Mechanism of Awareness of Hypoglycemia: Perception of Neurogenic (Predominantly Cholinergic) Rather Than Neuroglycopenic Symptoms

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IN BRIEF

The parasympathetic part of the autonomic nervous system mediates a large proportion of neurogenic symptoms of hypoglycemia (sweating, hunger, tingling). These mechanisms also mediate hypoglycemia awareness. Adrenergic mechanisms mediate other neurogenic symptoms such as shaking and tremulousness, heart pounding, and anxiety and nervousness. Hypoglycemia awareness is largely, if not exclusively, due to patients' ability to perceive and interpret neurogenic rather than neuroglycopenic symptoms.

Summary and Commentary by Walter P. Borg, MD, and William V. Tamborlane, MD

Objective. To study how to reproduce hypoglycemia-related symptoms, objectively discern neurogenic (autonomic) from neuroglycopenic symptoms, and address whether hypoglycemia awareness is the result of perceived neurogenic or neuroglycopenic symptoms.

Design. Randomized controlled study.

Subjects. Ten healthy young adults (7 men, 3 women, 22–29 years of age).

Measurements. Hypoglycemia awareness (i.e., a subjective perception of low blood glucose), 16 hypoglycemia-related symptoms, and 3 unrelated control symptoms were measured on four occasions in random sequence. The four occasions were as follows: *1)* during clamped euglycemia (~5 mM [90 mg/dl]); *2)* during clamped hypoglycemia (~2.5 mM [45 mg/dl]); *3)* during clamped hypoglycemia with combined α- and β-adrenergic blockade (phentolamine and propranolol); and *4)* clamped hypoglycemia with panautonomic adrenergic and chlorinergic blockade using phentolamine, propranolol, and atropine.

Cognitive function tests, which measured global cognitive function, attention, and memory, and hormone and metabolic measurements were also performed during each study. Blood pressure and heart rate were monitored throughout.

Results. Significant (analysis of variance $P < 0.001$) treatment effects on hypoglycemia awareness were noted. The mean ± SE score for this symptom did not change during euglycemia but did increase during hypoglycemia (2.1 ± 0.4). This increase was not reduced significantly by adrenergic blockade (1.6 ± 0.5) but was reduced significantly and substantially (~70%) by panautonomic blockade (0.6 ± 0.3).

Significant neurogenic adrenergic symptoms included shaking and tremulousness ($P < 0.001$), heart pounding ($P < 0.001$), and anxiety and nervousness ($P < 0.002$). Significant neurogenic cholinergic symptoms included sweating ($P < 0.001$), hunger ($P < 0.001$), and tingling ($P = 0.009$). Significant neuroglycopenic symptoms, those produced by hypoglycemia but not reduced by panautonomic blockade, included warmth ($P < 0.001$), weakness ($P = 0.011$), difficulty thinking and confusion ($P = 0.004$), and tiredness and drowsiness ($P = 0.003$).

Conclusions. The authors concluded that cholinergic mechanisms mediate an important, previously uncharacterized component of the neurogenic symptoms of hypoglycemia and hypoglycemia awareness. Hypoglycemia awareness is largely, perhaps exclusively, the result of whether patients perceive neurogenic rather than neuroglycopenic symptoms.

• COMMENTARY •

In the mid-1980s, the glucose clamp technique was adapted as a test to assess the response to hypoglycemia.[1] This paved the way for numerous studies that have greatly enhanced our knowledge about factors that influence the response to and recognition of hypoglycemia. Towler and colleagues' study is an excellent example of how the clamp technique can be combined with other complex infusion protocols to more precisely determine which components of the autonomic nervous system contribute to symptomatic hypoglycemia awareness.

Ten or fifteen years ago, hypoglycemic symptoms would have been broadly divided into early adrenergic warning symptoms and subsequent neuroglycopenic symptoms if blood glucose levels continued to fall. This study confirms that symptoms caused by mild-to-moderately reduced blood glucose levels are mediated by activating the autonomic nervous system. Cryer's group in St. Louis, from which this paper comes, has re-termed these "neurogenic" symptoms.

However, many warning symptoms (i.e., sweating, hunger, and tingling) appear to be mediated by cholinergic, rather than adrenergic, mechanisms because panautonomic blockade suppressed these symptoms but adrenergic blockade alone did not. Surprisingly, the same response pattern was seen for the more global symptoms of low blood glucose. Adrenergic blockade alone substantially decreased other symptoms, such as shaking and heart pounding.

These findings are difficult to interpret because the blocking

agents directly affect the central nervous system, which could make hypoglycemia harder to recognize. Towler's study illustrates this by the changes observed in cognitive function when blocking agents were infused before blood glucose was reduced. To overcome this obstacle, David Kerr, MD,[2] who was a member of our group, used the glucose clamp procedure in a different way. He directly examined the effects of the rise in counterregulatory hormones on symptoms scores in the absence of hypoglycemia.

Kerr compared hypoglycemic symptoms scores in 10 healthy subjects during a hypoglycemic clamp (plasma glucose lowered from 5.0 to 2.8 mM) with those during a euglycemic clamp combined with exogenous epinephrine, norepinephrine, cortisol, glucagon, and growth hormone infusions to mimic the plasma hormone profile observed during the hypoglycemic clamp study. Although the hormone infusions caused adrenergic symptoms to increase, as they did during the hypoglycemic clamp, hunger, sweating, and "feeling low" did not increase.

These data are entirely consistent with Towler's. His data also showed the importance of activating endogenous cholinergic mechanisms. The exogenous infusions of norepinephrine, which functions as a neurotransmitter, probably had little physiological effect.

A strength of this study is that the investigators addressed clinically relevant questions using a scientifically rigorous study design. Nevertheless, no one study can cover all the bases. For example, determining how cholinergic blockade alone affected the responses to hypoglycemia would have been interesting. Another caveat is that compared with how accurate many of the measurements in this study are, the symptoms scores are subjective and imprecise, and the scores during hypoglycemia increased only modestly (1–2 points on a 7-point scale).

The study results tend to downplay the importance of adrenergic symptoms in recognizing "feeling low" in nondiabetic subjects. Would the same be true for patients with insulin-dependent diabetes mellitus (IDDM), who have had ample opportunity to relate such adrenergic symptoms to low blood glucose readings on their monitors at home? With experience, even patients who lack neurogenic symptoms may be able to detect early neuroglycopenic symptoms, such as difficulty thinking, before more severe cerebral impairments intervene.

If the rise in plasma epinephrine levels that accompanies hypoglycemia is not critically important for recognizing hypoglycemia in patients with diabetes, does that imply that adrenergic blocking agents can be safely used in patients with IDDM? The ability of these agents to block responsive increases in fatty acids and lactate, and presumably other aspects of endogenous counterregulation, argue such a conclusion. ■

• REFERENCES •

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[2]Kerr D, Diamond MP, Tamborlane WV, Kerr S, Sherwin RS: Influence of hormones, independently of hypoglycemia, on cognitive function, warning symptoms and glucose kinetics. *Clin Sci* 85:197-202, 1993.

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Hypoglycemic Thresholds for Cognitive Dysfunction in IDDM

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Summary and Commentary by Irl B. Hirsch, MD

Objective. To determine the cognitive threshold for patients with poorly controlled insulin-dependent diabetes mellitus (IDDM).

Subjects. Ten nondiabetic volunteer subjects and 14 age-matched IDDM patients with poor glycemic control (HbA_{1c} 11.0 ± 0.5% [upper limit of normal 6.5%]).

Measurements. A stepped hypoglycemic clamp with a constant insulin infusion and a variable rate glucose infusion was initiated at 8:00 a.m. At the beginning of the study, blood glucose was clamped at 5.1 mM (92 mg/dl), decreased to 3.5 mM (63 mg/dl), and decreased again to 2.5 mM (45 mg/dl). A meal was consumed, and blood glucose levels rose to baseline and then to postmeal levels. A control study with blood glucose levels clamped at the basal level was performed to control for practice effects and the effects of fatigue.

The primary measurement was the P300 event-related potential, a measure of cognitive function and reaction time in response to visual stimuli. The P300 latency reflects the sensory and cognitive processing time associated with decision

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This study concluded that patients with poorly controlled IDDM and matched control subjects have similar cognitive impairment at blood glucose levels between 3.5 and 2.5 mM (63 and 45 mg/dl). Cognitive dysfunction was measured with P300 event-related potential and reaction time in response to visual stimuli. These measurements of neuroglycopenia are more sensitive than traditional symptom scores and cognitive function tests. Differences in study design may explain why this study's results differ from those of other reports.