Lactate and the Mechanism of Hypoglycemia-Associated Autonomic Failure in Diabetes

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

Hypoglycemia in diabetes is typically the result of the interplay of therapeutic insulin excess—caused by treatment with insulin, a sulfonylurea, or a glinide—and compromised physiological and behavioral defenses against falling plasma glucose concentrations (1,2). Compromised physiological defenses include loss of the normal decrease in β-cell insulin secretion and increase in α-cell glucagon secretion and attenuation of the normal increase in adrenomedullary epinephrine secretion during hypoglycemia. The compromised behavioral defense is failure to ingest carbohydrates because of loss of symptoms due to attenuation of the normal increase in sympathoadrenal, largely sympathetic neural, activity. The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent hypoglycemia (or sleep or prior exercise) causes both defective glucose counterregulation (by attenuating the epinephrine response in the setting of absent insulin and glucagon responses) and impaired awareness of hypoglycemia (by attenuating sympathoadrenal and the resulting symptomatic responses) and thus a vicious cycle of recurrent hypoglycemia.

Although additional intraislet mechanisms may be involved, it is reasonable to attribute both loss of the insulin and of the glucagon responses to hypoglycemia, the prerequisites to HAAF, to β-cell failure. Insulin normally restrains glucagon secretion and a decrease in insulin normally stimulates glucagon secretion during hypoglycemia. In the setting of absolute endogenous insulin deficiency—β-cell failure—there is no decrease in insulin and thus no increase in glucagon during hypoglycemia (2). However, the mechanism of the attenuated, central nervous system–mediated sympathoadrenal response to falling glucose levels (the key feature of HAAF) is not known. The systemic mediator, brain fuel transport, brain metabolism, and cerebral network hypotheses, which are not mutually exclusive, have been reviewed (2).

Although the precise mechanisms are far from clear (2), one focus is on the glucose metabolite lactate. Cerebral lactate uptake is a direct function of arterial lactate concentrations (3). Many of the studies summarized in this article involved infusions of lactate that raised plasma lactate concentrations to levels that occur only during exercise in humans (3). In addition, the methods involve some technical assumptions (4). Finally, several of the studies were conducted under hyperinsulinemic conditions, and insulin raises plasma lactate concentrations (5).

Lactate infusions resulting in approximately two- to fourfold plasma lactate elevations have been shown to reduce the epinephrine response to, and symptoms of, hypoglycemia in nondiabetic and diabetic humans (6–8). They also shift glycemic thresholds for these responses to lower plasma glucose concentrations (6,7) and cause brain lactate uptake (9,10). Arteriovenous measurements have revealed lactate release from the brain in the euglycemic state and either no brain lactate uptake (11) or brain lactate uptake sufficient to compensate for only about 25% of the calculated brain glucose energy deficit (12) during hypoglycemia in nondiabetic humans.

During insulin infusions that lowered plasma glucose concentrations to approximately 3.6 mmol/L in nondiabetic subjects and approximately 3.2 mmol/L in patients with type 1 diabetes and using [3-^{13}C]lactate nuclear magnetic resonance (NMR) spectroscopy, De Feyter et al. (13) found that [3-^{13}C]lactate infusions increased brain lactate, with no increase in brain oxidation of blood-borne lactate, to a greater extent in the patients. Aside from evidence that some of the five patients may have had impaired awareness of hypoglycemia, it is unclear whether HAAF was present or not. Plasma epinephrine and glucagon concentrations were similar in the two groups. This interesting lactate-related observation did not provide clear insight into the mechanism of the attenuated sympathoadrenal response to a given level of hypoglycemia that characterizes HAAF.

[3-^{13}C]Lactate NMR spectroscopy studies performed in nondiabetic rats by Herzog et al. (14) showed that exposure to recurrent hypoglycemia led to changes in brain metabolism such that increments in circulating lactate allowed the brain to function normally during subsequent hypoglycemia at a plasma glucose concentration of 2.5 mmol/L. Those changes included increased lactate flux through the brain, with only a small increase in brain lactate metabolism, following recurrent hypoglycemia compared with control studies in animals not subjected to prior hypoglycemia. But there was maintenance of brain glucose metabolism following recurrent hypoglycemia, perhaps signaled by increased lactate flux. The mechanism of the lactate effect to maintain brain glucose metabolism

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is not known, nor is it clear how it might relate to the mechanism of HAAF. Recurrent hypoglycemia is known to reduce the plasma epinephrine response to subsequent hypoglycemia—to produce a model of HAAF (15). It might be reasoned that a decrease in brain glucose metabolism at a plasma glucose concentration of 2.5 mmol/L, as occurred in the control animals in this study (those not subjected to prior recurrent hypoglycemia), signals a sympathoadrenal response. Correspondingly little or no decrease in brain glucose metabolism, as occurred in the experimental animals in this study (those subjected to prior recurrent hypoglycemia), does not signal a sympathoadrenal response. But this reasoning would be flawed. Neuroendocrine, including epinephrine, responses to falling plasma glucose concentrations are signaling events that are not caused by a decrease in whole-brain glucose metabolism (16). These responses occur at higher plasma glucose concentrations than those required to decrease the whole brain cerebral metabolic rate of glucose as measured with [1-^{11}C]glucose positron emission tomography in humans (16). Those higher plasma glucose levels—that do not decrease brain glucose metabolism—not only activate sympathoadrenal responses but also shift the glycemic thresholds for neuroendocrine responses to subsequent hypoglycemia to lower plasma glucose concentrations (17–19). The latter is a key cause of HAAF (2). It does not require a decrease in brain glucose metabolism.

In this issue, Chan et al. (20) report that direct application of lactate to the ventromedial hypothalamus (VMH) in rats increased VMH γ-aminobutyric acid (GABA) levels by about 10-fold and suppressed epinephrine (and glucagon) responses to hypoglycemia. Furthermore, VMH inhibition of lactate transport and of its utilization prevented the lactate-induced rise in VMH GABA; these and antagonism of GABA receptors increased epinephrine (and glucagon) responses to hypoglycemia. Finally, the authors observed that inhibition of lactate transport and utilization lowered elevated VMH GABA and increased epinephrine (and glucagon) responses during hypoglycemia in both prior recurrent hypoglycemia nondiabetic animals and in diabetic animals. While the effect of application of lactate to the VMH to increase VMH GABA could be pharmacologic, the latter findings suggest a physiologic effect of lactate. Given these authors' previous evidence that GABAergic tone within the VMH contributes to glucose counterregulatory failure in both prior recurrent hypoglycemia nondiabetic (21) and diabetic (22) animal models of HAAF, these interesting data suggest that lactate might suppress glucose counterregulation by increasing VMH GABA. Notably, however, VMH lactate concentrations were not significantly higher in the recurrent hypoglycemic or diabetic animals. The authors discuss their findings largely in the context of lactate as an alternative fuel to glucose despite the finding that increased brain lactate is not metabolized

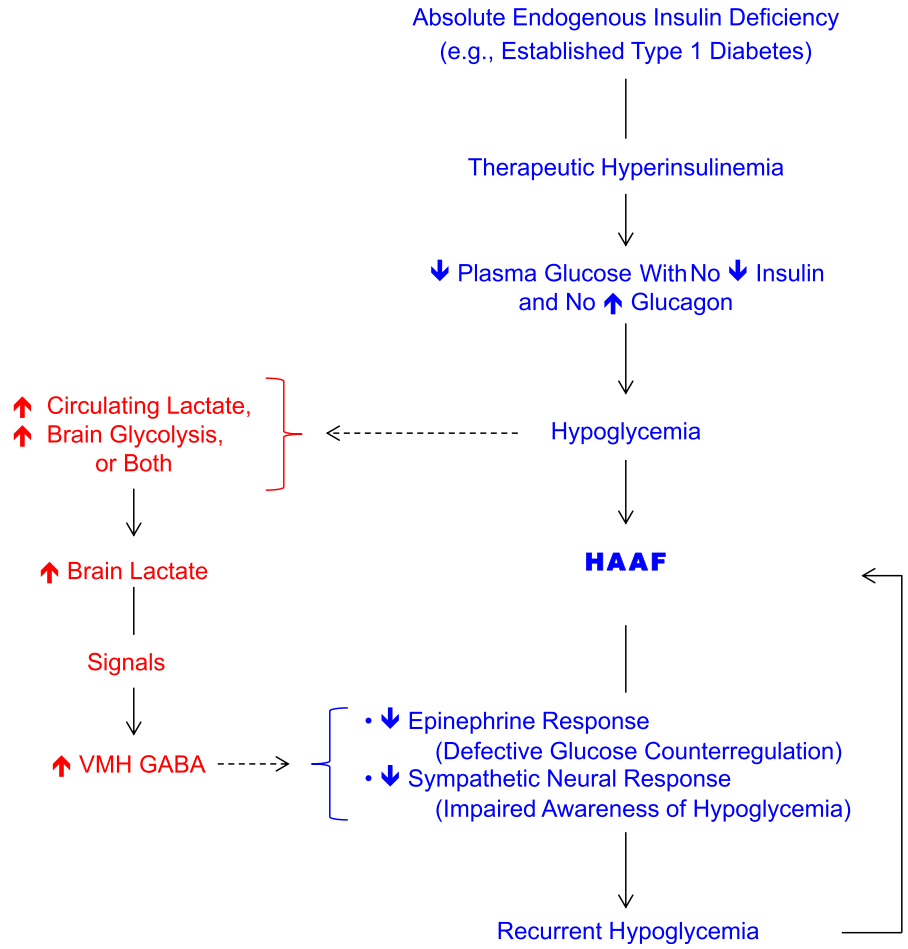

FIG. 1. General mechanism of HAAF in diabetes (*right*) (1,2) with a potential role of lactate in its pathogenesis (*left*). ↓, decreased; ↑, increased.

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(13,14) but serves as a signaling molecule to maintain brain glucose metabolism (14). They postulate different mechanisms of the putative lactate effect in the recurrent hypoglycemia and diabetic models.

Even in the aggregate, these data do not lead to a simple mechanism of the key feature of HAAF. Nonetheless, the application of sophisticated methods by knowledgeable investigators continues to provide insight into a potential role of lactate (Fig. 1).

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