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Defective counterregulation and hypoglycemia unawareness in diabetes: Mechanisms and emerging treatments

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Synopsis

For people with diabetes, hypoglycemia remains the limiting factor in achieving glycemic control. This article reviews recent advances in how the brain senses and responds to hypoglycemia. Novel mechanisms by which people with insulin treated diabetes develop hypoglycemia unawareness and impaired counterregulatory responses are outlined. Prevention strategies for reducing the incidence of hypoglycemia are discussed

Keywords

hypoglycemia; unawareness; glucose; diabetes; counterregulation; brain; hypothalamus; hypoglycemia-associated autonomic failure (HAAF)

Hypoglycemia - the clinical problem

Poorly-controlled diabetes is associated with vascular complications including renal failure, peripheral vascular disease, neuropathy, blindness, amputations, coronary artery disease and stroke. Multiple large clinical trials have shown the benefits of intensifying glycemic control in preventing or delaying microvascular complications. These trials, however, consistently report significantly higher rates of hypoglycemia in patients that intensify their glycemic control¹⁻⁵. Thus, hypoglycemia becomes the limiting factor for blood glucose management in patients with diabetes and precludes the attainment of microvascular benefits associated with tight glycemic control.

Incidence of Hypoglycemia

Compared to earlier self-reported and glucometer-based studies, continuous glucose monitor based studies more accurately assess the true incidence of hypoglycemia. In reasonably well-controlled patients with Type 1 diabetes (HbA1c 7.6%), biochemical hypoglycemia

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(<60mg/dl) averaged a disconcertingly high 2.1 times per 24 hours⁶. Of note, even in the group of people, who reported intact hypoglycemia awareness, biochemically confirmed hypoglycemia failed to elicit symptoms 62% of the time⁶. Thus, symptomatic hypoglycemia underestimates the true incidence of hypoglycemia and hypoglycemia awareness is not an “all or none” phenomena.

As discussed below, episodes of moderate hypoglycemia are not without clinical consequences. Recurrent episodes of moderate hypoglycemia can lead to decreased sympathoadrenal responses and decreased awareness of hypoglycemia, collectively termed hypoglycemia associated autonomic failure (HAAF)⁷, which leads to an increased risk of more frequent and more severe episodes of hypoglycemia.

Severe Hypoglycemia

Severe hypoglycemia is defined clinically as occurring when the patient requires assistance from another individual to correct hypoglycemia. For insulin treated diabetic patients, severe hypoglycemia has a high prevalence (46 and 25%) and high incidence (3.2 and 0.7 episodes per person-year) for people with Type 1 and Type 2 diabetes, respectively⁸. Severe hypoglycemia is associated with excess morbidity and mortality⁷. It can alter brain structure⁹ and cause brain damage^{10,11} [ENREF 9](#), cognitive dysfunction^{12,13} and even sudden death¹⁴. It is estimated that between 6 and 10% of patients with Type 1 diabetes die from hypoglycemia¹⁵⁻¹⁷ [ENREF 13](#). The mechanisms by which low glucose levels lead to sudden death has not been entirely worked out, but appears to be related to intensive sympathetic activation leading to fatal cardiac arrhythmias^{18,19}.

The Counterregulatory Response to Hypoglycemia

Since the brain is continuously dependent on peripheral glucose for metabolism, robust counterregulatory mechanisms exist to rapidly increase blood glucose levels in order to protect the body from the pathological consequences of hypoglycemia. In the setting of absolute or relative hyperinsulinemia, the counterregulatory response (CRR) is normally initiated when glucose levels fall below 80 mg/dl. The CRR to hypoglycemia normally includes suppression of endogenous insulin secretion and increase the secretion of glucagon, catecholamines (epinephrine, norepinephrine), cortisol, and growth hormone, which together act to increase plasma glucose levels by stimulating hepatic glucose production and limiting glucose utilization in peripheral tissues (Figure 1).

Glucagon Response to Hypoglycemia

Normally, as blood glucose levels fall, increased glucagon secretion from the pancreatic alpha cells along with decreased insulin secretion are the primary counterregulatory mechanisms by which hepatic glucose production is increased. Insulin-deficient diabetes results in an acquired defect of the glucagon response²⁰. Several mechanisms have been proposed to explain this phenomenon, including defective alpha cell glucose sensing, absent decrements in insulin secretion (intra-islet crosstalk), and reduced autonomic stimulation (recently reviewed^{21 22}). Elevated intra-islet somatostatin within the diabetic pancreas may also play a role in limiting the glucagon response to hypoglycemia because pharmacological antagonism of the somatostatin receptor can restore the glucagon response to hypoglycemia in diabetic rats²³.

Sympathetic and Adrenal Medullary Counterregulatory Response

In response to hypoglycemia, patients with Type 1 diabetes and advanced Type 2 diabetes are not able to suppress circulating (exogenous) insulin levels or increase glucagon secretion²⁰. Thus, patients with diabetes rely extensively on the sympathoadrenal system as

their primary counterregulatory defense against hypoglycemia¹⁹. Adrenergic activation leads to the release of norepinephrine at nerve terminals located throughout the periphery. Adrenergic stimulation of the adrenal glands stimulates epinephrine release. Activation of the adrenergic system combats falling glucose levels by increasing glucose production, reducing peripheral glucose utilization, and eliciting symptoms of hypoglycemia (figure 1).

Hypoglycemia Awareness

Exigent hypoglycemia is usually accompanied by characteristic signs and symptoms, which prompt the patient to take corrective action. Neurogenic symptoms occur as a result of activation of the autonomic nervous system by hypoglycemia, and lead to perception of hypoglycemia (hypoglycemia awareness) by the patient. These symptoms include sweating, hunger, tingling, tremors, palpitations, nervousness and anxiety. Interestingly, as characterized in adrenalectomized patients, these neurogenic symptoms of hypoglycemia are chiefly the result of sympathetic neural system activation, rather than epinephrine or norepinephrine release from the adrenal gland²⁴. Thus the unawareness of hypoglycemic symptoms in patients with diabetes is inexorably linked to exiguous sympathetic neuronal activation. On the other hand, neuroglycopenic symptoms result from brain's deprivation of glucose, and may be exhibited as warmth, weakness, altered mental status, drowsiness, seizures, or even coma or death²⁵. Autonomic symptoms of hypoglycemia tend to occur at higher thresholds (58 mg/dL) than neuroglycopenic symptoms, which tend to occur at 51 mg/dL²⁶. In the setting of progressive hypoglycemia, awareness of autonomic symptoms generally occurs prior to the development of profound neuroglycopenic symptoms, allowing the patient a window of opportunity to initiate corrective action to ameliorate hypoglycemia before global cognitive impairments limit behavioral responses and hypoglycemia becomes life-threatening.

Anatomy of Brain Glucose sensing

Although all brain cells utilize glucose, only a few specialized neurons in the brain truly sense and respond to reduced glucose supply. Rodent studies indicate that glucose is sensed in brain regions known to be important in metabolism and energy homeostasis, particularly in the hypothalamus, where glucose sensing neurons are located^{27,28}. Most studies to date indicate that it is the hypothalamus that principally initiates (or at least coordinates) the CRR to stimulate hormone secretion in the pituitary gland, pancreas, and adrenal glands resulting in a coordinated response. Clinical studies confirm the importance of the hypothalamus as a critical glucose sensing area because blood flow to the hypothalamus increases significantly during hypoglycemia, even before counterregulatory hormones rise²⁹. Within the hypothalamus, key regions that respond to changes in circulating glucose levels are the ventromedial hypothalamus (VMH) which contains the ventromedial nucleus (VMN) and the arcuate nucleus (ARC)³⁰. Studies show that glucose infusion into the VMH in the setting of peripheral hypoglycemia blunts the epinephrine response to hypoglycemia^{31,32}. These studies indicate that decreases in glucose are detected by the VMH and are required to fully activate the sympathoadrenal response to hypoglycemia (Figure 2).

The VMH contains glucose excitatory (GE, increase neuronal activity in response to glucose) and glucose inhibited (GI, decrease neuronal activity in response to glucose) neurons³³. Similarities and differences between GI and GE neurons with regard to glucose metabolic and electrophysiological properties have been reviewed³⁴. It is thought, that in response to hypoglycemia, concerted activation of GI neurons and suppression of GE neurons, as an initiating part of a neural network, result in a coordinated efferent process that activate the sympathoadrenal response (Figure 3).

Other glucose sensing neurons have been discovered in regions outside the hypothalamus. Within the brainstem, the nucleus tractus solitarius (NTS), the area postrema (AP), the dorsal motor nucleus of the vagus (DMN), and the subfornical region have been shown to contain glucose sensing neurons³⁵⁻³⁷. Other peripheral glucose sensing neurons (ie, within the portal/mesenteric vein, gut, and carotid bodies) ascend via afferent neurons to the brainstem (NTS) which projects anteriorly to the paraventricular nucleus (PVN) of the hypothalamus³⁰ (Figure 2). [ENREF 35](#)

Activation of the PVN appears to be critically important for activating several aspects of the stress counterregulatory responses including, 1) CRH release which acts on the anterior pituitary to release ACTH, 2) innervation of the dorsal motor nucleus of the vagus (DMN) to regulate the vagal parasympathetic efferent neurons, and 3) perhaps most importantly, direct activation of sympathetic nerves in the spinal cord (Figure 2). Failure to activate PVN neurons is a common finding in animal models that exhibit impaired counterregulatory responses to hypoglycemia^{38,39} [ENREF 35](#).

Cellular Biology of Brain Glucose sensing

The brain contains different isoforms of glucose transporters responsible for neuronal and astrocyte glucose uptake. The ubiquitous GLUT1 and the neural specific GLUT3 are the primary isoforms present in the brain that are responsible for glucose transport across the blood brain barrier and into the brain. Based on discrete regional expression, the potential contribution of other glucose transporters has been investigated. A role for GLUT2 in mediating CNS glucose sensing has been proposed⁴⁰. Also, a role for insulin-sensitive GLUT4 in mediating brain glucose sensing and the counterregulatory response to hypoglycemia was evident in recent reports from our lab showing that in response to hypoglycemia, brain GLUT4 knockout mice have 1) impaired epinephrine and glucagon responses, 2) impaired neuronal activation within the hypothalamus, and 3) impaired glucose sensing in GI neurons⁴¹. Further research is needed to understand how differential regional expression of the various glucose transporters regulate the CRR to hypoglycemia.

Once glucose enters the cells, it is phosphorylated by glucokinase, an enzyme which has been shown to play an important role in mediating hypothalamic glucose sensing^{42,43}. Metabolism of glucose increases the intracellular ATP to AMP ratio, which, in turn, regulates the activity of a key metabolic sensor, AMP-activated protein kinase (AMPK). During acute hypoglycemia, increased AMPK activity is hypothesized to lead to chloride ion (cystic fibrosis transmembrane conductance regulator, CFTR) channel closure, neuronal depolarization, and neurotransmitter release in GI neurons^{44,45} (Figure 3). In GE neurons, downstream of glucose metabolism, however, it is the activation of K-ATP channels that increases the sympathoadrenal response to hypoglycemia^{33,34,46}. Thus pharmacologic or genetic disruption of the metabolic^{41,42,44} or electrophysiological^{33,34,45} properties in these critical VMH glucose sensing neurons can lead to impaired hypoglycemic counterregulation.

Hormonal and neuro-hormonal regulation of CNS glucose sensing

The intrinsic glucose sensing/metabolism properties of glucose sensing neurons in the VMH can be acutely modified by the action of circulating hormones. Both leptin and insulin cross the blood-brain barrier and have been shown to acutely activate K-ATP channels in glucose sensing hypothalamic neurons⁴⁷. In the setting of hypoglycemia, insulin has been shown to act in the brain to augment the counterregulatory response⁴⁸. Furthermore, neuronal insulin receptor knockout (NIRKO) mice have impaired hypoglycemic counterregulation, characterized by a blunted epinephrine and norepinephrine response³⁹. Consistent with insulin exerting its effect primarily in the hypothalamus, NIRKO mice have impaired glucose sensing in VMH GI neurons and impaired activation of PVN neurons in response to

hypoglycemia³⁹. Together, these studies demonstrate that central insulin signaling plays an important role in regulating the normal counterregulatory response to hypoglycemia. Other, slower-acting hormones, including nuclear receptor transcription activators such as cortisol (discussed below), may also exert more long-term effects in regulating hypothalamic glucose sensing.

As blood glucose level fall, glucose levels within the brain also decrease. A fall in glucose levels within the VMH is associated with increased norepinephrine release in the VMH and the initiation of the counterregulatory response to hypoglycemia^{49,50}. Adrenergic receptors within the brain, particularly the VMH, are important mediators that trigger the sympathoadrenal response to hypoglycemia⁵¹. It is likely that increased or decreased catecholaminergic neurotransmitter output from other glucose sensing neurons (perhaps portal-mesenteric glucose-sensitive afferents⁵²) are integrated in the VMH to either amplify or suppress, respectively, the sympathoadrenal response to hypoglycemia.

Defective Counterregulation and Hypoglycemia Unawareness in People with Diabetes and Recurrent Hypoglycemia

As noted above, in people with Type 1 and advanced type 2 diabetes, impaired hypoglycemic counterregulation is noted by a failure to both suppress circulating insulin and increase glucagon secretion which [ENREF 45](#) leads to an increased reliance on the sympathoadrenal response as the primary counterregulatory responses^{53,54} [ENREF 46](#). Recurrent hypoglycemia further impairs the sympathoadrenal response as part of a vicious cycle, making diabetic patients vulnerable to more severe episodes of hypoglycemia^{7,20}. In addition, recurrent hypoglycemia induces impairments in brain glucose sensing on both a cellular basis in glucose sensing VMH neurons⁵⁵ as well as on a whole body basis, noted clinically by both impaired sympathoadrenal responsiveness and hypoglycemia unawareness (Figure 4). Hypoglycemia unawareness increases the incidence of severe hypoglycemia 6-fold for Type 1 diabetic patients⁵⁶ and 17-fold for Type 2 diabetic patients⁵⁷. Although approximately 20% of Type 1 diabetic patients report hypoglycemia unawareness⁵⁸, this value is most certainly an underestimation, as even diabetic patients who have intact hypoglycemia awareness are often unaware of biochemically confirmed hypoglycemia⁶.

The mechanisms by which recurrent hypoglycemia leads to altered CNS glucose sensing, impaired sympathoadrenal activation, and hypoglycemia unawareness remain an active area of investigation⁵⁹. Several potential mediators being investigated include 1) actions of hormones released during hypoglycemia (cortisol, epinephrine, opioids), 2) cell autonomous changes in substrate metabolism, and 3) altered neuronal circuitry/neurotransmitter release. These mechanisms are not mutually exclusive. Better understanding of these mechanisms will aid in developing therapeutic strategies to prevent hypoglycemia unawareness in insulin treated patients with diabetes.

Peripheral Mediators of HAAF and Hypoglycemia Unawareness

Cortisol—The hypothalamic-pituitary-adrenal axis involves a family of neuropeptides that regulate glucocorticoid (cortisol) secretion during stress. Corticotropin releasing hormone agonists have been shown to impair the counterregulatory response to subsequent hypoglycemia suggesting a possible mechanistic role in mediating HAAF⁶⁰. The hypoglycemia associated rise in systemic corticosteroids has been proposed to feedback to the hypothalamus and thereby potentially contribute to HAAF⁶¹⁻⁶³. It remains controversial as to whether the endogenous hypercortisolemia associated with the counterregulatory response is of sufficient magnitude to blunt the CRR to hypoglycemia^{64,65}.

Catecholamines—It has been well established that antecedent hypoglycemia induces a blunted epinephrine response to a subsequent episode of hypoglycemia. A study by Ramanathan et al.⁶⁶ showed that intravenous infusion of adrenergic blockers (phentolamine and propranolol) on day 1 of hypoglycemia prevented the induction of counterregulatory failure in the subsequent response on day 2 of hypoglycemia. This study implicates that HAAF is induced by antecedent sympathoadrenal responses to hypoglycemia, and possibly the antecedent sympathoadrenal response to exercise as discussed below. Extending these findings to their potential pharmacologic and therapeutic implications, an apparent dichotomy emerges whereby blocking the action of catecholamines (presumably within the CNS) may protect against subsequent hypoglycemic bouts by limiting the development of HAAF; but unfortunately, blocking the action of catecholamines in the periphery would tend to increase the severity of acute hypoglycemia. Perhaps future pharmacological treatment of recurrent severe hypoglycemia will involve development of selective adrenergic receptor modulators that favorably alter CNS mediated counterregulatory responses without adversely altering the beneficial peripheral effects of the sympathoadrenal response.

Opioids—Opioid signaling in the CNS has also been implicated in the development of impaired sympathoadrenal responses in people with Type 1 diabetes. Naloxone, an opioid receptor blocker, augmented the sympathoadrenal response to hypoglycemia⁶⁷ and when infused during antecedent hypoglycemia, it prevented the development of the hypoglycemia-associated reduced epinephrine response⁶⁸. Mechanistically, naloxone may preserve the counterregulatory response to hypoglycemia by reprogramming metabolic genes to use alternate fuels instead of glucose⁶⁹. Together, these pre-clinical and clinical studies implicate that the rise in endogenous opioids that occurs during hypoglycemia have a pathological role in mediating the adrenomedullary defect associated with HAAF and a potential therapeutic role for opioid receptor blockade to protect against HAAF.

Exercise—The inability to decrease circulating insulin during exercise puts people with Type 1 diabetes at increased risk for hypoglycemia during or after exercise. Furthermore, antecedent exercise can decrease sympathoadrenal responses to subsequent hypoglycemia⁷⁰. It is interesting that despite this reduced epinephrine responses to hypoglycemia following exercise, symptoms of hypoglycemia are not reduced, suggesting that there can be a distinction between hypoglycemia awareness and the counterregulatory adrenal response. Additionally, during stress, including hypoglycemia and exercise, the opioid β -endorphin is released to activate the sympathoadrenal response. In a recent study, healthy volunteers who exercised and had elevated endorphin levels had impaired epinephrine and norepinephrine responses during hypoglycemia the following day⁷¹. Thus, the impaired adrenomedullary response to hypoglycemia induced by antecedent hypoglycemia or exercise may be mediated by endogenous opioid action within the CNS. Thus, from a therapeutic perspective, blocking the actions of endogenous opioids may protect against exercise-induced autonomic failure.

Sleep—Nocturnal hypoglycemia is very common in patients with Type 1 Diabetes. It has a prevalence rate of up to 68%⁷² and has an incidence of once every third night⁷³. While sleeping, subjects with Type 1 diabetes have a significantly reduced epinephrine response to hypoglycemia⁷⁴ and reduced awakening from sleep during hypoglycemia, compared to non-diabetics⁷⁵. Thus the state of sleep induces a transient, additional, HAAF-like syndrome, characterized by hypoglycemia unawareness and an impaired adrenomedullary response to hypoglycemia.

If a diabetic patient is unable to wake up and take corrective actions, nocturnal hypoglycemia can be potentially life-threatening. Tattersall and Gill have reported the

unexplained overnight deaths of otherwise healthy young people with Type 1 diabetes⁷⁶, often referred to as the 'Dead in Bed syndrome'. Recently, the overnight death of a young man with Type 1 diabetes confirmed with continuous glucose monitoring that the dead in bed syndrome is associated with severe hypoglycemia^{14,76} ENREF 71.

Alternative Substrate Metabolism

Glycogen Supercompensation—It has been hypothesized that increased glycogen stores in astrocytes might contribute to hypoglycemia unawareness and impaired sympathoadrenal responses by supplementing glucosyl units for CNS metabolism during periods of systemic hypoglycemia. Studies in rats and humans have shown that brain glycogen content is increased following one or more episodes of hypoglycemia^{77,78} or 2-deoxyglucose induced neuroglycopenia⁷⁹. Currently, much controversy exists in this field since subsequent studies have shown that glycogen content in the rat brain is not elevated after acute or recurrent hypoglycemia⁸⁰ and that lower, not higher, glycogen levels exist in diabetic patients⁸¹. Hopefully improved techniques in measuring brain glycogen turnover *in vivo* both during and after hypoglycemia will resolve these apparent discrepant results. The more important question to be addressed is whether changes to brain glycogen levels (induced via physiological or pharmacological means) will offer people who suffer from recurrent hypoglycemia a beneficial therapeutic advantage in preserving both sympathoadrenal responses and hypoglycemia awareness.

Enhanced Glucose Metabolism—Alterations in glucose transport or glucose metabolism as a result of repeated exposure to hypoglycemia have been postulated to be a potential mediator of HAAF. Increased glucose transport to sustain metabolic demands during hypoglycemia is supported by studies in rats that show increased expression of glucose transporters in the brain after acute hypoglycemia⁸² and after recurrent hypoglycemia⁸³. The next important metabolic regulator in glucose sensing neurons is the enzyme glucokinase the expression level of which is also upregulated in the setting of recurrent hypoglycemia⁴². Consistent with an upregulation of glucose transport or glucokinase activity, recurrent hypoglycemia has been shown to increase hypothalamic glucose phosphorylation⁸⁴. Therefore, repeated exposure to hypoglycemia may upregulate the capacity for glucose metabolism (including increased glucose transporters, glucokinase activity, and glucose phosphorylation) during subsequent hypoglycemia. This process simultaneously limits neuroglycopenia and induces hypoglycemia unawareness at the cellular level in glucose sensing neurons, ultimately resulting in a diminished sympathoadrenal response.

While supported in some^{42,83,84} but not all⁸⁵ rodent models, altered glucose transport/metabolism as a cause for hypoglycemia unawareness is less well substantiated in humans. During hypoglycemia, Type 1 diabetic patients had similar glucose metabolism in the brain as compared to healthy controls⁸⁶. Patients with hypoglycemia unawareness seem to have normal global brain glucose metabolism; although several studies have identified specific brain regions that exhibit decreased glucose uptake, including the subthalamic brain region involving the hypothalamus⁸⁷, the prefrontal cortex⁸⁸, the amygdala and orbitofrontal cortex⁸⁹. Iatrogenic hypoglycemia that induces HAAF also did not increase global brain glucose transport in healthy patients⁹⁰, but was associated with significantly greater synaptic activity in the dorsal midline thalamus⁹¹. Further clinical studies utilizing enhanced PET and MRI technologies to examine regional brain glucose uptake/metabolism in patients with Type 1 diabetes with and without HAAF will help define the brain regions pathologically linked to this clinical syndrome.

Alternative Fuel Hypothesis—In the setting of reduced glucose supply from the periphery, the brain may be able to decrease its reliance on circulating glucose and maintain its metabolic processes by increasing uptake of alternate carbon fuels, such as ketones or lactate⁹². Lactate from astrocytes can be taken up into neurons via monocarboxylate transporters (MCT) and is hypothesized to support oxidative phosphorylation during times of glucose deficit^{85,92,93}. During a hypoglycemic clamp, Type 1 diabetic patients had twofold higher brain lactate concentrations than control subjects indicating increased brain uptake of lactate⁹⁴. If, in response to recurrent hypoglycemia, the brain has adapted in such a way as to meet its metabolic demands by utilizing relatively more lactate rather than circulating glucose, then the neurons' sufficed metabolic demands likely blunt its ability to sense and respond to subsequent hypoglycemia, resulting in impaired sympathetic activation and hypoglycemia unawareness (Figure 4).

Altered neuronal communication—Gamma-Aminobutyric Acid (GABA) is a potent inhibitory neurotransmitter. Hypothalamic GABA levels normally decrease during hypoglycemia⁹⁵, thereby relinquishing a tonic inhibitory effect on VMH neurons and allowing the generation of the counterregulatory response. Both diabetic rats and recurrently hypoglycemia rats have higher basal levels of VMH GABA that fail to decrease normally during subsequent hypoglycemia, which correlates with the reduced glucagon and epinephrine responses^{96,97}. These results indicate that altered GABA tone may be an important common mediator in the development of HAAF, especially in diabetic patients, and drugs that selectively target GABA secretion or receptor binding may improve sympathoadrenal responses to hypoglycemia.

Adaptations to Recurrent Hypoglycemia - adaptive or maladaptive?

Repetitive hypoglycemia induces a state of hypoglycemic tolerance, in which lower and lower blood glucose levels are needed to elicit symptomatic and counterregulatory responses. From a teleological perspective, brain adaptations that occur in response to repetitive hypoglycemia endeavor to maintain neuronal/cognitive function via sufficing CNS metabolic needs in the setting of another episode of hypoglycemia. Unfortunately, these adaptations ultimately reduce neuronal efferent signals, thereby limiting sympathoadrenal responses and induce a state of hypoglycemia unawareness⁷. Metabolic adaptations in patients with hypoglycemia unawareness allow cognitive function at dangerously low blood sugar levels, but do so at the perilous risk of a precipitous neuroglycopenic coma. By reducing awareness and counterregulation to subsequent hypoglycemia, HAAF jeopardizes patient safety and should therefore be considered a maladaptive response^{7,98}. However, hypoglycemic tolerance induced by recurrent hypoglycemia may induce some unexpected beneficial adaptations. Our laboratory has shown that adaptations associated with recurrent antecedent hypoglycemia protect the brain against severe hypoglycemia-induced brain damage and cognitive decline¹¹. Thus, similar to the phenomena of pre-conditioning, recurrent bouts of moderate hypoglycemia might, paradoxically, render an individual more prone to, but less vulnerable to, an episode of severe hypoglycemia. If a neuroprotective effect of hypoglycemic pre-conditioning were to be extrapolated to the clinical setting, it may explain the seemingly incongruous clinical findings that intensively treated patients, who experience recurrent hypoglycemia may be paradoxically protected from severe hypoglycemia-induced brain damage and cognitive dysfunction¹⁶. Of course recurrent hypoglycemia should not be advocated clinically, but defining the mechanisms of how recurrent hypoglycemia leads to beneficial adaptations could lead to the development of pharmacologic agents that will help protect against the morbidity and mortality associated with severe hypoglycemia^{11,99}.

Prevention of Hypoglycemia, Defective Counterregulation, and Hypoglycemia Unawareness

Identification of patients with risk factors for severe hypoglycemia is a critical step in the prevention of hypoglycemia. Type 1 diabetic patients with hypoglycemia unawareness and impaired counterregulation are more likely to be older, have diabetes of longer duration, and have lower HbA1c^{100,101}. Gender may also contribute to risk for hypoglycemia. The blunted counterregulatory response to hypoglycemia in women¹⁰², likely mediated by estrogen¹⁰³, uniquely increases the risk for hypoglycemia in women¹⁰⁴.

Strategies for the prevention of hypoglycemia includes frequent self-monitoring of blood glucose levels and patient education regarding insulin analogs, dose adjustments for anticipated exercise and carbohydrate consumption, and the use of technology for insulin administration and blood glucose monitoring (ie. insulin pumps and continuous glucose sensors).

Avoidance of Hypoglycemia

Recurrent antecedent hypoglycemia induces impaired sympathoadrenal responses and hypoglycemia unawareness. Fortunately, avoidance of hypoglycemia can completely restore hypoglycemia awareness, and partially restore the adrenomedullary response to hypoglycemia¹⁰⁵⁻¹⁰⁷. Studies showed an improved awareness after 3 days, and normalized hypoglycemia awareness with improved evidence of counterregulation in as little as 3 weeks of hypoglycemia avoidance. Thus, the adaptations that occur in response to recurrent hypoglycemia are reversible. As hypoglycemia begets hypoglycemia, so does hypoglycemia avoidance avoid hypoglycemia.

Patient Education

There are two types of patient education strategies that aim to decrease the incidence of hypoglycemia. Psychological-based instructional programs aim to improve the patients' accuracy in detecting hypoglycemia^{108,109}. Other educational programs advocate hypoglycemia avoidance strategies, dietary education, and flexible insulin dosing strategies to account for varied diet and activity levels^{110,111} [ENREF 100](#). Efficacy of these educational programs is noteworthy. In the setting of intensified blood glucose control (reducing HgbA1C from 8.1 to 7.3%), when rates of hypoglycemia would be expected to increase, educational programs markedly reduced the incidence of severe hypoglycemia from 0.37 to 0.14 events per patient per year¹¹¹. Thus, patient education appears to break the bond that hitherto invariably linked intensive glycemic control to increased incidence of hypoglycemia.

Choice of insulin analog therapy

Multiple clinical trials demonstrate that the newer insulin analogues reduce the incidence of hypoglycemia. With a shorter duration of action as compared to regular insulin, rapid acting insulin analogs decrease the incidence of post-prandial hypoglycemia^{112,113}. By not rising in the middle of the night, the flatter pharmacokinetics of long-acting insulin glargine help to decrease incidence of nocturnal hypoglycemia as compared with NPH insulin¹¹⁴. The newer ultra-long acting basal insulin degludec, appears to be particularly effective in lowering the risk of nocturnal hypoglycemia¹¹⁵.

Choice of Insulin delivery - use of continuous subcutaneous insulin infusion (CSII) pumps

If a patient's hemoglobin A1C<8.5% is not obtainable via multiple doses of injectable insulin, a clinical decision to initiate a trial of a continuous subcutaneous insulin infusion

pump is reasonable. A review analysis of 26 observational studies noted that the majority of CSII studies demonstrated significantly decreased rates of severe hypoglycemia¹¹⁶. A recent prospective study specifically recruiting patients with hypoglycemia unawareness showed that transitioning patients from multiple daily injections to CSII halved the hypoglycemic events rate and, remarkably, virtually eliminated the rate of severe hypoglycemia, from 1.25 to 0.05 events per year¹¹⁷. Thus, the use of CSII may reduce the amount of human error that occurs with multiple daily insulin injections and thereby reduce episodes of hypoglycemia.

Self-Monitoring of blood glucose - Glucose Continuous Glucose Monitors

A meta-analysis of nineteen trials indicate that continuous glucose monitors (CGM) improve glycemic control in adults with diabetes, but, in spite of hypoglycemia alarms, the effect on reducing incidence of hypoglycemia is marginal¹¹⁸. A more positive interpretation would be that the use of CGM improves HbA1C without increasing the incidence of hypoglycemia¹¹⁹, results very much unlike the DCCT³. Therefore, CGM technology may help dissociate intensive glycemic control from increased hypoglycemia.

Establishing closed-loop communication between CGM and insulin pumps may offer new technology-based opportunities to decrease the burden of hypoglycemia. For example, programming of insulin pumps to automatically suspend basal insulin infusion for two hours after a low blood sugar detected by CGM significantly decreases the duration of hypoglycemia¹²⁰. In addition to suspending insulin delivery, perhaps technology in the near future will allow dual chamber pumps to automatically infuse glucagon in response to a low or falling blood glucose in order to limit the incidence, duration, or severity of hypoglycemia¹²¹.

Whole Pancreas and Islet cell transplantation

Continuous glucose monitoring systems have confirmed that transplant recipients either have significantly decreased (in insulin requiring subjects) or completely eradicated (in insulin independent subjects) the amount of time spent in the hypoglycemic range (<60 mg/dL)¹²². The mechanisms for this striking reduction in the incidence of hypoglycemia include, 1) the elimination (or marked reduction) in exogenous insulin administration reduces the risk of iatrogenic hypoglycemia, 2) the provision of a regulatory decrement in endogenous insulin secretion, 3) the partial restoration of the glucagon counterregulatory response, and 4) the recovery of sympathoadrenal response and hypoglycemia awareness due to the avoidance of iatrogenic hypoglycemia^{123,124}. For patients with intractable, recurrent, severe hypoglycemia, whole pancreas or islet cell transplantation should be considered as a viable therapeutic option.

Relaxed A1C goals

Although the ADA and AACE differ with regards to HbA1c goals (<7.0 or <6.5, respectively) both societies acknowledge that these goals should only be attempted if they can be achieved safely “without significant/substantial hypoglycemia”. Given that significant/substantial, temporarily disabling, severe hypoglycemia occurs so frequently in people with both Type 1 and Type 2 diabetes⁸, it could be argued that these idyllic HbA1c goals are not appropriate for a relatively large percentage of people with diabetes. To decrease the incidence of hypoglycemia, both societies advocate less-stringent A1C goals (such as 8%) as being appropriate for patients with a history of severe hypoglycemia. Also, for young children who are often unable to recognize the symptoms of hypoglycemia, relaxed glycemic control guidelines are recommended¹²⁵. Additionally, relaxed HbA1C goals may be appropriate for patients in whom one severe hypoglycemic reaction might be particularly catastrophic (ie. frail elderly people with diabetes, patients with extensive comorbid conditions or advanced macrovascular complications). Finally, less-strict A1C

goals may be appropriate for individuals in whom the benefits of intensive glycemic control may not be realized (ie. patients with advanced microvascular complications or limited life expectancy). Therefore, ideal HbA1c target goals should not be generalized for all individuals with diabetes; but rather, healthcare practitioners should individualize realistic HbA1c goals on a case by case basis in order to minimize the potential morbidity and mortality of hypoglycemia.

Summary

Until a cure for diabetes is found, hypoglycemia will continue to be a major barrier for the achievement of long-term glucose control and will cause recurrent morbidity in individuals with diabetes. Numerous sedulous research studies have begun to uncover the mechanisms by which the CNS responds and adapts to hypoglycemia. Understanding these mechanisms will undoubtedly lead to better management and therapies that reduce the risk for hypoglycemia, while still allowing patients to achieve the benefits associated with tight glycemic control. Given this pervasive barrier of hypoglycemia for the treatment of diabetes, physicians should discuss hypoglycemia prevention strategies with their patients, so that they can have a better chance of achieving their glucose controls goals while avoiding the morbidity and mortality associated with hypoglycemia.

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KEY POINTS

- Hypoglycemia continues to be a major barrier for the achievement of long-term glucose control and will cause recurrent morbidity in individuals with diabetes.
- Numerous sedulous research studies have begun to uncover the mechanisms by which the CNS responds and adapts to hypoglycemia.
- Understanding these mechanisms will undoubtedly lead to better management and therapies that reduce the risk for hypoglycemia, while still allowing patients to achieve the benefits associated with tight glycemic control.
- Given this pervasive barrier of hypoglycemia for the treatment of diabetes, physicians should discuss hypoglycemia prevention strategies with their patients, so that they can have a better chance of achieving their glucose controls goals while avoiding the morbidity and mortality associated with hypoglycemia.

Figure 1. The counterregulatory response to hypoglycemia

Hypoglycemia is first sensed in various brain regions including the hypothalamus and brain stem. Low glucose in these brain regions stimulates the autonomic nervous system to release norepinephrine and acetylcholine at postganglionic nerve terminals and induce symptoms of hypoglycemia (hypoglycemia awareness). A principal counterregulatory response is the secretion of glucagon which may be stimulated by various mechanisms including independent α -cell glucose sensing, autonomic innervation, epinephrine stimulation, and a reduction of intra-islet insulin secretion. Via autonomic stimulation, epinephrine is released from the adrenal medulla. Not shown is the hypothalamic-pituitary-adrenal axis by which the release of ACTH from the pituitary stimulates cortisol release from the adrenal cortex. The cumulative effect of the sympathetic nervous system and counterregulatory hormones at the level of the liver is to increase hepatic gluconeogenesis and glycogenolysis while the effect at muscle and adipose tissue is to decrease peripheral glucose utilization.

Figure 2. Afferent glucose sensing pathways, neural integration, and efferent autonomic pathways that mediate the counterregulatory response to hypoglycemia

During hypoglycemia, the initiation and coordination of the counterregulatory response is mediated by a network of glucose sensing neurons in the hypothalamus, including the ventromedial nucleus (VMN), arcuate nucleus (ARC) and lateral hypothalamus (LH). Glucose sensing also occurs in the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus (DVN) in the hindbrain. The NTS also receives afferent information from peripheral glucose sensors, including the portal vein. Hypothalamic and hindbrain neural networks project to the paraventricular nucleus of the hypothalamus (PVN) in order to elicit autonomic and neuroendocrine counterregulatory responses. Although not directly glucose sensing, parvicellular neurons in the PVN initiate sympathetic autonomic responses via pre-ganglionic spinal efferents. Parasympathetic (vagal) innervation is relayed from the PVN to the dorsal vagal nucleus (DVN) which then relays to peripheral organs. In addition, the hypothalamic-pituitary-adrenal axis is also initiated from a distinct set of medial parvicellular neurons within the PVN that secretes corticotropin releasing hormone (CRH). CRH acts on the anterior pituitary (Pit) to stimulate the secretion of adrenocorticotropic hormone (ACTH) which circulates to the adrenal cortex to increase cortisol secretion. Interneurons involved in the neural glucose sensing and autonomic response network shown in black. Afferent glucose sensing pathways are shown in green. Efferent autonomic responses to hypoglycemia shown in brown. Post-ganglionic vagal parasympathetic efferent pathway shown in red. Hypothalamic-Pituitary-Adrenal axis shown in blue.

Figure 3. Glucose sensing neurons of the ventromedial hypothalamus (VMH)

A) VMH glucose excited (GE) neurons are activated in response to increasing glucose. In a setting of low glucose, decreased glucose entry into the GE neuron through glucose transporters (GLUT) leads to decreased phosphorylation by glucokinase (GK) leading to an increase in the AMP/ATP ratio, thus increasing the activity of AMPK and stimulating KATP channel activation. Activation of KATP channels leads to decreased membrane depolarization and decreased action potential frequency and neurotransmitter release, in particular GABA, thus leading to activation of the hypoglycemic counterregulatory response (CRR). B) VMH glucose inhibited (GI) neurons are activated in response to decreasing glucose. Decreased glucose entry into neurons leads to an increase in the AMP/ATP ratio, activation of AMPK which activates formation of nitric oxide (NO) which can act as a neurotransmitter. Increased AMP/ATP also inhibits a chloride channel, thought to be the cystic fibrosis transmembrane conductance regulator, (CFTR), leading to membrane depolarization, increased action potential frequency, and neurotransmitter release, including glutamate, which leads to activation of the counterregulatory response. GABA and glutamate can potentially be secreted from both GE and GI neurons upon their activation but a decrease in GABA levels is required for full activation of the counterregulatory response.

Figure 4. Preconditioning through recurrent hypoglycemia leads to cellular adaptation and HAAF

Hypoglycemia is a state of energy depletion that leads to metabolic stress. Sympathetic activation leads to symptoms of hypoglycemia awareness and the adrenomedullary response. The normal response to hypoglycemia is a cellular adaptation, assuming the energy depletion and metabolic stress was not enough to induce cell death. The mechanism by which cellular adaptation occurs is unclear but may include the use of alternate fuels (such as lactate) and/or an enhanced glucose transport/phosphorylation/metabolism. During a subsequent hypoglycemic episode, the adapted cell experiences less marked energy depletion and less metabolic stress thus making the cells less susceptible to death. Less intracellular energy depletion leads to impaired sympathetic activation resulting in hypoglycemia unawareness and a reduced adrenomedullary response to subsequent hypoglycemia, collectively known as hypoglycemia associated autonomic failure (HAAF). Preconditioning through recurrent hypoglycemia, paradoxically, acts to render an individual more prone to, but less vulnerable to, an episode of severe hypoglycemia.

Table 1
Clinical Indications for less strict HbA1c Goals (ie, goal HbA1c in 7-8% range)

Advanced Age
Pediatric Patients
Hypoglycemia Unawareness
Frequent Severe Hypoglycemia
Life Expectancy <5 years
Advanced Macrovascular Complications
Renal Failure
Extensive Comorbidities

Table 2
Recommended Review of Hypoglycemia at Clinic Visits

Monitoring	<p>Recent history of symptomatic or severe hypoglycemia</p> <p>Recent history of hypoglycemia unawareness</p> <p>Recommend frequent blood glucose measurements</p> <p>Monitor carbohydrate intake and insulin dosage, special events/considerations</p> <p>Review data: assess for patterns of hypoglycemia (time of day, association with types of meals/activities/exercise, weekdays versus weekends, post-menstrual)</p> <p>Recommend checking blood sugar before meals, at bedtime, and before driving</p> <p>Consider referral for diabetes education</p> <p>If nocturnal hypoglycemia is suspected, wake patient at 3am for a few nights to check blood glucose</p> <p>Consideration of a continuous glucose monitoring system with hypoglycemia alarms</p>
Meals	<p>Adjust insulin-to-carbohydrate ratio to avoid post-meal hypoglycemia</p> <p>Proper assessment of portion size and carbohydrate content</p> <p>Ideal insulin-to-carbohydrate ratio should reach target blood sugar three to four hours after meals</p> <p>Pre-meal glycemia may influence the timing delay between pre-meal insulin dosage and initiating of meal</p> <p>If pre-meal glucose is below target, reduce pre-meal insulin dose appropriately</p> <p>Alcohol has glucose-lowering effects and can mask symptoms of hypoglycemia; consider reducing basal insulin doses when consuming alcohol</p>
Insulin	<p>Insulin Basal long-acting + rapid-acting pre-meal insulin combinations less likely to cause hypoglycemia than intermediate acting + regular insulin preparations</p> <p>Consider less aggressive correction insulin doses. Use the '1,800 rule' rather than the '1,500 rule' (i.e. estimated mg/dl drop in glycemia per unit of insulin=1,800/total daily dose)</p> <p>Avoid repetitive, or stacking of, correction doses</p>
Exercise	<p>Consider type of exercise (timing, duration and intensity)</p> <p>Check blood sugars before and during prolonged exercise; snack if necessary</p> <p>Consider reducing basal insulin dosage prior to anticipated period of prolonged exercise</p> <p>Make adjustments for increased insulin sensitivity for 24 hours after exercise</p>
Treatment	<p>Readily available emergency supplies including sugar tablets, candy, sugar-paste in tube</p> <p>Prescription glucagon kits (non-expired) readily available</p> <p>People who have regular contact with patient (family members, colleagues, teachers, etc.) need to know signs of hypoglycemia and how to treat it</p> <p>Notification of emergency medical services (i.e. 911)</p>
Prevention	<p>Discussion between patient and physician regarding a period of less intensive glycemic management goals (i.e. relaxed/higher glycated hemoglobin goal, higher blood glucose targets pre-/post-meals, and when calculating correction factor, etc.)</p> <p>Review comorbidities that cause hypoglycemia including malabsorption (celiac or pancreatic insufficiency), renal failure, liver disease, adrenal insufficiency, hypothyroidism</p> <p>Scrupulous avoidance of hypoglycemia to restore hypoglycemia awareness</p> <p>Medical identification bracelet or necklace indicating that patient has diabetes and takes insulin</p>

Table 3
Investigational and Advanced and therapies for hypoglycemia prevention

Interventions	Rational	Reference
Bedtime Snacks: <ul style="list-style-type: none"> • Carbohydrate/Protein • Carbohydrate/Protein + Acarbose • Uncooked Cornstarch Bars 	Prevention of early nocturnal hypoglycemia	126,127
Insulin Pump & Continuous glucose monitors <ul style="list-style-type: none"> • Automatic basal insulin suspension • Dual Chamber insulin and glucagon pumps 	Prevention of iatrogenic insulin induced hypoglycemia	121,128
Alert Dogs	Dogs trained to recognize hypoglycemia and alert owners	129
Islet cell or whole pancreas transplantation	Restoration of the counterregulatory response	123,124
Medications: <ul style="list-style-type: none"> • Theophylline • Caffeine • Terbutaline • fluoxetine 	Increase hypoglycemic counterregulatory response and patient perception of hypoglycemia	126,130,131