Peripheral Signals Set the Tone for Central Regulation of Metabolism

In 1849, Claude Bernard suggested that the central nervous system (CNS) regulates blood glucose levels, after his classic experiments showing that “piquère” (pricking) of the floor of the fourth ventricle of rabbits produced hyperglycemia (1). Remarkably, he speculated that the effect was mediated by stimulation of the sympathetic innervation of the liver. The next major step was the work of Shimazu and colleagues (2), who showed in 1965–1966, in line with these prescient observations, that glycogenolytic enzymes in the liver were activated by splanchnic nerve stimulation and that specific regions of the hypothalamus had reciprocal effects on blood glucose levels and liver glycogen content (3). In this issue, Perrin et al. (4) suggest a key role for the hypothalamus in regulation of muscle glycogen synthesis through the autonomic nervous system (ANS).

Several regions of the brain are involved in regulation of food intake and energy homeostasis. Among them, the hypothalamus is the most important locus involved in the neural control of peripheral metabolism through the modulation of the ANS activity. The CNS indeed modulates hormone secretion (i.e. insulin and glucagon secretion by pancreatic islets) and metabolic activity of several tissues and organs (i.e. liver, adipose tissue, and muscle). The hypothalamus is in turn informed of the energy status of the organism by several metabolic and hormonal signals, establishing a feedback loop between the brain and the periphery (5) (Fig. 1).

According to the lipostatic model of the regulation of energy balance, peripheral signals proportional to the size of energy stores communicate energy status to the brain. Leptin and insulin are ideal candidates for this lipostatic function because their levels are closely associated with adiposity, and their central administration decreases food intake and increases energy expenditure (i.e. thermogenesis) (5).

Indeed, insulin and leptin receptors are expressed in several sites of the brain, including different hypothalamic nuclei such as, the ventromedial hypothalamus (VMH), the lateral hypothalamic area, the paraventricular hypothalamus, the arcuate nucleus (ARH), and in the brainstem (6). Leptin and insulin act mainly by modulating both the expression of neuropeptides (i.e. neuropeptide Y, agouti-related protein, proopiomelanocortin) in ARH and paraventricular hypothalamus and the neuronal electrical activity in some hypothalamic nuclei (i.e. VMH and ARH), resulting in modulation of ANS activity (6). Leptin stimulates fatty acid oxidation and thermogenesis in brown adipose tissue through activation of sympathetic nerves (7). However, the centrally mediated effect of insulin or leptin on peripheral nonadipose tissue metabolism has been poorly studied until recently. Indeed, we demonstrated that leptin injection stimulates fatty acid oxidation in muscle both directly and via the hypothalamic sympathetic nervous system (8) (Fig. 1).

The hypothalamic-ANS axis also modulates glucose homeostasis in peripheral tissues via insulin-independent mechanisms (9, 10). Acute administration of leptin either iv, intracerebroventricular (ICV) (11), or intrahypothalamic (into the VMH) (12, 13) increased glucose uptake in several tissues including muscle, brown adipose tissue, and heart through increased sympathetic nerve activity. Importantly, the increase in glucose uptake despite unchanged insulin levels indicated that leptin increases peripheral insulin sensitivity. Consistent with this hypothesis, administration of leptin IV (14, 15) or ICV (16) during hyperinsulinemic euglycemic clamps markedly enhances insulin action on glucose uptake and utilization. Moreover, acute or chronic IV administration of leptin alters hepatic glucose fluxes and enhances insulin’s ability to inhibit hepatic glucose production (14, 17). Although little is known about the pathways involved in the centrally mediated effects of leptin on peripheral insulin sensitivity, these effects are likely to involve activation of central melanocortinergic neurons (18). Altogether, these data demonstrate that leptin acts in the CNS to control glucose homeostasis in peripheral tissues as well as peripheral insulin sensitivity.

Less is known regarding the central effect of insulin on peripheral glucose homeostasis. Recent data from Rossetti’s lab show that ICV insulin or a small-molecule insulin mimetic suppresses hepatic glucose production despite insulin levels being clamped at basal circulating concentrations. Moreover, antagonism of hypothalamic insulin signaling (i.e. insulin receptor antisense, insulin receptor antibodies, or pharmacologic inhibition of phosphoinositide 3-kinase) in the presence of physiological hyperinsulinemia impaired the ability of peripheral insulin to suppress glucose production (19, 20). In these studies, peripheral glucose uptake was not affected in the basal or hyperinsulinemic state by ICV insulin or antagonism of hypothalamic insulin signaling, suggesting that central insulin-mediated effects are specific to the liver.

However, data presented in this issue (4) show that ICV administration of insulin markedly stimulates muscle glycogen synthesis at basal plasma insulin levels. Although, the effects of central insulin were not investigated during hyperinsulinemic conditions, these data for the first time suggest that central insulin, like leptin, can also modulate muscle glucose metabolism. The action of central insulin was mimicked by ICV administration of the pharmacological activator of AMP-activated protein kinase (AMPK), AICAR. ICV AICAR infusion increased both basal and insulin-stimulated

Abbreviations: AICAR, Pharmacological activator of AMPK; AMPK, AMP-activated protein kinase; ANS, autonomic nervous system; ARH, arcuate nucleus; CNS, central nervous system; ICV, intracerebroventricular; VMH, ventromedial hypothalamus.

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muscle glycogen synthesis, leading the authors to suggest that brain AMPK could be involved in central insulin and/or AICAR effects on peripheral insulin sensitivity. However, the phosphorylation of hypothalamic AMPK was not modified after the 3 h of insulin or AICAR infusion, making conclusions about the involvement of AMPK speculative. Furthermore, ICV insulin has been shown to decrease hypothalamic AMPK activity (21).

Caution should also be exercised in ascribing an effect of AICAR to AMPK activation. Indeed, AICAR also modulates adenosine re-uptake in neurons, which leads to changes in presynaptic glutamate release (excitatory neurotransmitter) that could induce changes in peripheral metabolism independent of the AMPK effect (22). Interestingly, insulin-stimulated muscle glycogen synthesis is reduced in vivo in α2-AMPK knockout mice, but this is likely to result from elevated circulating catecholamines (23). Despite some discrepancies among these studies, the above metabolic data indicate that elevation of brain insulin levels generates changes in skeletal muscle metabolism aimed at facilitating storage of energy as glycogen, as well as inhibiting liver glucose production.

Leptin and insulin are not the only metabolic factors that influence peripheral metabolism via central action (Fig. 1). Indeed, fatty acids (24–26) and glucose (4) can modulate not only food intake but also peripheral insulin sensitivity. Interestingly, the paper in this issue (4) showed that ICV glucose infusion at high concentration markedly decreased insulin-stimulated muscle glycogen synthesis and inhibited central effects of both insulin and AICAR, suggesting that central glucose decreases insulin sensitivity. Whether the hypothalamic pathways mediating these brain glucose effects involve hypothalamic AMPK is uncertain. AMPK has been proposed to function as a fuel sensor in the hypothalamus (21, 26–28), an evolutionarily conserved function of this pathway that is important even in yeast (29). Although high glucose has been shown to inhibit hypothalamic AMPK activity (21, 26), in contrast to the study in this issue (4), high glucose and insulin ICV had the same effect to suppress AMPK activity (21). The demonstration of a role of cerebral AMPK in the central effects of either AICAR, insulin, or glucose on peripheral glucose metabolism in muscle, will require molecular modulation of AMPK activity in the hypothalamus (dominant-negative, constitutively active AMPK, neuronal specific knockout, etc.).

Although some discrepancies remain among studies, possibly related to differences in technical procedures or strain of animals, these data indicate that hormonal and metabolic signals play a key role not only in the control of energy intake but also in peripheral glucose metabolism in muscle and liver through the ANS. The precise neurocircuitry and the molecular factor(s) that integrate these signals and mediate

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**FIG. 1.** The hypothalamus is an important target of a number of key hormonal and metabolic signals. These signals integrate through neuronal circuits to modulate the activity of the ANS, which regulates lipid and glucose metabolism as well as insulin sensitivity in peripheral tissues. The hypothalamic-adrenal axis also plays a role (not shown). Recent findings indicate that hypothalamic AMPK is involved in these fuel sensing mechanisms. Perrin et al. (4) show that insulin or AICAR injection into the brain acutely stimulates muscle glycogen synthesis whereas glucose has opposite effects. These and other findings support the concept that the CNS not only regulates food intake and body weight, but also plays a key role in regulating glucose homeostasis. *AMPK-mediated pathways; LCFA, long chain fatty acids.*
these needs to be clearly defined. Such studies are likely to provide important clues to the links between obesity and type 2 diabetes. The “treasure chest” could contain novel therapeutic approaches to prevent or ameliorate obesity and diabetes.

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