



Genetics, diet, and various types of bacteria that reside in the gut all modify susceptibility to obesity and metabolic conditions. In a recent study, researchers discovered that these factors are all interrelated, as illustrated in the figure and described further in this chapter. The top row depicts two genetically related strains of mice bred in different locations (129J and 129T) and an unrelated strain (B6J). Their gut bacteria (part of the “microbiota” or “microbiome”) are represented by multicolored pie charts. The bottom row shows these strains of mice after several generations of breeding in the same environment (“environmental normalization”) and the resulting similarities among their gut bacteria. From the B6J mice, the researchers found that a strong genetic susceptibility to obesity and metabolic syndrome can overshadow environmental factors. By contrast, environment prevailed over genetics for the 129 strains: bred apart, they differed in metabolic traits (top row), such as propensity for obesity and fatty liver (hepatosteatosi s). These differences disappeared after the 129 strains were bred in the same place and acquired similar gut bacteria (bottom row). Insights from this study may lead to new strategies to improve health by modulating gut bacteria.

Image courtesy of Dr. C. Ronald Kahn, Harvard Medical School and Joslin Diabetes Center. Reprinted from Cell Metab, Vol 22, Ussar S, Griffin NW, Bezy O, Fujisaka S, Vienberg S, Softic S, Deng L, Bry L, Gordon JI, Kahn CR, Interactions between gut microbiota, host genetics and diet modulate the predisposition to obesity and metabolic syndrome, p. 516-530, copyright 2015, with permission from Elsevier.

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 Approximately 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.^{1,2} 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, schools, health care, and other settings using a variety of approaches and technologies; 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 sponsors health information programs.³

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.

¹ Ogden CL, et al. NCHS Data Brief, No. 219. National Center for Health Statistics, Centers for Disease Control and Prevention. 2015.

² 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).

³ NIDDK Weight-control Information Network, <http://win.niddk.nih.gov/index.htm>

These represent examples of the NIDDK's broad spectrum of research efforts toward reducing the burden of obesity so that people can look forward to healthier lives.

BIOLOGICAL FACTORS IN HUMAN BODY WEIGHT

Belly Fat, or Hip Fat? And How Much? Mining the Genome for Answers: In recent international studies, researchers examining data from hundreds of thousands of people have discovered areas of the genome that are associated with obesity and other areas of the genome that help determine whether extra calories are more likely to be stored around the waist or hips. Researchers have long known that genetic and environmental factors, along with behaviors influenced by both, contribute to obesity. Genetic factors also direct where body fat accumulates. However, it has been difficult to identify genetic variants (genome sequence differences among individuals) associated with these conditions.

In one study, researchers scanned the genome for genetic variants associated with body mass index (BMI), a measure of weight relative to height, in more than 320,000 people, most of European ancestry. They identified variants in 97 different genomic regions, 56 of which were not previously known to be associated with BMI. Variants in two of the genomic regions differed between men and women, with stronger effects in women. Some were associated with other, obesity-related health conditions, but the effects were not always as expected. For example, although obesity is a strong risk factor for type 2 diabetes, one of the variants was associated with higher obesity risk and, surprisingly, lower diabetes risk; these findings may help explain why not everyone who is obese develops metabolic disease. The genomic region around any variant

could contain multiple genes; as a first step toward identifying those likely to cause the effects on BMI, the researchers examined the genes near each variant. They found that many of the genes were known from prior research to function in brain pathways relevant to obesity, and some are involved in processes such as transmitting signals between brain cells. Other genes are associated with insulin action, fat cell development, regulating whether genes are turned on or off, and other, disparate functions.

In the other study, researchers explored genetic contributors to body fat distribution, or why some people tend to accumulate belly fat, or fat in the abdominal area, while others store more fat in their hips—sometimes referred to as apple-shaped compared to pear-shaped, respectively. Abdominal fat, often estimated by waist circumference, tends to be more detrimental to health. For people of the same weight and height, an individual with a larger waist circumference relative to hip circumference, or waist-to-hip ratio, is at heightened risk for metabolic conditions, including diabetes. For this study, researchers analyzed data from over 220,000 individuals, most of European ancestry, and found genetic variants associated with waist-to-hip ratio in 49 regions across the genome. Of these, 33 were newly discovered to be related to body fat distribution. Variants in 19 of the genomic regions had larger effects on body fat distribution in women, while variants in one region showed a larger effect in men. The researchers then cataloged the genes and other DNA sequences in the genomic regions around each of the variants: some are known to play a role in insulin resistance (a condition related to diabetes); others are involved in blood vessel formation, fat tissue functions, and regulation of gene activity.

These new studies build on prior findings, more than doubling the number of regions of the genome now known to be associated with obesity and whether

body fat accumulates more at the waist or hips. Future research could determine which specific genes are responsible for the effects, and may also identify additional genetic variants that affect obesity and body fat distribution. Further study of individuals of diverse ancestry may also yield more insights. These lines of research will continue to enhance understanding and yield targets for potential new therapies.

Locke AE, Kahali B, Berndt SI,...Speliotes EK. Genetic studies of body mass index yield new insights for obesity biology. Nature 518: 197-206, 2015.

Shungin D, Winkler TW, Croteau-Chonka DC,...Mohlke KL. New genetic loci link adipose and insulin biology to body fat distribution. Nature 518: 187-196, 2015.

Ease of Weight Loss Influenced by Individual

Biology: Researchers have found evidence supporting the commonly held belief that people’s biology influences how much weight they lose when limiting calories. It is well known that, when people decrease their caloric intake, there is wide variability in the amount and rate of weight loss from person to person. However, the reasons behind this variability are not fully known. To examine the biology underlying these differences, NIDDK intramural researchers studied energy expenditure (calorie burning) and weight loss in 12 men and women with obesity. Using a whole-room indirect calorimeter—which allows energy expenditure to be calculated based on air samples—researchers took baseline measurements of participants’ energy expenditure in response to a day of fasting and a day of eating substantially more than usual (overfeeding). Fasting typically causes the body to reduce energy expenditure (burn fewer calories), while excess food can cause the body to increase energy expenditure (although usually not by enough to burn off all the extra calories). The researchers found that participants differed in how much their energy expenditure

changed in response to fasting or overfeeding. They next sought to determine whether these differences in individual biology correlated with differences in weight loss on a low-calorie diet.

Following the baseline period, the participants consumed a 50 percent calorie-reduced diet for 6 weeks. After accounting for age, sex, race, and baseline weight, the scientists found that the people who lost the least amount of weight during the calorie-reduced period were those whose energy expenditure had decreased the most when fasting and increased the least when overfeeding. In other words, their metabolism slowed down more when they fasted and did not increase as much when they overfed. Those participants had what the researchers called a “thrifty” metabolism—i.e., they saved calories. The people who lost the most weight had a “spendthrift” metabolism, in which energy expenditure decreased the least during fasting and increased the most during overfeeding. It is unknown if these biological differences are innate or develop over time. These findings show that when people who are obese try to lose weight by limiting calories, their metabolism influences how much weight they lose. Future research may help determine whether these insights could inform personalized approaches to help people who are obese achieve a healthy weight.

Reinhardt M, Thearle MS, Ibrahim M,...Votruba SB. A human thrifty phenotype associated with less weight loss during caloric restriction. Diabetes 64: 2859-2867, 2015.

HEALTHIER WEIGHT IN IMPOVERISHED CHILDREN

Head Start Participation Associated with Healthy Changes in Body Weight Among Impoverished

Overweight and Obese Children: A team of researchers found that preschoolers in Head Start

programs who were overweight or obese were more likely to reach healthier weights by kindergarten age than other groups of overweight and obese children. Head Start is a federally funded preschool program for children living in poverty. The researchers sought to determine whether Head Start might be a valuable setting for reducing childhood obesity because these programs serve impoverished children across the country, and because socioeconomically disadvantaged individuals are at greater risk for obesity.

For the study, the research team gathered children's weight and height measures from 12 Head Start programs in Michigan, both rural and urban, who agreed to participate, along with measures from other children for comparison. More than 19,000 children were in the Head Start group, including similar numbers of boys and girls, with race/ethnicities of 65 percent white, 11 percent black, and 14 percent Hispanic. The comparison groups, who were from a health care system in the same state, included 5,400 children who were on Medicaid, and over 19,000 children not on Medicaid. To examine the children's weight changes over time, taking into account the fact that children also grow in height, the researchers calculated body mass index (BMI), a measure of weight relative to height. They then examined how far the children's BMIs varied from what is considered healthy for their ages, based on standard growth charts for boys and girls. Among children who were obese or overweight, those in Head Start attained a healthier BMI during the first year of the study than children in the comparison groups, and were still at a healthier weight by the end of the second year. Children in Head Start who were underweight also reached healthier weights than those in comparison groups, although the data were more limited. It is not clear which aspects of Head Start may have contributed to these weight

changes, but the researchers suggested several possibilities. For example, Head Start programs are required to meet certain nutritional guidelines, provide space for active play, prohibit television watching, and facilitate access to health care. The results of this study provide evidence that Head Start programs may have beneficial effects on children's weight early in life.

Lumeng JC, Kaciroti N, Sturza J,...Reischl TM. Changes in body mass index associated with Head Start participation. Pediatrics 135: e449-456, 2015.

MULTIPLE BRAIN CELL PATHWAYS THAT REGULATE APPETITE

Although it may seem intuitive that one would feel hungry after not eating for a while, and full after eating, the body's regulation of the desire to eat is actually quite complex, involving multiple biological pathways in the brain. Two recent studies in mice, described below, give new insights into different pathways that increase appetite; these focused on different cells—AgRP and POMC neurons—that reside in the same region of the brain. In the study of AgRP neurons, scientists discovered other groups of cells along what is likely a major pathway toward increasing appetite when the body needs more energy from food. Unlike AgRP neurons, POMC neurons are known to suppress appetite. However, as revealed by the other study, in the presence of chemicals called cannabinoids, POMC neurons take on the opposite role, and, surprisingly, promote excessive eating.

Brain Cells That Forge a Path from Hunger to a Quest for Food: Researchers have mapped out a series of cells in the brain that relay signals to drive appetite in mice, illuminating potential targets for new obesity drug development. The research

team included scientists from universities and the NIDDK's Intramural Research Program.

To gain new insights into the circuits of the brain that control hunger and satiety (feeling full), the researchers began by engineering mouse brain cells called AgRP neurons to fire in response to blue light, and then, literally, shined light on these cells to activate them. Known to promote hunger, AgRP neurons work by blocking cells that would otherwise promote satiety—but the other cells' identity was unclear. Based on clues from past research, the scientists focused on brain cells containing MC4R, a molecule known to play a role in satiety. They stimulated the modified AgRP neurons with light, and observed cells elsewhere in the brain that responded by firing (emitting characteristic bursts of electrical activity). Some of these cells were MC4R-containing neurons in a part of the brain referred to as the PVH. The researchers then examined the roles of these PVH^{MC4R} cells in satiety. Activating PVH^{MC4R} neurons (with another technique) caused mice to eat less than normal after a fast, when they should have been hungry. Conversely, when the researchers inhibited PVH^{MC4R} neurons, the mice began poking a food-dispensing machine in their cage repeatedly to obtain more food pellets, even after a full meal. With further experiments, the researchers confirmed that AgRP neurons increase appetite by blocking the satiety-promoting activity of PVH^{MC4R} neurons. They then discovered the next brain region involved in this pathway. Using a fluorescent protein “tag,” they traced projections from PVH^{MC4R} neurons to neurons in another part of the brain, called the LPBN. Additional experiments demonstrated the importance of the connection between these groups of neurons for promoting satiety. By blocking PVH^{MC4R} cells and their LPBN cell partners, AgRP neurons are able to send the mice on a quest for food.

The researchers have thus mapped a series of cells along a pathway of appetite regulation that traverses different parts of the brain. Additional research, conducted by these scientists and others, shows that this is one of multiple brain pathways that affect eating behavior. Future research may show whether the results of this study apply to both females and males, as many of the experiments included only male mice. Future research could also determine whether AgRP, PVH^{MC4R}, and LPBN neurons work similarly in humans; if so, researchers may one day be able to target this pathway to develop obesity drugs that help people feel full after eating less food.

Garfield AS, Li C, Madara JC, ...Lowell BB. A neural basis for melanocortin-4 receptor-regulated appetite. *Nat Neurosci* 18: 863-871, 2015.

Hungry When You're Full? Cannabinoids Trigger a Surprising Switch in Brain Cells Known for Their Role in Suppressing Appetite:

Exploring how cannabinoids generate a strong urge to eat—even after a meal—researchers discovered, in mice, that these substances cause certain brain cells to abandon their characteristic role in appetite suppression and instead drive feeding behavior. Although cannabinoids are known as chemical components of marijuana, versions of cannabinoids are also made by the body, where they promote hunger, particularly for sweet and fatty food. The mechanisms by which they work, however, have not been well understood.

Because cells in the brain have docking sites, or receptors, for cannabinoids, a team of researchers thought that cannabinoids might block the activity of brain cells called POMC neurons, which have long been known for their role in feeling satiated. To test the theory, the researchers gave well-fed male mice doses of synthetic cannabinoids to stimulate one type of cannabinoid receptor, called CB₁R, and then observed how much the mice ate and the chemical's effects

on the brain. To their surprise, at doses that induced the mice to eat to excess, the synthetic cannabinoids activated—rather than dampened—POMC neurons. For example, these neurons ramped up their characteristic firing, the bursts of electrical activity that nerve cells use for signaling. Delving further into this paradox, the researchers examined levels of two molecules produced by POMC neurons that, intriguingly, have opposite effects. One is a hormone that inhibits eating; the other, β -endorphin, can increase feeding, although POMC neurons were not previously known to produce this hormone. In experiments with male mice, CB₁R activation amplified β -endorphin release from POMC cells in the brain but did not affect levels of the appetite-suppressing hormone. The researchers also tested the effects of a CB₁R-inhibiting drug, rimonabant. Once used for obesity treatment in some countries (although not in the United States), rimonabant is no longer marketed due to serious psychological side effects. When administered to mice, rimonabant blocked cannabinoid-induced food intake and diminished β -endorphin release in the brain.

This research in mice reveals an unexpected biologic switch in POMC neurons from suppressing appetite to promoting excessive hunger. With further study of CB₁R and innate cannabinoids in humans, investigators may be able to develop new and potentially safer therapeutics for obesity that target cannabinoid pathways.

Koch M, Varela L, Kim JG,...Horvath TL. Hypothalamic POMC neurons promote cannabinoid-induced feeding. [Nature](#) 519: 45-50, 2015.

CIRCADIAN RHYTHM AND CALORIE INTAKE

Time To Eat?: New research in mice suggests that restricting eating to a shorter period of the day

might be a valuable adjunct to traditional diet and exercise recommendations, and might potentially confer metabolic benefits or allow weight loss even without reducing caloric intake, eating a rigid diet, or taking weight-loss medications. Several studies have established that healthy metabolism is tied closely to circadian rhythms, and that the body handles food and digestion most effectively during daytime hours. These findings may help explain observational findings that people who work night shifts or eat at night are at an increased risk for obesity and metabolic diseases such as type 2 diabetes. The observations also lead to the question: can people improve their health by eating only during specific hours of the day? Clinical research to test the effects of varying people's mealtimes is currently lacking. However, previous research has shown that if mice are given food only during 8 hours of their active period (at night, because they are nocturnal animals), they are protected from obesity and diabetes, even if they are fed a high-fat diet that normally causes these conditions in mice with all-day access to the same food. In a new study, researchers sought to expand upon this result. For example, they sought to determine how severely feeding time had to be restricted to protect mice from the adverse metabolic effects of a high-fat diet. Working with male mice, they found through a number of experiments that mice with constant, continuous access to a high-fat diet gained significantly more weight than mice whose access was limited to 9 hours, to 12 hours, or even to 15 hours (*i.e.*, 9 hours fasting). The shorter the eating period, the better the protection, though protection was substantial even in the 15-hour-fed group. Animals with access to the high-fat diet for 9 hours weighed no more than mice given a normal healthy diet. Interestingly, for any given diet, time-restricted feeding did not change the number of calories the mice consumed: those with 9-hour access to high-fat food ate no less than those with

the same diet available for 24 hours. This suggests that circadian coordination of metabolism is responsible for the effect—not a reduction in calories consumed, but simply timing that consumption to correspond to the animals’ natural active period. That is, a dieting and exercise program was not necessary to limit weight, at least in male mice. Indeed, even on a healthy diet, time-restricted feeding came with a surprise benefit: although the mice weighed the same as mice with 24-hour access to the healthy diet, they had less body fat and more lean muscle mass. Taking the experiment further, the investigators examined whether it was necessary to restrict food intake every day. When male mice fed a high-fat diet were restricted to 9-hour access for 5 days per week and then given 24-hour access on weekends, they still fared considerably better than mice given 24-hour access to the diet every day, doing about as well as mice given food for 12 hours a day, 7 days a week. Importantly, the mice with 5 days of time-restricted feeding not only weighed less than the mice with 24-hour food access, but also experienced significant metabolic benefits: better insulin sensitivity, lower blood glucose (sugar), fewer signs of inflammation, more healthy brown fat, less unhealthy white fat, and healthier blood and liver levels of fat and cholesterol.

In another series of experiments, mice that had grown obese through 24-hour access to the high-fat food were switched to time-restricted feeding. These animals lost weight, and then plateaued, while those still receiving food 24/7 continued to gain. The metabolic benefits seen after switching the obese mice to time-restricted feeding were significant. For example, their insulin levels fell and glycemic control improved, although they remained somewhat less metabolically healthy than mice that had been fed continuously in a time-restricted fashion. In contrast, when time-restricted feeders were switched to 24-hour food access, they gained substantial

amounts of weight, although they retained some of the metabolic benefits they had previously earned in their period of time-restricted feeding. Further, the researchers found that the time-restricted feeding approach not only benefited animals on a high-fat diet. The benefit of time-restricted feeding was also quite substantial in mice given diets that may be more representative of those contributing to obesity in humans: not quite as high in fat, but including sucrose (table sugar), for example, or a diet elevated in fructose (often found in processed foods). It is unclear to what extent this approach would be beneficial to people, whether there might be differences between women and men in metabolic benefits derived, and whether people will be more or less able to adapt to changing their mealtimes as opposed to changing their diets. However, if the effects are similar to those in mice, the discovery may be of profound importance: people who have difficulty restricting calories or curtailing fattening foods may find it more manageable to simply restrict the time when they can consume them.

Chaix A, Zarrinpar A, Miu P, and Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metab 20: 991–1005, 2014.

GUT MICROBIOME, GENETICS, AND OBESITY

Nature, Nurture, and Nutrition—Gut Bacteria Native to Different Environments, Genetics, and

Diet Influence Metabolism: In a study in mice, researchers discovered that genetics, diet, and gut microbes acquired in different environments all interact to modify susceptibility to obesity and metabolic conditions. To examine genetic risk, the researchers compared mice known to be genetically related, strains 129J and 129T, and an unrelated strain, referred to as B6J. To investigate dietary

effects, they fed the mice regular mouse chow or a high-fat diet. Exploring potential environmental effects, and heeding the mantra “location, location, location,” they obtained mice from different vendors (the “J” and “T” in the strain names), and bred some of these mice for several generations in the same environment—their own research institution. They also catalogued the many different types of gut bacteria (the gut microbiome) in the mice.

Building on previous studies, the researchers found that all of these factors play a role in obesity and metabolism—and are interrelated. For example, the B6J mice had a strong genetic susceptibility to obesity and metabolic conditions. Regardless of birthplace, they gained more weight than both the 129T and 129J strains on either diet. The B6J mice also had worse metabolic health, including insulin resistance, impaired control of glucose (sugar) levels, inflammation, and liver damage. The genetically related 129T and 129J strains, when bred in separate locales, differed in weight gain and liver damage on a high-fat diet; thus, environment prevailed over genetics for some of their metabolic conditions. After the 129T and 129J strains were bred for several generations in the same place, these differences disappeared. The breeding environment, mouse genetic background, and diet all influenced the composition of gut bacteria, which in turn affected metabolism. From bacterial transplant experiments in the mice, the researchers found that some collections of gut bacteria confer better metabolic health than others to male recipient mice. They then discovered that specific types of gut bacteria were more abundant (and others less) in mice with higher body weight. Body fat, insulin levels, and markers of inflammation also correlated with the relative abundance of various types of gut bacteria.

This study provides new insights into obesity and metabolism. It also has implications for researchers

who are trying to confirm scientific results, in that genetically similar mice may exhibit different traits if bred in environments with different gut bacteria. Finally, this research may lead to strategies to improve health by modulating the composition of gut bacteria.

Ussar S, Griffin NW, Bezy O,... Kahn CR. Interactions between gut microbiota, host genetics and diet modulate the predisposition to obesity and metabolic syndrome. Cell Metab 22: 516-530, 2015.

BARIATRIC SURGERY RESEARCH

Bariatric Surgery May Help Reduce Urinary

Incontinence: A new study has shown that men and women with severe obesity experienced fewer urinary incontinence episodes after bariatric surgery, up to 3 years following the procedure. One of the many negative health consequences associated with obesity is urinary incontinence, which is the accidental loss of urine, caused by the loss of bladder control. People with severe obesity often do not gain sufficient health benefits from lifestyle interventions alone, and thus may turn to bariatric surgery to help them lose weight and reduce their risk for obesity-associated health conditions. Although bariatric surgery can rapidly lead to weight loss, and weight loss from diet and exercise has been associated with reduced incontinence in overweight and obese individuals, it has not been known if bariatric surgical procedures can reduce urinary incontinence episodes in people with severe obesity. To address this question, scientists with the multi-center Longitudinal Assessment of Bariatric Surgery (LABS) Consortium asked study participants to complete questionnaires designed to assess frequency of urinary incontinence. More than 90 percent of study participants underwent either Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding—two different commonly performed bariatric surgery procedures. Nearly

2,000 participants with severe obesity, 79 percent of whom were women, completed questionnaires within 30 days before bariatric surgery, and annually for 3 years after surgery for most participants. Prior to their surgery, 49 percent of women and 22 percent of men had reported prevalent (at least weekly) urinary incontinence. One year after surgery, the rates of prevalent urinary incontinence significantly dropped, to 18 percent of women and 10 percent of men. At 3 years after surgery, although rates rose to 25 percent of women and 12 percent of men, these were still both significantly lower than pre-surgery levels of prevalent incontinence. The researchers suggest that the improved continence could be a direct result of the dramatic weight loss often experienced by bariatric surgery patients. Supporting this idea, analysis of the results revealed that greater weight loss was associated with better continence, and that the amount of regained weight was associated with increased incontinence. Some study participants regained weight between the first and third years after surgery, which could explain the rise in reported urinary incontinence over that period of time. In addition, the scientists examined other independent factors among the participants, finding that older age, severe walking limitation, and recent pregnancy—known risk factors for urinary incontinence—reduced the likelihood for improvements after surgery. While the results are significant, researchers acknowledge that this observational study did not have a control group for direct comparison, and that self-reported assessments are not always completely accurate. The researchers do note, however, that the questionnaires used in this study have been previously validated for assessing urinary incontinence. The finding that urinary incontinence may be a health benefit of bariatric surgery could help inform people with severe obesity and their health care providers, as they weigh the risks and benefits of surgery as a treatment option.

Subak LL, King WC, Belle SH,....Huang AJ. Urinary incontinence before and after bariatric surgery. *JAMA Intern Med* 175: 1378-1387, 2015.

Redirecting the Flow of Bile to the Distal Small Intestine Could Provide Metabolic Health Benefits Similar to Bariatric Surgery:

A new study in mice suggests that diversion of bile acids directly to the distal segment of the small intestine could lead to weight loss and metabolic benefits that are similar to gastric bypass bariatric surgery. For some people with severe obesity who are unable to lose sufficient weight through lifestyle changes alone, bariatric surgery could be an effective therapeutic option. Roux-en-Y gastric bypass (RYGB) surgery, currently the most common bariatric surgery procedure performed in the United States, connects the upper stomach to the middle part of the small intestine (called the jejunum), so that food bypasses a large portion of the gastrointestinal tract in which digestion and nutrient absorption normally take place. RYGB can have dramatic health benefits, including significant weight loss, improved control of blood glucose (sugar) levels, or even reversal of type 2 diabetes. Recent evidence suggests that bile acids help mediate some of the metabolic effects of RYGB. Bile acids, released from the gall bladder into the upper portion of the small intestine (called the duodenum), normally aid in the digestion and absorption of nutrients, and also act as hormones in the gut, influencing metabolism and other physiological processes.

To determine whether bile acids can directly lead to weight loss and metabolic benefit in the absence of RYGB, researchers tested in male mice different surgical procedures connecting the gall bladder to the three portions of the small intestine: the duodenum (GB-D); the jejunum (GB-J); or the ileum (GB-IL), which is farthest from the stomach. The GB-J and GB-IL procedures diverted bile flow,

while the GB-D procedure did not alter bile flow and served as a surgical control. They compared mice that underwent these procedures with mice that had RYGB, as well as with mice that did not have any surgical procedures. All mice were fed a high-fat diet to induce obesity. At 2 weeks following surgery, the GB-IL mice and RYGB mice consumed significantly less food than mice in the other groups. After 8 weeks, GB-IL mice exhibited sustained weight loss equal to or even greater than RYGB; GB-D and GB-J mice lost weight initially, but regained weight over time and eventually reached the weight of the normal control mice. Total circulating bile acid levels were elevated several-fold in the GB-IL mice over each other group. The researchers then examined various indicators of metabolic health in the different groups of mice. The GB-IL and RYGB procedures led to several health improvements over the other groups, including sustained weight loss, reduced overall body fat, improved blood glucose control and insulin sensitivity, lower levels of circulating fats, and protection from fat accumulation in the liver. Circulating cholesterol levels were only lower in GB-IL mice. By contrast, triglycerides in the blood were at about the same level among all groups. Because the gut microbiome—the community of bacterial species that symbiotically inhabit the gastrointestinal tract in mice and humans—is known to affect bile acid function, the scientists compared the microbiomes of the groups of mice that received bile diversion procedures. They found that 8 weeks after surgery, the pattern of GB-IL gut bacterial species more closely resembled that of lean mice than of the other surgical groups or control obese mice. These results suggest that surgical diversion of bile to the ileum yields many of the health benefits of RYGB, without the risks associated with dramatic alterations to the gastrointestinal tract. However, the researchers point out that there is still risk associated with

surgically diverting bile flow. While promising as a potential treatment for severe obesity, additional research will be necessary to determine if bile diversion surgical procedures could provide similar benefit to humans, or whether these findings could lead to therapeutic approaches that can harness the metabolic potential of bile acids without the need for invasive surgery.

Flynn CR, Albaugh VL, Cai S,...Abumrad NN. Bile diversion to the distal small intestine has comparable metabolic benefits to bariatric surgery. [Nat Commun](#) 6: 7715, 2015.

BURNING CALORIES: BROWN FAT, BEIGE FAT, AND BODY TEMPERATURE

Mimicking a Meal To Reduce Weight Gain:

Researchers have determined that tissue-selective delivery of a molecule called fexaramine (Fex) reduced weight gain and improved the metabolism of mice with diet-induced obesity without changes in appetite. Fex is a specific and potent activator of FXR, a factor that, when activated, “turns on” genes in diverse tissues including the kidney, stomach, intestines, and liver. It is known that FXR plays a complex, but not fully understood, role in metabolism. FXR is selectively activated in the intestine in response to a meal. It was unknown whether experimentally activating FXR only in the intestines could mimic eating a meal and lead to improvements in metabolism without consumption of calories. This selective activation was attractive to scientists because it could potentially avoid side effects that often result from drugs that systemically affect the body.

First, the scientists demonstrated that oral delivery of Fex to male mice resulted in intestinally restricted FXR activation due to its poor absorption into the bloodstream. They then gave the mice daily

treatment of Fex for 5 weeks and fed them a normal or a high-fat diet. Mice on a normal diet showed similar weight gain and metabolic characteristics whether or not they received Fex. However, mice on a high-fat diet who received Fex showed a reduction in weight gain and improved metabolic profiles, including reduced glucose (sugar) and cholesterol levels. The Fex treatment improved insulin sensitivity and glucose tolerance in the mice, as well as reduced levels of inflammatory factors that accompany obesity.

To further understand these effects, the scientists examined the adipose (fat) tissue of the mice. Mammals have different types of fat tissue: calorie-storing white adipose tissue (WAT) is the most abundant; brown adipose tissue (BAT), which burns calories to generate heat; and beige fat tissue, which exhibits some characteristics of classic BAT cells but also has distinct properties, and can appear within WAT depots in response to various triggers. Treatment with Fex led to increased energy expenditure in BAT, increased core body temperature, and the “browning” of WAT; the WAT took on characteristics of energy-burning BAT. Combined with the reduction in diet-induced weight gain and inflammation and improvement in metabolic profiles, these results suggest that Fex activation of FXR in the intestines mimics eating a meal in male mice. The selective activation may mean that Fex is safer than agents that activate FXR throughout the body, thus making Fex an attractive candidate for further development and testing in human clinical trials as a new approach in the treatment of obesity and metabolic syndrome. Further research will also be needed to determine if the results of this study hold true in females.

Fang S, Suh JM, Reilly SM,...Evans RM. Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. Nat Med 21: 159-165, 2015.

A New Role for a Class of Immune Cells in Regulating Beige Fat Development:

Two studies have revealed a critical role for an immunological cell type, called ILC2 cells, in the development and activity of calorie-burning beige fat. Mammals harbor different kinds of adipose (fat) tissue in various regions of the body. White adipose tissue (WAT)—the most abundant type of fat—stores calories, while brown adipose tissue burns calories to generate heat. A third, calorie-burning type of fat, called beige fat, emerges within WAT depots—a process referred to as “browning” of WAT—in response to cold exposure, nervous system triggers, or muscle activity. The metabolic potential of beige fat has led many scientists to believe that it could serve as a target for treatment strategies for obesity and associated metabolic diseases in humans, but the mechanisms controlling beige fat induction are not well understood.

Previous research showed that molecular signals from certain immunological cells within WAT activate pathways that induce beige fat formation. One such signal, called IL-33, has been shown to be present in WAT, and to protect mice from insulin resistance and other metabolic conditions associated with obesity. In an effort to further understand the role of IL-33 in weight gain and metabolism, two research teams recently discovered that, in mice, a type of immune cell, called group 2 innate lymphoid cells (ILC2s), which are known to respond to IL-33, plays an essential role in beige fat induction and energy balance—the state of balance between energy consumption (eating food), energy storage (fat), and energy expenditure (burning fat to fuel activity and generate body heat).

In one study, scientists treated male and female mice with IL-33 and found a robust induction of beige fat cells within areas of WAT under the skin (subcutaneous WAT depots). When exposed to

cold temperature, which triggers the browning of WAT, IL-33-treated mice exhibited a greater increase in overall calorie burning (whole-body energy expenditure) than did untreated mice. The researchers then used mice that were genetically modified to produce a fluorescent “marker” protein exclusively in ILC2s, enabling the scientists to track the formation of these cells as they arise. IL-33 treatment in these mice led to dramatic induction of active ILC2s as compared to untreated mice. In addition, the scientists found that IL-33 treatment led to increased numbers of “adipocyte precursor” cells—cells that could either develop into white or beige fat cells, depending on what signals they receive—in WAT. These precursor cells were characterized and shown to exhibit molecular hallmarks of beige fat, indicating that IL-33 triggers the expansion of adipocyte precursor cells in WAT that are committed to becoming beige fat cells. Moreover, IL-33 treatment in mice genetically modified to lack ILC2s failed to stimulate production of the precursor cells and beige fat cells, indicating a crucial role for ILC2s in the browning of WAT. Together, these results show that IL-33 induces ILC2s in WAT, which promotes the browning of WAT through the expansion of beige fat-committed adipocyte precursor cells. Based on additional experiments in this study and research from other scientists, it is likely that this newly identified pathway works in parallel with other cells and molecules to induce the browning of WAT.

In a separate study, scientists independently demonstrated that IL-33 induces ILC2s in WAT, and further addressed the role of these cells in energy balance using male mice. The scientists fed mice a high-fat diet, which leads to obesity, and found that WAT from the resulting obese mice contained fewer ILC2s than did normal-weight mice. Mice genetically modified to lack IL-33 gained more weight and fat mass on a normal diet than did normal

mice. In addition, mice lacking IL-33 had far fewer beige fat cells within WAT than did normal mice. Mice genetically engineered to lack ILC2s, when treated with IL-33, failed to induce browning of WAT. However, when ILC2s from normal donor mice were transplanted into mice lacking ILC2s, the browning phenomenon in WAT was restored. To identify the possible “browning” signals sent from ILC2s, the researchers compared the genes turned on in mouse ILC2s to those turned on in similar cells (ILC3s) that are not involved in the induction of beige fat. The analysis revealed one gene specific to ILC2s, whose protein product can activate a potential signal called methionine-enkephalin (or MetEnk). IL-33 treatment led to increased production of MetEnk by ILC2s. Mice treated with MetEnk exhibited increased browning of WAT, as well as increased body energy expenditure. Isolated WAT cells treated with MetEnk turned on beige fat genes, suggesting that MetEnk itself can directly promote the browning of WAT. To begin to address whether ILC2s similarly function in people, the scientists compared WAT biopsies from a small number of donors. They found that WAT from people who were obese (six women and one man) contained significantly lower levels of ILC2s than did WAT from people of normal weight (three women and four men).

Together, these studies suggest that IL-33 induces production of ILC2s in WAT. ILC2s then generate MetEnk, which signals the formation and activity of beige fat cells. Based on previous research, it is clear that these cells and signals work together with other immune cell pathways to induce the browning of WAT. While preliminary experiments revealed a correlation between larger numbers of ILC2s and lower body weight in people, additional studies will be needed to continue elucidating the roles of these cells and proteins. If human beige fat development works in a similar manner, IL-33, ILC2s, MetEnk, and their partners and pathways could be useful

therapeutic targets to protect against obesity and metabolic diseases.

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Improved Utility of Mice as Models of Human

Obesity: NIDDK scientists have improved the predictive value of mice as experimental models of human obesity by integrating body temperature into the analysis of factors affecting energy use and regulation. For decades, researchers studying obesity and metabolism have used the mouse as a model experimental system for understanding the mechanisms regulating energy balance, which is governed by a variety of factors, such as energy intake (calories from food), energy expenditure (calorie burning), metabolism, and heat production. To better reflect the complex control of energy use and expenditure in humans and understand how it contributes to weight maintenance and obesity, scientists in the NIDDK's Intramural Research Program used sophisticated technologies in mice to measure and integrate several factors that contribute to energy balance. Included in their analyses was body temperature—a measure that had not been previously integrated in similar studies—as well as the energy effects of physical activity, food intake, and basal metabolic rate. The scientists housed individual mice at 22 degrees Celsius (72 degrees Fahrenheit) for 3 days, and then adjusted the ambient (environmental) temperature to a range from 4 degrees Celsius (40 degrees Fahrenheit) to

33 degrees Celsius (91 degrees Fahrenheit) for 1 day each. For each ambient temperature, they took continuous energy measurements at the light and dark phases, which were both 12 hours each day. (Because mice are nocturnal, they are more active in the dark phase than they are in the light.) They then analyzed the series of energy measurements across different times and environmental temperatures. The scientists found that in male mice, body temperature was constant from 18 to 28 degrees Celsius, but was lower at 4 and 12 degrees Celsius. It was elevated during the dark phase compared to the light phase at all of the ambient temperatures. The light/dark cycle and physical activity, and to a lesser extent ambient temperature, were the factors that most affected body temperature. The researchers found that physical activity actually raised the body temperature that the mice were trying to maintain, as compared with their body temperature during periods of inactivity; the elevation was not just due to an overproduction of body heat from exercise. The researchers then compared heat loss in different living mice (normal, shaved mice, or genetically furless) with that of male or female mice that had just died, and found that fur provides a relatively minor contribution to insulation as compared with physiological mechanisms active while mice are alive. These findings provide a more comprehensive view of how mice respond to different environmental temperatures and reveal the complex interactions between body temperature, environmental temperature, and energy expenditure, which could help scientists enhance the utility of mice as research models of human obesity.

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A Technological Partnership Between the NIH and the USDA Aims To Help People Achieve and Maintain a Healthy Weight



The National Institutes of Health (NIH) and the U.S. Department of Agriculture (USDA) have partnered to add the NIH Body Weight Planner, developed by NIDDK scientists, to the

USDA's SuperTracker online food and activity tool as a goal-setting resource to help people achieve and stay at a healthy weight. Created in 2011, the SuperTracker tool empowers people to build a healthier diet, manage weight, and reduce risk of chronic disease. Users can determine what and how much to eat; track foods, physical activities, and weight; and personalize with goal setting, virtual coaching, and journaling. With science-based technology drawing on years of research, the new addition of the Body Weight Planner in 2015 will now enable SuperTracker's more than 5.5 million registered users to tailor their plans to reach a goal weight during a specific timeframe, and maintain that weight afterward.

The mathematical model behind the Body Weight Planner, an online tool published by the NIH in 2011, was created to accurately forecast how body weight changes when people alter their diet and exercise habits. The Planner's calculations reflect the discovery that the widely accepted paradigm that reducing 3,500 calories will shed one pound of

weight does not account for slowing of metabolism as people change their diet and physical activities. Computer-based simulations used in the online tool were developed in the laboratory of Dr. Kevin Hall, a scientist in the NIDDK's Intramural Research Program. The Planner's calculations more accurately model changes in a person's body by taking into consideration differences between people, such as age, height, weight, amount of body fat, whether they are male or female, and resting metabolic rate. The complex "dynamic" model incorporates these various parameters; the model also accounts for changes in metabolism during weight loss, and the variation in these changes among people. The mathematical model was validated using data from multiple controlled studies in people. Based on this research, the NIH and USDA worked together to incorporate the Body Weight Planner into the SuperTracker to enhance the web-based tool. This technological partnership could assist those striving for a healthier weight—the NIH Body Weight Planner helps users develop a realistic plan for reaching their goals, and the USDA SuperTracker helps them to achieve it.

For more information, please visit the following websites:

NIH Body Weight Planner: www.niddk.nih.gov/health-information/health-topics/weight-control/body-weight-planner/Pages/bwp.aspx

USDA SuperTracker: www.supertracker.usda.gov

