Comment on: Straznicky et al. Neuroadrenergic Dysfunction Along the Diabetes Continuum: A Comparative Study in Obese Metabolic Syndrome Subjects. Diabetes 2012;61:2506–2516

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In the recent article by Straznicky et al. (1), the authors demonstrate that the onset of diabetes is associated with increased central sympathetic outflow, altered norepinephrine disposition, and blunted sympathetic responsiveness to carbohydrates. In fact, insulin resistance highly correlated with neuroadrenergic function, as shown by the independent correlation of insulin-stimulated glucose uptake (M/I) with whole-body norepinephrine spillover. Muscle sympathetic nerve activity (MSNA), on the contrary, failed to correlate with insulin resistance. This apparently surprising result can, however, find a logical explanation (2), which actually reinforces the data of Straznicky et al. Sympathetic overactivity, similarly to insulin resistance, should not be viewed as an on-off perturbation, but it most probably interferes with glucose metabolism following its own time course. An initial, primary prevalence of sympathetic over parasympathetic activity might be responsible for an increased metabolic state, accompanied by increased insulin sensitivity (3) (Fig. 1, circle A). As in many other hormone-regulated pathways, this state is followed by a downregulation of the β-adrenergic metabolic responsiveness (Fig. 1, circle B) (reduced basal metabolic rate and facultative thermogenic effect of food), eventually accompanied by increased tendency toward anabolic processes and reduced ability to dissipate energy, i.e., weight gain (particularly at the visceral level), and finally insulin resistance (Fig. 1, circle C). Again, as in many other hormone-regulated pathways, sympathetic activity attempts to overcome (with norepinephrine overflow) the β-adrenergic receptor downregulation, maintaining overall MSNA activity apparently unmodified. Finally, this could represent the onset of a vicious cycle, in which insulin resistance further stimulates sympathetic activity and worsens insulin resistance itself (Fig. 1, circle D).

According to this hypothesis, the effects of sympathetic activation on insulin-mediated glucose metabolism are time dependent and, therefore, impact differently according to the stage of autonomic imbalance. At the stage the current study was performed, the increase of arterial norepinephrine concentration progressively downregulates β-receptors and, consequently, reduces insulin sensitivity: this explains why the two parameters strongly correlate. Reduction of β-receptors, in turn, nicely explains why MSNA increase is only partial, as suggested by the similar burst frequency and median burst amplitude in impaired glucose tolerant and diabetic subjects. As a consequence, no correlation between MSNA and insulin-mediated glucose metabolism can be expected. In conclusion, we believe that this study strongly supports the hypothesis of a continuous changing in the interrelationship between autonomic function and glucose metabolism from the early stage of insulin resistance to the onset of diabetes and, eventually, to the development and progression of autonomic diabetic neuropathy (4).

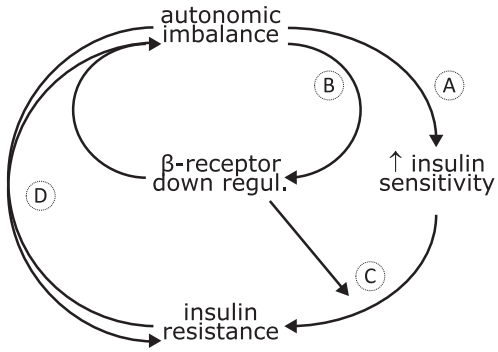

FIG. 1. Schematic representation of the time course of the relationship between autonomic dysfunction and insulin sensitivity.

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