Where Does Insulin Resistance Start?

The brain

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During the last two decades, many studies have focused on the pivotal role of the hypothalamus in the control of energy metabolism (1). Hypothalamic nuclei, particularly the arcuate and the ventromedial, receive numerous peripheral inputs from adipokines (leptin, adiponectin, and resistin) and free fatty acids. These signals of "nutrient abundance" lead to the activation of multiple hypothalamic pathways that overlap and generate a plethora of central and peripheral responses (2). In this context, the central neuronal signals generated by insulin have been the most extensively studied (3).

The pivotal experiment performed by Woods et al. (4) in the late 1970s showed that intracerebral infusion of insulin in baboons reduced food intake and body weight and paved the way for intense scientific investigation over subsequent years by highlighting the key role of insulin at the central nervous system (CNS) level. Insulin receptors (5) and components of the insulin signaling pathway (6) are widely distributed in the brain. Insulin interacts with its binding sites by crossing the blood-brain barrier through a receptor-mediated and saturable transport mechanism (7), although it has been hypothesized that insulin is also synthesized in the brain (7).

Considerable evidence has been generated to indicate that insulin can modulate the expression of neuropeptides involved in the regulation of food intake within the CNS (8) and also can influence glucoregulation via CNS connections that regulate hepatic glucose production (9), glycogen synthesis in the skeletal muscle (10), and fat metabolism in adipocytes (11). By activating its receptors, insulin directly suppresses prepro-NPY mRNA transcription in the arcuate nucleus, leading to a reduction in NPY and a decrease in food intake (12), whereas intracerebroventricular delivery of insulin increases the expression of pro-opiomelanocortin (POMC) (13) (Fig. 1). This hypothalamic mode of insulin action resembles the well-known effect of leptin, suggesting that these two hormones act in concert in the hypothalamus (14). Leptin is an adipokine that primarily is produced by adipocytes. Leptin production and plasma levels are correlated with adipocyte size and triglyceride content, which increase in obesity and overfeeding and decrease with weight loss. Similar to insulin, leptin crosses the blood-brain barrier through a saturable transport mechanism (15). The activation of neuronal leptin receptors involves the Janus kinase/signal transducer and activator of transcription (Jak-STAT) pathway that culminates in the translocation of STAT3 into the nucleus and the transcription of neuropeptides (15). The main effects of leptin in the CNS are the inhibition of NPY and AgRP neurons and the activation of POMC neurons in the arcuate nucleus. Thus, leptin reduces food intake, stimulates thermogenesis, and enhances lipid oxidation and insulin sensitivity in peripheral organs (15). Like insulin, leptin is a signal of "nutrient abundance," even if its ability to signal excess energy storage is weak. Obese individuals have high plasma leptin levels but an impaired response to the increased levels of this adipokine, suggesting the presence of "leptin resistance." This pathological condition is associated with impaired leptin transport across the blood-brain barrier, causing reduced hypothalamic leptin signaling. This results in an increase in food intake and triglyceride storage, mainly in adipose tissue and liver, and generates a vicious cycle leading to excessive fat weight gain.

Both leptin and insulin signaling are known to directly target POMC and AgRP neurons, through a complex interaction that only recently has started to be elucidated (16). By activation/inhibition of a series of intracellular converging cascades in the CNS, leptin and insulin cross-talk via the phosphatidylinositol (PI) 3-kinase pathway (16). Blockade of PI 3-kinase activation by LY294002 promotes the inhibition of both insulin and leptin-induced anorexia in animals (17). Therefore, the PI 3-kinase pathway may be considered the main mediator of leptin and insulin effects on food intake. However, the activation of PI 3-kinase by insulin and leptin may differ at the level of individual cells (18). The two hormones act in concert on POMC neurons, whereas they display contrasting effects in AgRP neurons (18).

The transcriptional control of neuropeptide expression is not the only way by which insulin and leptin may regulate the neuronal circuits controlling food intake. The activation of PI 3-kinase may, in fact, regulate electrical activity via stimulation of ATP-sensitive potassium (K_{ATP}) channels in the neuronal target cells (19). This activation leads to an outward flow of K^+ ions, inducing hyperpolarization and a reduced activity of the target neuron. However, at this level, insulin and leptin may regulate electrical activity in different ways, as documented in some POMC neurons (19,20). This divergent ability of the two hormones to modulate electric activity of hypothalamic neurons is well depicted by the comparison of the two phenotypes obtained by the brain-specific knockout of insulin and leptin receptors, respectively. Only insulin receptor neuronal deletion is associated with a constitutive severe state of obesity (21). Mice lacking the insulin receptor in the brain developed obesity only after a high-fat diet was administered (22).

The neuronal integrity of the insulin receptor signaling also is required for the maintenance of normal glucose homeostasis. In fact, mice with a neuron-specific insulin receptor knockout

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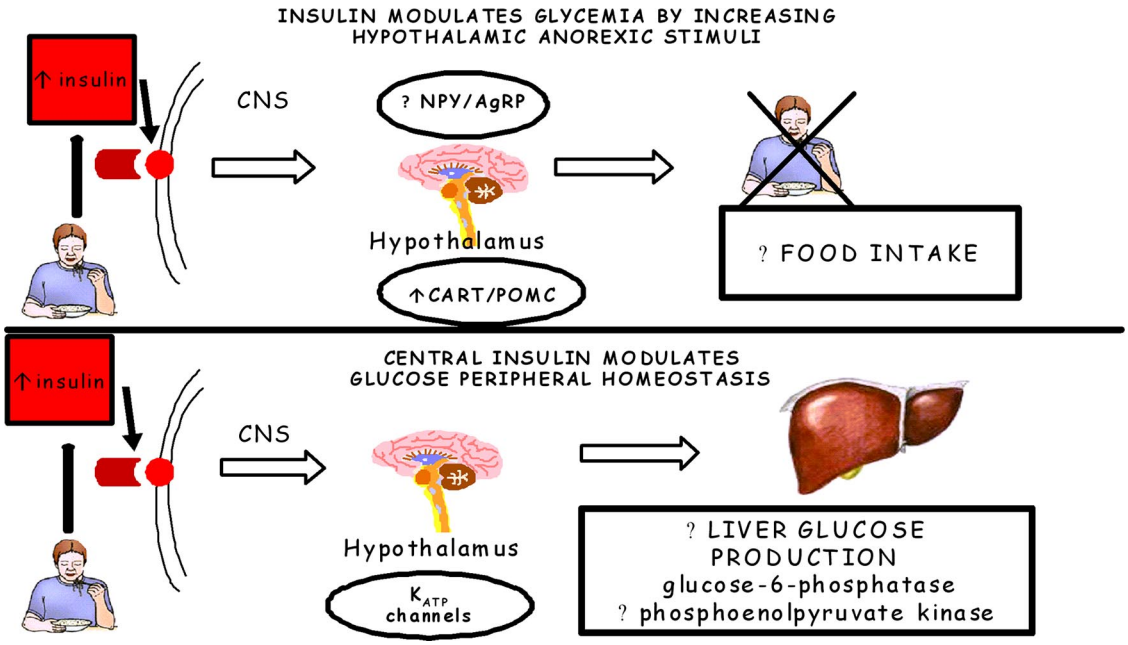

Figure 1—*The upper part of the figure shows the mechanism by which insulin acting at the brain level, and precisely at the hypothalamus, may modulate glycemia by reducing food intake. The lower part shows how insulin receptor signaling is required for the maintenance of normal glucose homeostasis. K_{ATP} channels in hypothalamic neurons are activated by insulin and influence hepatic glucose production, an effect that is mediated by the autonomous nervous system.*

developed glucose intolerance and insulin resistance (21). Consistent with this, antisense oligodeoxynucleotide directed against the insulin receptor caused not only hyperphagia and increased fat mass, but also a state of insulin resistance (23). Changes in glucose homeostasis may simply reflect, and be secondary to, the concomitant changes in energy balance. Therefore, to investigate the central effects of insulin, independent of its pleiotropic peripheral actions, Obici et al. (9) administered intracerebroventricular agonists and antagonists of insulin signaling in the presence of basal circulating insulin levels to detect whether hepatic insulin action was affected. They found that infusion of either insulin or small-molecule insulin mimetic agents into the third cerebral ventricle suppressed glucose production. Conversely, central antagonism of insulin signaling impaired the ability of circulating insulin to inhibit glucose production. This neuronal action of insulin on glucose production has been shown to be mediated by central K_{ATP} channels, because the sulfonylurea tolbutamide abolished this effect (9).

Additional studies have substantiated the hypothesis that insulin controls glucose metabolism at the CNS level. Thus, K_{ATP} channels in hypothalamic neurons are activated by insulin and influence hepatic glucose production by decreasing glucose-6-phosphatase and phosphoenolpyruvate-carboxikinase, effects that are mediated by the autonomous nervous system (24) (Fig. 1).

It has been shown that neuronal insulin receptor activation directly regulates hepatic interleukin-6 (25) by a mechanism involving AgRP-expressing neurons in the hypothalamus. Insulin acts centrally on AgRP neurons, causing activation of PI 3-kinase. The consequent activation of K_{ATP} channels results in the reduced release of AgRP. Silencing of these cells modulates hepatic metabolism, leading to increased interleukin-6 expression and decreased glucose-6-phosphatase expression (26). To further investigate the contribution of brain-insulin signaling versus peripheral insulin signaling on the development of insulin resistance, Koch et al. (11) generated two acutely inducible insulin receptor–deficient mouse models: one with a reduction of insulin receptor number in all tissues of the body, including the CNS, and another lacking the insulin receptor only in the peripheral nervous system. These models of inducible insulin resistance are of considerable interest, because the results are devoid of any developmental compensation and, thus, bypass any changes that arise from deletion of the insulin receptor during embryonic development. By comparing the phenotypes of the two groups of animals, it was found that central neuronal insulin also has an important role in the control of lipogenesis in peripheral adipocytes (11) and increases fat mass, fat cell size, and adipose tissue lipoprotein lipase expression. Therefore, this study demonstrated differential, partially counterbalancing actions of insulin in the CNS: a well-known catabolic function via control of food intake, but also an anabolic function via stimulation of lipogenesis. A salient point was that the mice lacking CNS insulin signaling suffered from more severe hyperglycemia than the mice in whom insulin signaling was impaired only at the peripheral level, confirming the pivotal role of the neuronal insulin receptor in the control of peripheral glucose metabolism (11).

According to these findings, impaired glucose metabolism and obesity may arise from disruptions of hypothalamic insulin signaling (Fig. 2). It is still not clear how the genetic background and the environment may affect these neuronal pathways. High-energy or fat-enriched diets may work, not only through an impaired ability of insulin to activate the peripheral PI 3-kinase pathway, but also by negatively modifying the intracellular insulin signaling in the hypothalamus (27). Recent studies have demonstrated that cerebral insulin resistance also may occur in humans. By means of a magneto-encephalo-

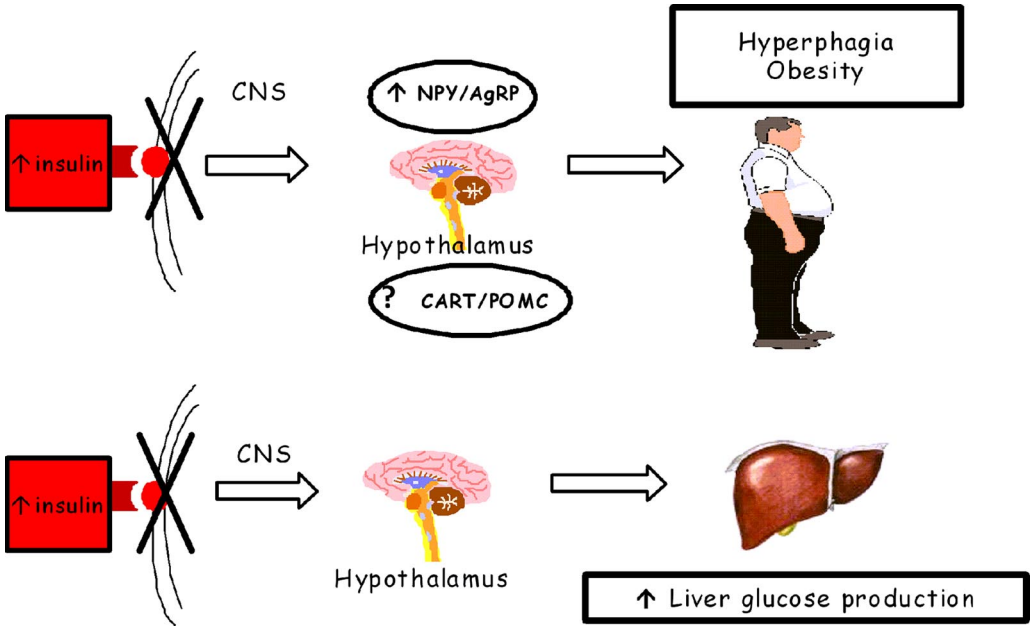

Figure 2—*The consequences of central insulin resistance are depicted. An impairment of insulin signaling in the CNS may lead to hyperphagia, weight gain, and consequently to hyperinsulinemia* (upper part)*, but also to a dysregulation of plasma glucose levels for the potentiation of gluconeogenesis.*

graphic approach during a two-step hyperinsulinemic-euglycemic clamp, an impaired cortical neuronal response to insulin was demonstrated in obese subjects and in individuals with the Gly972Arg polymorphism in IRS-1, a genetic condition associated with type 2 diabetes. However, the reduced neuronal response to insulin in the two pathological conditions (obesity versus genetic predisposition to develop type 2 diabetes) showed a different magneto-encephalographic pattern, suggesting that *1*) different mechanisms can lead to cerebral insulin resistance and 2) central insulin resistance may not only be a consequence of, but also a starting point for, the development of obesity and type 2 diabetes (28).

In summary, the brain is an insulin-sensitive tissue and, in association with other nutrient and adiposity signals, such as fatty acids (29), amino acids (30), and leptin, may play an important role in the regulation of energy balance and glucose homeostasis. Hence, an impairment of the fuel-sensing mechanisms in the CNS may lead to both weight gain and dysregulation of plasma glucose levels. Diet, rather than obesity per se, seems to play a greater role in inducing a state of central insulin resistance (31). However, the ensuing obesity may further reduce the neuronal sensitivity to peripheral signals, such as insulin and leptin. These pathological processes, in turn, exacerbate obesity and the hyperinsulinemic state, leading to overt hyperglycemia, and thus generate a vicious cycle that, in combination with β-cell dysfunction, progresses to diabetes. The future will divulge whether restoration of central neuronal signaling will be beneficial for both obesity and diabetes.

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