Brain glucose sensing and body energy homeostasis: role in obesity and diabetes

BARRY E. LEVIN,1,2 AMBROSE A. DUNN-MEYNELL,1,2 AND VANESSA H. ROUTH2,3
1Neurology Service, Veterans Affairs Medical Center, East Orange 07018;
and 2Department of Neurosciences and 3Pharmacology and Physiology,
New Jersey Medical School, Newark, New Jersey 07103

Levin, Barry E., Ambrose A. Dunn-Meynell, and Vanessa H. Routh. Brain glucose sensing and body energy homeostasis: role in obesity and diabetes. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1223–R1231, 1999.—The brain has evolved mechanisms for sensing and regulating glucose metabolism. It receives neural inputs from glucosensors in the periphery but also contains neurons that directly sense changes in glucose levels by using glucose as a signal to alter their firing rate. Glucose-responsive (GR) neurons increase and glucose-sensitive (GS) decrease their firing rate when brain glucose levels rise. GR neurons use an ATP-sensitive K⁺ channel to regulate their firing. The mechanism regulating GS firing is less certain. Both GR and GS neurons respond to, and participate in, the changes in food intake, sympathoadrenal activity, and energy expenditure produced by extremes of hyper- and hypoglycemia. It is less certain that they respond to the small swings in plasma glucose required for the more physiological regulation of energy homeostasis. Both obesity and diabetes are associated with several alterations in brain glucose sensing. In rats with diet-induced obesity and hyperinsulinemia, GR neurons are hyporesponsive to glucose. Insulin-dependent diabetic rats also have abnormalities of GR neurons and neurotransmitter systems potentially involved in glucose sensing. Thus the challenge for the future is to define the role of brain glucose sensing in the physiological regulation of energy balance and in the pathophysiology of obesity and diabetes.

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IT IS CLEAR THAT THE BRAIN both monitors and regulates the energy needs of the body. What is less clear is the way in which the periphery signals its energy needs to the brain. We now know that both carbohydrate and adipose stores are monitored by the brain using combinations of metabolic and neural signals from the periphery. These signals enter the brain and trigger neuroendocrine and autonomic responses that maintain energy homeostasis over a fairly wide variety of environmental perturbations. However, in the highly interconnected conditions of obesity and non-insulin-dependent diabetes mellitus (NIDDM), there appear to be major resettings of normal homeostatic mechanisms. In particular, the brain’s ability to monitor and respond to alterations in glucose metabolism becomes aberrant in both individuals predisposed to become obese (obesity prone) and those already obese and diabetic. Such dysregulation also occurs in insulin-dependent diabetes mellitus (IDDM). Whereas much is known about the way in which the brain senses glucose, much remains to be learned about the way in which this information is used to regulate energy homeostasis under physiological circumstances. This review is intended to bring the reader up to date with what is known and act as a potential stimulus for future research into the rapidly expanding field.

Of all the macronutrients, the brain must maintain carbohydrate metabolism within narrow boundaries over short time frames because it uses glucose as a primary fuel and carbohydrate stores are extremely limited (102). The brain monitors plasma glucose levels by both direct (3, 81) and indirect means (30). Oomura et al. (81) and Anand et al. (3) identified neurons within areas of the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH) that altered their firing rates when plasma glucose levels changed. These areas
were explored first because of their proposed roles as “feeding” and “satiety” centers (105), respectively, making it logical that they might monitor peripheral glucose levels as a means of controlling ingestion (70). Later, Oomura et al. (82) showed that directly applied glucose altered the firing rate of select neurons. They defined “glucose-responsive” (GR) neurons as those that increased and “glucose-sensitive” (GS) neurons as those that decreased their firing rates when ambient glucose levels rose. In areas such as the LH, VMH, and nucleus of the solitary tract, 20–40% of neurons sampled showed glucose-sensing properties (36, 72, 83, 100). However, there are other brain areas not thought to be involved in ingestive behavior that also contain glucose-sensing neurons and/or neurons with the potential machinery to sense glucose.

On the basis of observations that changes in glucose use affect food ingestion, Mayer (70) proposed the glucostatic hypothesis (70) whereby glucose-sensing neurons participated in the short-term regulation of energy intake. Later, Louis-Sylvestre and Le Magnen (65) found that 6–8% dips in plasma glucose were associated with meal initiation. Certainly large reductions in plasma glucose levels or glucose availability can stimulate food intake (86). But to date, it remains uncertain whether the brain can actually detect small changes in plasma glucose or if this might be a primary stimulant of meal initiation. However, central neurons do respond to larger changes in peripheral glucose levels transmitted from portal vein glucosensors by direct neural inputs (30) and by a direct action of glucose that enters the brain by a transport-mediated process (111). Most brain glucose is used primarily as substrate for the energy needs of neurons and glia and does not alter the firing rate of the majority of neurons. However, the fact that a small group of neurons within brain areas tied to ingestive behavior that also contain glucose-sensing properties (36, 72, 83, 100). However, there are other brain areas not thought to be involved in ingestive behavior that also contain glucose-sensing neurons and/or neurons with the potential machinery to sense glucose.

GR neurons. GR neurons are illustrated in Fig. 1. These neurons increase their firing rate when ambient glucose levels rise and cease firing when glucose is removed (82). This response is modulated by a K+-channel that is sensitive to the intracellular ratio of ATP to ADP. Thus it is called the ATP-sensitive K+-channel (KATP) (109). The KATP channel is inactivated by direct binding of ATP, whereas phosphorylation of the channel increases its activity (89). This channel was first identified in pancreatic β-cells where binding of ATP derived from intracellular glucose metabolism inactivates (closes) the channel. This increases intracellular K+, resulting in Ca2+ influx, cellular depolarization, and insulin release (109). The KATP channel is actually a functional unit composed of a pore-forming unit (Kir6.2) for K+ (109) and a binding site for sulfonylureas, a class of insulin secretagogues. The Kir6.2 pore-forming unit is a member of the inwardly rectifying K+-channel family (32, 96). The sulfonylurea receptor (SUR) is a member of the ATP-binding cassette family and is essential for KATP channel function (32). As with ATP derived from intracellular glucose metabolism, occupation of the SUR inactivates the channel and stimulates insulin secretion. Conversely, drugs known as the K+ channel openers have the opposite effect. They open the KATP channel causing K+ efflux, cellular hyperpolarization, and prevention of insulin secretion (29).

In addition to the pancreatic β-cell the KATP channel resides on smooth and cardiac muscles and other nonneural tissues. The KATP channel is present on brain GR neurons but not glia (20). The Kir6.2 pore-forming unit (20, 32, 35, 63) and both a high (SUR1)- and low (SUR2)-affinity form of the SUR have been cloned and identified in brain (21, 33, 49, 51, 63, 114). A presumptive endogenous ligand for the SUR, α-endosulfine, was also identified in the brain (84) but little is known about

**Fig. 1.** Hypothetical model of ATP-sensitive K+-channel (KATP) complex on glucose-responsive (GR) neurons. Neuronal cell bodies may contain a glucose transporter (possibly GLUT-2) and/or a hexokinase (possibly glucokinase (GK)), which regulates entrance of glucose into cell and rate of glycolysis, respectively, at physiological concentrations found in brain. Hexokinase is located in plasma membrane close to KATP channel. Channel is composed of a low-affinity sulfonylurea receptor (SUR2) and Kir6.2 pore-forming unit. This arrangement provides relatively high ratios of ATP to ADP at the channel during glycolysis. Binding of ATP inactivates channel, whereas phosphorylation increases its activity. At axon terminals of GABA, glutamate, or other transmitter neurons, KATP channel consists of a high-affinity SUR (SUR1) and Kir6.2 pore-forming unit. Either binding to channel of ATP derived from glycolysis or occupation of SUR would inactivate channel, leading to increased firing of neuron or transmitter release at terminal.
ATP levels would fall. This would activate the K\textsubscript{ATP} channel, causing egress of intracellular K\textsuperscript{+} and neuronal hyperpolarization. This would antagonize the excitatory toxicity of glutamate released under such circumstances.

Both high-affinity SUR binding sites (21, 49, 51, 74) and the message for the high-affinity SUR1 and the Kir6.2 pore-forming unit (20, 35) are widely distributed throughout the brain. However, brain sites that are critically integrated into pathways regulating autonomic function, metabolism, and energy balance contain a relative paucity of high-affinity SUR binding sites (21, 49, 51). On the other hand, low-affinity SUR binding sites make up ~20–40% of total binding sites in these areas (49, 51). This matches the proportion of GR neurons that are present in these same brain areas (100). Because selective destruction of neuronal cell bodies in such areas abolishes low- but not high-affinity SUR binding, we have proposed that the low-affinity SUR site is located on neuronal cell bodies (21). This low-affinity site should be the SUR2, and we have now used in situ hybridization to show that SUR2 mRNA is localized in these same areas and in the same relative abundance as low-affinity SUR sites (unpublished data).

At least some high-affinity SUR sites appear to be located on GABA (20–22) and glutamate (44) nerve terminals. Raising ambient glucose concentrations at these terminals causes them to release their transmitters. On the other hand, both dopamine (63) and norepinephrine neurons (31) are GR with regard to cell firing rate, but their terminals do not appear to contain the K\textsubscript{ATP} channel (21). Areas such as the substantia nigra contain both dopamine neurons with cell body K\textsubscript{ATP} channels (63) and axon terminals of GABA neurons, which also contain both the Kir6.2 and the high- and low-affinity SUR binding sites (20, 22, 56). Raising ambient glucose levels or infusion of the sulfonylurea glyburide releases the inhibitory transmitter GABA (22), and this opposes the direct action of glucose on the K\textsubscript{ATP} channel to stimulate firing of nigral dopamine neurons (56, 63). The resultant firing rate of nigral dopamine neurons thus becomes highly dependent on ambient glucose concentrations. At lower concentrations, transient stimulation of dopamine neuron firing prevails, whereas at higher concentrations, GABA-induced inhibition predominates (56). Similarly, one might predict that low concentrations of sulfonylureas would stimulate GABA release by acting on the high-affinity SUR1 site, whereas higher concentrations should act at the low-affinity SUR2 site to stimulate firing of the dopamine cell body directly. Similar interactions can be expected in any area that contains both neuronal cell bodies and axon terminals of neurotransmitter neurons that contain a full complement of GR mechanisms.

Finally, there are probably several types of GR neurons that differ in their firing characteristics, conductances, and sensitivities to glucose, sulfonylureas, and/or ATP (89, 98, 100). In a given population, individual neurons may contain different proportions of the SUR1, SUR2, and Kir6.2 units of the K\textsubscript{ATP} channel (63). Some of the observed differences in glucose responsiveness may also be due to the fact that there are various subconductances of the K\textsubscript{ATP} channel. Thus the conductance of an individual channel on a given neuron may

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vary from moment to moment depending on ambient conditions (89).

GR neurons have several transmitter peptide phenotypes. Dopamine (20), norepinephrine (20), GABA (20), and glutamate (43) all express the K\textsubscript{ATP} channel. In the hypothalamic arcuate nucleus (Arc), several neurons also express Kir6.2 (20). Arc neurons also contain a functional K\textsubscript{ATP} channel (Fig. 2). Of particular interest are those Arc neurons that coexpress both the K\textsubscript{ATP} channel and neuropeptide Y (NPY) (20). These neurons exemplify a class of neurons that are potentially capable of monitoring and integrating a multitude of metabolic and neural signals from both the periphery and brain. Arc NPY neurons express not only Kir6.2 (20) but also leptin receptors (28) and possibly insulin receptors (67). A functional relationship is suggested by the fact that GR neurons from this area of the hypothalamus are hyperpolarized by the actions of both leptin (103) and insulin (90) on the K\textsubscript{ATP} channel. Arc NPY neurons project to the hypothalamic paraventricular nucleus (PVN), which is linked to both neuroendocrine and autonomic afferent pathways (7). Central NPY injections induce a host of anabolic events, including increased food intake (104) and food-induced insulin release (110), decreased brown adipose thermogenic capacity (27), and a shift from lipid to carbohydrate oxidation (11). Restriction of energy intake (15) and glucoprivation (2) both increase NPY expression selectively in Arc NPY neurons. This supports the idea that they are specialized to respond to alterations in energy availability. Hypothalamic glucose-sensing neurons, including those in the Arc (9), also respond to a host of neurotransmitters and peptides, including monoamines (38), GABA (38), vasopressin, and oxytocin (37). Thus numerous intrinsic and extrinsic signals related to energy homeostasis converge on cells such as the Arc NPY neurons where they are integrated and passed on to downstream effector areas responsible for energy intake, expenditure, and storage. It is highly likely that there are many other types of such integrator neurons throughout the brain that can monitor multiple metabolic signals and participate in the regulation of energy homeostasis.

GS neurons. These neurons respond to increasing glucose levels by decreasing their firing rate. Whereas they have been characterized electrophysiologically, less is known of the mechanism(s) regulating their firing. Oomura et al. (83) proposed that GS activity is regulated by the Na\textsubscript{+}/K\textsuperscript{+}-ATP pump (83). Unfortunately, there are no markers for GS neurons comparable to the K\textsubscript{ATP} channel in GR neurons that allow direct characterization of their location and phenotype. Increased c-Fos expression is seen within several hypothalamic, amygdalar, and brainstem areas involved in autonomic activity when glucopenia is induced (80, 85). Although this is an indirect index of neuronal activation, it does not necessarily mean such neurons are GS, merely that they are in the pathway of neurons activated by glucoprivation. On the other hand, direct electrophysiological measurement of firing rate during local glucoprivation has identified GS neurons in areas such as the LH (5) and amygdala (75). GS neurons also receive inputs from peripheral glucose-sensing afferents (99). Besides their direct activation by reduced glucose availability, GS neurons in these areas can also be conditioned to respond to food-related cues independent of ambient glucose levels (5, 75). Finally, these areas are integrated into circuits known to mediate the affective and reward components of ingestion with those that modulate its metabolic effects (40, 41). Thus GS neurons may represent an important interface between systems controlling the affective and metabolic component of energy homeostasis (Fig. 2).

ROLE OF GLUCOSE-SENSING NEURONS
IN ENERGY BALANCE

There is little question that the brain senses and responds to excessively high and low levels of plasma glucose. However, it has been much more difficult to show that glucose levels within the physiological range are used by the brain to regulate energy balance. Alterations in plasma glucose of 2 mM alter brain glucose levels by 0.2–0.3 mM within 10 min, and this is associated with changes in firing of glucose-sensing
neurons (100). But these levels are still far greater than the <0.5 mM changes in plasma glucose postulated to trigger meal initiation (65). Whereas both the LH feeding and VMH satiety centers (105) contain relatively high proportions of GS and GR neurons, respectively (5, 100), there is no convincing evidence that alterations in glucose availability in either area can initiate or terminate meals. Intraportal (8) and intrace-rebroventricular (18) glucose infusions produce small but significant reductions in food intake but it is unclear whether such infusions are within the physiological range.

On the other hand, neurons in the VMH and LH, as well as other hypothalamic areas involved in autonomic regulation are definitely activated in response to both severe hypo- and hyperglycemia (3, 36, 81). Relatively large intravenous or intracarotid glucose infusions produce generalized sympathetic nervous system activation in some humans (92) and animals (47, 48, 58–60) and this can be independent of changes in plasma insulin levels (47, 59). Selective increases in sympathetic nerve activity in thermogenic tissues such as brown adipose depots can be elicited by intracarotid (95), intracerebroventricular (42), and direct glucose infusions into the PVN (94) and VMH (93) (but see Ref. 12). This might underlie the increased energy expenditure produced by an oral glucose load (101). Similarly, intravenous (78) or intracarotid (77) glucose infusions variably increase parasympathetic (vagal) output to the pancreas and liver. Local infusion of glucose into the LH but not VMH increases vagal output to the pancreas (79). Again, there is the question of the physiological relevance of such studies compared with the changes in brain glucose that follow food intake, the usual physiological cause of increased plasma glucose levels.

Similar issues arise when trying to evaluate the role of small changes in plasma and brain glucose in modulating physiological functions. Both peripheral (25) and central glucoprivation (86) stimulate food intake. But the stimuli for this are far outside the usual variations in plasma glucose postulated to initiate ingestion (65). Similarly, systemic, intracerebroventricular (23), and local LH (but not VMH) glucopenia (24) reduce neural activity to brown adipose, suggesting that glucopenia might reduce energy expenditure. Importantly, the brain detects and responds to severe glucoprivation by mounting a neuroendocrine counter-regulatory response that mobilizes remaining glucose stores. This response can be mimicked by infusion of 2-deoxyglucose into the VMH (14). On the other hand, either VMH lesions (13) or VMH glucose infusions (12) prevent the counterregulatory response to systemic hypoglycemia. This implicates the VMH as critical to this response. The LH (113) and brain stem (19) also appear to be important for such responses.

Glucose-modulated receptor binding. By as yet unknown means, changes in plasma glucose are paralleled by alterations in ligand binding to a variety of receptors in the brain. For example, $\alpha_2$-adrenoceptor binding in various forebrain areas shows a positive correlation with plasma glucose levels across a physiological range of 3–14 mM (4, 57). A similar correlation with plasma glucose levels (and with $\alpha_2$-adrenoceptor binding) also occurs with binding to a class of putative anorectic receptors in the brain (4). Finally, binding to low-, but not high-affinity SUR sites is reduced in select forebrain areas by only 1 h of intracarotid glucose infusions (51). This latter phenomenon suggests that relatively short-term changes in glucose levels can alter the function of the glucose-sensing mechanism ($K_{\text{ATP}}$ channel) that allow GR neurons to sense glucose. These changes can be mimicked in vitro with glucose concentrations from 0 to 10 mM (51). Again, the mechanism for such changes is unknown but could be related to changes in the phosphorylation state of the receptors induced by intracellular glucose metabolism.

BRAIN GLUCOSE SENSING IN OBESITY AND DIABETES

Obesity and NIDDM. In rodent models, obesity and NIDDM are inextricably linked because of the presence of hyperinsulinemia and insulin resistance (58, 61). There is also a very high incidence of NIDDM in obese humans (107). Thus it is often difficult to separate the effects of hyperinsulinemia from those related to other metabolic aspects of obesity when assessing brain function in these cases. This is important because insulin affects $K_{\text{ATP}}$ channel function (90) as well as transmitter and peptide systems that could indirectly alter channel function (55, 97).

We have used the rat model of diet-induced obesity (DIO) to investigate abnormalities of glucose regulation in obesity. When outbred rats are fed a diet moderately high in calorie, fat, and sucrose content, one-half develop DIO and the rest are diet-resistant (DR), gaining no more carcass fat than controls fed a low-fat diet (58, 60, 62). Inbreeding studies suggest that this is a polygenic trait, similar to some human obesity (53). DIO rats have reduced sympathetic input to their pancreas (62) but have an exaggerated sympathetic response to both intravenous (58, 60) and intracarotid glucose infusions (48). By contrast, intracarotid glucose infusions selectively increase c-Fos expression in neurons of the VMN, PVN, and Arc only in DR rats (54). This apparent paradox can be explained by postulating that glucose-induced activation of forebrain GR neurons normally inhibits, whereas glucose-induced inhibition of GS neurons normally increases, sympathetic activity. Thus increased forebrain glucose levels would have no effect on sympathetic activity in DR rats because of simultaneous activation of GR neurons and inhibition of GS neurons. But in obesity-prone rats, sympathetic stimulation would occur because of their impaired activation of inhibitory GR neurons, whereas GS neurons were normally inactivated.

DIO rats also exhibit several other signs of reduced central glucose sensitivity. They do not upregulate forebrain $\alpha_2$-adrenoceptor binding normally to increased plasma glucose levels (57). Obesity-prone rats...
increased. When the caloric density and dietary fat content is unique to the propensity of such animals to become obese, the dysregulation of glucose-modulated NPY expression may contribute to the development of increased metabolic efficiency and obesity when obesity-prone rats are exposed to a high-energy diet. Such defective glucose sensing and the development of glucose-reduced central sensitivity to glucose may be a predisposing factor to the development of hyperglycemia increases c-Fos expression in these neurons (54), they have not directly been shown to be GR. Somewhat paradoxically, both fasting and glucopenia increase NPY (2), whereas glucopenia increases c-Fos expression in these neurons (71). The failure of DIO Arc neurons to respond to altered glucose levels might contribute to the basal overexpression and failure to increase NPY message in energy-restricted obesity-prone rats (52). A similar dysregulation of Arc NPY occurs in both obese Zucker (fa/fa) rats (10) and ob/ob mice (106). Such dysregulation of glucose-modulated NPY expression may contribute to the propensity of such animals to become obese when the caloric density and dietary fat content is increased.

have reduced or absent low-affinity SUR binding throughout their forebrains (49) and do not downregulate these few receptors normally to raised glucose levels (51). Finally, VMH neurons in obesity-prone rats have defective KATP channel sensitivity to both ATP and sulfonylureas (88). Interestingly, obese Zucker (fa/fa) rats have no identifiable VMH KATP Channel (91). Thus reduced central sensitivity to glucose may be a predisposing factor to the development of increased metabolic efficiency and obesity when obesity-prone rats are exposed to a high-energy diet.

Arc NPY neurons may be a potential link between such defective glucose sensing and the development of DIO. Arc neurons have a functional KATP channel (Fig. 3) and are activated by raising forebrain glucose levels in DR but not DIO rats (54). Although Arc NPY neurons do express Kir6.2 (20) and have glucose-induced increases in c-Fos expression (54), they have not directly been shown to be GR. Somewhat paradoxically, both fasting and glucopenia increase NPY (2), whereas glucopenia increases c-Fos expression in these neurons (71). The failure of DIO Arc neurons to respond to altered glucose levels might contribute to the basal overexpression and failure to increase NPY message in energy-restricted obesity-prone rats (52). A similar dysregulation of Arc NPY occurs in both obese Zucker (fa/fa) rats (10) and ob/ob mice (106). Such dysregulation of glucose-modulated NPY expression may contribute to the propensity of such animals to become obese when the caloric density and dietary fat content is increased.

IDDM. As with NIDDM, IDDM also profoundly affects brain glucose sensing and other systems that modulate its glucose sensing capabilities. Streptozotocin-induced IDDM decreases brain glucose uptake (73), increases hexokinase activity in areas such as the PVN (39), and produces major alterations in both high- and low-affinity SUR binding (50). Hyperglycemia in insulin-deficient diabetic (BB) or streptozotocin-treated or Wistar fatty rats is associated with increased Arc NPY expression (1, 112). This overexpression occurs even when hyperglycemia is not associated with insulin deficiency (68). On the other hand, insulin itself inhibits NPY upregulation during energy restriction (97). Thus there is a complex interaction between glucose and insulin in the regulation of Arc NPY and energy metabolism in IDDM.

Finally, tight control of patients with IDDM is associated with repeated episodes of hypoglycemia and this leads to defective brain glucose sensing. Even a single bout of hypoglycemia reduces the awareness of and the counterregulatory response to hypoglycemia (17). In rats, there is a similar attenuation of the sympathoadrenal counterregulatory response in some but not all rats subjected to repeated bouts of hypoglycemia (108). Preliminary data (N. Tkacs, personal communication) suggest that this depressed counterregulatory response can be reproduced by central infusions of 2-deoxyglucose, suggesting that impairment of brain glucose-sensing function is responsible for this defect.

SUMMARY AND CONCLUSIONS

The brain has evolved mechanisms for sensing the energy needs of the body. Because plasma glucose levels change more rapidly than most signals that reflect the body's metabolic status and because the brain is dependent on a constant supply of glucose for its energy needs, it has a vested interest in maintaining glucose levels within a fairly narrow range. Although the brain may be able to sense and respond to elevated postigestive glucose levels or to reduced levels seen during iatrogenically induced hypoglycemia, it is less clear how brain glucose sensing might affect other facets of energy intake, expenditure, and storage. Moreover, there are a number of abnormalities in brain glucose-sensing neurons, the transmitters and peptides that affect them, and the physiological responses to changes in glucose levels that occur in both obesity and diabetes. But there is as yet no direct link established between these defects of glucose sensing and the pathophysiology of obesity and diabetes. However, we now have many of the tools needed to increase our knowledge of these critical issues affecting energy homeostasis.

Address for reprint requests and other correspondence: B. E. Levin, Neurology Service (127C), VA Medical Center, E. Orange, NJ 07018-1095 (E-mail: levin@umdnj.edu).
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