 15% (SDP200) and 30% (SDP400). Adipose tissue mass was decreased in both SDP groups, and fat-free mass was increased in the SDP400 group. Compared to CON, animals in both SDP groups had increased energy expenditure and increased faecal energy content. Animals in the SDP400 group had increased glucose clearance and insulin sensitivity. In conclusion, the addition of SDP to a high-fat diet reduced diet-induced obesity, possibly via mechanisms that include decreased energy intake, increased energy expenditure, and increased energy excretion, suggesting their potential use as supplements to ameliorate current trends in overweight and obesity. ARC, Horizon Science.
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Early-life short-term voluntary exercise attenuates obesity in adult OLETF rats

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OLETF rats lacking functional CCK_1 receptors are a model of early-onset hyperphagia-induced obesity, used to study the early origins and neurobiology of obesity. OLETF pups present high body weight, adiposity (adipocyte hypertrophy) and leptin already during the suckling period. In the present study, we attempted to bias their obesity tendency towards a more "lean" adulthood providing access to running wheels from weaning until day 45, a critical period regarding adipocyte development. Long-term influences of the manipulation were examined in males and females. Early voluntary exercise reduced long-term intake, adiposity and leptin in OLETF males together with a sharp reduction in adipocyte size. Control males presented stable intake, but reduced body fat and increased plasma creatinine, suggesting increased muscle mass. OLETF females showed only a tendency to reduced body fat, primarily by slight reduction in adipocyte number. Control females showed an increase in intake, body weight and creatinine, but a reduction in body fat via reduction in adipocyte number. Overall, OLETF rats presented higher adiponectin levels than controls in both basal and post-exercise conditions. A follow-up study showed that early long-term access to running wheels (from days 22 to 70) successfully reduced obesity levels in 4-month-old OLETF females. The results suggest an effective early time frame, where OLETF males can be "re-programmed" by voluntary exercise; these results can only be observed in OLETF females after prolonged exercise. Findings also expose sex-different peripheral mechanisms in coping with energy challenges.
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Physically active lifestyle does not decrease the risk of fattening

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Increasing age is associated with declining physical activity and a gain in fat mass. The objective was to observe the consequence of the age-associated reduction in physical activity for the maintenance of energy balance as reflected in the fat store of the body. Young adults were observed over an average time interval of more than 10 years. Physical activity was measured over two-week periods with doubly labeled water and doubly labeled water validated tri-axial accelerometers, and body fat gain was measured with isotope dilution. Body mass index increased from $22.8 \pm 2.0\,kg/m^2$ at baseline to $24.3 \pm 2.6\,kg/m^2$ at follow-up ($P < 0.01$). Total energy expenditure (TEE) showed a non-significant decrease and resting energy expenditure (REE) showed a non-significant increase, in combination resulting in a significant decrease of activity energy expenditure from 4.21 ± 1.05 MJ/d to 3.92 ± 1.19 MJ/d ($P < 0.05$). The physical activity level (TEE/REE) decreased significantly ($P < 0.01$) from 1.81 ± 0.16 (range 1.51–2.15) to 1.75 ± 0.11 (range 1.58–2.03). There was a significant association between the change in physical activity and the change in body fat, where a high initial activity level was predictive for a higher fat gain. In conclusion, the change from a physically active to a more sedentary routine does not induce an equivalent reduction of energy intake and requires cognitive restriction to maintain energy balance.
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Single protein casein and gelatin diets induce similar effects on energy expenditure, but different effects on substrate balance and appetite

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Incomplete protein diets exert greater satiety than complete protein diets do. Here we compared the incomplete protein gelatin, with complete protein casein, in single protein diets with 25% or 10% of energy (En%) from protein with respect to energy expenditure (EE), substrate balances and appetite profile over 24 h. During a 36-h respiration chamber stay, 23 healthy subjects (22.2 ± 2.3 kg/m^2; 25 ± 7 year) received randomly four subject-specific iso-energetic diets being 10En% or 25En% casein or gelatin diets. Three days before, subjects consumed a diet with similar macronutrient composition at home. EE was neither different between the two 25En% diets, nor between the two 10En% diets. On the 25En% casein compared with the 25En% gelatin diet, subjects were in a higher P(rotein) balance (0.56 ± 0.05 vs 0.30 ± 0.04 MJ/d, $P < 0.0001$), lower C(arbohydrate) balance (0.86 ± 0.14 vs 1.37 ± 0.17MJ/d $P < 0.01$), and similar negative F(at) balance. On the 10En% casein compared with the 10En% gelatin diet, subjects were in a less negative P balance (-0.07 ± 0.03 vs -0.17 ± 0.03 MJ/d $P < 0.05$); positive C balances and F balances did not differ. Hunger was 44% more suppressed on the 10En% gelatin compared with the 10En% casein diet ($P < 0.05$). In conclusion, greater hunger suppression of the incomplete protein diet was confirmed; elevated energy expenditure at higher dosages did not differ; the complete protein diet showed higher protein anabolism, while in the incomplete protein diet gluconeogenesis may have played a role.

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The adaptive response to forced weight gain. A role for leptin?

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While many humans and rodents become obese when exposed to a high-fat diet, involuntary overfeeding induces an adaptive decrease in voluntary food intake that persists well beyond the cessation of overfeeding and contributes to the normalization of body weight. Our primary goal is to define the mechanism underlying this adaptive response to weight gain and determine if defects in this mechanism contribute to diet-induced obesity. When male Long Evans rats were implanted with indwelling gastric cannula and overfed a liquid low-fat (10% fat) diet for 17 days, overfed rats exhibited increased weight gain ($P < 0.01$) but a marked decrease in voluntarily food intake that persisted for at least 4 days beyond the cessation of overfeeding ($P < 0.05$). Leptin levels were increased 8-fold on the final day of overfeeding ($P < 0.01$), yet returned to baseline within 2 days after overfeeding despite the persistent hypophagia. To more specifically assess the role of leptin in the adaptive response to involuntary weight gain, lean and obese Zucker rats were tested in an identical paradigm. While obese Zucker rats reduced voluntary food intake during the overfeeding regimen ($P < 0.05$), their food intake immediately returned to baseline upon cessation of overfeeding. Contrastingly, food intake in lean Zucker rats remained below baseline for 6 days following overfeeding ($P < 0.05$). These data indicate that leptin is not required to reduce food intake during overfeeding, but is required to persistently reduce food intake and efficiently normalize body weight following overfeeding.

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β-Mercaptoacetate-induced feeding is not altered by endogenous, central or peripheral leptin

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Leptin is a circulating hormone from adipose tissue that acts centrally to decrease food intake. The lipoprivic control stimulates feeding in response to the blockade of fatty acid oxidation by drugs such as β-mercaptoacetate (MA). In previous work, we found that chronic central leptin treatment does not alter the feeding response induced by MA. Here we further examine the possible reciprocity of these signals of fat excess and deficit in four acute experiments. (1) We examined circulating leptin levels 1 h after acute MA injection to test the hypothesis that MA reduces circulating leptin levels; it did not. (2) We examined the MA response in rats of differing adiposity (as determined by DEXA) and therefore of differing circulating levels of leptin. Fat mass was increased by 69% in the fatter rats but the feeding response to MA was not changed. (3) We examined the MA response in rats at 1 h and 24 h after central leptin injections and at neither acute time-point was the feeding response to MA changed. (4) We examined the MA response in rats on the 2nd day of peripheral leptin treatment (1 mg/kg, i.p.) when both body weight and food intake were significantly reduced. Again, there was no difference in the feeding response to MA between leptin- and saline-treated rats. Thus, the acute manipulation of endogenous, central or peripheral leptin does not alter the hyperphagia induced by MA. These findings suggest that leptin and MA activate independent pathways and support our previous finding that chronic leptin treatment does not alter MA-induced feeding. Supported by DK 081546.

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The role of plasma leptin in the response to and recovery from a 24-h fast

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A period of overnutrition may be a key adaptive strategy to reverse weight loss following food deprivation. Plasma leptin levels fall in response to fasting, and this effect is thought to mediate many of the physiologic and behavioral responses to the fast. However, it is unknown whether refeeding hyperphagia is related to low plasma leptin levels. In this study, we examined the time course of decreased plasma leptin levels during a fast and recovery upon refeeding, and also asked whether the hyperphagia observed upon refeeding is dependent on the fasting-induced fall in leptin levels. We observed a gradual, linear decrease in leptin levels over the course of a 24-h fast, reaching the lowest point at the end of the fast (~35% of baseline). Upon refeeding, leptin levels also recovered gradually, returning to baseline 8 h after access to ad libitum food. As expected, fasted rats showed a substantial hyperphagic response upon refeeding (~2× baseline) during the first 2 h, and a small but significant hyperphagia at some of the later time-points. In a second study, we provided physiologic dose leptin replacement to 24-h fasting rats via osmotic minipumps. Leptin replacement had no impact on the large initial refeeding hyperphagia, however, subsequent hyperphagia was attenuated by leptin replacement, and body weight recovery was impaired. Our data suggest that the plasma leptin response to fasting is important for some elements of recovery, but that the initial food intake response to a fast is not dependent on reduced leptin levels.

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Maternal high fat diet during development leads to pancreatic islet expansion in the nonhuman primate offspring

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Our lab has shown that maternal high fat diet (HFD) consumption causes increased liver triglycerides and oxidative damage in nonhuman primate fetal offspring that persists into postnatal life. Our goal was to investigate the impact of maternal HFD on the development of pancreatic islets. Adult macaques were fed a control diet (CTR) or HFD for 2–4 years. Offspring were studied in the early 3rd trimester or at 14 months of age. After birth, infant animals were kept with the mothers on the same diet until weaning. At 7 months of age HFD offspring were weaned onto the HFD (HFD/HFD) or the CTR diet (HFD/CTR). CTR offspring were all maintained on the CTR diet (CTR/CTR). At 14 months of age HFD/HFD offspring were heavier and had increased fat mass. Both HFD/HFD and HFD/CTR had elevated fasting insulin levels. There was a significant decrease in several transcription factors important for islet neogenesis, including PDX1 and NKX6.2 and NeuroD, in the pancreas of HFD fetuses. However, this did not persist in the postnatal offspring. Quantification of islets by size in the postnatal offspring revealed significantly more medium and large islets in the HFD/HFD group, suggesting a shift in islet type. Further stereological analysis of the postnatal pancreas revealed a trend toward an increase in the mean islet area in both the HFD/HFD and HFD/CTR offspring. This suggests that maternal HFD or early postnatal HFD consumption could increase the susceptibility to insulin resistance and diabetes later in life.

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Food viscosity influences respiratory quotient, energy expenditure and caloric compensation in rats

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Previous work from our lab has suggested that experience with low viscosity diets can influence body weight gain, caloric compensation, and core body temperature. The objective of this study was to determine the effects of food viscosity on respiratory quotient, energy expenditure, and activity in rats. Sixteen naïve male Sprague–Dawley rats consumed low- and high-viscosity dietary supplements that were matched in terms of caloric and nutritive content. The rats were placed in metabolic chambers and consumed either a low- or high-viscosity 10 g premeal followed by a lab chow test meal to evaluate caloric intake compensation, respiratory quotient (RQ), energy expenditure (EE), and activity. After each premeal trial in metabolic cages, rats were returned to their home cages where half received 10 days of exposure to 10 g of the low viscosity supplement for 2 h, daily while the other half received no exposure. Following exposure in the home cage, premeal tests were repeated. A total of four premeal trials were conducted. The results suggested that caloric compensation was weaker when animals received a low viscosity compared to a high viscosity premeal. In addition, changes in RQ and EE were affected by premeal viscosity and by exposure to the premeal. These data suggest that changes in metabolic parameters may contribute to differences in caloric compensation and energy balance produced by exposure to low viscosity diets.

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Restrained eating impairs the ability to acquire flavour-nutrient associations

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Several reports have suggested that restrained women fail to acquire flavour-based associations in learning studies. To test this further, we conducted 2 studies of flavour-nutrient learning (FNL) in women classified as high or low on the Three Factor Eating Questionnaire restraint and disinhibition scales. In Experiment 1, women ($n = 78$) evaluated and consumed ad libitum a novel flavoured sorbet on days 1 (Pre-) and 6 (Post-training), and consumed a 400 g drink with the same flavour and either added maltodextrin (Energy: 159 kcal) or nothing added (Control: 7 kcal). Unrestrained women both showed increased liking for the sorbet flavour, and consumed more sorbet, Post-training in the Energy condition, but restrained women showed small increases in liking and intake in both conditions, suggesting insensitivity to caloric content. Experiment 2 used a within-subjects design based on consumption of two different flavoured breakfast yoghurts, one high (110 kcal/100 g) and one low in energy (55 kcal/100 g). Women ($n = 48$) rated and consumed ad libitum the two versions on separate days at Pre- and Post-training, but consumed a fixed amount (300 g) on 2 training days with each version. Again, unrestrained women rated the high-energy flavour more pleasant, and consumed more of it, at Post-training whereas restrained women showed an equal increases in liking and intake of both versions. These data confirm that restrained eating impairs the ability to modulate behaviour in response to small changes in diet energy, suggesting that restraint may increase the risk of passive over-consumption.

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Neonatal maternal separation may suppress dopaminergic activity in the reward pathway, affect palatable food intake in rats

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We have reported that intake of palatable food is suppressed in adolescent rats that experienced neonatal maternal separation (MS), exhibiting depression-like behaviors. In this study, we examined the dopaminergic activity in the reward pathway and the HPA axis responding to stress in the adolescent MS rats. Sprague–Dawley pups received a 3 h maternal separation daily during the first 2 weeks of life (MS) or left undisturbed (NH). Rats were sacrificed on PND 40 with/without 1 h of restraint stress. Cardiac bloods were collected for corticosterone assay and the brain tissues were processed for c-Fos immunohistochemistry in the hypothalamic PVN or for mRNA in situ hybridization of tyrosine hydroxylase (TH), rate limiting enzyme of dopamine synthesis, in the ventral tegmental area. The nucleus accumbens and midbrain tissues were dissected for HPLC analysis of dopamine. The PVN Fos expression responding to restraint stress was not affected by MS experience. Restraint increased plasma corticosterone both in NH and MS rats, although the basal level of plasma corticosterone was elevated in MS compared with NH. TH expression was increased by restraint stress in NH, but not in MS pups. Stress-induced dopamine release appeared to be blunted in the reward pathway of MS pups. Together with our previous finding, it is suggested that MS experience may suppress dopaminergic activity in the reward pathway and affect palatable food intake.

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Circulating GLP-1 and CCK-8 reduce food intake by non-vagal mechanisms

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CCK and GLP-1 are secreted by intestinal endocrine cells in response to luminal nutrients. Consequently, plasma concentrations of both peptides increase postprandially. Reduction of food intake by intraperitoneal (IP) CCK injection is abolished or attenuated by vagotomy, and at least one report suggests that reduction of food intake by IP GLP-1 also is vagally mediated. However, endogenous secretion or IP CCK or GLP-1 injection likely produce much higher local peptide concentrations than are achieved in the systemic circulation. Though vagal mediation of food intake reduction by IP peptide injection is established, vagal participation in feeding reductions in response to elevated plasma CCK and GLP-1 is uncertain. Here we report that intravenous infusion of GLP-1 (1.25, 2.5, 5.0 or 10.0 μg/rat) or CCK-8 (1.4 or 2.8 μg/rat) reduced 30 min intake of 15% sucrose of intact rats. Reductions of intake by intravenous CCK and GLP-1 were not attenuated either by bilateral subdiaphragmatic vagotomy or systemic capsaicin treatment. Further, at the 10 μg/rat dose, GLP-1 reduced food intake more in vagotomized and capsaicin-treated rats than in controls. On the other hand, reduction of food intake by IP CCK was abolished in these same groups of vagotomized and capsaicin-treated rats. We conclude that abdominal vagal afferents mediate reduction of food intake by IP CCK, but are not required for feeding effects of circulating CCK or GLP-1. Furthermore, it appears that vagal lesions increase responsiveness of non-vagal substrates mediating reduction of food intake by circulating GLP-1.

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Synphilin-1 regulates AMPK signaling

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Synphilin-1 is a cytoplasmic protein with unclear function. We recently generated a human synphilin-1 transgenic mouse model that displays some key features of obesity and diabetes including increased food intake, body weight and body fat, hyperinsulinemia, hyperleptinemia and glucose insensitivity. In our synphilin-1 transgenic mice, human synphilin-1 was highly expressed in hypothalamic nuclei: ARC and PVN, main sites regulating food intake and body weight. Pair feeding synphilin-1 mice to amounts consumed by intact non-transgenic mice significantly attenuated the obesity and diabetes. We found here that expression of human synphilin-1 in N1E-115 mouse neuroblastoma cells increased AMP-activated kinase (AMPK) phosphorylation. Increasing evidence indicates that AMP-activated kinase (AMPK) is a central neuronal energy sensor that plays a major role in maintaining energy homeostasis. We further found that synphilin-1 reduced the inhibitory effect of insulin on AMPK phosphorylation compared with the effect in vector only control cells. These results indicate that synphilin-1 alters AMPK-related signaling pathways. These studies provide novel insight into the molecular mechanisms underlying synphilin-1 induced hyperphagia and obesity and indentify new biological functions of synphilin-1.

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Meal patterns, satiety, and food choice in a rat model of Roux-en-Y gastric bypass surgery

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Gastric bypass surgery efficiently reduces excess body weight and reverses type-2 diabetes in obese patients. Decreased energy intake is the main cause of weight loss, but the mechanisms involved are poorly understood. The aim was to characterize the changes in ingestive behavior in a rat model of Roux-en-Y gastric bypass surgery (RYGB). Male SD rats made obese on a high-fat (60%) diet underwent either RYGB or sham surgery and were given Ensure or a choice of chow and high-fat. Five months after surgery, RYGB rats had lost 21 ± 3% body weight and all excess adiposity, while sham rats gained 29 ± 7% of pre-surgical body weight (∼450 g). Intake of Ensure was significantly ($p < 0.01$) reduced by 65% at 5 d and of the 2-choice diet by 18% at 20 d after surgery compared with sham rats. Decreased Ensure intake at 20 d was the result of drastically reduced meal size (−63%), with only partial compensation by increased meal frequency (+107%), resulting in a significantly increased satiety ratio (+63%, all $ps < 0.05$). Three months after surgery, this "nibbling" and hypophagic phenotype had almost normalized. While sham rats preferred high-fat over chow (99 ± 2%), RYGB rats progressively decreased preference for fat (86 ± 5% at 30 d, 52 ± 2% at 120 d, $p < 0.01$). The results confirm reports of 'nibbling' behavior and fat-avoidance in RYGB patients and provide a basis for more mechanistic studies in this rat model.

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Olfaction is critical for conditioned sucrose preference in sweet-taste impaired T1R3 knockout mice

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Knockout (KO) mice missing the T1R3 sweet-taste receptor protein are initially indifferent to sucrose but develop strong preferences in 24-h tests. This is attributed to their learning to associate T1R3-independent orosensory cues with the sugar's post-oral reinforcing effect. The current study investigated the role of olfaction in this conditioned sucrose preference. T1R3 KO and C57BL/6J wild-type (WT) mice were given 24-h sucrose vs. water tests with ascending sugar concentrations (0.5–32%). The mice were then given olfactory bulbectomy (OBX) or sham surgery (Sham) followed by a second series of preference tests. In Test 1, the KO mice were indifferent to 0.5–8% sucrose but preferred 16–32% sucrose to water; WT mice preferred all concentrations. In Test 2, the KO Sham mice ($n = 11$) preferred all sucrose solutions to water although less than WT Sham mice ($n = 11$) at 0.5–4% concentrations. In contrast, KO OBX mice ($n = 12$) were indifferent to 0.5–2% sucrose and showed weaker preferences for 4–16% sucrose than WT OBX mice ($n = 12$). WT OBX mice preferred all sucrose solutions although less than WT Sham mice at 0.5–4% concentrations. OBX mice underconsumed sucrose at lower concentrations compared to Sham mice, but consumed more sucrose at 16% and 32% concentrations. These findings suggest that olfactory stimuli mediate the learned preference T1R3 KO mice display for dilute sucrose solutions. Their learned preference for concentrated sugar solutions may be mediated by texture or T1R3-independent taste cues.

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The functional architecture of dehydration anorexia

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Anorexia is a significant reduction of appetite that occurs in the presence of plentiful food supplies, the consequences of which are reduced food intake and body weight. Anorexia is an important complication for a number of clinical conditions that can lead to poor outcomes and in severe cases, death. The underlying mechanisms that generate anorexia in these situations are many and unclear. For the past decade we have used the anorexia that develops during cellular dehydration (DE-anorexia) as a tool to investigate the functional organization of the neural circuits. DE-anorexia in rats develops within 24 h of drinking hypertonic saline, and is rapidly reversed once drinking water is again made available. Together with a presentation of a neural network model for how DE-anorexia develops, this talk will discuss new data supporting the notion for the up-regulation of satiety mechanisms as a key factor in the reduced feeding evident in DE-anorexic animals.

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