SPECIAL ARTICLE

# Stress and Autonomic Nervous System in Type II Diabetes
## A Hypothesis

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Many investigators have begun to speculate that the sympathetic nervous system is involved in the pathophysiology of type II (non-insulin-dependent) diabetes mellitus (1–4). Recalling the early observations of Claude Bernard, who found that hyperglycemia could be produced in normal rabbits by lesioning the area of the hypothalamus, several groups have noted that hyperglycemia can be produced by chemical stimulation of the brain with morphine as well as with a variety of endogenous neuropeptides and can be abolished by bilateral adrenalectomy (1,5). Similarly, hyperglycemia has been shown to result from slow intravenous infusion of epinephrine (6) as well as from certain forms of stress that produce prolonged sympathetic discharge (7).

Indeed, there is mounting experimental evidence of altered sympathetic nervous system activity in type II diabetes. Exaggerated suppression of insulin secretion and profound hyperglycemia in response to epinephrine have been repeatedly noted in several animal models of type II diabetes (8–10). This hyperresponsivity to epinephrine appears to coincide with an exaggerated insulin response to phentolamine in these animals, suggesting the presence of enhanced sensitivity of $\alpha_2$-receptors in the pancreas and possibly at other sites as well (9,10). There is also substantial evidence of altered adrenergic sensitivity in humans with type II diabetes. As in animals, adrenergic blockade with phentolamine produces a much larger increase in insulin secretion in diabetic individuals than it does in healthy control subjects (11,12). Furthermore, patients with type II diabetes appear to have higher levels of circulating catecholamines than do normal individuals (12). Finally, the elevated levels of endogenous opioid peptides that have been reported in animal models (13) as well as in human type II diabetes (14) may also be a sign of abnormal sympathetic nervous system activity. Opioid peptides act as neuromodulators for presynaptic inhibition in sympathetic ganglia (15) and opioid receptors are found on sympathetic nerve terminals, providing a site for postsynaptic inhibition. Acute opiate blockade can reverse circulatory shock (16), can potentiate the cardiovascular effects of psychologic stress (17), and can increase blood pressure in patients with pheochromocytoma (18). Therefore, the high levels of endogenous opioid peptides found in the pancreas and plasma in type II diabetes may actually serve to attenuate the hyperglycemic effects of sympathetic nervous system activity. We have recently shown that opiate blockade with naltrexone will aggravate stress hyperglycemia in diabetic but not normal mice, lending support to this notion (19).

Whether these changes in sympathetic nervous system activity are associated with the onset of type II diabetes or are secondary to hyperglycemia, interventions to reduce sympathetic nervous system activity should, in theory, be useful in modulating hyperglycemia excursions. In recent studies, $\alpha_2$-blockade has been shown to improve glucose tolerance and increase insulin secretion in diabetic obese mice (20) and increase both meal-stimulated insulin secretion and glucose disposal in patients with type II diabetes (21). Long-term $\alpha_2$-blockade has been observed to produce clinically significant improvements in glycohemoglobin and fasting plasma glucose (21,22). The relevance of these observations is highlighted by the report that clonidine, which binds to $\alpha_2$-receptors, inhibits the binding of the oral hyperglycemic agent glyburide in the pancreas, suggesting that part of the effect of glyburide on insulin

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secretion may be related to an effect on adrenergic activity (23).

Both psychologic and physical stress stimulate sympathetic nervous system activity (24). Therefore, if sympathetic nervous system activity is altered in type II diabetes, patients with this disease may be extremely sensitive to the effects of psychologic stress. The possible role of psychologic stress in the etiology of diabetes was first suggested by Willis (25) and later noted by Maudsley (26). Although the effects of stress on type I (insulin-dependent) diabetes are controversial (27,28), there is mounting evidence that stress is important in glycemic control in type II diabetes. Stress has been shown to precipitate hyperglycemia in several animal models of type II diabetes (8,29). Moreover, exaggerated hyperglycemia can be classically conditioned in at least one animal model of the disease. By temporally pairing a known stressor (shaking) to the sound of a metronome, the metronome itself can become a potent hyperglycemic stimulus in obese diabetic, but not lean, mice (30). This suggests that psychologic as well as physical stressors can severely disrupt glucose metabolism when type II diabetes is present. There are, unfortunately, no human data that directly support or refute this hypothesis. Previous research on the effects of stress on glycemic control has not differentiated the effects of stress on type I from those on type II diabetes. However, available data suggest that stress reduction techniques may have a singular utility in the treatment of type II diabetes. As early as 1892, Osler (31) advised the use of rest and opiates in the treatment of "hyperglycemia of obesity," which probably corresponds to what is considered to be type II diabetes today. It has recently been shown that relaxation training can reduce hyperglycemia in human type II diabetes (32,33) but not type I diabetes (34–36) and that some benzodiazepines can reduce hyperglycemia in response to stress in an animal model of type II diabetes (37). Preliminary data from our laboratory indicate that some benzodiazepines may also improve glucose tolerance in human type II diabetes.

In summary, there is evidence from both animal and human studies of increased α-adrenergic sensitivity in the endocrine pancreas and other tissues in type II diabetes. The resultant exaggeration of sympathetic nervous system effects would impair both insulin secretion and glucose utilization, the pathophysiologic hallmarks of the disease. This hypothesis does not require the presence of unusual psychologic stress for metabolic disregulation to occur in that the metabolic effects of even normal sympathetic nervous system activity appear to be exaggerated. Thus, type II diabetes may be, in part, a problem of neurally regulated homeostasis in which stress and the autonomic nervous system interact in contributing to the development and/or the course of the disease. This hypothesis is consistent with the early theoretical speculations of Claude Bernard and the clinical observations of Willis, Osler, and Maudsley. Further investigation will determine its relevance to our understanding of the etiology and treatment of type II diabetes.

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