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Regulation of gonadotropin-releasing hormone neurons by glucose

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Abstract

Reproduction is influenced by energy balance, but the physiological pathways mediating their relationship have not been fully elucidated. As the central regulators of fertility, gonadotropin-releasing hormone (GnRH) neurons integrate numerous physiological signals, including metabolic cues. Circulating glucose levels regulate GnRH release and may in part mediate the effects of negative energy balance on fertility. Existing evidence suggests that neural pathways originating in the hindbrain, as well as in the hypothalamic feeding nuclei, transmit information concerning glucose availability to GnRH neurons. Here we review recent evidence suggesting that GnRH neurons may directly sense changes in glucose availability by a mechanism involving adenosine monophosphate-activated protein kinase (AMPK). These findings expand our understanding of how metabolic signaling in the brain regulates reproduction.

Metabolic cues regulate reproductive function

Fertility is closely coupled to nutrition. The reproductive system must sense changes in bodily energy status to prevent reproduction during times of food scarcity, and to take advantage during times of plenty. Metabolic regulation of fertility is particularly important in females, in whom gestation and lactation have an exceptional energetic cost. More than three decades ago, based on observations in menarcheal adolescents and female athletes, a critical body composition hypothesis was proposed, positing that females must surpass a threshold level of adiposity to attain puberty and remain fertile[1,2]. The discovery of the adipocyte-derived hormone leptin seemed to substantiate this hypothesis, as leptin is permissive for fertility[3]. However, more recent observations indicate that in addition to being susceptible to metabolic signals reflecting long-term nutritional stores, the reproductive system monitors energy availability on a minute-to-minute basis by sensing levels of circulating nutrients, including glucose and fatty acids[4,5].

GnRH neurons comprise the final common pathway by which the brain controls reproduction. These neurons secrete GnRH in discrete pulses that elicit corresponding pulses of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release from the pituitary. Signals that indicate fuel availability, and particularly deficiency, can be sensed

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centrally and transmitted to GnRH neurons to modulate their activity and thereby GnRH release. Metabolic control of GnRH pulsatility has been demonstrated primarily by measuring LH pulses as a surrogate for GnRH release[6]. These studies have found that food deprivation suppresses pulsatile LH secretion in rats[7–9], sheep[10,11], monkeys[12], and humans[13], consistent with inhibition of pulsatile GnRH release. In mice and hamsters, in which assessment of LH pulses is extremely difficult due to the small blood volume of these species, fasting suppresses estrous cyclicity[14–16] and LH levels[17]. Similar findings were obtained from multiunit activity recordings of coordinated electrical discharges in the mediobasal hypothalamus; these discharges, which are associated with LH pulses and considered an electrophysiological correlate of GnRH pulses, are reduced in frequency by fasting in monkeys[18] and goats[19,20].

Glucose: a critical link between metabolism and reproduction

Numerous studies support the idea that glucose in particular mediates the effects of fasting to suppress GnRH-stimulated LH release. Reducing central glucose availability via intracerebroventricular (ICV) infusion of insulin or glucose antimetabolites (2-deoxyglucose, 2-DG, or 5-thioglucose, 5-TG) suppresses LH levels and pulse frequency in rats[21,22], goats[23], monkeys[24], and sheep[25]. Additionally, 2-DG infusion increases the interval between bursts of multiunit activity in the mediobasal hypothalamus of goats, suggesting a slowing of GnRH pulse frequency[23]. Administration of glucose restored LH pulsatility in insulin-induced hypoglycemic rats[26,27] and sheep[28], suggesting that low glucose rather than high insulin mediates the suppression of LH. In addition to the negative effect of reduced glucose, increased glucose may positively influence GnRH/LH secretion. Goats provided with dietary supplementation exhibited parallel increases in serum glucose levels and LH pulse frequency, whereas pulses declined as food availability, and thus glucose, was reduced[29]. These studies provide a strong case that glucose can act as a signaling molecule in the brain to both positively and negatively modulate reproductive function.

Many of the aforementioned studies employed insulin to induce hypoglycemia, suggesting that insulin may participate in concert with glucose to regulate GnRH neuronal function. In reproductively normal women, insulin administration increases the LH pulse frequency, consistent with a stimulatory effect of insulin on GnRH pulsatility[30]; this finding argues against a potential effect of insulin to reduce GnRH pulse frequency during insulin-induced hypoglycemia. A recent study demonstrated that GnRH neuron-specific deletion of the insulin receptor had no effect on fertility[31]. In contrast, neuronal insulin receptor knockout mice exhibit subfertility attributable to reduced central stimulation of LH secretion[32]. Together, these studies suggest that insulin signaling in presynaptic neurons may be important for normal GnRH neuronal function. Here we will focus on the central reproductive effects of glucose, which have been characterized in greater detail.

Where and how glucose is detected in the brain, and how this information is conveyed to GnRH neurons, remain important questions with significant implications in the modern environment of overnutrition. Substantial evidence points to a system of hindbrain fuel detectors in the area postrema[33], which, via intermediate signals that may include opioids[24,34,35], catecholamines[36], corticotropin-releasing hormone[37,38], and gamma-aminobutryic acid (GABA)[35,39], transmit information about metabolic status to GnRH neurons in the forebrain (reviewed in [4,5]). Other potential sites for the relay of metabolic signals are the nutrient-sensing neurons of the arcuate, ventromedial, and lateral hypothalamus, some of which are known to project to and alter the function of GnRH neurons via neuropeptidergic signaling[40]. Lastly, several new studies suggest that GnRH neurons may directly sense information about glucose availability[41,42]. Here we review

these studies, as well as evidence implicating AMPK in nutrient-sensing and metabolic control of GnRH neurons.

Neuronal glucosensing

The high metabolic activity of the brain requires a constant supply of glucose. Glucose enters the brain via facilitated transport through glucose transporters in the blood brain barrier, reaching an extracellular concentration of approximately 10–30 percent of the blood level. Specialized neurons in the brain translate changes in the ambient glucose concentration into changes in membrane potential and firing rate; this ability is distinct from the near ubiquitous neuronal inhibition that occurs in response to aglycemia, and is confined to specific neuronal subpopulations[43]. Such glucosensing neurons are subdivided into two classes: glucose-inhibited (GI) neurons, which hyperpolarize when the extracellular glucose concentration is increased, and glucose-excited (GE) neurons, which depolarize when glucose is increased. These neurons have been well characterized in the arcuate, ventromedial, and lateral hypothalamic nuclei, where they are involved in the control of glucoregulatory responses and potentially the regulation of feeding behavior[44,45]. Some of the most well-studied glucosensing neurons express neuropeptides in addition to classical neurotransmitters; for example, proopiomelanocortin (POMC) neurons are GE[46], and orexin and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons are GI[47,48]. Of interest, GnRH neurons contain receptors for and have been shown to be responsive to these neuropeptides[40], suggesting that the glucosensing network responsible for maintaining peripheral metabolic homeostasis may also relay metabolic information to the reproductive system.

Mechanisms of neuronal glucosensing

It is widely held that the primary mechanism of glucosensing by GE neurons mirrors that of the pancreatic beta cell, in which ATP-sensitive potassium (K_{ATP}) channels and glucokinase play an integral role[49]. The K_{ATP} channel is comprised of four Kir6.2 pore-forming subunits and four sulfonylurea (SUR1) subunits; the latter confer sensitivity to sulfonylureas, such as tolbutamide, which close K_{ATP} channels. Extracellular glucose is transported into cells and serves as a substrate for ATP generation by glycolysis. The rate-limiting step in glycolysis is hexokinase-mediated conversion of glucose to glucose-6-phosphate; beta cells and some neurons express an isoform of this enzyme called glucokinase, which has a high K_m and thus is not saturated at physiological glucose levels. ATP blocks membrane K_{ATP} channels, resulting in decreased potassium efflux and membrane depolarization. In beta cells, depolarization leads to insulin release; in neurons, it can increase the action potential firing rate. As greater glucose influx leads to increased ATP generation and K_{ATP} closure-mediated depolarization, neuronal firing rate is relatively proportional to the extracellular glucose concentration. Numerous studies support this model of neuronal glucosensing, although it is not without debate[50]. Reducing the extracellular glucose concentration around ventromedial hypothalamic neurons activates channels exhibiting properties consistent with K_{ATP} channels. Mice with deletion of the pore-forming subunit of the K_{ATP} channel lack functional glucose-excited neurons in the ventromedial hypothalamus and have impaired counterregulatory and feeding responses to glucoprivation[51]. Further, expression of a mutant, ATP-insensitive Kir6.2 subunit in POMC neurons abolished glucosensing in this cell type. With regard to a role for glucokinase, pharmacological inhibition of this kinase inhibits GE and stimulates GI neurons; conversely, its activation stimulates GE and inhibits GI neurons[52,53]. In addition to roles in glucosensing, K_{ATP} channels are involved in neuronal leptin and insulin signaling. Both leptin and insulin activate K_{ATP} channels in a phosphoinositide-3-kinase-dependent manner[54]. K_{ATP} channels are thus thought to perform diverse functions in transmitting metabolic information from the periphery.

Among other putative mechanisms of glucosensing is the adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor that, like K_{ATP} channels, is postulated to play an integrative role in central metabolic signaling[55]. AMPK is activated allosterically by 5'AMP and via phosphorylation by AMPK kinase (AMPKK). AMP binding to AMPK makes it a better substrate for AMPKK, and a worse substrate for inactivating phosphatases; ATP antagonizes all effects of AMP. Thus, AMPK activation is determined by the intracellular ratio of AMP to ATP. AMPK consists of a catalytic α subunit, of which two isoforms have been identified, and regulatory beta and gamma subunits. In the central nervous system, AMPK α2 is expressed at higher levels than α1. AMPK subunit expression is mainly neuronal, although it has also been identified in astrocytes. In contrast to K_{ATP} channels, which are widely expressed, AMPK localization is restricted to distinct brain subregions[55]. In addition to regulation by intracellularly-generated adenine nucleotides, AMPK is amenable to regulation by peripheral hormones. Leptin inhibits, whereas ghrelin and adiponectin enhance, AMPK activation in the brain[56]. These findings have let to a surge of interest in AMPK as a regulator of energy homeostasis at both the cellular and whole-body levels.

GI neurons of the ventromedial hypothalamus sense glucose at least in part via activation of AMPK[57]. Low glucose activates AMPK, which phosphorylates and activates cystic fibrosis transmembrane regulator chloride channels, hyperpolarizing and inhibiting these cells. This process is amplified by AMPK-dependent generation of nitric oxide (NO). NO activates soluble guanylyl cyclase, increasing intracellular cyclic GMP and activating AMPK through some yet undetermined upstream kinase[57]. This mechanism differs from that of GI orexin neurons, which utilize a glucose-activated tandem-pore potassium current (distinct from the K_{ATP} current)[47]. A subset of orexin neurons exhibit time-dependent closure of these background channels, which may be an adaptive mechanism to maintain responsiveness to glucose changes over a wide range of baseline concentrations[58]. In addition to reported roles in GI neurons, one study has demonstrated a contribution of AMPK to glucosensing by GE neurons[59]. Genetic deletion of the AMPK α2 subunit from AgRP and POMC neurons completely abolished glucosensing in these cell types. Interestingly, AMPK α1 knockout mice are subfertile, but exhibit no apparent metabolic phenotype, indicating that subfertility in these mice is not secondary to metabolic dysregulation[60]. AMPK thus appears to play a role in both GE and GI neurons and has been independently linked with fertility.

Additional metabolism-independent mechanisms for glucosensing have been proposed, in light of the observation that, in some cells, responses to glucose can be dissociated from its metabolism to ATP[50]. One such mechanism is electrogenic glucose entry, whereby glucose transport into cells is coupled to ion movement. An example is the sodium-glucose cotransporter (SGLT). SGLTs concurrently transport sodium and glucose into cells, generating depolarizing inward currents. An exception is SGLT3, which generates inward current without concomitant glucose transport, acting as a “glucose receptor” on the cell surface[61]. However, this receptor has not yet been identified in glucosensing neurons. Glial cells have also been implicated in glucosensing. A rise in extracellular glucose increases glycolysis in astrocytes, which release lactate that can excite GE neurons via closure of K_{ATP} channels[48]. Further, a recent study has suggested a role for tanycytes, glial-like cells that line the cerebral ventricles and communicate with parenchymal cells, in glucosensing by hypothalamic neurons[62]. Glucose application to third ventricular tanycytes in a slice preparation evokes ATP release and the generation of ATP-dependent calcium waves that travel along the tanycyte processes. Due to their proximity and extension of processes to the arcuate and ventromedial nuclei, these tanycytes are poised to mediate the responses of glucosensing neurons. Interestingly, there is evidence for glial, and in particular tanycyte, modulation of GnRH neuronal function[63].

Glucosensing by GnRH neurons

Zhang et al. first demonstrated glucosensing in GnRH neurons[41]. Using extracellular recordings from GnRH neurons in brain slices exposed to high potassium to stimulate firing activity and high Ca^{2+}/low Mg^{2+} solution to minimize presynaptic neurotransmitter release, over half of cells (5/9) demonstrated a reduction in firing frequency in response to a switch from 2.5 to 1mM glucose. This study also independently demonstrated Kir6.2 mRNA in 60% and glucokinase mRNA in 30% of GnRH neurons by single-cell quantitative PCR. In vivo treatment with estradiol potentiated the K_{ATP} current, demonstrated by application of the K_{ATP} antagonist tolbutamide and the agonist diazoxide. The demonstration of glucosensing, the cellular machinery for K_{ATP}-dependent glucosensing, and an intrinsic K_{ATP} current strongly suggest that glucosensing in GnRH neurons involves a similar mechanism as that reported for neurons of the arcuate and ventromedial hypothalamus, although this link was not directly established. This first evidence for direct sensing of glucose by GnRH neurons contributed a novel component to the model of fuel detection by the reproductive system.

A subsequent study by Huang et al. also addressed the role of K_{ATP} channels in the regulation of GnRH/LH secretion, particularly with regard to their role in mediating suppression of LH by fasting[17]. As predicted, LH was suppressed by a 48-hour fast. The K_{ATP} channel antagonist tolbutamide was administered intracerebroventricularly to either fed or fasted mice and evoked a 2-fold increase in LH in both groups. If K_{ATP} channel opening was the cause of suppressed LH, one would predict a greater LH increase in response to tolbutamide in fasted mice; thus, K_{ATP} channels did not appear to contribute to the response to fasting. The authors further corroborated this finding by demonstrating that there was no attenuation of fasting-induced LH suppression in sulfonylurea-1 null mice, which lack functional K_{ATP} channels. While supporting a role for K_{ATP} channels in GnRH neuronal regulation, these findings suggested K_{ATP} activation is not the mechanism by which fasting suppresses GnRH/LH secretion.

A recent report confirmed and extended the findings of Zhang and demonstrated that the majority of GnRH neurons (~70–80%) can be inhibited by reducing the extracellular glucose concentration[42] (Figure 1A,C). This response persisted in the presence of blockers of receptors for fast GABAergic and glutamatergic neurotransmission, suggesting, as in the Zhang study, that glucosensing is intrinsic to the GnRH neuron. This study also attempted to directly link glucosensing and K_{ATP} channels by testing the response of GnRH neurons to low glucose in the presence of tolbutamide. Although acute application of tolbutamide evoked firing in a subset of GnRH neurons, confirming the presence of functional K_{ATP} channels, tolbutamide unexpectedly failed to attenuate the response to low glucose. This finding suggested that K_{ATP} channels are not the primary mediator of glucosensing in GnRH neurons. Moreover, the effects of different steroids (administered *in vivo*) on glucosensing were tested; estradiol did not appear to affect glucosensing properties, which would have been predicted by the previously reported estradiol enhancement of K_{ATP} current[41]. In contrast, the non-aromatizable androgen dihydrotestosterone (DHT) attenuated glucosensing; this finding may have implications for sex differences in responses to metabolic cues, or in the context of hyperandrogenemic infertility in females. While K_{ATP} channels may not be required for glucose responsiveness of GnRH neurons, they have been shown to have important functions beyond metabolic signaling, including a role in the mediation of steroid negative feedback[64]. What function glucokinase might serve in GnRH glucosensing remains to be fully explored; 30% of GnRH neurons express glucokinase mRNA, but this is less than the percentage that exhibited glucosensing[42]. Glucokinase-dependent glucosensing may act as a secondary mechanism in a subset of cells, as many of the signals controlling reproduction show physiological redundancy. Future studies could

examine the role of glucokinase in GnRH neuronal function by employing glucokinase-modulating agents, or mice with targeted deletion of glucokinase from GnRH neurons.

AMPK: a novel regulator of GnRH neuronal function

Whereas blockade of K_{ATP} channels failed to alter glucosensing, pharmacological antagonism of AMPK using compound C attenuated glucosensing in GnRH neurons[42]. Acute application of the AMPK agonist AICAR inhibited GnRH neurons (Figure 1B, D), supporting the idea that inhibition by low glucose was due to AMPK-mediated inhibition. Metformin, an antihyperglycemic agent that activates AMPK through a mechanism distinct from that of AICAR, similarly inhibited GnRH neuron firing activity. GnRH neurons from DHT-treated mice were less sensitive to inhibition by AICAR, consistent with their attenuated response to low glucose. Mechanistically, AMPK and low glucose activated a similar current with a reversal potential of −50 mV; this current was unaffected by blockade of action-potential dependent synaptic transmission with tetrodotoxin, providing further evidence that glucosensing is intrinsic to the GnRH neuron. The possibility that this current was carried by chloride was ruled out, suggesting, rather, that it was a mixed cation current.

Several other recent studies have identified a role for AMPK in GnRH neuronal regulation. Three studies demonstrated the expression of AMPK in GT1–7 immortalized GnRH neurons [65–67]. AICAR, metformin, and globular adiponectin were shown individually to inhibit GnRH release from these cells by an AMPK-dependent mechanism[65–67]. In GT1–7 cells, AMPK activation inhibited the hyperpolarization-activated cation current. The discrepancy between this finding, which involves inhibition of a cation current, and that mentioned above, which suggested activation of a cation current, may be related to the cell type; cultured immortalized GT1–7 cells may function differently than GnRH neurons recorded in acutely prepared brain slices. Two recent studies examined the effects of in vivo treatment with AMPK activators. The first examined estrous cyclicity and food intake following ICV infusion of AICAR[65]. AICAR caused AMPK phosphorylation in the hypothalamus as expected, and transiently increased food intake, consistent with reports that hypothalamic AMPK stimulates feeding[68]. Another study demonstrated effects of in vivo treatment with metformin on the firing activity of GnRH neurons from control and prenatally androgenized female mice, the latter of which have increased baseline GnRH neuron activity[69]. While metformin had no effect on the firing activity of GnRH neurons from control mice, it suppressed firing activity in the prenatally androgenized mice, restoring it to control levels. Further, GnRH neurons from metformin-treated (androgenized or control), but not untreated, mice were excited by the AMPK antagonist compound C in vitro, suggesting AMPK was activated in cells from these mice. Low glucose failed to inhibit firing in the majority of cells from metformin-treated mice. Together, these findings suggested that metformin administered in vivo activated AMPK in GnRH neurons, leading to a suppression of activity in mice in which GnRH neurons were excessively active. The above studies provide further support that AMPK activation has an inhibitory effect on GnRH neurons.

Concluding remarks

Several questions remain unanswered with regard to AMPK regulation of GnRH neuronal activity. Importantly, although AMPK expression was demonstrated in the GT1–7 cell line, it has not been assessed in GnRH neurons from adult mice. A limitation of the studies done in mice is that manipulations were solely pharmacological, and nonspecific actions of AICAR, metformin, and compound C are possible, although the observation that all three had experimentally consistent effects would argue against such non-specificity. The above studies imply that presynaptic neuronal activity is not required for the response of GnRH

neurons to low glucose, and thus AMPK is likely expressed in GnRH neurons. However, it is also possible that astrocytes are involved in the GnRH neuronal response to low glucose. AMPK expression has been demonstrated in astrocytes[70], and astrocytes may transmit metabolic information to alter neuronal function. Thus, identifying the site of AMPK localization is essential. Another remaining question is the identity of the specific subtype of mixed cation current activated by AICAR and low glucose, as well as the signaling pathways that lead to its activation.

A role for AMPK in glucosensing by GnRH neurons could be confirmed using mice deficient in various AMPK subunits. Further, in order to fully integrate direct glucosensing by GnRH neurons into a model of fuel-sensing, we must establish the physiological relevance of this phenomenon. Presumably, the sensitivity of GnRH neurons to low glucose contributes to the suppression of GnRH pulsatility by central or peripheral glucoprivation, but these hypotheses must be tested empirically through pharmacological or genetic manipulation of AMPK together with fasting, insulin, or glucose anti-metabolites administered to the whole animal. Drawing once again from the energy homeostasis field, 2-deoxyglucose administration and insulin-induced hypoglycemia have been shown to activate central AMPK, and compound C inhibits glucoprivic feeding[68]. These findings suggest that the same stimuli that have previously been shown to suppress LH (and therefore GnRH) pulses also activate central AMPK, consistent with the proposed working model. Lastly, as AMPK is known to be the target of ghrelin, adiponectin, and other peripheral metabolic hormones[56], the effects of these cues on GnRH neurons should be examined, as well as the AMPK-dependence of their actions.

In summary, the worked described here suggests that direct glucosensing may contribute to the response of the reproductive system to fluctuations in nutrient availability. Combined with previous work implicating distal brain regions in the metabolic control of GnRH neurons, these findings suggest a model (Figure 2) in which direct glucosensing functions together with afferent signals to ensure that reproduction occurs only in the presence of an adequate nutrient supply.

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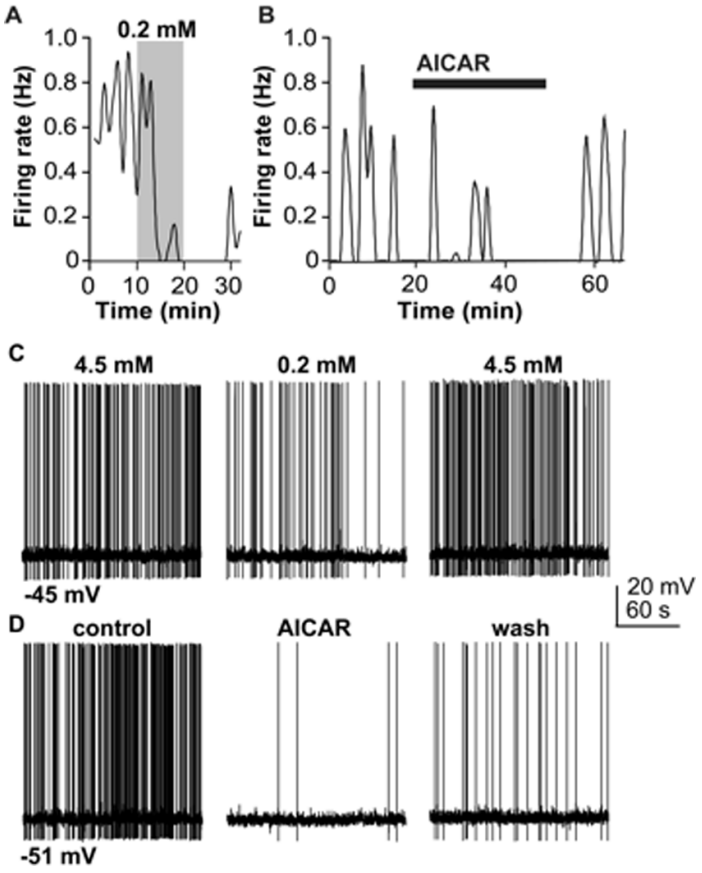

Figure 1.

GnRH neurons are inhibited by both low glucose and AICAR. (a). Plot of firing rate (binned in 60-second intervals) of a GnRH neuron from an ovariectomized mouse in response to a reduction from 4.5 mM to 0.2 mM glucose. Shaded region indicates time of low glucose exposure. Low glucose slowly inhibits the firing rate; this effect is not immediately reversed upon restoration of 4.5 mM glucose. The decrease at the return to high glucose in this example was typical of many GnRH neurons; this observation was found to be a coincidental aspect of the temporal nature of the response to low glucose, rather than a further suppression by restoration to normal glucose. (b). AICAR, which activates AMPK, inhibits GnRH neuron firing in 4.5 mM glucose. (c, d). Whole-cell, current-clamp recordings demonstrating low glucose (c) and AICAR (d) suppression of GnRH neuron action potential firing rate. mV, millivolts. Adapted from reference 43 with permission.

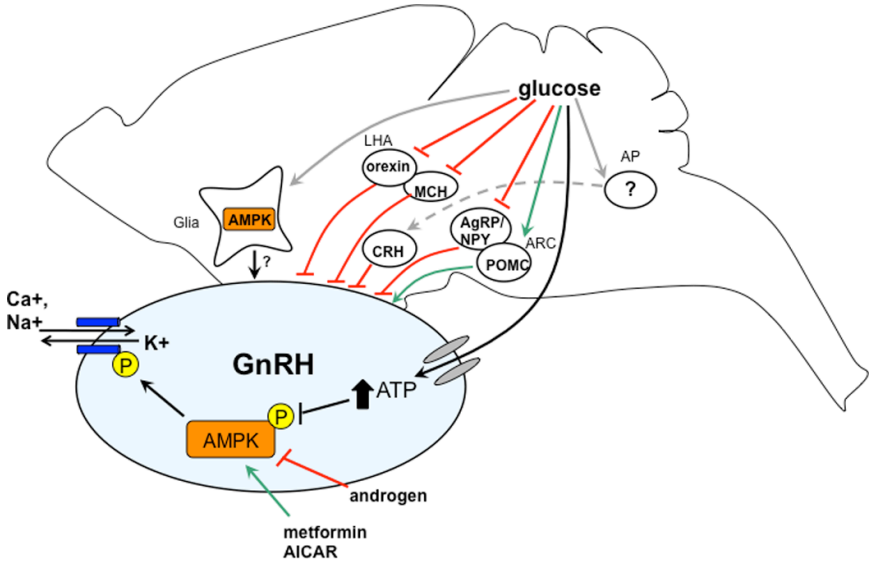

Figure 2.

Putative sites of glucose action in the brain to regulate GnRH neuronal function. Glucose may act on distal brain regions in the hindbrain area postrema (AP), and in the arcuate (ARC) and lateral hypothalamus (LHA), which project (both directly and indirectly) to GnRH neurons. In addition, glucose may alter the function of GnRH neurons through direct action mediated by AMPK, or through effects on proximal glial cells.