The mechanisms that underlie glucose sensing during hypoglycaemia in diabetes

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Abstract

Hypoglycaemia is a frequent and greatly feared side-effect of insulin therapy, and a major obstacle to achieving near-normal glucose control. This review will focus on the more recent developments in our understanding of the mechanisms that underlie the sensing of hypoglycaemia in both non-diabetic and diabetic individuals, and how this mechanism becomes impaired over time. The research focus of my own laboratory and many others is directed by three principal questions. Where does the body sense a falling glucose? How does the body detect a falling glucose? And why does this mechanism fail in Type 1 diabetes? Hypoglycaemia is sensed by specialized neurons found in the brain and periphery, and of these the ventromedial hypothalamus appears to play a major role. Neurons that react to fluctuations in glucose use mechanisms very similar to those that operate in pancreatic B- and A-cells, in particular in their use of glucokinase and the $K_{ATP}$ channel as key steps through which the metabolic signal is translated into altered neuronal firing rates. During hypoglycaemia, glucose-inhibited (GI) neurons may be regulated by the activity of AMP-activated protein kinase. This sensing mechanism is disturbed by recurrent hypoglycaemia, such that counter-regulatory defence responses are triggered at a lower glucose level. Why this should occur is not yet known, but it may involve increased metabolism or fuel delivery to glucose-sensing neurons or alterations in the mechanisms that regulate the stress response.


Keywords hypoglycaemia, glucose-excited neurons, glucose-inhibited neurons, ventromedial hypothalamus, AMP-activated protein kinase

Abbreviations ACTH, adrenocorticotrophic hormone; AgRP, agouti-related peptide; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; APF, action potential frequency; Arc, arcuate nucleus; ATP, adenosine triphosphate; CRH, corticotrophin-releasing hormone; CSF, cerebrospinal fluid; DMH, dorsomedial hypothalamus; ECF, extracellular fluid; GABA, gamma-aminobutyric acid; GE, glucose-excited neuron; GH, growth hormone; GI, glucose-inhibited neuron; GLUT, glucose transporter; GK, glucokinase; HAAF, hypoglycaemia-associated autonomic failure; $K_{ATP}$, ATP-sensitive potassium channel; KO, knock out; MCT2, monocarboxylate transporter 2; MRNA, messenger ribonucleic acid; NO, nitric oxide; NOS, nitric oxide synthase; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; rt-PCR, reverse transcription polymerase chain reaction; T1DM, Type 1 diabetes mellitus; VDCC, voltage-dependent calcium channel; VMH, ventromedial hypothalamus; VMN, ventromedial nucleus

Introduction

Shortly after the introduction of insulin in the management of T1DM, clinicians became aware of the potential for insulin therapy to induce iatrogenic hypoglycaemia. Despite the introduction of insulin analogues and improved delivery systems, hypoglycaemia remains the major adverse effect of insulin therapy and has emerged as a major limitation to achieving near-normal glucose control, which is required to reduce the risk of microvascular complications [1]. An increasing awareness of hypoglycaemia in clinical practice provided the initial stimulus to a series of excellent and detailed human physiological studies in the 1980s and 1990s, which greatly increased our understanding of the counter-regulatory defence systems that prevent and correct hypoglycaemia and, importantly, how these differed over time in individuals with T1DM (for a detailed review of this area see [2]). However, in order to understand the mechanisms that underlie glucose sensing, a
prerequisite to understanding why this homeostatic system becomes defective in T1DM, investigators have in recent years increasingly used more basic in vitro techniques and animal models. This is an area of research that is developing rapidly, and focuses on three basic questions. Where does the body detect hypoglycaemia? How does the body detect hypoglycaemia? And why does this mechanism become defective over time in T1DM? This review will focus on the more recent developments in this field, which are beginning to answer these three important questions.

**Where does the body sense a falling glucose?**

Glucose is an integral part of whole-body energy homeostasis and is tightly regulated by numerous endocrine, neuronal and behavioural systems, which ensure that glucose levels in the blood are maintained within a narrow physiological range. It is perhaps not surprising, given the fundamental importance of glucose to the organism, that the capacity to sense glucose is not limited to any single organ system. Apart from the classical glucose sensor, the pancreatic B-cell, glucose-sensing neurons in the periphery have, to date, been found in the intestine [3], hepatoportal vein [4–9] and carotid body [10]. Within the brain, glucose-sensing neurons are found in certain distinct regions, namely VMH [27–30] (which includes the arcuate and ventromedial nuclei), the PVN [31] and the DMH [32]. Perhaps the most studied of these regions is the VMH. Chemical destruction of the VMH in a rodent model with ibotenic acid was shown to cause a ~75% reduction in the hormonal counter-regulatory response to acute hypoglycaemia [29]. Later, it was shown in awake rats that local perfusion of the VMH with 2-deoxyglucose (a non-metabolizable form of glucose that effectively causes ‘local hypoglycaemia’) stimulated a classical systemic counter-regulatory response [30], whereas local perfusion of the VMH with glucose during systemic hypoglycaemia markedly suppressed the hormonal counter-regulatory response [28]. Taken together, these three studies provided good evidence for the VMH playing a key role in the sensing of hypoglycaemia.

The glucose-sensing neurons share certain common features. Within the brain, they localize to regions adjacent to the third or fourth ventricle or to the circumventricular organs (these are regions of the brain where the blood–brain barrier is ‘leaky’ or absent). This potentially allows glucose-sensing neurons direct sampling, and hence monitoring, of glucose levels in the blood, brain and CSF. This is important because the presence of the blood–brain barrier ensures that brain glucose levels are only ~10–30% of the levels seen in the blood [33–35]. Thus, glucose-sensing neurons are able to integrate changes in
Review article

How does the body detect a falling glucose?

In 1953, Jean Mayer proposed the ‘glucostatic hypothesis’ [36]. Hypothalamic ‘glucoreceptors’, it was proposed, could sense fluctuations in glucose and translate that signal into a change in neural activity [36]. The defining feature of these neurons should be their use of glucose, not simply as a fuel, but as a signalling molecule that regulates their activity. All neurons use glucose as their major fuel source and all neurons will ultimately alter their firing rates when glucose homeostasis is significantly disrupted, but glucose-sensing neurons alter their membrane potential, action potential frequency and/or rate of neurotransmitter release over the more physiological ranges of glucose to which they are exposed. Such specialized neurons were first demonstrated by Oomura and colleagues in 1969 [22]. These neurons are ‘glucose’-sensing in so far as glucose is the major metabolic substrate for the brain, but the fact that these neurons can use other fuels, such as lactate produced either by astrocytes [37–39], delivered locally [40,41] or systemically [42–45] to alter their function, suggests that it is more likely to be intracellular ATP that determines the activity of these neurons. This is intriguing because neuronal levels of ATP are generally thought to be well maintained, thus it is also likely that subcellular compartmentalization of the glucose-sensing apparatus must exist to provide sensing capability. Such compartmentalization has been shown within pancreatic β-cells [46].

GE neurons

There are thought to be two predominant subtypes of glucose-sensing neurons, namely GE neurons (whose activity increases as glucose levels rise) and GI neurons (whose activity decreases as glucose levels rise) [47]. The mechanisms through which these neurons sense alterations in glucose remain incompletely understood. Classical glucose sensing in the pancreatic islet served as a model for the initial research in this field [48]. In the pancreatic β-cell, glucose is transported into the cell through a high-capacity glucose transporter (GLUT) to allow rapid equilibration of extracellular and cytosolic glucose. The rate of glucose metabolism, which is closely coupled to insulin secretion, is determined by glucokinase (GK), the enzyme in the rate-limiting step of glycolysis [49]. Metabolism of glucose leads to several intracellular events, the culmination of which is an increase in cytosolic calcium. One of the key steps in this signalling pathway is the depolarization of the β-cell that follows closure of ATP-sensitive potassium (K_ATP) channels in the plasma membrane [48]. The exciting discovery of glucokinase and K_ATP channels in glucose-sensing regions in the brain lead to the hypothesis that these enzymes might also serve key roles in glucose sensing, particularly in GE neurons [48,50]. K_ATP channels have been demonstrated throughout the brain, including hypothalamic regions thought to be involved in glucose sensing [27,51–53]. Using single-cell rt-PCR to analyse glucose-sensing neurons (identified electrophysiologically in a hypothalamic slice preparation), investigators have shown that they express mRNA for Kir6.2 and SUR1, the two subunits that comprise the K_ATP channel in the pancreatic β-cell [54]. In addition, electrophysiological studies of the rat [27,55–57] and mouse [58] have demonstrated that sulphonylureas (agents that block the K_ATP channel) can alter the response of GE neurons to changes in ambient glucose, and Kir6.2 KO mice show impaired glucose counter-regulation to systemic hypoglycaemia [58]. Finally, in vivo perfusion of the VMH of rodents with glibenclamide (a K_ATP channel blocker) suppresses [59], whereas diazoxide (a K_ATP channel opener) amplifies [60], hormonal counter-regulatory responses to acute hypoglycaemia. However, K_ATP channels are present on many different neurons and so while they may be required for glucose sensing they are unlikely to have a regulatory role.

In the pancreatic β-cell, GK is the critical regulator of glycolytic production of ATP and K_ATP channel activity [49]. The pancreatic form of GK is also present in areas of the brain involved in glucose sensing [61–63]. GK mRNA is expressed in ~70% of GE neurons [54], and glucokinase also has been shown to play a regulatory role in GE neuron-sensing ability [54,57,61,64]. In addition, the selective down-regulation of GK in GE neurons in primary VMH neuronal cultures led to the loss of all demonstrable GE and GI neurons [65]. However, extracellular levels of glucose are only about 10–30% of the levels found in blood. Microdialysis studies in rats [33,34,66] and human subjects [67] have shown that the ECF glucose levels to which neurons are exposed are in the range of 1–2 mM, and fall to a similar degree during acute hypoglycaemia (~0.5 mM) [33]. Both euglycaemic and hypoglycaemic ECF glucose levels are beneath the range of glucose levels in which GK usually acts in a regulatory manner, thus for GK to perform this role in glucose-sensing neurons it almost certainly has to operate within a distinct subcellular compartment.

Glucose signalling in the pancreatic β-cell also requires the GLUT Type 2 (GLUT-2). GLUT-2 mRNA has been found in brain glucose-sensing regions [54,68]; in transgenic mice, central GLUT-2 has been shown to be involved in the counter-regulatory response to hypoglycaemia. Intriguingly, reintroducing GLUT-2 to glia cells, but not to neurons, restored the defective counter-regulatory response to hypoglycaemia [69]. Taken together, these studies provide good evidence that the glucose-sensing mechanism used by the GE neuron has many similarities with the pancreatic β-cell. In particular, GK and
the $K_{ATP}$ channel appear to be key points through which an increase in the ambient glucose leads to altered firing of GE neurons (Fig. 2).

**GI neurons**

In contrast, GI neurons show a decrease in activity as glucose levels rise [47]. It is perhaps easier to think of GI neurons as those glucose-sensing neurons that become more active when glucose levels fall, and as such they may use signalling mechanisms more relevant to the pancreatic A-cell. Unfortunately, like the A-cell, the signalling pathways used by the GI neuron are not well understood (Fig. 3). This may reflect the fact that they are few in number, comprising only 3–14% of neurons in the ventromedial hypothalamic nucleus [61, 70]. However, recent evidence suggests that GI neurons may be more prevalent: when improved slice techniques are used in conjunction with novel methods for identifying GI neurons (e.g. membrane potential dyes), as many as ~30–40% of all neurons in the VMH are reported to be GI neurons [71]. GK mRNA is expressed in around 40% of GI neurons, and may also serve a regulatory role in these neurons. [65].

More recently, evidence has also emerged that AMP-activated protein kinase (AMPK) plays a key role in the sensing pathway used by GI neurons (Fig. 3). AMPK has been described as an intracellular ‘fuel gauge’ in that it is activated in response to a rise in the intracellular ratio of AMP to ATP and acts to switch off energy-consuming anabolic processes and switch on energy-producing catabolic processes [72]. Within the brain, AMPK expression is thought to be predominantly neuronal in distribution, with very little expression evident in astrocytes [73]. Czanabal et al. [71] demonstrated that in VMN GI neurons exposed to 2.5 mM glucose, AICAR (an activator of AMPK), mimicked the excitatory effect of low glucose (0.5 mM) on action potential frequency. Both low glucose and AICAR were shown to mediate their effects, in part, through an increase in nitric oxide (NO) production in GI neurons. Conversely, increased NO production in response to a low glucose was blocked by compound C, an inhibitor of AMPK [71]. In a related series of studies, Mountjoy et al. [74] reported that activation of AMPK with AICAR or inhibition with compound C altered neuronal activity in GI, but not GE, neurons in an ex vivo hypothalamic cell culture system obtained from the mediobasal (including VMN and Arc) hypothalamus. In this study, AMPK had no effect on the $K_{ATP}$ channel [74], but others have suggested that AMPK may instead act on a chloride channel to depolarize the plasma membrane [75]. In rodent studies, in vivo pharmacological activation of AMPK in the VMH during acute hypoglycaemia amplifies the glucose counter-regulatory response in normal Sprague-Dawley rats [76], and restores the hormonal counter-regulatory response to hypoglycaemia in rats with defective counter-regulation [77]. Conversely, down-regulation of AMPK in the VMH using specific RNA interference suppresses the counter-regulatory response to acute hypoglycaemia [78]. In addition, mice that selectively lack the alpha-catalytic subunit of AMPK in POMC or AgRP neurons (both neuronal types are located in the medio-basal hypothalamus and are involved in feeding behaviors), show reduced feeding and body weight in response to hypoglycaemia [79].
behaviour and energy homeostasis) lose the responsiveness of these neurons to changes in extracellular glucose [79].

What these studies all indicate is that the brain contains specialized neurons that exist in distinct locations and are able to monitor and react to alterations in the glucose concentration to which they are exposed. These neurons, by virtue of specific sensing systems, translate the rate or quantity of glucose oxidation into a neural signal that alters neuronal firing rates and, in the case of hypoglycaemia, leads to the stimulation of a systemic glucose counter-regulatory defence response. The glucose-sensing neurons seem to use signalling mechanisms that are very similar to those used by pancreatic B- and A-cells. The GE neuron, which seems to operate more under conditions of eu- or hyperglycaemia, may use glucokinase as its key regulatory step, and the GI cell, in its attempt to translate that signal into altered neuronal firing rates. In contrast, while the GI neuron (which operates more under hypoglycaemic conditions) may still use glucokinase as a regulatory enzyme, it appears more dependent on alterations in intracellular AMPK activity that, in turn, may act via a chloride channel to alter neuronal firing rates. It is highly likely that these two neuronal populations communicate with each other, perhaps via the inhibitory neurotransmitter GABA [80], to co-ordinate their responses to a changing blood glucose. Potentially, the counterbalance between GI and GE neuronal activity forms the most sensitive means of regulating and maintaining blood glucose within a narrow physiological range and ensuring an adequate supply of glucose to the brain.

**Counter-regulation in T1DM**

In health, a fall in plasma glucose level is rapidly detected and a sequence of counter-regulatory responses triggered, which mainly involve: (1) suppression of insulin secretion; (2) counter-regulatory hormone release, which rapidly promotes endogenously glucose production and limits peripheral glucose utilization; and (3) subjective awareness of hypoglycaemia. In T1DM, these compensatory systems are disrupted at every level. Firstly, for most individuals, insulin delivery from its subcutaneous depot is unregulated and continues despite the fall in plasma glucose. Thus, insulin delivery from its subcutaneous depot is unregulated and continues despite the fall in plasma glucose. As a result, individuals with T1DM are very reliant on the sympathoadrenal (primarily adrenaline and noradrenaline) response to low blood glucose. However, within 10 years of diagnosis of T1DM, hypoglycaemia fails to stimulate the release of glucagon, the major counter-regulatory hormone (Table 1) [81]. As a result, individuals with T1DM are particularly dependent on the sympathoadrenal (primarily adrenaline and noradrenaline) response to low blood glucose. However, within 10 years of diagnosis, the majority of patients develop additional impairments in sympathoadrenal and other neurohormonal responses against hypoglycaemia (Table 1) [81]. In addition, symptom awareness becomes impaired in individuals with T1DM. The term hypoglycaemia-associated autonomic failure (HAAF) was introduced by Cryer to incorporate both defective glucose counter-regulation and hypoglycaemia unawareness [1]. The presence of HAAF associated with more frequent hypoglycaemia, was shown to lower the glucose level at which hormonal counter-regulation of this and it has been shown in both humans [93–95] and rodents [77,96–97] that single or multiple episodes of

<table>
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<th>Duration of diabetes</th>
<th>Glucagon (%)</th>
<th>Epinephrine (%)</th>
<th>Cortisol (%)</th>
<th>GH (%)</th>
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<td>&lt; 1 year</td>
<td>27</td>
<td>9</td>
<td>0</td>
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<td>1–5 years</td>
<td>75</td>
<td>25</td>
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<td>5–10 years</td>
<td>100</td>
<td>44</td>
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<td>&gt; 10 years</td>
<td>92</td>
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Unfortunately, this response also appears to become defective over time in T1DM [81]. The major reason for the development of this defect is thought to be the experience of hypoglycaemia itself. In the Diabetes Control and Complications Trial, which compared intensive with standard insulin therapy in T1DM, the major single factor predicting severe hypoglycaemia in the study cohort was reporting a previous episode of severe hypoglycaemia [91]. Intensive insulin therapy, which is associated with more frequent hypoglycaemia, was shown to lower the glucose level at which hormonal counter-regulation was initiated in T1DM [92]. Hypoglycaemia per se is the likely cause of this and it has been shown in both humans [93–95] and rodents [77,96–97] that single or multiple episodes of
antecedent hypoglycaemia lead to suppressed adrenaline responses to a subsequent episode of hypoglycaemia.

Data gleaned from studies in rodents suggest that this defect arises through changes in key brain glucose-sensing regions such as the VMH. Recurrent hypoglycaemia has been shown to markedly suppress the counter-regulatory response to 2-deoxyglucose (a non-metabolized form of glucose) perfused into the VMH of rats [98]. It has also been shown that the glucose level at which you first see activation of glucose-inhibited neurons in the VMH is lower in rats that have experienced prior recurrent hypoglycaemia [99]. Moreover, in vivo activation of AMPK in the VMH of rats who have experienced prior recurrent hypoglycaemia can restore hormonal counter-regulatory responses to a subsequent hypoglycaemic challenge [77]. Similarly, opening of KATP channels in the VMH of recurrently hypoglycaemic rats leads to the restoration of normal counter-regulatory responses to subsequent hypoglycaemia. If our model is correct, these studies suggest that the balance between GE and GI neuronal activity is altered by recurrent hypoglycaemia. We would anticipate that GE neurons (acting to suppress counter-regulation) are more likely to be active and/or that GI neurons (acting to amplify counter-regulation) are less likely to be active following recurrent hypoglycaemia. The net effect is that full glucose counter-regulation is initiated at a lower glucose level. This gives individuals less time to react to, and seek treatment for, hypoglycaemia.

Why does this mechanism fail in Type 1 diabetes?

The question we then need to ask is: why does this happen? The most obvious explanation is that following recurrent hypoglycaemia, glucose-sensing neurons are ‘seeing’ higher glucose and/or ATP levels during a subsequent hypoglycaemic challenge. This change may arise through an increased supply of fuel through altered glucose [100], or alternate fuel transport [101]. However, while these changes suggest an increased capacity to transport fuels across the blood–brain barrier and into glucose-sensing neurons, the data from human studies have been mixed, with some indicating increased whole-brain glucose [102], or acetate [103], uptake after chronic hypoglycaemia and others showing no change [104].

Another possibility is that the brain is able to obtain additional metabolic substrates from more local sources. Recently, it has emerged that brain glycogen may act as a fuel reserve during acute hypoglycaemia [105]. Moreover, brain glycogen levels may actually increase in response to an acute episode of hypoglycaemia [105,106]. This ‘super-compensation’ of brain glycogen may then provide the additional fuel reserve that leads to defective glucose sensing during a subsequent episode of hypoglycaemia. This theory is attractive, but against it is the fact that brain glycogen levels appear to be very low and a fraction of the levels seen in other tissues such as muscle and liver. Also, ‘super-compensation’ of glycogen may actually have arisen because of the model employed in these studies where pre-study infusions of glucose and insulin, rather than hypoglycaemia per se, may have led to the described phenomenon. Further research is needed in this area.

It has also emerged that mechanisms for regulating the magnitude of the neuroendocrine response to acute hypoglycaemia exist within the brain. The CRH family of ligands and receptors form an ancient and highly conserved means of regulating the neuroendocrine stress response. Within the brain, at key sites involved with autonomic activation, CRH acting through the CRH-R1 receptor appears to lead to an amplification of the autonomic response to stress whereas Urocortin (part of the CRH family of peptides), acting through the CRH-R2 receptor, suppresses the autonomic response to stress. We were recently able to show that such a mechanism might change following recurrent hypoglycaemia, with an upregulation of CRH-R2-mediated suppressive effects in the VMH. The net effect would be to suppress the counter-regulatory response to subsequent hypoglycaemia.

We should not be surprised that there is no single answer to the phenomenon of HAAF. Hypoglycaemia represents a profound physiological stress and is likely to activate numerous physiological defence systems that affect both biological and behavioural responses. Our understanding of these physiological defences remains limited, but it is reasonable to conclude that recurrent hypoglycaemia may lead to an increase in the capacity of glucose-sensing regions of the brain to use glucose and/or alternate fuels, as well as to a change in the mechanisms that fine-tune the hypoglycaemic stress response. The net effect of these changes is to suppress the glucose counter-regulatory response to a subsequent episode of hypoglycaemia.

What relevance are studies in rodents to human disease?

The ultimate aim of all basic research is its translation into the human model. In hypoglycaemia research, electrophysiological studies of hypothalamic slice preparations and rodent models offer much, but one must always be wary of over-interpreting data. The limitations of cell-based and rodent studies are well recognized. However, this does not make the work irrelevant to human disease. Glucose homeostasis, in particular, is fundamental to the survival of a vast range of species from single-cell organisms to humans. AMPK, for instance, is a critical part of the process whereby the yeast cell responds to a period of fuel deprivation, and likewise in rodents clearly plays a major role in glucose sensing during hypoglycaemia. Thus, it appears likely that such ancient and conserved systems may be important in human disease. Another example is glucokinase, which, as reviewed earlier, has been shown in rodents to play a regulatory role in glucose sensing in hypothalamic neurons.
This finding led to human studies where fructose, a modulator of glucokinase activity, was delivered systemically during hypoglycaemia and was shown to amplify the counter-regulatory response in both non-diabetic [109] and TIDDM [110] subjects. Finally, the recognition that recurrent hypoglycaemia might lead to adaptive changes that increase the ability of the brain to use alternate fuels has prompted trials in TIDDM subjects using medium-chain fatty acids that may provide neuroprotection, particularly during the night, while not leading to a deterioration in overall glucose control.

In summary, our understanding of where and how glucose is sensed has increased significantly in the last 20 years. We now recognize that a network of specialized neurons exist that continually monitor the ambient glucose level and that these neurons act in such a way as to try to maintain glucose homeostasis. These neurons appear to use sensing mechanisms very similar to those used within the pancreatic islet, with GK, the KATP channel and AMPK all playing key roles in central glucose sensing. While this information has come largely from rodent studies using a combination of in vivo and in vitro techniques, it is anticipated that newer imaging techniques such as positron emission tomography and magnetic resonance spectroscopy will allow the translation of these findings into the human model and determine their relevance to human disease. The development of novel therapies or treatment strategies designed to minimize the risk of hypoglycaemia in insulin-treated individuals with diabetes relies on the information that these studies will provide.

Competing interests
None to declare.

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The image contains a page from a scientific publication. The text on the page is related to research on the hypothalamus, hippocampus, and related brain regions, focusing on age-related differences and the role of AMP-activated protein kinase (AMPK) in glucose sensing and metabolism. The page includes references to various studies and journals, discussing topics such as hypoglycemia-sensing in the ventromedial hypothalamus, the role of AMPK in energy homeostasis, and the effects of intensive insulin therapy on glycemic thresholds.

Some key points from the text include:
- The importance of glucose and feeding-relevant peptides in the arcuate nucleus for glucose and feeding-relevant regulation.
- The role of glucokinase in the processing of glucose in the arcuate nucleus.
- The AMPK pathway and its role in the hypothalamus, particularly in glucose inhibition of neurons.
- The effects of intensive insulin therapy on glycemic thresholds and counterregulatory hormone release.
- The role of AMPK in the regulation of glucose homeostasis and the impact of AMPK activation on glucose sensitivity.

The text is a review article from the journal *Diabetes Medicine*, focusing on the role of AMPK in the regulation of glucose homeostasis and the impact of AMPK activation on glucose sensitivity.

The page also includes references to various studies and journals, discussing topics such as hypoglycemia-sensing in the ventromedial hypothalamus, the role of AMPK in energy homeostasis, and the effects of intensive insulin therapy on glycemic thresholds.


