Multifactorial Origin of Hypoglycemic Symptom Unawareness in IDDM

Association With Defective Glucose Counterregulation and Better Glycemic Control

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To assess potential relationships between unawareness of hypoglycemic symptoms and both defective glucose counterregulation and therapy-associated altered glycemic thresholds, symptoms and hormonal responses to hypoglycemia were quantitated during standardized insulin infusion tests in 41 patients with insulin-dependent diabetes mellitus (IDDM). The glycemic thresholds for both neurogenic and neuroglycopenic symptoms (and those for both epinephrine and pancreatic polypeptide release) were at lower plasma glucose concentrations in both patients with defective (n = 9, 22%) and those with adequate glucose counterregulation and, among the latter, in patients with lower compared with higher glycosylated hemoglobin levels. The data are consistent with the concept that both defective glucose counterregulation and improved glycemic control contribute to excessive hypoglycemia in IDDM by reducing awareness of symptoms of developing hypoglycemia and by impairing physiological defenses against hypoglycemia. Thus, hypoglycemic symptom unawareness is multifactorial in origin and may be partly reversible. *Diabetes* 40:680–85, 1991

Hypoglycemia is a major problem for people with insulin-dependent diabetes mellitus (IDDM). In addition to recurrent morbidity and some mortality, it engenders both fear and guilt and is the limiting factor in attempts to achieve euglycemia in IDDM (1–4). Understanding of the risk factors for hypoglycemia in IDDM has been broadened from simple insulin excess to the interplay of absolute or relative insulin excess and compromised glucose counterregulation (2–4). The latter includes the syndromes of defective glucose counterregulation, hypoglycemia unawareness, and altered glycemic thresholds.

Defective glucose counterregulation has been associated with and best attributed to combined deficiencies of the glucagon and epinephrine secretory responses to plasma glucose decrements. It has been shown in prospective studies (5,6) to be associated with at least a 25-fold increase in the risk for severe iatrogenic hypoglycemia. Although it has not been documented by prospective studies, it is reasonably assumed that the absence of warning symptoms of developing hypoglycemia also contributes to this high frequency of iatrogenic hypoglycemia (7–11). Indeed, hypoglycemia unawareness segregates with defective glucose counterregulation (10), with which it shares a pathophysiological feature—a reduced epinephrine response to hypoglycemia. The pathogenesis of hypoglycemic symptom unawareness is not entirely clear. It cannot be attributed to a deficient adrenomedullary (epinephrine) response entirely, because one of the neurogenic warning symptoms that is often reduced or absent is sweating, which is cholinergic, albeit sympathetic, in origin. However, hypoglycemic symptom unawareness could be attributed to a more generalized reduction in the sympathochromaffin (sympathetic neural and adrenomedullary) response to plasma glucose decrements (3,4). Finally, although patients with poorly controlled IDDM have been shown to suffer symptoms of hypoglycemia at higher plasma glucose concentrations than nondiabetic individuals (12), those with very-well-controlled IDDM have been found to often tolerate low plasma glucose levels without symptoms and to require lower glucose concentrations to activate glucose counterregulatory systems (13–16). Clearly, the latter could contribute to an increased frequency of iatrogenic hypoglycemia, although this, like the effect of hypoglycemic unawareness, has not been demonstrated in prospective studies.

To date, the interrelationships among defective glucose

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counterregulation, therapy-associated alterations of glycemic thresholds for symptoms and glucose counterregulation, and hypoglycemic symptom unawareness have not been examined simultaneously in patients with IDDM. Accordingly, we assessed counterregulatory status (adequate vs. defective) and both neurogenic and neuroglycopenic symptoms with an insulin infusion test (5) in a relatively large group of patients with IDDM. Thus, we were able to relate glycemic thresholds for symptoms to both counterregulatory status and the degree of antecedent glycemic control.

RESEARCH DESIGN AND METHODS

Forty-one subjects with IDDM for at least 1 yr and no other chronic disease participated in the study, which was approved by the University of Virginia Institutional Review Board. All subjects gave written informed consent. No subject had evidence of neuropathy or was taking any medication other than insulin. Subjects were studied at the Clinical Research Center of the University of Virginia as part of a 4-day research protocol assessing the relationship between stress and blood glucose. Intermediate and long-acting insulins were discontinued 84 h before testing, and overnight euglycemia was maintained at ~5.6 mM with a previously described open-loop insulin infusion algorithm (17).

At 0800, the subjects were connected to the Biostator glucose-controlled insulin infusion system (Miles, Elkhart, IN) for continuous glucose monitoring and insulin (human regular, Lilly, Indianapolis, IN) infusion at the rate of 40 $mU \cdot kg^{-1} \cdot h^{-1}$. The insulin infusion was continued for 120 min unless the subject's plasma glucose level fell below 1.9 mM or severe manifestations of hypoglycemia (e.g., severe lethargy, disorientation, confusion, or inappropriate behavior) were observed. White et al. (5) and Bolli et al. (6) have previously demonstrated that such testing of a subject's ability to counterregulate can prospectively identify those persons with IDDM at high risk for severe hypoglycemic events during intensive outpatient insulin therapy.

Venous blood was sampled every 10 min for the determination of plasma glucose, glucagon, epinephrine, norepinephrine, and pancreatic polypeptide concentrations. Plasma glucose was determined with a glucose oxidase method (Beckman glucose analyzer, Fullerton, CA). Plasma glucagon and pancreatic polypeptide concentrations were determined by radioimmunoassay (18,19), and plasma epinephrine and norepinephrine concentrations were determined by a single-isotope–derivative method (20). Glycosylated hemoglobin levels, obtained at the beginning of the study, were determined with boronate affinity-column chromatography. The normal range for this assay is 4.4–6.9% in our laboratory.

All subjects were asked to rate, on a scale of 1–7, the extent to which they were experiencing four neurogenic and five neuroglycopenic symptoms at each 10-min interval. The neurogenic symptoms included sweaty hands, pounding heart, trembling and shakiness, and dry mouth. The neuroglycopenic symptoms included blurred vision, confused thinking, slurred speech, difficulty concentrating, and numbness.

Data were initially analyzed after dividing the subjects into groups based on their ability or inability to complete the entire 120-min protocol as described above, i.e., whether they exhibited adequate or defective glucose counterregulation (5). All data are expressed as group means ± SE for each sampling time. Mean plasma glucose thresholds for each variable were identified by calculating the first significant difference between the mean time-0 sampling and subsequent samplings with a Dunnett's test to compensate for multiple comparisons (21). Between-group comparisons were performed with a *t* test. When a threshold for a given variable could not be defined (i.e., the threshold, if present, must have been at a plasma glucose concentration lower than that tested), the mean nadir glucose level for the group was used in these comparisons. Identical analyses were performed on data from two groups formed by splitting of the patients into two equal groups based on the median glycosylated hemoglobin values (11%) in the subjects with adequate counterregulation.

Because subjects with adequate glucose counterregulation would not be expected to exhibit continuously falling plasma glucose levels throughout the 120-min study, analyzing the data only in terms of 10-min intervals may have masked changes in the variables measured. Thus, in an attempt to reduce bias introduced by subjects' plasma glucose concentrations, which plateaued or rose during the course of the study, each variable was also analyzed at 0.56-mM plasma glucose intervals from 5.6 to 2.2 mM. Variables for each subject were recorded only at the first (nearest to the 0.56-mM level) occurrence of a plasma glucose value within each interval. Glycemic thresholds and group comparisons were then calculated as described above.

RESULTS

Glucose counterregulatory status and symptoms of hypoglycemia. Nine subjects (22%) exhibited defective glucose counterregulation. Mean ± SE baseline plasma glucose concentrations were not different between those with adequate (CR^+) and defective (CR^-) counterregulation (5.5 ± 0.1 vs. 5.2 ± 0.2 mM). During the insulin infusion test, the mean nadir plasma glucose concentration was 2.7 ± 0.2 mM at 120 min in CR^+ subjects, which is significantly ($P < 0.001$) higher than that of 2.1 ± 0.1 mM at 70 min in CR^- subjects. The rate of fall of plasma glucose was significantly ($P < 0.001$) greater in CR^- subjects (0.47 ± 0.06 mM/10 min) than in CR^+ subjects (0.24 ± 0.06 mM/10 min), and mean glucose levels were significantly lower in CR^- subjects than in CR^+ subjects by 20 min.

There were no significant differences in age (33 ± 2 vs. 33 ± 3 yr), duration of IDDM (12 ± 2 vs. 15 ± 5 yr), daily insulin dose (0.68 ± 0.04 vs. 0.53 ± 0.03 $U \cdot kg^{-1} \cdot day^{-1}$), glycosylated hemoglobin (11.5 ± 0.6 vs. 10.0 ± 0.5%), or pretest (120-min) insulin infusion doses (37.3 ± 5.7 vs. 47.2 ± 5.8 $mU \cdot kg^{-1} \cdot h^{-1}$) between the CR^+ and CR^- groups, respectively. Estimated glycemic thresholds for release of epinephrine (3.1 ± 0.1 mM), norepinephrine (2.8 ± 0.1 mM), pancreatic polypeptide (2.8 ± 0.1 mM), and glucagon (2.7 ± 0.1 mM) could be defined only in the CR^+ subjects. Thus, the thresholds for release of these hormones, if present, must have occurred at plasma glucose levels less than the mean nadir value of 2.1 mM in the CR^- subjects, which is significantly lower than those in the CR^+ subjects.

The thresholds for epinephrine and pancreatic polypeptide release are illustrated in Fig. 1.

Estimated glycemic thresholds for symptoms of hypoglycemia in relation to glucose counterregulatory status are also shown in Fig. 1. In the CR^+ subjects, total symptoms and neuroglycopenic symptoms increased over those at baseline at 80 min at a mean plasma glucose concentration of 3.0 ± 0.1 mM. Neurogenic symptoms increased over those at baseline at 100 min at a mean plasma glucose concentration of 2.8 ± 0.1 mM. Glycemic thresholds could be estimated for several individual symptoms—pounding heart (3.1 ± 0.1 mM), trembling or shakiness (3.0 ± 0.1 mM), confused thinking (3.1 ± 0.1 mM), slurred speech (2.8 ± 0.1 mM), and difficulty concentrating (3.0 ± 0.1 mM)—in the CR^+ subjects (Table 1). In sharp contrast, glycemic thresholds could be defined only for trembling or shakiness (2.1 ± 0.2 mM) in the CR^- subjects. Clearly, therefore, the glycemic thresholds for both neurogenic and neuroglycopenic symptoms were at lower plasma glucose concentrations in the subjects with defective glucose counterregulation compared with those with adequate glucose counterregulation.

Antecedent glycemic control and symptoms of hypoglycemia. The subjects with adequate glucose counterregulation were separated into two groups on the basis of the median glycosylated hemoglobin value of 11%. The mean glycosylated hemoglobin levels were therefore 9.1 ± 0.4 and 13.80 ± 0.76% in the two groups. Mean baseline plasma glucose concentrations were not different between those with lower and higher glycosylated hemoglobin levels (5.3 ± 0.2 vs. 5.7 ± 0.1 mM). However, during the insulin infusion test, the nadir plasma glucose levels were significantly ($P < 0.04$) lower in the lower–glycosylated hemoglobin group (2.4 ± 0.1 vs. 2.9 ± 0.2 mM). The rates of fall of plasma glucose did not differ (0.24 ± 0.06 vs. 0.2 ± 0.01 mM/10 min).

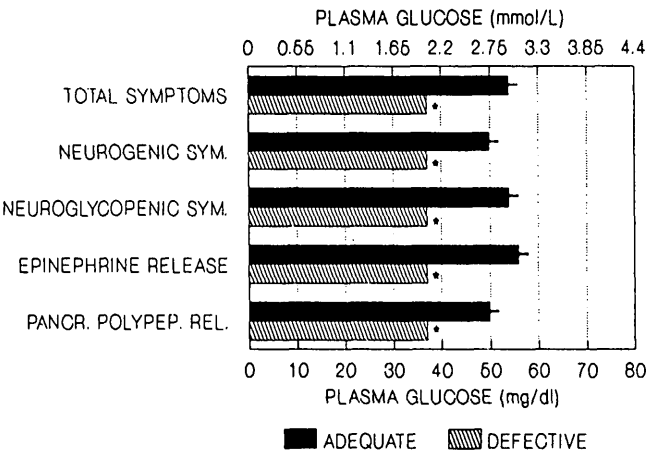

FIG. 1. Mean ± SE estimated glycemic thresholds for symptoms (Sym) and for epinephrine and pancreatic polypeptide release (Pancr Polypep Rel) during insulin-induced decrements in plasma glucose concentration in insulin-dependent diabetic patients with adequate glucose counterregulation (n = 32) and with defective glucose counterregulation (n = 9). *Thresholds could not be defined for these parameters in patients with defective glucose counterregulation and were therefore at plasma glucose levels lower than mean nadir glucose concentrations of 2.1 ± 0.1 mM. Maximum estimate of thresholds is shown. All differences in thresholds between these 2 groups are statistically significant.

TABLE 1
Glycemic thresholds (mM) for symptoms of hypoglycemia in insulin-dependent diabetic subjects

	Adequate counterregulation (n = 32)	Defective counterregulation (n = 9)
All symptoms	3.0 ± 0.1	<2.1
Neurogenic symptoms	2.8 ± 0.1	<2.1*
Sweaty hands	<2.7	
Pounding heart	3.1 ± 0.1	<2.1
Trembling, shakiness	3.0 ± 0.1	2.1 ± 0.2
Dry mouth	<2.7	<2.1
Neuroglycopenic symptoms	3.0 ± 0.1	<2.1
Blurred vision	<2.7	<2.1
Confused thinking	3.1 ± 0.1	<2.1
Slurred speech	2.8 ± 0.1	<2.1*
Difficulty concentrating	3.0 ± 0.1	<2.1
Numbness	<2.7	<2.1

$P < 0.001$ except as noted.
*$P < 0.002$ vs. adequate counterregulation.

There were no differences in age, duration of IDDM, daily insulin dose, or pretest (120-min) insulin infusion doses between the groups with lower and higher glycosylated hemoglobin. Estimated glycemic thresholds for release for epinephrine (3.3 ± 0.2 mM at 70 min), pancreatic polypeptide (3.0 ± 0.2 mM at 100 min), and glucagon (3.0 ± 0.2 mM at 110 min) could be defined in the higher–glycosylated hemoglobin group. Estimated glycemic thresholds for the release of epinephrine (2.6 ± 0.1 mM at 100 min) and pancreatic polypeptide (2.5 ± 0.1 mM at 110 min) could be defined in the lower–glycosylated hemoglobin group. Thus, in subjects with lower glycosylated hemoglobin levels, the thresholds for epinephrine and pancreatic polypeptide release were at lower plasma glucose concentrations than in subjects with higher glycosylated hemoglobin levels (Fig. 2).

Estimated glycemic thresholds for symptoms of hypoglycemia in relation to antecedent glycemic control are also shown in Fig. 2. In the higher–glycosylated hemoglobin group, thresholds could be defined for total symptoms (3.3 ± 0.2 mM), neurogenic symptoms (3.2 ± 0.2 mM), and neuroglycopenic symptoms (3.3 ± 0.2 mM) at 70, 70, and 80 min, respectively. Similarly, thresholds could be defined for most of the individual symptoms—pounding heart (3.2 ± 0.2 mM), trembling or shakiness (3.2 ± 0.2 mM), blurred vision (3.4 ± 0.2 mM), confused thinking (3.3 ± 0.2 mM), and difficulty concentrating (3.3 ± 0.2 mM) (Table 2). In sharp contrast, thresholds could not be defined for any symptoms or symptom groups in the lower–glycosylated hemoglobin group. Clearly, therefore, glycemic thresholds for both neurogenic and neuroglycopenic symptoms, if present, were at lower plasma glucose concentrations in the subjects with better antecedent glycemic control compared with those with poorer antecedent glycemic control.

Analyses of the data across 0.6 ± 0.3-mM plasma glucose intervals confirmed the findings above. Plasma epinephrine and pancreatic polypeptide concentrations became statistically elevated at the plasma glucose interval 2.8 mM, and plasma glucagon became significantly elevated at the glucose interval 2.2 mM, but only in subjects with adequate glucose counterregulation. Total, neurogenic, and neuroglycopenic symptoms increased significantly only in the CR^+

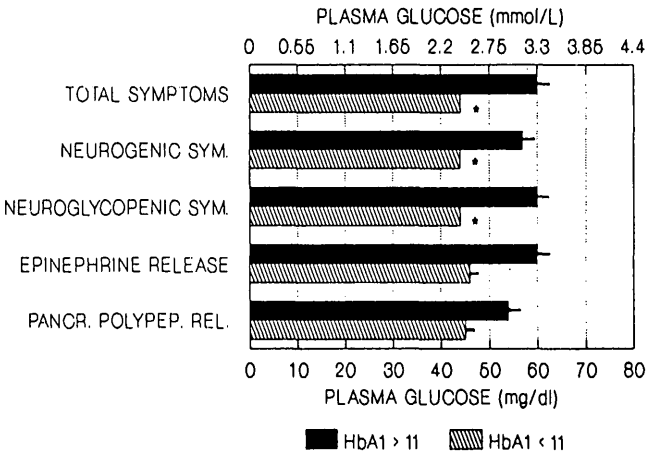

FIG. 2. Mean ± SE estimated glycemic thresholds for symptoms (Sym) and epinephrine and pancreatic polypeptide release (Pancr Polypep Rel) during insulin-induced decrements in plasma glucose in insulin-dependent diabetic patients with adequate glucose counterregulation and glycosylated hemoglobin (HbA_1) levels >11% (n = 16) and with HbA_1 levels <11% (n = 16). *Thresholds could not be defined for indicated parameters in patients with lower HbA_1 levels and were therefore at plasma glucose levels lower than mean nadir glucose concentrations of 2.4 ± 0.2 mM. Maximum estimate of thresholds is shown. All differences in thresholds between these 2 groups are statistically significant.

subjects at the plasma glucose interval of 2.8 mM. Similar findings were observed for the lower– and higher–glycosylated hemoglobin groups. Total, neurogenic, and neuroglycopenic symptoms increased significantly only in the higher–glycosylated hemoglobin group (at the plasma glucose interval of 2.8 mM), and mean changes (from the interval of 5.5 mM to the interval of 2.8 mM) in these variables were significantly greater in the higher– than in the lower–glycosylated hemoglobin group.

DISCUSSION

These data indicate that both defective glucose counterregulation (5,6) and better antecedent glycemic control (13–16) are associated with relative hypoglycemic symptom unawareness in IDDM. In a rather large group of patients with IDDM, those with defective glucose counterregulation, defined with a standard insulin infusion test with published criteria (5), had lower estimated glycemic thresholds for symptoms than those with adequate glucose counterregulation. Stated differently, as a group, those with defective glucose counterregulation had fewer and/or less-intense symptoms at a given plasma glucose concentration during hypoglycemia; i.e., they were less aware of symptoms of hypoglycemia than those with adequate glucose counterregulation. This is a new finding. Similarly, as a group, patients with better long-term glycemic control, as evidenced by lower glycosylated hemoglobin levels, had lower estimated glycemic thresholds for symptoms than those with poorer antecedent glycemic control. In other words, those with better glycemic control had fewer and/or less-intense symptoms at a given plasma glucose concentration during hypoglycemia; i.e., they were less aware of symptoms of hypoglycemia than those with poorer glycemic control. This confirms previous data (13–16). Therefore, these data are most consistent with the concept that both defective glucose counterregulation and better glycemic control contribute to excessive iatrogenic hypoglycemia in IDDM by reducing awareness of developing hypoglycemia and by impairing physiological defenses against hypoglycemia.

TABLE 2
Effect of antecedent glycemic control on glycemic thresholds (mM) for symptoms of hypoglycemia in insulin-dependent diabetic subjects with adequate glucose counterregulation

	Glycosylated hemoglobin <11% (n = 16)	Glycosylated hemoglobin >11% (n = 16)
All symptoms	<2.5	3.4 ± 0.2
Neurogenic symptoms	<2.5	3.2 ± 0.2
Sweaty hands	<2.5	<2.9
Pounding heart	<2.5	3.2 ± 0.2
Trembling, shakiness	<2.5	3.2 ± 0.2
Dry mouth	<2.5	<2.9
Neuroglycopenic symptoms	<2.5	3.4 ± 0.2
Blurred vision	<2.5	3.5 ± 0.2
Confused thinking	<2.5	3.4 ± 0.2
Slurred speech	<2.5	<2.9
Difficulty concentrating	<2.5	3.4 ± 0.2
Numbness	<2.5	<2.9

$P < 0.001$.

Note that the glycosylated hemoglobin levels in the patients with defective glucose counterregulation were not significantly different from those in the patients with adequate glucose counterregulation. Therefore, better glycemic control does not explain the new finding of glycemic thresholds at lower plasma glucose concentrations in patients with defective compared with adequate glucose counterregulation.

Although only defective glucose counterregulation has been demonstrated prospectively to increase the risk of iatrogenic hypoglycemia (5,6), the finding that this syndrome is associated with hypoglycemic symptom unawareness (10) provides support for the assumption that hypoglycemic symptom unawareness also contributes to the high frequency of hypoglycemia during the intensive therapy of IDDM. If so, the finding of an association between hypoglycemic symptom unawareness and improved glycemic control (13–16) suggests that effective intensive therapy would contribute to the high frequency of iatrogenic hypoglycemia by reducing awareness of developing hypoglycemia and by causing intermittent hyperinsulinemia.

The method we used to define glycemic thresholds warrants comment. These were derived from continuously declining plasma glucose curves and defined as the plasma glucose concentration at which there was a significant increase in the parameter of interest over its baseline values. Because there must be a signal-to-response interval, this approach must lead to estimated threshold values at lower plasma glucose levels than those that triggered the measured response as discussed previously (22). Furthermore, we used venous plasma glucose measurements, which would be expected to be lower than arterial glucose levels under hyperinsulinemic conditions as also discussed previously (22). Therefore, the glycemic thresholds estimated here are at lower plasma glucose concentrations than the biological thresholds and those reported when a stepped hypoglycemic clamp approach and arterialized venous sampling were used to calculate thresholds (12,22). Nonethe-

less, the estimated glycemic thresholds we present in this study do permit comparisons of these within our experimental groups. Clearly, however, they should not be compared uncritically with data from other studies.

A pathophysiological common denominator of defective glucose counterregulation, altered glycemic thresholds during intensive therapy, and hypoglycemic symptom unawareness is a reduced sympathochromaffin response to plasma glucose decrements (2–16). Evidence of a reduced parasympathetic response (increments in plasma levels of pancreatic polypeptide) to hypoglycemia has been demonstrated in defective glucose counterregulation (23) and might be anticipated in the other two syndromes. Indeed, in this study, the thresholds for both epinephrine and pancreatic polypeptide release and for symptoms during hypoglycemia were at lower plasma glucose concentrations in both the group with defective glucose counterregulation and the group with lower glycosylated hemoglobin levels. Therefore, it is reasonable to suggest that a reduced autonomic nervous system response to hypoglycemia, regardless of its specific mechanisms, underlies the reduced neurogenic symptoms of hypoglycemia in affected patients. However, we found both defective glucose counterregulation and better antecedent glycemic control to also be associated with reduced neuroglycopenic symptoms of hypoglycemia. Indeed glycemic thresholds for neuroglycopenic and neurogenic symptoms were similar in both analyses. Therefore, factors in addition to reduced autonomic responses must be involved in the pathogenesis of hypoglycemia unawareness in these disorders. Those factors could include central nervous system adaptation (e.g., increased fractional extraction of glucose by the brain) to previous recurrent hypoglycemia (12,24), although the latter has not been demonstrated in humans.

An additional potential mechanism of hypoglycemia unawareness not addressed in this study is decreased responsiveness to autonomic activation. Berlin et al. (25,26) have found decreased cardiac chronotropic sensitivity to isoproterenol to be associated with a blunted heart rate response to hypoglycemia and patient reports of perception of hypoglycemia at lower plasma glucose concentrations and fewer neurogenic symptoms of hypoglycemia. Because the latter includes sweating, the data are not consistent with reduced β-adrenergic sensitivity alone; reduced cholinergic sensitivity would also need to be postulated.

Clearly, hypoglycemia unawareness in patients with IDDM can be multifactorial in origin. These data indicate that both the syndrome of defective glucose counterregulation and the component of the syndrome of therapy-associated altered glycemic thresholds, in which the thresholds are shifted to lower plasma glucose concentrations during improved glycemic control, are associated with and could be the cause of hypoglycemic symptom unawareness in IDDM. Defective glucose counterregulation appears to be a persistent syndrome. It is demonstrable during poor metabolic control (5,6), and the reduced counterregulatory hormonal responses are not reversed during intensified therapy (27,28). However, altered glycemic thresholds are a function of the degree of metabolic control (13–16) and are presumably reversible. If so, less tight metabolic control would be expected to result in increased awareness of hypoglycemic symptoms. This would at least partially explain the observation that the syndrome of hypoglycemia unawareness can be partial; i.e., a given patient can be aware on some occasions but unaware on others (11). It would also provide a possible approach to the treatment of hypoglycemia unawareness. Although they both involve a reduced autonomic response to a given degree of hypoglycemia, the specific mechanisms of these syndromes are not known and need not be the same. In theory, the threshold abnormality could lie in the afferent, central, or efferent components of the autonomic nervous system. Additional potential mechanisms of hypoglycemia unawareness include decreased responsiveness to autonomic activation (25,26) and decreased perception of both neurogenic and neuroglycopenic symptoms (24) as mentioned earlier.

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