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Comment to: Grassi G, Dell'oro R, Quarti-Trevano F et al (2005) Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia 48:1359–1365

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To the Editor: In the July issue of *Diabetologia*, Grassi and colleagues report that in patients with the metabolic syndrome muscle sympathetic activity is increased [1]. This is an important study, as it highlights two observations: (1) that the increased sympathetic activity accompanying the metabolic syndrome is detectable when blood pressure is normal; and (2) that increased sympathetic activity correlated positively and strongly with BMI, waist circumference, and insulin resistance (HOMA index), and less so with diastolic blood pressure (BP). It did not correlate with systolic BP, triglycerides, or cholesterol.

Three explanations are put forward by the authors to explain the mechanisms responsible for the increased sympathetic activity: (1) that it is stimulated by hyperinsulinaemia; (2) that it is the result of increased BMI; or (3) that by producing restricted perfusion of muscle it is the cause, rather than the result, of insulin resistance. An accompanying commentary by Landsberg builds on the first of these mechanisms, explaining the increase in sympathetic activity as essentially a response to overfeeding with the overall purpose of increasing energy expenditure [2]. This explanation is entirely plausible on theoretical grounds, and indeed there is evidence that increased sympathetic activity may decrease dietary thermogenesis.

However, if explanation (1) were true, then insulin resistance has already set in before the increase in sympathetic activity and so a rationale for the insulin resistance must then be sought. Explanations (2) and (3) are most interesting, particularly if considered jointly. For instance, the increase in BMI may by itself, or through an intermediary, cause the increase in sympathetic nervous system activity, which in turn acts on skeletal muscle blood vessels to decrease muscle perfusion. However, this requires a mechanism by which BMI or an intermediary activates the

sympathetic nervous system. As pointed out by the authors themselves, both visceral obesity and hypertension have sympathostimulating effects [1], but again an accompanying insulin resistance may play the key role.

Neither the primary article by Grassi and colleagues [1], nor the commentary by Landsberg [2] mention the involvement of vascular dysfunction as a member of the constellation of pathologies that constitute the metabolic syndrome. There is now abundant evidence to suggest that obesity and the relative physical inactivity that contributes to, and accompanies obesity, cause an early vascular dysfunction where the vasodilatory responses to insulin and exogenous vasodilators are grossly impaired (recently reviewed in [3]). We also know that under normal conditions, physiological insulin acts to increase muscle perfusion by capillary recruitment in human subjects, and in animals this is both an early and very sensitive process (see review [4]). More importantly, insulin-mediated capillary recruitment is impaired in obesity, and when deliberately impaired in animal models by acute interventions, there is an accompanying decrease in insulin-mediated glucose uptake by muscle (albeit an acute muscle insulin resistance) (see review [4]). What is not known is how the process of vascular dysfunction is initiated. Recent work by Kim et al. [5] suggests that a parallel attack by elevated plasma fatty acids or inflammatory cytokines occurs on insulin signalling in both the vasculature and the myocytes. Then, because of impaired tissue perfusion, insulin and glucose are unable to gain full access and insulin resistance results. The origin of these cytokines may be the adipocytes themselves (see, for example [6]). The resultant insulin resistance and/or the elevated plasma insulin may then be responsible for activation of the sympathetic nervous system [2].

A number of studies in animals and humans have shown that insulin resistance is accompanied by decreased muscle perfusion, reflected by diminished insulin or glucose delivery [4, 7]. Perhaps even more intriguingly, a recent study reports that exercise has a positive effect in ameliorating vascular dysfunction [8]. Further to this, Grassi and colleagues have previously shown that physical activity exerts

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marked and long-lasting sympathoinhibitory effects [1]. Thus, it goes without saying that regular exercise has the power to reverse the entire sequence.

Finally, and as correctly proposed by Landsberg [2], the increase in sympathetic activity may be part of a homeostatic process to correct for overeating, and it may turn out that an increase in muscle perfusion is part of this action. What is clear is that vasodilators in general cannot be used to ameliorate insulin resistance in muscle.

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