Embargoed until Nov. 14, 1 p.m. PST
Press Room, Nov. 13-17: (619) 525-6640

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COMMON LINKS BETWEEN OBESITY AND DRUG ABUSE FOUND

Animal studies suggest the same chemicals and brain circuits may be key to both, and that long-term brain changes make kicking the habit hard

SAN DIEGO — New animal research helps explain why some eat without hunger or to excess. The studies explore the biological effects of poor eating habits, showing that high-fat diets cause lasting brain changes that may impair healthy eating. Additional studies show that food and drugs of abuse engage many of the same brain systems. The findings were presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health.

More than one billion adults worldwide are overweight, according to the World Health Organization. With increased risk for chronic disease and rising health care costs tied to obesity, today's studies are valuable in helping generate future prevention and treatment techniques.

Specifically, today's new findings show that:

- Animals fed a high-fat diet show long-term brain changes in the pleasure centers of the brain, illustrating the biological challenges for obese individuals (Teresa Reyes, PhD, abstract 299.18, see summary attached).
- The same substance may signal satiation and pleasure. The stomach hormone ghrelin, which normally indicates when an animal is hungry or full, fueled cravings for sugar that resemble those for drugs (Karolina Skibicka, PhD, abstract 191.6, see summary attached).
- A chemical released in the body during food restriction is a contributing factor in drug-seeking behavior. Research shows that drug-exposed rats are less likely to relapse when that chemical signal is blocked, suggesting a potentially novel treatment for recovering drug addicts (Uri Shalev, PhD, abstract 368.25, see summary attached).
- A sex difference may exist in addictive behavior. When given a choice between food and cocaine, male rats preferred sweets and female rats favored cocaine (Kerry Kerstetter, abstract 266.6, see summary attached).

Other recent findings discussed show that:

- A predisposition to obesity and food addiction might be hardwired at or around birth, and good nutrition in early life is essential for development of brain centers involved in regulating weight (Sebastien Bouret, PhD, see attached speaker's summary).

"Life experiences change the nervous system, and today's findings demonstrate why regulating food intake and body weight is such a challenge," said press conference moderator Ralph DiLeone, PhD, of Yale University School of Medicine, an expert on the neural mechanisms of food intake and behavior.

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

– more –

Related Presentation:

Minisymposium 621: **Neural Components of Feeding Control: From Signaling to Hedonics and Emotions**
Tuesday, Nov. 16, 1:30–4 p.m., Room 29D
# # #

Abstract 299.18 Summary

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Long-Term, High-Fat Diet Alters Mice Brains

Study suggests brain changes may contribute to cycles of weight gain

The brains of mice fed a high-fat diet for an extended period of time showed irreversible changes in areas associated with reward and pleasure, a new study has found. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our data show that chronic consumption of a high-fat diet leads to significant changes in brain chemistry," said senior author Teresa Reyes, PhD, of the University of Pennsylvania, School of Medicine.

Fatty foods tap the pleasure centers of the brain, the same areas triggered by cocaine or heroin. Reyes and her colleagues explored whether these pathways could be modified on a molecular level by eating a high-fat diet for a long period of time. The researchers found that the genes involved with reward were altered in mice fed a high-fat diet for more than six months. The authors suggest the changes, which may promote cravings for fatty foods, could have far-reaching consequences.

Many people struggle with unhealthy cycles of weight loss and gain. This study illustrates the biological challenges of breaking out of this cycle. "These results provide further insight into the health consequences of long-term, high-fat diets, and suggest one explanation for why some people face such difficulty in the path to weight loss and healthier eating," Reyes said.

Research was supported by the National Institute of Mental Health.

Scientific Presentation: Sunday, Nov. 14, 2–3 p.m., Halls B–H

299.18, Epigenetic memory of chronic exposure to high fat diet in reward-associated CNS circuitry
Z. VUCETIC, **T. M. REYES**; Univ. of Pennsylvania, Philadelphia, Pa.

TECHNICAL ABSTRACT: Regulation of gene expression in response to environmental stimuli (such as nutrition or drugs of abuse) can be achieved via epigenetic mechanisms that modify regulatory DNA regions (cytosine methylation) or alter histone structure (methylation, acetylation). Using a mouse model, we have previously found that 15-week exposure to 60 percent high fat (HF) diet induces epigenetic silencing (specifically, increased DNA methylation and histone H3-Lys9 methylation and decreased H3-Lys acetylation) of tyrosine-hydroxylase (TH), dopamine reuptake transporter (DAT) and mu-opioid receptor (MOR) genes in brain regions associated with reward (nucleus accumbens (NAC), ventral tegmental area (VTA), prefrontal cortex (PFC) and hypothalamus). The goal of this study was to assess the reversibility of these HF-diet induced epigenetic changes after withdrawal from HF diet. Dietary-induced obese mice (n= 8-10/group) were removed from HF diet and placed on control diet for one, two, and four weeks. At the end of each time point, gene expression (by real-time PCR) and epigenetic analysis (using chromatin (ChIP) and methyl-DNA (MeDIP) immunoprecipitation assays) were performed in microdissected brain regions. Reduced expression of TH, DAT and MOR observed in DIO-animals starts to reverse after two weeks of dieting but does not reach the levels seen in controls even after four weeks. At the same time (two weeks on control diet) we observed an increase in H3-Lys4 acetylation suggesting partial reactivation of epigenetically repressed state of TH, DAT and MOR promoters in obese mice. In contrast, during the four weeks of dieting, promoters of TH, DAT and MOR genes remain hypermethylated in reward-associated regions (NAC, VTA and PFC) as assessed by MeDIP analysis. These studies suggest that long-term exposure to high-fat diet has permanent effects on gene regulatory mechanisms that mediate reward and could not be easily reversed by dieting alone. Epigenetic changes in brain-associated genes may represent a form of molecular memory of nutritional insults that could ultimately have long-term effects on dysregulation of reward-related behaviors in obesity.

Abstract 191.6 Summary

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Stomach Hormone Can Fuel or Suppress Rats' Sugar Cravings

Study shows chemical associated with appetite also activates the brain's pleasure center

Researchers have found that rats either seek out sweets or lose interest, depending on the action of a stomach hormone called ghrelin. Ghrelin is one of many chemicals in the body that tell the brain when to trigger hunger or fullness. New results about this hormone's influence were presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Recent research showed that, in addition to moderating normal eating habits, ghrelin acts on the brain's reward and pleasure centers — areas also activated by drugs and sex.

In this study, researchers used tests typically found in alcohol and drug addiction experiments to determine the role of ghrelin in food addiction. While rats pressed a lever hundreds of times to earn a tiny bit of sugar, rats given ghrelin worked almost twice as hard to get the same treat, as though they had not eaten. Yet when the hormone was blocked in hungry rats, they were less willing to labor for a sweet reward, as if they were full. The researchers also found that increasing or decreasing ghrelin influenced whether the animals preferred environments they associated with candy consumption. These findings may help explain why people eat when not hungry and have implications for potential weight-control treatments.

"Our results indicate that ghrelin plays an important role in food intake that is driven by the pleasure of food rather than by hunger," said lead author Karolina Skibicka, PhD, of University of Gothenburg in Sweden. "We believe that future therapies for obesity that limit the intake of sugary and fatty foods could be enhanced with drugs that suppress ghrelin's effects on the reward system."

Research was supported by the Swedish Institute, the Swedish Research Council for Medicine, the European Union 7th Framework, and ALF Göteborg.

Scientific Presentation: Sunday, Nov. 14, 9–10 a.m., Halls B–H

191.6, Role of ghrelin in sugar reward: Effects of GHS-R1A stimulation and antagonism on sucrose self-administration and conditioned place preference in rats
K. P. SKIBICKA[1], E. EGECIOGLU[1], S. L. DICKSON[1]; [1]Dept. Physiology/Endocrinology, Inst. Neurosci. and Physiol., The Sahlgrenska Acad. At Univ. of Gothenburg, Göteborg, Sweden

TECHNICAL ABSTRACT: Energy imbalance, through its effects on the CNS, is a well-established regulator of food intake. The decision to eat, however, is often strongly influenced by non-homeostatic factors such as food palatability and food reward and hence, the incentive/motivational value of food that can override the homeostatic signals. Ghrelin, a gut-derived circulating orexigenic hormone, has a prominent role in homeostatic feeding through its action on hypothalamic arcuate and caudal brainstem ghrelin receptors (GHS-R1A). Recently, however, it has emerged as a potent modulator of the midbrain dopamine system with a role in alcohol and cocaine reward. Here we sought to determine the role of ghrelin and its receptors in motivation for food reward utilizing behavioral paradigms typically applied in studies of alcohol and drug addiction. Specifically we examined the role of peripheral and central GHS-R1A stimulation and blockade for the sucrose progressive ratio operant conditioning (measure of motivation and goal directed behavior) and also high fat/sugar food-induced conditioned place preference. Additionally we investigated whether ghrelin-induced changes in food motivation are mediated by the central endocannabinoid system, an orexigenic system that also modulates dopamine signaling, increases the rewarding value of food and has been implicated previously in ghrelin's orexigenic effects. Both peripheral and central injection of ghrelin significantly increased operant responding for sucrose. Conversely, peripheral or central delivery of the GHS-R1A antagonist JMV2959 significantly decreased operant responding for sucrose. In addition we show that ghrelin and JMV2959 increase and decrease free feeding of non-palatable food respectively. Our data also suggest a differential role of the central cannabinoid system in ghrelin-induced feeding, where the CB1 receptors signaling is required for the free feeding effects of ghrelin but is not essential for its motivational effects. Finally we also show that blockade of GHS-R1A disrupts high sugar/high fat food conditioned place preference. Together our data indicate that central ghrelin system plays an important role in non-homeostatic feeding and the motivation to obtain food. The central GHS-R1A emerges as a common denominator in chemical drug and food addiction, providing new therapeutic opportunities for treating problematic overeating as well as substance use disorders.

Abstract 368.25 Summary

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Appetite-Related Chemical Also Affects Drug-Seeking

Study shows hungry rats more resistant to drug relapse in absence of chemical signal

A behavioral study of food-deprived rats shows that the animals were less likely to return to heroin-seeking habits when given a compound that blocks specific brain receptors. These results, which have implications for drug treatments, were presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

More than 2.4 million Americans are in some sort of rehabilitation program for drug use. Yet 40 to 60 percent of drug addicts relapse when trying to get sober, often because of stressful situations. Scientists use animal models of drug use to further understand addict-like behavior and relapse, training rats to press a lever to self-administer heroin or other illicit drugs. Previous studies employed food deprivation as the stress "trigger" for potential relapse in drug-deprived animals. These studies showed that rats exposed to a short period of intense hunger quickly seek out drugs, mimicking the behavior of a relapsed addict.

The new results suggest that a molecule known as NPY, which is released into the body in times of food restriction, also acts as a trigger for drug-seeking. In this study, Concordia University researchers found that rats given a chemical that blocks the NPY brain receptors don't search for heroin. Moreover, the authors observed no side effects from the drugs in the rats, such as weight loss or behavioral changes.

"Our findings suggest a novel approach to the treatment of drug addiction, at least for addicts who also have eating disorders," said Uri Shalev, PhD, the study's lead author.

Research was supported by the Natural Science and Engineering Council of Canada, funds from the Canada Research Chair to the United States, and the Fonds de la recherche en santé du Québec.

Scientific Presentation: Monday, Nov. 15, 8–9 a.m., Halls B–H

368.25, The novel neuropeptide Y Y5 receptor antagonist, Lu AA33810, attenuates food deprivation-induced reinstatement of heroin seeking
U. SHALEV[1], T. MARIC[1], M. W. WALKER[2], F. SEDKI[1]; [1]Concordia Univ., Montreal, QC, Canada; [2]Lundbeck Research, USA, Paramus, NJ

TECHNICAL ABSTRACT: *Objectives* Neuropeptide Y (NPY) is a 36-amino acid neurotransmitter that is released during periods of food deprivation (FD) and serves as an orexigenic signal that powerfully stimulates feeding via Y1 and Y5 receptor subtypes. We have recently demonstrated that central infusions of NPY facilitate both heroin and cocaine self-administration, enhance the locomotor activating properties of cocaine, and elicit the reinstatement of previously extinguished heroin-reinforced behavior in an animal model of relapse to drug abuse. Previously, we reported that FD-induced reinstatement of heroin seeking is blocked by the anorexigenic hormone, leptin. We hypothesized that leptin's effect was mediated through its modulating effect on NPY release in the brain. However, we found that the NPY Y5 receptor antagonist, L152-804 (20.0 µg, i.c.v.), failed to block FD-induced reinstatement of heroin seeking. Recently, a novel NPY Y5 receptor antagonist, Lu AA33810, has been introduced, with high specificity to the Y5 receptor, and anxiolytic-like and antidepressant-like effects in rats. Here we examined the effects of Lu AA33810 on acute food deprivation-induced reinstatement of heroin seeking behavior. *Material and Methods* Long Evans male rats were trained to self-administer heroin (0.10 mg/kg/infusion, i.v.) over a period of 10 days (three three-hour sessions/day) on a fixed-ratio 1 schedule of reinforcement. Heroin self-administration training was followed by a minimum of 4 days of extinction training. Subsequently, rats were exposed to two counterbalanced reinstatement test sessions, that consisted of 3-hour sessions under extinction conditions, which were preceded by either 21 hour FD or 21 hour of unlimited access to food. Rats received injections of the novel NPY Y5 receptor antagonist (Lu AA33810; 0.0, or 30.0 mg/kg/rat, i.p.) 30 min before each test. *Results* The NPY Y5 receptor antagonist, Lu AA33810, significantly attenuated food deprivation-induced reinstatement of heroin seeking behavior (lever presses) in the absence of the drug. *Conclusion* Our preliminary results indicate that blocking the NPY Y5 receptor subtype, using a dose known to inhibit Y5 agonist-induced feeding, attenuates acute food deprivation-induced reinstatement of heroin seeking. We suggest that activation of the NPY Y5 receptors is critically involved in FD-induced reinstatement of drug seeking. Further research is currently being conducted in order to reveal the effective dose-range for Lu AA33810, and its effects on reinstatement induce by other known triggers for relapse, namely, drug-associated cues and priming.

Abstract 266.6 Summary

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Animal Study Suggests Sexes Differ in Choice between Food and Cocaine

Results show male rats prefer food, female rats favor cocaine

When given a choice between sweets and cocaine, male rats prefer sweets, while female rats would rather self-administer cocaine, a new study has found. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Human studies of cocaine dependence indicate that women enter drug treatment faster than men and report shorter cocaine-free periods," said lead author Kerry Kerstetter, of the University of California, Santa Barbara. "Given that male and female rats also exhibit differences in their responses to cocaine, we reasoned that they would exhibit differences when presented with a choice between food and the drug."

In the study, rats were trained to press one lever for food and a separate lever for cocaine; they were then offered a choice between the two. Female rats pressed the cocaine lever significantly more times than the male rats, while the male rats mainly selected the food. When higher doses of cocaine — more than double — were offered, both sexes chose cocaine more often, but female rats still preferred the drug more than the males.

"It appears that females are more likely than males to sacrifice food for low doses of cocaine," Kerstetter said.

Research was supported by the National Institute of Drug Abuse and by the National Alliance for Research on Schizophrenia and Affective Disorders Young Investigator Award to Tod E. Kippin.

Scientific Presentation: Sunday, Nov. 14, 2–3 p.m., Halls B–H

266.6, Effect of sex and dose in selecting between food and cocaine
K. A. KERSTETTER[1], M. BALLIS[1], S. M. DUFFIN-LUTGEN[1], J. TRAN[1], A. M. BEHRENS[1], T. KIPPIN[1,2]; [1]UCSB, Santa Barbara, CA; [2]Neurosci. Res. Inst., Univ. of California Santa Barbara, Santa Barbara, CA

TECHNICAL ABSTRACT: Sex differences in the profile of cocaine dependence have indicated that women relative to men transition faster from first use to entering treatment and report shorter cocaine-free periods. In addition, female rats relative to males display greater propensity to acquire cocaine self-administration and show enhanced cocaine self-administration under a progressive ratio schedule. Choice paradigms have shown that male rats will prefer sweetened water to cocaine, and that when food is made available it will reduce cocaine self-administration. Given that males and females exhibit differences in their response to cocaine, we reasoned that they should exhibit differences when presented with a choice between food and cocaine. To address this issue, the present study examined the effect of sex, estrous cycle, and cocaine dose on the choice between food and cocaine during an alternative reinforcement schedule. Rats were trained to respond on the "food" lever for food (45 mg pellets) and were trained to respond on the "cocaine" lever for cocaine (0.4 or 1.0 mg/kg/0.1 ml infusion/4 sec) on a FR1 (20s TO) schedule - during training only 1 lever was extended with the available lever and reinforcer alternating between successive days. After training, rats completed "discreet-trial tests" during which both levers were extended and rats could choose between the two reinforcers. When presented with the choice between food and cocaine (0.4mg/kg/inf) females earned significantly more cocaine infusions than males; with males predominately selecting food over cocaine. For the higher dose of cocaine (1.0mg/kg/inf), both male and female had increased cocaine choice during discrete trials, relative to the 0.4mg/kg/inf dose of cocaine, however females again selected cocaine over food significantly than did males. There was no effect of estrous cycle on choice behavior. Present findings indicate that sex modulates the relative motivation for cocaine and food under choice conditions; accordingly, it appears that females are more sensitive than males to cocaine reinforcement relative to food reinforcement with females, but not males, forgoing food reinforcement for low doses of cocaine.

Speaker's Summary

Speaker: Sebastien Bouret, PhD (301) 402-3035
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Developmental Plasticity of Brain Feeding Pathways (621.2)
Minisymposium: Neural Components of Feeding Control" From Signaling to Hedonics and Emotions
Tuesday, Nov. 16, 1:35–1:55 p.m., San Diego Convention Center, Room 29D

The devastating health and emotional impact of obesity is no longer confined to just adults. Recent statistics show that 22 million children under five are estimated to be overweight worldwide. Recent findings in pediatric research have uncovered a significant piece of the obesity puzzle: beyond merely the effects of diet and lack of exercise, a child's risk of obesity can also be determined during the critical perinatal stage, that is, the period during and around birth. Central to this field is the concept of "perinatal programming," defined broadly as a process where a stimulus at a critical period of development may have long-term or even lifetime effects. Data from both human studies and animal models have revealed that obesity risk is greatly influenced by two major factors: the nutritional and hormonal conditions of the mother during pregnancy and the nutritional and hormonal conditions of the child in early infanthood, with both perinatal malnutrition as well as over-nutrition being risk factors for the child becoming overweight or obese. We have also known for decades that the brain, and particularly a region of the brain called the hypothalamus, plays a key role in regulating food intake and body weight. A collection of brain cells (neurons) in the hypothalamus coordinates our need to eat in relation to how well our body is fed via cross talk with hormone signals arising from the gastrointestinal tract and adipose tissue.

The critical brain growth and development period takes place during the intra-uterine life up to the first years of life. During this time, the brain is highly sensitive and a change in environment, particularly in regard to hormones and nutrition, could have an adverse effect on the organ. Experimental evidence suggests that development of programming in brain circuitry that controls appetite by the perinatal environment could predispose an individual to become overweight or obese. For example, we have recently shown that the fat hormone leptin and the gut hormone ghrelin work on the brain (on the hypothalamus) during early life to regulate the growth of nerve cells (axons) that control eating. In addition, nutritional manipulation of hormone secretion during perinatal life has generated considerable concern, and the developing brain appears to be a particularly sensitive target for these environmental changes, with both perinatal undernutrition and overnutrition having adverse consequences on the architecture of brain circuits involved in appetite regulation.

These intriguing results suggest that predisposition to obesity might be hardwired at or around birth and that adequate nutrition during early life is essential for proper development of brain centers involved in food intake and body weight regulation.