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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

the pentose pathway. Each of these pathways require glucose phosphorylation as the first step, thus depend on some form of hexokinase or glucokinase activity. The main mechanism by which this pathway is thought to exert its effects is through the post-translational modification of proteins by a key product of this pathway, glucosamine. This modification is mediated by the enzyme O-glucosamine-transferase (OGT). Lagerlof et al. (Lagerlof et al., 2016) have now reported that post-natal ablation of OGT in forebrain neurons (including hypothalamic neurons) using the αCaMKII promoter to drive Cre-recombinase crossed with floxed-OGT causes hyperphagia and obesity. The main hypothalamic area driving this phenotype appears to be the paraventricular nucleus (PVN), whose ablation has previously been demonstrated to cause obesity due to hyperphagia (Shor-Posner et al., 1985). These studies, consistent with results of heterozygous pGK ablation to promote hyperphagia and other obese phenotypes (Yang et al., 2007), provide the strongest evidence to date that glucose signaling in the hypothalamus regulate energy balance and that impairments in these mechanisms can cause obesity.

Related to the role of hypothalamic glucose signaling in regulating energy balance, substantial evidence suggests that hypothalamic lipid metabolism, which would be expected to oppose glucose metabolism (and thus signaling) promotes obesity. The first clear evidence to support this hypothesis was the discovery that the drug C75, which inhibits fatty acid synthase (FAS), reduces food intake and body weight (Loftus et al., 2000), apparently by enhancing the production of hypothalamic malonyl-CoA, which leads to the metabolic switch toward glucose metabolism and away from lipid metabolism by blocking Cpt1 activity, the rate limiting step for lipid metabolism. Subsequent studies corroborated that the anorectic effects of C75 were mediated by the enhancement of hypothalamic glucose metabolism (Wortman et al., 2003). A similar FAS inhibitor, cerulenin, produced anti-obesity effects similar to those of leptin and activation of the melanocortin system, but independent of those systems, and apparently not mediated by toxic effects (Makimura et al., 2001). Conversely, overexpression of hypothalamic malonyl-CoA decarboxylase, which reduces the levels of malonyl-CoA, leads to robust obesity and hyperphagia (He et al., 2006). The rate-limiting enzyme for lipid metabolism, Cpt1a (the liver form of this enzyme which however is also expressed in the hypothalamus) is induced by fasting in association with a metabolic shift away from glycolysis toward lipid metabolism (Poplawski et al., 2010). Furthermore, genetic and pharmacological inhibition of hypothalamic Cpt1a inhibits food intake and hepatic glucose production (Obici et al., 2003), and reverses obesity phenotypes in diet-induced obesity (Pocai et al., 2006). Conversely overexpression of hypothalamic Cpt1a enhances obese phenotypes (Mera et al., 2014). Together these studies strongly support the hypothesis that, as in the periphery, hypothalamic glucose and lipid metabolism are antagonistic, with glucose metabolism promoting satiety and lipid metabolism promoting obese phenotypes. As indicated above, since plasma glucose levels are normally elevated after feeding whereas lipid levels are normally observed during fasting, these observations are consistent with normal physiology.

2. Role of hypothalamic glucose signaling in the regulation of glucose homeostasis

As indicated above recent studies have demonstrated a key role for hypothalamic neurons expressing pGK in regulating glucose homeostasis and feeding behavior, apparently largely through glucose-inhibited neurons in the ventromedial nucleus of the hypothalamus (Stanley et al., 2016). Similarly, in mice lacking a key component of the K-ATP channel, the Sur-1 regulatory protein, hypothalamic electrophysiological responses, as well as counter-regulatory and feeding responses to hypoglycemia, were not observed (Miki et al., 2001). These studies are consistent with a large number of studies demonstrating a role for neurons in the ventromedial nucleus in glucose homeostasis, particularly in the context of counter-regulatory responses to hypoglycemia (Borg et al., 2003, 1997, 1995, 1994). Counter-regulatory responses entail rapid release of adrenal epinephrine, norepinephrine, glucocorticoids, and pancreatic glucagon, as well as inhibition of pancreatic insulin and peripheral insulin sensitivity, all of which serve to enhance plasma glucose (Cryer, 1993). Lesions highly localized to the hypothalamic ventromedial nucleus (produced by the excitotoxin ibotenic acid and verified histologically) dramatically reduce these counter-regulatory responses to hypoglycemia (Borg et al., 1994). Conversely, highly localized inhibition of glucose metabolism in the hypothalamic ventromedial nucleus by targeted infusion of 2-deoxyglucose (2-DG; verified by autoradiography) induces robust systemic counter-regulatory responses (Borg et al., 1995). Conversely localized infusion of glucose into the ventromedial nucleus prevent counter-regulatory responses to systemic hypoglycemia (Borg et al., 1997). Of particular interest the effect of hypothalamic glucose to prevent systemic responses to hypoglycemia were reproduced by infusion of lactate into the ventromedial hypothalamus (Borg et al., 2003), consistent with evidence that lactate mimics effects of glucose on both glucose-stimulated (Yang et al., 1999) and glucose-inhibited (Yang et al., 2004) hypothalamic neurons. Further, 2-DG stimulates electrical activity of glucose-inhibited hypothalamic neurons (Yang et al., 2004). Since lesions of the ventromedial nucleus block systemic responses to hypoglycemia (Borg et al., 1994), these studies are generally consistent with the hypothesis that glucose-inhibited neurons in the ventromedial nucleus (whose activity is increased by hypoglycemia and glucopenia) apparently mediate counter-regulatory responses to hypoglycemia, consistent with the observation that activation and inhibition of neurons expressing pGK in the ventromedial nucleus reduce and enhance insulin secretion, respectively (Stanley et al., 2016).

A key role for hypothalamic glucose signaling in regulating glucose homeostasis (as well as energy balance) is further supported by studies examining the role of the melanocortin system, driven by hypothalamic neurons expression POMC, in these functions. Hypothalamic POMC neurons are located just ventral and somewhat medial to the ventromedial nucleus, extending to some extent into the lateral arcuate nucleus (Mizuno et al., 1998). Expression of hypothalamic POMC is reduced by fasting and genetic (leptin-deficient) obesity, in the latter case associated with hyperglycemia (Mizuno et al., 1998). Transgenic restoration of neuronal POMC completely corrects hyperglycemia in these genetically obese mice, in association with correction of hepatic gene expression associated with hepatic glucose production, but only partially corrects obese phenotypes (Mizuno et al., 1998). These results were corroborated with a converse study, in which reduction of leptin signaling in POMC neurons impaired glucose homeostasis (Berglund et al., 2012). While expression of POMC is clearly stimulated by the adipose hormone leptin (Mizuno et al., 1998), several lines of evidence support that POMC neurons are also stimulated by glucose (Belgardt et al., 2009). Of particular importance, Parton et al. (2007) demonstrated that expression of a dominant negative construct of the K-ATP channel specifically in POMC neurons inhibits glucose stimulation of POMC neurons and causes impaired glucose tolerance. Furthermore a high-fat diet impaired sensitivity of POMC neurons to glucose (associated with diet-induced obesity), a phenomenon apparently associated with expression of uncoupling-protein 2 (UCP2) (Parton et al., 2007). Indeed, leptin and glucose appear to be mutually permissive and likely act together to produce overlapping effects on hypothalamic neurons

(Poplawski et al., 2010). Furthermore neurons in the ventromedial nucleus activate POMC neurons (Sternson et al., 2005), presumably reflecting effects of glucose-stimulated neurons in the ventromedial nucleus.

3. Role of glucose signaling in food-induced reward

Food-induced reward has been increasingly implicated in the etiology of overeating and obesity (Kenny et al., 2013; Volkow et al., 2013, 2011). Intake of palatable foods engage reward systems, particularly the mesolimbic dopamine system (Geiger et al., 2009, 2008). Chronic intake of high fat, high sugar foods leads to changes in dopamine signaling and reward dysfunction that mimic the changes seen in drug addicts (Johnson and Kenny, 2010; Wang et al., 2001). Therefore, it is crucial to understand the mechanisms underlying the hedonic response to palatable foods and the long-term effects of consuming such foods.

Glucose consumption is rewarding independent of its sweet taste. Animals unable to sense sweet taste prefer glucose to the sweet-tasting but non-digestible sucralose and intragastric infusions of glucose are sufficient to induce preference for a neutral flavor, a classic measure of reward (de Araujo et al., 2008; Ren et al., 2010). Furthermore, glucose is uniquely rewarding among carbohydrates. For example, although animals do not show an initial preference for glucose or fructose in a two-bottle choice test, intragastric glucose infusions in mice produce a conditioned flavor preference whereas intragastric infusion of fructose and galactose do not (Ackroff and Sclafani, 1991; Sclafani et al., 2015; Sclafani and Ackroff, 2012). Similarly, in humans, only glucose increases connectivity between the hypothalamus and striatum and alters striatal activity (Page et al., 2013). These results may be due to differential activation of brain reward pathways by glucose and fructose. Glucose intake activates the mesolimbic dopamine system (de Araujo et al., 2012; Tsurugizawa and Uneyama, 2014). Systemic infusion of D1, D2, and NMDA receptor antagonists diminishes glucose flavor preference, and rats with a history of glucose binging have increased D1R and decreased D2R expression in the nucleus accumbens (NAc), an area classically implicated in mediating reward (Colantuoni et al., 2001; Dela Cruz et al., 2014). Fructose reward, on the other hand, is likely mediated through orexin-containing neurons in the lateral hypothalamus (LH) instead (Rorabaugh et al., 2014). It is possible that the two sugars activate different reward systems in the brain based on their opposing effects on circulating hormones insulin, leptin, GLP-1, and ghrelin, which can independently activate the dopaminergic system (Hommel et al., 2006; Naleid et al., 2005; Page et al., 2013; Teff et al., 2004).

Although glucose signaling may mediate glucose reward, the evidence suggests that glucose sensors in the central and peripheral nervous systems mediate the rewarding effects of glucose via parallel nutrient sensing (Burdakov et al., 2013). There are glucose sensing neurons at every level of nutrient processing, from the portal vein to the hypothalamus to limbic brain areas like the ventral tegmental area (VTA) (Watts and Donovan, 2010). Here we will briefly review what is currently known about the role of glucose signaling in food reward and highlight areas for further research.

4. Role of dopamine in glucose-induced reward

In the gut, duodenal transport of glucose into the hepatic-portal blood system is required for glucose-induced DA release in the dorsal striatum (Han et al., 2015). There are peripheral glucose sensors in the portal-mesenteric vein and denervation of the portal vein eliminates the effect of portal glucose infusion on satiety (Hevener et al., 1997; Mithieux et al., 2005). Furthermore, portal glucose infusion induces neuronal activity in the arcuate nucleus (particularly in POMC neurons), LH, and nucleus of the solitary tract, in addition to corticolimbic areas including the nucleus accumbens, providing evidence that peripheral glucose sensing information may be transmitted to the CNS (Adachi et al., 1984; Delaere et al., 2013; Shimizu et al., 1983). However, it has not yet been shown that these afferents are required for the behavioral components of glucose-induced reward. Given that DA activation mimics the post-ingestive rewarding effects of sucrose, it is likely that a similar system mediates glucose reward (Domingos et al., 2011). Another area for further research regarding the role of portal glucose sensing in reward is the precise circuitry underlying the activation of dopaminergic systems.

The neurons of the VMH are the classical glucose sensors of the CNS. POMC neurons are excited by glucose and induce satiety, whereas AgRP neurons are inhibited by glucose and induce hunger (Aponte et al., 2011; Fan et al., 1997; Krashes et al., 2011; Levin et al., 2004; Ollmann et al., 1997). Both populations produce their actions via melanocortin receptors (MCRs) on neurons in the PVN and other structures: the POMC propeptide is proteolytically processed into a-melanocyte-stimulating hormone, an MCR agonist, and AgRP is an inverse agonist at the MCRs. Both POMC and AgRP neurons appear to project to the VTA and the central MCRs, MC3R and MC4R, have been founded in the VTA, SN, and other limbic areas (Dietrich et al., 2012; King and Hentges, 2011; Kishi et al., 2003; Liu et al., 2003; Roselli-Rehfuss et al., 1993). To our knowledge, no study has directly implicated the glucose-sensing role of the VMH neurons in food reward, but as described above, there is ample evidence that these neurons modulate food reward through projections to the medial and central amygdala, as well as the VTA dopamine system (Roseberry et al., 2015).

Infusion of an MCR agonist, melanotan II (MTII), into the CeA decreases preference for a high fat diet and into the VTA decreases preference for nutritive and non-nutritive sweet solutions (Boghossian et al., 2010; Yen and Roseberry, 2015). In both studies, activation of MCRs recapitulated the effect of POMC neuron stimulation. In the latter study, it is interesting that preference for both sucrose and sucralose solutions was decreased, suggesting that MCRs in the VTA may regulate the hedonic aspect of sweet taste rather than the post-ingestive rewarding effects of sucrose or glucose intake. Another important finding from the Yen and Roseberry study is that rats with exposure to 10 percent sucrose appeared to have a desensitized melanocortin system, as a higher dose of MTII was required for attenuation of sucrose preference and food intake. This suggests that long-term exposure to a palatable diet may modify MCRs to make the targets of POMC neurons less sensitive to satiety-inducing signaling.

The effect of AgRP on food reward is less clear, as icv injection of the peptide has been shown to bias food preference in opposing directions in different tasks (Davis et al., 2011; Tracy et al., 2008). Similarly, studies in MC3R and MC4R knockout mice have not revealed a clear role for these receptors in food reward. MC4R knockout mice are classically obese, with concomitant hyperphagia and hyperinsulinemia (Huszar et al., 1997). In fact, mutations in the MC4R gene account for the highest monogenic cause of obesity in humans (Farooqi et al., 2003). However, there have been conflicting reports on the effect of MC4R knockout in food reward. Studies have shown that loss of MC4Rs results in both increased food self-administration, as well as decreased high fat diet self-administration, sucrose intake, and fat intake (Cui et al., 2012; Panaro and Cone, 2013; Vaughan et al., 2006).

MC3R ablation has a less obvious effect on body weight. Although the mice have increased fat mass and decreased lean mass, there are not consistent increases in body weight, although

mice with a double MC3R and MC4R knockout have a significantly increased body weight compared to either individual knockout (Chen et al., 2000). Only female MC3R knockout mice exhibit decreased sucrose intake and increases in dopamine in the VTA (Lippert et al., 2014). Further studies are needed to characterize the sexually dimorphic effects of MC3Rs in the VTA and to clarify the effect of eliminating MCR signaling in the VTA on food reward and preference.

Another locus for glucose signaling in reward is the LH, which contains at least two non-overlapping populations of neurons that are glucose sensitive. The melanin concentrating hormone neurons (MCH) are excited by glucose whereas the orexin-containing hormones are inhibited by it (Burdakov, 2005). The orexin neurons mediate the classic view of the hypothalamus as a "hunger" center as they are transiently inhibited by increases in glucose and loss of orexin neurons leads to obesity (González et al., 2008; Hara et al., 2001; Venner et al., 2011; Williams et al., 2008) The orexin neurons mediate food reward-seeking and a sub-population projects to the VTA (González et al., 2012; Harris et al., 2005). Recent electrophysiology data suggests that low glucose levels during fasting promotes firing of VTA-projecting orexin neurons, specifically those that release glutamate onto DA neurons (Sheng et al., 2014). These results strongly support the role of LH orexin neurons in motivated food behaviors. However, LH orexin neurons also have an important role in sensing amino acids and other metabolic products, suggesting that they mediate food reward in the context of nutrient balance, rather than for any one nutrient (Burdakov et al., 2013; Karnani et al., 2011). For example, in the presence of pyruvate and lactate, orexin neurons become insensitive to glucose levels (Venner et al., 2011). Therefore, orexin-mediated activation of the DA system may initiate food-seeking behaviors based on more general nutritional availability, not just glucose availability per se.

The LH MCH neurons oppose the actions of the orexin neurons in feeding and energy balance. Loss of the MCH neurons leads to hypophagia and leanness and infusion of MCH into the accumbens shell potentiates feeding, possibly via diminished synaptic events in accumbal medium spiny neurons (Georgescu et al., 2005; Sears et al., 2010; Shimada et al., 1998). Conversely, infusion of a MCH1R antagonist into the NAc attenuates feeding and mice lacking the MCH precursor Pmch have decreased food intake and hyper-sensitive dopamine systems (Georgescu et al., 2005; Mul et al., 2011). When optogenetically stimulated, the MCH neurons are not rewarding nor do they induced DA release in the striatum. However, upon pairing with a sweet taste, MCH stimulation is preferred to sucrose intake, and ablation of the LH MCH neurons prevents the post-ingestive effects of sucrose, suggesting that the MCH neurons are necessary and sufficient for sucrose-induced reward (Domingos et al., 2013). Recent work by Sclafani and colleagues shows mice lacking the MCH-1R have intact glucose-paired flavor preference, so the effect of MCH neurons on sugar reward is likely not mediated through the MCH peptide itself (Sclafani et al., 2016).

Finally, the midbrain dopaminergic neurons themselves may directly sense changes in glucose levels. DA neurons of the substantia nigra are sensitive to changes in glucose levels within the normal physiological range, suggesting that changes in brain glucose levels may be sufficient to trigger dopaminergic responses to glucose intake (Levin, 2000). Dopamine neuronal activity is also modulated by hormone signals of nutritional availability like ghrelin and leptin, suggesting that midbrain dopamine neurons may be another node of neural integration of metabolic signals (Hommel et al., 2006; Naleid et al., 2005). This raises the question of what information is sent to these neurons from other glucose-sensing nuclei in the brain and what information these neurons receive directly.

Given the evidence for reward dysfunction after access to a high-fat diet (Johnson and Kenny, 2010; Wang et al., 2001), and the role of lipid metabolism in regulating obese phenotypes, the role of lipid metabolism in regulating food-induced reward is of particular interest. Recently, Cansell et al. showed that infusion of triglycerides into the carotid artery decreases locomotion, motivation to work for food, palatable food preference, and amphetamine-induced locomotion, suggesting an attenuation of dopamine function in the striatum (Cansell et al., 2014). Correspondingly, knockdown of lipoprotein lipase, the enzyme that hydrolyzes triglycerides into fatty acids, in the nucleus accumbens was sufficient to reverse the effects of system triglycerides on food seeking and preference. However, it is unclear which neurons in the NAc mediate this effect and how intracellular fatty acid signaling modulates the activity of those neurons. There is also evidence that gut lipids, such as oleoylethanolamine (OEA), may link fatty acid sensing in the gut to striatal dopamine release via the vagal nerve (Tellez et al., 2013). However, as with portal sensing of glucose, further research is needed to elucidate how the vagal nerve signal is communicated to the brain's reward system.

In summary, there is ample evidence that glucose signaling activates reward systems to promote intake of foods that can be easily metabolized to glucose, independent of sweet taste. However, much remains unknown about which site(s) of glucose-sensing are most important for the rewarding effects of glucose and the precise circuitry that mediates those effects. Furthermore, much of the research on glucose-reward has focused on the brain's dopamine system, although several other reward-related neurotransmitters have been implicated in food reward, including serotonin. More studies on the role of other neurotransmitter systems in food reward would better inform our understanding of reward-related systems in the brain, particularly as they relate to food intake.

5. Opioid-mediated reward via β-endorphin

The proteolytic processing of POMC to form αMSH produces another peptide, β-endorphin, that is also released when POMC neurons in the VMH are excited. β-endorphin is an endogenous opioid peptide that acts at the mu and delta opioid receptors (MOR and DOR, respectively). The MORs and DORs are expressed in many brain areas that receive POMC projections, including the LH, VTA, amygdala, and NAc (Le Merrer et al., 2009; Leriche et al., 2007; Mansour et al., 1995). β-endorphin has been implicated in pain and stress, as well as in reward processes associated with drugs of abuse including ethanol, nicotine, and cocaine (Dikshtein et al., 2013; Kieffer, 1999; Nguyen et al., 2012). Compared to other opioid peptides, β-endorphin has restricted expression in the brain (Le Merrer et al., 2009). Since POMC neurons are sensitive to glucose, β-endorphin release is a plausible mechanism of glucose-induced reward.

Early pharmacological experiments seemed to suggest that β-endorphin opposed the effects of its co-released peptide αMSH in feeding. For example, intracerebroventricular (icv) infusion of β-endorphin, as well as selective infusion of the peptide into the paraventricular nucleus of the hypothalamus and the NAc, stimulates food intake (Grossman et al., 2003; Leibowitz and Hor, 1982; Sugawara and Nikaido, 2014). However, transgenic mice in which the β-endorphin segment of the POMC pro-peptide has been deleted have a propensity toward hyperphagia-induced obesity, contrary to what would be expected from loss of a hunger signal (Appleyard et al., 2003). The discordance between the pharmacological and genetic studies of β-endorphin may be explained in two ways. First, genetic knockout of β-endorphin only targets the peptide at its site of action, whereas pharmacological

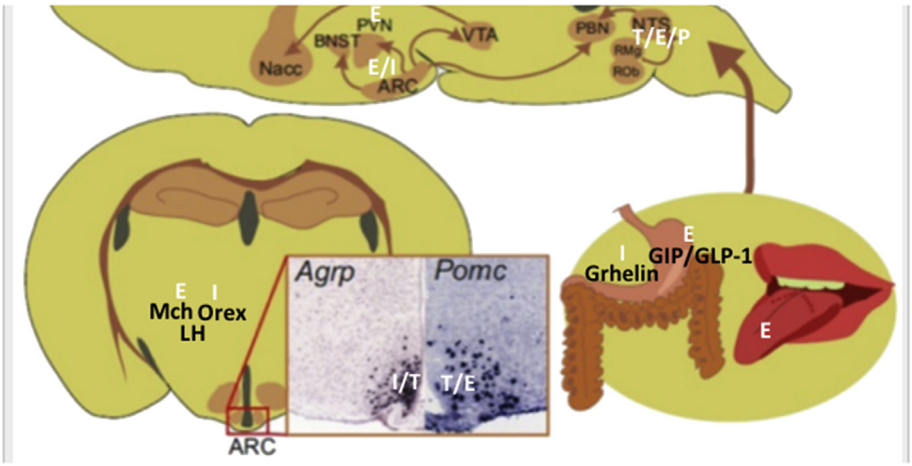

Fig. 1. Sagital (top) and coronal (bottom) areas influenced by glucose. I: glucose-inhibited; E: glucose-excited; T: lesioned by (Gold)-Thio-glucose. P: expresses POMC.

manipulations may introduce β-endorphin in brain regions where it is not normally expressed but may still act on the opioid receptors. Alternatively, β-endorphin may differentially regulate food intake in the short and long term. This latter explanation is supported by evidence that the orexigenic effects of β−endorphin only last for a few hours − or a few days when given chronically at a subthreshold dose − in contrast to the sustained satiating effects of αMSH administration (Dutia et al., 2012). Therefore, in the long run, β-endorphin may be important for homeostatic balance, but the mechanism through which it regulates long-term food intake it not yet clear.

Opioids are a promising system to study regarding food reward because they do not simply alter food intake (Zhang and Kelley, 2002). Zhang et al. found that infusion of DAMGO, a MOR agonist, into the NAc increases consumption of *palatable* foods, particularly those high in fat (Zhang et al., 1998). Woolley et al. found that the same manipulation selectively increased intake of a preferred flavor over a nutritionally equivalent alternative. Similar results have been observed in the central nucleus of the amygdala (Woolley et al., 2006). Infusion of naltrexone, an opioid receptor antagonist, into the CeA decreases intake of a preferred food and infusion of DAMGO into the CeA increases "wanting" for a sucrose solution (Bodnar et al., 1995; Mahler and Berridge, 2012).

That the opioid signaling in the NAc mediates the hedonic value of rewards such as food has long been hypothesized (Zhang and Kelley, 2002). However, recent data have extended the possible role of opioid function in food reward. There are in fact hedonic "hotspots" in the NAc, but there are also neurons in subregions of the NAc that mediate aversion and wanting through the same opioid receptors as in the "hotspots" (Castro and Berridge, 2014). Furthermore, there is a MOR-mediated bidirectional connection between the NAc and the CeA that regulates food intake, explaining the functional overlap (Kim et al., 2004). Recent optogenetic data suggests that activation of CeA is not inherently rewarding, but does produce incentive salience for a paired sucrose solution (Robinson et al., 2014). Therefore, it is possible that the CeA-NAc connection mediates food reward with opioid signaling in the NAc controlling the hedonics and opioid signaling in the CeA conferring motivational drive to pursue a food stimulus.

Could β-endorphin be acting at both the NAc and CeA to drive consumption of rewarding foods? POMC afferents and/or mRNA have been identified in both the amygdala and the NAc, so β-endorphin is present in those brain regions (King and Hentges, 2011; Leriche et al., 2007). Furthermore, during post-fasting sucrose consumption, mice lacking β-endorphin do not show any deficits in the total number of licking bouts − a marker of motivation to consume a food item − but they do have shorter licking bouts, particularly with a higher percentage of sucrose or after a longer fast, indicative of impairments in hedonic valuation of a solution (Mendez et al., 2015). Although this hints that β-endorphin may be acting at the NAc and not the CeA during consumption of rewarding foods, selective regional manipulations of β-endorphin function need to be performed to confirm that hypothesis.

Another unanswered question is whether opioid signaling in the NAc and CeA specifically underlies glucose-induced reward. Intermittent glucose binging increases MOR expression in the NAc shell and there is a positive linear relationship between glucose intake and MOR expression (Colantuoni et al., 2001). This sensitization of MOR signaling in the NAc may explain the escalation in glucose intake that occurs during extended access binging paradigms. This finding also provides evidence that excess glucose consumption can modify opioid signaling in reward-related areas, but does not rule out the possibility that overconsumption of other palatable foods − fructose, fatty acids − may cause similar changes in the brain, although consumption of a high-fat diet has been shown to *decrease* MOR mRNA in the NAc and other reward regions (Vucetic et al., 2011).

In conclusion, glucose signaling in the brain, particularly the hypothalamus, has been strongly implicated in the regulation of energy balance, glucose homeostasis, and food-induced reward (see Fig. 1). In the context of the obesity epidemic, further assessment of these mechanisms would seem to be highly relevant to public health in the 21st century.

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