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Hypoglycemia-Associated Autonomic Failure in Diabetes: Maladaptive, Adaptive, or Both?

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COMMENTARY

In this issue of *Diabetes*, Joy et al. (1) report that in healthy individuals hyperinsulinemic hypoglycemia, compared with hyperinsulinemic euglycemia, reduced endogenous nitric oxide (NO)-mediated endothelial vasodilation, activated inflammatory processes, impaired fibrinolytic balance, and increased proatherothrombotic mechanisms and that repeated episodes of hypoglycemia on two consecutive days further impaired vascular function by additionally reducing both endogenous and exogenous NO-mediated endothelial function. Because the data during both day one and day two hyperinsulinemic-hypoglycemic clamps were contrasted with day one hyperinsulinemic-euglycemic clamps, the data implicate hypoglycemia, rather than hyperinsulinemia, in the development of these responses. However, their mechanisms, particularly any relationship with the documented sympathoadrenal responses to hypoglycemia and the attenuated sympathoadrenal responses to hypoglycemia following recent antecedent hypoglycemia (2,3), were not determined. These translational data support the notion that iatrogenic hypoglycemia may contribute to the pathogenesis of atherosclerotic vascular disease in diabetes (4,5) and extend that to include a further effect of recurrent hypoglycemia.

Iatrogenic hypoglycemia causes recurrent morbidity in most people with type 1 diabetes and many with advanced type 2 diabetes and is sometimes fatal. Notably, 8% of the deaths of patients with diabetes who participated in the Diabetes Control and Complications Trial (DCCT) were attributed to hypoglycemia (6). Hypoglycemia attenuates sympathoadrenal and symptomatic responses to the same level of subsequent hypoglycemia (2,3) and thus causes hypoglycemia-associated autonomic failure (HAAF) in diabetes (3,7,8). HAAF includes both defective glucose counterregulation and impaired awareness of hypoglycemia. This phenomenon is the result of a shift in the glycemic thresholds for sympathoadrenal and symptomatic responses to falling plasma glucose concentrations. Patients with tightly controlled, frequently hypoglycemic diabetes have these responses at lower-than-normal falling glucose levels (9), whereas patients with poorly controlled, frequently hyperglycemic diabetes have these responses at higher-than-normal falling glucose levels (9,10). HAAF, the result of recent antecedent hypoglycemia, is clearly maladaptive as it is associated with a 25-fold (11) or greater (12) increased risk of severe iatrogenic hypoglycemia during intensive glycemic therapy of diabetes.

Iatrogenic hypoglycemia is also maladaptive in that it causes cardiac arrhythmias (13), and severe hypoglycemia is associated with death (14,15), including arrhythmic death (15). Although hypoglycemia causes an attenuated sympathoadrenal response to the same level of subsequent hypoglycemia (2,3,6,7), that does not preclude a greater sympathoadrenal response to more marked hypoglycemia. If HAAF led to an episode of marked hypoglycemia that triggered a massive sympathoadrenal discharge that caused a fatal arrhythmia, HAAF would again be maladaptive. This scenario need not be frequent. It would occur only once in a lifetime.

Sudden death of patients with diabetes caused by a sympathoadrenal discharge triggered by hypoglycemia, deduced in humans (14,16), has been supported by studies of the mechanism of cardiovascular death during marked hyperinsulinemic hypoglycemia in rats (17,18). The electrocardiographic findings included premature atrial and ventricular contractions but the sequence of progressive atrioventricular block and bradycardia most often preceded death (17). These sequences were sympathoadrenal catecholamine mediated, as was evidenced by the finding that nonselective β-adrenergic antagonism (with propranolol), but not α-adrenergic antagonism, prevented atrioventricular block and reduced hypoglycemic mortality from 33% to zero.

Interestingly, however, hypoglycemic mortality was 21% in control rats, 36% in streptozotocin diabetic rats,

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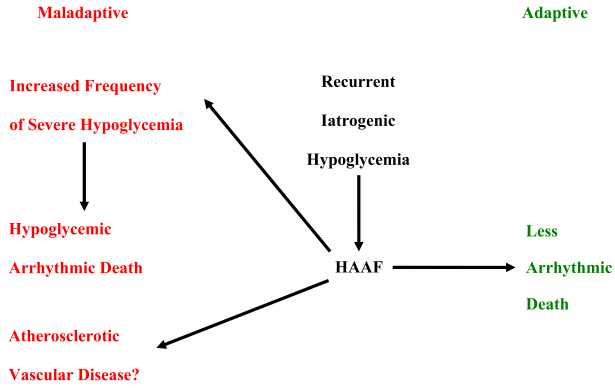

Figure 1—Maladaptive and adaptive aspects of HAAF in diabetes.

and 4% in rats exposed to prior recurrent moderate hypoglycemia (17). As expected from the earlier human studies (2,3), the plasma epinephrine response to hypoglycemia was attenuated in the latter animals (17). Similarly, hypoglycemic mortality was reduced in diabetic rats exposed to prior recurrent moderate hypoglycemia (18). These findings suggest an adaptive aspect of HAAF. This possibility was also supported by the finding of a lower risk of death in patients with type 2 diabetes assigned to intensive glycemic therapy who experienced more hypoglycemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (19) and a somewhat similar pattern in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (20).

Thus, available data suggest that recurrent iatrogenic hypoglycemia and the resulting HAAF in diabetes (6,7) are both maladaptive and adaptive (Fig. 1). HAAF is maladaptive in that it increases the frequency of severe hypoglycemia (11,12) and, therefore, could play a role in the occurrence of a fatal hypoglycemic arrhythmic death (13–15) and may contribute to the pathogenesis of atherosclerotic vascular disease (1,4,5). On the other hand, HAAF appears to be adaptive in that it reduces the most devastating effect of severe hypoglycemia—death (17–20).

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