



WORKSHOP ON THE PREVENTION OF OBESITY IN INFANCY & EARLY CHILDHOOD

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Early intervention to prevent obesity has the potential to improve health and reduce health care costs associated with obesity-related diseases now and in the future. In fall of 2013, the NIDDK and other Institutes sponsored a workshop on the Prevention of Obesity in Infancy and Early Childhood. This workshop brought together a diverse group of scientists to discuss what is known about obesity in children and infants and how childhood obesity might best be treated or prevented. This workshop aimed to provide the scientific background for future NIH supported research on interventions to prevent inappropriate weight gain during infancy and early childhood.

Obesity

Obesity has risen to epidemic levels in the United States. Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK's mission.

More than one-third of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.^{1,2} Nearly 17 percent of children and teens ages 2 through 19 are also obese, and thus at increased risk for developing serious diseases both during their youth and later in adulthood.³ Obesity disproportionately affects people from certain racial and ethnic groups and those who are socioeconomically disadvantaged.

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Diet, activity, and aspects of our environment may also modify biologic factors in ways that promote obesity. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions. The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental approaches in families, schools, health care settings and other community settings; medical and surgical interventions; and combinations of these strategies. In parallel, Institute-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches. To help bring research results to those affected by obesity and their families, health professionals, and the general public, the Institute also sponsors health information programs.

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK

Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. These represent examples of NIDDK's broad spectrum of research efforts toward reducing the burden of obesity so that people can look forward to healthier lives.

BARIATRIC SURGERY AND WEIGHT LOSS

Surgically Remodeling the Intestines—and the Bacteria Within—To Treat Obesity: Gaining new insight into Roux-en-Y gastric bypass surgery, a treatment for obesity, researchers studying a mouse

¹ *Statistics Related to Overweight and Obesity.*

<http://win.niddk.nih.gov/statistics/index.htm>

² Ogden CL, et al. *NCHS data brief, no 131. National Center for Health Statistics. 2013.*

³ Ogden CL, et al: *JAMA* 307: 483-490, 2012. *For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).*

model found that restructuring of the digestive tract leads to weight loss and metabolic benefits in part by altering the communities of bacteria that normally live in the intestines. Gastric bypass, a form of bariatric surgery, is thought to work in a number of ways, but the mechanisms are not well understood. Among various changes observed after gastric bypass are alterations in gut bacteria.

Thus, a team of researchers sought to determine whether the changes in types of bacteria (gut microbes) in the intestines after gastric bypass contribute to weight loss. To do this, they started with groups of obese mice that had been fed a high-fat diet, performed gastric bypass surgery on some of the mice and sham surgery (as a control) on others, and then analyzed intestinal bacteria. Despite access to unlimited food after surgery, the mice that had gastric bypass lost 29 percent of their initial body weight and maintained their lower weight throughout the study. These mice also had reduced visceral body fat, the type of fat most associated with metabolic disease, and other metabolic benefits. Their resident gut microbes changed rapidly after surgery, as different types of bacteria flourished in the newly renovated intestinal habitat. By contrast, a group of mice that had only sham surgery, which did not alter the intestinal tract, regained all of their initial body weight after recovering from surgery. These mice also had more body fat, and their gut bacteria differed from those of the gastric bypass group. The researchers then tested whether putting mice on a low-calorie diet would lead to similar changes in gut bacteria. Dieting did not have quite the same effect: the relative abundances of various types of bacteria from the mice on a diet differed from those of the gastric bypass group. Finally, the researchers investigated whether the unique collection of gut microbes resulting from gastric bypass could cause weight loss—even without gastric bypass surgery. They extracted bacteria from mice that had undergone gastric bypass and administered the bacteria to other mice that had not been treated surgically. Although the recipient mice did not lose as much weight as the gastric bypass group, the bacterial transfer did lead to some weight loss, along with reduced body fat.

This study indicates that changes in gut bacteria contribute to the weight loss and reduced body fat from gastric bypass surgery in mice. Because changes in gut bacteria have also been observed in people after surgery, this study also has implications for understanding how gastric bypass works in humans. Further research into the effects of gut microbes on weight and metabolism after gastric bypass in people may lead to interventions that achieve similar health benefits without the cost and risks of surgery.

Liou AP, Paziuk M, Luevano JM Jr, Machineni S, Turnbaugh PJ, and Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med 5: 178ra41, 2013.

EFFECTS OF DIET AND EXERCISE

Health Effects of Diet and Exercise for Adults with Type 2 Diabetes and Obesity: Researchers in the Look AHEAD (Action for Health in Diabetes) clinical trial found that an intensive lifestyle intervention for weight loss was not sufficient to stave off heart disease and stroke in overweight and obese adults with type 2 diabetes, but it did yield a number of other health benefits.

Because type 2 diabetes is a devastating disease, increasing risk for cardiovascular disease and other complications, and because obesity also heightens risk for many diseases and disorders, researchers have been exploring ways to improve health for individuals with these conditions. Based on prior, short-term studies, weight loss has been recommended for overweight and obese patients with type 2 diabetes, but the effects on cardiovascular disease (CVD) over the long term had not been known. To conduct the Look AHEAD clinical trial, investigators at 16 centers around the United States recruited 5,145 volunteers. The participants were women and men of diverse racial/ethnic backgrounds, ages 45 to 75 at the start of the study, who had type 2 diabetes and were overweight or obese. The researchers designed a lifestyle intervention that aimed for a seven percent weight loss through decreased calorie intake, and in particular, reduced calories from dietary fat, along with 175 minutes of moderate intensity physical activity per

week. The intervention included regular group and individual counseling sessions, liquid meal replacement products for some meals, and a toolbox of additional strategies to assist those having difficulty with weight loss. Half of the participants were randomly assigned to receive this lifestyle intervention. For comparison, the other half of the participants were assigned to a much less intensive program of diabetes support and education, comprised of several group sessions focused on diet, exercise, and social support. For all participants, the investigators recorded CVD events: instances of death from any cardiovascular cause, non-fatal heart attack or stroke, and hospitalization for a condition called angina. They also monitored other health conditions.

After nearly 10 years of follow up, the researchers found that the numbers of CVD events were not significantly different between the intensive lifestyle intervention group and the diabetes support and education group. This similar number of CVD events was observed even though there were improvements in a number of disease risk factors in the lifestyle intervention group, with less use of medication. These benefits included greater weight loss; improved blood pressure; increased fitness, as measured by an exercise test; and improved blood glucose (sugar) control.

Additional analyses of data from the first several years of the Look AHEAD trial have identified many other health benefits of the lifestyle intervention. For example, the researchers investigated whether the intervention led to partial or complete remission of type 2 diabetes over the first four years of the study, and, as reported recently, they found that it did, although at modest rates. After one year, about 11.5 percent of those in the intervention group experienced at least partial remission of their diabetes, as defined by blood glucose levels decreasing to prediabetes or normal levels without need for diabetes medications. By the fourth year of the study, 7.3 percent of participants in the lifestyle intervention had at least partial remission of their diabetes. Those in the control group experienced a smaller remission rate of only two percent at both time points. Remission in the intensive lifestyle intervention group was more likely among those who had lived with diabetes for

less than two years at the study's outset, and who had relatively low (although still diabetic) glucose levels, did not yet need insulin therapy for their diabetes, and had greater weight loss and fitness improvements during the study. The association between remission and shorter duration of type 2 diabetes suggests that starting healthy lifestyle changes early in the course of the disease may lead to better outcomes.

In another recently reported analysis, researchers analyzing the first four years of Look AHEAD data found that the lifestyle intervention reduced levels of obstructive sleep apnea, a serious breathing disorder during sleep that is associated with obesity. Among other benefits, researchers have previously reported a decrease in urinary incontinence, improvements in quality of life, and less of a decline in physical mobility as a result of the lifestyle intervention. At this point, because there was not a reduction in CVD events, the intervention phase of Look AHEAD has concluded. However, researchers are continuing follow up of the study participants to evaluate longer-term effects. This research will help inform decisions about management of type 2 diabetes, to help people improve their health and quality of life.

Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 369: 145-154, 2013

Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 308: 2489-2496, 2012.

“Maintain, Don’t Gain”—A Weight Management Approach To Help Those Already Overweight or Obese: Researchers have achieved promising results in an intervention to help overweight and obese African American women prevent further weight gain, using a combination of primary care and community settings, along with technology accessible to those who are socioeconomically disadvantaged. The intervention aimed not for weight loss, but rather to improve the overall well-being of the participants and maintain their current body shape—a message that they hoped would resonate with the participants. By helping overweight

and moderately obese individuals avoid further weight gain, the researchers hoped to prevent the additional health risks associated with extreme obesity. The researchers recruited women from primary care centers in a socioeconomically disadvantaged area in the South. Participants were randomly assigned either to the intervention or, for comparison, to their usual care. For 12 months, the women in the intervention group received tailored behavior change goals (for example, no sugar-sweetened beverages), weekly self-monitoring with computer-generated telephone calls, monthly counseling calls from a registered dietician, skills training materials, and a one-year YMCA membership.

Measuring weight at the end of the 12 month intervention, and then again at 18 months, the researchers found that the women in the intervention group better maintained their initial weight: 53 percent had weights at or even below their weight at the start of the study, compared to 39 percent of those in usual care. On average, the women in the intervention group had a slight weight loss of approximately two pounds, while those in the usual care group on average gained that amount of weight. Many of the women had other health risk factors at the outset of the study, but the intervention did not affect blood pressure, blood glucose, or several other cardiovascular risk factors. Importantly, although recruiting from a primary care system, the intervention was largely delivered in the community with dieticians and relatively inexpensive electronic health technologies. This strategy circumvents issues related to insufficient reimbursement, time, and training that may hinder effective weight management solely by primary care physicians. This strategy could also be implemented broadly in communities disproportionately affected by obesity. Longer-term studies may help researchers determine whether—by fending off the usual weight gain over time—this intervention could reduce type 2 diabetes and other obesity-associated diseases.

Bennett GG, Foley P, Levine E, et al. Behavioral treatment for weight gain prevention among black women in primary care practice: a randomized clinical trial. JAMA Intern Med 173: 1770-1777, 2013.

BODY WEIGHT AND THE BRAIN

Let's Not Sugar Coat It: Evidence Is Emerging that Fructose and Glucose Elicit Different Brain Responses:

Researchers have found that in humans, ingestion of glucose, but not fructose, activates brain pathways and stimulates hormones that promote feelings of satiety, fullness, and reward. Consumption of the simple sugar fructose in the United States has risen significantly over the past few decades, concomitant with an increase in the prevalence of obesity. Several studies have provided evidence suggesting that fructose consumption does not have the same effects as glucose on circulating hormones that modulate hunger and satiety. While research using animal models has demonstrated that fructose affects regions of the brain (*e.g.*, the hypothalamus) that help regulate feeding behavior, corresponding analyses in humans have been technologically challenging to perform. Scientists have now used a new method of determining the effects of fructose or glucose on specific regions of the human brain by using functional magnetic resonance imaging (fMRI) to quantify cerebral blood flow—a proxy measure for brain activity. Twenty normal-weight participants, after fasting, drank beverages containing either glucose or fructose; the resulting effects on the brain were analyzed, along with circulating hormones (from blood samples), and other changes. Glucose consumption led to reduced blood flow in the hypothalamus and other regions of the brain associated with hunger, changes which were not seen with fructose consumption. Glucose ingestion led to a significantly greater induction of circulating insulin and GLP-1, two hormones that promote satiety, than did fructose consumption. Although both sugars induced functional connectivity—a statistical measurement of the communication between parts of the brain—between the hypothalamus and various other brain regions, only glucose consumption induced functional connectivity to the striatum, a reward center of the brain. Participants who drank the glucose beverage reported feeling full and satiated, but those who drank the fructose beverage did not.

Together, these data support the idea that in people, glucose, but not fructose, promotes satiety, in part because of its effects on the activity of specific regions of the brain, which differ from those of fructose. This study was limited by several potential issues, including technical constraints, the small number of participants, and the complicating fact that the study design does not reflect real-world conditions (e.g., people typically consume sugars and other nutrients in combination, not individually). Although the role of fructose's effects on the brain in the development of obesity was not directly explored, these results suggest that previous findings in animal models are relevant to humans, with respect to differences between fructose and glucose. Future research could shed light on how these effects may relate to food consumption and health.

Page KA, Chan O, Arora J, et al. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA 309: 63-70, 2013.

Discovery of Body Weight Regulation by the Protein MRAP2: Researchers discovered that the MRAP2 protein regulates growth and body weight in animals, and MRAP2 deficiency may contribute to severe obesity in humans. Two research teams studied MRAP2 because its suspected biological partner, a protein called MC4R, is known to be critical in metabolism; people born with genetic deficiencies in MC4R develop severe obesity as children. To investigate MRAP2 further, one team generated mice with a genetic mutation that caused a deficiency of this protein. Without MRAP2, the mice became extremely obese, even when their food was limited so they could eat only as much as normal mice. The MRAP2-deficient mice only attained a normal weight when the researchers further restricted their allotted food to less than what a typical mouse would eat—a finding that may help explain why weight control through dieting is a constant challenge for people with genetic predisposition to obesity.

Because MRAP2-deficient mice fed normal portions still became obese, the researchers realized that

MRAP2 may affect body weight in ways other than through appetite and food intake. They thus examined whether MRAP2 influences how much the mice move, their calorie burning, or body temperature, but found no differences between mice with and without MRAP2. Although these results alone do not clarify the mechanism by which MRAP2 functions, additional studies by both teams, using mice and another experimental organism, zebrafish, revealed several clues. MRAP2, like MC4R, works in the brain; MRAP2 and MC4R physically interact; and MRAP2 influences MC4R's activity. Finally, one of the research teams analyzed genomic data from people whose obesity began in childhood, and found that a few of these individuals had rare genetic variants that may impair MRAP2. The variants were not seen in non-obese people.

This research sheds light on a potential rare genetic form of obesity and yields insights that may lead to the design of new therapeutics that target MRAP2.

Asai M, Ramachandrapa S, Joachim M, et al. Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. Science 341: 275-278, 2013.

Sebag JA, Zhang C, Hinkle PM, Bradshaw AM, and Cone RD. Developmental control of the melanocortin-4 receptor by MRAP2 proteins in zebrafish. Science 341: 278-281, 2013.

Researchers Identify Malfunctioning Satiety Signal in Mice Fed a High-fat Diet and Its Link to Dopamine in the Brain: A group of scientists has identified a chemical produced in the gut that regulates the sense of satiety, or fullness, in mice after dietary fat consumption by inducing dopamine release in the brain, a process that is disrupted after excessive high-fat feeding. The feeling of satisfaction following ingestion of food is caused by a chemical in the brain called dopamine. A significant amount of dopamine is usually released by the brain after eating, resulting in a sense of gratification or reward. For unknown reasons, however, prolonged eating of a high-fat diet leads to desensitization of this signal,

which is believed to contribute to overeating in order to compensate for a dampened feeling of satisfaction.

Researchers studying this phenomenon in a mouse model identified a chemical produced by the gut in response to eating that can cause dopamine release in the brain. However, if the mice are fed high-fat diets for several weeks, the levels of this chemical, called oleoylethanolamine (OEA), are reduced. When the group supplied OEA directly to the intestine, the mice reduced their fat intake and lost weight, supporting OEA's role in promoting satiety. The scientists, interested in how OEA was signaling to the brain in these mice, found that OEA's effects require a factor called PPAR α . They also found that the signal generated by OEA and PPAR α is probably transmitted through the vagus nerve, which carries signals between the intestines and the brain, because infusion of OEA directly into the stomach did not seem to affect mice that lacked functional vagus nerves. The scientists next enabled the mice to self-administer fat directly to their stomachs, bypassing the mouth and therefore the ability to taste the incoming food. When mice on prolonged high-fat diets were fed in this manner, they were less likely to keep self-administering the fat than the mice on low-fat diets, suggesting that the dopamine-mediated reward response was impaired in the high-fat fed mice. But when mice on the high-fat diet were given OEA, they self-administered more fat, suggesting that OEA restores the dopamine-mediated reward signal associated with eating that had weakened in these mice.

This study supports a model whereby a long-term, high-fat diet suppresses the production of OEA in the gut, resulting in a decrease in the production of dopamine in the brain and a dampening of the reward signals that usually accompany eating foods high in fat. This could mean that the desire to eat high-fat foods is strongly affected by these chemical signals originating in the gut, which could point to new therapeutic options for suppressing appetite and treating obesity in people.

Tellez LA, Medina S, Han W, et al. A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science* 341: 800-802, 2013.

GENETICS OF OBESITY

Gene Linked to Obesity Has Role in Different Types of Human Behavior: Researchers discovered that a gene with a known role in obesity also plays an unexpected role in human behavior. The gene, called *SH2B1*, is a key regulator of leptin sensitivity in mice; leptin is a hormone that suppresses appetite. Previous research showed that mice lacking the *SH2B1* gene have impaired leptin and insulin signaling, making them severely obese and insulin resistant. To investigate the role of *SH2B1* in human metabolism, scientists examined whether obese people had mutations in their *SH2B1* gene. They studied people with severe early-onset obesity (developed before age 10) who also had higher than expected levels of insulin resistance for their weight. They identified four different types of mutations in the *SH2B1* gene that were not found in people who are normal weight. The mutations were inherited from their overweight or obese parents. The people with these mutations had excessive appetites and at adulthood were a shorter height than average. A surprising finding was that they also had behavioral abnormalities, as reported by their families and health care providers. These abnormalities included delayed speech and language development, aggressive behavior, and a tendency toward social isolation. Further experiments showed that some of the identified mutations impaired leptin signaling while others did not, suggesting that the SH2B1 protein may be exerting some of its effects through cellular pathways that are independent of leptin. This research sheds new light on the human *SH2B1* gene and suggests that it not only plays a role in obesity, but may also be an important factor in controlling certain types of human behavior.

Doche ME, Bochukova EG, Su HW, et al. Human SH2B1 mutations are associated with maladaptive behaviors and obesity. *J Clin Invest* 122: 4732-4736, 2012.

PREDICTING BODY WEIGHT AND EFFECTS OF DIET AND ACTIVITY WITH MATHEMATICAL MODELING

“The Biggest Loser” Study Predicts Sustained Weight Loss Through Modest Changes in Diet and Exercise: With a validated computational model for predicting weight loss, a research study has quantified the dramatic diet and exercise intervention strategy employed in “The Biggest Loser” television program. It found that this intervention would not be sustainable over time, but a more modest and feasible diet and exercise could maintain the weight loss. “The Biggest Loser” program, although highly successful, has been criticized for portraying an extreme diet and exercise intervention regimen that could raise unrealistic expectations for weight loss. The program shows obese adults losing large amounts of weight over several months, initially isolated on a ranch, followed by an extended period at home.

Scientists took advantage of this cost-efficient opportunity to study the television program’s 16 obese contestants already engaged in an intensive lifestyle intervention. As part of the program, researchers measured body fat, total energy expenditure and resting metabolic rate—the energy burned during inactivity—three times: at the start of the program, at week 6, and at week 30, which was at least 17 weeks after participants returned home. Participation in the program led to an average weight loss of 128 pounds, with about 82 percent of that coming from body fat, and the rest from lean tissue like muscle. Preserving lean tissue, even during rapid and substantial weight loss, helps maintain strength and mobility and reduces risk of injury, among other benefits.

A scientist at NIDDK then used a mathematical computer model of human metabolism to calculate the diet and exercise changes underlying the observed body weight loss. Because the TV program was not designed to directly address how the exercise and diet interventions each contributed to the weight loss, the computer model simulated the results of diet alone and exercise alone to estimate their relative contributions.

At the competition’s end, diet alone was calculated to be responsible for more weight loss than exercise, with 65 percent of the weight loss consisting of body fat and 35 percent consisting of lean mass like muscle. In contrast, the model calculated that exercise alone resulted in participants losing only fat, and no muscle. The simulation of exercise alone also estimated a small increase in lean mass despite overall weight loss. In addition, the simulations suggest that the participants could sustain their weight loss and avoid weight regain by adopting more moderate lifestyle changes—like 20 minutes of daily vigorous exercise and a 20 percent calorie restriction—than those demonstrated on the television program.

These findings suggest that a more moderate weight loss strategy, rather than the extreme lifestyle intervention depicted in “The Biggest Loser,” would be preferable for sustained weight loss in many people who are obese.

Hall KD. Diet versus exercise in “The Biggest Loser” weight loss competition. Obesity (Silver Spring) 21: 957-959, 2013.

Mathematical Model Predicts Effects of Diet and Physical Activity on Childhood Weight: Scientists have created and confirmed the accuracy of a mathematical model that predicts how weight and body fat in children respond to adjustments in diet and physical activity. Excess weight in children can lead to lifelong health problems, such as type 2 diabetes and high blood pressure. However, the amount of energy (calorie) intake that leads to excess weight and development of obesity in growing children has been difficult to quantify. The challenge of taking into consideration healthy weight gain from normal growth has impeded the development of accurate mathematical models to simulate and predict body weight changes in children and adolescents.

NIDDK researchers have now modified a mathematical model, originally designed for and validated in adults, to account for children’s unique physiology, including changes in body composition (the amounts of body fat and other body tissues) as they grow. The researchers

analyzed data from children ages 5 to 18 years to create the model, and tested it by comparing predictions to actual changes in children as measured in clinical studies that were not used to build the model. The model accurately simulated observed changes in body composition, energy expenditure, and weight. Model simulations also suggest that obese children may be eating far more calories for each pound gained, compared to adults. For example, children under age 10 were predicted to require more than twice the calories per pound of extra weight than an adult would need to gain a pound. Additionally, the model suggests that there may be therapeutic windows of weight

management when children can “outgrow” obesity without requiring weight loss, especially during periods of high growth potential in males who are not severely obese at the onset of treatment. While the model may help to set realistic expectations, a controlled clinical trial will be needed to determine if it is an effective tool for weight management.

Hall KD, Butte NF, Swinburn BA, and Chow CC. Dynamics of childhood growth and obesity: development and validation of a quantitative mathematical model. Lancet Diabetes Endocrinol 1: 97-105, 2013

Turning Up the Heat—Important New Insights into the Biology of Brown Fat

New discoveries about the properties of brown and beige fat could inform research to develop potential new approaches for reducing obesity and its associated diseases.

Mammals harbor different kinds of adipose (fat) tissue in various regions of the body. Calorie-storing white adipose tissue (WAT) is the most abundant, and can be found surrounding internal organs, where it is referred to as visceral or abdominal fat, and just under the skin, a location termed subcutaneous. In contrast to the fat-storing WAT, brown adipose tissue (BAT) burns calories to generate heat. The heat-generating activity of brown fat is induced by cold weather, and contributes to a phenomenon known as “non-shivering thermogenesis” in which heat is produced as a by-product of specific biochemical processes that aid mammals in staying warm during hibernation.

Recent research has identified a second type of inducible brown fat cell (alternately called beige, brite (for brown in white), or recruitable BAT cells) that exhibits some of the characteristics of classic brown fat. The beige fat cells appear within portions of white fat and muscle tissue, in response to cold or other nervous system triggers. Because of the calorie-burning capability of both types of brown fat, many scientists believe that BAT could serve as an ideal target for the development of treatment strategies for obesity in humans. However, while rodents maintain patches of brown fat near the neck throughout life, classic brown fat largely disappears after infancy in humans. Interest in the therapeutic potential of BAT has been rekindled with the discovery of alternative inducible forms of BAT present in adult humans. New reports shed important new light on the anatomy, physiology, and molecular properties of human and rodent fat tissue.

In one recent study, while investigating the molecular control of brown fat activity, researchers uncovered

a novel way that mammals regulate body heat—by promoting beige fat production when classic brown fat mass is reduced. Scientists genetically modified mice to lack the protein BMPR1A in a region of the developing embryo from which the bulk of BAT arises. Removing BMPR1A in these cells dramatically reduced the size of many BAT patches (also known as BAT depots). Unexpectedly, the body temperatures of adult mice lacking BMPR1A were no different from their normal littermates. Furthermore, after prolonged exposure to cold temperatures, body temperatures initially dropped in normal and genetically modified mice, but subsequently came back to normal, presumably due to brown fat activation. While the normal mice recovered in 48 hours, the mice lacking BMPR1A also recovered but required 11 days to return to normal. This surprising result suggested that cold-inducible beige fat cells might be recruited to compensate for the loss of other BAT. Further analysis showed that beige fat was indeed induced in WAT. The researchers confirmed this finding with other mouse models in which BAT activity was disrupted. This study identified a novel and complex interplay between brown and beige fat, and suggests that this compensatory relationship must be taken into account when designing brown fat-targeted therapeutics for altering energy balance.

In another study, researchers sought to better understand if beige fat cells can respond to cold exposure directly, or, as has been previously thought, only to cold-generated signals sent from the nervous system and interpreted by WAT. The scientists used mice genetically modified to lack key proteins, called β -adrenergic receptors, that interpret signals sent from the brain in response to cold temperature. These mice were then exposed to moderately cold conditions, and different fat depots were isolated to see whether genes involved in heat production (thermogenesis) were turned on. In beige fat cells without β -adrenergic receptors, thermogenic genes were turned on, but at

levels much lower than normal. Surprisingly, these genes were also turned on to a similar extent in subcutaneous WAT with and without the β -adrenergic receptors. To investigate these effects in the absence of influence from the nervous system and brain, the researchers grew isolated white fat and beige fat cells in the laboratory, exposed them to cold temperature, and found that even in isolation, specific thermogenic genes were turned on, and could be turned off again by returning the cells to normal temperature. Cellular respiration—one measure of a cell's energy output—also increased with cold exposure. Isolated classic brown fat cells did not exhibit the same responses to direct cold exposure, suggesting that their activity is induced by indirect factors (*i.e.*, the nervous system). While most of these experiments were done in mice or with mouse cells, the researchers also tested isolated human cells from subcutaneous fat, and found that these cells similarly turned on thermogenic genes in response to cold temperature. Together, these results reveal a previously unknown direct response to cold temperature by white and beige fat cells. Scientists will now explore the mechanism of the direct response to determine whether this system can be exploited to develop weight loss strategies.

Studies in mice have greatly illuminated the basic biology of fat tissue and how the body coordinates the thermogenic response to cold temperature. The applicability of findings from rodent models to human biology, however, is always a concern, and technical limitations have impeded progress in identifying and characterizing human BAT.

To begin to address this issue, a third study characterized the complex anatomy and molecular nature of fat tissue derived from the human neck. Scientists isolated samples of fat tissue from the necks of 31 participants who had given consent and were already undergoing surgery for other reasons. The researchers then carefully examined five different depots at progressively deeper positions within the neck. Molecular and cellular analyses revealed that

broadly, the fat tissue closer to the surface exhibited properties similar to mouse WAT, whereas the deeper fat depots more closely resembled mouse BAT. Importantly, however, there was considerable variability between individuals. The researchers isolated a population of cells and, using specific conditions, induced them to become brown fat cells. These brown fat cells could indeed turn on thermogenic genes in response to a chemical that “tricks” the cells into thinking that the body was exposed to cold temperatures. Moreover, cells from the deeper fat tissues of two individuals had the capacity to burn about 100 times more calories—as determined by oxygen consumption rate—than subcutaneous fat tissue, and about half as much as mouse BAT. Together, these results suggest that adipose depots deep in the human neck most closely resemble rodent BAT in anatomy and function.

These reports greatly advance the current understanding of brown, beige, and white adipose tissues, describing novel properties and complex relationships within the heat regulation system. The detailed anatomical, molecular, and functional characterization of human neck adipose tissue will aid in the translation of findings in rodents to human biology, and provides critical new information that can potentially be used to develop therapeutic strategies to alter energy balance in people.

Cypess AM, White AP, Vernochet C, et al. Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. *Nat Med* 19: 635-639, 2013.

Schulz TJ, Huang P, Huang TL, et al. Brown-fat paucity due to impaired BMP signalling induces compensatory browning of white fat. *Nature* 495: 379-383, 2013.

Ye L, Wu J, Cohen, P, et al. Fat cells directly sense temperature to activate thermogenesis. *Proc Natl Acad Sci USA* 110: 12480-12485, 2013.

