Mechanisms of Hypoglycemia-Associated Autonomic Failure in Diabetes

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Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes. It causes recurrent illness in most people with type 1 diabetes mellitus and in many with advanced type 2 diabetes mellitus and is sometimes fatal. It generally precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the benefits of glycemic control. Various mechanisms, discussed in this review, cause a vicious cycle of recurrent hypoglycemia.

Compromised defenses against hypoglycemia

As plasma glucose levels fall, the physiologic defenses against hypoglycemia are a decrease in the secretion of the glucose-lowering pancreatic beta-cell hormone insulin, an increase in the secretion of the glucose-raising pancreatic alpha-cell hormone glucagon, and in the absence of an increase in glucagon, an increase in the secretion of the glucose-raising adrenomedullary hormone epinephrine. The normal behavioral defense is carbohydrate ingestion, prompted by neurogenic (autonomic) symptoms that largely originate from a sympathetic neural response. These defenses are illustrated in Figure 1. Their effectiveness ensures a continuous supply of glucose to the brain.

In people with diabetes, therapeutic insulin excess caused by treatment with insulin, sulfonylureas, or glinides can initiate a hypoglycemic episode. Marked absolute therapeutic insulin excess can occasionally cause hypoglycemia in patients with intact defenses against hypoglycemia (Fig. 2). Typically, however, hypoglycemia occurs during less marked or even relative therapeutic insulin excess (insulin levels insufficient to cause hypoglycemia under most conditions but high enough to cause it in the context of decreased exogenous glucose delivery or endogenous glucose production, increased glucose use, or increased sensitivity to insulin) in patients with compromised defenses against hypoglycemia. Such patients — those with established type 1 diabetes or advanced type 2 diabetes — have beta-cell failure or absolute endogenous insulin deficiency (Fig. 2). As plasma glucose levels fall, the compromised physiologic defenses include failure of insulin levels to diminish (in the absence of endogenous insulin secretion, circulating insulin levels are a function of the absorption and clearance of injected insulin, not insulin secretion), failure of glucagon secretion to increase, and attenuated epinephrine secretion (Fig. 2). This combination of compromised physiologic defenses causes the clinical syndrome of defective glucose counterregulation, which increases the risk of recurrent severe hypoglycemia by a factor of 25 or more.

The compromised behavioral defense, as plasma glucose levels fall, is the failure to ingest carbohydrates because of the absence of symptoms of hypoglycemia;
their absence reflects the attenuation of the sympatoadrenal response (largely the sympathetic neural response)\(^1\) (Fig. 2). That attenuation causes the clinical syndrome of hypoglycemia unawareness (or impaired awareness of hypoglycemia), which increases the risk of recurrent severe hypoglycemia by a factor of 6 or more.\(^1\)

A pivotal finding is that hypoglycemia attenuates defenses (including increased epinephrine secretion and symptomatic defenses) against subsequent hypoglycemia in nondiabetic persons\(^10\) and patients with type 1 diabetes.\(^7\) That led to the concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes (Fig. 2). According to this concept, recent hypoglycemia (or sleep or prior exercise) causes both defective glucose counterregulation (by attenuating the adrenomedullary epinephrine response, in the context of an insulin concentration that is not reduced and glucagon secretion that is not increased) and hypoglycemia unawareness (largely by attenuating the sympathetic neural response) and thus a vicious cycle of recurrent hypoglycemia.\(^1,7,8\) With regard to the pathophysiological mechanisms of HAAF, one needs to explain not only the lack of a decrease in insulin and of an increase in glucagon but also the attenuated sympatoadrenal — adrenomedullary and sympathetic neural — responses to declining glucose concentrations.
Loss of Insulin and Glucagon Responses

The mechanism underlying the failure of circulating insulin levels to fall as glucose levels fall in patients with type 1 diabetes or advanced type 2 diabetes is straightforward. In the absence of endogenous insulin secretion (beta-cell failure), circulating insulin levels are simply a function of the absorption and clearance of injected insulin.\(^1\)

The mechanism of the lack of an increase in glucagon is different from that of the attenuation of the sympathoadrenal responses.\(^1\) Loss of the glucagon response precedes attenuation of the epinephrine response,\(^1,6,11\) is independent of diabetic autonomic neuropathy,\(^1,7\) and is not corrected by scrupulous avoidance of hypoglycemia.\(^1,12\)

The lack of an increase in alpha-cell glucagon secretion is also best attributed to beta-cell failure — specifically, the lack of a decrease in the alpha-cell inhibitory signal of beta-cell insulin\(^1-13\) (Fig. 3). The evidence for this conclusion has been reviewed previously\(^13\) and is summarized here. First, loss of the insulin response and loss of the glucagon response are correlated\(^6,11,14,15\) and they develop early in the course of type 1 diabetes\(^6,11\) but late in the course of type 2 diabetes.\(^8\) Second, the glucagon response to hypoglycemia is not critically dependent on innervation. Normal glucagon secretion in response to hypoglycemia occurs in humans with a transplanted (denervated) pancreas,\(^16\) as well as in humans with spinal cord transections\(^17\) (and, thus, no sympathoadrenal outflow from the brain to the islets) and dogs with a denervated pancreas;\(^18\) glucagon secretion is also normal in the perfused rodent pancreas and perfused rodent and human islets. Thus, loss of the glucagon response cannot be attributed to

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**Figure 2. Schematic Diagram of Hypoglycemia-Associated Autonomic Failure (HAAF) in Diabetes.**

Although marked insulin excess can cause occasional episodes of hypoglycemia in patients with relative beta-cell failure, less marked insulin excess often causes hypoglycemia in patients with hypoglycemia-associated autonomic failure (defective glucose counterregulation and hypoglycemia unawareness). Adapted from Cryer.\(^4\)
islet denervation, and the causative abnormality in type 1 diabetes and advanced type 2 diabetes must reside within the islets.

Third, because there is a glucagon response to administered amino acids in patients with type 1 diabetes,\textsuperscript{5,19,20} loss of the glucagon response to hypoglycemia must be the result of reduced signaling of functional alpha cells to secrete glucagon during hypoglycemia. Fourth, because insulin normally regulates glucagon secretion in a reciprocal fashion in humans\textsuperscript{20-25} and laboratory animals, it follows that loss of beta-cell insulin secretion would result in loss of the signal of a decrease in insulin to increase alpha-cell glucagon secretion, despite a low glucose level in the alpha cells (Fig. 3). This mechanism for loss of the glucagon response to hypoglycemia does not exclude the possibility of additional intra-islet mechanisms, such as excessive delta-cell secretion of somatostatin.\textsuperscript{26}

These data support the conclusion that in diabetes characterized by an absolute deficiency of endogenous insulin secretion — type 1 diabetes and advanced type 2 diabetes — the lack of a decrease in insulin and the lack of an increase in glucagon are prerequisites for defective glucose counterregulation but do not cause defective glucose counterregulation or hypoglycemia unawareness. Those two components of HAAF in diabetes develop only when the sympathoadrenal and symptomatic responses to hypoglycemia become attenuated\textsuperscript{1} (Fig. 2).
ATTENUATION OF SYMPATHOADRENAL RESPONSES

Attenuated sympathoadrenal responses to hypoglycemia are commonly caused by recent hypoglycemia but can also be caused by sleep or prior exercise. Unlike the loss of the insulin and glucagon responses at the islet level, the alteration resulting in attenuated sympathoadrenal responses must reside within the central nervous system (CNS) or its afferent or efferent connections.

One limitation of research on the mechanism underlying attenuated sympathoadrenal responses in humans has been the need for noninvasive methods of measuring human brain function. As discussed below, new techniques of positron-emission tomography (PET), magnetic resonance imaging, and magnetic resonance spectroscopy are now addressing that need. Other limitations are the failure of many studies to document which patients with diabetes have HAAF (i.e., documented attenuation of the plasma epinephrine and neurogenic symptom responses to controlled hypoglycemia) and which patients do not and the failure to study the putative mechanisms of HAAF in both patient groups and nondiabetic controls. A more efficient approach is to study a putative mechanism of HAAF in nondiabetic persons both before a period of hypoglycemia, when normal plasma epinephrine and neurogenic symptom responses to controlled hypoglycemia can be documented, and after a period of hypoglycemia, when attenuated responses can be documented. Incidentally, the findings that attenuated sympathoadrenal and symptomatic responses to hypoglycemia can be induced by recent hypoglycemia in nondiabetic persons and can be reversed by scrupulous avoidance of hypoglycemia in patients with diabetes underscore the fact that these key features of HAAF are functional rather than structural (i.e., neuropathic) in origin.

Hypotheses regarding CNS-mediated mechanisms of the attenuated sympathoadrenal responses to hypoglycemia that cause HAAF include the systemic-mediator hypothesis, the brain fuel–transport hypothesis, the brain-metabolism hypothesis, and the cerebral-network hypothesis.

Systemic-Mediator Hypothesis

This hypothesis holds that increased circulating cortisol levels or perhaps some other factor during recent hypoglycemia acts on the brain to attenuate the sympathoadrenal and symptomatic responses to subsequent hypoglycemia. However, neither prior cortisol elevations similar to those that occur during hypoglycemia nor inhibition of the cortisol response to prior hypoglycemia with metyrapone prevents the attenuated epinephrine and symptomatic responses to subsequent hypoglycemia in humans.

Brain Fuel–Transport Hypothesis

According to this hypothesis, recent hypoglycemia causes increased blood-to-brain transport of glucose (or of an alternative metabolic fuel) and thus attenuates sympathoadrenal and symptomatic responses to subsequent hypoglycemia. This hypothesis was initially based on the finding that hypoglycemia persisting for 3 days or longer results in increased expression of glucose transporter 1 (GLUT-1) in the cerebral vasculature and in increased brain glucose uptake in rats. However, hypoglycemia for just 2 hours results in attenuated sympathoadrenal and symptomatic responses to subsequent hypoglycemia in humans. In addition, brain glucose uptake (calculated from arteriovenous glucose differences across the brain and estimates of cerebral blood flow [the Kety–Schmidt technique]) was reported to be maintained during a subsequent episode of hypoglycemia in nondiabetic persons with a prior episode and in patients with type 1 diabetes who had relatively low glycated hemoglobin levels and thus probably more recent hypoglycemia. In both instances, however, the difference in calculated brain glucose uptake was due to greater estimated cerebral blood flow rather than increased arteriovenous glucose differences across the brain.

The glucose-transport hypothesis was not supported by PET measurements. Global blood-to-brain glucose transport, measured with [1-13C] glucose PET, was not reduced in patients with poorly controlled type 1 diabetes and was not increased after nearly 24 hours of interprandial hypoglycemia, which produces a model of HAAF (including attenuated epinephrine and neurogenic symptom responses to hypoglycemia) in nondiabetic persons. Furthermore, global blood-to-brain [13C]3-O-methylglucose transport and [18F]deoxyglucose transport, both measured with PET, were not increased in patients with type 1 diabetes who were thought to have hypoglycemia unawareness.

The brain fuel–transport hypothesis may be...
flawed. The premise is that hypoglycemia causes a decrease in the rate of cerebral glucose metabolism, which in turn causes an increase in sympathoadrenal activity, and that prior hypoglycemia may somehow increase the cerebral transport of glucose to the brain, minimizing the decrease in the rate of cerebral glucose metabolism and thus attenuating the increase in sympathoadrenal activity. However, there is no evidence that a decrease in the rate of cerebral glucose metabolism causes an increase in sympathoadrenal activity (that response could be a signaling event), and it is unclear how low the plasma glucose concentration has to be to limit oxidative brain metabolism, but it may be quite low. The rate of blood-to-brain glucose transport exceeds the rate of cerebral glucose metabolism even at plasma glucose concentrations of 65 mg per deciliter (3.6 mmol per liter) in humans.30,42

Extrapolation of the linear relationship between plasma and brain glucose concentrations, the latter measured with 13C magnetic resonance spectroscopy, in nondiabetic persons and patients with type 1 diabetes during euglycemia and hypoglycemia, as reported by van de Ven and colleagues,45 suggests that the plasma glucose concentration at which the brain glucose concentration would become zero — at which point brain glucose metabolism would have to decrease — is less than 36 mg per deciliter (2.0 mmol per liter). An increase in blood-to-brain glucose transport would not increase brain glucose metabolism unless it shifted from below to above that unknown, but seemingly low, glycemic threshold.

There was no significant difference in brain glucose concentrations between the nondiabetic persons and the patients with type 1 diabetes in the study by van de Ven and colleagues,45 suggesting no difference in blood-to-brain glucose transport. Assuming the patients with type 1 diabetes did not have HAAF (epinephrine responses in these patients were similar to those in nondiabetic persons, and symptoms of hypoglycemia were not reported), commentators suggested that blood-to-brain glucose uptake might have been increased in patients with HAAF, if they had been included in the study.46 That inference was made on the basis of two observations: a 15% higher occipital–cortical brain glucose concentration in patients with type 1 diabetes than in nondiabetic persons, as measured with 1H magnetic resonance spectroscopy under nonphysiologic conditions (infusions of somatostatin, insulin, and 50% glucose) with hyperglycemia (approximately 300 mg per deciliter [16.7 mmol per liter]),47 and no significant difference in cortical brain glucose metabolism, as measured with 13C magnetic resonance spectroscopy under similar nonphysiologic conditions with hyperglycemia, between patients with type 1 diabetes and nondiabetic persons.48 Although the patients with type 1 diabetes were assumed to have HAAF, they were not shown to have attenuated epinephrine and symptomatic responses to hypoglycemia.

Notably, the same investigative group found no effect of recurrent episodes of hypoglycemia, which produced a model of HAAF (attenuated epinephrine and neurogenic symptom responses to hypoglycemia), on brain glucose concentrations measured with 1H magnetic resonance spectroscopy under similar nonphysiologic conditions with hyperglycemia.49 Because the brain glucose concentration is a direct function of the plasma glucose concentration,45 the unaltered brain glucose concentration does not support the conclusion that increased blood-to-brain glucose transport might be the mechanism of HAAF.46

If the normally small astrocytic brain glycogen pool increases substantially (reflecting glycogen supercompensation) after hypoglycemia, that expanded source of glucose within the brain could result in an attenuated sympathoadrenal response during subsequent hypoglycemia.50 However, the evidence in rats that brain glycogen content increases substantially after hypoglycemia has not been confirmed,51 and the glycogen-supercompensation hypothesis has not been supported in humans.52 Brain glycogen was not increased in patients with type 1 diabetes who were selected for hypoglycemia unawareness. Because brain glycogen synthesis is a direct function of the plasma glucose concentration and blood-to-brain glucose transport, increased blood-to-brain glucose transport should result in increased brain glycogen. That was not the case in the patients selected for hypoglycemia unawareness.52

Neurons oxidize lactate,53 but that lactate is largely derived from glucose within the brain.1 An increase in blood-to-brain lactate transport is a plausible mechanism of HAAF, although, as discussed above regarding glucose, this idea assumes that a decrease in brain oxidative metabolism causes an increase in sympathoadrenal
activity and, if so, lactate metabolism would have to be sufficient to raise brain oxidative metabolism. Lactate infusions resulting in increases in circulating lactate levels by a factor of approximately 4 in nondiabetic persons and by approximately 2 in nondiabetic persons and patients with type 1 diabetes reduced epinephrine responses to, and symptoms of, hypoglycemia in both the nondiabetic persons and the patients with type 1 diabetes. Plasma lactate concentrations roughly double during hyperinsulinemia. Arteriovenous measurements have revealed lactate release from the brain in the euglycemic state and either no lactate uptake or a small amount of lactate uptake, sufficient to compensate for only about 25% of the calculated brain glucose energy deficit during hyperinsulinemic hypoglycemia in humans.

Studies of systemic lactate infusions with 13C magnetic resonance spectroscopic measurements in nondiabetic persons have shown brain lactate uptake when arterial lactate levels are increased by a factor of 4 and increased lactate transport to the brain when plasma lactate levels are increased by a factor of 2. Indeed, increased brain lactate concentrations without increased oxidation of lactate have been reported in patients with type 1 diabetes. Lactate infusions that caused only a small increase in brain lactate metabolism were found to result in maintenance of brain glucose metabolism during subsequent hypoglycemia in rats subjected to recurrent hypoglycemia.

Brain-Metabolism Hypothesis

This hypothesis holds that recent hypoglycemia alters CNS metabolic regulation, resulting in attenuated sympathoadrenal responses to declining plasma glucose concentrations and thus HAAF. Studies of the cellular and molecular biology and pathophysiology of CNS control of glucose counterregulation in rodent models have focused largely, but not exclusively, on the ventromedial hypothalamus. Potential mechanisms include decreased glucose sensing by glucose-excited or glucose-inhibited neurons in the hypothalamus, elsewhere in the brain, and in the periphery; decreased activation of AMP kinase; increased glucokinase activity; loss of a decrease in the counterregulatory inhibitor γ-aminobutyric acid; loss of an increase in the counterregulatory stimulator glutamine; increased urocortin release; and reduced actions of insulin on the brain.

One or more of these basic clues from a variety of studies may ultimately lead to clinical strategies that prevent hypoglycemia. Pending that, there are clues from studies in humans that may lead to strategies that lower the barrier of hypoglycemia in diabetes (Fig. 4).

Several agents, such as glucagon, glucagon-stimulating amino acids, β1-adrenergic agonists (e.g., terbutaline), and adenosine antagonists (e.g., caffeine), are known to raise glucose concentrations. Their therapeutic potential is limited because their glucose-raising actions are not increased in response to falling glucose levels. Nonetheless, the judicious use of such agents could prove beneficial if their efficacy and safety were demonstrated in randomized clinical trials.

Five potential treatments for reversing glucose counterregulatory defects — selective serotonin-reuptake inhibitors (SSRIs), adrenergic antagonists, an opiate-receptor antagonist, fructose, and a selective ATP-sensitive potassium (KATP)—channel agonist — are of particular interest. All enhance counterregulatory responses to falling glucose concentrations.

SSRIs increase the counterregulatory responses to hypoglycemia in humans and rats. A randomized clinical trial of an SSRI for the prevention of iatrogenic hypoglycemia may be warranted. Combined α-adrenergic and β-adrenergic blockade prevents the attenuation of sympathoadrenal responses the day after hypoglycemia in humans. If that were shown to be predominantly an effect of β1-adrenergic blockade, a trial of a β1-adrenergic antagonist for the prevention of hypoglycemia in patients with type 1 diabetes would be reasonable and might reduce mortality. β1-adrenergic blockade would not impair the β2-adrenergic actions of catecholamines, such as their glucose-raising and symptom-generating effects. Infusion of the opioid-receptor antagonist naloxone increases the plasma epinephrine response to hypoglycemia and, when administered during hypoglycemia, prevents attenuation of the plasma epinephrine response to subsequent hypoglycemia in humans. Fructose infusion amplifies epinephrine and glucagon responses and increases glucose production during hypoglycemia in humans. Finally, administration of a selective Kir6.2/SUR-1 KATP—channel agonist increases the epinephrine response to hypoglycemia in rats. However, systemic administration of the nonselective KATP—channel agonist diazoxide suppresses the glucagon re-
Cure diabetes

Prevent diabetes

Develop plasma glucose regulation:
Insulin replacement
Insulin secretion

Eliminate Hypoglycemia

Reverse compromised glucose counterregulatory defenses

Glucagon
Amino acids
β2-adrenergic agonist

Adrenergic antagonist
Selective serotonin-reuptake inhibitor
Opiate antagonist

Adenosine antagonist
GABA-release inhibitor
Fructose
KATP-channel agonist
Other

Figure 4. Elimination of Hypoglycemia from the Lives of People with Diabetes.

Prevention or cure of diabetes or provision of plasma-glucose–regulated insulin replacement or secretion would eliminate hypoglycemia. In the meantime, available drugs might reduce the burden of iatrogenic hypoglycemia. GABA denotes γ-aminobutyric acid, and KATP ATP-sensitive potassium. Adapted from Cryer.66

Recent hypoglycemia attenuates sympathoadrenal responses to subsequent hypoglycemia in nondiabetic persons60 and in patients with diabetes,7 an example of habitation of the sympathoadrenal response to hypoglycemia in humans. Hypoglycemia has been found to increase synaptic activity in the human dorsal midline thalamus, among other brain sites,31,75,76 and to increase synaptic activity to a greater extent after recent hypoglycemia only in the dorsal midline thalamus (Fig. 5),31 the site of the posterior paraventricular nucleus of the thalamus.78 Indeed, slightly subphysiologic glucose concentrations (65 mg per deciliter) increase synaptic activity in the dorsal midline thalamus predominantly, perhaps selectively, in humans.80 Thus, thalamic synaptic activation may be involved in the pathogenesis of the attenuated sympathoadrenal and symptomatic responses to hypoglycemia that are the key features of HAAF in diabetes.31,80

Inactivation of the medial prefrontal cortex has also been reported to prevent habitation to restraint-induced stress in rats.81 Increased synaptic activity in the medial prefrontal cortex (anterior cingulate) occurs during hypoglycemia in humans.31,75,76 Thus, the medial prefrontal cortex, among other regions, may be

Cerebral-Network Hypothesis

According to this hypothesis, recent hypoglycemia acts through a network of interconnected brain regions to inhibit hypothalamic activation and thus attenuate the sympathoadrenal and symptomatic responses to subsequent hypoglycemia.1,31 The cerebral-network hypothesis is largely based on findings from functional neuroimaging in humans during hypoglycemia,43,44 particularly [15O]water PET measurements of regional cerebral blood flow as an index of regional brain synaptic activity,31,75,76 and the psycho-physiological concept of habituation of the response to a given stress and its proposed mechanism.77 The posterior paraventricular nucleus of the thalamus is a brain site at which previous stress, such as stress induced by restraint, acts to attenuate responses to subsequent episodes of that stress in rats.78 Lesions in the posterior paraventricular nucleus of the thalamus block habituation of the hypothalamic–pituitary–adrenocortical response to repeated restraint.78 Habituation of the sympathoadrenal response to repeated restraint-induced stress has also been documented in rats.79

Response and has no effect on the epinephrine response to hypoglycemia in nondiabetic humans.22
part of the cerebral network involved in the attenuated sympathoadrenal and symptomatic responses to hypoglycemia that characterize HAAF in diabetes.

A greater decrease in [18F]deoxyglucose uptake, measured with the use of PET, in the subthalamic region of the brain, centered on the hypothalamus, during hypoglycemia has been reported in patients with type 1 diabetes and hypoglycemia unawareness, as compared with those without hypoglycemia unawareness.44 Indeed, the array of differences in the patterns of [18F]deoxyglucose uptake during hypoglycemia between patients with hypoglycemia unawareness and those without it44 is consistent with the participation of a widespread cerebral network in the pathogenesis of HAAF in diabetes.

**Figure 5. Increased Thalamic Response to Hypoglycemia in a Model of HAAF.**

A model of HAAF in humans shows a greater increase in dorsal midline thalamus activation, as measured with the use of [18F]water positron-emission tomography, during hypoglycemia on day 2 than during hypoglycemia on day 1, with interprandial hypoglycemia occurring between the measurements on day 1 and day 2. Areas with the greatest activity are yellow, and those with the least activity are dark red. Adapted from Arbeláez et al.31

## Summary

The key feature of HAAF in diabetes is attenuated sympathoadrenal responses to hypoglycemia, most often caused by recent hypoglycemia. In the context of the lack of a decrease in insulin and of an increase in glucagon — both plausibly attributed to beta-cell failure — attenuation of the sympatheic response causes defective glucose counterregulation. Attenuation of the sympathetic neural response largely causes hypoglycemia unawareness. The precise mechanisms of the attenuated sympathoadrenal responses are not known, but there are provocative clues, ranging from evidence that available drugs might lower the burden of iatrogenic hypoglycemia and that lactate can affect brain metabolism to the notion of alterations in a cerebral network in the pathogenesis of HAAF.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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