Insulin can get a bum rap. Although a mainstay of diabetes treatment, when secretion increases in response to a low-fat, high-carbohydrate diet or insulin resistance, insulin has been purported to raise blood pressure, potentiate cardiovascular risk, and, to make matters worse, promote weight gain (1,2). But many in the lay public, popular media, and health care are not aware (or choose not to acknowledge) that insulin predated leptin as an adipostat hormone— one that circulates in the blood in proportion to body weight and binds to key brain centers to lower body weight (3). However, to rehabilitate insulin’s reputation and validate its beneficial role in weight regulation requires strong evidence because “obesity” and “insulin” are so frequently entwined.

Until recently, the mechanistic role of insulin in the central nervous system control of body weight had been worked out exclusively in animal models (4–8), whereas evidence for its effect in humans remained circumstantial and controversial. For example, an inverse association of postprandial insulin secretion at breakfast and a reduction in subsequent food intake at lunch has been reported in humans (9) and is consistent with insulin’s role as an anorectic hormone. In contrast, intensive diabetes therapy that includes increasing insulin dosage is frequently accompanied by unwanted weight gain and even obesity (10). Hence the conundrum: is insulin good or bad for body weight in humans? To answer the question of how central insulin action regulates energy balance, insulin would need to be administered directly to brain centers involved in determining food intake and energy expenditure without increasing peripheral levels, which can lead to hypoglycemia. In addition, since brain biopsies are not an option in human studies, a noninvasive technique to measure brain responsiveness would also be required. Fortunately, imaging technologies have recently emerged that allow direct or indirect study of human brain function. These include positron emission tomography and functional magnetic resonance imaging (11).

In this issue of Diabetes, Jauch-Chara et al. (12) address these challenges by combining intranasal application of insulin and a novel brain imaging method. They conducted a prospective study on 15 healthy, normal-weight men and compared brain responses and food intake among those receiving intranasally administered insulin and placebo. Intranasal administration delivers the drug to the olfactory mucosa, thereby allowing direct access to the brain. Indeed, studies of intranasally delivered insulin and other hormones have shown rapid penetration to the cerebrospinal fluid (13) as well as changes in brain response, including effects on appetite (14). The dose of 40 IU of rapid-acting insulin chosen for this study did not change peripheral insulin or glucose levels and had previously been shown to decrease body weight in men when given repeatedly (14). But rather than use positron emission tomography or functional magnetic resonance imaging to assess brain responses, the authors used magnetic resonance spectroscopy to measure changes in ATP and phosphocreatine (PCr) levels in the motor cortex. Changes in these cellular components reflect the balance of cellular fuel production versus use and represent one mechanism that might underlie nutrient-induced alterations in food intake and body weight (Fig. 1) (15–17). Compared with placebo, men receiving intranasal insulin had increased ATP and PCr concentrations and reduced food intake during an ad libitum breakfast roughly 90 min later. Importantly, stimulated brain levels of ATP and PCr correlated inversely with subsequent food intake, suggesting that insulin-mediated alterations in brain “energetics” played a role in this response. The authors note that hunger ratings remained unaffected by insulin, and they speculate that insulin’s effects on appetite might be subconscious. However, eating less during an ad libitum meal suggests that intranasal insulin increased fullness, an effect that most likely would have been demonstrated if subjects had been forced to eat the same amount of calories with each study meal (isocaloric feeding).

This study provides new evidence for insulin’s beneficial role on body-weight regulation in humans: that of a measured metabolic intermediate response (ATP) to insulin in the brain that predicts food intake. It also provides support for the role of brain energetics in determining food intake in studies of nutrient sensing and weight regulation. The implications of this study could also be extended to other fields in which obesity and energetics have been linked, such as neurodegenerative diseases (rev. in 18). It has been shown that patients with obesity and/or type 2 diabetes, states of insulin resistance, and relative insulin deficiency are at increased risk for neurodegenerative diseases (19,20) and that intranasal insulin improves cognition and memory in Alzheimer’s disease patients (21). The possibility that intranasal insulin could result in ATP and PCr increases in obese patients, improvement in cognition and memory, and reduction in risk for neurodegenerative disease is a topic that merits further investigation.

Although its results are intriguing, this report has several limitations. First, the study population was limited to normal-weight men, thereby lacking generalizability to women and other weight categories. Indeed, in the previously cited study of intranasally delivered insulin reducing body weight in men, women who received the same dose did not lose fat mass or body weight (14). A second limitation is that subjects were not studied under...
circumstances of weight perturbation (such as after under- or overfeeding) to assess the directionality of the ATP and PCr response, a factor that is important in determining causation. Third, insulin is known to act on transcription of hypothalamic neurotransmitters regulating food intake (6,22) as well as leptin receptor signaling through phosphatidylinositol 3-kinase (23). As a result, it is unclear if the changes reported by Jauch-Chara et al. (12) represent a causative mechanism or are an epiphenomenon. Finally, the study lacks anatomic specificity because measuring
ATP and PCr in the motor strip of the cortex is well removed from the brain centers currently thought to play important roles in determining energy expenditure and the behavioral control of food intake.

We are still far from understanding what specific part or parts of the brain are responsible for determining the "set point" for body weight in humans, the pathways with which these parts communicate with one another, why this system becomes disturbed to cause obesity, and how to treat these defects to allow sustained weight loss. The article by Jauch-Chara et al. expands our understanding of this system by providing an important translational link between animals and humans regarding the role of energetics in body weight regulation. But, also thanks to this report, insulin's physiological and therapeutic reputation as a weight-loss hormone has gotten a boost, and that's nothing to sniff at.

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