Reply to R Jindal

Dear Sir:

We would like to thank Ripu Jindal for his comments and perspective regarding our recently published article that showed blunted sympathetic neural responsiveness to glucose ingestion in obese, insulin-resistant compared with obese, insulin-sensitive subjects with metabolic syndrome (1). Jindal raises 2 important issues: 1) the chronology of sympathetic activation and 2) the interrelation between autonomic responsiveness, insulin resistance, and weight gain.

Long-term prospective trials that have examined the cause-effect relation of sympathetic activation and insulin resistance consistently show that sympathetic activation precedes and predicts future weight gain and development of insulin resistance (2–4). Masuo et al (2) examined young, lean, normotensive Japanese men annually over 10 y and found that elevated plasma venous norepinephrine concentrations at baseline predicted subsequent weight gain, blood pressure elevation, and insulin resistance. In Norwegian men followed over a 20-y period, elevated arterial norepinephrine concentrations and heightened sympathetic response to cold pressor testing at baseline were both positively associated with future weight gain and HOMA-IR (homeostasis model assessment–insulin resistance index) (3, 4). Although seemingly counterintuitive, sympathetic activation may be causally linked to obesity via β-adrenoceptor desensitization (5) and insulin resistance, mediated through increased lipolysis; decreased glucose utilization in skeletal muscle; and catecholamine-induced alterations in the inflammatory milieu (6). In established obesity, metabolic and medical conditions, such as obstructive sleep apnea, contribute significantly to increased sympathetic neural drive and further aggravate insulin resistance, hence establishing a vicious cycle. Parallel to the evidence of sympathetic activation is a growing body of data that shows blunted sympathetic neural responsiveness to physiologic and pharmacologic perturbations in obesity, which is the focus of our current article.

In our study, sympathetic responsiveness to glucose ingestion was inversely related to measures of central adiposity and the insulin response (insulin AUC0–120 and absolute change in plasma insulin concentration) and positively to whole-body insulin sensitivity index and fitness level (1). Because calf blood flow and baroreflex responses to oral glucose did not differ between insulin-resistant and insulin-sensitive subjects, we hypothesized that a central nervous system action of insulin on sympathetic outflow was deficient in the insulin-resistant group. In the brain, insulin resistance can manifest itself through changes in brain insulin uptake and/or insulin receptor function. Reduced cerebrospinal fluid to plasma insulin ratio has been reported with increasing BMI and HOMA-IR index, suggesting that obesity in humans is characterized by a relative central nervous system insulin deficit (7). These data are supported by findings in genetically obese rats, which exhibit reduced brain capillary insulin binding and cerebrospinal fluid insulin uptake compared with lean rats (8). Hyperinsulinaemia is the primary signal leading to increased central sympathetic outflow after carbohydrate ingestion, which accounts for ≈30% of the thermic effect of food or 3% of daily energy expenditure. Insulin also acts in the brain via the melanocortin system to suppress food intake, increase energy expenditure, and hence limit weight gain. Therefore, central insulin deficiency or resistance would be expected to promote weight gain. Accordingly, impaired glucose-induced thermogenesis has been previously reported in obesity (9).

Jindal suggests that blunted sympathetic responsiveness may be of some benefit vis-a-vis heightened vagal activity and reduced inflammation and insulin resistance. He also rightly points out that, in Pima Indians, Hispanic, and some white populations, insulin resistance may protect against further weight gain. Inconsistent findings regarding insulin resistance and weight gain have been reported in the literature and may be attributed to ethnic diversity, genetic predisposition, and the interaction between obesity and insulin resistance (10). The complex nature of insulin’s actions, which involve direct and indirect mechanisms acting both centrally and peripherally, could dictate how acute insulin response might affect weight gain.

The pertinent clinical question arising from our work is whether therapeutic interventions that improve peripheral or central insulin resistance modify sympathetic responsiveness. To this end, we have shown in a follow-on study that moderate weight loss (8.6% of body weight) markedly reversed blunted sympathetic neural responsiveness to glucose, but only in insulin-resistant subjects (11). The ratio of the norepinephrine spillover AUC0–120 to the insulin AUC0–120, which gives an index of sympathetic responsiveness for a given increase in insulin concentration, increased from 3.6 ± 0.4 to 5.0 ± 1.0 (P = 0.05) in the insulin-resistant subjects but did not change in the insulin-sensitive group. Further intervention trials using insulin-sensitizing agents are needed to confirm the role of insulin resistance in mediating blunted sympathetic responsiveness in metabolic syndrome obesity. Intranasal insulin delivery may offer another therapeutic avenue to test whether manipulating brain insulin concentrations affects sympathetic nervous system function in this clinical setting.

Neither author had a conflict of interest to declare.

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REFERENCES

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