How does the brain know when the stomach and intestines contain food to be digested? Researchers recently gained insights by studying the vagus nerve (the tenth cranial nerve), which transmits information from the gut to the brain through many different nerve cells (neurons). They discovered that some of these cells, called GLP1R neurons, sense when the stomach and intestines have stretched in size to accommodate a meal just eaten, while others, called GPR65 neurons, detect nutrients to be digested.

As shown in this image of a section of mouse intestine, fibers from GPR65 neurons, labeled in pink, spread throughout intestinal structures that absorb nutrients. These fibers are thus ideally situated to detect food, so that the neurons can signal the brain accordingly. Fibers from GLP1R neurons permeate other parts of the gut. Described further in this chapter, this study sheds new light on brain-gut communication.

Image courtesy of Dr. Stephen Liberles and Erika Williams, Harvard Medical School. Image credit: Dr. David Strochlic. Reprinted from Cell, vol. 166, Williams EK, Chang RB, Strochlic DE, Umans BD, Lowell BB, Liberles SD, Sensory neurons that detect stretch and nutrients in the digestive system, pages 209-221, copyright 2016, with permission from Elsevier.
Obesity

Obesity has risen to epidemic levels in the United States. Individuals with obesity 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 to have obesity based on body mass index (BMI), a measure of weight relative to height. Approximately 17 percent of children and teens ages 2 through 19 also have obesity, and thus may be at increased risk for developing serious diseases both during their youth and later in adulthood. 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 interventions in families and in health care and other settings, using a variety of approaches and technologies; surgical interventions; and combinations of 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 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.

The Brain’s Regulation of Appetite and Digestion

New Insights into How the Brain Handles Hunger:
Researchers have discovered new details about how the brain controls food intake in mice, suggesting a possible therapeutic target for curbing appetite. In the central nervous system, hormones called melanocortins can activate signaling through the melanocortin 4 receptor (MC4R), affecting metabolism, food intake, and calorie burning (energy expenditure), as well as other physiological factors such as blood pressure. Genetic changes that inactivate the gene for MC4R can cause severe obesity. Without MC4R, food intake and body fat increase, while energy expenditure decreases and the body becomes less able to respond to the hormone insulin. Unfortunately, past attempts to activate MC4R’s effects as a potential obesity treatment also resulted in higher blood pressure, limiting its use as a therapy.

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3 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).
A team of scientists thus sought new insights into MC4R and proteins it partners with, as possible avenues to new treatment strategies. MC4R was known to work through a signaling protein called Gα, to affect energy expenditure and glucose metabolism in the brain. However, Gα did not appear to be responsible for MC4R’s effects on reducing food intake, which originate in a different part of the brain, called the paraventricular nucleus (PVN). Thus, scientists hypothesized that another MC4R-triggered pathway was involved in food intake. To determine what this pathway might be, researchers investigated MC4R’s interactions with a pair of other signaling proteins, which they referred to collectively as Gq/11α. To determine if Gq/11α plays a role in regulating food intake, the researchers created genetically engineered mice lacking Gq/11α in the PVN and looked at the mice’s behavior, weight, and metabolism. Mice lacking Gq/11α ate more food and, later, developed severe obesity compared to mice that still produced Gq/11α. This increased weight was especially prominent in female mice. Additionally, a chemical that usually reduces food intake when injected into the PVN had a reduced effect in mice lacking Gq/11α in the PVN, demonstrating that Gq/11α was involved in curbing appetite. The mice lacking Gq/11α also developed elevated cholesterol levels. However, the lack of Gq/11α in the PVN had no effect on heart rate and blood pressure. These results confirmed that melanocortin’s effects on food intake and cholesterol levels in the PVN were mediated through Gq/11α, a different pathway than that which mediates melanocortin’s effects on blood pressure.

Overall, these results provide new clarity to the question of how hunger and obesity are regulated by the brain. They also offer new avenues for possible therapeutic interventions, since therapies that are specific to the Gq/11α pathway may be able to suppress appetite without unwanted cardiovascular side effects.


The Inner Workings of a Brain Cell That Drives Eating and Weight Gain: Seeking insights that could lead to novel obesity treatments, scientists discovered a molecular pathway in mouse brain cells that begins with activation of cell-surface proteins, called G protein-coupled receptors (GPCRs), and ends with the cells’ release of a powerful appetite-inducing molecule, AgRP. In planning their research, the team of scientists chose to study certain cells in the brain, called AgRP neurons, that produce several factors to promote food intake, including their namesake AgRP molecules. The scientists focused on the cells’ GPCRs because these types of proteins transmit important signals in cells throughout the body to maintain health. GPCRs are also the targets of many medications on the market today for many conditions—and are thus tantalizing prospects for potential future drug development.

The researchers decided to investigate one type of GPCR, the Gα-coupled version, to elucidate its function in AgRP neurons. However, because there are many different forms of GPCRs in many different cells, including multiple forms even within AgRP neurons, they needed a way to zoom in on these particular GPCRs. They adapted a technique, developed previously by others, to create a “designer” Gα-linked GPCR in mice that could only be produced in AgRP neurons and could only be activated by a particular chemical. Then, they tested the effects of this GPCR on food intake, using male mice that had the designer Gα-coupled GPCR in their neurons. Would administering the activating chemical to mice that had just eaten—and thus should be full—cause them to start eating again? It did. Following a single dose of the chemical to activate the Gα-coupled GPCR, the mice not only greatly increased their food intake over the next several hours, but they also continued overeating for the three days of the experiment. Their voracious appetite was not without consequences—the mice gained weight. With further experiments, the researchers mapped additional molecular steps along the pathway from the initial Gα-GPCR activation to the ultimate release of appetite-inducing AgRP molecules. Finally, they confirmed that the insights gained from their designer Gα-GPCR also applied to a native Gα-GPCR in AgRP neurons.

This study brings to light the role of Gα-coupled GPCRs in the brain’s regulation of food intake and body weight. In this and previous research on AgRP neurons, the scientists also investigated another type of GPCR, and found that it, too, prompted mice to eat, but through a different molecular pathway. With multiple ways to provoke eating, the inner workings of these cells may pose a challenge to well-intentioned dieters, but they also present an opportunity. If future research reveals similar findings in people, scientists could develop drugs that interfere with steps along these brain cell pathways,
with the goal of suppressing appetite to help individuals lose excess weight.


**A Nutrient Sensor in Brain Cells Regulates Feeding:**

New research in mice has revealed a key enzyme that acts as a control switch for feeding. Obesity is a worldwide epidemic and a major public health concern. Maintaining energy balance—or the balance between calorie intake and calorie burning—is crucial to keeping a healthy weight and preventing obesity. In addition to lifestyle habits, such as diet and exercise, numerous genes and signaling molecules influence energy balance. The brain regulates food intake by responding to signals in the body, but how the brain interprets these signals is unclear. Previous studies have shown the enzyme O-GlcNAc transferase (OGT) is important in the development of brain cells (neurons) and is regulated by nutrients and insulin, but its precise role in the adult brain was unknown. In this study, researchers investigated the function of OGT in male mice by knocking out the gene that encodes OGT (“OGT knockouts”) within a very specific set of neurons in the brains of adult mice. They then compared food intake and weight in mice without OGT to normal mice.

They found that brain-specific loss of OGT caused a rapid weight gain in mice. Within 3 weeks, the genetically modified mice tripled their body fat. Although these mice ate only as frequently as their unmodified counterparts, they ate more at each meal. The researchers observed that if they restricted food access, the knockout mice maintained a normal weight. However, when free access to food was reintroduced, the mice quickly became obese. When they examined the brains more closely, they found that the loss of OGT was occurring in a particular region of the brain known to be involved in appetite regulation, called the paraventricular nucleus (PVN) of the hypothalamus. Further studies showed that upon deleting OGT, the PVN neurons became far less active, as if they had been silenced. Because disrupting OGT in PVN neurons inhibited the activity of these cells and caused the mice to overeat, the team reasoned that stimulating these cells would have the opposite effect and decrease food intake. To test this theory, they genetically manipulated PVN cells further in knockout mice to produce light-sensitive proteins on their membranes. When they stimulated the cells with a beam of light, the cells became activated and fired signals to other parts of the brain, causing a reduction in food intake.

Taken together, these findings identify OGT in PVN neurons as a potential off-switch to control overeating. While more studies are needed to determine if these cells work the same way in humans, OGT in PVN neurons represents a new potential therapeutic target for human obesity.


**How the Brain Knows When the Stomach Has Stretched and There Is Food To Digest:**

Exploring a biological data cable that transmits information from the gut to the brain, researchers discovered nerve cells in mice that detect nutrients to be digested, and other nerve cells that sense when the stomach and intestines have stretched in size to accommodate food just eaten. To regulate digestion and other processes, many nerve cells (neurons), bundled together to form the vagus nerve, monitor organs throughout the body and report back to the brain. Long fibers from this group of neurons permeate the stomach, intestines, or other organs at one end of the vagus nerve, while fibers at the other end reach up to connect to the brain. It has not been clear, however, which of these neurons transmit which signals.

To identify cells within the vagus nerve that carry different signals, a team of researchers developed a strategy, using a set of fluorescent biological tags, for observing individual neurons and their activity. They first genetically engineered neurons in male and female mice to produce a fluorescent protein that would glow when the cells were activated—that is, transmitting signals—and then examined hundreds of neurons under different conditions. The researchers found that some neurons were activated in response to stretch in the stomach and intestines, while others were activated by the presence of nutrients, as seen by their fluorescent glow. Next, the researchers sought to reveal the identity of these neurons. They focused on a few types of neurons they suspected might play a role based on signaling proteins they produced, called GLP1R and GPR65. The researchers genetically
engineered neurons so they would glow when activated, and used additional fluorescent tags, which glowed in a different color, to mark cells containing GLP1R or GPR65, so they could spot these among other neurons. With other techniques, they also mapped the nerve fibers of these cells in the digestive tract. They found that GLP1R neurons projected their fibers into stomach and intestinal muscle, and that these cells became activated in response to stomach and intestinal stretching. By contrast, GPR65 neurons spread their fibers through intestinal structures that absorb nutrients and respond to food in the intestine. Thus, GLP1R and GPR65 neurons monitor and transmit different signals related to digestion. In other experiments, the researchers found that both types of neurons, when activated, could affect gut motility—the contractions and pressure that help digestion.

By identifying which neurons sense nutrients and stretch in the digestive tract and affect gut motility, this research sheds new light on the connections between body and mind. This study may also lead to new insights into digestive disorders.


NEW DIRECTIONS IN OBESITY TREATMENTS

Brain Stimulation with Electric Current Leads to Changes in Food Consumption and Body Weight in a Preliminary Study of Adults with Obesity: In an intriguing preliminary study, researchers found that a method for stimulating brain activity with electricity, transcranial direct current stimulation (tDCS), affected food choices of people with obesity and led to a small amount of weight loss over several days. Given the challenges of weight loss with lifestyle changes alone, researchers have begun to explore novel treatment approaches, beyond medication and bariatric surgery, that could be combined with or facilitate healthy eating and physical activity. These approaches include modulation of brain activity, because the brain plays major roles in hunger and satiety, in the feeling of reward when eating delicious food, and in other aspects of eating.

In this study, a team of researchers tested tDCS, a non-invasive but still experimental method for stimulating activity in specific regions of the brain with electricity, to see if it might help people with obesity. Nine volunteers, including both men and women, resided in one of NIDDK’s intramural metabolic research centers on two separate occasions for the study, where they received either tDCS or a sham (control) treatment, and where their food consumption could be carefully examined. For the tDCS, the researchers placed electrodes on the participants’ heads to target a part of the brain involved in behavioral regulation and reward. During their visits to the research center, which lasted 8 days each, the volunteers spent the first 5 days on a weight-maintaining diet that was prepared for them. For the next 3 mornings, they were randomly assigned to receive either tDCS or the sham treatment. After their treatments, they ate all of their food from special computerized vending machines; they could choose whatever they wanted to eat and drink from the vending machines, and could eat whenever and as much as they wished. Their food choices, the amounts they consumed, and their body weights were recorded. Five of the volunteers received an inactive form of tDCS on their first visit to the research center, and active tDCS on the second visit. These individuals consumed significantly fewer calories from fat and soda and lost more weight during the visit in which they received the active tDCS. The four volunteers who received the sham treatment on both visits to the center did not experience these changes.

This study provides preliminary evidence that tDCS might affect food consumption and help reduce body weight in people who are obese. The results are consistent with several previous small studies that found potential effects of tDCS on eating behavior. However, because the current study included only a small number of participants, and the effects of the treatment were monitored for only 3 days, much more research would need to be done to test the safety and effectiveness of this procedure for weight loss.


Naturally Occurring Compound Shows Potential as a Treatment for Obesity and Diabetes: Researchers have used an innovative drug-discovery approach to identify a naturally occurring compound, called withaferin A, that mitigates obesity and its metabolic...
effects in mice. Fat cells secrete a hormone called leptin, which signals to the body to stop eating when energy stores are sufficient. When leptin was first discovered in the 1990’s, it was thought that the hormone may be useful to treat obesity. However, except in rare cases of obesity caused by leptin deficiency, obese individuals actually have high levels of leptin, but they are resistant to leptin’s actions. Thus, in obese individuals who are leptin resistant, the hormone is unable to curb appetite, resulting in overeating and additional weight gain. In new research, scientists were interested in identifying potential therapies that could combat leptin resistance and thus promote weight loss. Rather than using a common approach of screening thousands of potential drugs against a single molecular target to identify promising compounds for further testing, the researchers used an innovative drug-screening approach by building on their previous research that identified a naturally occurring compound, called celastrol, which increased leptin sensitivity and promoted weight loss in mice. They looked for compounds that induced a similar gene expression profile—i.e., the genes that are turned on and off—in cells as when they are treated with celastrol. They reasoned that such compounds may similarly improve leptin sensitivity. This approach led to the discovery of withaferin A.

The researchers next examined whether treatment with withaferin A, like celastrol, could reduce body weight in different male mouse models. Withaferin-A treatment of mice that were obese and leptin-resistant because of eating a high-fat diet led to a 23 percent reduction in body weight and a 35 percent reduction in fat mass compared to control mice; treated animals also ate substantially less food. Withaferin-A treatment also resolved the animals’ fatty liver disease, a condition associated with obesity. In contrast, withaferin A did not reduce the body weight of lean mice, which are not leptin resistant, and only marginally affected the body weight of mice that do not make leptin because of a genetic mutation, and thus would not be expected to be affected by a therapy that improves leptin sensitivity. These results suggest that, like celastrol, withaferin A improves leptin sensitivity in mice and promotes weight loss. Further experiments showed that withaferin A (unlike celastrol) also had anti-diabetic properties. For example, withaferin-A treatment improved glucose tolerance, insulin sensitivity, and blood glucose levels in the mice that were obese and leptin-resistant as a result of eating a high-fat diet. Surprisingly, withaferin A also improved glucose tolerance and blood glucose levels in the mice lacking leptin, suggesting that withaferin A’s effects on glucose metabolism are independent of its ability to improve leptin sensitivity. This research identifies a novel compound that improves leptin sensitivity, promotes weight loss, and has beneficial effects on glucose metabolism in mice. Additional research is needed to determine the cellular mechanisms by which withaferin A exerts these effects, as well as whether it will have similar benefits in people without causing unwanted side effects. Future research could build on these promising findings in mice, as well as on the screening approach used by the scientists as a way of identifying other potential therapies for obesity and diabetes.


Custom-made Fat Tissue That Burns Calories:
In research that might lead to a new obesity and diabetes treatment approach, scientists developed a novel technique in mice for directing stem cells from body fat to grow in special gels and form fat tissue that burns—rather than stores—calories. Based on earlier findings that some types of body fat, called brown and beige fat, can generate heat by burning stored calories, researchers have proposed various strategies for creating more of these types of tissues to reduce excess weight and boost metabolism. Pursuing one such strategy, a multidisciplinary research team sought to grow beige fat tissue in the lab and test whether it would improve weight and health in mice.

They began by extracting stem cells from white fat tissue, the more abundant type of fat best known for storing calories. Next, they devised a way to coax these cells into becoming beige fat, taking into account the importance of a cell’s surrounding environment in determining its fate. In the body, critical signals come not only from molecules that enter into cells, but also from the biological structures on which cells sit, including the proteins on these structures. Thus, to grow the stem cells, the researchers developed a special gel matrix that included fragments of proteins they had carefully selected to help guide stem cell maturation into beige fat. After immersing the stem cells in chemicals known to induce beige
fat characteristics, the researchers mixed the cells with the gel components to help seal their fate, and transplanted the mixture into male mice. The technology worked. Cells grown in the special gel turned on a key beige fat gene, UCP1, used for generating heat from calorie burning, and did so more effectively than cells grown in other ways. Mice transplanted with this new beige fat gained less weight than other mice on a high-fat diet. They also had less fat in their bloodstream; higher body temperatures after exposure to cold; and improved blood sugar levels, a sign of reduced risk for diabetes.

In the future, scientists could test this new technology to see whether it works with human cells. If it does, a person’s own excess fat tissue might one day be used as a source of stem cells for generating beige fat—turning a problem into a potential solution.


INSIGHTS INTO WEIGHT LOSS MAINTENANCE

Research Reveals Persistent Metabolic Slowing as Potential Catch-22 in Maintaining Significant Weight Loss: A long-term follow-up study of participants in a televised weight loss competition suggests that there is a persistent change in how the body handles calories that can interfere with efforts to maintain weight loss. Scientists in the NIDDK Intramural Research Program originally studied metabolic changes in 16 extremely obese men and women who lost weight through intensive diet and exercise in the televised “The Biggest Loser” competition. They have now conducted a follow up study with 14 of these people 6 years after the end of the 30-week competition. A key finding in the original study was that, between the start and end of the competition, participants’ weight loss was accompanied by greater than predicted and substantial reduction in their resting metabolic rate (RMR)—a measure of the minimum amount of calories the body will burn per day. Lowering RMR is a way for the body to resist weight loss and to be able to function on fewer calories, and is advantageous in circumstances such as starvation. However, in the context of losing excess fat weight, this metabolic adaptation may contribute to weight regain, especially if it persists.

In the new study, the NIDDK scientists obtained data on body composition so that—using an equation developed in the original study that also takes into account factors such as age and gender—they could calculate a new predicted RMR for each person. They also measured each person’s actual RMR. When they compared the data from the beginning of the competition, the end of the competition, and 6 years later, they found that all but one participant had regained at least some of their lost weight. At the same time, participants’ RMRs had, on average, remained at the same reduced level seen at the end of the competition, rather than increasing as would be predicted with weight regain. This alarming result suggests that metabolic adaptation following diet- and exercise-induced weight loss persists and does not fully reverse even as weight is regained, adding to people’s struggle to maintain weight loss. Encouragingly, when examining individual results, the researchers found that the persons who maintained greater weight loss at the 6-year mark also experienced greater ongoing metabolic slowing—suggesting that the observed RMR adaptation does not completely counter weight loss. Maintaining a lower body weight nonetheless requires continued attention to physical activity and dietary changes, given the body’s tendency to burn fewer calories after weight loss.


DISCOVERIES PROVIDE INSIGHTS ON EATING BEHAVIOR

How What You Eat Can Affect How Much You Eat: Scientists identified one way the gut microbiome influences obesity and metabolism. A link between the bacteria that populate the intestines (part of the gut microbiome) and obesity had been previously discovered, but the details of how the microbiome influenced body weight were not known. To delve into this question, researchers built on a previous observation: changes in the amount of short-chain fatty acids (by-products of digestion in the gut) can be associated with overfeeding, obesity, and metabolic syndrome (factors that increase risk of heart disease and diabetes). In this new study, the scientists found that male rats fed a high-fat diet showed a striking increase in the amount of acetate, a short-chain fatty acid, in their bodies, and became
insulin resistant, a condition associated with metabolic syndrome. Determining the origin and consequences of the increase in acetate resulted in an exciting discovery of how the gut microbiome affects metabolism.

By measuring the acetate in tissues of the rat, the scientists found the highest amount in the gut; treating the rats with antibiotics to kill the gut bacteria, or removing the colon (part of the gut), reduced the amount of acetate dramatically. Consistent with previous research, they also found that rats fed a high-fat diet had a mix of bacteria in their microbiome that was somewhat different from the gut bacteria of rats fed a normal diet. A fecal transfer—transplanting the gut microbiome from rats eating the high-fat diet into rats on a normal diet—also transferred the increase in acetate production. Together, these observations indicate that the gut microbiome was responsible for generating the increased acetate. To determine the chronic effects of increased acetate, rats on a normal diet received acetate infusions for 10 days. After this period, the rats had increased insulin secretion by the pancreatic β (beta) cells in response to insulin, were insulin resistant, and more than doubled their daily caloric intake and weight gain. Interestingly, the researchers discovered that the acetate stimulated the parasympathetic nervous system through the brain.

These results suggest a model: exposure to a diet high in calories leads to increased acetate production by bacteria in the gut. The acetate enters the blood and travels to the brain. As a result, the brain signals to the pancreas to increase insulin secretion and storage of fat, and signals to the stomach to release the hunger hormone ghrelin. This process appears to lead to overfeeding and insulin resistance, creating a feedback loop. Additional research will be necessary to determine whether the same mechanism operates in humans and to identify which bacteria in the gut microbiome contribute to the production of acetate. Nevertheless this study describes a novel link between the gut microbiome, obesity, and metabolic syndrome that could be targeted in the development of therapeutics for obesity and diabetes.


**Tracking Both the What and the When of the Human Diet:** Researchers have developed an innovative smartphone application (“app”) to provide valuable insights into the content and timing of the human diet, and showed that many adults eat over a span of 15 hours or more each day; through a very small pilot study, they have also begun to explore whether limiting the hours of daily eating and drinking may help achieve weight loss. Measuring just what people normally eat and drink during their daily lives is surprisingly difficult. Standard approaches, such as surveys or food diaries, depend on accurate recollection and measurement by study participants, and can be a significant burden, particularly if a person wishes to indulge in between-meal snacks. Further, research suggests that when people eat—not just what—may have a significant impact on metabolic health: shift workers have a higher burden of obesity and diabetes; and in animals, 24-hour access to food promotes poorer metabolic health. To get a clearer idea both of what people eat and when, the new study took advantage of smartphone technology. Participants—156 healthy adult men and women—were asked to use the cameras on their phones to take pictures of everything they ate or drank, regardless of calorie content (including water), for 3 weeks. None of the participants was a shift-worker. An app specially designed for the study logged the date and time of each picture, and sent the image to study researchers for analysis. The image was then automatically deleted from the smartphone to prevent it from later influencing the participant’s eating, and to reduce memory-hogging on his or her device. An estimated caloric value of each item was recorded by study staff. (Participants who forgot to take a picture before they took a bite were asked to submit information via text entry.) If participants did not finish an item, they submitted a second picture showing the leftovers. This part of the study was designed to shed light on how people eat: the participants received no dietary guidance.

Results showed that although the majority of participants described themselves as three-meal-a-day eaters, the actual number of times people consumed calories varied substantially, averaging from a little more than 3 to a little more than 10. The median portion of the day during which people ate was nearly 15 hours (i.e., one half of participants generally ate during a shorter period of the day than that, and one half during a longer one). The study also found that consumption was generally heaviest in the evening hours: less than one-quarter of calories were typically consumed before noon, while over one-third were
typically consumed after 6 p.m. The average weight of the subjects remained quite stable over the course of the study; this suggests the simple act of taking the pictures and using the app did not induce participants to make significant changes in their eating habits. However, there are some important caveats: the study was relatively short, and the participants relatively young (average age about 28) and not especially diverse—more than three-fourths of the group were either non-Hispanic white or of Asian descent. Thus, it will be important to learn whether the observed eating patterns are similar to those that would be found in a more representative cohort of Americans.

Because experiments in animal models have shown that reducing food availability to 12 hours or less may have metabolic benefits, the researchers sought to test whether this might work in people. They began with a very preliminary study of just a few people, to see whether such a test would be feasible. They recruited eight participants (five men, three women) from the first study who consumed calories for 14 hours or more per day and who were also overweight or obese to participate in a 16-week follow-up study. These eight people were asked to confine consumption of calories to a consistent 10- to 12-hour window that they themselves were allowed to select. They were instructed to stick to their chosen window, but given no guidance about what kinds of things they should eat and drink, or how much. All eight significantly reduced their eating period—by an average of more than 4.5 hours. Although they were not counseled to eat less, they also consumed 20 percent fewer calories, on average, and most of the people lost several pounds. At the same time, they reported feeling they had more energy, reduced hunger at bedtime, and better sleep satisfaction. Notably, all of the participants expressed interest in continuing this approach, and all of these improvements generally persisted for at least a year, 8 months after the active phase of the intervention had ended. Follow-up studies with larger numbers of people will be needed to confirm these preliminary findings, and to see whether this sort of intervention might be effective in a more diverse group of people. If so, shortening the period of daily caloric intake may turn out to be a valuable approach to helping people lose weight and potentially improve other aspects of their health. In the publication of their study findings, the researchers noted that they are continuing to gather data using the app, and provided information for people interested in their research to learn more and, if they wish, sign up to participate.


**BARIATRIC SURGERY RESEARCH**

*Weight Loss and Health Benefits from Bariatric Surgery in Teens with Severe Obesity:* In a study of teens with severe obesity, bariatric surgery resulted in substantial weight loss and improvements in health and quality of life 3 years after the surgeries were performed; the study also identified risks associated with the surgeries. These findings are from the Teen Longitudinal Assessment of Bariatric Surgery, or Teen-LABS, study.

Obesity increases risk for type 2 diabetes, cardiovascular disease, and many other serious conditions. Previous research has shown that adults with severe obesity (also known as extreme obesity) can experience dramatic health benefits from bariatric surgery. However, very little has been known about the effects of this surgery in adolescents, particularly over the long-term—even though it is used in clinical practice for this age group. Thus, researchers designed Teen-LABS, an observational study that enrolled adolescents who were already planning to have bariatric surgery. Their goal was to collect outcome data on health risks and benefits that could help with treatment decisions.

Conducted at five U.S. clinical centers, Teen-LABS enrolled 242 people ages 13-19. Prior to surgery, all were obese, and nearly all had severe obesity, based on body mass index (BMI), a measure of weight relative to height. The majority of the participants in the study were Caucasian females, a demographic representative of patients who seek bariatric surgery at these clinical centers. The study focused on those who underwent either of two bariatric surgical procedures: gastric bypass (used for a majority of the teens), or sleeve gastrectomy. Before surgery, the participants’ average weight was 328 pounds. Three years after surgery, their weight decreased by an average of 90 pounds, or 27 percent. Some of the participants had type 2 diabetes, some had
kidney disease, and many had high blood pressure or abnormal levels of blood lipids (cholesterol or triglycerides) prior to surgery. The study found that 95 percent of the teens who had type 2 diabetes had reversal of their disease, 86 percent of those with kidney damage experienced improvements in kidney function, and most of the teens with high blood pressure or lipid abnormalities saw improvements in these conditions 3 years after surgery. Additionally, 26 percent of the teens were no longer obese 3 years after surgery. Although a majority still had some level of obesity, not as many had severe obesity.

The study also identified risks. During the study period, 13 percent of participants needed additional abdominal surgery, most commonly gallbladder removal. The study also found that although fewer than 5 percent of the teens were iron-deficient before surgery, more than half had low iron stores 3 years later.

These results contribute important knowledge about the benefits and risks of bariatric surgery in adolescents. However, further research will be critical to determine the longer-term effects of bariatric surgery on health and well-being, including whether health improvements are sustained and whether additional risks emerge. This information will help teens, their parents, and their health care providers make more informed treatment decisions, so that young people with obesity can have improved health during adolescence and as they become adults.


Weight-loss Surgery Contributes to Type 2 Diabetes Remission: A study has shown that one type of weight-loss surgery is more effective than another at inducing long-term type 2 diabetes remission in people who have obesity. When approaches to weight loss such as diet, exercise, and medications are ineffective in inducing enough weight loss to produce health benefits, some people with severe obesity turn to surgical options for weight loss—so-called bariatric surgery. While bariatric surgery can be a useful tool to promote and sustain substantial weight loss, increasing evidence suggests it can also be beneficial in treating diabetes. Because type 2 diabetes is associated with excess weight and is a major public health concern, researchers set out to understand better the effects of two different types of bariatric surgery, Roux-en-Y gastric bypass (RYGBP) and laparoscopic gastric banding (LAGB), on diabetes remission using the large observational study, Longitudinal Assessment of Bariatric Surgery-2 (LABS-2).

Many of the LABS-2 study participants had type 2 diabetes prior to surgery; of these individuals, 466 underwent RYGBP and 140 underwent LAGB. When the team examined diabetes remission rates in LABS-2 participants who underwent RYGBP versus those who had LAGB, they found that, after 3 years, both types of surgery resulted in a subset of participants in each group entering diabetes remission. In other words, both procedures were effective to an extent, such that 68.7 percent of the RYGBP participants, and 30.2 percent of the LAGB participants had blood glucose (sugar) levels that were no longer in the range of diabetes, and they did not need diabetes medications. They also found that the greater the post-surgical weight loss, the greater the chances of diabetes remission after both procedures. Not surprisingly, they observed that individuals in both groups who had better blood glucose control prior to surgery had better remission outcomes. However, when they analyzed changes in certain hormones that typically coincide with weight loss, such as a reduction of overall leptin levels and improved insulin sensitivity, they found something unexpected—these metabolic markers were only associated with diabetes remission after LAGB, not RYGBP. When they examined the relationship between weight loss and diabetes remission more carefully by accounting for weight-loss differences between the two groups, they found a nearly twice as high remission rate for individuals who underwent RYGBP. In other words, weight loss was not the only factor contributing toward diabetes remission after RYGBP. This suggests that RYGBP may have added benefits beyond weight loss on glucose control.

This study found that factors in addition to weight loss may play a role in the greater likelihood of diabetes remission following RYGBP compared to LAGB. Longer-term studies are needed to confirm this.

Obesity—a condition affected by many different factors, including genetics, lifestyle, and even various types of gut bacteria—has soared to epidemic levels in the United States. With this in mind, the NIDDK sponsored two workshops in December 2015 to further explore different aspects of obesity.

Understanding Behavioral Traits Linked to Differences Among Individuals in Physical Activity and Sedentary Behavior
The health benefits of regular exercise and reduced sedentary time are well established. Moreover, it is widely acknowledged that physical activity is an integral part of preventing obesity and maintaining weight post weight-loss. While significant health-promotion efforts have been made throughout the years, substantial room remains for increasing physical activity and reducing sedentary behavior for weight management. To understand behaviors related to variation in physical activity better and to identify promising research opportunities, the first workshop, entitled “Behavioral Phenotyping of Physical Activity and Sedentary Behavior,” was held December 1-2.

The meeting’s objective was to enhance understanding of and identify research gaps in behavioral and psychological factors that influence individual variation in physical activity and sedentary behavior across the lifespan. Speakers summarized the state of the science and identified numerous research gaps. While some promising phenotypes to explain individual variability were discussed, it was clear that more research is needed. A report is currently being developed to describe the rationale and outcomes of the workshop.

Obesity and the Bacteria and Other Microbes That Live in the Gut (the Gut Microbiome)
Energy balance is the relationship between “energy in”—food intake—and “energy out”—calories burned. Increasing evidence suggests that gut microbial composition—or the gut microbiome—may alter this balance and contribute to the development of obesity. Recent data indicate that the gut microbiome can predict body composition (lean or obese) with 90 percent accuracy compared to 60 percent accuracy with genetics alone. Moreover, evidence suggests the microbiome plays a critical role in weight loss interventions, but the precise functional nature of this role has not been clearly established.

To address unmet needs in this area of obesity research, the NIDDK together with the National Heart, Lung, and Blood Institute, the National Cancer Institute, and the Office of Dietary Supplements organized a second workshop, entitled “Functional Role of Microbiome in Obesity,” held on December 14-15. The meeting brought together experts in microbiome and obesity research, NIH staff, and selected trainees doing research in these areas. A number of research gaps were identified and specific recommendations for potential future research directions were made. Proceedings of the workshop will be published in a scientific journal.