Published in final edited form as:

Obesity (Silver Spring). 2014 February ; 22(0 1): S1–S17. doi:10.1002/oby.20646.

Hyperphagia: Current Concepts and Future Directions Proceedings of the 2nd International Conference on Hyperphagia

Steven B. Heymsfield¹, Nicole M. Avena², Leslie Baier³, Phillip Brantley¹, George A. Bray¹, Lisa C. Burnett⁴, Merlin G. Butler⁵, Daniel J. Driscoll⁶, Dieter Egli^{4,7}, Joel Elmquist⁸, Janice L. Forster⁹, Anthony P. Goldstone¹⁰, Linda M. Gourash⁹, Frank L. Greenway¹, Joan C. Han¹¹, James G. Kane¹², Rudolph L. Leibel⁴, Ruth J.F. Loos¹³, Ann O. Scheimann¹⁴, Christian L. Roth¹⁵, Randy J. Seeley¹⁶, Val Sheffield¹⁷, Maïthé Tauber¹⁸, Christian Vaisse¹⁹, Liheng Wang⁴, Robert A. Waterland²⁰, Rachel Wevrick²¹, Jack A. Yanovski¹¹, and Andrew R. Zinn²²

¹Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana, USA

²Department of Psychiatry, University of Florida College of Medicine, Gainesville, Florida, USA

³Diabetes Molecular Genetics Section, Phoenix Epidemiology and Clinical Research Branch, NIDDK, NIH, Phoenix, Arizona, USA

⁴College of Physicians and Surgeons, Columbia University, New York, New York, USA

⁵Kansas University Medical Center, Kansas City, Kansas, USA

⁶Division of Genetics and Metabolism, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida, USA

⁷New York Stem Cell Foundation, New York, New York, USA

⁸UT Southwestern Medical Center, Dallas, Texas, USA

⁹The Pittsburgh Partnership, Pittsburgh, Pennsylvania, USA

¹⁰Metabolic & Molecular Imaging Group, MRC Clinical Sciences Centre, Imperial College London, UK

¹¹Section on Growth and Obesity, National Institute of Child Health and Human Development, NIH, Bethesda, Maryland, USA

¹²Prader-Willi Syndrome Association (USA), Sarasota, Florida, USA

© 2013 The Obesity Society

Correspondence: Steven B. Heymsfield (Steven.Heymsfield@pbrc.edu).

Disclosure: The authors report no conflict of interest.

Author Contributions

All authors provided lectures and written summaries of their selected topics. The draft manuscript was reviewed and edited by all listed authors.

Additional Supporting Information may be found in the online version of this article.

¹³The Genetics of Obesity and Related Metabolic Traits Program, The Charles Bronfman Institute for Personalized Medicine, The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York, New York, USA

¹⁴Division of Pediatric Gastroenterology, Nutrition and Hepatology at Johns Hopkins School of Medicine, Baltimore, Maryland, USA

¹⁵Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, Washington, USA

¹⁶Center of Excellence in Obesity and Diabetes, University of Cincinnati, Cincinnati, Ohio, USA

¹⁷Pediatrics and Medical Genetics, University of Iowa College of Medicine, Iowa City, Iowa, USA

¹⁸Department of Endocrinology, Hôpital des Enfants and Paul Sabatier Université, Toulouse, France

¹⁹University of California, San Francisco, School of Medicine, San Francisco, California, USA

²⁰USDA/ARS Children's Nutrition Research Center, Department of Pediatrics and Molecular & Human Genetics, Baylor College of Medicine, Houston, Texas, USA

²¹Department of Medical Genetics, University of Alberta, Edmonton, Canada

²²McDermott Center for Human Growth and Development, UT Southwestern Medical Center, Dallas, Texas, USA

Abstract

Objective—Hyperphagia is a central feature of inherited disorders (e.g., Prader–Willi Syndrome) in which obesity is a primary phenotypic component. Hyperphagia may also contribute to obesity as observed in the general population, thus raising the potential importance of common underlying mechanisms and treatments. Substantial gaps in understanding the molecular basis of inherited hyperphagia syndromes are present as are a lack of mechanistic of mechanistic targets that can serve as a basis for pharmacologic and behavioral treatments.

Design and Methods—International conference with 28 experts, including scientists and caregivers, providing presentations, panel discussions, and debates.

Results—The reviewed collective research and clinical experience provides a critical body of new and novel information on hyperphagia at levels ranging from molecular to population. Gaps in understanding and tools needed for additional research were identified.

Conclusions—This report documents the full scope of important topics reviewed at a comprehensive international meeting devoted to the topic of hyperphagia and identifies key areas for future funding and research.

Overview

Conference background

Steven B. Heymsfield, M.D., Phillip Brantley, Ph.D., and Merlin G. Butler, M.D., Ph.D.—The 2nd International Conference on Hyperphagia held on October 17th–19th, 2012 was followed by the 26th Annual Prader–Willi Syndrome Association Scientific Day

Conference on October 19th–20th at the Pennington Biomedical Research Center, Baton Rouge, Louisiana. The Prader–Willi (PWS) syndrome conference has been held for 26 years with the aim of discussing research and to arrange collaborations among scientists attending the meeting and engaged in PWS research. The concept of holding a hyperphagia conference was stimulated by discussions and activities of those who organized and participated in the ongoing PWS conferences over the years and the need to develop a separate conference based on hyperphagia, a cardinal feature of those with PWS. Historically, before the discovery of accurate genetic testing protocols (i.e., methylation analysis) which correctly assigns the diagnosis of PWS in 99% of affected individuals, the clinical diagnosis could not be established using consensus diagnostic criteria until the development of hyperphagia, rapid weight gain, and obesity in early childhood.

The increased prevalence of obesity in our society has generated emphasis on research to better understand the causation, early recognition, and treatment (including for hyperphagia), stimulating the need to organize and arrange the 2nd International Conference on Hyperphagia held at the Pennington Biomedical Research Center, an institute for obesity research (basic and applied) and in co-sponsorship with the Prader–Willi Syndrome Association (USA) and the Foundation for Prader–Willi Research. The 1st International Conference on Hyperphagia was held in Baltimore, Maryland on June 4th–5th, 2009. Invited international experts, speakers, and other professionals discussed several themes ranging from animal models of obesity to rare genetic disorders with hyperphagia and obesity as major findings. The theme of the initial conference was to encourage awareness and to support research and collaboration by accepting grant proposals after the conference through the Best Idea Grant (BIG) for Hyperphagia initiative. For grant submission, collaboration with other researchers in attendance with different expertise was required; three grant proposals were accepted for funding. Because of the success of the initial hyperphagia conference and generated enthusiasm, the decision was made to plan for the 2nd International Conference on Hyperphagia which was held in October 2012.

The theme of the 2nd International Conference on Hyperphagia was to expand on the topic of hyperphagia, as the hunger or drive to eat excessively is a critical factor in the worldwide obesity problem. Hyperphagia is the extreme unsatisfied drive to consume food and a hallmark characteristic of PWS along with several other obesity-related genetic disorders. Given the rationale and obesity epidemic, the interest in the study of PWS and other rare or uncommon single gene causes of obesity has the potential to gain specific knowledge to address obesity in the general population.

Additionally, the second conference was held to allow 25 invited scientists from throughout the world to discuss their latest research findings related to appetite and obesity research. This interaction was intended to generate points of contact and create opportunities to share and exchange research ideas for collaboration and initiatives to address hyperphagia and obesity. The research community involved in the meeting also believes that PWS presents a “Window of Opportunity” to study appetite control in the extreme situation of PWS and uncover new science with application to the general population.

The Hyperphagia Conference featured top national and international scientists in the field of hyperphagia and obesity research and held over a three day period. The latest information on various aspects of appetite control included: intracellular nutrient control of hunger; common and novel genetic causes of hyperphagia; animal and cell models of hyperphagia; addictive behavior and hyperphagia; and novel investigative approaches to the study of hyperphagia. A panel of experts also discussed the pros and cons of certain treatment avenues for hyperphagia and questions generated by the attendees were helpful in developing recommendations for research agendas.

The three day conference was grouped into five sessions: Overview; Animal and *In Vitro* Studies; Genetics and Epigenetics; Treatment; and Research Challenges. On the evening of Wednesday, October 17th, Drs. S.B. Heymsfield and P. Brantley presented the Conference Background and Introduction followed by dinner with Keynote Addresses by Drs. R. Seeley (*Hypothalamic, Brainstem, and Intracellular Nutrient Signals Controlling Food Intake*) and J. Yanovski (*Defining Hyperphagia*). On the second day of the conference, Thursday, October 18th, Dr. P. Brantley presented the Welcome and Conference Overview and Mr. J. Kane presented on *Hyperphagia: A Patient's Perspective*. Next, the first speaker in *Session I: Causes of Hyperphagia* was Dr. D. Driscoll who presented on *Prader-Willi Syndrome—The “Window of Opportunity” PWS as a Unique Vehicle for Research into Hyperphagia*, followed by Dr. R. Loos on *Common Genetic Variants Causing Hyperphagia and Obesity* then Dr. L. Baier on *Novel Genetic Defects Causing Hyperphagia*; Dr. C.L. Roth on *Craniopharyngioma and Hyperphagia*, and Dr. A. Zinn on *SIM1 Gene and Hyperphagia*. In *Session II: Developing Treatments Pros and Cons: Panel Facilitated Discussions*, a panel consisting of Drs. A. Goldstone, L. Gourash, and F. Greenway presented on the *Pros & Cons: Drugs vs. Behavior* followed by a second group of panelists, Drs. A. Goldstone, C. Vaisse, and A. Scheimann presenting on *Pros & Cons: Bariatric Surgery* with a final group of panelists, Drs. T. Inge, K. Manning, and R. Seeley discussing the *Pros & Cons—Discussion* with questions generated from the attendees. *Session III* section was presented by Dr. M. Tauber on *How to Run a Clinical Trial for Genetic and Hypothalamic Obesity with Hyperphagia*. *Session IV: Animal and Cell Models of Hyperphagia* included presentations by Drs. R. Wevrick on *How can Animal Models for Prader–Willi Syndrome help us find Treatment for Hyperphagia?* and Dr. V. Sheffield on *Hyperphagia in Animal Models of Bardet–Biedl Syndrome*. The second day of the conference concluded with Discussions and a Poster Session with dinner and Keynote Speaker, Dr. N.M. Avena presenting on *Addictive Behavior and Hyperphagia*.

On the final day of the conference, Friday, October 19th, the session entitled *Novel Techniques for Investigating Obesity* began with Dr. J. Elmquist presenting on *Novel Genetic and Neuroanatomical Techniques to Dissect Feeding Pathways in Animal Models* then followed by Dr. R. Leibel on *Using Induced Pluripotent Stem Cells to Investigate Neuronal Phenotype in Genetic Obesity* and Dr. R. Waterland on *Developmental Epigenetics and Obesity*. The last session of the morning was entitled *Research Challenges* directed by Drs. S. Heymsfield and A. Goldstone by facilitating panel discussions on research challenges and research agendas followed by a tour of the Pennington Biomedical Research Center. *The 26th Annual PWSA (USA) Scientific Day Conference* immediately

commenced after lunch at the same facility and settings. Information about the meeting organizers and funding sources is presented in the Supporting Information.

Defining hyperphagia

Jack A. Yanovski, M.D., Ph.D—Hyperphagia is often described as a hallmark of a group of inherited disorders associated with obesity. Hyperphagia is also considered present at times in otherwise healthy adults, some of whom become obese over time. A critical next step in further evaluating the mechanisms and treatments for hyperphagia is to establish an accepted definition and measurement method for both human and animal studies.

Several terms are used to describe excessive energy intake in humans, even for normal weight individuals, including most often “overeating” and “feasting.” When evaluated in experimental settings, most adults will eat an amount dependent on served portion size as well as their habitual intake and thus overeating can be studied in the laboratory. Biological drives such as rapid growth during puberty are typically accompanied by “overeating.” Overeating can also be present in the absence of physiological hunger. Loss of control over food intake is part of the formally defined “binge eating disorder” that has explicit research diagnostic criteria in the DSM-IV-R (1). When we consider categorizing overeating behaviors along a continuum of severity of eating pathology, we see a sequence beginning with overeating/feasting and then moving on to eating in the absence of physiological hunger, loss of control over eating, binge eating, and finally the most extreme form of overeating, hyperphagia. At the time of this meeting there were 8,646 PubMed publications since 1943 including the term “hyperphagia.”

Conditions that are often included when the term hyperphagia is used include binge eating disorder, hormonal imbalances such as glucocorticoid excess, leptin signaling abnormalities, syndromes associated with obesity and cognitive impairment (e.g., PWS), and many mouse models of obesity. There are several approaches frequently used to describe hyperphagia:

- By quantifying “overeating” as energy intake relative to a control group; eating beyond amount predicted for body size and body composition; and evaluating food intake pre- vs. post-treatment (e.g., before and after people with leptin deficiency are given recombinant leptin);
- Relative to a control group, by evaluating “hunger” (e.g., with visual analog scales in patients with PWS and controls); time to reach satiation relative to a control group; and duration of satiety;
- Measuring preoccupation with food or “hyperphagic drive”; food seeking behaviors (e.g., night eating, etc.); and
- Evaluating psychological symptoms such as distress and functional impairment.

Hyperphagic drive for food, behaviors, and severity can be evaluated with Dykens’ Questionnaire (2) that is designed to be completed by a caregiver and is thus suitable for children and for those with cognitive impairments. Other scales that quantify hyperphagia symptoms by asking subjects directly include, but are not limited to the Three-Factor Eating Inventory (3), Power of Food Scale (4), and the Dutch Eating Behavior Questionnaire (5).

Scientists working in this area are often focused on one aspect of the larger problem of hyperphagia and evaluate: preoccupation with food; food seeking; impaired satiety; psychic distress; eating in the absence of hunger; and binge eating. The following questions are therefore posed:

- Is it useful to define hyperphagia separately from overeating in animal and human studies? My answer is “yes,” but how this distinction should be made is still an open question.
- If so, how should overeating and hyperphagia be defined for animal and human studies? Statistically significant at $P < 0.05$? Weight gain? Requirement for satiety or satiation defect? Associated symptoms?
- How might we standardize and create objective assessments for hyperphagic drive, severity, and behaviors to facilitate cross-sample and cross-species comparisons?

For video presentation, see: <http://youtu.be/chnBReFMEPo>

Prader–Willi syndrome: A unique vehicle for research into obesity and hyperphagia

Daniel J. Driscoll, M.D., Ph.D—PWS is the most frequently diagnosed genetic cause of obesity. It also was the first recognized human disorder related to genomic imprinting. PWS occurs by one of three main mechanisms resulting in the failure of expression of genes located on the paternally inherited chromosome 15: 1) paternal deletion of the 15q11.2 region; 2) both chromosome 15s from the mother (maternal uniparental disomy 15); and 3) a defect in the imprinting process in 15q11.2 (6).

The obesity in PWS typically begins between 2 and 4 years of age if the diet is not appropriately managed. Remarkably, as neonates there is an almost complete absence of an appetite drive. The appetite gradually increases in early childhood such that by about 8 years of age the individual with PWS has an insatiable appetite. Through careful longitudinal studies, we have been able to discern seven distinct nutritional phases and sub-phases in PWS (7).

The initial nutritional phase, phase 0, occurs *in utero* with decreased birth weight, length, and fetal movements. In the first phase the infant is hypotonic and not obese. Sub-phase 1a (median age range = 0–0.75 years) is characterized by poor appetite, feeding, and weight gain. Sub-phase 1b (0.75–2.08 years) occurs when the infant is growing steadily along a growth curve and appears to be growing at a normal rate with an improving appetite.

The second main phase occurs when the weight starts to increase and crosses growth percentile lines. This generally begins between 18 and 36 months of age. Sub-phase 2a (2.08–4.50 years) is when the child’s weight increases such that they cross 1–2 or more growth percentile lines without a significant increase in calories. During this phase the children do not have an increased appetite or increased interest in food. Therefore, these observations indicate that the precipitant for the onset of the early-onset obesity is not a result of hyperphagia, but rather a different etiology. Sub-phase 2b (4.5–8.0 years) occurs when the child has increased their daily calories and has become more overweight/obese if the diet is not appropriately regulated. Individuals in this sub-phase have an abnormally

increased appetite and interest in food and typically food seek, but do not yet have the insatiable appetite and frequent food seeking exhibited in phase 3.

The third phase (8.0 years to adulthood) is the development of an insatiable appetite accompanied by very aggressive food-seeking. This is the classical phase that most people typically associate with PWS, but its onset is actually quite variable in PWS. It may appear as early as 3 years of age or as late as 15 years. In fact, a small minority of individuals with PWS never do go into this phase. The fourth phase occurs in adulthood when an individual who was previously in phase 3 no longer has an insatiable appetite and can feel full. Families and care takers note a significant improvement in appetite and weight control. Most adult individuals with PWS have not yet entered this phase, and may never do so. Longer longitudinal studies are necessary to fully understand this last phase.

For the last 11 years we have been conducting a natural history study of the nutritional phases, first at the University of Florida and then through the auspices of the NIH funded Rare Disease Clinical Research Network. We have been correlating the nutritional phases in PWS with the data accumulated on caloric intake, basal metabolic rates, DEXA body fat measurements, and levels of various appetite regulating hormones. Results of these studies will be discussed further.

PWS can serve as an ideal model system to help dissect metabolic and hormonal components in appetite regulation and the development of obesity. The diagnosis is typically made in early infancy due to hypotonia and failure to thrive prior to the onset of obesity and hyperphagia. There are robust genetic tests to confirm the diagnosis. PWS is a well-known condition to geneticists and neurologists who typically are consulted in the neonatal period due to the hypotonia and poor feeding. The existence of well-organized and highly motivated PWS support groups nationally and internationally has provided invaluable support to families, health care providers, and researchers. This, combined with a good understanding of the natural history of the various nutritional phases in PWS, should help scientists unravel the mysteries of the early-onset obesity and hyperphagia in PWS. An improved understanding of the factors associated with the various nutritional phases of PWS will not only benefit the treatment and management of PWS, but also should provide valuable insights into obesity in the general population.

For video presentation, see: http://youtu.be/KM_IBTDGztQ

Hyperphagia: A patient's perspective

James G. Kane, M.B.A

Hyperphagia is everywhere: In today's society food is everywhere. Social events, shopping trips, schools, and work places all have food at every turn. The ever-present pursuit of food by someone with PWS prevents them from functioning in any way in society without absolute control through one to one supervision. Absolute total control is necessary.

Hyperphagia is relentless: A person with PWS is always thinking about food. As 7-year-old Matt said, "*I try and I try, but my hand reach in the refrigerator and I can't stop it!*" Planning, scheming, and certain to stay one step ahead of even the best supervisor, a person

with PWS is cycloptically focused on food. The excitement of a new job or new school is a very genuine emotion. However the joy will quickly be undermined by the search for food. Always insatiable, always front, and center to a person with PWS, the search for food is paramount.

Hyperphagia is an overwhelming burden: The extreme 24/7 level of food seeking creates stress on families, caregivers, and support systems that is extraordinary and unique in the disabilities world (8). It is even more of a burden on the child or adult with the syndrome.

Hyperphagia is life-threatening: People with PWS are also saddled with a low energy requirement related to lower muscle mass, decreased metabolism, and reduced physical activity. Energy expenditure may be 40% to 70% reduced in non-growth hormone treated individuals with PWS compared with non-obese controls. The maintenance diets generally allow only 800–1,200 calories per day. Any intake over that level may lead to weight gain. It is not unusual for a person with PWS, who is living in the controlled environment of a group home, to gain twenty pounds on a week-long home visit, even to a home with a family that is knowledgeable, diligent, and controls food by managing a restricted diet and locked cabinets. Without absolute, total control over access to food, including locked refrigerators and food pantries, and planned menus, people with PWS develop severe obesity and the multitude of associated life-threatening complications that can occur.

Hyperphagia is the relentless, overwhelming, life-threatening force, which sentences people with PWS to a frustrated lifetime of control and restricted lifestyle, denying them the possibility of achieving any independence or realization of hopes or fulfillment of capabilities, all common human instincts. John Hudson Symon wrote the following shortly before his death: *“My father was a doctor and my mother was a nurse. If I was left alone I would eat everything I could. I would think about food all the time, food is everywhere—on TV, at school, at home, and in the junk mail. I would even hide food and sneak food that belonged to my brothers and sisters. I had no control. I could feel sharp teeth tearing at my stomach like piranhas—and still do. I know that I need someone to keep the cupboards locked and I need someone to keep me active to control my weight. I want to have some fun in my life. I have the right to have the same CHOICES in life that you do.”*

Hyperphagia in PWS is the *Window of Opportunity* for researchers to study the puzzle of appetite control and regulation. For PWS families, it is the locked door to freedom, independence, and a better quality of life.

Animal and In Vitro Studies

Hyperphagia in animal models of Bardet–Biedl syndrome

Val Sheffield, M.D., Ph.D—An effective approach to the molecular dissection of complex diseases is to investigate Mendelian disorders that have phenotypic overlap with complex disease. An outstanding example of such a disorder and a major focus of our laboratory is the heterogeneous autosomal recessive Bardet–Biedl syndrome (BBS). Primary diagnostic features of BBS are obesity, retinal degeneration, polydactyly, hypogonadism, renal anomalies, and cognitive impairment. In addition, BBS patients have an increased incidence

of diabetes and hypertension. Mutation carriers of BBS are predisposed to hypertension, diabetes mellitus, and obesity suggesting that the biological systems in which BBS genes play a role can contribute to non-syndromic disorders. Our work, along with the work of others, has led to the identification of multiple genes that independently cause this disorder, as well as the identification of two protein complexes (9–11). We and others have now shown that there are at least sixteen BBS genes. We have also created animal models of BBS (12–15). My laboratory has developed zebrafish gene-knockdown models of the known BBS genes (12), and seven mouse knockout or knockin models (*Bbs1*, *Bbs2*, *Bbs3*, *Bbs4*, *Bbs6*, *Bbs7*, *Bbs8*, and *Bbs11*) (13–16). The development of animal models in our laboratory has been pursued for five primary reasons: 1) To understand the molecular and cellular pathophysiology; 2) to confirm the disease-causing role of specific genes; 3) to identify phenotypes associated with specific genetic mutations; 4) to explore genetic interactions; and 5) to pursue treatments for the disease.

An initial clue suggesting a function for BBS proteins and the pathophysiology of BBS came from mouse models indicating that BBS genes/proteins play a role in cilia function. The spermatozoa of BBS mouse models do not form flagella (13–16). Furthermore, data from us and others show conservation of BBS genes in ciliated organisms, but not in non-ciliated organisms. These findings indicated that BBS genes play a role in cilia formation, maintenance, and/or function. My collaborators and I have shown that seven of known BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, and BBS9) form a stable complex (known as the BBSome) that transiently associates with PCM-1, a core component of centriolar satellites (10). This function of the BBSome is linked to the Rab8 nucleotide exchange factor, Rabin8, which localizes to the basal body and contacts the BBSome through BBS1. This interaction facilitates GTP loading of Rab8. Rab8^{GTP} targets vesicles to the cilium to promote ciliary membrane elongation.

Mouse studies have greatly contributed to our understanding of obesity in BBS. BBS knockout mice have hyperphagia, decreased activity, and increased circulating levels of leptin (17,18). Our studies show that BBS knockout mice are leptin resistant with respect to metabolic responses. In addition, we have demonstrated hypertension in some BBS knockout mice. The hypertension results from increased renal sympathetic nerve activity associated with high circulating leptin levels. Collectively, these studies show that BBS mice have a novel mechanism of obesity and hypertension resulting from selective leptin resistance. These models are proving useful in the development of novel treatments (19).

Hyperphagia and craniopharyngioma

Christian L. Roth, M.D—One of the most recalcitrant examples of excessive weight gain is hypothalamic obesity (HO) in patients with hypothalamic lesions and tumors such as craniopharyngioma (CP). CP is an embryological tumor located in the hypothalamic and/or pituitary region, frequently causing not only hypopituitarism, but also leading to damage of medial hypothalamic nuclei due to the tumor and its treatment by surgery and irradiation. After surgery, hyperphagia and obesity occur on average in about 50% of all CP patients, although study results vary from 6% to 91%. Risk factors for developing obesity in CP patients include: large hypothalamic lesions and tumors that reach the floor of the third

ventricle and the area beyond mammillary bodies; hydrocephalus; aggressive resection; and hypothalamic irradiation. Clinical features of the full HO syndrome include severe obesity with uncontrolled appetite, potentially caused by central leptin resistance and deficient downstream pathways, fatigue, decreased sympathetic activity, low energy expenditure, and increased energy storage in adipose tissue. Similar clinical features are also observed in patients suffering from HO syndrome due to a genetic abnormality (i.e., melanocortin-4 receptor defect, PWS).

In our own clinical series, CP patients with severe obesity had lesions affecting several medial hypothalamic nuclei such as hypothalamic arcuate (ARC), ventromedial (VMN) and dorsomedial (DMN) nuclei (20). In particular, VMN damage can lead to disinhibition of the vagal tone, resulting in excess stimulation of pancreatic β -cells, hyperinsulinemia, and obesity. However, there is also evidence that HO is related to a reduced sympathetic nervous output leading to decreased physical activity and energy expenditure (20). Several previous studies including our own data show that the secretion of satiety regulating peptides, such as ghrelin and peptide YY, may be altered in CP patients. Thus, using functional magnetic resonance imaging (fMRI)—a powerful tool for observing the human brain's *in vivo* responses to stimuli—we assessed pre- and post-meal responses to visual food cues in brain regions of interest in CP patients. Following the test meal, BMI matched controls showed suppression of activation by high-calorie food cues while CP patients showed trends toward higher activation. These data support the hypothesis that perception of food cues may be altered in CP patients with HO, especially after food intake.

Mechanisms leading to the profoundly disturbed energy homeostasis are complex and need to be elucidated. Using lesion specific data obtained from pediatric CP patients with refractory HO, our group created a combined medial hypothalamic lesion (CMHL) rat model in which the ARC, VMN, and DMN are destroyed bilaterally to mimic the metabolic effects of CP. This model leads to a more severe HO phenotype than lesions of single nuclei and is characterized by excessive weight gain as well as markedly increased body adiposity and food intake. Moreover, similar to that of CP patients, ambulatory activity levels are lowered, the degree of hyperleptinemia and hyperinsulinemia is inappropriate for the degree of obesity, and plasma alpha-melanocyte stimulating hormone (MSH) levels are reduced, a feature that is not present in rats receiving VMN lesions only (21).

There is an urgent need to find an efficacious treatment for HO. Recently, we used the CMHL rat model to test the efficacy of three pharmaceutical agents that act downstream of the mediobasal hypothalamus to reduce food intake and body weight. These agents include the melanocortin 3/4 receptor agonist MTII, the glucagon-like peptide (GLP)-1 agonist exendin-4, and the psychomotor stimulant methylphenidate. Peripheral administration of MTII reduced food intake and body weight relative to sham-vehicle-treated controls ($P < 0.05$). Indirect calorimetry established that the effect of MTII was due to both a reduction in food intake, as well as an increase in energy expenditure. Similar to MTII, both sham-lesioned and CMHL rats exhibited significant reductions in both food intake (lesion -20.8% , control -13.7%) and body weight when treated with exendin-4 relative to saline-controls. Finally, using a crossover design study, we found that treatment with methylphenidate in

both sham and CHML rats caused a significant decrease in food intake (CMHL -23% , $P = 0.008$; control -20% , $P = 0.002$) and body weight compared to saline-treated controls.

In summary, the CMHL model most accurately mimics the complex metabolic abnormalities observed in obese CP patients and provides a foundation for testing pharmacological approaches to treat obesity in children with hypothalamic dysfunction. Follow-up studies are required to further elucidate the effects of these three potential candidates for the treatment of HO.

Hyperphagia and addictive behavior

Nicole M. Avena, Ph.D—The increase in the prevalence of obesity, along with the convenient availability of highly-palatable, calorically dense foods, has led some to suggest that hedonic hyperphagia (i.e., eating for pleasure, as opposed to caloric need) may be a cause of increased body weight. It is well known that overeating of palatable food can have powerful effects on brain reward systems (22); however, it is debated whether excessive intake of palatable food can produce signs of dependence such as those seen in response to drugs of abuse (23). In an effort to better understand this concept, several studies have been conducted using laboratory animal models to assess whether overeating of palatable foods can produce behaviors and changes in reward-related brain systems that are similar to those seen with some drugs of abuse. In the case of binge consumption of 10% sucrose, observed behaviors include tolerance (24), signs of opiate-like withdrawal (24–26), enhanced motivation to obtain sucrose (27), and a heightened sensitivity to (28), and consumption of (29) drugs of abuse. Accompanying brain changes include alterations in dopaminergic (26,30), cholinergic (30), and opioid systems (26) in the nucleus accumbens, which are similar to the effects seen in response to some drugs of abuse. While rats bingeing on sucrose show these behavioral and neurochemical signs of addiction, they maintain a normal body weight. However, studies addressing overconsumption of palatable foods have been extended to compare the effects of overeating a variety of nutrients and palatable foods in addition to sucrose. Findings produced by these studies show that when rats overeat fat-rich diets they can gain excess body weight, but different behavioral signs of addiction are seen (31). Recently, clinical studies have used psychometrics and brain imaging techniques to study overeating within clinical populations. The results of these studies also suggest that aspects of drug-like dependence can be observed in response to excessive intake of palatable foods in some individuals (32,33). Collectively, these findings show aberrant behaviors and brain changes that can develop when rats or humans excessively eat palatable foods and suggest differences in aspects of addiction that emerge when body weight and the type of palatable food are considered.

For video presentation, see: <http://youtu.be/iQVIA6aPkBg>

Hypothalamic, brainstem, and intracellular nutrient signals controlling food intake

Randy J. Seeley, Ph.D—Adult mammals do a masterful job of matching caloric intake to caloric expenditure over time. This maintenance of energy balance requires a complex and redundant homeostatic system critically involving a number of systems in the CNS. Unfortunately, over the past decade, there have been dozens of neuropeptide and

neurotransmitter systems linked to the control of energy balance that might be involved. One way to begin organizing functional circuits is to identify which of these systems are the direct targets for afferent signals about the status of adipose mass in the periphery. Such “adiposity signals” (like leptin and insulin) have concentrations of receptors in the arcuate nucleus of the hypothalamus.

A key question is why animals when exposed to a high-fat diet gain weight and become resistant to the effects of leptin to reduce food intake. Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors where fatty acids can act as activators. PPAR- γ agonists such as rosiglitazone are used as important treatments for diabetes but are associated with weight gain. Our work indicates that the central administration of a single dose of rosiglitazone can produce increased food intake and increased weight gain that persists over several weeks. We have further shown that CNS administration of PPAR- γ antagonists can reduce food intake and body weight when animals are maintained on a high-fat diet. In particular, we have observed that while high-fat diets render animals insensitive to the CNS effects of leptin, PPAR- γ antagonists can restore normal leptin sensitivity. These data indicate an important role for hypothalamic PPAR- γ receptors in the ability of high-fat diets to reduce leptin’s ability to reduce food intake. The details of my presentation with references are provided in the video presentation of my lecture at <http://youtu.be/ptc9DxBQLp0>

Novel genetic and neuroanatomical techniques to dissect feeding pathways in animal models

Joel Elmquist, D.V.M., Ph.D—The brain plays a critical role in regulating food intake, body weight, and blood glucose levels. Dysfunction of this central regulation results in obesity and type II diabetes. Therefore, to understand the causes and to develop treatments for obesity and diabetes, it is first necessary to unravel the brain pathways regulating coordinated energy homeostasis. Metabolic cues and neurotransmitters act on key collections of neurons both within and outside the hypothalamus to regulate food intake, body weight, and glucose homeostasis. However, the inherent complexity of these CNS circuits has made it extremely difficult to definitively identify the key neurons that are required to maintain glucose homeostasis and energy balance. Over the past several years, the ability to manipulate gene expression in a neuron-specific fashion has become feasible. Recent findings using mouse models allows for neuron-specific manipulation of genes regulating energy balance and glucose homeostasis. Those studies may provide insights into the mechanisms through which the nervous system regulates food intake, body weight, and blood glucose levels.

Using induced pluripotent stem cells to investigate neuronal phenotypes in genetic obesity

Liheng Wang, Lisa C. Burnett, Dieter Egli, Ph.D., and Rudolph L. Leibel, M.D—Hypothalamic, brainstem, and other neurons act centrally to regulate energy homeostasis in response to circulating and neural signals. These cells are not directly accessible in human subjects. We seek to generate such cells *in vitro* using stem cell-based approaches. We have selected monogenic and syndromic forms of human obesity in which to test the feasibility of

such an approach. PWS is caused by a loss of a paternally expressed, imprinted region on chromosome 15q (6). BBS, Joubert (JBST) and Alstrom (ALMS) syndromes are caused by mutations of a specific group of proteins that are components of the primary cilium (34). The primary cilium on neurons “convenes” important signal receptors including Smo, Sstr3, ACIII, Lepr, and Mchr1 (34–38). Specifically, how BBS/JBST/PWS mutations affect the function of hypothalamic neurons is not well understood. To investigate the neurobiology of obesity in BBS and PWS, we have established *in vitro* models by reprogramming skin fibroblasts from BBS/PWS/JBST patients into induced pluripotent stem cells (iPSCs) and further differentiate these cells into neurons by dual SMAD (Smad represent several proteins that act as transcription factors with the abbreviation derived from gene name fusion (sma in *Caenorhabditis elegans* and Mad in *Drosophila*)) inhibition (39,40). The iPSCs derived from unaffected healthy subjects are used as controls. We have found that maternal imprinting is preserved in PWS iPSCs and iPSC-derived neurons (in collaboration with Daniel J. Driscoll, UF). Neurogenesis was unaffected in BBS iPSC-derived neurons. However, BBS10 mutant neurons possessed longer cilia than control iPSC-derived neurons. The JBST lines which carry hypomorphic mutations in *RPGRIPL* showed defective ciliogenesis manifested as fewer, shorter cilia based on ACIII and ARL13B staining. The BBS neurons displayed relative insulin resistance (decreased p-AKT (p-AKT is phosphorylated AKT with the “Ak” representing the name of a mouse that developed spontaneous thymic lymphomas and with “t” standing for thymoma) levels in response to insulin). We also observed impaired leptin signaling in red fluorescence protein (RFP)-leptin receptor (LEPR) overexpressing BBS and JBST fibroblasts compared with control fibroblasts while lentivirus-mediated expression of the wild type BBS transgene rescued leptin signaling in BBS mutant fibroblasts. These findings suggest that BBS proteins participate in both insulin and leptin signaling.

Genetics and Epigenetics

Common genetic variants causing hyperphagia and obesity

Ruth J.F. Loos, Ph.D—Large-scale genome-wide associations studies (GWAS) have so far identified more than 55 loci associated with obesity-susceptibility traits, including body mass index (BMI), WHR, body fat percentage, and extreme and early-onset obesity (41–48). In ongoing analyses by the GIANT (Genetic Investigation of Anthropometric Traits) consortium, which combined the data of up to 340,000 individuals from 125 genetic association studies, the number of loci associated with BMI and waist to hip ratio (WHR) is set to more than triple. Although these loci explain only a fraction of the overall variation in obesity-susceptibility, they may harbor genes that are involved in pathways relevant to obesity. As the genome-wide association approach is hypothesis-generating, the role of most of these loci and of the genes they harbor in relation to obesity risk remains to be elucidated. While the ongoing large-scale effort by the GIANT consortium is starting to reveal several loci that harbor genes in pathways that have so far been less apparent, i.e., in glucose and insulin homeostasis, mitochondrial processes, lipid metabolism, and the immune system, the previous observation that many BMI loci contain genes that have a potential neuronal role continues to be consistently confirmed. This begs the question whether any of these loci increase the risk of obesity through increasing food intake or through influencing related behaviors and sensations, such as increasing the feeling of hunger, reducing satiation,

amongst others. Studying the association between the obesity-susceptibility loci in relation to such markers of food intake in epidemiological studies is however a challenging undertaking for several reasons. First, most obesity-susceptibility loci have been identified through meta-analyses including data from 30,000 to up to 340,000 individuals. As such, to examine associations between the obesity-susceptibility loci with food intake traits, the study sample size will need to be of a similar large-scale magnitude to provide sufficient statistical power to either confirm or refute the hypotheses. Second, food intake and related behaviors or sensations are often inaccurately measured, using questionnaire data, in particular in large-scale studies (49,50). Furthermore, self-reported data are subjective and often biased by individuals' BMI or obesity status (51–53). These difficulties in assessing the food intake related makers will again affect the statistical power to observe associations. Third, our earlier question assumes that increased food intake is indeed associated with increased BMI. However, this association is often weak in epidemiological settings, often because of the inaccurate and biased self-reported data (54). As a consequence of these methodological challenges, no convincing associations have so far been reported between any of the obesity-susceptibility loci and markers of food intake. Nevertheless, there is evidence from animal and human case studies that some of the loci harbor genes that affect food intake. For example, some loci harbor genes (*MC4R*, *BDNF*, and *POMC*) in which mutations lead to monogenic obesity through hyperphagia (55–57). For other loci (*SH2B1*, *NPC1*), animal models have shown that deficiency of the derived protein affects weight gain through influencing energy intake (58). These observations had already been made before the GWAS discoveries, but studies focusing on the newly identified loci and their role in food intake are emerging, with the *FTO* gene being studied the most (59,60).

While GWAS and subsequent epidemiological studies are limited in their ability to follow-up on traits that are inaccurately measured (such as food intake, but also physical activity, etc), they are able to examine the association of the obesity-susceptibility genes with metabolic traits and diseases to gain insights in the pathways in which they may be involved. By integrating data across metabolic traits, it has become apparent that some obesity-susceptibly loci increase the risk of various traits and diseases through diverse pathways. A few BMI-increasing loci show even significant association with decreased metabolic risk. Such loci might be particularly informative when trying to identify the pathways in which they are involved. Another approach toward understanding the genetic basis of obesity is by studying traits that intermediate in the causal pathways. Preliminary results of a GWAS of circulating leptin levels shows that besides *LEP* also other loci affect leptin levels, some of which show intriguing associations with related metabolic traits.

Novel genetic defects causing hyperphagia

Leslie Baier, Ph.D—Studies in monozygotic twins have provided compelling evidence that BMI is a highly heritable trait. The high rates of obesity in populations from developed and developing countries have led to the assumption that common variation in the human genome underlies this common disease. However, analysis of more than 1 million common variants using techniques such as GWASs have not identified a single variant that has a large effect size on BMI across multiple ethnic groups. Instead, dozens of common variants have been identified that are significantly and reproducibly associated with BMI in studies

which include thousands of subjects such as the GIANT consortium (41), but each variant individually has only a minor impact on BMI. This has led many investigators to reconsider the assumption that common variation must underlie common disease, and potential roles for rare and/or ethnic specific variants are being explored.

Much of our current knowledge of rare variants affecting hyperphagia in humans originated in rodent studies. In particular, the discovery of the hormone leptin and its downstream signaling pathway led to the identification of specific causative variants that underlie rare monogenic forms of childhood obesity (61). Following the systemic release of leptin and its subsequent interaction with the LEPR on the surface of neurons of the arcuate nucleus region of the hypothalamus, the downstream signals that regulate satiety and energy homeostasis are then propagated via proopiomelanocortin (POMC), cocaine-and-amphetamine-related transcript (CART), and the melanocortin system which includes the melanocortin 4 receptor (MC4R). These genes involved in regulating hunger and satiety have been directly sequenced in cohorts of extremely obese children, primarily in the laboratories of Stephen O'Rahilly and Sadaf Farooqi (57). Candidate gene studies have determined that functional mutations within the leptin gene (LEP) itself is exceedingly rare; in contrast, loss of function mutations in the gene that encodes the LEPR have been found in 3% of probands with severe early-onset obesity in a study that included consanguineous families. Null mutations in POMC lead to obesity, but heterozygous mutations in POMC, including loss of function mutations in the post-translationally modified products alpha and beta MSH are not consistently associated with severe childhood obesity. Dozens of different, rare missense variants in the single exon of MC4R have been identified, the majority of which are consistent with a dominant inheritance of monogenic obesity. Missense variants in MC4R occur in nearly 6% of patients with severe, early onset obesity, making heterozygous, loss of function mutations in MC4R the most common cause of monogenic obesity in humans.

Similar to the leptin/MC4R pathway, the brain-derived neurotrophic factor (BDNF) and its tyrosine kinase receptor (TrkB) were also initially studied in mouse models. Both genes are expressed in hypothalamic nuclei and their protein products were found to have a role in satiety and locomotor activity. BDNF homozygosity in mice is lethal, but heterozygous mice with reduced BDNF expression exhibit abnormal eating behavior leading to an obese phenotype. Similarly, TrkB hypomorphic mice, which express full-length TrkB at about 25% of normal levels, display excessive feeding behavior. Rare *de novo* mutations in the BDNF and TrkB have been observed in humans who exhibit hyperphagia and severe obesity, and more recently, a common Val66Met polymorphism in BDNF has been associated with BMI in human populations (55).

In addition to performing candidate gene analysis to identify rare variation in extreme case samples, recent investigations have included genome-wide detection of large, rare deletions in extreme cases. One of these studies has uncovered overlapping deletions on chromosome 16p11.2 (61). The various deletions encompassed several genes but all included SH2B1, which is involved in leptin and insulin signaling. Deletion carriers are hyperphagic and severely insulin resistance, even after accounting for their degree of body fatness.

While studies in children with extreme obesity have proven successful in identifying rare variants for hyperphagia, not all “novel” variants are necessarily rare across all populations. Allele frequency varies considerably among different ethnic groups, and many minority groups, who were not included in the large GWAS meta-analyses for obesity performed to date, have very high rates of this disease. The Pima Indians of Arizona are an interesting population in that they have one of the world’s highest prevalence rates of obesity, and have minimal European admixture, suggesting that they may have some “novel” (i.e., non-Caucasian) genetic contributors to this disease. For example, the protein coded by HCRTR2 is a G-protein coupled receptor that binds the hypothalamic neuropeptides orexin A and orexin B and is involved in regulating feeding behavior. A variant with a risk allele frequency of 0.48 in HCRTR2 is associated with BMI in Pima Indians, but this variant has a frequency of 0.04 in Africans and is monomorphic (for the non-risk allele) Caucasians. Alternatively, similar genes may be contributing to hyperphagia in different ethnic groups, but the inherited casual variant may differ. For example, common non-coding variation in both the SIM-1 and LEPR loci are reproducibly associated with BMI in Native Americans (62,63), whereas in Caucasians rarer coding variants and/or large chromosomal deletions or rearrangements have been associated with obesity (64).

Even within a genetically similar population, different casual variants within a single gene can exist. For example, sequencing of MC4R in a population-based study of 7900 Pima Indians from a single community detected 10 different missense variants, four of which have not been previously reported in other ethnic groups (65). A total of 237 of the 7,900 Pima Indians carried a missense MC4R variant (population-based frequency of 3%) as compared to a frequency of 1 in 1,000 carriers in the general UK population (population-based frequency of 0.1%). These distinct rare casual variants in close genetic proximity can confound large GWAS analyses. To complicate associations in this region even further, many populations also have common variation near the MC4R locus that is associated with BMI (41). Pima Indians have common variation near the 5’UTR of MC4R that is associated with BMI, where the risk allele frequency is 0.47 in Pima Indians and 0.12 in Caucasians. This variation is distinct from the common variation near the MC4R locus previously reported by the GIANT study; Pima Indians are essentially monomorphic for the non-risk allele of the variant associated with BMI in Caucasians.

Obesity, in particular childhood obesity, is perhaps our largest public health concern and many resources are being devoted to identifying the heritable basis for this disease. Excellent studies have shown the importance of rare variants in the early development of this disease, but unfortunately the most common cause of extreme childhood obesity is haploinsufficiency of the MC4R gene. The complexity of the signaling of the melanocortin system, including effects on the cardiovascular system, makes it a difficult target for drugs without substantial risk for side effects. Among the other well-studied obesity genes, BDNF and POMC both code for ligands and are therefore not traditional drug targets. Many of the gene products along this pathway are also difficult to manipulate because they are expressed in the CNS. Therefore, future research must include identifying new pathways that are more accessible for therapy.

Genetic research in obesity, similar to genetic research for other polygenic complex diseases, is moving toward whole genome sequencing as a more thorough, hypothesis-free investigation. As Next Generation sequencing costs are decreasing, it will become more feasible to sequence the large numbers of subjects required for identifying genes for polygenic diseases. Sequencing of whole genomes will also allow better detection of variation that is more complex than the simple polymorphisms which were analyzed by GWASs. It is estimated that 8% of individuals have a large (>500 kb) deletion or duplication that occurs at an allele frequency of <0.05%. Copy-number variants (CNVs) are also important in that they have been subjected to sudden, rapid, and often adaptive, evolution in human populations.

Epigenetics is also an emerging field in the genetics of polygenic disease. Technology that allows large-scale exploration of epigenetic factors such as DNA methylation, histone modification, RNA processing, and microRNA expression is becoming available. However, it must be remembered that the most important outcome of understanding the genetic heritability of a disease such as obesity is using this information for prevention or treatment. Given our current understanding of the genetic basis for common, polygenic obesity, this may be a daunting task.

Hyperphagia and SIM1 gene

Andrew R. Zinn, M.D., Ph.D—Energy homeostasis is tightly regulated genetically. A large number of loci with modest effects, e.g., *FTO*, contribute to the heritability of BMI and related phenotypes, and mutations of a small number of genes have been found to cause monogenic obesity (66). Most of the Mendelian obesity genes were first identified in mouse models, with human mutations subsequently detected from directed screening of individuals with severe and/or familial obesity. For some of these genes, e.g., *MC4R*, mutations with major effects on protein function cause monogenic obesity, whereas subtle variation contributes to BMI as a complex trait. Both modest-effect and especially Mendelian obesity genes have highlighted the role of the central nervous system and hypothalamic leptin-melanocortin signaling pathways in energy homeostasis.

SIM1 encodes a member of the bHLH-PAS family of transcription factors expressed in the developing and adult hypothalamus (67). Homozygous *Sim1* knockout mice, which die perinatally, lack the paraventricular nucleus of the hypothalamus (PVN), a major site of Mc4r action in feeding regulation (68). Heterozygous mutation of *SIM1* was first associated with hyperphagia in a girl with severe, early onset obesity and normal energy expenditure (64). Subsequent studies showed that heterozygous *Sim1* knockout mice showed hyperphagia with normal energy expenditure, exacerbated by high fat diet, and decreased PVN oxytocin and vasopressin expression (69). PVN oxytocin neurons projecting to the hindbrain have been previously implicated in satiety in response to MC4R signaling and dietary fat, and intracerebroventricular oxytocin partially rescued the hyperphagia of *Sim1* heterozygotes (70). Consistent with these data, a recent study showed that acute inhibition of oxytocin-expressing *Sim1* PVN neurons in mice increases food intake, whereas activation of these neurons inhibits feeding (71).

Classical lesioning of the PVN resulted in hyperphagia, and *Sim1* heterozygous mice were initially proposed to be hyperphagic on the basis of reduced number of PVN neurons (72). However, we did not observe a reduced number of PVN neurons in *Sim1* heterozygotes (70). In addition, *Sim1* expression in adult PVN neurons suggested that it has post-developmental, physiologic functions. Consistent with this hypothesis, transgenic overexpression of *Sim1* ameliorated high fat diet-induced hyperphagia without altering PVN morphology (73). Furthermore, viral-mediated overexpression of *Sim1* in adult mice reduced food intake, whereas inhibition of *Sim1* expression increased feeding (74). Finally, conditional postnatal knockout of *Sim1* caused hyperphagia, with no loss of PVN neurons or gross changes to their hindbrain projections (75). These lines of evidence strongly supported a physiologic role for *Sim1* in regulation of food intake.

In order to inactivate *Sim1* in adult mice with fully formed, mature hypothalamic circuits, we generated a tamoxifen-inducible *Sim1* knockout mouse. Using this system, we confirmed that *Sim1* inactivation increased food intake and weight gain without affecting gross PVN neuron survival. Induced *Sim1* knockout also caused increased water intake, probably via decreased vasopressin expression (central diabetes insipidus).

Sim1 and its as yet unidentified transcriptional targets are thus potential targets for treating hyperphagia. Unlike other genes such as *MC4R* that modulate both food intake and autonomic nervous system activity, *SIM1* appears to selectively or preferentially regulate feeding. CHIP-Seq experiments are in progress to determine *Sim1* genomic binding sites in cultured cells; the inducible *Sim1* knockout mice will be useful for validating *Sim1* PVN target genes *in vivo*.

Developmental epigenetics and human disease

Robert A. Waterland, Ph.D—Epigenetics describes the study of mitotically heritable and stable alterations in gene expression potential that are not caused by changes in DNA sequence (76). Animal models and the human neurodevelopmental disorder PWS demonstrate that epigenetic dysregulation can cause obesity. The extent to which epigenetic mechanisms contribute to the worldwide obesity epidemic, however, remains unclear. Understanding the epigenetic contribution to human disease is substantially more complex than studying genetic pathogenesis. A major reason is the inherent tissue-specificity of epigenetic regulation. Unlike in genetic studies of obesity, in which an individual's genotype can be assessed from peripheral blood or buccal DNA, such easily obtainable samples will in most cases not be indicative of epigenetic variation in tissues of primary importance to body weight regulation. Elucidating epigenetic mechanisms in human obesity is further complicated by multiple interactions among environment, genetics, epigenetics, and obesity. Effects of environment, moreover, must be considered in a developmental perspective; developmental periods when epigenetic mechanisms are undergoing establishment or maturation constitute critical windows when environment can affect these processes, with lifelong consequences (77).

For these reasons, we have been developing mouse models in which to study early environmental influences on developmental epigenetics and obesity. The agouti viable yellow (*A^{vy}*) mouse provides an excellent model in which to study the effects of maternal

obesity on the offspring. *A^{vy/a}* mice are spontaneously hyperphagic and become extremely obese as adults, but remain fertile. Using this model, we recently showed that maternal obesity promotes obesity in her offspring, and that this transgenerational amplification of obesity is prevented by a pro-methylation dietary supplement (78). We have now replicated and expanded these studies.

Given its central role in regulating food intake and energy expenditure (79), the hypothalamus is an obvious tissue in which to explore a potential epigenetic basis for induced alterations in body weight regulation. Our current hypothesis is that maternal obesity alters the intrauterine environment, affecting developmental epigenetics of hypothalamic body weight regulation in the fetus, leading to permanent changes in food intake and/or energy expenditure. The hypothalamus is comprised of distinct regions, or “nuclei,” with specialized functions, gene expression patterns (79), and epigenetic regulation (80). Additionally, the nervous system includes diverse cell types; the simplest classification distinguishes neurons and glia, which are epigenetically distinct (81,82). To better understand how maternal obesity causes persistent changes in regulation of body weight and body composition, it will be necessary to characterize epigenetic effects within specific nuclei and cell types of the hypothalamus. Moreover, since fetal life is a critical period for not only epigenetic but also neuroanatomic development, studying these processes in an integrated fashion will likely be necessary to gain a clear understanding of how maternal obesity affects the establishment of hypothalamic body weight regulation.

Treatments

How can animal models for Prader-Willi syndrome help us find treatments for hyperphagia?

Rachel Wevrick, Ph.D—Eating disorders that cause unhealthy increases or decreases in body weight are a rising cause of morbidity, mortality, and health care costs worldwide. Four percent of North Americans are estimated to suffer from some type of serious eating disorder and about 36% are obese. The etiology of disordered eating encompasses environmental, sociological, and genetic components. Moreover, inadequate perinatal nutrition can program epigenetic changes that predispose the individual to obesity and diabetes in adult life (83,84). While the heritability of body mass index (a surrogate marker for obesity) in adults is estimated at 40–70%, genetic factors contribute to over 80% of the variation in children and adolescents. Mutations in specific genes cause about 5–10% of cases of childhood-onset obesity, and these genes have revealed important pathways that regulate energy balance. Many obesity susceptibility genes act in the central nervous system, and interact with each other and with an environment that provides easy access to cheap, calorically dense, highly palatable food.

PWS is a rare disorder that illustrates the importance of genetics in regulation of body weight. Constant hunger and obsession with food are cardinal findings in PWS: life-threatening obesity is inevitable if the environment is not strictly controlled. Affected individuals also face intellectual disability, excessive daytime sleepiness, and low sex hormone levels. Not only do people with PWS consume very large amounts of food if permitted, but their food perceptions, satiety responses, and emotional reactions to food are

highly aberrant. PWS can cause indiscriminate eating, such as eating pet food or spoiled food, and stealing or hoarding food. Most caregivers need to lock up food to prevent binge eating, which can lead to stomach rupture, gastric necrosis, and death. Functional brain imaging studies in PWS reveal over-activation of reward circuits and decreased activity in cortical inhibitory circuits in response to eating or just pictures of food. This suggests an underlying imbalance in the cognitive control of food motivation, food consumption, and satiety. Similar circuits are altered in women with bulimia, suggesting that the pathways disrupted in PWS may overlap with those important in other eating disorders. While brain imaging identifies abnormal circuits, it provides no information about cause and effect or about the biochemical pathways involved. Despite decades of research and the identification of genes inactivated in PWS, the molecular pathogenesis of compulsive eating in PWS remains poorly understood. Although PWS occurs in only 1 in 15,000 people, solving the puzzle of this very severe genetic eating disorder will provide a new molecular entry point into more common complex and heterogeneous eating disorders.

At least six PWS candidate genes have been identified and three of these genes (*SNORD116*, *MAGEL2*, and *NECDIN*) produce aberrant phenotypes when the orthologous genes are disrupted in mice. Deletion of the entire cluster of PWS candidate causes high rates of lethality shortly after birth, limiting the usefulness of this mouse model. Mice lacking only *Snord116* have abnormal feeding behavior, mice lacking only *Magel2* have increased fat mass and decreased voluntary activity, and mice lacking *Necdin* have increased fat mass when fed a high fat diet. Elucidating the intricate neural circuits that interact with peripheral organs to maintain appropriate food intake and body weight may provide new opportunities to develop effective therapies for people with PWS and others with rare or common eating disorders.

Inactivation of one (or more) PWS candidate genes causes excessive eating and binge eating in people with PWS. At least one of the PWS genes participates in a neural pathway that modulates reward-based eating behavior. However, few rigorous studies of feeding behavior and of the neural pathways important in feeding have been performed in PWS model mice. Studies of PWS genes in model organisms will provide novel insight into the neural pathways that are critical to the pathogenesis of severe eating disorders.

Hyperphagia and related behavior in Prader–Willi syndrome

Linda M. Gourash, M.D. and Janice L. Forster, M.D—Those confronted with the day-to-day challenges of behavior management for PWS require an accurate understanding of the characteristically persistent, extraordinary and often dangerous behaviors of persons with PWS. Because of the complexity of the disorder, some reductionist thinking is needed to organize caregivers' moment-to-moment responses but wholly incorrect paradigms lead to mismanagement. Existing neuroscience and behavioral phenomenology of PWS inform our understanding of PWS hyperphagia presented in an automotive analogy (Car Model) for parents, teachers, and professional careers.

PWS is characterized by the body's inability to adapt to homeostatic dysregulation (global feedback failure). Failure to suck and feed in the neonatal period is an early indicator of faulty drives (lack of hunger, the first and most important organizing drive in life) and leads

to failure to thrive. Scheduled feeding of prescribed calories leads to survival with subsequent growth. Weight gain precedes the increase in calories, and an increased interest in food becomes apparent around the same time that the first tantrum occurs. Both of these behaviors indicate the timely development of the reward drive, which is a manifestation of orbitofrontal maturation. From this point on, hyperphagia leads to weight gain through impaired satiety mechanisms and food becomes the major organizer of thought and behavior. It is also apparent that the abnormal appetitive drive (reward drive) and failed satiety mechanisms involve more than just food; collections of preferred items and over use of all commodities, telephone and internet use, grooming and tobacco products ensue, requiring external controls for management just as with food. Personality traits, such as excessive, repetitive questioning, and perseverative behaviors, also lack a typical response to habituation and satiety and require external cues and environmental interventions for management. These behaviors are apparent by age 10 years.

Controlled food access is an essential management tool for weight regulation in PWS. But controlling food access does not manage the preoccupation with food or food-related behaviors in PWS. Behavioral disturbance in PWS (impulsive tantrum or shut down) is related to disappointment (emotional response) when the outcome of a situation (cognitive prediction/idea) is discrepant from expectations (contextual conditioning via learning and memory). In the macrosphere of economics, food security pertains to the knowledge of where the source of nourishment will originate across the day. It can be applied to population studies of obesity because typical individuals will eat more of available calories (compensation) when balanced meals (needing) and preferred sources (wanting) are not present. For the person with PWS, psychological food security manages food preoccupation and behavior. Managing expectations by knowing what is available to eat (the menu and amount), when it will be served (the schedule), and controlling access and supervision (no chance of getting more) leads to psychological contentment (satisfaction). FOOD SECURITY, summarized in the mantra, “NO DOUBT, NO HOPE, NO DISAPPOINTMENT” provides the necessary feedback to override failed satiety mechanisms. Because disappointment is avoided, behavioral control is better maintained and intake and behavior can be managed in concert. When food ceases to be the major organizer of thought and behavior in persons with PWS, individuals have greater freedom to use their brain for other developmentally appropriate tasks, such as learning, socializing, and engaging in creative processes.

Treatment will involve drugs in addition to control of the food environment and behavioral modification

Frank Greenway, M.D—HO is caused by bilateral damage to the ventromedial hypothalamus and results in obesity that is usually resistant to diet, exercise, and behavior modification. HO releases the vagus nerve from inhibitory influences, and the increased vagal traffic increases insulin output, reduces blood sugar, and results in hyperphagia. The hypothalamic damage also reduces sympathetic tone and metabolic rate in addition to increasing food intake. Since most obesity medications act in the hypothalamus, they have limited use in treating HO.

Dextroamphetamine has been used to treat HO because of its ability to increase sympathetic tone. A study was reported in which five subjects were given 12.5–20 mg/day for 24 months. During the treatment period they gained 0.4 kg/months compared to the 10 months prior to treatment when they gained 2 kg/months ($P = 0.009$). On dextroamphetamine, the subjects had improved attention, improved behavior, and were more active physically (85).

Octreotide has been used to treat HO because it can reduce the exaggerated insulin response seen with hypothalamic damage. A study was reported in which eight children with HO were gaining 1 kg/month for six months. These children were treated with octreotide for 6 months. Their peak insulin response to an oral glucose tolerance test (OGTT) dropped from $281 \pm 47 \mu\text{U/mL}$ to $114 \pm 35 \mu\text{U/mL}$ ($P = 0.04$) and their weight decreased 0.8 kg/month ($P = 0.04$). In a randomized placebo controlled trial, 18 children with HO were treated with 5–15 $\mu\text{g/kg/day}$ of octreotide or placebo subcutaneously for 6 months. The octreotide group gained 1.6 ± 0.6 kg compared to a gain of 9.1 ± 1.7 kg in the control group ($P < 0.001$), and the peak insulin during an OGTT was less in the octreotide group (135 ± 39 vs. $324 \pm 65 \mu\text{U/mL}$) (86).

Triiodothyronine at hyperthyroid levels caused weight loss in individuals with HO due to the action of thyroid hormone outside the brain to increase metabolic rate (87). Caffeine and ephedrine also caused a 10% weight loss in three subjects with HO (88). These observations suggest that drugs acting on peripheral targets to decrease insulin levels and increase metabolic rate might have promise in the treatment of HO.

Beloranib is a candidate obesity drug being developed by Zafgen. Beloranib is an inhibitor of methionine aminopeptidase-2 (MetAP2) which works in the periphery to reduce fatty acid synthesis, reduce insulin levels and food intake while increasing fat mobilization, fatty acid oxidation, and energy expenditure based on comparisons similar to pair feeding. MetAP-2 inhibition is thought to work by reducing activity of ERK1/2, decreasing insulin levels and inflammation while increasing FGF21 and fat oxidation. Ob/ob mice have a leptin deficiency on a C57 black 6 (C57B6) background. Beloranib treatment returns body weight in ob/ob mice to the weight of the wild-type C57B6 mice. In a human phase 1b trial in which beloranib was given at a dose of 0.9 mg/m² intravenously twice weekly, obese human females lost 1 kg/week over the 4-week trial and the drug was well tolerated. Since beloranib acts peripherally to decrease insulin levels, fatty acid synthesis, and increase energy expenditure, it was hypothesized that it would effectively treat HO. HO was created using gold thioglucose (GTG) in mice. Forty-eight days after the GTG treatment, the control group treated with saline gained 20% of their body weight while the mice treated with GTG increased their food intake and gained 50% of their body weight. A pilot study was then conducted in which 8 GTG treated mice were treated with vehicle and 10 were treated with beloranib 0.1 mg/kg/day subcutaneously for 10 days. Body weight in the beloranib treated group fell by 1%/day from baseline in the 10 days of treatment and food intake returned to the level of the non-GTG treated controls. The vehicle treated group gained 3% of their body weight.

Thus, HO with its impaired sympathetic tone, increased insulin secretion, and hyperphagia represents a challenge to treatment with modification of the food environment, behavioral

modification, or medication. Although prior attempts addressing the reduced sympathetic tone or the increase in insulin secretion alone to treat the hyperphagia of HO have been met with limited success, beloranib, a candidate obesity drug acting outside the brain to lower both insulin levels and increase energy expenditure, has shown promise to successfully induce weight loss and reduce food intake in a pilot trial of HO in GTG mice. If further studies with beloranib in HO confirm and extend the results of the pilot study, beloranib may represent a potential medication to accompany modification of the food environment and behavioral modification in the treatment of HO including the PWS.

For video of this session, see: <http://youtu.be/GZk5n7BGKGQ>

Is bariatric surgery an appropriate treatment option for patients with genetic or hypothalamic obesity?

Introduction

Anthony P. Goldstone, M.D., Ph.D: Several bariatric surgical procedures are available and include laparoscopic banding, Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and biliopancreatic diversion. The Swedish Obese Subject (SOS) Study has reported excellent weight loss results in obese patients over a 15-year follow-up period, the magnitude of which depended on type of bariatric procedure (89). The amount of weight loss, beneficial and adverse effects, and hormonal-metabolic consequences all vary by type of bariatric surgery as recently reviewed by Stefater et al. (90), and recently reported in functional neuroimaging studies by Scholtz et al. (91) (Table 1).

These variable effects of bariatric surgical procedures are important considerations that will be discussed further in the next two presentations. There have been a number of reports on patients with hyperphagia treated with bariatric surgical procedures and some of these reports are summarized in Table 2. However these conclusions are usually based on small studies or case reports.

Christian Vaisse, M.D., Ph.D: Bariatric surgery is currently the most effective therapy for patients with severe obesity, but outcomes after different types of bariatric surgery are variable and the mechanisms of resultant weight loss are poorly understood (90). In addition to environmental, as well as psychological and behavioral factors, genetic variations, in particular those underlying the hyperphagic obesity of the patients, could influence the outcome of these procedures.

Genetic factors account for 40–70% of an individual's predisposition to obesity (92). The known genetic variants predisposing to obesity include common genetic variants with small effects as well as several extremely rare recessive obesity-causing mutations in genes of the hypothalamic leptin-melanocortin system, including homozygous null mutations in leptin, the LEPR, POMC, and the MC4R (92). Assessing the outcome of bariatric surgery in individuals with complete loss of function of these genes may allow for establishing the importance of the integrity of the central leptin-melanocortin pathway for weight loss after bariatric surgery. Indeed, work in mice suggests that obesity associated with a complete genetic ablation of MC4R is refractory to bariatric surgery (93). In line with this

observation, we have recently described the outcome of bariatric surgery in an adolescent with compound heterozygosity and complete functional loss of both alleles of the MC4R (94). The patient underwent laparoscopic adjustable gastric banding and truncal vagotomy at 18 8/12 years of age, which resulted in initial, but not sustained weight loss suggesting that, in humans, MC4R is required for long-term weight loss following bariatric surgery. Interestingly, adjustable gastric banding seems to lead to sustained weight loss in a severely obese patient carrying a homozygous null mutation in the LEPR (Dr. K. Clement, personal communication). This could indicate that the neuronal mechanism through which bariatric surgery (or at least gastric banding) elicits its long-term effects could be within the leptin responsive primary order neurons (i.e., downstream of the LEPR but upstream of the MC4R). Confirmation of these findings in additional patients and mechanistic follow-up experiments in rodent models could help further outline the central mechanisms underlying the long-term response to bariatric surgery in humans.

In addition to the very rare patients with obesity due to complete loss of function of genes of the leptin-melanocortin pathway, 2.5% of severely obese patients carry a pathogenic heterozygous mutation in the MC4R gene, making this the most common known genetic cause of severe obesity. A number of studies have evaluated the long-term outcome of these patients after bariatric surgery. We first reported that weight loss after bariatric surgery (RYGB) in patients heterozygous for well characterized pathogenic MC4R mutations was not significantly different from non-carriers in a one year follow-up (95), a result further confirmed by larger studies (93,96). We are currently assessing more precisely the effect of MC4R mutations on the long-term (five-year) outcome after bariatric surgery in the large multicenter LABS cohort.

In summary, preliminary data suggest that the outcome of bariatric surgery may in certain cases be influenced by the nature of the genetic cause underlying the hyperphagic obesity of the patients, which may allow for insights into the mechanism through which it exerts its central effects. Of more clinical relevance, heterozygous mutations in MC4R, the most common genetic cause of severe obesity does not seem to affect the long-term outcome of bariatric surgery and patients with such mutations should be considered candidates for these procedures.

For video presentation of this session, see: <http://youtu.be/UhGkWB2ttL4>

Ann O. Scheimann, M.D., M.B.A: Lifespan is shortened in PWS with terminal events ranging from a high of ~30% for pneumonia and on to respiratory failure (~25%), sudden death (~20%), congestive heart failure (~10%), and several types of gastrointestinal fatal events. Among the gastrointestinal risks, patients with PWS have an underlying defect in satiety, an altered pain threshold, a decreased ability to vomit, and an increased risk of gastric dilation and necrosis.

These collective risks and disturbances are important when considering surgical weight loss treatments for patients with PWS. Several surgical operations are available and include restrictive procedures (e.g., vertical banded gastroplasty, laparoscopic banding, sleeve gastrectomy, etc.) and malabsorptive procedures (e.g., gastric bypass, biliopancreatic

diversion with and without duodenal switch, etc.). Insertion of a gastric balloon is another short-term non-surgical option.

Small scale studies have been reported for both restrictive and malabsorptive procedures. Restrictive procedure reports for patients with PWS began in the early nineteen seventies and surgery was followed by weight loss and clinical improvements, although complications and death are noted in these studies. Similarly, reports of PWS patients treated with malabsorptive procedures began during the early nineteen eighties and describe weight loss followed by weight regain in some cases and complications ranging from minor adverse events to death. Of the few comparative reports, patients 5-years post procedure tended to have lost substantially less weight or even gained weight compared to non-PWS obese controls who on average lost 10–25% of their baseline weight. An example is the study by Yu et al. of 11 PWS and Bardet Biedl patients treated with laparoscopic sleeve gastrectomy that overall lost weight and had improvement in comorbidities (97). In another report of one 16-year-old male patient with BBS (98) there was a lowering of BMI from 52.8 kg/m² to 34.85 kg/m² over 3½ years post-operatively with improvements in hypertension, hyperuricemia, and mobility. Weight loss had stabilized by the second post-operative year. Similarly, a single report of an 18-year-old male with MC4R deficiency (94) treated with a laparoscopic truncal vagotomy showed initial weight loss followed by weight regain above baseline one year postoperatively.

Bariatric surgery has also been used to treat the hyperphagia and obesity associated with hypothalamic lesions. In the study of Rottembourg et al. (99) seven patients with HO were treated with several different bariatric surgical procedures and most lost considerable weight, although adverse events (e.g., pancreatitis) were noted and long-term weight gain above baseline was found in four patients at seven years post-operatively who had been treated with laparoscopic gastric bypass.

Another option is short-term use of a gastric balloon as in the study of DePeppo et al. (100) in which 12 patients were treated with the BioEnterics IntraGastric Balloon (BIB). Subjects experienced a significant reduction in BMI and adiposity while there was one death due to gastric perforation.

In sum, a variety of bariatric surgical procedures are available to treat patients with hyperphagic obesity. There is a paucity of data regarding outcomes after bariatric surgery for hyperphagic disorders aside from PWS. All of the long-term studies of outcomes after bariatric procedures in PWS have demonstrated weight regain unlike the sustained weight loss seen in non-PWS obese patients undergoing bariatric surgery. The BIB-balloon enteric procedure is not recommended for weight loss in PWS due to the risks for development of gastric dilation/necrosis. Clearly, more data with detailed information is needed on the surgical treatment of hyperphagia. In the meantime, non-bariatric approaches including diet and exercise that show promise in patients with PWS (101), particularly when applied early in life, can potentially help to avoid long-term obesity.

For video presentation of this session, see: <http://youtu.be/UhGkWB2ttL4>

How to run a clinical trial for genetic and hypothalamic obesity with hyperphagia

Maïthé Tauber, M.D., Ph.D—The issue of how to run a clinical trial for genetic and HO with hyperphagia is crucial. The example of PWS gives some useful indications.

First the age of the study population is important as there are different nutritional phases with age with the paradigm of PWS. The possible interactions with psychotropic medications often taken by these persons need to be investigated.

From an ethical point of view, we think that it is not possible to stop the strict control to food access which is mandatory for these persons. Even for a clinical trial, the evaluation of eating behavior and food intake when persons are exposed to food *ad libitum* is not recommended.

As eating behavior is part of the “general” behavior troubles a complete evaluation is needed including food intake, eating behavior, and general behavior. The evaluation of the effect of the study drug includes calorie intake, food preferences, adapted questionnaires of food intake, and eating behavior (to age and disease if available, i.e., the PWS hyperphagia questionnaire). Visual analogic scales for hungry and satiety are helpful. Specific tools can be developed to assess food related emotion. Foraging, craving, storage behaviors have to be noted.

Whether the study is performed ambulatory at family home or group homes or in patients admitted in dedicated centers or hospitals is also important. We have built a home-made grid for persons with PWS to routinely/daily evaluate behavior when patients are admitted in our dedicated center, including the key features of PWS. These grids are filled by the careers and score by our team psychologist.

From a pathophysiological point of view, in addition to these clinical evaluations, blood samples are generally performed, before and after the start of therapy, fasting, and post meals. Blood sample difficulties and/or limitations particularly for persons with obesity and/or, assays difficulties are challenging questions. In addition what is the signification of a plasma value for specific neuropeptides or hormones?

It is now undoubtedly interesting to combine brain imaging and particularly functional studies such as PET scan or fMRI in various conditions at rest or after stimulations. Regarding certain brain imaging protocols requiring radiation, how many images can be made from an ethical point of view due to the radiation risk?

Finally, the dose and modalities of administration of treatment should be discussed given the fact that persons with PWS are often very sensitive to psychotropic treatments and requiring lower doses than other patients. Escalating and monitoring dosage studies may then be necessary.

Moreover, rare diseases add another line of complexity to design studies and sufficient statistical power due to small sample size.

Research Challenges

Steven B. Heymsfield, M.D., Anthony P. Goldstone, M.D., Ph.D

Two topics were the focus of the closing discussion, future collaborations and animal models.

- **Future Collaborations.** One aim is to develop useful animal models as a means of determining pathophysiology and identifying contributing genetic factors for causation and to evaluate drug targets leading to clinical trials and treatments. Several international collaborations of this type are in progress.

A second aim is to create a brain bank, and one effort is underway to develop this area for patients with PWS. Other banks could serve as sources of tissues, cell lines, stem cells, and material for genetic analyses. With brain, logistics can present a formidable problem with collection, handling, harvesting, and transportation once complex approvals have been met.

Some discussion followed about the advantages of a cell line bank modeled after one now in place at Columbia University for patients with diabetes and severe obesity. Appropriate consent forms must be developed that effectively manage intellectual property issues and tissue use. The cost of maintaining such banks is also important and may pose a barrier to further development.

One idea was to develop standardized consents and advanced directives forms that could be presented to families by providers who could be trained at their annual meeting.

A third and related area for collaboration is to develop standardized evaluation methods for quantifying clinical aspects of hyperphagia, including extensive patient and family histories, aspects of food intake behavior, and medical histories. This information might be specific for the condition (e.g., PWS) being evaluated. Such standardized procedures would be invaluable when testing potential treatments and for FDA and other agency reviews. A critical need is for extensive phenotyping to accompany banked material that can maximize their usefulness.

A fourth area of collaboration could be bariatric surgery treatment for hyperphagia. Perhaps a registry and network could be created that would then allow for un-biased reporting of treatment outcomes.

Taken collectively, these collaborations could form the basis of an international consortium that would meet at convenient times, such as at The Obesity Society or International Congress of Obesity meetings. Consortia could facilitate the development of data, tissue banks, and to further establish collaborations and research.

- **Animal Models.** Is there an appropriate animal model for evaluating pharmacologic therapies for hyperphagia? Could such an animal model provide proof-of-principle and a “go-no” decision for drug development? The discussion centered on the likelihood that hyperphagic mechanisms may be diverse and that no single animal model can achieve these goals. Might other models than the mouse be considered, such as the pig? Some drug companies may be willing to collaborate

on these efforts. Optimally, the best approach was to test new therapies early in their development in hyperphagic humans once safety has been assured in pre-clinical evaluations.

Acknowledgments

Authors graciously thank Ms. Sydney Smith for her coordination of manuscript preparation. The extensive meeting arrangements and follow-up were coordinated through the skilled efforts of Ms. Anne Haney. Meeting organizers are listed in the Supporting Information.

Funding agency: DJD: NIH 1K24 HD01361; NIH 1K23 DK081203; Department of Defense W81XWH-08-1-0025; 1U54 RR019478; NIH CTSA 1UL1RR029890; JE: NIH R01DK53301, NIH RL1DK081185, and NIH P01DK088761; RW: “Best Idea Grant for Hyperphagia Research” from the Prader–Willi Syndrome Association; AZ: Supported by NIH grants DK079986 and DK081185; NA: USPHS Grant DA-03123, Kildehoj-Santini, University of Florida Foundation; LB: This research was funded by the intramural program of NIDDK; JY: This research was funded by the intramural program of NICHD.

References

1. Mirch MC, McDuffie JR, Yanovski SZ, et al. Effects of binge eating on satiation, satiety, and energy intake of overweight children. *Am J Clin Nutr.* 2006; 84:732–738. [PubMed: 17023698]
2. Dykens EM, Maxwell MA, Pantino E, Kessler R, Roof E. Assessment of hyperphagia in Prader–Willi syndrome. *Obesity.* 2007; 15:1816–1826. [PubMed: 17636101]
3. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res.* 1985; 29:71–83. [PubMed: 3981480]
4. Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite.* 2009; 53:114–118. [PubMed: 19500623]
5. van Strien T, Frijters JER, Bergers GPA, Defares PB. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. *Int J Eat Disord.* 1986; 5:295–315.
6. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader–Willi syndrome. *Genet Med.* 2012; 14:10–26. [PubMed: 22237428]
7. Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader–Willi syndrome. *Am J Med Genet A.* 2011; 155:1040–1049. [PubMed: 21465655]
8. Mazaheri MM, Rae-Seebach RD, Preston HE, et al. The impact of Prader–Willi syndrome on the family’s quality of life and caregiving, and the unaffected siblings’ psychosocial adjustment. *J Intellect Disabil Res.* 2013; 57:861–873. [PubMed: 23057501]
9. Seo S, Zhang Q, Bugge K, et al. A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet.* 2011; 7:e1002358. [PubMed: 22072986]
10. Nachury MV, Loktev AV, Zhang Q, et al. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. *Cell.* 2007; 129:1201–1213. [PubMed: 17574030]
11. Seo S, Baye LM, Schulz NP, et al. BBS6, BBS10, and BBS12 form a complex with CCT/TRiC family chaperonins and mediate BBSome assembly. *Proc Natl Acad Sci USA.* 2010; 107:1488–1493. [PubMed: 20080638]
12. Yen HJ, Tayeh MK, Mullins RF, Stone EM, Sheffield VC, Slusarski DC. Bardet–Biedl syndrome genes are important in retrograde intracellular trafficking and Kupffer’s vesicle cilia function. *Hum Mol Genet.* 2006; 15:667–677. [PubMed: 16399798]
13. Davis RE, Swiderski RE, Rahmouni K, et al. A knockin mouse model of the Bardet–Biedl syndrome 1 M390R mutation has cilia defects, #ventriculomegaly, #retinopathy, and obesity. *Proc Natl Acad Sci USA.* 2007; 104:19422–19427. [PubMed: 18032602]
14. Nishimura DY, Fath M, Mullins RF, et al. Bbs2-null mice have neurosensory deficits, a defect in social dominance, and retinopathy associated with mislocalization of rhodopsin. *Proc Natl Acad Sci USA.* 2004; 101:16588–16593. [PubMed: 15539463]

15. Mykytyn K, Mullins RF, Andrews M, et al. Bardet-Biedl syndrome type 4 (BBS4)-null mice implicate Bbs4 in flagella formation but not global cilia assembly. *Proc Natl Acad Sci USA*. 2004; 101:8664–8669. [PubMed: 15173597]
16. Fath MA, Mullins RF, Searby C, et al. Mkks-null mice have a phenotype resembling Bardet-Biedl syndrome. *Hum Mol Genet*. 2005; 14:1109–1118. [PubMed: 15772095]
17. Rahmouni K, Fath MA, Seo S, et al. Leptin resistance contributes to obesity and hypertension in mouse models of Bardet-Biedl syndrome. *J Clin Invest*. 2008; 118:1458–1467. [PubMed: 18317593]
18. Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC. Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. *Hum Mol Genet*. 2009; 18:1323–1331. [PubMed: 19150989]
19. Drack AV, Dumitrescu AV, Bhattarai S, et al. TUDCA slows retinal degeneration in two different mouse models of retinitis pigmentosa and prevents obesity in Bardet-Biedl syndrome type 1 mice. *Invest Ophthalmol Vis Sci*. 2012; 53:100–106. [PubMed: 22110077]
20. Roth CL. Hypothalamic obesity in patients with craniopharyngioma: profound changes of several weight regulatory circuits. *Front Endocrinol (Lausanne)*. 2011; 2:49. [PubMed: 22654811]
21. Roth CL, Blevins JE, Ralston M, et al. A novel rodent model that mimics the metabolic sequelae of obese craniopharyngioma patients. *Pediatr Res*. 2011; 69:230–236. [PubMed: 21372758]
22. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev*. 2013; 14:2–18. [PubMed: 23016694]
23. Avena NM, Gearhardt AN, Gold MS, Wang GJ, Potenza MN. Tossing the baby out with the bathwater after a brief rinse? The potential downside of dismissing food addiction based on limited data. *Nat Rev Neurosci*. 2012; 13:514. [PubMed: 22714023]
24. Colantuoni C, Rada P, McCarthy J, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res*. 2002; 10:478–88. [PubMed: 12055324]
25. Avena NM, Bocarsly ME, Rada P, Kim A, Hoebel BG. After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. *Physiol Behav*. 2008; 94:309–315. [PubMed: 18325546]
26. Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Brain Res Mol Brain Res*. 2004; 124:134–142. [PubMed: 15135221]
27. Avena NM, Long KA, Hoebel BG. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. *Physiol Behav*. 2005; 84:359–362. [PubMed: 15763572]
28. Avena NM, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neuroscience*. 2003; 122:17–20. [PubMed: 14596845]
29. Avena NM, Carrillo CA, Needham L, Leibowitz SF, Hoebel BG. Sugar-dependent rats show enhanced intake of unsweetened ethanol. *Alcohol*. 2004; 34:203–209. [PubMed: 15902914]
30. Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience*. 2005; 134:737–744. [PubMed: 15987666]
31. Bocarsly ME, Berner LA, Hoebel BG, Avena NM. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: implications for nutrient-specific food addiction behaviors. *Physiol Behav*. 2011; 104:865–872. [PubMed: 21635910]
32. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite*. 2009; 52:430–436. [PubMed: 19121351]
33. Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry*. 2011; 68:808–816. [PubMed: 21464344]
34. Lancaster MA, Gleeson JG. The primary cilium as a cellular signaling center: lessons from disease. *Curr Opin Genet Dev*. 2009; 19:220–229. [PubMed: 19477114]
35. Zaghoul NA, Katsanis N. Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy. *J Clin Invest*. 2009; 119:428–437. [PubMed: 19252258]
36. Stratigopoulos G, LeDuc CA, Cremona ML, Chung WK, Leibel RL. Cut-like homeobox 1 (CUX1) regulates expression of the fat mass and obesity-associated and retinitis pigmentosa GTPase

- regulator-interacting protein-1-like (RPGRIPL) genes and coordinates leptin receptor signaling. *J Biol Chem.* 2011; 286:2155–2170. [PubMed: 21037323]
37. Guo DF, Rahmouni K. Molecular basis of the obesity associated with Bardet–Biedl syndrome. *Trends Endocrinol Metab.* 2011; 22:286–293. [PubMed: 21514177]
38. Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC. Requirement of Bardet–Biedl syndrome proteins for leptin receptor signaling. *Hum Mol Genet.* 2009; 18:1323–1331. [PubMed: 19150989]
39. Dimos JT, Rodolfa KT, Niakan KK, et al. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. *Science.* 2008; 321:1218–1221. [PubMed: 18669821]
40. Chambers SM, Fasano CA, Papapetrou EP, Tomishima M, Sadelain M, Studer L. Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling. *Nat Biotechnol.* 2009; 27:275–280. [PubMed: 19252484]
41. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010; 42:937–948. [PubMed: 20935630]
42. Wen W, Cho YS, Zheng W, et al. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet.* 2012; 44:307–311. [PubMed: 22344219]
43. Okada Y, Kubo M, Ohmiya H, et al. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet.* 2012; 44:302–306. [PubMed: 22344221]
44. Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet.* 2010; 42:949–960. [PubMed: 20935629]
45. Kilpelainen TO, Zillikens MC, Stancakova A, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. *Nat Genet.* 2011; 43:753–760. [PubMed: 21706003]
46. Meyre D, Delplanque J, Chevre JC, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet.* 2009; 41:157–159. [PubMed: 19151714]
47. Scherag A, Dina C, Hinney A, et al. Two new loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German Study Groups. *PLoS Genet.* 2010; 6:e1000916. [PubMed: 20421936]
48. Bradfield JP, Taal HR, Timpson NJ, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. *Nat Genet.* 2012; 44:526–531. [PubMed: 22484627]
49. Bingham SA, Gill C, Welch A, et al. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. *Br J Nutr.* 1994; 72:619–643. [PubMed: 7986792]
50. Kroke A, Klipstein-Grobusch K, Voss S, et al. Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, #urinary |nitrogen, and repeated 24-h dietary recall methods. *Am J Clin Nutr.* 1999; 70:439–447. [PubMed: 10500011]
51. Bingham S, Welch A, Cassidy A, Runswick S. The use of 24 h urine nitrogen to detect bias in the reported habitual food intake of individuals assessed from weighed dietary records. *Proc Nutr Soc.* 1991; 50:32A.
52. Johansson G, Wikman A, Ahren AM, Hallmans G, Johansson I. Underreporting of energy intake in repeated 24-hour recalls related to gender, age, #weight |status, day of interview, #educational | level, reported food intake, smoking habits and area of living. *Public Health Nutr.* 2001; 4:919–927. [PubMed: 11527517]
53. Ferrari P, Slimani N, Ciampi A, et al. Evaluation of under- and overreporting of energy intake in the 24-hour diet recalls in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr.* 2002; 5:1329–1345. [PubMed: 12639236]
54. Togo P, Osler M, Sorensen TI, Heitmann BL. Food intake patterns and body mass index in observational studies. *Int J Obes Relat Metab Disord.* 2001; 25:1741–1751. [PubMed: 11781753]

55. Gray J, Yeo GSH, Cox JJ, et al. Hyperphagia, #severe |obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene. *Diabetes*. 2006; 55:3366–3371. [PubMed: 17130481]
56. Farooqi IS, Keogh JM, Yeo GSH, Lank EJ, Cheetham T, O’Rahilly S. Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene. *N Engl J Med*. 2003; 348:1085–1095. [PubMed: 12646665]
57. Farooqi IS, O’Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat Clin Pract End Met*. 2008; 4:569–577.
58. Xie C, Turley SD, Pentchev PG, Dietschy JM. Cholesterol balance and metabolism in mice with loss of function of Niemann-Pick C protein. *Am J Physiol*. 1999; 276:E336–E344. [PubMed: 9950794]
59. Tung YC, Yeo GS. From GWAS to biology: lessons from FTO. *Ann NY Acad Sci*. 2011; 1220:162–171. [PubMed: 21388413]
60. Muller TD, Tschop MH, Hofmann S. Emerging function of fat mass and obesity-associated protein (fto). *PLoS Genet*. 2013; 9:e1003223. [PubMed: 23300491]
61. Farooqi IS. Genetic, molecular and physiological insights into human obesity. *Eur J Clin Invest*. 2011; 41:451–455. [PubMed: 21391993]
62. Traurig M, Mack J, Hanson RL, et al. Common variation in SIM1 is reproducibly associated with BMI in Pima Indians. *Diabetes*. 2009; 58:1682–1689. [PubMed: 19401419]
63. Traurig MT, Perez JM, Ma L, et al. Variants in the LEPR gene are nominally associated with higher BMI and lower 24-h energy expenditure in Pima Indians. *Obesity*. 2012; 20:2426–2430. [PubMed: 22810975]
64. Holder JL Jr, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Genet*. 2000; 9:101–108. [PubMed: 10587584]
65. Thearle MS, Muller YL, Hanson RL, et al. Greater impact of melanocortin-4 receptor deficiency on rates of growth and risk of type 2 diabetes during childhood compared with adulthood in Pima Indians. *Diabetes*. 2012; 61:250–257. [PubMed: 22106157]
66. Ramachandrapa S, Farooqi IS. Genetic approaches to understanding human obesity. *J Clin Invest*. 2011; 121:2080–2086. [PubMed: 21633175]
67. Fan CM, Kuwana E, Bulfone A, et al. Expression patterns of two murine homologs of *Drosophila* single-minded suggest possible roles in embryonic patterning and in the pathogenesis of Down syndrome. *Mol Cell Neurosci*. 1996; 7:1–16. [PubMed: 8812055]
68. Michaud JL, Rosenquist T, May NR, Fan CM. Development of neuroendocrine lineages requires the bHLH-PAS transcription factor SIM1. *Genes Dev*. 1998; 12:3264–3275. [PubMed: 9784500]
69. Holder JL Jr, Zhang L, Kublaoui BM, et al. Sim1 gene dosage modulates the homeostatic feeding response to increased dietary fat in mice. *Am J Physiol Endocrinol Metab*. 2004; 287:E105–E113. [PubMed: 14982752]
70. Kublaoui BM, Holder JL Jr, Gemelli T, Zinn AR. Sim1 haploinsufficiency impairs melanocortin-mediated anorexia and activation of paraventricular nucleus neurons. *Mol Endocrinol*. 2006; 20:2483–2492. [PubMed: 16728530]
71. Atasoy D, Betley JN, Su HH, Sternson SM. Deconstruction of a neural circuit for hunger. *Nature*. 2012; 488:172–177. [PubMed: 22801496]
72. Michaud JL, Boucher F, Melnyk A, et al. Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. *Hum Mol Genet*. 2001; 10:1465–1473. [PubMed: 11448938]
73. Kublaoui BM, Holder JL Jr, Tolson KP, Gemelli T, Zinn AR. SIM1 overexpression partially rescues agouti yellow and diet-induced obesity by normalizing food intake. *Endocrinology*. 2006; 147:4542–4549. [PubMed: 16709610]
74. Yang C, Gagnon D, Vachon P, et al. Adenoviral-mediated modulation of Sim1 expression in the paraventricular nucleus affects food intake. *J Neurosci*. 2006; 26:7116–7120. [PubMed: 16807340]
75. Tolson KP, Gemelli T, Gautron L, Elmquist JK, Zinn AR, Kublaoui BM. Postnatal Sim1 deficiency causes hyperphagic obesity and reduced Mc4r and oxytocin expression. *J Neurosci*. 2010; 30:3803–3812. [PubMed: 20220015]

76. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet.* 2003; 33 (Suppl):245–254. [PubMed: 12610534]
77. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr.* 2007; 27:363–388. [PubMed: 17465856]
78. Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S. Methyl donor supplementation prevents transgenerational amplification of obesity. *Int J Obes (Lond).* 2008; 32:1373–1379. [PubMed: 18626486]
79. Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. *Cell.* 2004; 116:337–350. [PubMed: 14744442]
80. Hoivik EA, Bjanesoy TE, Mai O, et al. DNA methylation of intronic enhancers directs tissue-specific expression of steroidogenic factor 1/adrenal 4 binding protein (SF-1/Ad4BP). *Endocrinology.* 2011; 152:2100–2112. [PubMed: 21343250]
81. Iwamoto K, Bundo M, Ueda J, et al. Neurons show distinctive DNA methylation profile and higher interindividual variations compared with non-neurons. *Genome Res.* 2011; 21:688–696. [PubMed: 21467265]
82. Skene PJ, Illingworth RS, Webb S, et al. Neuronal MeCP2 is expressed at near histone-octamer levels and globally alters the chromatin state. *Mol Cell.* 2010; 37:457–468. [PubMed: 20188665]
83. Seki Y, Williams L, Vuguin PM, Charron MJ. Minireview: epigenetic programming of diabetes and obesity: animal models. *Endocrinology.* 2012; 153:1031–1038. [PubMed: 22253432]
84. Bale TL, Baram TZ, Brown AS, et al. Early life programming and neurodevelopmental disorders. *Biol Psychiatry.* 2010; 68:314–319. [PubMed: 20674602]
85. Mason PW, Krawiecki N, Meacham LR. The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. *Arch Pediatr Adolesc Med.* 2002; 156:887–892. [PubMed: 12197795]
86. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab.* 2003; 88:2586–2592. [PubMed: 12788859]
87. Fernandes JK, Klein MJ, Ater JL, Kuttlesch JF, Vassilopoulou-Sellin R. Triiodothyronine supplementation for hypothalamic obesity. *Metabolism.* 2002; 51:1381–1383. [PubMed: 12404183]
88. Greenway FL, Bray GA. Treatment of hypothalamic obesity with caffeine and ephedrine. *Endocr Pract.* 2008; 14:697–703. [PubMed: 18996788]
89. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med.* 2007; 357:741–752. [PubMed: 17715408]
90. Stefater MA, Wilson-Pérez HE, Chambers AP, Sandoval DA, Seeley RJ. All bariatric surgeries are not created equal: insights from mechanistic comparisons. *Endocr Rev.* 2012; 33:595–622. [PubMed: 22550271]
91. Scholtz S, Miras AD, Chhina N, et al. Obese patients after gastric bypass surgery have different brain reward responses to high-caloric food and healthier eating behaviour compared to gastric banding. *Gut.* 2013 [Epub ahead of print]. 10.1136/gutjnl-2013-305008
92. Ranadive SA, Vaisse C. Lessons from extreme human obesity: monogenic disorders. *Endocrinol Metab Clin North Am.* 2008; 37:733–751. [PubMed: 18775361]
93. Hatoum IJ, Stylopoulos N, Vanhoose AM, et al. Melanocortin-4 receptor signaling is required for weight loss after gastric bypass surgery. *J Clin Endocrinol Metab.* 2012; 97:E1023–E1031. [PubMed: 22492873]
94. Aslan IR, Ranadive SA, Ersoy BA, Rogers SJ, Lustig RH, Vaisse C. Bariatric surgery in a patient with complete MC4R deficiency. *Int J Obes.* 2011; 35:457–461.
95. Aslan IR, Campos GM, Calton MA, Evans DS, Merriman RB, Vaisse C. Weight loss after Roux-en-Y gastric bypass in obese patients heterozygous for MC4R mutations. *Obes Surg.* 2011; 21:930–934. [PubMed: 20957447]
96. Valette M, Poitou C, Le Beyec J, Bouillot JL, Clement K, Czernichow S. Melanocortin-4 receptor mutations and polymorphisms do not affect weight loss after bariatric surgery. *PLoS One.* 2012; 7:e48221. [PubMed: 23185251]

97. Yu H, Di J, Jia W. Laparoscopic sleeve gastrectomy in Chinese female patient with Prader-Willi syndrome and diabetes. *Surg Obes Relat Dis.* 2013; 9:e25–e27. [PubMed: 22951076]
98. Daskalakis M, Till H, Kiess W, Weiner RA. Roux-en-Y gastric bypass in an adolescent patient with Bardet–Biedl syndrome, a monogenic obesity disorder. *Obes Surg.* 2010; 20:121–125. [PubMed: 19847573]
99. Rottembourg D, O’Gorman CS, Urbach S, et al. Outcome after bariatric surgery in two adolescents with hypothalamic obesity following treatment of craniopharyngioma. *J Pediatr Endocrinol Metab.* 2009; 22:867–872. [PubMed: 19960898]
100. De Peppo F, Di Giorgio G, Germani M, et al. BioEnterics intragastric balloon for treatment of morbid obesity in Prader-Willi syndrome: specific risks and benefits. *Obes Surg.* 2008; 18:1443–1449. [PubMed: 18449615]
101. Messersmith NV, Slifer KJ, Pulbrook-Vetter V, Bellipanni K. Interdisciplinary behavioral intervention for life-threatening obesity in an adolescent with Prader–Willi syndrome—a case report. *J Dev Behav Pediatr.* 2008; 29:129–134. [PubMed: 18408535]

TABLE 1

Changes in energy homeostasis and eating behavior after bariatric surgery

	LAGB	VSG	RYGB	BPD
Weight loss	++	++	+++	+++
Hunger	↓↓	↓↓	↓↓	↓↓
T2DM resolution	+	++	+++	+++
Gastric restriction	+	–	–	–
Gastric emptying	↓ →	→	? →	? →
Malabsorption	–	–	–	++
Vagus nerve involved	+	+/-	+/-	+/-
Duodenal exclusion	–	–	+ (mimicked by DEL)	+
Ghrelin	↑	?↓total →acyl	?↓total →acyl	?↓total →acyl
GLP-1/PYY	?↑/→	↑↑/↑↑	↑↑/↑↑	↑↑/↑↑
Bile acids	→	↑	↑	? ↑
Dietary habits	↓ bread ↑ soda	↓↓ fat	↓↓ fat, sugar	?
Food reward/hedonics	? →	→	? →↓	?
Food intolerance	Vomiting	-	Some dumping	Some dumping
Energy expenditure	?	→	? ↑→	?

Adapted from Stefater et al. (90). Abbreviations: LAGB laparoscopic gastric banding; VSG vertical sleeve gastrectomy; RYGB Roux-en-Y gastric bypass; BPD biliopancreatic diversion; T2DM type 2 diabetes mellitus; DEL duodenal endoluminal liner.

TABLE 2

Efficacy of bariatric surgery in conditions associated with hyperphagia

	LAGB	VSG	RYGB	BPD
Binge eating disorder	?✓ ?-ve	n/a	?✓ ?-ve	n/a
Craniopharyngioma	? ✓✗	? ✓✗	? ✓✗	n/a
PWS	✗	✗ (✓)	✗ (✓)	✗ (✓)
MC4R mutation	✗	✓	✓	n/a
LEPR mutation	n/a	n/a	✓	n/a
Undiagnosed childhood/adolescent severe obesity (ongoing data collection)	Sweden	Saudia Arabia	TeenLabs, USA	n/a
Common genetic variants	FTO -ve UCP2 +ve	n/a	FTO, MC4R SNPs no effect M-C4R I251L +ve	FTO no effect
BBS/WAGR/Alstroms	n/a	n/a	n/a	n/a
Knockout animal models	n/a	MC4R, Ghrelin ✓	PYY -ve	n/a

Abbreviations: ✓ procedure still effective for weight loss; ✗ procedure ineffective for weight loss; -ve/+ve procedure less/more effective for weight loss compared to control group; LAGB laparoscopic gastric banding; VSG vertical sleeve gastrectomy; RYGB Roux-en-Y gastric bypass; BPD biliopancreatic diversion; n/a not available.