Multiple hypothalamic circuits sense and regulate glucose levels

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Karnani M, Burdakov D. Multiple hypothalamic circuits sense and regulate glucose levels. Am J Physiol Regul Integr Comp Physiol 300: R47–R55, 2011. First published November 3, 2010; doi:10.1152/ajpregu.00527.2010.—The hypothalamus monitors body energy status in part through specialized glucose sensing neurons that comprise both glucose-excited and glucose-inhibited cells. Here we discuss recent work on the elucidation of neurochemical identities and physiological significance of these hypothalamic cells, including caveats resulting from the currently imprecise functional and molecular definitions of glucose sensing and differences in glucose-sensing responses obtained with different experimental techniques. We discuss the recently observed adaptive glucose-sensing responses of orexin/hypocretin-containing neurons, which allow these cells to sense changes in glucose levels rather than its absolute concentration, as well as the glucose-sensing abilities of melanin-concentrating hormone, neuropeptide Y, and proopiomelanocortin-containing neurons and the recent data on the role of ventromedial hypothalamic steroidogenic factor-1 (SF-1)/glutamate-containing cells in glucose homeostasis. We propose a model where orexin/hypocretin and SF-1/glutamate neurons cooperate in stimulating the sympathetic outflow to the liver and pancreas to increase blood glucose, which in turn provides negative feedback inhibition to these cells. Orexin/hypocretin neurons also stimulate feeding and reward seeking and are activated by hunger and stress, thereby providing a potential link between glucose sensing and goal-oriented behavior. The cell-type-specific neuromodulatory actions of glucose in several neurochemically distinct hypothalamic circuits are thus likely to be involved in coordinating higher brain function and behavior with autonomic adjustments in blood glucose levels.

hypocretin; hypothalamus; neuron; orexin

About half a century ago, subgroups of hypothalamic neurons were found to show specialized excitatory or inhibitory firing responses to extracellular glucose, revealing a strategy for how the brain can directly monitor body energy status (3, 69, 70). Glucose sensing in these glucose-excited and glucose-inhibited neurons was not a general energy-related response, because during examination of a large number of neurons in several brain areas, glucose-responding cells were observed only in the hypothalamus and brain stem, but not in other areas, such as the thalamus or cortex (1, 60, 69, 70, 80, 83, 111). More recent work suggests that glucose-sensing neurons may also be found in substantia nigra (113). It is important to emphasize that the effects of glucose on at least some of the glucose-sensing neurons are fundamentally different form the general effects of glucose on neuronal firing due to energy availability. While it may be argued that glucose-excited neurons are simply a more sensitive version of non-glucose-sensing neurons, which would also be stimulated by glucose, especially if they are energy depleted, glucose-inhibited neurons respond in the opposite way to that expected from the general stimulatory fuel injection effects of glucose, and their operation is thus clearly different from a general energy-related effect. Glucose-sensing cells are also found outside the brain, in tissues such as the endocrine pancreas [glucose-excited β-cells and glucose-inhibited α-cells (7, 81)] and the gut [glucose-excited L-cells (79)], but in this review we will predominantly focus on a selection of recent studies of glucose sensing in the hypothalamus. Our aim is not to provide a comprehensive overview of mechanisms of glucose sensing in the brain and periphery, but to highlight key findings and caveats in the recent work linking glucose sensing to specific neurochemically defined hypothalamic neurons and the implications of these findings for whole body glucose homeostasis. For detailed discussions of the electrophysiological and molecular mechanisms of glucose sensing in the brain and in peripheral glucose-sensing cells of the pancreas and the intestine, readers are referred to other recent reviews (e.g., 6, 21, 40, 58, 54, 63, 81, 102). To put the subject into a more general physiological perspective, we will begin with a brief overview of the nature and sources of glucose changes in the brain.

Physiological Fluctuations in Brain Glucose Levels

Simultaneous measurements of extracellular glucose levels in blood and brain show that brain [glucose] is generally lower than plasma [glucose], yet changes in blood [glucose] cause rapid parallel changes in brain [glucose] (83, 92). A thorough review of data on brain glucose levels (30) suggests that during euglycemia, brain glucose levels are ∼0.7–2.5 mM, and a
maximum of ~5 mM may be reached under severe plasma hyperglycemia. In turn, plasma hyperglycemia can cause the brain glucose to fall to 0.2–0.5 mM. This triggers counterregulatory responses where pancreatic glucagon and adrenal catecholamine secretion, as well as hepatic glucose production, are stimulated through activation of sympathetic nerves. Apart from the counterregulatory responses, which are orchestrated by glucosensors in both the brain and periphery (58, 85), hypocretin also induces feeding in mammals [glucoprivic feeding (93)]. Glucoprivic feeding has recently been suggested to involve glucose-sensing neurons in the ventromedial hypothalamus (VMH), since it was reduced by blockade of VMH glucokinase, a critical molecular component of some glucose-sensing neurons (31).

Although brain glucose levels are generally lower than those in the blood, it is commonly assumed that glucose concentrations can approach those in the blood at circumventricular organs, areas where the blood-brain barrier is highly permeable, such as the median eminence of the hypothalamus (35). However, it has recently been shown that this does not necessarily apply to brain structures in close vicinity, such as the arcuate nucleus (ARC) (31), perhaps because of tanyocyte barriers separating the ARC from the median eminence (64, 74).

Generally speaking, a meal will increase blood glucose and thus also brain glucose, but the extent to which this happens depends on the food. The potency of foods to increase blood glucose is measured as the glycemic index (48), and a major factor affecting this is the macronutrient composition of the food. In particular, meals high in protein or fat generally have a low glycemic index, i.e., they elevate blood glucose less than carbohydrate-rich meals. Another source of blood glucose is the endogenous production of glucose by the liver, which is also under hypothalamic control as reviewed below. Hepatic glucose production is controlled by the pancreatic hormones insulin and glucagon as well as, but to a lesser extent, directly by autonomic innervation (77). Insulin and parasympathetic innervation increase hepatic glucose uptake and glycogen synthesis, whereas glucagon and sympathetic innervation promote glycogenolysis, gluconeogenesis, and glucose release. Blood glucose is also affected by glucose uptake into muscle and adipose tissue, both of which are increased by insulin and sympathetic innervation (67). Below, we will first discuss the neurochemical identities and functional features of glucose-sensing hypothalamic neurons, and then focus on recent studies suggesting that they are key regulators of sympathetic drive that controls uptake and release of glucose in peripheral tissues.

Glucose-Sensing Capabilities of Neurochemically Defined Hypothalamic Neurons

The lateral hypothalamus. Most recent work focused on lateral hypothalamic (LH) cells that contain the peptide transmitters orexins/hypocretins, which are not expressed anywhere else in the brain (29, 86). Orexin/hypocretin-containing neurons project widely throughout the brain, with especially dense innervation of regions regulating arousal, metabolism, and reward (75). Lack of orexins/hypocretins produces the symptoms of narcolepsy/cataplexy, hypophagia, hypoactivity, and late onset obesity (23, 42). Orexin/hypocretin neurons are most active during wakefulness and almost silent during slow-wave sleep (32, 52). Several lines of evidence indicate that the activity of orexins/hypocretin neurons promotes wakefulness, sympathetic outflow, exploratory locomotor activity, reward seeking, and food consumption (13, 14, 44, 53, 91, 97, 99, 100, 109). Interestingly, recent studies also suggest that underactivity and overactivity of the orexin/hypocretin system could be linked to depression and anxiety, respectively (16, 17, 47, 98).

Whole animal studies looking at genetic markers of neuronal activation and orexin/hypocretin mRNA expression following in vivo manipulation of glucose levels concluded that orexin/hypocretin neurons are activated by systemic hypoglycemia (22, 61, 86) and could thus be glucose inhibited, especially considering that they are not directly modulated by insulin (110). During initial cellular level investigations of the effects of glucose on rat LH neurons, it was found that orexin-A/hypocretin-1 was not present in glucose-inhibited neurons (55); and a more recent electrophysiological study also failed to elicit responses to glucose in rat orexin/hypocretin neurons (71). In contrast, at least three different groups independently reported acute inhibition of orexin/hypocretin neurons by glucose, using calcium imaging in rat orexin/hypocretin neurons (65), or whole cell patch-clamp recordings from isolated mouse orexin/hypocretin cells (110), or mouse orexin/hypocretin cells in brain slices (41, 108).

The published discrepancies in the ability of glucose to inhibit orexin/hypocretin neurons could, in theory, be related to species differences (more responsive in the mouse, less responsive in the rat), which remain to be investigated in detail. If the rat orexin/hypocretin neurons are not electrically responsive to glucose, as suggested by the data in Ref. 71, then the calcium imaging data, which do show glucose-induced drops in calcium concentration in ~ 50% of rat orexin/hypocretin neurons (65), would suggest a possible dissociation between biochemical and electrical effects of glucose in these cells in the rat. As an alternative to the species differences explanation, the reported absence of acute glucose responses in orexin/hypocretin neurons in cytosol-sparing (cell-attached or perforated patch) recordings (71), but their presence in whole cell recordings (19, 110), could in theory be explained by a currently unidentified cytosolic factor, which suppresses the glucose-sensing ability of these cells in in vitro preparations, but whose influence is removed in the whole cell configuration due to the exchange of solution between the cytosol and the pipette in this recording mode.

The mechanism of glucose-induced inhibition of mouse orexin/hypocretin cells is not well understood but involves activation of background K+ channels (reviewed in Ref. 20). Interestingly, the glucose responses of orexin/hypocretin cells display a unique sugar selectivity, which suggests that the sensing pathway in orexin/hypocretin cells may be distinct from pathways involving glucose-binding proteins such as GLUT2, hSGLT3, and SGLT1 (39). The glucose responses of orexin/hypocretin neurons are also insensitive to glucokinase inhibitors and cannot be mimicked by the intracellular ATP or extracellular lactate, suggesting that they do not require conventional glucose-metabolizing machinery (39, 40).

Interestingly, at physiological temperatures, ~70% of orexin/hypocretin cells exhibit only transient, or adaptive, responses to sustained physiological rises in glucose levels (Fig. 1). Importantly, this allows orexin/hypocretin neurons to adjust their baseline potential to background glucose levels, and thus to...
membrane potential back to baseline despite the continuing presence of orexin/hypocretin cell is transiently inhibited by glucose but then adapts its response to a second change in glucose levels. (Composited from Figs. 1, 4, and 5 of Ref. 108 with permission from Proc Natl Acad Sci USA).

This steep temperature sensitivity is consistent with classical sensory organs such as the eye, this adaptation allows orexin/hypocretin neurons to adjust their glucose sensitivity to background glucose levels (108). In other words, the glucose dose-response curve of orexin/hypocretin cells is not fixed, but can slide along the glucose concentration axis depending on the glucose baseline. Analysis of membrane currents and membrane resistance during the glucose adaptation response of orexin/hypocretin cells suggests that the cellular mechanism of this adaptation involves a time-dependent closure of the hyperpolarizing ion channels originally opened by glucose, rather than opening of an additional population of depolarizing channels (108). How these channels become less active with time after they are opened by glucose is currently unknown, but this process is highly temperature sensitive [very slow or undetectable at room temperature but prominent at 35°C (108)]. This steep temperature sensitivity is consistent with a process involving internalization/endocytosis of the glucose-activated channels and/or putative glucose receptors; this possibility, as well as alternative explanations (e.g., phosphorylation-induced desensitization), remain to be examined.

Because orexin/hypocretin neurons are thought to stimulate wakefulness and signal reward deficiency, their inhibition by glucose may, in theory, be involved in anxiolytic, rewarding, and soporific effects of sugar ingestion (reviewed in Ref. 18), as well as in the regulation of blood glucose levels (see Hypothalamic Glucose-Sensing Neurons as Regulators of Peripheral Glucose Handling). In terms of arousal and reward, there is a theory that proposes a functional separation of the orexin/hypocretin system into a lateral population that regulates reward and a medial population that regulates arousal (43). At least in the mouse, inhibition of orexin/hypocretin cells by glucose does not appear to follow such a clear topographic separation; the glucose responses are observed in most if not all orexin/hypocretin cells across both lateral and medial parts of the lateral hypothalamic area, suggesting that glucose may affect both arousal and reward-related parts of the orexin/hypocretin system (108). However, analysis of the time course of glucose responses in mouse hypothalamus suggests that the medial group of orexin/hypocretin cells contains a greater proportion of adaptive orexin/hypocretin neurons than the lateral group (108). It is thus tempting to speculate that adaptive and nonadaptive glucose-sensing responses may be differentially involved in arousal or reward.

Another population of widely projecting lateral hypothalamic cells use the peptide transmitter melanin-concentrating hormone (MCH) (10). Although, like orexins/hypocretins, MCH is often considered an appetite-promoting transmitter, in many other respects the physiological roles of MCH neurons appear to be the opposite of those of orexin/hypocretin cells. In mice, knockout of MCH increases energy expenditure and reduces body weight (88), and these characteristics are also seen in animals lacking the MCH receptor -1 (MCH1R) (57).

Central injection of MCH in rats increases the quantities of rapid eye movement and especially slow-wave sleep (106), while deletion of MCH or MCH1R in mice leads to increased wheel-running activity (115). These data suggest that endogenous MCH promotes sleep and suppresses locomotor activity and energy expenditure, i.e., the opposite of actions of orexins/hypocretins. It should be noted that, while MCH neurons are often referred to as appetite promoting, their role in the control of food intake is not entirely clear cut. For example, in mice, knockout of MCH increases food intake during the day but decreases it at night with the net daily result being a reduction in food intake (88). Although most (57, 78, 82), but not all (76), studies show that brain injections of MCH increase food intake, mice lacking the MCH receptor actually exhibited increased food intake (24, 57). Feeding-related effects of MCH thus appear to be complex, and may be influenced by its possible roles in anxiety and depression (15, 37). A closely related issue, which remains to be resolved, is whether MCH neurons are a functionally homogenous population or comprise subsets of cells with different profiles of ion channels and receptor expression and differential projection patterns, giving rise to several different behavioral roles, as recently proposed for orexin/hypocretin neurons (43).

Examination of the effects of changes in glucose on the electrical excitability of MCH neurones using whole cell recordings in mouse brain slices suggests that most MCH neurones are directly and dose-dependently depolarized and ex-
cited by glucose within the physiological concentration window (19). Based on the above-mentioned effects of MCH on locomotor activity and body energy balance, these data imply that glucose-induced excitation of MCH neurones may promote sleep and suppress energy expenditure. To the best of our knowledge, the glucose-sensing abilities of MCH neurons have not yet been examined in species other than mouse or with different recording techniques.

**ARC of the hypothalamus.** This hypothalamic region is currently probably the best understood in terms of the control of appetite and metabolism. The generally accepted model is that the ARC of the hypothalamus, neuropeptide Y (NPY) neurons promote weight gain by stimulating appetite and suppressing energy expenditure, whereas ARC proopiomelanocortin (POMC) neurones cause weight loss by inhibiting feeding and stimulating energy expenditure (26, 87). A key feature of this model is that NPY and POMC neurones are oppositely regulated by signals of body energy status, such as leptin (26–28, 87, 105). Whether the NPY and POMC neatly correspond to glucose-inhibited and glucose-excited neurones, respectively, which would fit in nicely into the above model, is still debated. For example, Muroya et al. (66) concluded that 94% of ARC cells that decreased their calcium levels in response to glucose were immunonecactive for NPY. Whole cell patch-clamp recordings also indicated that a significant proportion (40%) of NPY neurones are glucose inhibited (34). But, in contrast, perforated patch recordings of Clare et al. (25) failed to show inhibitory effects of glucose on NPY cells. These discrepancies appear to show a similar methodology correlation to discrepancies in the studies of orexin/hypocretin neurones noted above; in both NPY and orexin/hypocretin cells, glucose-induced inhibition appears to be readily observed in whole cell recordings but, paradoxically, not in the less invasive perforated patch recordings. Interestingly, for arcuate glucose-excited POMC neurones, the differences in the literature appear to follow the opposite methodology correlation. Specifically, Fioramonti et al. (34) did not observe any glucose responses in most POMC neurones when using the cytosol-disrupting whole cell recordings. In contrast, using the cytosol-preserving loose patch or perforated patch recordings shows that the majority of POMC neurones are excited by glucose in the physiological concentration range (25, 46, 72). We would like to propose that the operation of glucose-excited neurones requires a highly diffusible cytosolic messenger [presumably ATP (59), but see Ref. 2] and can thus be particularly easily disrupted especially in small cells by experimental techniques that wash out the cytosol (such as the whole cell recording with large-tipped pipettes). In contrast, glucose-inhibited neurones use a completely different (but as yet undetermined) intracellular signaling pathway (see Refs. 39 and 40), and we would like to speculate that this pathway is boosted in whole cell recordings, possibly due to diffusion of a suppressor substance(s) away from cytosol into the pipette.

** Ventromedial nucleus of the hypothalamus.** This hypothalamic area is probably the most studied in terms of brain glucose sensing and has long been known to contain both glucose-excited and glucose-inhibited neurones. However, in terms of neurochemistry of glucose sensing, the ventromedial nucleus of the hypothalamus (VMH) is currently understood much less than the ARC and LH. Single cell gene expression analysis suggests that some VMH neurones, including glucose-excited cells, are GABAergic; however, the GABAergic marker GAD is not expressed in a clear relationship to glucose-sensing capacity (49, 59). Recent data show that most VMH neurones express a protein called steroidogenic factor-1 (SF-1) and that SF-1-expressing neurones have key roles in glucose homeostasis (103, 114). However, how SF-1 expression relates to glucose-excited and glucose-inhibited neurones of the VMH is currently unclear, although there is some interesting recent data that indirectly suggest that some of the glucose-inhibited VMH neurones may express SF-1 and glutamate (see discussion at the end of Hypothalamic Glucose-sensing Neurons as Regulators of Peripheral Glucose Handling). Perhaps the most critical issue to resolve here is how gene expression and glucose-sensing identities of VMH neurones relate to their projection targets, since there is emerging evidence that different subregions of the VMH are differentially connected to other key feeding centers, such as the ARC (96).

### Need for Better Functional and Molecular Markers of Glucose Sensing

After glucose sensing has been linked to specific populations of vital neurones described above, more and more researchers have moved into this field, creating an increasing demand for clear criteria for classifying neurones as glucose excited and glucose inhibited. In terms of functional experiments, a key source of uncertainty stems from the fact that glucose is used as an energy fuel by all neurones, either directly or indirectly by stimulating lactate production by astrocytes (71, 73). Thus, experimental alterations of glucose levels can often elicit general energy-related and/or neuroprotective responses that are unrelated to specific glucose sensing. An example of this is silencing of neurones by very low glucose, which is a widespread response found in both glucose-sensing and non-glucose-sensing neurones and often involving neuroprotective opening of ATP-inhibited K (KATP) channels, and consequent hyperpolarization, induced by the fall in glucose (and thus cytosolic ATP) levels (9, 60). Although in glucose-excited neurones the hyperpolarization induced by 0 mM glucose is likely to be much faster than in non-glucose-sensing neurones, and thus the speed of hyperpolarization has been used by some researchers to identify glucose-sensing cells, this criterion can be very sensitive to experimental variables such as location of cells in the recording chamber and in the tissue (for brain slice recording). For these reasons, a more robust, and more physiological, criterion for classifying a glucose-excited neurone as glucose sensing would perhaps be a test of whether its firing can be significantly affected by changes in extracellular glucose in the physiological glucose range in the brain, e.g., 1 to 2.5 mM (83), although there is currently no agreement on how large the effects on firing should be to pass this qualifying test. As mentioned in the introduction, the functional definition of glucose-inhibited neurones is much more clear, because their membrane potential responses to glucose occur in the opposite direction (hyperpolarization) from the general energy-related effects of glucose (depolarization).

In terms of molecular definitions of brain glucose-sensing cells, no molecules unique to glucose-sensing cells have yet been identified. Several markers of glucose-sensing ability have been proposed, including KATP channels, glucokinase, AMP kinase, and the GLUT2 transporter (25, 101, 111), but...
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the correlation between the expression of these proteins and the brain locations of glucose-sensing neurons is imperfect (5, 49, 50). For glucose-inhibited neurons, the need for molecular markers is particularly critical since even the final effector channels remain to be defined in exact molecular detail (20). It is probably accurate to say that it is currently unknown exactly what makes glucose-sensing neurons distinct from other neurons at the molecular level.

Hypothalamic Glucose-Sensing Neurons as Regulators of Peripheral Glucose Handling

Although ARC neurons send signals to key central and peripheral regulators of energy balance (95, 62), the roles of glucose sensing in the POMC and NPY cells in glucose homeostasis remain somewhat unclear, despite recent attempts to inactivate NPY/POMC glucosensing through targeted genetic manipulations [(25, 72), but see discussion in Refs. 54 and 40]. In orexin/hypocretin and MCH neurons, an equivalent analysis has not been performed due to the lack of knowledge of molecular components of glucose sensing in these cells (19, 20, 38). However, the original study by Yamanaka et al. (110) that described the intrinsic inhibitory responses of orexin/hypocretin cells to glucose also observed a lack of fasting-induced stimulation of arousal in mice lacking orexins/hypocretins, suggesting that disinhibition of orexin/hypocretin cells by falling glucose may have a role in the initiation of foraging. In this section, we will not discuss the involvement of glucose-sensing neurons in behavior and higher brain function further but instead discuss recent findings on their interactions with peripheral tissues relevant to glucose homeostasis, focusing in particular on recent work on control of glucose homeostasis by LH orexin/hypocretin neurons and VMH SF-1 neurons.

As reviewed in Refs. 33 and 104, orexin/hypocretin neurons can control basal metabolic rate in addition to alertness and reward seeking. Intracerebroventricular administration of orexin-A/hypocretin-1 increases energy expenditure even in anesthetized rats (107). A number of experiments (4, 89) showed that intracerebroventricular or intrathecal administration of orexin/hypocretin stimulates sympathetic outflow and increases plasma epinephrine and norepinephrine levels. Anatomical data employing pseudorabies virus transsynaptic tract tracing (36, 51, 95) or electron microscopy and cholera toxin B subunit tracing (56), show that orexin/hypocretin cells project polysynaptically to various sympathetic outflow systems. Two recent papers have demonstrated the potential physiological significance of these findings in relation to glucose homeostasis.

The data of Yi et al. (112) suggested that orexin/hypocretin neurons, especially those in the perifornical area, can stimulate endogenous glucose production and increase blood glucose through sympathetic nervous control. They retrodialyzed bicuculline into the LH and found that orexin/hypocretin neurons were specifically activated in the perifornical area. This led to stimulation of hepatic glucose production, which was inhibited by intracerebroventricular pretreatment with an orexin/hypocretin receptor antagonist. An increase in endogenous glucose production was also induced by intracerebroventricular injection of orexin-A/hypocretin-1, and this increase was inhibited by hepatic sympathetic denervation.
whether MCH neuron activity increases or decreases sympathetic outflow to these organs.

The VMH is especially important for the counterregulatory response (84). Local glucoprivation in the VMH results in pancreatic glucagon secretion (12) and glucose infusion into the VMH suppresses glucagon secretion in response to falling blood glucose (11). In turn, the blunting of the counterregulatory response by repetitive hypoglycemia is associated with an impairment of glucosensing in VMH glucose-inhibited neurons (94). Although the precise cellular mechanisms of the counterregulatory response are not fully understood, and other factors, such as glucosensors in the portal vein, play a critical role (45), these data suggest that, like the orexin/hypocretin neurons, the VMH glucose-sensing neurons may control sympathetic outflow. As the glucose-sensing VMH cells are not currently neurochemically identified, it is not yet straightforward to demonstrate a connection to sympathetic innervation targets by tracing techniques. However, some hypotheses can be formulated from data looking at the expression of GAD-67 (glutamic acid decarboxylase, a GABAergic marker) in VMH neurons that are likely to be glucose excited (59) and experiments looking at systemic effects of inactivation of glutamate release from VMH SF-1 neurons (103). The former study suggests that VMH glucose-excited neurons are GABAergic, whereas the latter shows that the counterregulatory release of glucagon upon fasting, which is stimulated by the sympathetic system, requires glutamate release from VMH SF-1 neurons. Therefore, we hypothesize that glucose-inhibited VMH neurons that increase sympathetic outflow and control glucagon secretion are glutamatergic (Fig. 2), whereas at least some of VMH glucose-excited neurons are GABAergic [in line with the recent demonstration that glucose stimulates GABA release in the VMH, (116)].

Perspectives and Significance

Many glucose-sensing neurons of the hypothalamus have now been assigned neurochemical identities and are beginning to be linked to specific higher and lower functions of the nervous system (Fig. 2). Most, if not all, of the glucose-sensing neurons of the hypothalamus are well placed to affect peripheral glucose utilization in liver, muscle, and adipose tissue through the autonomic nervous system (Fig. 2). Most, if not all, of the glucose-sensing neurons that are likely to be glucose excited (59) and experiments looking at systemic effects of inactivation of glutamate release from VMH SF-1 neurons (103). The former study suggests that VMH glucose-excited neurons are GABAergic, whereas the latter shows that the counterregulatory release of glucagon upon fasting, which is stimulated by the sympathetic system, requires glutamate release from VMH SF-1 neurons. Therefore, we hypothesize that glucose-inhibited VMH neurons that increase sympathetic outflow and control glucagon secretion are glutamatergic (Fig. 2), whereas at least some of VMH glucose-excited neurons are GABAergic [in line with the recent demonstration that glucose stimulates GABA release in the VMH, (116)].

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Review

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