Hypoglycemia-associated autonomic failure in diabetes

PHILIP E. CRYER
Division of Endocrinology, Diabetes and Metabolism, and the General Clinical Research Center and the Diabetes Research and Training Center, Washington University School of Medicine, St. Louis, Missouri 63110

Cryer, Philip E. Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 281: E1115–E1121, 2001.—Hypoglycemia is the limiting factor in the glycemic management of diabetes. The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response to falling glucose levels in the setting of an absent glucagon response) and hypoglycemia unawareness (by reducing the autonomic and the resulting neurogenic symptom responses) and thus a vicious cycle of recurrent hypoglycemia. Perhaps the most compelling support for HAAF is the finding that as little as 2–3 wk of scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness and improves the reduced epinephrine component of defective glucose counterregulation in most affected individuals. Insight into this pathophysiology has led to a broader view of the clinical risk factors for hypoglycemia to include indexes of compromised glucose counterregulation and provided a framework for the study of the mechanisms of iatrogenic hypoglycemia and, ultimately, its elimination from the lives of people with diabetes.

glucagon; epinephrine; sympathetic nervous system

GLUCOSE IS AN OBLIGATE METABOLIC FUEL for the brain (10, 11). Because it cannot synthesize glucose or store more than a few minutes’ supply as glycogen, the brain requires a continuous supply from the circulation. At physiological plasma glucose concentrations, rates of facilitated (GLUT-1) glucose transport across the blood-brain barrier exceed rates of brain glucose metabolism. However, if the arterial plasma glucose concentration falls below the physiological range, blood-to-brain glucose transport becomes limiting to brain glucose metabolism and thus brain function and, ultimately, survival. Given the survival value of maintenance of the plasma glucose concentration, it is hardly surprising that physiological mechanisms that ordinarily very effectively prevent or correct hypoglycemia have evolved (10, 11).

Defenses against hypoglycemia include an array of neuroendocrine responses, including decrements in insulin and increments in glucagon and epinephrine, among others, and symptoms that prompt behavioral responses such as the ingestion of food (10, 11). These are so effective that hypoglycemia is a distinctly uncommon clinical event. Clinical hypoglycemia can be caused by 1) a variety of drugs in addition to those used to treat diabetes mellitus, including alcohol, 2) several critical illnesses, including hepatic and renal failure and sepsis, 3) cortisol and growth hormone deficiencies, 4) ectopic production of an insulin-like growth factor, and 5) endogenous hyperinsulinism, among other disorders; but these are all uncommon (10). In sharp contrast, hypoglycemia is a fact of life for many of the millions of people with drug-treated diabetes mellitus (10). As discussed later, this is the result of both the pharmacokinetic imperfections of those therapeutic agents and compromised defenses against developing hypoglycemia.

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Were it not for the potentially devastating effect of hypoglycemia on the brain, diabetes would be rather easy to treat. Enough insulin, or any effective drug, to lower plasma glucose concentrations to or below the normal
range would eliminate the symptoms of hyperglycemia (polyuria, polydipsia, weight loss despite polyphagia), prevent the acute hyperglycemic complications (ketoacidosis or the hyperosmolar syndrome), almost assuredly prevent the long-term microvascular complications (retinopathy, nephropathy, and neuropathy) (40, 44), and likely reduce atherosclerotic risk to baseline (27, 37). But the effects of hypoglycemia on the brain are real, and the glycemic management of diabetes is therefore complex. In the short term, iatrogenic hypoglycemia causes recurrent physical and psychosocial morbidity and some mortality. In the long term, because it precludes true glycemic control, it limits the well-established microvascular and potential macrovascular benefits of attempts to achieve near euglycemia.

Hypoglycemia is a problem for people with diabetes that has not been solved. Current understanding of the pathophysiology of glucose counterregulation, the mechanisms that normally prevent or rapidly correct hypoglycemia, in diabetes and a conceptual framework for its further study are summarized in the paragraphs that follow.

**PHYSIOLOGY OF GLUCOSE COUNTERREGULATION**

Declining arterial plasma glucose concentrations within and below the physiological postabsorptive concentration range of 70–110 mg/dl (3.9–6.1 mmol/l) trigger a characteristic series of responses (10, 11). Insulin secretion decreases as glucose levels decline within the physiological range. This favors increased hepatic (and renal) glucose production and decreased glucose utilization by insulin-sensitive tissues such as skeletal muscle. The secretion of glucagon, epinephrine, growth hormone, and cortisol increases as glucose levels fall just below the physiological range. Glucagon stimulates hepatic glycogenolysis and thus glucose production. Epinephrine stimulates hepatic glycogenolysis and hepatic and renal gluconeogenesis (largely by mobilizing gluconeogenic precursors including lactate, the amino acids alanine and glutamine, and glycerol) and limits glucose utilization by insulin-sensitive tissues. Glucagon and epinephrine act within minutes to raise plasma glucose concentrations. In contrast, the actions of growth hormone and cortisol to support glucose production and limit glucose utilization are delayed for ~6 h. Lower plasma glucose concentrations cause symptoms of hypoglycemia. These include neurogenic (autonomic) symptoms that are the result of the perception of physiological changes triggered by the central nervous system-mediated sympatho-adrenergic response to hypoglycemia. Adrenergic (catecholamine-mediated) neurogenic symptoms include tremor, palpitations, and anxiety, and cholinergic neurogenic symptoms include sweating, hunger, and paresthesias. These also include neuroglycopenic symptoms, the direct result of glucose deprivation from brain neurons, such as fatigue, a sensation of warmth (despite observable pallor and diaphoresis), difficulty thinking and speaking, and behavioral changes. At slightly lower glucose levels, cognitive function is impaired measurably. Prolonged severe hypoglycemia can cause a seizure, coma, or even death.

Despite the reproducibility of the glycemic thresholds for these responses to falling arterial plasma glucose concentrations from laboratory to laboratory in healthy humans (10, 11, 19, 30, 33), the fact that these thresholds are dynamic rather than static warrants emphasis. As discussed later, they shift to higher plasma glucose levels during chronic hyperglycemia (1, 7, 10) and to lower plasma glucose levels after recurrent hypoglycemia (10, 13, 15, 25, 29).

The principles of glucose counterregulation (10, 11) are three. 1) The prevention and correction of hypoglycemia are the result of both dissipation of insulin and activation of glucose counterregulatory systems. These are not due solely to waning of insulin. 2) Whereas insulin is the dominant glucose-lowering factor, there are redundant glucose-raising (counterregulatory) factors. These collectively constitute a fail-safe system that prevents or minimizes failure of the glucose counterregulatory process upon failure of one, or perhaps more, of its components. 3) There is a hierarchy among the glucoregulatory factors. There is a ranked series of counterregulatory factors, some more critical to the effectiveness of the fail-safe system than others, that act in concert with decrements in insulin to prevent or correct hypoglycemia.

In defense against falling plasma glucose concentrations (10, 11), decrements in insulin are fundamentally important. Among the glucose-counterregulatory factors, glucagon plays a primary role. Albeit demonstrably involved, epinephrine is not normally critical, but it becomes critical when glucagon is deficient. Growth hormone and cortisol are involved in defense against prolonged hypoglycemia, but neither is critical to the correction of even prolonged hypoglycemia or to the prevention of hypoglycemia after an overnight fast. There is evidence that glucose autoregulation, i.e., glucose production as an inverse function of ambient plasma glucose levels independent of hormonal and neural regulation, is involved in glucose counterregulation, albeit only during severe hypoglycemia. To the extent that they are involved, autoregulation and neural regulation must play minor roles.

**PATHOPHYSIOLOGY OF GLUCOSE COUNTERREGULATION IN DIABETES**

**Frequency and impact of iatrogenic hypoglycemia.** Patients with established (i.e., C-peptide-negative) T1DM attempting to achieve some degree of glycemic control suffer untold numbers of episodes of asymptomatic hypoglycemia; plasma glucose concentrations may be less than 50 mg/dl (2.8 mmol/l) 10% of the time (10). They suffer an average of two episodes of symptomatic hypoglycemia per week, thousands of episodes over a lifetime of diabetes, and episodes of severe, at least temporarily disabling, hypoglycemia approximately once a year. Indeed, an estimated 2–4% of deaths of
people with T1DM have been attributed to hypoglycemia (10).

Although quantitative data from patients treated to near euglycemia are limited, the rates of severe hypoglycemia are at least 10-fold lower in T2DM treated aggressively with insulin and even lower in those treated with oral hypoglycemic agents (42, 44). Nonetheless, hypoglycemia was found to become progressively more limiting to glycemic control over time in T2DM in the United Kingdom Prospective Diabetes Study (43). Furthermore, the frequencies of severe hypoglycemia are similar in T2DM and T1DM, matched for duration of insulin therapy (26). Given progressive insulin deficiency in T2DM (42), these findings indicate that hypoglycemia becomes a progressively more frequent clinical problem, approaching that in T1DM, as patients approach the insulin-deficient end of the spectrum of T2DM.

Iatrogenic hypoglycemia causes recurrent physical and psychosocial morbidity and some mortality (10). The physical morbidity of an episode of hypoglycemia ranges from unpleasant symptoms through aberrant behaviors and cognitive impairment to seizure or coma. Permanent neurological damage occurs, albeit rarely. The psychosocial morbidity of hypoglycemia, fear, guilt, anxiety, etc., can also be a barrier to glycemic control. In the long term, because it precludes true glycemic control, hypoglycemia limits the well-established microvascular and potential macrovascular benefits of aggressive glycemic therapy of diabetes.

Insulin excess. The conventional risk factors for iatrogenic hypoglycemia (10) are based on the premise that absolute or relative insulin excess, whether it is injected or secreted insulin, is the sole determinant of risk (10). Absolute or relative insulin excess occurs when 1) insulin or insulin secretagogue or sensitizer doses are excessive, ill-timed, or of the wrong type; 2) exogenous glucose delivery is decreased, as after missed meals or snacks and during the overnight fast; 3) endogenous glucose production is decreased, as after alcohol ingestion; 4) glucose utilization is increased, as during exercise; 5) sensitivity to insulin is increased, as late after exercise, in the middle of the night, and after weight loss, increased fitness, or improved glycemic control or during treatment with an insulin sensitizer; and 6) insulin clearance is decreased, as in renal failure. However, although they must be considered carefully by patients suffering from recurrent iatrogenic hypoglycemia and by their care givers, these conventional risk factors explain only a minority of episodes of severe iatrogenic hypoglycemia, at least in T1DM (39).

Clearly, therefore, one must look beyond the conventional risk factors to understand the pathogenesis of the majority of episodes of severe hypoglycemia.

Insulin excess plus compromised glucose counterregulation. In T1DM (and perhaps in advanced T2DM as discussed later) iatrogenic hypoglycemia is the result of the interplay of relative or absolute insulin excess and compromised glucose counterregulation (10). As plasma glucose concentrations decline, insulin levels do not decrease (they are simply the result of passive absorption of exogenous insulin from subcutaneous injection sites), and glucagon levels do not increase. The mechanism of the loss of the glucagon response is not well understood, but it is tightly linked to and, as discussed later, possibly the result of insulin deficiency. Thus the first and second physiological defenses against developing hypoglycemia are lost. Furthermore, the epinephrine response, the third defense, is typically attenuated. This is largely the result of recent antecedent hypoglycemia, which shifts the glycemic threshold for the epinephrine response to subsequent hypoglycemia to lower plasma glucose concentrations (13).

Given the fact that circulating insulin levels are unregulated and do not fall as glucose levels fall, the combination of absent glucagon and attenuated epinephrine responses causes the clinical syndrome of “defective glucose counterregulation.” Patients with T1DM and combined deficiencies of their glucagon and epinephrine responses, compared with those with deficient glucagon but normal epinephrine responses, have been shown, in prospective studies, to be at 25-fold or more greater risk of severe iatrogenic hypoglycemia (3, 45). The reduced autonomic response, including the sympathetic neural as well as the adrenomedullary response, causes the clinical syndrome of “hypoglycemia unawareness” (or impaired awareness of hypoglycemia), loss of the warning, largely neurogenic, symptoms of developing hypoglycemia. Unawareness compromises the behavioral defenses against developing hypoglycemia (e.g., food ingestion) and is also associated with a high frequency of iatrogenic hypoglycemia (24).

HYPOGLYCEMIA-ASSOCIATED AUTONOMIC FAILURE IN DIABETES

The concept of hypoglycemia-associated autonomic failure (HAAF) in T1DM (Fig. 1) posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response in the setting of an absent glucagon response) and hypoglycemia unawareness (by reducing the autonomic (sympathetic neural and adrenomedul-

![Hypoglycemia-Associated Autonomic Failure](https://example.com/hypoglycemia-associated-autonomic-failure.png)

Fig. 1. Schematic representation of the concept of hypoglycemia-associated autonomic failure in diabetes. Modified from Ref. 9 with permission of the American Diabetes Association.

AJP-Endocrinol Metab • VOL 281 • DECEMBER 2001 • www.aipendo.org
Hypoglycemia to lower plasma glucose concentrations resulted in autonomic (including epinephrine), symptomatic, and cognitive dysfunction responses to subsequent hypoglycemia. In patients with T1DM, recent antecedent hypoglycemia has been shown to 1) shift glycemic thresholds for autonomic (including epinephrine), symptomatic, and cognitive dysfunction responses to subsequent hypoglycemia to lower plasma glucose concentrations (13, 20); 2) impair glycemic defense against hyperinsulinemia, undoubtedly a biological reflection of the reduced epinephrine response at a given level of hypoglycemia (13); and 3) reduce detection of hypoglycemia in the clinical setting (32). Perhaps the most compelling support for the concept of HAAF is the finding, in three independent laboratories (8, 14, 18), that as little as 2–3 wk of scrupulous avoidance of iatrogenic hypoglycemia reverses hypoglycemia unawareness and, at least in part, improves the epinephrine component of defective glucose counterregulation in most affected patients.

The phenomenon of HAAF provides a conceptual framework for the study of hypoglycemia in diabetes. Among the many fundamental issues that need to be clarified, four are addressed in the paragraphs that follow. 1) What is the mediator of HAAF? 2) What is the mechanism of HAAF? 3) To what extent is HAAF present in T2DM? 4) What is the mechanism of the absent glucagon response to hypoglycemia, a key component of HAAF?

**Mediator of HAAF.** On the basis of their findings that antecedent cortisol infusion (rather than hypoglycemia) mimics the phenomenon (16) and that deficient cortisol secretion minimizes the effects of antecedent hypoglycemia (17), Davis and colleagues have suggested that the cortisol response to antecedent hypoglycemia mediates HAAF. Indeed, they have reported that antecedent exercise, which releases cortisol, reduces autonomic, including adrenomedullary (plasma epinephrine) and sympathetic neural (plasma norepinephrine and muscle sympathetic nerve activity measured with microneurography) responses, among other neuroendocrine responses, to subsequent hypoglycemia (22), findings consistent, in part, with that suggestion. We (28) also found prior exercise to reduce the epinephrine response to hypoglycemia, but the effect was rather small and limited to that endpoint. Plasma norepinephrine, pancreatic polypeptide (an index of parasympathetic activation), and glucagon responses to hypoglycemia were not reduced. Notably, symptomatic responses to hypoglycemia were not reduced by prior exercise-stimulated cortisol secretion in either study (22, 28). Thus it appears that an additional factor, or factors, may be involved in the mediation of HAAF.

**Mechanism of HAAF.** Chronic hypoglycemia (days to weeks) increases brain microvascular GLUT-1 mRNA and protein and increases brain glucose uptake in rodents (e.g., Ref. 36). Using the Kety-Schmidt technique, Boyle and colleagues reported that 56 h of interprandial hypoglycemia increased brain glucose uptake (calculated from the arteriovenous glucose difference across the brain and cerebral blood flow) during hypoglycemia in nondiabetic humans (6) and that brain glucose uptake during hypoglycemia was preserved in patients with well controlled (i.e., frequently hypoglycemic) T1DM (5). These data are consistent with the hypothesis that increased blood-to-brain glucose transport is the mechanism of HAAF. We tested that hypothesis directly by measuring blood-to-brain glucose transport and cerebral glucose metabolism with [1-14C]glucose and positron emission tomography (PET) and cerebral blood flow with [15O]water and PET after ~24 h of hypoglycemia and after euglycemia. Antecedent hypoglycemia reduced autonomic (including epinephrine) and symptomatic responses to hypoglycemia as expected. However, global blood-to-brain glucose transport, cerebral glucose metabolism, and cerebral blood flow were not increased after hypoglycemia (34). These data do not support the hypothesis that recent antecedent hypoglycemia increases blood-to-brain glucose transport during subsequent hypoglycemia. They do not exclude regional increments in glucose transport. Alternatively, the fundamental alteration may lie beyond the blood-brain barrier (4).

**HAAF in T2DM.** Iatrogenic hypoglycemia is substantially less frequent in T2DM compared with T1DM. The rates of severe hypoglycemia (requiring the assistance of another individual) are more than 10-fold lower, even during aggressive treatment of T2DM with insulin, and even lower in patients treated with oral hypoglycemic agents (42). This is likely a reflection of intact glucose counterregulatory mechanisms early in the course of T2DM. Nonetheless, iatrogenic hypoglycemia becomes progressively more limiting to glycemic control over time in T2DM (43). Indeed, the rates of severe hypoglycemia have been reported to be similar in T2DM and T1DM matched for duration of insulin therapy (26). Given progressive loss of insulin secretion in T2DM (42), these findings indicate that hypoglycemia becomes an increasingly frequent clinical problem, approaching that in T1DM, in advanced T2DM.

Given this background, we tested the hypothesis that the glucagon response to hypoglycemia is reduced in patients approaching the insulin-deficient end of the spectrum of T2DM (35). That hypothesis was confirmed. Patients with T2DM were selected for the need for long-term treatment with insulin (and the absence of antibodies to glutamic acid decarboxylase, a marker of autoimmune T1DM) and were shown to have reduced C-peptide levels. In these insulin-deficient patients with T2DM, the glucagon response to hypoglycemia was virtually absent compared with the response of matched nondiabetic controls (35). In addition, recent antecedent hypoglycemia was shown to shift the glycemic thresholds for autonomic (including epinephrine) and symptomatic responses to hypoglycemia to lower plasma glucose concentrations in patients with T2DM. Thus patients with advanced T2DM, like those with T1DM, are at risk for HAAF and the resultant vicious cycle of recurrent iatrogenic hypoglycemia.

**Mechanism of the absent glucagon response.** Because of the key role of glucagon in the prevention or correc-
tion of hypoglycemia, as discussed earlier, loss of the glucagon response to falling plasma glucose concentrations in T1DM (and advanced T2DM) is a critical component of defective glucose counterregulation and HAAF. First reported nearly three decades ago (23), the mechanism of this defect is unknown. It is a selective defect; glucagon responses to other stimuli are largely, if not entirely, intact. Therefore, it must represent a signaling abnormality rather than destruction of the pancreatic α-cells. It is an acquired defect that is linked tightly with loss of endogenous insulin secretion (21) but not with classical diabetic autonomic neuropathy (13). Potential mechanisms include a unique form of impaired autonomic signaling of the glucagon secretory response (38), reduced α-cell glucose sensing per se, or loss of intraislet signaling by insulin (2). Interest in this clinical problem has led to a renewed focus on the mechanisms of the normal glucagon response to hypoglycemia.

We tested the intraislet insulin hypothesis (a decrease in β-cell insulin secretion, and thus a decrease in tonic intraislet α-cell inhibition by insulin is normally a signal for increased glucagon secretion in response to hypoglycemia) in healthy subjects. Prevention of the normal decrease in insulin secretion, by infusion of the β-cell secretagogue tolbutamide, selectively prevented the glucagon response to hypoglycemia despite an entirely normal autonomic (adrenomedullary, sympathetic neural, and parasympathetic neural) response and a low α-cell glucose concentration (2). This was reflected biologically in that higher rates of glucose infusion were required to maintain the hypoglycemic clamps. Taken together, the available data suggest a fundamental interaction between decrements in α-cell glucose and intraislet insulin in the normal glucagon response to hypoglycemia. If so, loss of the signal of a decrease in intraislet insulin would plausibly explain the loss of the glucagon response to hypoglycemia in insulin-deficient diabetes.

REDUCING AND ELIMINATING THE RISK OF IATROGENIC HYPOGLYCEMIA IN DIABETES

Recognition of the fact that iatrogenic hypoglycemia is the result of the interplay of insulin excess, which must occur from time to time because of the pharmacokinetic imperfections and less-than-physiological nature of current regimens, and compromised glucose counterregulation leads logically to a reassessment of the risk factors for iatrogenic hypoglycemia in T1DM and in advanced T2DM. Although the conventional risk factors that result in relative or absolute insulin excess summarized earlier (those relating to drug dose, timing and type, carbohydrate ingestion, effects of other drugs including alcohol, exercise, and sensitivity to or clearance of insulin) must continue to be considered carefully, these explain only a minority of episodes of severe iatrogenic hypoglycemia (39). More potent risk factors (10, 21, 31, 41) include 1) insulin deficiency, 2) a history of severe hypoglycemia, hypoglycemia unawareness, or both, and 3) aggressive glycemic therapy per se, as evidenced by lower hemoglobin A1C levels, lower glycemic goals, or both. These are clinical surrogates of compromised glucose counterregulation. Insulin deficiency indicates that insulin levels will not decrease and predicts accurately that glucagon levels will not increase as glucose levels fall. A history of severe hypoglycemia indicates, and that of hypoglycemia unawareness or even aggressive therapy per se implies, recent antecedent hypoglycemia, which compromises the autonomic (including epinephrine) and symptomatic responses to falling glucose levels by shifting the glycemic thresholds for these responses to lower plasma glucose concentrations. The result is defective glucose counterregulation and hypoglycemia unawareness, the central features of HAAF in diabetes.

It is possible, with techniques available currently, to minimize the risk of iatrogenic hypoglycemia and pursue glycemic control by practicing hypoglycemia risk reduction (12). That involves addressing the issue of hypoglycemia, applying the principles of aggressive therapy (patient education and empowerment, frequent self-monitoring of blood glucose, flexible drug regimens, rational individualized glycemic goals, and ongoing professional guidance and support) and consideration of both the conventional risk factors and those for compromised glucose counterregulation that impair physiological and behavioral defenses against developing hypoglycemia. With respect to the latter, a history of severe hypoglycemia should prompt consideration of a fundamental change in the treatment regimen, because the risk of recurrence is high (41). A history of hypoglycemia unawareness, which implies antecedent hypoglycemia (and defective glucose counterregulation) should prompt a 2- to 3-wk period of scrupulous avoidance of iatrogenic hypoglycemia. Hypoglycemia unawareness and, at least in part, the reduced epinephrine component of defective glucose counterregulation are reversible in most affected patients (8, 14, 18).

Nonetheless, iatrogenic hypoglycemia remains the limiting factor in the glycemic management of diabetes. Despite steady progress, e.g., new short-acting insulins and oral agents, new long-acting insulins, and new glucose sensors, it is not practical to eliminate hypoglycemia from the lives of people with T1DM and many with T2DM with currently available methods (12). Pending the prevention and cure of diabetes, elimination of hypoglycemia will require the development of methods that provide plasma glucose-regulated insulin replacement or secretion (e.g., closed-loop insulin replacement with a continuous glucose sensor, a computer, and an insulin infusion pump or implantation of cells that provide glucose-regulated insulin secretion). In the nearer term, we need to learn to provide insulin in a much more physiological fashion, to prevent, correct, or compensate for compromised glucose counterregulation, or both, if we are to more fully realize the benefits of glycemic control safely in people with diabetes.
K. Muehlhauser is thanked for preparing the manuscript.
My work cited in this review was supported in part by US Public Health Service Grants R37-DK-27085, M01-RR-00036, P60-DK-20579, and T32-DK-07120, and by a fellowship award from the American Diabetes Association.

REFERENCES


