L. Landsberg

Insulin resistance and the metabolic syndrome

Published online: 10 June 2005
© Springer-Verlag 2005

In this issue of *Diabetologia*, Grassi and colleagues report increased muscle sympathetic nerve activity in patients with a collection of cardiovascular risk factors known as the metabolic syndrome [1]. They present evidence that the increase in sympathetic activity in this syndrome is related to insulin resistance and is associated with decreased baroreflex sensitivity.

Why is this important? Because the metabolic syndrome is associated with significant cardiovascular risk, and understanding the pathogenesis of this constellation of factors can help define therapeutic strategies to reverse or mitigate the risk. There are four critical features of the metabolic syndrome: (1) obesity, particularly the central or abdominal form of obesity; (2) insulin resistance and hyperinsulinaemia; (3) hypertension; and (4) a characteristic dyslipidaemia consisting of high triglycerides and low HDL cholesterol [2]. Moreover, these abnormalities are associated; they occur together with increased frequency, as demonstrated in population studies. Additional risk factors that may be associated with the syndrome include type 2 diabetes, hyperuricaemia, microalbuminuria and coagulation abnormalities that constitute a pro-thrombotic diathesis. The clinician can readily diagnose the metabolic syndrome using the well-established criteria that were applied in the study of Grassi et al. [1] to identify appropriate subjects. These criteria use waist circumference as a reasonable surrogate for the abdominal form of obesity. The current worldwide epidemic of obesity highlights the importance of this syndrome.

What are the threads that tie the seemingly diverse manifestations of this syndrome together? The defining features of obesity and insulin resistance are relatively well-understood and, together, can rationally and convincingly explain the hypertension and dyslipidaemia [3]. For the last 100 years, hypertension has been known to be closely as-

sociated with obesity. It has been known for four decades that obesity and type 2 diabetes are associated with hyperinsulinaemia; the latter reflects enhanced pancreatic beta cell secretion in the face of an impairment of muscle glucose uptake, the defining abnormality of insulin resistance. When the pancreatic beta cell reserve falters, IGT or overt type 2 diabetes develops. It has been known for over two decades that insulin stimulates sympathetic activity [4] and, more recently, that this stimulation occurs at levels of insulin that are well within the physiological range [5]. For the last 15 years it has been known that obese humans have increased sympathetic activity [6], and Grassi and colleagues recently demonstrated that sympathetic activation is greater in subjects with the central, as opposed to the peripheral, form of obesity [7]. It is a reasonable inference, therefore, that insulin stimulates the sympathetic nervous system in obese individuals and that insulin-mediated sympathetic stimulation exerts a pro-hypertensive effect in this group. This inference is strengthened by the correlation of measures of insulin resistance with both blood pressure and sympathetic activity in this study and in other clinical and population-based studies. The effect of insulin and the sympathetic nervous system should be regarded as pro-hypertensive, since not all obese individuals are hypertensive, as demonstrated here and elsewhere, despite increased sympathetic activity. Nor is this mechanism involving insulin an exclusive one; leptin, which also stimulates sympathetic activity [8, 9], and angiotensinogen, produced in (central) adipocytes [10], have been implicated as well. In the present study of Grassi and colleagues, since the subjects with the metabolic syndrome were obese, it seems reasonable to infer that the enhanced sympathetic activity reported was secondary to obesity.

The dyslipidaemia of the metabolic syndrome appears to reflect the direct effects of elevated insulin levels on triglyceride synthesis and release [3]. Obese individuals also have decreased adrenal medullary activity (in contrast to increased sympathetic nervous system activity), and lower levels of epinephrine secretion from the adrenal medulla in this population have been shown to contribute to the lipid abnormality [11].

L. Landsberg (✉)
Department of Medicine,
Northwestern University Medical School,
Chicago, IL, 60611, USA
e-mail: l-landsberg@northwestern.edu
Tel.: +1-312-503-0340
Fax: +1-312-503-7757

But a more fundamental question emerges: what is the link between insulin and the sympathetic nervous system? Why should insulin, the major anabolic hormone of the fed state, stimulate the sympathetic nervous system? The answer lies in the relationship between sympathetic activity and dietary intake. During fasting, sympathetic activity is decreased and metabolic energy expenditure diminishes [12]. This conservative reaction makes teleological sense: in the face of limited food supply a decrease in energy consumption would lengthen survival. The converse—increased sympathetic activity with overfeeding—has also been well established [13]. Although the latter association defies such a facile teleological explanation, since the value of increasing energy intake and dissipating the increased calories as heat is not immediately obvious, closer inspection does provide a solid physiological rationale. Overfeeding is associated with an increase in caloric expenditure that is termed dietary thermogenesis. Mammals may have developed the capacity for dietary thermogenesis as an evolutionary adaptation to dietary deficiencies, particularly diets low in protein. By overeating a low protein diet, an organism might be able to satisfy basic nitrogen requirements for growth and development, without the accompanying liability of excessive fat accumulation [14]. Whatever the evolutionary origins, it is clear that dietary thermogenesis can act as a buffer against the development of obesity.

What is the role of insulin? Insulin functions as a signal to the brain that links sympathetic outflow with dietary intake. Insulin-mediated glucose metabolism in regulatory hypothalamic neurons is the proximate mechanism. These neurons regulate the activity of tonically active sympathetic centres in the brainstem [15]. Importantly, obese individuals are not resistant to the central nervous system effects of insulin on sympathetic stimulation.

How can these considerations help elucidate the metabolic economy of the obese population? It seems obvious that the insulin-mediated synthesis and storage of fuels cannot continue indefinitely in the face of persistently elevated levels of insulin, since cellular disruption would result from unrestrained triglyceride or glycogen deposition in fat or muscle. Thus, on a cellular level, insulin resistance limits fuel storage, perhaps by alterations in the configuration of membrane structural components secondary to excessive fuel storage. At the level of the whole organism, in the presence of insulin resistance, sympathetic stimulation of energy production serves to limit further fuel storage (weight gain) by increasing energy output. From this perspective, insulin resistance is a homeostatic mechanism aimed at antagonising a relentless increase in nutrient storage, and the hypertension that so commonly attends obesity is the unfortunate by-product of mechanisms (sympathetic stimulation) recruited in obese persons to stabilise body weight and restore energy balance [16].

Looked at in a slightly different light, both decreased metabolic heat production (lower metabolic rate, decreased capacity for dietary thermogenesis) on the one hand, and decreased insulin sensitivity on the other, may be viewed as conservative ‘thrifty’ traits that provide a selective advantage in the setting of intermittent famine. Decreased met-

abolic rate conserves calories, while insulin resistance conserves protein, the latter by directing substrate disposal in muscle away from glucose, the major nutrient of the central nervous system. Under these circumstances, the use of lipids by muscle makes more glucose available for the brain, thus making it less reliant on gluconeogenesis from muscle protein breakdown [17]. Although serving well in periods of famine, these ‘thrifty’ traits predispose to obesity and the metabolic syndrome in the presence of an abundant food supply.

Are there therapeutic implications that can be derived from a better understanding of the metabolic syndrome? Since insulin resistance is at the core, increasing insulin sensitivity is critical. Although drugs of the thiazolidinedione class antagonise insulin resistance and play a role in the treatment of type 2 diabetes, the mainstays of treating insulin resistance in the metabolic syndrome are diminished energy intake, exercise and weight loss. These so-called ‘lifestyle’ interventions directly increase muscle glucose uptake, increase insulin sensitivity, and diminish sympathetic activity, thereby addressing the fundamental physiological alterations that underlie this syndrome. If lipid abnormalities and hypertension remain in the face of these lifestyle changes, they should be treated aggressively with drugs to improve the lipid profile and reduce the blood pressure. Since comprehension is the handmaiden of conviction, elucidation of the fundamental mechanisms may help health care professionals to more effectively advise patients with the metabolic syndrome.

References

1. Grassi G, Dell’Oro R, Quarti-Trevano F et al (2005) Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. *Diabetologia* DOI 10.1007/s00125-005-1798-z
2. Hansen BC (1999) The metabolic syndrome X. *Ann NY Acad Sci* 892:1–24
3. Landsberg L (2004) The metabolic syndrome: diabetes, obesity and hypertension. In: Birkenhäger WH, Robertson JJS, Zanchetti A (eds) *Handbook of hypertension*, vol. 22. Elsevier, Amsterdam, pp 245–261
4. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L (1981) Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes* 30:219–225
5. Hausberg M, Mark AL, Hoffman RP, Sinkey CA, Anderson EA (1995) Dissociation of sympathoexcitatory and vasodilator actions of modestly elevated plasma insulin levels. *J Hypertens* 13:1015–1021
6. Troisi RJ, Weiss ST, Parker DR, Sparrow D, Young JB, Landsberg L (1991) Relation of obesity and diet to sympathetic nervous system activity. *Hypertension* 17:669–677
7. Grassi G, Dell’Oro R, Facchini A, Trevano FQ, Bolla GB, Mancia G (2004) Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. *J Hypertens* 22:2363–2369
8. Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI (1997) Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest* 100:270–278
9. Kazumi T, Kawaguchi A, Katoh J, Iwahashi M, Yoshino G (1999) Fasting insulin and leptin serum levels are associated with systolic blood pressure independent of percentage body fat and body mass index. *J Hypertens* 17:1451–1455

10. Giacchetta G, Faloia E, Sardu C et al (2000) Gene expression of angiotensinogen in adipose tissue of obese patients. *Int J Obes* 24 [Suppl. 2]:S142–S143
11. Ward KD, Sparrow D, Landsberg L, Young JB, Vokonas PS, Weiss ST (1994) The relationship of epinephrine excretion to serum lipid levels: the normative aging study. *Metabolism* 43:509–513
12. Young JB, Landsberg L (1977) Suppression of sympathetic nervous system during fasting. *Science* 196:1473–1475
13. Young JB, Landsberg L (1977) Stimulation of the sympathetic nervous system during sucrose feeding. *Nature* 269:615–617
14. Landsberg L (2001) Insulin-mediated sympathetic stimulation: role in the pathogenesis of obesity-related hypertension (or, how insulin affects blood pressure, and why). *J Hypertens* 19:523–528
15. Landsberg L, Young JB (1985) Insulin-mediated glucose metabolism in the relationship between dietary intake and sympathetic nervous system activity. *Int J Obes* 9:63–68
16. Landsberg L (1986) Diet, obesity and hypertension: a hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. *Q J Med* 236:1081–1090
17. Reaven GM (1999) Insulin resistance: a chicken that has come to roost. *Ann NY Acad Sci* 892:45–57