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Mechanisms and significance of brain glucose signaling in energy balance, glucose homeostasis, and food-induced reward

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ABSTRACT

The concept that hypothalamic glucose signaling plays an important role in regulating energy balance, e.g., as instantiated in the so-called "glucostat" hypothesis, is one of the oldest in the field of metabolism. However the mechanisms by which neurons in the hypothalamus sense glucose, and the function of glucose signaling in the brain, has been difficult to establish. Nevertheless recent studies probing mechanisms of glucose signaling have also strongly supported a role for glucose signaling in regulating energy balance, glucose homeostasis, and food-induced reward.

1. The glucostat hypothesis: role of glucose signaling in regulating energy balance

As early as 1916 Carlson hypothesized that glucose plays a key role in regulating energy balance (Carlson, 1916). This hypothesis was substantially formalized by Jean Mayer in the 1950s, in which he articulated compelling arguments that glucose signaling in the hypothalamus regulates food intake and thereby regulates energy balance (Mayer, 1953; Mayer and Bates, 1952). The basic hypothesis that Mayer articulated was that the gradual fall in plasma glucose after a meal eventually triggers appetite, and that the rise of glucose immediately after a consuming a meal produces satiety, mediated by neurons in the hypothalamus (Mayer, 1953; Mayer and Bates, 1952). Mayer and other investigators focused particularly on neurons in the ventromedial hypothalamus (VMH) because it had been definitively demonstrated that lesions in that part of the brain produces robust obesity, entailing both hyperphagia and obesity even in pair-fed animals (Hetherington and Ranson, 1940), implicating reduced metabolic rate as a contributor to the obesity syndrome. Key support for this "glucostat" hypothesis was that i.p. injection of the glucose analog gold-thioglucose (GTG) produces robust obesity associated with lesions in the VMH, dependent on the glucose moiety (Mayer, 1953). The glucostat hypothesis stimulated significant research, including the discovery of neurons in the VMH and that are uniquely sensitive to changes in glucose concentrations (Oomura et al., 1969). A key implication of the glucostat hypothesis is, of course, that impaired hypothalamic sensitivity to glucose could be a cause of obesity.

Based on the paradigm established by Oomura et al., mechanisms mediating glucose signaling in the hypothalamus have been examined in great detail, generally based on the mechanisms mediating glucose signaling in pancreatic beta cells (Ashford et al., 1990; Yang et al., 1999). Thus drugs that stimulate insulin secretion by blocking ATP-dependent potassium channels also excite glucose-stimulated hypothalamic neurons (Ashford et al., 1990; Yang et al., 1999). Furthermore the pancreatic form of glucokinase (pGK), generally considered a key element in glucose signaling in beta cells, is expressed in the VMH and inhibition of this enzymatic activity blocks glucose signaling in these neurons (Yang et al., 1999, 2004). Expression of pGK is largely confined to hypothalamic areas known to be involved in regulating energy balance and glucose homeostasis (e.g., ventromedial, arcuate, and paraventricular

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nuclei of the hypothalamus) although pGK is expressed in other brain areas as well (Jetton et al., 1994; Lynch et al., 2000; Yang et al., 1999).

In the pancreas, glucose signaling that induces insulin secretion is mediated by glucose metabolism, in turn entailing the property of pGK to drive glycolysis in proportion to plasma glucose levels, in contrast to related hexokinases (Matschinsky et al., 1998). In pancreatic beta cells glucose signaling is generally thought to entail production of ATP, which in turn blocks K-ATP channels, leading to depolarization of the cell (Ashcroft and Rorsman, 1990). K-ATP channels may support a similar function in hypothalamic neurons that sense glucose (Ashford et al., 1990). On the other hand K-ATP channels are ubiquitously expressed in neurons and other electrically excitable cell types, many of whose electrical activity is reduced at very low concentrations of glucose, presumably functioning to conserve energy (Mobbs et al., 2001). This very general response to low glucose must be distinguished from the response to physiological changes at much higher post-prandial levels of glucose, in highly specialized cells such as pancreatic beta cells and specific hypothalamic neurons that express pGK (Mobbs et al., 2001).

The role of pGK in glucose signaling was definitively established in humans by the discovery that mutations in pGK accounted for some forms of human Mature Onset Diabetes of the Young (MODY), a congenital form of diabetes associated with reduced glucose-induced insulin secretion (Fajans et al., 1994). Subsequent studies in mice corroborated that heterozygous ablation of pGK also cause roughly a doubling of plasma glucose with normal insulin concentrations, due to a roughly 50% reduction in plasma insulin relative to plasma glucose concentrations i.e., an apparent 50% reduction in beta cell sensitivity to glucose (Bali et al., 1995; Grupe et al., 1995). Unfortunately homozygous ablation of pGK leads to neonatal death, probably due to diabetic ketoacidosis consequent to insulinopenia (Bali et al., 1995; Grupe et al., 1995), limiting the ability to assess effects of complete ablation of the enzyme (in contrast, for example, to the leptin receptor).

Nevertheless, heterozygous ablation of pGK does produce neuroendocrine phenotypes similar to those produced by hypoglycemia, fasting, and genetic obesity due to leptin deficiency (presumably reflecting reduced hypothalamic neuronal sensitivity to glucose) including impaired reproductive function, elevated glucocorticoid secretion, food intake, and hypothalamic NPY, as well as reduced hypothalamic POMC (Yang et al., 2007). Interestingly, it has been so far impossible to generate mice in which pGK is specifically ablated in neurons using floxed pGK crossed with neuron-specific enolase driving Cre-recombinase, suggesting that pGK in neurons is also required for normal insulin secretion or some other essential function (Yang et al., 2007). However recent studies using much more powerful genetic resources have demonstrated that electromagnetic stimulation of pGK-expressing neurons in the ventromedial nucleus reduces insulin secretion and stimulates food intake, whereas inhibition of these neurons produces the opposite effects, increasing insulin secretion and inhibiting feeding (Stanley et al., 2016). These surprising results suggest that the pGK neurons targeted in these studies are predominantly glucose-inhibited neurons, whose activation and inhibition would be expected to produce the observed phenotypes. Previous studies have demonstrated that glucose-inhibited neurons can be observed in the ventromedial nucleus and glucose signaling in these neurons, as with glucose-stimulated neurons, is mediated by pGK and subsequent glycolysis (Yang et al., 2004). Nevertheless the majority of neurons in the ventromedial nucleus are stimulated by glucose (Oomura et al., 1969), and glucose signaling in these neurons is also apparently mediated by pGK (Yang et al., 1999), so it is unclear why the dominant effect of activating or inhibiting pGK neurons in the this hypothalamic brain area would produce effects almost certainly mediated by glucose-inhibited neurons. Thus at present the role of hypothalamic glucose-stimulated neurons remains to be established.

Despite many tantalizing lines of support for the glucostat hypothesis, that hypothalamic glucose signaling regulates energy balance, definitive proof of glucose signaling in the hypothalamus in the regulation of energy balance has remained elusive. Nevertheless a recent study has apparently provided strong evidence for the hypothesis (Lagerlof et al., 2016). As indicated above several lines of evidence have suggested that glucose signaling in the hypothalamus, as with pancreatic beta cells, is mediated by glucose metabolism producing ATP, which then blocks the K-ATP channel, leading to depolarization of the neuron (Ashford et al., 1990). While an attractive hypothesis, some studies suggest that glucose signaling in the hypothalamus might be independent of ATP production. For example lactate mimics effects of glucose signaling, whereas pyruvate does not, in both glucose-stimulated (Yang et al., 1999) and glucose-inhibited neurons (Yang et al., 2004). The failure of pyruvate to mimic effects of glucose suggests that glucose signaling in these neurons may be independent of ATP production.

Indeed these studies support a likely role of astrocytes in mediating hypothalamic glucose sensing. Key support of this hypothesis is the existence of the activity-dependent astrocyte-neuronal lactate shuttle, in which astrocytes supply lactate to neurons to support electrical activity (Pellerin et al., 1998). A major element of this mechanism is that astrocytes are better positioned than neurons to transport glucose across the blood-brain barrier, then effectively supplying the relevant glucose-derived carbon bonds via transport of lactate to neurons (Pellerin et al., 1998). That this mechanism is relevant to hypothalamic glucose sensing (and its role in the regulation of peripheral glucose homeostasis, as described below) was strongly supported by the observation that infusion of glucose into the hypothalamus reduced peripheral blood glucose, dependent on the conversion of glucose to lactate, then conversion to pyruvate (Lam et al., 2005). Other studies have demonstrated that key elements of glucose sensing are in fact expressed in tanocytes (highly specialized hypothalamic glia) and microglia (Kim et al., 2011). Of particular importance glucokinase is expressed in tanocytes. Together these studies strongly support a major role in hypothalamic glial cells in mediating glucose sensing.

Similar results were observed in the regulation of hypothalamic AgRP, which is induced by fasting, leptin deficiency (Mizuno et al., 1999), and hypoglycemia (Briski et al., 2010). Of particular interest, transgenic expression of AgRP causes obesity (Klebig et al., 1995). Consistent with these observations, in vitro studies in a clonal hypothalamic cell demonstrated that glucose inhibits AgRP expression (Cheng et al., 2008). Of particular interest, the ketone 3-hydroxybutyrate is metabolized to produce ATP in this cell line, but rather than mimicking the effect of glucose to inhibit AgRP gene expression, 3-hydroxybutyrate actually opposed the effect of glucose and stimulated AgRP expression (Cheng et al., 2008). These results are consistent with normal physiology, in which plasma glucose is relatively elevated in the fed state, whereas 3-hydroxybutyrate is elevated in the fasted state. Thus as with electrical responses to glucose in hypothalamic neurons, molecular responses to glucose signaling relevant to energy balance appear not be to mediated by ATP production, although evidence continues to support a role for glucose metabolism.

A recent paper has provided probably the best evidence to date for the glucostat hypothesis, implicating glucose metabolism, but not hypothalamic ATP production, in regulating appetite and energy balance. This elegant study addressed the role of the hexosamine pathway (Lagerlof et al., 2016), which is the main alternative to the other two main glucose metabolism pathways, glycolysis and