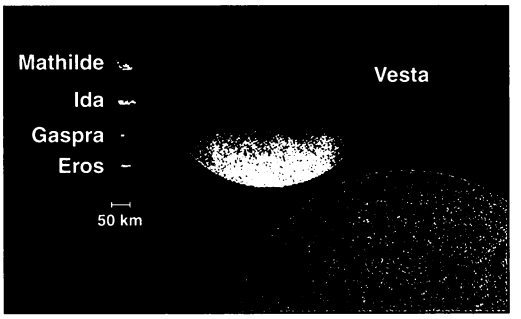
the 34-km-long asteroid cataloged as 433 Eros (see the figure, this page) (*14*). Now entering the second half of its year-long assignation, NEAR is returning a bounty of information about the asteroid's surface morphology, composition, topography, and internal structure (*1*). Eros is likely a fragment of a once larger parent; the collision that spawned Eros may have set its course for the inner solar system. Why Eros lacks small craters, why it has a remarkably uniform color, and how it maintains a seemingly homogeneous but porous interior remain to be resolved.



Off to asteroid worlds. A growing album of small asteroids have now been encountered by spacecraft (**left**). All of them are likely collision fragments from once larger parent bodies. The largest asteroids, such as the 900-km Ceres and 500-km Vesta (**right**), are sizable enough to be direct protoplanetary survivors that can give clues about the solar system's beginnings. These worlds are premier targets for exploring our planetary origins.

NEAR's long-term residence at Eros also provides the opportunity for performing the first ever in situ elemental abundance analysis of an S-class asteroid. Early results from the x-ray spectrometer reveal elemental ratios that are forging the first direct link between S asteroids and their long suspected ordinary chondrite analogs. These findings come at a time when other spacecraft (*15*), telescopic (*16*), and laboratory (*17*, *18*) research has increasingly attributed the subtle reddening of spectral slopes and the muting of absorption bands for ordinary chondrite materials to a "space weathering" process. Confirmation awaits results from the complementary gamma-ray spectrometer, and many details of the space weathering mechanism and time scale remain to be worked out, but NEAR may be close to completing a long chapter on asteroid-meteorite relationships.

As asteroids start their third century, they are emerging from the astronomical realm into the domain of geology and geophysics. Key objectives for asteroid science will be to establish even stronger ties to the origin and geologic context of our meteorite samples and to probe farther back to the earliest stages of protoplanet formation and evolution.

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2. A numerical relationship found by Johann Titius and popularized by Johann Bode in 1772 gives approximate distances to the planets as measured in astronomical units (AU). One AU is the average Earth-sun distance equal to 1.496×10^8 km. The sequence is $0.4 + 0, 0.3 \times 2^n$, where $n = 0, 1, 2, 3, 4, 5$, and 6, yielding 0.4, 0.7, 1.0, 1.6, 2.8, 5.2, 10.0, and 19.6 for Mercury through Uranus, with no 18th century planet known at 2.8 AU.
3. Letter from Piazzi to Barnaba Oriani in Milan, dated 24 January 1801. Modern historical account given by C. J. Cunningham, *Introduction to Asteroids* (Willmann-Bell, Richmond, VA, 1988).
4. Ceres was the Roman goddess of harvests.
5. An ephemeris (plural: ephemerides) is a table listing specific data for a moving object as a function of time. Ephemerides usually contain right ascension and declination, apparent angle of elongation from the sun, and brightness of the object; other quantities frequently included are the object's distances from the sun and Earth, phase angle, and moon phase.
6. Two planetary objects are in resonance if the ratio of their orbital periods can be expressed by integers. For example, the Kirkwood gap at 2.5 AU corresponds to the location where an object orbits the sun exactly three times faster than Jupiter, giving the integer ratio 3:1.
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PERSPECTIVES: BIOMEDICINE

Staying Slim with Insulin in Mind

Michael W. Schwartz

When Banting and Best first administered insulin to patients with uncontrolled diabetes, they established its crucial importance in the regulation of blood glucose concentration. Secreted by the β-islet cells of the endocrine pancreas, insulin exerts its glucose-lowering effects by stimulating glucose uptake in tissues such as skeletal muscle, suppressing fatty acid release from adipose (fat) tissue, and inhibiting production of glucose by the liver (see the figure). Muscle, liver, and fat, therefore, are widely viewed as the principal "insulin-sensitive" tissues in the body. The brain, in contrast, has historically been considered "insulin-insensitive" because its ability to use glucose does not require insulin. Therefore, the notion that insulin participates in the central nervous system (CNS) control of food intake and body weight was received with a good deal of skepticism when it was first proposed by Woods and Porte more than 20 years ago (*1*). Since then, however, support for this hypothesis has steadily accumulated, including the demonstration that insulin is transported across the blood-brain barrier, that it is effective in suppressing food intake when given directly into the brain, and that insulin receptors are concentrated in brain areas involved in energy homeostasis (*2*). Now, Brüning and colleagues (*3*) provide important evidence to support this hypothesis with their report on page 2122 of this issue. They show that mice lacking insulin receptors in the brain have an increased body fat content (adiposity), demonstrating that insulin signaling in the brain is essential for normal regulation of adiposity.

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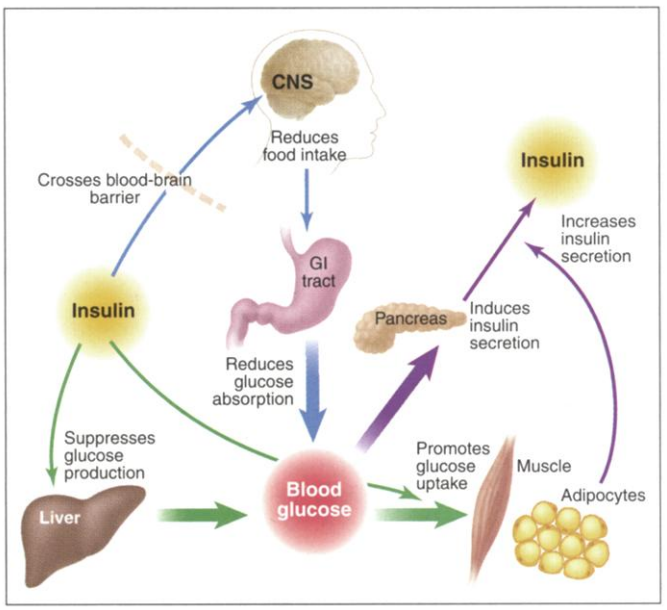
The hypothesis that body fat stores are subject to negative-feedback regulation was formally introduced by Kennedy in 1953 (*4*). He proposed that humoral signals, generated in proportion to body fat stores, act in the brain to lower food intake and body weight. Hence, weight loss induced, for example, by restricting food intake was suggested to decrease circulating "adiposity signals" and thereby to increase the drive to eat until the deficit in body adiposity is corrected. To qualify as an adiposity signal, candidate molecules should circulate and traverse the blood-brain barrier at levels proportionate to body fat content. Within the brain, they should influence the activity of key neurons to promote anorexia and weight loss, and a deficiency of such signals should stimulate feeding behavior. Insulin was the only known molecule to meet these criteria until the discovery in 1994 of leptin (*5*), a hormone secreted by fat cells (adipocytes)

that also circulates at levels proportionate to fat stores and acts in the brain to reduce food intake and body weight.

Several observations seem to contradict the notion of insulin as a physiological signal to the brain that promotes weight loss. For one, insulin deficiency in type 1 diabetes does not cause weight gain, but rather is associated with severe, progressive weight loss. This apparent paradox is reconciled by recognizing that in addition to its effects on blood glucose and food intake, insulin is a potent stimulus for the synthesis and storage of fat. Thus, untreated insulin-deficient type 1 diabetes is characterized by the expected increases in blood glucose (hyperglycemia) and food intake (hyperphagia), but ingested calories are not stored as fat and instead are expended or lost in the urine. Therefore, severe insulin deficiency does not coexist with weight gain, as insulin is required to maintain and increase energy storage in the body. This situation contrasts sharply with the severe obesity syndrome that accompanies leptin deficiency (*5*).

Whereas leptin deficiency and insulin deficiency have opposing effects on body weight, their effects on food intake and hypothalamic function are similar. Hyperphagia occurs in both conditions and is associated with increased hypothalamic signaling by orexigenic (appetite-stimulating) peptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), and decreased signaling from anorexigenic peptides such as melanocortins (*6*). Despite pronounced differences in body fat storage, therefore, the consequences of reduced CNS signaling by leptin and insulin parallel one another closely.

Thus, insulin enhances fat storage through stimulation of the adipocyte, while promoting weight loss through leptin-like actions in the brain. One way to investigate the specific contribution of brain insulin signaling to the control of body adiposity is to delete insulin receptors in the brain using Cre-loxP genetic engineering technology (*7*). The hypothesis that insulin is an adiposity signal to the CNS predicts that a selective loss of neuronal insulin receptors should induce excessive fat storage. The finding by Brüning and co-workers (*3*) that mice with a neuron-specific deficiency in insulin receptors (NIRKO mice) have increased body fat content and are predisposed to the obesity-promoting effects of a high-fat diet provides direct support for this hypothesis. As these responses are mediated only in part by increased food intake (detected in female but not male mice consuming a regular chow diet), brain insulin signaling appears to be essential for normal control of both energy intake and energy expenditure.



Insulin weighs in. Insulin regulates blood glucose and body adiposity. **(Left)** Insulin lowers blood glucose concentration by suppressing its production by the liver and promoting its uptake into "insulin-sensitive" tissues such as muscle and fat. Insulin also crosses the blood-brain barrier to enter the CNS, where it reduces food intake and consequently reduces absorption of glucose and other nutrients into the body. **(Right)** Glucose-induced insulin secretion from the pancreas increases in proportion to body adiposity, owing to the capability of expanding fat stores to induce resistance to insulin's glucose-lowering effects.

The energy-deprived state activates a host of adaptive neuroendocrine responses in addition to a heightened drive to eat, and reduced signaling by insulin and leptin is implicated in these responses as well. For example, starvation acutely suppresses reproductive function by inhibiting hypothalamic neurons that drive the pulsatile release of pituitary gonadotrophins. Because leptin administration partially restores reproductive capabilities to fasted mice (*8*), leptin deficiency is implicated in this response. The restorative effect of leptin was incomplete, however, suggesting that other factors help to mediate the inhibitory effects of food deprivation on the reproductive axis. The finding that NIRKO mice have a similar hypothalamic impairment of reproduction (*3*) suggests that reduced neuronal signaling by both insulin and leptin is involved in this adaptive response to starvation. Although levels of gonadal steroids were not reported, deficiency of these hormones is a likely concomitant of the reproductive deficit in NIRKO mice, and this in and of itself can cause weight gain. The extent to which obesity in these animals is the product of hypogonadism, rather than being a direct consequence of reduced insulin signaling in the brain, is a question that requires further study.

The pervasive notion that insulin causes obesity, like the tenet that the brain is insulin-insensitive, has hindered acceptance of insulin as a signal to the brain that limits weight gain. Although the concept that insulin triggers weight gain has little scientific merit, it remains a key selling point for advocates of diets that are low in carbohydrate and high in protein and fat. It is true that obesity is strongly associated with increased circulating insulin levels (hyperinsulinemia), but this relation is most likely due to obesity-induced insulin resistance, rather than to obesity-promoting effects of insulin, because increased insulin secretion actually protects against subsequent weight gain in obese humans (*9*). If hyperinsulinemia has adverse consequences, obesity does not appear to be among them.

Although leptin appears to play a quantitatively more important part than insulin in the CNS control of energy homeostasis, the phenotype of mice lacking neuronal insulin receptors indicates that brain insulin signaling is involved. Recent studies demonstrate that obesity induced by a high-fat diet causes hypothalamic resistance to leptin (*10*) and impairs insulin transport into the brain (*11*). Combined with evidence that leptin and insulin can influence glucose homeostasis through actions at a central site (*3*, *12*), the stage is now set for studies to determine if impaired CNS signaling by insulin and leptin contribute to the pathogenesis of two common metabolic diseases, obesity and type 2 diabetes.

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