

# Metabolic syndrome and hypertension: what are the outstanding problems?

**Murray David Esler, MBBS, PhD, FAA, FRACP**

*Baker Heart Research Institute - Melbourne - AUSTRALIA*

*Recent studies in clinical and experimental obesity suggest that the hypertension enmeshed within the metabolic syndrome is neurogenic, ie, initiated and sustained by activation of the sympathetic nervous outflow to the kidneys. Whether the stimulus for this is hyperinsulinemia, leptin excess, or perhaps coexistent obstructive sleep apnea remains problematic. Weight reduction and an aerobic exercise program remain pivotal in normalizing obesity-related hypertension. If these fail, the ideal anti-hypertensive drug should target the underlying neural pathophysiology of the hypertension, but should not contribute to weight gain by inhibition of thermogenesis or worsen the existing insulin resistance. Centrally acting sympathetic nervous inhibitors of the imidazoline-receptor binding class appear to meet these prerequisites, though no definitive empirical evidence is yet available to establish them as the preferred drug class.*

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**Address for correspondence:**

Prof Murray Esler, Baker Heart Research Institute, Commercial Road, Prahran 3181, AUSTRALIA

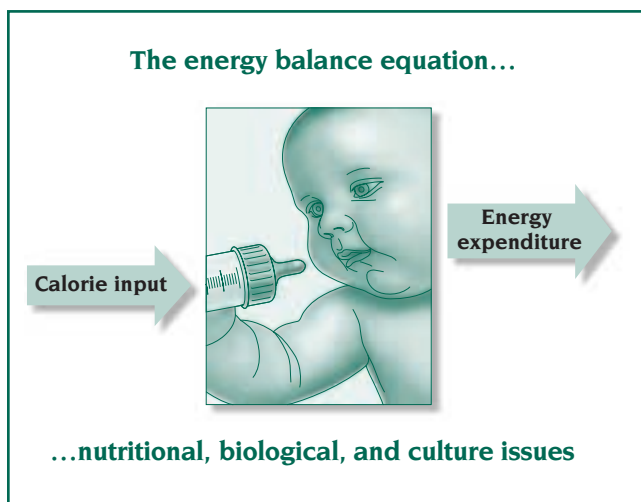
(e-mail: murray.esler@baker.edu.au)

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**A**s obesity prevalence soars in industrialized countries and progressively increases in the third world, with the appearance of altered patterns of nutrition and a reduction in work-related energy expenditure, obesity-related hypertension has become a truly global health issue. Although there is a validity to the central concept commonly proposed for the origins of obesity—a mismatch in the energy balance equation with an excess of dietary calorie intake over body energy expenditure (*Figure 1*)—this simple thermodynamic formulation leaves complex issues untouched.

*Dietary calorie intake* is modified by social, economic, and cultural issues. Further, the composition of the diet no doubt matters, as exemplified by recent evidence suggest-

ing that calorie-restricted diets identical in energy content, but differing in carbohydrate and fat content, differ also in propensity for weight loss (greater on the low carbohydrate diet). *Energy expenditure* is influenced by demographic change (such as third-world transition from a labor-intensive agricultural economy to an industrial base), by patterns of transportation (exemplified by the benefits of cycling as an anti-obesity factor in the Dutch), by the degree of adoption of household labor-saving devices, by changed recreational habits, particularly in childhood (computer games instead of physical games), and by genetic influences on metabolic rate.<sup>1</sup> The prevalence of childhood obesity is escalating, having whimsically, but not entirely unrealistically, been attributed to “potato chips and computer chips.”



**Figure 1.** Although there is validity to the central concept commonly proposed for the origins of obesity, a mismatch in the energy balance equation—with an excess of dietary calorie intake over body energy expenditure—this simple thermodynamic formulation leaves complex societal issues untouched.

**Metabolic syndrome and hypertension: what are the outstanding problems? - Esler**

Obesity and hypertension are intimately associated, and both very commonly coexist in individual patients with insulin resistance, hyperinsulinemia, and hyperlipidemia, this clustering of adverse health factors being designated as the metabolic syndrome.<sup>2</sup> The pathophysiological mechanisms by which hypertension is linked so strongly with obesity (in particular with central obesity) and with hyperinsulinemia have remained uncertain. Understanding these processes might provide a more rational basis for drug treatment of obesity-related hypertension. Attempts at reduction in body weight, although pivotal in the treatment of obesity-related hypertension, more often than not fail, so that antihypertensive drug therapy is needed. But what are the preferred drugs?

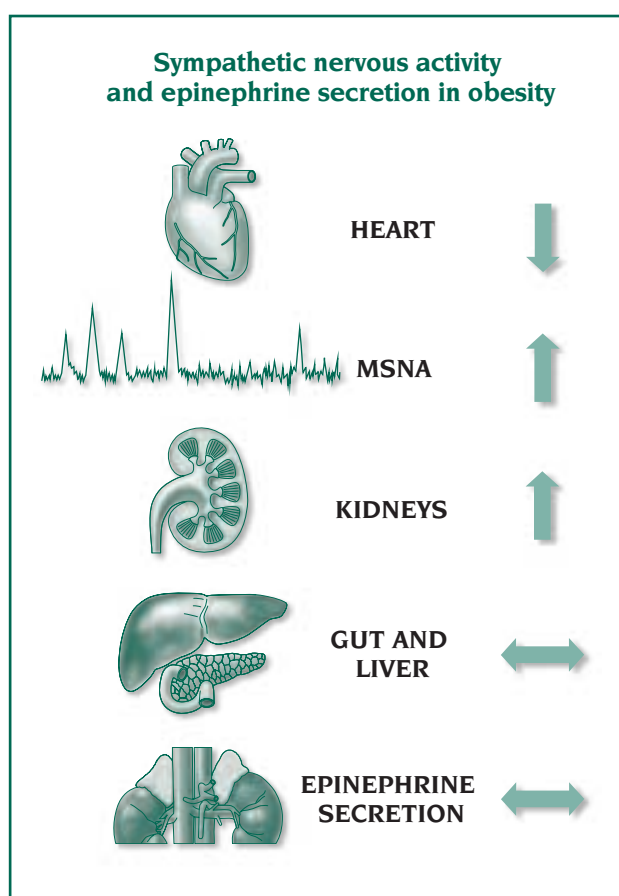
**SYMPATHETIC NERVOUS SYSTEM ACTIVITY IN OBESITY**

On this issue there have been two enduring hypotheses. The first hypothesis, from Bray et al,<sup>3</sup> is that sympathetic nervous system underactivity is present in human obesity, as it commonly is in animal models,<sup>1</sup> and through consequential failed stimulation of thermogenesis provides a metabolic basis for the obesity. The second hypothesis, attributable to Landsberg,<sup>4</sup> is that, in obesity, sympathetic nervous activation occurs with chronic overeating where it facilitates energy balance and weight stabilization, but at the cost of adverse consequences attributable to chronic stimulation of the sympathetic nervous system, in particular, elevation in blood pressure.

Methods involving measurements of rates of sympathetic nerve firing, clinical microneurography, and of organ-specific norepinephrine spillover to plasma provide the most

secure basis for studying regional sympathetic nervous function in patients with obesity and obesity-related hypertension (*Figure 2*).<sup>5,6</sup> Clinical microneurography can measure nerve firing rates in subcutaneous sympathetic nerves distributed to skin and skeletal muscle. Multifiber recordings of "bursts" of nerve activity synchronous with the heart beat and, more recently, single

nephrene spillover rate, a measure of overall sympathetic nervous activity, and the rate of secretion of epinephrine from the adrenal medulla are typically normal. In contrast, renal norepinephrine spillover on average is approximately twice normal, evidence of activation of the sympathetic outflow to the kidneys (*Figure 2*).<sup>7,8</sup> The sympathetic nerves passing to the skeletal muscle vas-



**Figure 2.** The sympathoadrenal medullary changes in human obesity show complex regional patterning. The sympathetic outflows to the kidneys and skeletal muscle vasculature are activated, that to the gut is unremarkable, epinephrine secretion also is normal, but there is inhibition of the sympathetic outflow to the heart. Activation of the renal sympathetic outflow is thought to importantly contribute to the initiation and maintenance of obesity-related hypertension. MSNA, multifiber muscle sympathetic nerve activity recorded in the outflow to the skeletal muscle vasculature.

fiber traces, are generated.<sup>5</sup> Sympathetic neurotransmitter release to plasma from an individual organ, regional norepinephrine "spillover," can be studied using the principle of isotope dilution, with intravenous infusion of tritiated norepinephrine and sampling from the venous drainage of the organ in question.<sup>6</sup>

In obese people with normal blood pressure, the whole-body norepi-

culature are also stimulated, evident in the sympathetic microneurogram as increased multiunit nerve firing.<sup>6</sup> These findings of sympathetic nervous system activation in human obesity unequivocally support the Landsberg position.<sup>4</sup> Perhaps surprisingly, the sympathetic outflow to the heart is subnormal, cardiac norepinephrine spillover being approximately 50% of that of healthy lean people (*Figure 2*).<sup>7,8</sup> The low sym-



pathetic activity in the heart in established obesity, however, would have only a trifling impact on total energy balance, outweighed by increases in sympathetic activity in the kidneys and skeletal muscle vasculature, since the heart is responsible for approximately 2% to 3% only of whole-body energy expenditure.

### **MECHANISMS OF SYMPATHETIC NERVOUS ACTIVATION IN OBESITY**

Since positive energy balance with overeating initiates thermogenesis by stimulation of the sympathetic nervous system, as suggested by Landsberg,<sup>4</sup> the activation of sympathetic activation seen in obesity could perhaps represent an adaptive response to overeating, helping to stabilize body weight by stimulating thermogenesis, but at the price of sympathetic nervous activation in the kidneys and vasculature secondarily elevating blood pressure. How might this sympathetic nervous activation be mediated? Hyperinsulinemia and hyperleptinemia accompanying obesity are candidates, but as yet the evidence for both is inconclusive.

#### **Sympathetic activation or hyperinsulinemia: which comes first?**

In the clustering of hypertension with overweight, hyperlipidemia, insulin resistance, and hyperinsulinemia in the "metabolic syndrome," whether the hyperinsulinemia is a cause or a consequence of the sympathetic nervous activation is still debated. With infusion of insulin in humans to acutely produce hyperinsulinemia, and clamping of blood glucose concentrations, activation of the sympathetic nervous outflow recorded in skeletal muscle is seen with microneurography.<sup>9</sup> This effect

of insulin is mediated through the central nervous system (CNS) either as a reflex response to vasodilatation or as a direct effect of insulin on forebrain areas regulating sympathetic outflow.<sup>10</sup> While fasting serum insulin concentrations are higher in the obese, we have previously reported that serum insulin and renal norepinephrine spillover values are not quantitatively related overall,<sup>7</sup> arguing against hyperinsulinemia per se causing the elevated renal sympathetic nervous activity. Further, euglycemic insulin infusion in humans (lean hypertensive patients were studied) does not appear to activate the renal sympathetic nerves.<sup>10</sup> It seems that the renal sympathetic nervous activation in obesity has its origins in altered CNS regulation of sympathetic nervous outflow, but involving mechanisms other than hyperinsulinemia.

A viewpoint gaining favor is that the hyperinsulinemia of the metabolic syndrome is a secondary phenomenon, resulting from the underlying hemodynamic abnormalities present.<sup>11</sup> Glucose utilization by skeletal muscle under the influence of insulin, which is the process largely determining measured insulin resistance, is dictated by muscle blood flow. Reduced skeletal muscle blood flow in hypertension resulting from neural vasoconstriction may possibly be the primary cause of the insulin resistance and the attendant hyperinsulinemia.<sup>11</sup>

#### **Leptin in obesity: important in rodents, but not in human obesity?**

It has been proposed that the sympathetic nervous activation of obesity might be driven by high plasma levels of leptin. Leptin, a 16-kDa protein derived principally from adipose tissue has been implicated in body weight homeostasis. In ro-

dent, leptin has been demonstrated to promote negative energy balance and weight loss, an effect attributed to both suppression of appetite and sympathetically mediated thermogenesis.<sup>12</sup> With intravenous infusion of leptin in rats, activation of the sympathetic outflows to the kidneys and hindlimb vasculature is seen,<sup>12</sup> without any increase in heart rate, suggesting that the cardiac sympathetic nerves are not stimulated. These effects have a close parallel in the pattern of sympathetic nervous change seen in human obesity,<sup>5,7,8</sup> suggesting that leptin stimulation of the sympathetic nervous system may be the underlying explanation.

Our own observations in human obesity, however, do not support this interpretation. We find plasma leptin concentrations in lean and obese normotensive men to be weakly related only to measures of whole-body and regional sympathetic activity.<sup>13</sup> Unlike in some rodent models of obesity, the biological role of leptin in human obesity therefore is uncertain. Paradoxically, we find release of leptin from the brain in men with obesity, not seen in lean men, accompanied by increased turnover of serotonin.<sup>14,15</sup> This is noteworthy in that it suggests a functional coupling in human obesity, perhaps as an adaptive response, albeit futile, of two brain systems known to cause satiety.

#### **Obstructive sleep apnea**

Hypertension is particularly common in obese people with episodic nocturnal airways obstruction. Apneic episodes at night are accompanied by intense sympathetic nervous activation, elegantly documented by Narkiewicz, Somers, and colleagues using microneurography.<sup>16</sup> With time, and by an unknown mechanism, this episodic nocturnal sympathetic stimulation seems to

evolve into ongoing, continuous sympathetic nervous activation. The claim has been made that heightened sympathetic activity in the obese is seen only in those with obstructive sleep apnea,<sup>16</sup> although this is disputed.

### **IS OBESITY-RELATED HYPERTENSION NEUROGENIC?**

Activation of the sympathetic nervous system, involving the sympathetic outflows to the kidneys, heart, and skeletal muscle vasculature, is a now very well documented pathophysiological finding in lean young and middle-aged patients with essential hypertension.<sup>5,6,8</sup> Their hypertension is conceived as being "neurogenic," initiated and sustained by the increased sympathetic nervous cardiovascular drive.

Obesity-related hypertension also seems to have an important neurogenic component,<sup>5,8</sup> being characterized by activation of the sympathetic outflows to the kidneys and skeletal muscle vasculature. A large number of studies, reviewed by DiBona,<sup>17</sup> have demonstrated the importance of the renal sympathetic nerves in the development of hypertension in various experimental models. The neurogenic hypothesis of human obesity-related hypertension, which emphasizes activation of the renal sympathetic outflow as a prime mover in the blood pressure elevation, is supported by evidence from obesity-induced hypertension in dogs, where sympathetic activation during overfeeding is accompanied by a marked retention of sodium despite increases in glomerular filtration rate (GFR) and renal plasma flow.<sup>18</sup>

There is, however, a problem. In patients with obesity-related hypertension there is a comparable, but

no greater, elevation of renal norepinephrine spillover to that present in the normotensive obese.<sup>8</sup> The higher renal sympathetic nervous activity in the obese thus may be important in the development of their hypertension, but it would seem to be a *necessary* rather than a *sufficient* cause. The search for predisposing genetic or other factors among overweight people determining who might become hypertensive so far has proven futile.

### **ARE THERE CONSEQUENCES OF SYMPATHETIC ACTIVATION THAT GO BEYOND BLOOD PRESSURE ELEVATION?**

Catecholamine toxicity to the myocardium, in the form of focal necroses and myocyte deterioration, can be demonstrated when high doses of these agents are administered in experimental animals. Similarly, elevated catecholamine secretion in patients with pheochromocytoma sometimes leads to cardiomyopathy. Given this background, the question has been put: while the sympathetic activation present in obesity-related hypertension no doubt contributes to the blood pressure elevation, are there adverse consequences which go beyond this? In patients with heart failure, certainly, the case for adverse effects of high sympathetic tone in the failing heart, and protection from them with  $\beta$ -adrenergic blockade, is proven.<sup>19</sup>

For obesity-related hypertension, as the sympathetic nervous activation spares the heart, the adverse effects of ongoing sympathetic activation no doubt are more circumscribed. It is only potentially noxious extracardiac effects of sympathetic activation that are of relevance, such as the undesirable metabolic consequences of neural vasoconstriction

in skeletal muscle impairing glucose delivery to muscle, causing insulin resistance and hyperinsulinemia,<sup>11</sup> and perhaps in liver, retarding postprandial clearing of lipids, contributing to hyperlipidemia.<sup>20</sup>

### **REVERSAL OF HYPERTENSION ON A LOW-CALORIE DIET: IS IT DUE SPECIFICALLY TO DIETARY ENERGY RESTRICTION OR TO WEIGHT LOSS?**

Blood pressure is often quickly lowered in our patients with obesity-related hypertension when placed on a calorie-reduced diet, even before there is any material loss in weight. The explanation probably lies in the effects of dietary energy intake on the sympathetic nervous system. In the mid-1970s, Landsberg and Young<sup>21</sup> made the totally unexpected discovery in rats that calorie restriction reduced sympathetic nervous system activity, while overfeeding caused sympathetic activation. These findings were counterintuitive ("doesn't everyone feel their sympathetic nervous system being switched on if they miss a meal or two?"). The early phase of blood pressure reduction on a low-calorie diet coincides with sympathetic nervous inhibition,<sup>22</sup> with subsequent further blood pressure fall as body weight drops.

### **HOW DOES AN EXERCISE PROGRAM LOWER BLOOD PRESSURE IN THE METABOLIC SYNDROME?**

It took many years of research to establish that regularly performed physical exercise produces long-term lowering of blood pressure, and to demonstrate that inhibition of the sympathetic nervous system is an important underlying mechanism of this, most clearly evident in the



sympathetic nerves of the kidneys.<sup>23</sup> The process by which regular exercise lowers sympathetic nervous activity remains uncertain, although stimulation of skeletal muscle mechanoreceptors in exercising muscle may possibly be involved. An exercise program has multifaceted benefit in hypertensive patients with the metabolic syndrome, improving insulin sensitivity and reducing blood pressure, in the long term this blood pressure reduction being a result of both weight loss and of sympathetic nervous system inhibition.

#### WHAT ANTIHYPERTENSIVES ARE BEST IN THE METABOLIC SYNDROME?

Might the findings on the neural pathophysiology of obesity related-hypertension have any implications for its rational treatment? Given that sympathetic activation in obese hypertensive patients seems to contribute both to the blood pressure elevation and perhaps to other adverse metabolic and cardiovascular effects, might it be appropriate to specifically recommend therapies inhibiting the sympathetic nervous system?

There are three principal points of clinical relevance to the choice of antihypertensive drugs for the hypertension of the metabolic syndrome.

#### Does the action of the antihypertensive drug reverse the neural pathophysiology?

Centrally acting sympathetic suppressants, imidazoline-receptor-binding agents such as rilmenidine and moxonidine, inhibit sympathetic outflow, including in the renal sympathetic nerves,<sup>24</sup> and might be preferred on theoretical grounds.

#### Would an antiadrenergic antihypertensive promote weight gain?

A negative thermogenic effect of  $\beta$ -adrenergic blockers has been demonstrated experimentally, and weight gain has been observed clinically with  $\beta$ -blockers. Although perhaps expected, weight gain has not been documented with the suppression of sympathetic outflow produced by imidazoline-receptor-binding agents.

#### Which antihypertensives would unfavourably modify insulin resistance?

A diabetogenic effect has been unequivocally demonstrated for both diuretics and  $\beta$ -adrenergic blockers. The effect of imidazoline-receptor-binding agents, ACE inhibitors, angiotensin receptor blockers, and dihydropyridine calcium channel blockers on insulin resistance is neutral, or marginally positive, tending to increase insulin sensitivity.

A rational case could thus be made for perhaps preferring imidazoline-receptor-binding agents, but avoiding diuretics and  $\beta$ -adrenergic blockers in hypertensive patients with the metabolic syndrome. Large-scale trials would be needed to formally test this proposition.

"Tailoring" of antihypertensive therapy to pathophysiology, however, at present cannot be the primary therapeutic principle, in part because knowledge of both hypertension pathophysiology and the precise mechanisms of drug action remains imperfect. The same point can be made for pharmacogenomic profiling of hypertensive patients, which remains in its infancy. Overriding clinical considerations commonly apply in the choice of initial therapy, such as the presence of coex-

isting illnesses carrying particular pharmaceutical recommendations. Whether obesity-related hypertension has a specific sensitivity to antiadrenergic drugs, in fact, has not been adequately investigated. Despite these caveats, the two non-pharmacological measures most commonly applied in the treatment of obesity-related hypertension—dietary calorie restriction and an exercise program—are well known to suppress sympathetic nervous system activity.<sup>22,24</sup>

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