Elimination of Hypoglycemia From the Lives of People Affected by Diabetes

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Iatrogenic hypoglycemia is a problem for people affected by diabetes (1). It causes recurrent morbidity in most people with type 1 diabetes and many with advanced type 2 diabetes, and it is sometimes fatal. It generally precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the vascular benefits of glycemic control. And, it compromises defenses against subsequent falling plasma glucose concentrations and therefore causes a vicious cycle of recurrent hypoglycemia.

Hypoglycemia in diabetes is fundamentally iatrogenic, the result of therapeutic hyperinsulinemia caused by treatment with a sulfonylurea, a glinide, or insulin. But because of the effectiveness of the normal glucose counterregulatory mechanisms, hypoglycemia is typically the result of the interplay of therapeutic hyperinsulinemia and compromised physiological and behavioral defenses against falling plasma glucose concentrations in people with diabetes (1).

The compromised physiological defenses include loss of the normal decrements in insulin, increments in glucagon, and increments in epinephrine as glucose levels fall in absolute endogenous insulin deficient diabetes (1). Loss of decrements in insulin and of increments in glucagon develop early in people with type 1 diabetes but only later in people with type 2 diabetes. In view of increasing evidence that β-cell insulin secretion normally restrains α-cell glucagon secretion (2) and that a decrease in insulin normally signals an increase in glucagon secretion during hypoglycemia (3), loss of both the insulin and the glucagon responses is plausibly attributable to β-cell failure (1). That construct fits nicely with the fact that iatrogenic hypoglycemia becomes a major problem early in people with type 1 diabetes but only later in people with type 2 diabetes (1). Given the evidence that insulin also acts on the hypothalamus to restrain glucagon secretion, there may also be a central nervous system component to the loss of the glucagon response (4). However, that cannot be the sole explanation since the denervated (transplanted) human pancreas and the denervated dog pancreas (as well as the perfused pancreas and perifused islets) release glucagon in response to low glucose concentrations in the absence of innervation (1). In any event, people with absolute endogenous insulin deficient diabetes are largely dependent on epinephrine for defense against falling glucose levels. However, the increments in epinephrine are often attenuated. That is a critical component of the pathophysiology of glucose counterregulation in diabetes. In the setting of absent insulin and glucagon responses, attenuated increments in epinephrine cause the clinical syndrome of defective glucose counterregulation with a 25-fold or greater increased risk of severe hypoglycemia (1). Attenuated increments in sympathoadrenal, largely sympathetic neural, activation cause the clinical syndrome of hypoglycemia unawareness with a sixfold increased risk of severe hypoglycemia (1).

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent iatrogenic hypoglycemia (as well as sleep or prior exercise) causes both defective glucose counterregulation (by reducing the epinephrine response to subsequent hypoglycemia in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by reducing the sympathoadrenal response to subsequent hypoglycemia) and thus a vicious cycle of recurrent hypoglycemia (1). Perhaps the most compelling evidence for the clinical impact of HAAF is the fact that hypoglycemia unawareness and to some extent the attenuated epinephrine component of defective glucose counterregulation are reversed after as little as 2–3 weeks of scrupulous avoidance of hypoglycemia in most affected subjects (5–8).

The mechanism(s) of the attenuated central nervous system-mediated sympathoadrenal response to falling glucose levels, the key feature of HAAF in type 1 diabetes and advanced type 2 diabetes, is not known (1). Much of the relevant investigative focus has been on the hypothalamus and its environs in experimental animals (e.g., ref. 9). However, recent studies in humans have raised the possibility that a cerebral network, operating through the thalamus, may be involved in the pathogenesis of HAAF (10–12).

The current clinical approach to minimizing the risk of iatrogenic hypoglycemia includes *1*) acknowledging the problem in subjects at risk, *2*) applying the principles of aggressive glycemic therapy, and *3*) addressing the risk factors for hypoglycemia (1). With respect to the latter, a history of hypoglycemia unawareness should prompt a 2- to 3-week period of scrupulous avoidance of hypoglycemia with the anticipation that awareness will return (1,5–8). Given the vascular benefits of glycemic control, mean glycemia as close to the nondiabetic range as can be safely maintained is generally in the best interest of people with diabetes (1). During effective therapy with lifestyle changes or with glucose-lowering drugs other than a sulfonylurea, a glinide, or insulin, the glycemic goal might be a normal A1C. But such therapies are seldom effective over a lifetime of diabetes. During therapy with a sulfonylurea, a glinide, or insulin, the glycemic goal might be an A1C <7%. The latter can sometimes be safely achieved

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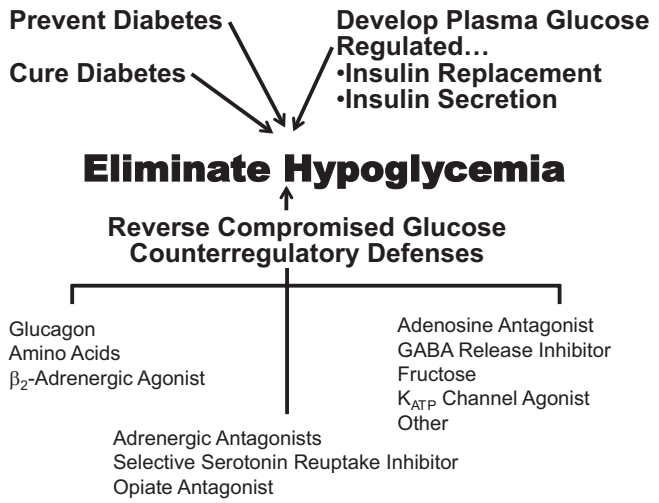

FIG. 1. Elimination of hypoglycemia from the lives of all people affected by diabetes. GABA, γ-aminobutyric acid.

early in type 2 diabetes or shortly after diagnosis in type 1 diabetes, but it is often not possible later. Nonetheless, despite increasing management efforts and expense as insulin secretion declines and the glucose-lowering regimen required to maintain tight glycemic control becomes increasingly complex slowly in type 2 diabetes and rapidly in type 1 diabetes, hypoglycemia and its associated morbidity becomes more frequent and sometimes fatal. Recent estimates suggest that 6–10% of individuals with type 1 diabetes die from hypoglycemia (1). Increased mortality has been reported during more aggressive glucose–lowering therapy compared with less aggressive glucose–lowering therapy in individuals with type 2 diabetes (13), in those with hyperglycemia in intensive care units (14), and in individuals with type 2 diabetes and A1C levels in the lower and higher deciles (15). That excess mortality may or may not be the direct result of iatrogenic hypoglycemia, but some aspect of aggressive glycemic therapy must be responsible. In addition, there are long-term benefits from reducing A1C from higher to lower—albeit still above recommended—levels (16). Perhaps, therefore, a reasonable glycemic goal is the lowest A1C that does not cause severe hypoglycemia (that which requires the assistance of another person), preserves awareness of hypoglycemia, and causes an acceptable number of documented episodes of symptomatic hypoglycemia at a given stage in the evolution of the individual's diabetes. Ultimately, glucose levels that are low enough to prevent symptoms of hyperglycemia become a reasonable goal in individuals with limited life expectancy or functional capacity in whom glycemic control is unlikely to be beneficial.

Clearly, the current clinical approach is inadequate in most individuals with type 1 diabetes and many with advanced type 2 diabetes. Iatrogenic hypoglycemia remains the limiting factor in the glycemic management of their diabetes (1). How then, apart from sacrificing glycemic goals completely, will hypoglycemia be eliminated from the lives of all people affected by diabetes in the future (Figure 1)?

Prevention and cure of diabetes will eliminate iatrogenic hypoglycemia, but no one knows when those goals will be accomplished. The development of successful plasma glucose regulated insulin replacement or secretion will almost assuredly eliminate iatrogenic hypoglycemia (17). These therapeutic regimens are coming, probably closed-loop insulin replacement (18) before islet transplantation (19). But some of us have been saying that these regimens are coming for decades. We don't know when either will become available to appreciable numbers of people with diabetes. Pending these major developments, we should seek to reverse compromised glucose counterregulatory defenses to at least minimize the risk of iatrogenic hypoglycemia. As discussed in the following paragraphs, several potential clinical approaches have been probed in humans. However, none have been shown to be both effective and safe in suitably powered randomized controlled trials.

Parenteral administration of glucagon is commonly used to treat iatrogenic hypoglycemia in diabetes (20); its infusion could be used to prevent hypoglycemia (21). Oral and parenteral amino acids stimulate glucagon secretion, and oral alanine has been shown to prevent nocturnal hypoglycemia in type 1 diabetes (22–24). Similarly, oral administration of the epinephrine simulating β_2-adrenergic agonist terbutaline has been shown to prevent nocturnal hypoglycemia in type 1 diabetes (22–24). Apart from its use as a component of a closed-loop system (21), the use of glucagon, amino acids, or terbutaline to minimize the risk of hypoglycemia suffers from the fact that their glucose-raising actions are not plasma glucose-regulated. Nonetheless, their judicial application could prove beneficial if it were documented in randomized controlled trials.

Among other possibilities, adenosine antagonists, such as caffeine, raise catecholamine levels and enhance symptoms of hypoglycemia in people with diabetes (25,26). Modafinil, a drug that decreases extracellular γ-aminobutyric acid levels, increases symptoms of hypoglycemia (27). Fructose infusion, thought to increase glucokinase activity, increases the epinephrine and glucagon responses to hypoglycemia in nondiabetic individuals (28). Ventromedial hypothalamic microinjection of the nonselective K_{ATP} channel agonist (opener) diazoxide enhances epinephrine and glucagon responses to hypoglycemia in a rat model of HAAF (29), and systemic administration of a selective Kir6.2/SUR-1 K_{ATP} channel agonist enhances the epinephrine response to hypoglycemia in nondiabetic and diabetic rats (30). However, oral diazoxide suppresses the glucagon response and has no effect on the epinephrine response to hypoglycemia in humans (31). Although ventromedial hypothalamic glutamate release is thought to mediate the sympathoadrenal response to hypoglycemia in rats (32), antagonism of glutamate signaling with the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (33) or with the amino-3-hydroxy-5-methy1–4-isoazol propionate (AMPA) receptor antagonist caroverine (34) does not decrease sympathoadrenal responses to, or symptoms of, hypoglycemia in nondiabetic individuals.

Three potential approaches to reversing compromised glucose counterregulatory defects—adrenergic antagonists, a selective serotonin reuptake inhibitor, and an opiate antagonist—are of particular interest because they enhance counterregulatory responses to falling glucose levels, i.e., the responses are plasma glucose-regulated, and they prevent the key feature of HAAF. Combined α- and β-adrenergic blockade with the α-adrenergic antagonist phentolamine and the β-adrenergic antagonist propranolol prevents the effect of hypoglycemia to attenuate the sympathoadrenal response to subsequent hypoglycemia, the key feature of HAAF, in nondiabetic individuals (35). Selective serotonin reuptake inhibitors increase the

sympathoadrenal response to hypoglycemia (36,37). In rats, sertraline both enhances the epinephrine response to hypoglycemia and prevents the attenuated epinephrine response to hypoglycemia in diabetic animals (37). In humans, oral fluoxetine enhances the plasma epinephrine and muscle sympathetic nerve activity responses to hypoglycemia in both nondiabetic and diabetic individuals (36). Infusion of the μ-opiate antagonist naloxone increases the response to hypoglycemia in humans (38). Administration of naloxone during hypoglycemia prevents the effect of hypoglycemia to attenuate the epinephrine response to hypoglycemia the following day in nondiabetic individuals (39) and individuals with type 1 diabetes (40).

In this issue of *Diabetes*, Poplawski et al. (41) report their novel approach to dissection of the hypothalamic alterations in HAAF. They used quantitative PCR to identify a series of mouse ventromedial hypothalamic genes that were induced by insulin-induced hypoglycemia. They then found that a subset of those genes did not respond to hypoglycemia following four episodes of recurrent hypoglycemia but did respond to hypoglycemia if naloxone (which prevents HAAF in humans [39,40]) was administered during each episode of prior recurrent hypoglycemia. Those genes included those that regulate pyruvate dehydrogenase kinase isoenzyme 4, glycerol 3-phosphate dehydrogenase 1, angiopoietin-like 4, and cyclin-dependent kinase inhibitor 1a (p21). In addition, carnitine palmitoyltransferase 1A was inhibited after recurrent hypoglycemia, and that was prevented by naloxone. The authors provide an admittedly speculative but nonetheless provocative metabolic interpretation of their data. Unfortunately, the effects of recurrent hypoglycemia were not shown to be associated with the key feature of HAAF, an attenuated epinephrine response to hypoglycemia, and the impact of naloxone on gene responses to a single episode of hypoglycemia was not assessed. Clearly, however, the generic approach of Poplawski et al. could be used both to further explore the mechanisms of the effect of naloxone and to explore the mechanisms of the various other interventions mentioned earlier.

Pending the prevention and cure of diabetes or the development of plasma glucose-regulated insulin replacement or secretion that might eliminate hypoglycemia from the lives of all people affected by diabetes, the potential exists to minimize the risk of iatrogenic hypoglycemia by reversing the compromised physiological and behavioral defenses against falling plasma glucose concentrations that characterize type 1 diabetes and advanced type 2 diabetes. Several approaches that have been probed in humans are summarized in this article. It would seem that people with diabetes would be served if these or other approaches were subjected to suitably powered randomized controlled trials.

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