

WHAT FUELS FAT

The human body's ability to store energy as fat seems haywire in a world full of food. Understanding how our complex energy-regulating systems can falter and lead to obesity is revealing new ways to fight excess weight

KEY CONCEPTS

- Our bodies' ability to stockpile energy for future use was critical to survival when food was scarce. Now, in a world of plenty, obesity is the life-threatening problem for an increasing number of people.
- Scientists are working to understand the mechanisms the human body uses to regulate its storage of energy in the form of fat, as well as how these systems can become unbalanced and lead to obesity.
- As the components of this regulatory system are identified, they are providing new targets for drug treatments that could restore energy balance and help to reverse obesity.

—The Editors

By Jeffrey S. Flier & Eleftheria Maratos-Flier

At the dawn of humanity, and for much of our history since, meals were literally catch-as-catch-can. Because humans evolved in a world where food was available only intermittently, survival required that we have the capacity to store ingested energy for times when none was around. Adipose tissue, familiarly known as fat, is the organ specialized for that task.

Our ability to store fat remains essential to life and can allow a person to survive starvation for several months. In very recent human history, however, the amount of energy packed away as fat has been increasing in many populations. When fat storage approaches a level that compromises a person's health, we call it obesity.

In part, this trend is the result of humanity's technological progress—in the face of abundant food and a reduced need for physical activity, it is all too easy to take in more energy than one needs. Yet some people seem to be more susceptible than others to becoming obese when exposed to this plentiful environment, which suggests that variations in individual physiology

may also be influencing how much energy a person consumes, expends and stores as fat.

Many critical variables within the body, such as blood pressure, body temperature, blood sugar and water balance, are tightly controlled by automatic mechanisms, but whether body weight is similarly regulated has long been the subject of vigorous debate. Scientists have only recently begun to make significant advances in identifying pathways of cellular signaling and activity that might participate in such a regulatory system for fat.

These new insights into how the body senses and responds to its energy needs and stores are helping researchers to understand how inherited genetic variations can subtly or powerfully affect those mechanisms and how they can also be upset by environmental influences as well as by excess fat itself. As the discoveries accumulate, scientists gain a clearer picture of the complex physiological systems involved in controlling fat accumulation and new targets for interventions that could help individuals attain greater control in their own battles against bulge.



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Is There a Fat-o-Stat?

Any system of physiological regulation requires a way for the body to sense the quantity of a specific substance present and to translate that information into actions that keep that variable within a desired range. The moment-to-moment energy needs of human cells, for example, are met by glucose, derived from food, circulating in the bloodstream. Normally the body keeps glucose levels within very tight limits. When blood glucose rises, specialized cells in the pancreas detect the change and secrete extra insulin, which triggers responses in muscle and adipose that cause those tissues to take in and utilize more glucose, while the liver responds by decreasing its own glucose production.

The adipose cells convert the excess energy they have taken in to triglyceride, a fatty acid. When food is not available and insulin levels fall, the fat cells release triglycerides back into the bloodstream, where they are transported to the liver and broken down into ketones, which can serve as fuel for muscle and the brain.

Studies of both animals and humans have long suggested that the mammalian body has mechanisms for monitoring the amount of energy it has stored as fat and for regulating that resource to remain near a particular level. If an animal has been at a stable weight, for example, significantly altering its energy intake will produce physical and behavioral changes that appear to be geared toward restoring weight to the previous level. An animal whose food is suddenly restricted tends to reduce its energy expenditure both by being less active and by slowing energy use in cells, thereby limiting weight loss. It also experiences increased hunger so that once the restriction ends, it will eat more than its prior norm until the earlier weight is attained. Likewise, after intentional overfeeding, an animal will start to expend more energy and exhibit reduced appetite, with both states persisting until weight falls to the previous level.

The consequences of having no regulatory system for controlling body weight would be substantial. Just a 1 percent excess of energy consumption over expenditure, for instance, could cause an average-size man to gain 60 pounds over 30 years. But do humans have an active system that maintains our stored energy balance, analogous to the mechanisms that control circulating glucose levels? The answer is yes. Though imperfect, such a system does exist and investigators, including our respective research groups, are making encouraging

progress toward identifying its components.

As the pieces of this puzzle come together, a general observation can be made that may disappoint but will probably not surprise anyone who has struggled to lose weight: the human body's regulation mechanisms seem to be slightly biased in favor of preserving fat rather than eliminating it. In light of fat's value to survival, this tendency makes evolutionary sense. Over time, evolution could even have favored slight variations in relevant genes that produced the "thriftiest" management of precious energy stores.

Differences in obesity susceptibility among subgroups of people can also sometimes be tied to differing versions of particular genes. Very recently, for example, genome-wide scans performed on nearly 40,000 study subjects around the world identified a gene called *FTO* whose variation was linked to obesity. In every country studied, carriers of one version of the *FTO* gene were on average three kilograms heavier than others in their population and had nearly double the risk for becoming obese. At this point, the function of the *FTO* gene and how it might promote obesity are completely unknown, but its association with increased body weight suggests that it might have a role in weight regulation.

Genes do not function in a vacuum, however, and the genes of the human population in general have not changed over the past few decades. Explaining the relatively recent epidemic of obesity will therefore require a much better understanding of how variant genes interact with a person's environment to influence body weight as well. Some important environmental factors are obvious, such as the reduced need for physical exertion to survive and the increased quantity and quality of available food. Many other environmental variables are less self-evident and still poorly comprehended, such as the effect of nutrition during fetal development on body weight in later life. Stress, sleep deprivation and even viral infections and the composition of benign microbial communities within the body are additional factors that may affect an individual's fat regulation.

Identifying the genes that are normally involved in the body's management of fat is nonetheless allowing researchers to clarify some of the fundamental mechanisms at work. Not surprisingly, following the trail of protein signals encoded by those genes often leads to the master command center for many physiological processes, the brain.

[THE AUTHORS]



Jeffrey S. Flier and Eleftheria Maratos-Flier are husband and wife, and each heads a laboratory within the division of Endocrinology, Diabetes and Metabolism at Beth Israel Deaconess Medical Center in Boston. Both are professors of medicine at Harvard Medical School, and Flier became dean of that school on September 1. The authors investigate the physiology of obesity and diabetes, and each has uncovered key components of the systems that regulate the body's energy balance. Flier is especially interested in the functions of leptin and insulin, both in health and disease, and Maratos-Flier has characterized the multiple roles of melanin-concentrating hormone. Recently, she also identified the critical part played by a liver protein in triggering fat cells to release stored energy.

COMMAND CENTER

The human brain regulates weight by integrating information about the body's energy needs and the status of its stores, then initiating changes in behavior and energy processing in response. Specialized brain areas stimulate feelings of appetite or satiety to cause more energy, in the form of food, to be taken in or to terminate a meal. Over time, the brain can also raise or lower the body's overall energy use and reallocate energy away from systems, such as reproduction, that are not essential for short-term survival.

INFORMATION

STORED ENERGY STATUS

- Circulating leptin, a hormone generated by fat cells, indicates how much fat they contain

METABOLIC STATUS

- Circulating glucose represents energy immediately available to cells
- Various indicators of liver activity signal that ingested energy is being processed

FEEDING STATUS

- Neural and chemical signals from the gut indicate whether digestive organs are full of food

RESPONSES

ALTER BODY'S ENERGY INTAKE

- Direct meal timing and size through appetite and satiety signals

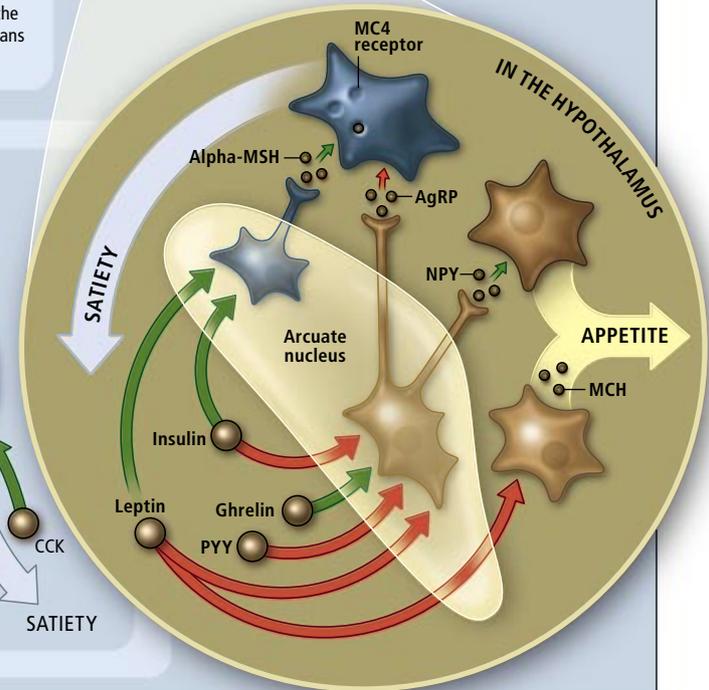
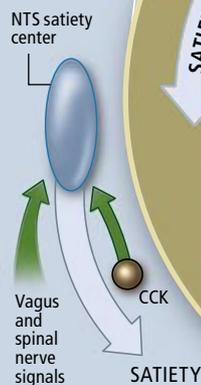
ALTER BODY'S ENERGY USE

- Reduce or increase physical activity
- Slow or speed cellular energy use
- Suppress or restore growth, reproduction and immune function

APPETITE CONTROL

In the arcuate nucleus (ARC) of the hypothalamus (*far right*), indicators of energy and feeding status in the form of gut peptides such as ghrelin and PYY, and hormones including leptin and insulin, act upon groups of neurons associated with appetite (*brown*) or satiety (*blue*). Each substance either stimulates (*green arrows*) or dampens (*red arrows*) the neurons' responses. When stimulated, the ARC cells release peptides such as NPY, AgRP and alpha-MSH, which act on a second set of hypothalamic neurons that induce appetite or satiety. Leptin and insulin act through both types of cells simultaneously to promote satiety while suppressing appetite. Nerve signals and the gut peptide cholecystikinin (CCK) also communicate feeding status directly to the nucleus tractus solitarius (NTS), a satiety center (*right*) in the brain stem.

IN THE BRAIN STEM



Information Integration

Very little happens anywhere in the human body without the brain playing a part by monitoring the situation and exerting its influence. The brain can thus be expected to have a critical role in regulating weight through its direction of appetite, motivation and physical activity, as well as its management of how energy is allocated within the body.

Indeed, a small region at the base of the brain called the hypothalamus has been known for many years to be central to these energy-regulating activities. In animal studies, placing tiny lesions in this area can cause obesity or leanness depending on their precise location. Such observations have led to certain parts of the hypothalamus being labeled as "satiety" or "feeding" centers.

By stimulating appetite or the feeling of satiety, the brain can directly manage the body's energy balance from day to day. Over longer periods, signaling from the brain can also suppress nonessential systems, such as growth and reproduction, when fat stores are too low and energy must be conserved for survival. For the brain to command any of these mechanisms in response to the body's needs, however, it must receive updated information about how much stored energy is available.

What might this signal be, and how might it work? Many different molecules have been shown to influence appetite as their levels in the bloodstream rise and fall, including various breakdown products of food, such as glucose, and gut-derived hormones, such as insulin and cholecystikinin (CCK). But a critical regulator

MIXED MESSAGES

Important signals that stimulate energy-regulating responses by the brain and tissues of the body emanate from digestive organs and from fat itself. They constitute both short-term indicators of the body's feeding status, such as nerve impulses and secreted peptides generated just before and after meals, as well as longer-term information about the status of the body's stored energy. In addition to leptin, which reports body fat levels to the brain, fat cells secrete nearly a dozen other hormones—collectively known as adipokines. At least two of these directly alter tissue responses to insulin, which regulates how much glucose cells take in and use as fuel.

● EMPTY STOMACH

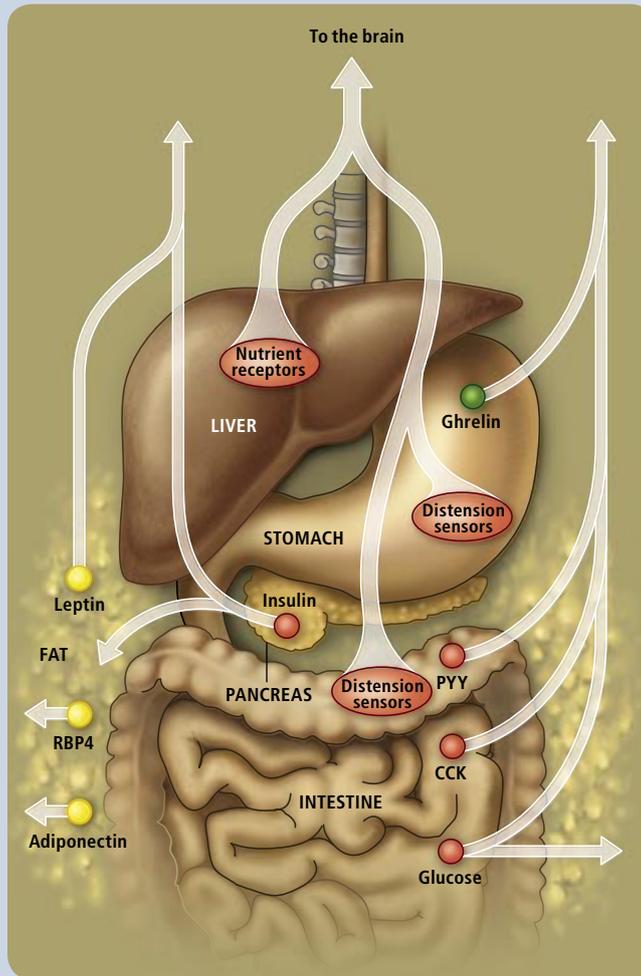
- Ghrelin is produced by glands in the stomach 20 to 30 minutes before eating. The trigger for its release is unclear, but ghrelin may signal the stomach's readiness for a meal to the brain

● FULL OF FOOD

- Stomach and intestinal distension is transmitted via spinal and vagus nerves to the brain
- Nutrient receptors in the liver also send neural signals indicating that ingested food is being broken down
- Circulating levels of insulin, secreted from the pancreas, and glucose, derived from ingested food, reflect feeding status and readily available energy
- Cholecystokinin (CCK) and PYY are peptides manufactured by the intestines and secreted into the bloodstream after a meal

● STORED ENERGY

- Leptin is manufactured by adipose tissue in amounts proportionate to the fat it contains
- Secreted retinol-binding protein 4 (RBP4) also rises with fat levels and reduces other tissues' responsiveness to insulin
- Adiponectin enhances cellular responses to glucose and insulin, but this adipokine's levels fall in obesity



Discovery of leptin opened the door to exploration of a whole new biological pathway.

of how much energy is maintained in storage proved elusive until Jeffrey Friedman of the Rockefeller University and his colleagues discovered leptin in 1994.

Decades earlier a spontaneous syndrome of severe obesity with increased appetite and decreased energy expenditure appeared in certain mice bred at the Jackson Laboratory in Maine. Because a mouse had to inherit the trait from

both parents, the syndrome itself was called ob/ob. Despite hundreds of studies attempting to understand obesity in these mice, Friedman's group was the first to identify the inherited gene mutation responsible. The researchers also determined that the newly identified gene was predominantly active in fat cells and gave rise to a protein that was not made in functional form in the mice harboring the ob mutation. The obesity

syndrome seemed to be caused by the absence of this substance.

The researchers named the protein leptin, from the Greek root *leptos*, for “thin,” and quickly demonstrated that replacing the missing leptin by daily injections lowered the weight of affected mice by reducing their appetite and increasing their energy expenditure. Very soon, others furthered this remarkable discovery by finding a similar loss-of-function mutation in the human leptin gene among people with extremely rare cases of severe, early-onset obesity. Administering leptin to these subjects helped them to lose weight just as it had the mice.

These experiments demonstrated for the first time a physiological system whereby fat cells produce a hormonal signal that reflects their state of energy storage—the more triglyceride a fat cell contains, the more leptin it generates—and to which the brain responds by altering appetite and energy expenditure. When this energy-status signal is absent, either because the genetic mutation prevents functional leptin proteins from being manufactured or because the body actually has low fat stores, the brain believes that the body is starving and behaves accordingly by promoting hunger and energy conservation.

The discovery of leptin opened the door to exploration of a whole new biological pathway of cellular signaling and responses. The brain was clearly a major target of leptin secreted into the bloodstream by fat cells, and researchers, including ourselves, have begun to learn many of the detailed neural circuits and cell types through which leptin acts. As might be expected, many of them are in the hypothalamus [see illustration on page 75].

In a structure called the arcuate nucleus of the hypothalamus, within the area previously identified as a satiety center, leptin simultaneously affects two neighboring neuron populations that control appetite in opposite ways. One set of neural cells produces a peptide called alpha-MSH that reduces appetite and, consequently, body weight. The other set of neurons produces two neuropeptides, NPY and AgRP, both of which stimulate feeding and promote obesity. Leptin’s interactions with both these cell groups are quite elegant. Neurons that produce MSH connect to neurons elsewhere in the hypothalamus that carry a surface protein known as the melanocortin 4 receptor (MC4R), whose activation reduces appetite and promotes weight loss. AgRP, the peptide that promotes feeding, is an antagonist of this receptor, meaning that it

prevents receptor activation. Thus, leptin acts to trigger MC4 receptors both by stimulating them directly via the MSH-producing neurons and by inhibiting their antagonist.

At the same time, leptin also affects the brain area previously viewed as a feeding center, the lateral hypothalamus, in an interesting way. One group of cells in that region produces a small protein called melanin-concentrating hormone (MCH). In 1996 our research group discovered that levels of this peptide are raised in the ob/ob mouse type, suggesting that leptin normally inhibits production of the peptide. We also established that increased MCH promotes food intake and obesity and found that even ob/ob mice, if they lack the ability to manufacture MCH, are substantially less obese. We had thus found another clear example of the physiological system through which leptin acts as a signal that regulates hypothalamic neuropeptides, which in turn exert control over appetite and energy balance.

The same cells and circuits affected by leptin, moreover, are also acted on by numerous other circulating factors. The hypothalamus and related brain areas integrate all this information coming from diverse sources to produce a real-time picture of the body’s energy status and orchestrate responses to manage energy resources. For a better understanding of what these signals, including leptin, are telling the brain, researchers are also studying how and where they originate.

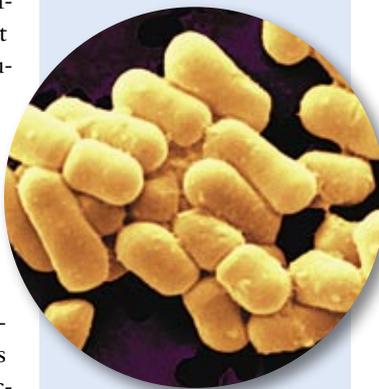
Visceral Responses

A full belly is a simple but sure sign that the body has recently taken in energy as food, and stomach distension has long been known to reduce appetite. One way that this physical state is communicated to the brain is via distension-sensitive nerve fibers that carry signals from the stomach and intestine, ultimately reaching appetite-control centers. Neural signals reflecting the energy-processing state of the liver may also be transmitted to the brain via the vagus nerve.

Insulin is also believed to act directly on neurons in the hypothalamus to suppress appetite, and several other hormones manufactured in the intestine and released into the bloodstream after meals are known to travel to the brain and produce the same effect. Among these, cholecystokinin is an important factor in causing short-term satiety, but its actions are limited to signaling termination of individual meals. Another peptide called PYY, released from the small intestine, does the same.

HUNGRY HELPERS

A person’s internal “environment” might influence how much of a meal gets turned into body fat. Trillions of benign microbes inhabit the human gut, helping to break down food, but the mix of species residing in different individuals can vary. Researchers at Washington University in St. Louis have shown that in obese people, a division of bacteria known as firmicutes predominates, whereas bugs from the division bacteroidetes are more populous in lean individuals. Moreover, the “fat” microbe set has the ability to extract more nutrients, hence calories, from food than the lean set. Whether the difference in microbiota is a contributor to obesity, a consequence, or both, remains to be determined.



FRIENDLY FIRMICUTES:
Lactobacillus fermentum

So far only one gut-generated peptide that acts to spur appetite has been identified: ghrelin is made and released in the stomach before feeding and may signal anticipation of a meal [see illustration on page 76].

In people who are already obese, it is possible that dysfunctional generation of such short-term signals indicating whether food has recently been consumed, or is about to be, could skew the brain's energy-regulation mechanisms. Losing as little as 10 pounds, for example, can cause ghrelin output to rise, provoking increased hunger.

Over the long term, signals emanating from body fat itself might also contribute to abnormal energy management. For many years, fat was viewed primarily or exclusively as a passive site for energy storage and release in the form of fatty acids, but with the discovery of leptin, adipose tissue was recognized as an endocrine gland whose activity has widespread effects on health [see box on opposite page].

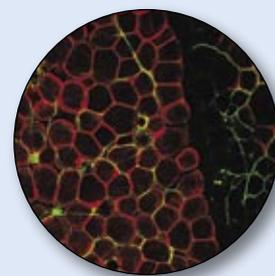
Leptin is still the only fat-derived hormone conclusively shown to participate directly in regulation of fat stores, but a group of others, often collectively referred to as adipokines, are under investigation as well. Adiponectin, for example, is a molecule produced and secreted exclusively by fat cells that normally circulates in the bloodstream in high concentrations. Adiponectin levels are lower than average in obese subjects for unknown reasons, and experimental mice lacking adiponectin are extremely heavy, although the mechanism underlying this effect is also mysterious. Some intriguing research suggests that under certain circumstances adiponectin might have a direct appetite-stimulating effect in the brain. Although such findings are very preliminary, they point to the possibility that adiponectin, too, could serve as a direct signal from fat cells to the brain indicating a need to take in energy. As such, it might offset leptin's appetite-suppressing role in energy regulation.

Origins of Obesity

Much remains to be discovered about the extremely complex circuitry regulating the body's energy use and storage as well as how disruptions within it might help perpetuate existing obesity or predispose an individual to becoming obese in the first place. The discovery of leptin in mice led to the identification of a few humans whose severe obesity could be explained by a single genetic defect. Such "monogenic" obesities are quite rare but very informative. For example, a handful of patients have been identi-

SELF-REGULATING CELLS?

In obesity, overstuffed fat cells excrete more leptin, a signal of abundant energy stores to which the brain responds by cutting appetite. But do fat cells also put out calls for more energy when they are running low? Research published in July indicates that another hormone generated by fat cells, adiponectin, might play that role. Takashi Kadowaki and his colleagues at the University of Tokyo showed that in mice, fasting raises adiponectin levels in spinal fluid and the hormone's presence in the central nervous system triggers the brain's release of the appetite-stimulating peptide NPY. If adiponectin is confirmed to be a starvation signal, to which the brain responds by increasing food intake, then it would represent the second fat-generated molecule directly involved in regulating fat stores.



FAT CELLS in lean (*top*) and obese (*bottom*) mice.

fied with severe obesity attributable to mutations in the genes for leptin, the leptin receptor, or POMC, a precursor of the appetite-depressing hypothalamic peptide MSH.

Mutations that cause loss of functioning MC4 receptors—the targets of MSH—are also very important, accounting for between 3 and 5 percent of patients with severe obesity. In most of those individuals, only one of two copies of the gene is affected, leaving them with about 50 percent of normal MC4 receptor function.

The majority of people with obesity, however, have no known genetic mutations that could explain their condition. Moreover, their leptin levels are actually higher than those of lean individuals, which sounds counterintuitive if leptin is supposed to cause appetite suppression. Indeed, this discovery led to the idea that most obese patients may have leptin resistance—for some reason, leptin's signal that fat stores are abundant is not being heard by some part of the energy-regulation pathway. Consistent with this theory is the fact that attempts to administer leptin therapeutically have produced disappointingly poor responses in typical obese patients lacking specific leptin-associated gene mutations.

Finding the molecular basis for leptin resistance is therefore a matter of substantial research interest. Two proteins have been implicated strongly as contributing to leptin resistance by acting in the brain and possibly in peripheral tissues. One is called SOCS3 and is produced by hypothalamic neurons that normally respond to leptin. SOCS3 can block leptin's ability to signal to those cells. The other protein, PTP1B, squelches leptin signaling inside the cells. In mouse experiments, reducing levels of SOCS3 or PTP1B in all tissues, or even just in neurons, makes mice more sensitive to leptin and resistant to obesity. The precise role of these proteins in human leptin resistance is still unknown, but based on these observations in animals it is tempting to speculate that such molecules produced by leptin-sensitive neurons serve the purpose of modulating leptin signaling so that the cells do not become overwhelmed by it. In obese individuals, chronically high leptin levels could therefore cause these proteins to start overcompensating to protect the cells, initiating a cycle of increasing resistance to leptin signaling.

Such physiological feedback mechanisms could help perpetuate and worsen obesity, and variations in genes involved in fat-regulating pathways may have a similar role in unbalancing the system. Indeed, we believe that varia-

Fat's Fuzzy Role in Disease

A clear association between obesity and a variety of serious illnesses, including diabetes, hypertension, cardiovascular disease and even cancer, has been established, although many aspects of the relation between fat and illness are still unexplained. The most common medical definition of obesity is nonetheless based on evidence of adverse health effects in people above certain weights. The body mass index (BMI) is calculated as a person's weight in kilograms divided by height in meters squared. Because higher mortality is seen at BMIs greater than 30, that number has become the accepted cut-off for obesity. A BMI between 25 and 30 is called overweight, reflecting some connection with adverse health effects.

These epidemiological relations between BMI and illness can vary in different subpopulations, however. And no precise number can allow doctors to determine what amount of excess fat will cause illness in a given patient. Some people experience health problems at the relatively low BMI of 25, whereas others remain healthy at BMIs higher than 30 [see "Can Fat Be Fit?" by Paul Raeburn, on page 70].

Nor does all fat appear to have equal effects. Adipose tissue accumulates underneath the skin in most body areas, as well as in and around internal organs, especially in the abdomen. Many studies strongly suggest that diabetes and cardiovascular diseases in particular are tightly linked to that intra-abdominal, or visceral, fat. In some cases even significant excess fat in the hips and thighs—producing the proverbial "pear" shape—is relatively unlikely to cause those diseases when excessive abdominal fat is not also present. Conversely, excess abdominal fat is associated with diabetes and other metabolic imbalances, even in the absence of abundant lower-body fat, as in the "apple"-shaped body type.

The basis for the influence of location on fat's health effects is not

fully understood. One theory focuses on the fact that abdominal fat is well placed to release fatty acids and possibly other substances and signals into the portal vein that directly bathes the liver, thereby potentially affecting the functioning of that critical organ. A second theory is based on the fact that fat depots in different parts of the body generate varying amounts of certain chemical signals, and the higher relative volumes emanating from visceral fat may account for its more adverse effects.

Several specific fat-generated signals are also strongly implicated in obesity-related health problems. Adipose tissue produces triggers of inflammation, for example, which could contribute to risk for cancers, cardiovascular disease, diabetes and other immune disorders. The hormone adiponectin, in contrast, has desirable actions in several tissues to improve glucose and lipid processing by cells. Because circulating adiponectin levels fall in obesity, however, the loss of its beneficial effects is associated with the development of insulin resistance, which contributes to diabetes, and vascular disease. A more direct role in insulin resistance is attributed to the adipokine known as retinol-binding protein 4 (RBP4), which fat cells manufacture in greater amounts in obesity. Animal studies show that RBP4 causes liver and other cells to become less sensitive to insulin. A very recent report also confirmed that visceral fat generates greater amounts of RBP4 than subcutaneous adipose tissue elsewhere in the body.

As these few examples illustrate, many of the same molecules and mechanisms under investigation for their role in the body's energy regulation are also involved in other processes vital to health. Advances in understanding obesity will likely result in new insights into obesity-related diseases and their treatment as well.

—J.S.F. and E.M.-F.

APPLES ARE UNHEALTHY when the word refers to body shape. Excess abdominal fat indicates excessive fat packed in and around internal organs, a situation strongly linked to metabolic and cardiovascular disease. In contrast, fat accumulated mainly on hips and thighs, creating a "pear" shape, is less likely to cause illness.



tions in genes that influence body weight through as yet undiscovered mechanisms are a likely source of at least some susceptibility to obesity. Whether there are many such genes whose variation affects weight to a small extent or a few dominant genes whose variation affects weight in most people remains to be seen. With powerful techniques for scanning human genes within large populations becoming more widely available, discovery of new weight-regulatory pathways and new insights into known mechanisms

is bound to accelerate. At present, however, the prevalence of obesity and its complications are continuing to rise, making it clear that highly effective therapies are not yet available.

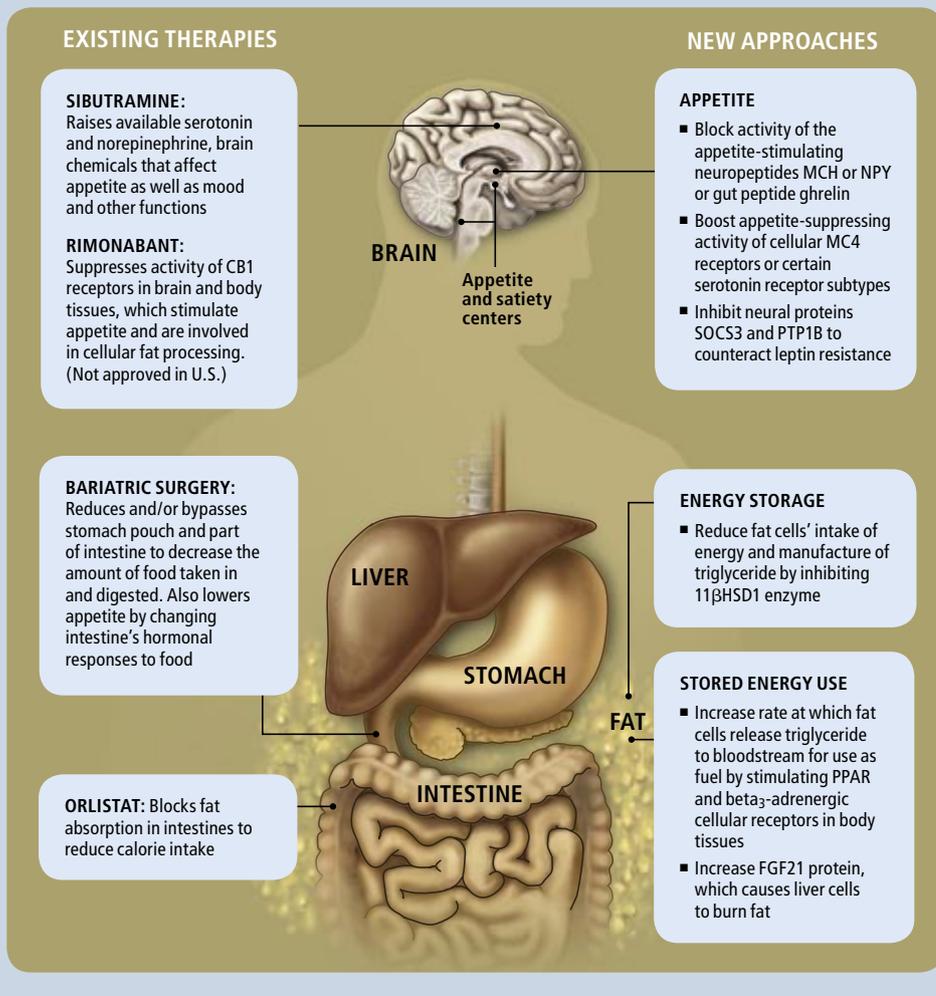
Intervening in Obesity

Simple recommendations such as reducing food intake, changing the composition of one's diet and increasing physical exercise are always appropriate for an obese person. And by themselves, such behavior changes can help individu-

OVERRIDING OBESITY

As the mechanisms that can give rise to obesity become clearer, so do the reasons why losing body fat and keeping it off through behavioral changes alone can be difficult for many individuals. Existing therapies are only modestly effective, and developing new drugs that are safe for prolonged use has been difficult because energy-regulation systems are intertwined with other vital processes in the body and brain, creating a risk of serious side effects. Therapeutic approaches currently in development attempt to more precisely target the molecules and mechanisms that control how much energy the body takes in as food or how much energy it stores and burns.

Successful therapy for obesity will eventually involve multiple drugs acting through independent pathways.



als lose up to 10 percent of their body weight, although maintaining that weight loss is often difficult.

Bariatric surgery is now performed on hundreds of thousands of patients every year. In general, these operations either tie off part of the stomach with a band to limit its size or actually reroute the gut to both reduce the stomach pouch and bypass part of the intestine. Both procedures are substantially more successful than any current drug therapies at promoting and maintaining weight loss. Recent research also sug-

gests that gastric bypass may cause a reduction in appetite, in part by altering levels of gut hormones such as ghrelin and PYY, which indicates that drugs to accomplish the same end might someday substitute for these operations in many patients.

Any new drug to treat obesity will be held to very high standards of efficacy, tolerability and safety. Because the pathways regulating energy storage are so critical to other processes in the body and brain, developing drug interventions that meet all those criteria is challenging. Unfor-

tunate experiences with past drug candidates that were effective but ultimately proved to be addictive or unsafe could in fact push regulatory agencies to be even more demanding than may seem reasonable. In addition to treating obesity by reducing body fat content, a drug will have to improve obesity-associated complications, such as diabetes and hypertension, or at least not cause them to become worse. Any therapy will also have to be safe for extended use because stopping treatment would likely allow weight to return to previous levels. A high risk exists as well for obesity drugs to be misused by people seeking inappropriately low body weights for nonmedical reasons.

Just recently, a new medication that has been available in Europe for some time, rimonabant, failed to gain approval from U.S. Food and Drug Administration advisers because of concern about increased incidence of depression and anxiety in people taking it. The drug works by blocking activation of a cell-surface receptor in the brain and peripheral tissues known as CB1. This receptor mediates the “munchies” brought on by smoking marijuana, as well as the actions of lipid molecules made in various tissues. The trade-offs between safety and efficacy in using this class of compounds over an extended period are therefore not yet clear.

At present, only two prescription drugs are approved in the U.S. for long-term use to treat obesity. Sibutramine, available since 1997, acts to prolong the exposure of neurons in the brain to the neurotransmitters norepinephrine and serotonin, resulting in reduced appetite and modest weight loss. This drug’s use is limited by the fact that blood pressure and pulse tend to rise rather than fall during therapy. Orlistat, available since 1999 and now offered in an over-the-counter form under the brand name alli, lowers an individual’s total calorie intake by acting in the gut to reduce fat absorption, with modest effects on weight and obesity complications.

Many other approaches to the development of obesity drugs are being pursued based on the numerous pathways for regulating appetite and weight that have been discovered in recent years. Potential therapies include inhibitors of the appetite-stimulating molecules MCH, NPY and ghrelin, appetite-suppressing mimics of PYY, and activators of the melanocortin 4 and serotonin receptor subtypes. Any of those options would be targeted toward lowering energy intake, as the existing drugs do. But because the body tends to compensate for fat loss by going

into energy-conservation mode, complementary drugs that boost the rate at which energy is expended might also be necessary.

Several research groups are looking into ways of increasing the rate at which fat cells release stored energy or of preventing its storage from taking place. One approach focuses on stimulating a class of cell-surface receptors—known as beta₃-adrenergic receptors and PPAR nuclear receptors—which trigger tissues’ release of a substance called uncoupling protein 1. That signal is a call for energy, which is heard by certain fat cells and increases the rate at which they send triglycerides back into the bloodstream. Yet this technique may work only on a special type of fat tissue known as brown adipose, which is abundant in rodents and in newborn human infants, but by adulthood very few brown adipose cells remain in human fat.

Another promising approach involves blocking enzyme activities that promote fat storage. One example, the enzyme 11 beta HSD-1 (11βHSD1), causes the steroid cortisol to be converted from a dormant form to a biologically active one inside adipose and liver cells. This locally active cortisol, in turn, prompts those cells to manufacture more triglyceride. Our laboratory group has shown that experimental mice overproducing 11βHSD1 in their adipose cells also generated excess corticosterone (the mouse version of cortisol) in those cells and grew to be significantly obese. Interestingly, the mice developed abdominal obesity in particular, as well as diabetes, high blood pressure and high blood lipids, a suite of symptoms resembling the human condition known as metabolic syndrome.

Although studies of obese human subjects have yet to produce such a clear-cut association between 11βHSD1 activity and excess fat storage, inhibitors of that enzyme already exist and are in development for use in treating metabolic syndrome. They may prove to be useful interventions for obesity as well.

Many experts believe that successful drug therapy for obesity will eventually involve multiple drugs acting through independent pathways, in combinations tailored to individual patients, as is now the case for treating hypertension and diabetes. Of course, as with other common diseases such as hypertension, it would be preferable to treat people with changes in diet and lifestyle alone. But if that approach fails, and morbid consequences result, safe drug therapies would be no less appropriate for obesity than for other illnesses. ■

MORE TO EXPLORE

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