Iatrogenic Hypoglycemia as a Cause of Hypoglycemia-Associated Autonomic Failure in IDDM

A Vicious Cycle

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Three hypoglycemia-associated clinical syndromes in people with insulin-dependent diabetes mellitus (IDDM)—defective glucose counterregulation, hypoglycemia unawareness, and elevated glycemic thresholds for symptoms and activation of counterregulatory systems during effective intensive therapy—have much in common. They segregate together, are associated with increased frequency of severe iatrogenic hypoglycemia, and share several pathophysiological features, including reduced autonomic nervous system responses to a given degree of hypoglycemia. In the setting of reduced glucagon responses, the reduced adrenomedullary epinephrine responses play a key role in the pathogenesis of iatrogenic hypoglycemia in affected patients. Thus, these syndromes are examples of hypoglycemia-associated autonomic failure in IDDM, a disorder distinct from classical diabetic autonomic neuropathy. The pathogenesis of hypoglycemia-associated autonomic failure is not known, need not be the same in all three syndromes, and could be multifactorial even in a given syndrome. The recent finding that short-term antecedent hypoglycemia results in reduced symptomatic and autonomic (including adrenomedullary) responses to subsequent hypoglycemia in nondiabetic humans leads logically to the following hypothesis concerning one potential pathogenetic mechanism: recent antecedent iatrogenic hypoglycemia is a major cause of hypoglycemia-associated autonomic failure in IDDM, and hypoglycemia-associated autonomic failure, by reducing both symptoms of and defenses against developing hypoglycemia, results in recurrent severe hypoglycemia, thus creating a vicious cycle. If this hypothesis is confirmed, it will suggest strategies to reduce the frequency of iatrogenic hypoglycemia in people with IDDM. *Diabetes* 41:255–60, 1992

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Received 22 July 1991 and accepted for publication 1 November 1991.

Iatrogenic hypoglycemia is a major problem for people with diabetes mellitus, particularly those with insulin-dependent diabetes mellitus (IDDM) (1–3). They suffer an average of one to two episodes of symptomatic hypoglycemia per week. Ten to 25% suffer at least one episode of severe, temporarily disabling hypoglycemia, often with seizure or coma, in a given year. Four percent of deaths of people with IDDM have been attributed to hypoglycemia. In addition to this recurrent physical morbidity and some mortality, the fear of developing hypoglycemia often causes recurrent or persistent psychological morbidity. Clearly, iatrogenic hypoglycemia is a problem that has not been solved.

Circumstances that result in absolute or relative insulin excess constitute the conventional risk factors for iatrogenic hypoglycemia in IDDM. These include insulin doses that are excessive or ill timed, missed meals or snacks and overnight fasts, excessive physical activity, excessive alcohol ingestion, and conditions that increase sensitivity to or decrease clearance of administered insulin (1,2). However, despite thorough analysis of many episodes of severe hypoglycemia, these conventional risk factors account for only a minority of episodes (2). Thus, it is reasonable to shift the investigative focus to the risk factors that compromise glycemic defenses against mild-to-moderate hyperinsulinemia in IDDM (1). The mechanistic relationships among the latter factors are the subject of this article.

The premises of my hypothesis are three. First, there are three clinically, possibly pathogenetically interrelated hypoglycemia-associated clinical syndromes in people with IDDM. Second, autonomic, specifically adrenomedullary, hypofunction plays a fundamental role in the

pathogenesis of iatrogenic hypoglycemia in affected patients. Third, although epinephrine and pancreatic polypeptide secretory responses, markers of sympathochromaffin and parasympathetic activation, respectively, to a given degree of hypoglycemia are reduced, these syndromes are distinct from classical diabetic autonomic neuropathy.

These hypoglycemia-associated clinical syndromes (defective glucose counterregulation, hypoglycemia unawareness, and elevated glycemic thresholds for symptoms and activation of glucose counterregulatory systems during intensive therapy that effectively lowers overall plasma glucose concentrations) are herein collectively termed *hypoglycemia-associated autonomic failure*.

THE AUTONOMIC NERVOUS SYSTEM

Biologically effective plasma epinephrine concentrations are derived from the adrenal medullae (4). With the sympathetic nervous system, the adrenal medullae are an integral component of the sympathochromaffin (sympathoadrenal) system (4–6). Sympathetic postganglionic neurons and adrenomedullary chromaffin cells differentiate from a common embryological precursor and share various biochemical processes including regulated synthesis, storage, and release of catecholamines (5). The adrenal medullae can therefore be conceptualized as sympathetic postganglionic neurons without axons that release their products, including epinephrine, into the circulation rather than into synaptic clefts (5,6). These products function as hormones rather than neurotransmitters.

The sympathochromaffin system and the parasympathetic nervous system constitute the autonomic nervous system (5). Hypofunction of the sympathochromaffin system including the adrenal medullae, of the parasympathetic nervous system, or both that results from diabetes mellitus is, by definition, a form of diabetic autonomic failure. However, it need not be the result of classical diabetic autonomic neuropathy. The abnormality could lie in the afferent, central, or efferent components of the autonomic nervous system and need not involve nerve fiber loss.

PHYSIOLOGY OF GLUCOSE COUNTERREGULATION

The prevention or correction of hypoglycemia is normally the result of both suppression of insulin secretion and activation of glucose counterregulatory systems (1,7). Whereas insulin is the dominant glucose-lowering factor, there are redundant glucose counterregulatory factors, and there is a hierarchy among the glucoregulatory factors.

In defense against decrements in plasma glucose, dissipation of insulin is fundamentally important. Hyperinsulinemia of sufficient magnitude will cause hypoglycemia despite the actions of the counterregulatory factors. However, the latter determine whether less-marked hyperinsulinemia results in hypoglycemia, particularly severe symptomatic hypoglycemia (7). Among the counterregulatory factors, glucagon plays a primary role. Epinephrine is not normally critical, although it is involved, but it becomes critical when glucagon is deficient. Growth hormone and cortisol are involved in defense against prolonged hypoglycemia, and glucose autoregulation (hepatic glucose production as an inverse function of the ambient glucose concentration independent of hormonal and neural regulatory factors) may be operative during severe hypoglycemia. Nonetheless, hypoglycemia develops or progresses when both glucagon and epinephrine are deficient and insulin is present despite intact growth hormone and cortisol secretion and autoregulatory mechanisms. The same reasoning applies to the potential roles of other hormones, neurotransmitters (including norepinephrine), and substrates other than glucose. They may be involved, but they must stand low in the hierarchy of redundant glucoregulatory factors.

The glycemic thresholds for secretion of the key glucose counterregulatory hormones during decrements in plasma glucose lie within or just below the physiological plasma glucose concentration range (8,9). The arterialized venous glycemic thresholds for glucagon and epinephrine release are normally ~3.8 mM, well above the thresholds for symptoms of hypoglycemia (~3 mM) and those for cognitive impairments resulting from hypoglycemia (~2.8 mM). As discussed later, it is clear that these thresholds are dynamic rather than static and can change rather rapidly.

With respect to glycemic thresholds, a semantic issue warrants comment. If, during decrements in plasma glucose, a lower-than-normal plasma glucose concentration is required to elicit a given response, the glycemic threshold for that response is higher or elevated, because a more-intense hypoglycemic stimulus is required to elicit that response. Conversely, if a higher-than-normal plasma glucose concentration elicits a given response, the glycemic threshold for that response is lower or reduced. This usage differs from that in our initial report (8) but is, in my view, correct (23).

HYPOGLYCEMIA-ASSOCIATED CLINICAL SYNDROMES

Defective glucose counterregulation. Deficient glucagon secretory responses to plasma glucose decrements are the rule in people with IDDM (1,10,11). Although this is an acquired defect, it develops in the first few years of clinical IDDM (11). It appears to be a selective defect because the glucagon secretory responses to other stimuli are largely, if not entirely, preserved. Although it is closely associated with absolute insulin deficiency (12), its mechanism is unknown. Many patients, the majority of those with relatively long-standing IDDM, also exhibit deficient epinephrine secretory responses to plasma glucose decrements (1,11). Like the deficient glucagon response, this acquired defect is selective and of unknown mechanism.

People with IDDM who have combined deficiencies of their glucagon and epinephrine responses to plasma glucose decrements have the syndrome of defective glucose counterregulation (1,13). They have been shown in prospective studies (13,14) to be at markedly increased risk (≥25-fold) for severe iatrogenic hypoglycemia during intensive therapy of their IDDM compared

with patients with deficient glucagon but not epinephrine responses. Similarly, combined deficiencies of glucagon and epinephrine responses to hypoglycemia have been found to characterize patients selected for clinical histories of recurrent severe hypoglycemia (15). Although pancreatic polypeptide and epinephrine responses to hypoglycemia are reduced (16), defective glucose counterregulation is not associated with classical diabetic autonomic neuropathy (13,17). For example, in the series of patients, Ryder et al. (17), none of the patients with defective glucose counterregulation had classical diabetic autonomic neuropathy.

Thus, in the setting of deficient glucagon secretory responses, which are the rule in IDDM, deficient adrenomedullary epinephrine secretory responses to decreasing plasma glucose concentrations play a key role in the pathogenesis of severe iatrogenic hypoglycemia.

Unfortunately, some authors (e.g., 18,19) have used the term *defective glucose counterregulation* to refer to the syndrome of elevated glycemic thresholds during effective intensive therapy (discussed later). That usage cannot be endorsed because it introduces confusion. Rather, the term should be limited to the different syndrome just summarized, which was first described by White et al. (13), who coined the term *defective glucose counterregulation* (16,20).

Hypoglycemia unawareness. Many people with IDDM (as many as half of those with long-standing disease; 3) develop the syndrome of hypoglycemia unawareness (1,3,17,21,22). Affected patients no longer have the warning (autonomic or neurogenic) symptoms of developing hypoglycemia and therefore fail to act (e.g., to eat) to prevent its progression to severe hypoglycemia with disabling neuroglycopenia. This syndrome is also associated with increased frequency (at least 5-fold) of severe clinical hypoglycemia (22).

Hypoglycemia unawareness is thought to be the result of deficient sympathochromaffin—sympathetic neural as well as adrenomedullary—responses to falling plasma glucose concentrations (1,21,23). Direct evidence of reduced sympathetic neural, as opposed to adrenomedullary, responses is, to my knowledge, lacking. However, one cannot explain all of the reduced symptoms on the basis of impaired sympathochromaffin responses without invoking reduced responses of the sympathetic nervous system (including both its adrenergic and cholinergic postganglionic elements) (23). Patients with hypoglycemia unawareness require lower plasma glucose concentrations to trigger increments in plasma epinephrine levels (i.e., have higher glycemic thresholds for epinephrine release) compared with unaffected patients (24). Pancreatic polypeptide responses to a given degree of hypoglycemia are also reduced in patients with hypoglycemia unawareness (R. E. J. Ryder, unpublished observations). Nonetheless, like defective glucose counterregulation, with which it cosegregates (17), hypoglycemia unawareness is not associated with classical diabetic autonomic neuropathy (17,21,22). For example, in the series of patients, Ryder et al. (17), none of the patients with hypoglycemia unawareness had classical diabetic autonomic neuropathy.

Elevated glycemic thresholds during effective therapy. During decrements in plasma glucose, people with poorly controlled IDDM (25–27) or even those with moderately controlled IDDM (28) can suffer symptoms of hypoglycemia at plasma glucose concentrations higher than those required to produce symptoms in nondiabetic people or those with well-controlled IDDM. Such patients have lowered glycemic thresholds (i.e., a lesser hypoglycemic stimulus is required to elicit symptoms and counterregulatory responses). Conversely, people with well-controlled IDDM often tolerate subnormal plasma glucose levels without symptoms. They require lower plasma glucose concentrations (i.e., have elevated glycemic thresholds) to elicit both symptoms and counterregulatory, including epinephrine, responses than patients with less-well-controlled IDDM or even nondiabetic individuals (18,26). Such elevated glycemic thresholds are also a feature of defective glucose counterregulation (27) and of hypoglycemia unawareness (24), as mentioned earlier. Although pancreatic polypeptide and epinephrine responses to a given degree of hypoglycemia are reduced (27), there is no evidence that elevated glycemic thresholds during effective therapy are associated with classical diabetic autonomic neuropathy (26,27).

The extent to which elevated glycemic thresholds for symptoms and for activation of glucose counterregulatory systems contribute to the approximately threefold increased frequency of severe iatrogenic hypoglycemia during effective intensive therapy of IDDM (2) is not known. It is conceivable that elevated glycemic thresholds might be an adaptive phenomenon (29). If the mechanism were increased fractional extraction of glucose by the brain (as suggested by studies of the effects of antecedent hypoglycemia in animals; 30,31), it would be appropriate that symptoms were absent and counterregulatory systems were not activated at relatively low glucose levels. On the other hand, the syndrome would be maladaptive and would increase the risk of clinical hypoglycemia, if the glycemic thresholds for neuroglycopenic manifestations including cognitive dysfunction (in contrast to those for neurogenic symptoms and counterregulatory activation) were not elevated. Evidence that the thresholds for EEG activation (32), neuroglycopenic symptoms (33,34), and cognitive dysfunction (33,34) are not elevated in well-controlled patients has been presented. However, others have reported elevated glycemic thresholds for neuroglycopenic and neurogenic symptoms (27) and for cognitive dysfunction (35) in better-controlled patients. Thus, this fundamentally important issue remains controversial.

HYPOGLYCEMIA-ASSOCIATED AUTONOMIC FAILURE

The three hypoglycemia-associated clinical syndromes just summarized (defective glucose counterregulation, hypoglycemia unawareness, and elevated glycemic thresholds during effective therapy) have much in common. First, they cosegregate, i.e., they tend to occur in the same patients (17,22,27). Second, they are associated with a high frequency of iatrogenic hypoglycemia (13–17,21,22). Third, they share several pathophysiolog-

ical features. These include elevated glycemic thresholds for neurogenic symptoms (17,18,21,22,24,25,27,32) and for autonomic activation, including epinephrine (13–16,18,21,22,25,27,32,34) and pancreatic polypeptide (16,17,22,27) responses. In the setting of deficient glucagon responses to plasma glucose decrements, which are the rule in IDDM (1,10,11), the deficient epinephrine responses play a key role in the pathogenesis of severe iatrogenic hypoglycemia (13–15) in patients affected by the syndromes. Thus, these three syndromes are clinically, and therefore perhaps pathogenetically, interrelated. Therefore, it is reasonable to group them without implying a single pathogenesis as the syndromes of *hypoglycemia-associated autonomic failure*. This term implies not only that the syndromes are associated in a causal way with a high frequency of iatrogenic hypoglycemia but also, albeit hypothetically at this point, that antecedent iatrogenic hypoglycemia might be involved in the pathogenesis of functional autonomic (including adrenomedullary) failure as discussed shortly.

Hypoglycemia-associated autonomic failure appears to be distinct from classical diabetic autonomic neuropathy in several ways. First, the two disorders do not cosegregate, i.e., they tend to occur in different patients (13–15,17,18,21–25,27,32). Second, in hypoglycemia-associated autonomic failure, the deficient autonomic responses appear to be specific for the stimulus of hypoglycemia (1,23,36), whereas reduced sympathetic and parasympathetic responses to multiple stimuli characterize classical diabetic autonomic neuropathy (37,38). Third, whereas substantially reduced adrenomedullary epinephrine responses to a given degree of hypoglycemia are a central feature of hypoglycemia-associated autonomic failure (13–19,21,22,24,26,27,32–36), plasma epinephrine responses are reduced little, if at all, in classical diabetic autonomic neuropathy. Although Hilsted et al. (37,38) found slightly lower epinephrine responses to hypoglycemia in patients with classical diabetic autonomic neuropathy compared with those without, the epinephrine responses of the former patients were greater than those of nondiabetic control subjects. This is consistent with evidence that classical diabetic autonomic neuropathy is largely an axonal lesion (39,40), probably the result of nerve fiber loss. Fourth, in sharp contrast with hypoglycemia-associated autonomic failure, there is clear evidence that classical diabetic autonomic neuropathy does not cause excessive iatrogenic hypoglycemia in IDDM (2,37,38,41). Fifth, recent data (42–44) suggest, but do not prove, that hypoglycemia-associated autonomic failure might be, at least in part, reversible for reasons discussed shortly. There is no evidence that classical diabetic autonomic failure is reversible.

The pathogenetic mechanisms of the syndromes of hypoglycemia-associated autonomic failure are not known. Although likely different from that of classical diabetic autonomic neuropathy, they need not necessarily be the same in all three syndromes and might well be multiple in a given syndrome (27). Although it is tempting to postulate a central nervous system alteration, the alteration or alterations could also lie in the afferent or efferent limbs of the autonomic nervous system.

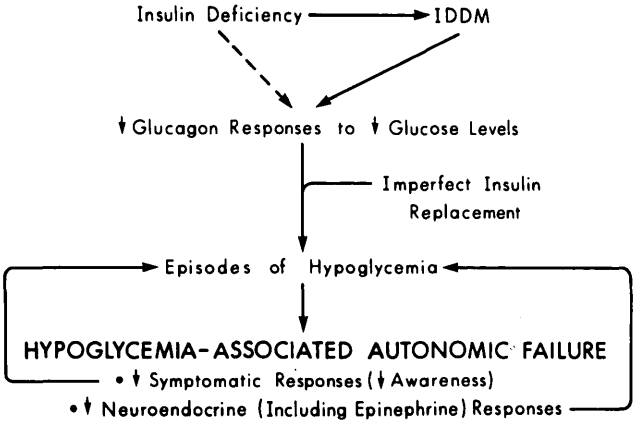

FIG. 1. Diagram of 1 hypothetical mechanism of the pathogenesis of hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus (IDDM). The hypothesis is that recent antecedent iatrogenic hypoglycemia is a major cause of hypoglycemia-associated autonomic failure in IDDM, and hypoglycemia-associated autonomic failure, by reducing both symptoms of and defenses against developing hypoglycemia, results in recurrent severe hypoglycemia, thus creating a vicious cycle.

It is conceivable that antecedent iatrogenic hypoglycemia itself might be one factor, perhaps a major factor, in the pathogenesis of hypoglycemia-associated autonomic failure. There is now clear evidence that recent antecedent hypoglycemia results in substantially higher glycemic thresholds for symptomatic and autonomic responses to subsequent hypoglycemia (42–44). For example, we (42) found that a single 2-h episode of afternoon hypoglycemia reduced the symptomatic and neuroendocrine (including autonomic) responses to hypoglycemia the following morning in nondiabetic humans. Fundamentally similar findings with different experimental designs have been reported by Widom and Simonson (43) and Davis and Shamoon (44). One important difference, however, is that we (42) found reduced neuroglycopenic and neurogenic symptom responses after antecedent hypoglycemia. Widom and Simonson found reduced neurogenic, but not neuroglycopenic, symptom responses.

If this phenomenon occurs in people with IDDM, the following hypothesis shown in Fig. 1 is quite plausible. In the setting of deficient glucagon secretory responses to plasma glucose decrements (1,10,11) and unavoidably imperfect insulin replacement (1) in IDDM, episodes of iatrogenic hypoglycemia occur commonly. These would be expected to result in elevated glycemic thresholds for both symptoms of hypoglycemia (i.e., decreased awareness) and counterregulatory, including epinephrine, responses to hypoglycemia (i.e., decreased defenses against hypoglycemia). Decreased awareness and decreased defenses would then act in concert to result in recurrent episodes of iatrogenic hypoglycemia. Thus, a vicious cycle would be established in which iatrogenic hypoglycemia, by reducing both symptoms of and defenses against subsequent hypoglycemia, causes recurrent iatrogenic hypoglycemia. If this hypothesis is supported by future research, it would suggest a rather

straightforward approach to reduction of the frequency of iatrogenic hypoglycemia in IDDM, specifically a relatively short period of scrupulous avoidance of hypoglycemia.

Again, it should be emphasized that hypoglycemia-associated autonomic failure is likely multifactorial in origin. For example, the syndrome of defective glucose counterregulation was first defined in people with poorly controlled IDDM but was later expressed clinically as frequent severe iatrogenic hypoglycemia during intensive therapy (13). Thus, it seems unlikely that the key abnormality, a reduced epinephrine secretory response to a given degree of hypoglycemia, was induced by iatrogenic hypoglycemia just before initial testing, although that construct is not entirely inconceivable.

In summary, three seemingly disparate hypoglycemia-associated clinical syndromes in people with IDDM are now known to have several features in common. These include elevated glycemic thresholds for symptoms and for autonomic, including adrenomedullary, activation. Thus, the syndromes of defective glucose counterregulation, hypoglycemia unawareness, and elevated glycemic thresholds during effective therapy are examples of hypoglycemia-associated autonomic failure in IDDM, a disorder distinct from classical diabetic autonomic neuropathy. One testable hypothesis concerning the pathogenesis of the disorder is that recent antecedent iatrogenic hypoglycemia is a major cause of hypoglycemia-associated autonomic failure and hypoglycemia-associated autonomic failure, by reducing both symptoms of and defenses against developing hypoglycemia, results in recurrent severe hypoglycemia, thus creating a vicious cycle.

ACKNOWLEDGMENTS

My cited work was supported in part by United States Public Health Service (USPHS) Grants R01-DK-27085, M01-RR-00036, and P60-DK-20579 as well as support for postdoctoral fellows from USPHS Grant T32-DK-07120 and the American Diabetes Association.

I gratefully acknowledge the substantive input of several collaborators and postdoctoral fellows, many of whose names appear in the list of references in my cited work, including the technical assistance of Suresh D. Shah among others; the assistance of the nursing staff of the Washington University General Clinical Research Center, headed by Carolyn E. Havlin, in the performance of our studies; and the assistance of Mary Kharibian in the preparation of this manuscript.

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