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Should the sympathetic nervous system be a target to improve cardiometabolic risk in obesity?

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Lambert EA, Straznicky NE, Dixon JB, Lambert GW. Should the sympathetic nervous system be a target to improve cardiometabolic risk in obesity? Am J Physiol Heart Circ Physiol 309: H244–H258, 2015. First published May 15, 2015; doi:10.1152/ajpheart.00096.2015.—The sympathetic nervous system (SNS) plays a key role in both cardiovascular and metabolic regulation; hence, disturbances in SNS regulation are likely to impact on both cardiovascular and metabolic health. With excess adiposity, in particular when visceral fat accumulation is present, sympathetic activation commonly occurs. Experimental investigations have shown that adipose tissue releases a large number of adipokines, cytokines, and bioactive mediators capable of stimulating the SNS. Activation of the SNS and its interaction with adipose tissue may lead to the development of hypertension and end-organ damage including vascular, cardiac, and renal impairment and in addition lead to metabolic abnormalities, especially insulin resistance. Lifestyle changes such as weight loss and exercise programs considerably improve the cardiovascular and metabolic profile of subjects with obesity and decrease their cardiovascular risk, but unfortunately weight loss is often difficult to achieve and sustain. Pharmacological and device-based approaches to directly or indirectly target the activation of the SNS may offer some benefit in reducing the cardiometabolic consequences of obesity. Preliminary evidence is encouraging, but more trials are needed to investigate whether sympathetic inhibition could be used in obesity to reverse or prevent cardiometabolic disease development. The purpose of this review article is to highlight the current knowledge of the role that SNS plays in obesity and its associated metabolic disorders and to review the potential benefits of sympathoinhibition on metabolic and cardiovascular functions.

obesity; sympathetic nervous system

THE PREVALENCE AND DEGREE of obesity has markedly escalated over recent decades and has reached epidemic proportions worldwide. It is well recognized that obesity is associated with reduced quality of life and increased risk of premature death and predisposes individuals to the development of a number of chronic illnesses including cardiovascular disease, type 2 diabetes, dyslipidemia, insulin resistance, hyperglycemia, hypertension, degenerative joint diseases, obstructive sleep apnea (OSA), gastroesophageal reflux disease, nonalcoholic fatty liver, and various forms of cancer (79). Obesity has also been linked to increased stress, depressive illness, cognitive impairment, and increased risk for dementia later in life, independent of other comorbidities (132a). Given the association between obesity and significant chronic illness, obesity research remains a priority. Previous studies investigating the morbidity of obesity and obesity-related conditions indicated that the extent of body fat accumulation does not necessarily correlate with risk, but rather the distribution of fat seems to be the more crucial factor, with visceral fat accumulation relating directly to cardiovascular disease development (109). This may be explained by the fact that visceral obesity, which is commonly associated with metabolic abnormalities, may induce more dysregulation of adipose tissue-secreting factors compared with subcutaneous fat (109). While the level and extent of obesity and obesity-related illness are undoubtedly influenced by diet, exercise, sedentary behavior, and genetics, the physiology of obesity extends beyond these factors and involves the integration of an array of central nervous and peripheral sig-
nals. Of particular importance is the role played by the sympathetic nervous system (SNS). Indeed, a number of experimental and clinical studies have documented that SNS activation is a hallmark of obesity and likely contributes to the elevated cardiometabolic risk associated with the condition. Sympathetic nervous activation may precede the development of weight gain or may occur as a consequence of excess adiposity and, importantly, play a role in the development of hypertension, diabetes mellitus, hyperlipidemia, atherosclerosis, and end-organ damage, not only in obese humans but also in animal models of diet-induced obesity (59). Given evidence documenting the detrimental cardiovascular, renal, and metabolic effects of sustained SNS activation, reducing sympathoexcitation may offer clinical benefit in the treatment of obesity. In this review we highlight the current knowledge of sympathetic nervous dysfunction in obesity and its cardiovascular and metabolic sequelae and examine how available strategies to treat either excess weight or metabolic disturbances alter sympathetic tone and potentially improve the cardiovascular and metabolic comorbidities related to obesity.

Sympathetic Activity in the Obese State

Given the role of the SNS in energy balance, the concept of elevated sympathetic drive in the context of obesity was slow to emerge. Respiratory chamber studies showed that muscle sympathetic nerve activity (MSNA) was positively and independently associated with 24-h energy expenditure and sleeping and resting metabolic rates, as well as being inversely related to the 24-h respiratory quotient in Caucasian subjects (149, 151). Therefore, one could predict that diminished basal SNS activity, in not providing the normal calorie-consuming thermogenic response to overeating, may cause positive energy balance and possibly contribute to the development of obesity. The inconsistency concerning the state of SNS function in obesity was emphasized in a review of the literature over two decades ago. Young and Macdonald (183) found that there were numerous studies proposing that SNS in subjects with obesity was either low, normal, or elevated. The heterogeneity of the results most likely occurred because of inadequacy of the methods used (in particular, venous or urinary norepinephrine concentrations) and because SNS activity is typically regionalized, where the efferent outflow throughout the body is not uniform. By using more robust methods such as whole body and regional plasma norepinephrine kinetics, Vaz et al. (171) demonstrated that sympathetic nerve activity in humans with obesity varied between different vascular beds, with a substantial elevation observed in the kidneys and, perhaps surprisingly, a lower activity in the heart. Elevated MSNA, which can be reliably recorded by microneurography, was first demonstrated by Grassi and colleagues (48) and was subsequently confirmed in many other studies (4, 70, 84, 85). One longitudinal study has shown that even a modest weight gain of 5 kg was associated with increased MSNA in young men who were not obese (45). Whether augmented sympathetic activity to the skeletal muscle bed translates into elevated sympathetic vasoconstrictor activity is at present unclear because complete α-adrenergic receptor blockade by phentolamine was found to cause equivalent vasodilatation in subjects with obesity and lean normotension (1). However, animal studies recently documented that sympathetic nerve-mediated vasoconstriction is augmented in rat mesenteric resistance arteries during diet-induced obesity. This hyperactivity results from an upregulation of purinergic mechanisms in addition to adrenergic signaling mechanisms through an increase in the density of the sympathetic perivascular nerve plexus and release of ATP. A decrease in the sensitivity to sensory vasodilatory neurotransmitters may also complicate these effects (57). It is not clear yet whether the increase in the SNS activity is confined to the kidney and skeletal muscle or whether it also includes increased SNS activity to metabolically active tissues, such as brown and white adipose tissue and the liver. Additionally, it is recognized that a marked interindividual variability in MSNA exists in humans and resting MSNA may not always reflect sympathetic activity during day-to-day activities or be linked specifically to elevated blood pressure (74).

Is Sympathetic Activity a Cause or a Consequence of Obesity?

Obesity as a cause of sympathetic activation. In 1986, before the demonstration of increased MSNA and norepinephrine spillover in obesity, Landsberg (91) proposed that sympathetic nervous activation could represent an insulin-mediated adaptative response to overeating, promoting thermogenesis and acting as a buffer against weight gain. Reaven (131) posited that insulin resistance was the key abnormality leading to hyperinsulinemia, sympathetic activation, and hypertension. The observation that a modest weight gain of 5 kg was associated with increased MSNA in healthy young men who were not obese (45) suggested that sympathetic activation occurs as a consequence of excess weight gain. Accordingly, a recent preclinical study demonstrated that in rabbits fed a high-fat diet, sympathetic activation to the kidneys occurred as early as 1 wk after the commencement of feeding (7). In addition to elevated baseline sympathetic tone, individuals with obesity present reduced cardiac and sympathetic baroreceptor reflexes (50), contributing to increased blood pressure variability and reduced variability of heart rate, which are markers of end-organ damage and have been shown to be associated with increased cardiovascular morbidity (101). Animal studies using obese Zucker rats (141) have shown that the deficits in baroreflex control of SNS develop in adulthood long after the onset of obesity at a stage when other deficits in cardiovascular regulation are present. Impaired baroreflex function in obese Zucker rats involve alterations in the region of the brain stem (the nucleus tractus solitarius), developing during the progression of obesity that may lead to deficits in short- and long-term control of blood pressure (56).

Sympathetic activity as a cause of obesity. Prospective cohort studies have provided insight into the temporal sequence of pathogenic events associated with obesity and indicated that SNS activation may be a prime mover and antecedent in the development of obesity. In fact, increased plasma norepinephrine concentration and a hyperkinetic circulation in young adulthood have been shown to predict future weight gain and the development of insulin resistance (75, 104). Chronic sympathetic activity may downregulate adrenergic sensitivity and blunt sympathetic-mediated thermogenesis. While this scenario is possible, it remains controversial (76). Alternatively, genetic polymorphisms that influence adrenergic sensitivity may lead to upregulation of sympathetic
outflow in young adulthood (103). Offspring studies enabled the effects of genetic predisposition to be studied before the development of obesity and obesity-related disease development and indicated that parental hyperdynamic circulation is positively linked to body mass index (BMI) and measures of adiposity in offspring (123). Furthermore, elevated MSNA has been demonstrated in insulin-sensitive offspring of parents with type 2 diabetes compared with matched controls whose parents did not have diabetes (71). Moreover, those insulin-resistant offspring may have elevated sympathetic responsiveness to exogenous and endogenous hyperinsulinemia, as quantified by power spectral analysis of heart rate variability (43). Collectively, these data suggest that autonomic dysfunction may be one of the early pathophysiological changes that precedes the development of insulin-resistance and obesity.

Abnormal Sympathetic Response to Food Ingestion in Obesity

Postprandial activation of the peripheral nervous system may play a role in the maintenance of energy balance. The presumed physiological role of postprandial sympathetic activation is to induce peripheral vasoconstriction for maintaining adequate blood pressure in response to splanchnic vasodilation. Additionally, the postprandial sympathetic response induces a facultative thermogenesis that accounts for around 3 to 4%, corresponding to 50–100 calories, of daily energy expenditure. Hence, postprandial sympathetic activation potentially plays a modulating role in body weight homeostasis, but this depends on the size and composition of the meal, with carbohydrates having the clearest effect (169). The primary signal leading to increased SNS activity and enhanced thermic effect of food is believed to be hyperinsulinemia, as increased plasma insulin levels in the absence of hyperglycemia can also raise plasma norepinephrine concentrations, whereas fructose ingestion, which induces carbohydrate oxidation without causing hyperinsulinemia, does not increase SNS activity (165). Following glucose ingestion, we have demonstrated that obese individuals who are insulin resistant have a blunted sympathetic nervous system response as they displayed a reduced or minimal rise in MSNA compared with insulin-sensitive individuals (161). Similar findings were present in obese individuals with type 2 diabetes, as the rise in norepinephrine spillover following glucose ingestion was blunted compared with that in patients with impaired glucose tolerance (157). The inability of the SNS to respond appropriately to glucose may represent a reduced delivery of insulin in the central nervous system. This blunted response may reduce the facultative thermogenesis and therefore contribute to weight gain (161). However, this remains unclear because postprandial sympathetic nervous activation did not seem to relate to either insulin secretion or thermogenesis (172).

Impaired Sympathoinhibitory Mechanisms in Obesity

In parallel to sympathoexcitatory mechanisms in obesity, there is some emerging evidence derived from animal studies indicating that attenuated sympathoinhibitory responses to circulating gut hormones, different from those mediated by the baroreflex, may also be important. Apart from adipose tissue, leptin is also stored and released from the gastric epithelial cells of the stomach. Gastric leptin may subserve a distinct functional role to that of adipose leptin and therefore regulate short-term mechanisms including satiety. Studies from Sartor and Verberne (134) demonstrated that gastric leptin triggers the release of cholecystokinin, a gastrointestinal peptide hormone that is released from enterocyte cells lining the gastrointestinal mucosa in response to the fat and protein components of a meal. In turn, cholecystokinin induces a vagally mediated effect on sympathetic vasomotor function, resulting in a modest hypotensive response that is accompanied by splanchnic and renal sympathoinhibition and lumbar sympathoexitation, effects that are dependent on an intact vagus nerve (134). It was suggested that diets high in fat may alter the release of cholecystokinin and therefore present a blunted splanchnic sympathoinhibitory response to cholecystokinin. In addition, while gastric leptin induced sympathoexcitatory responses in control animals, these responses were sympathoinhibitory in those on a high-fat diet. It is believed that these changes seen in obesity may disrupt sympathoexcitatory mechanisms, as these hormones may no longer be as efficacious in inducing the sympathoexcitatory effects required to maintain cardiovascular homeostasis; diminished vasodilator effects in the renal and splanchnic beds may lead to increased vascular resistance, which could contribute to the development of hypertension (135). While these sympathoexcitatory mechanisms have been characterized in animal models of obesity, there is little evidence for such mechanisms being operative in human obesity.

Adipose Tissue as a Key Factor for Sympathetic Activity

Obesity is characterized by excessive accumulation of fat, a highly dynamic endocrine and paracrine organ that releases many cytokines and bioactive mediators, including, among others, leptin, adiponectin, interleukin-6, and tumor necrosis factor-α, which are capable of influencing body weight homeostasis as well as insulin resistance, diabetes, lipid levels, blood pressure, coagulation, fibrinolysis, inflammation, and atherosclerosis (37) and may influence SNS activity (63). Adipokines that have been demonstrated to be involved in the deleterious consequences of obesity, and the metabolic syndrome include leptin, nonesterified free fatty acids (NEFAs) (Fig. 1), adipocytokine angiotensinogen, resistin, and (reduced) adiponectin. While an unbalanced interplay between a variety of these adipokines may lead to impaired insulin signaling, inflamma-
tion and/or altered sympathetic nervous regulation (148), of particular interest, are leptin and NEFAs.

Leptin is principally produced in adipocytes, and its concentration in plasma is in proportion to the fat mass. Leptin produced from adipocytes acts in a negative feedback loop to suppress the appetite, thereby preventing weight gain as pos-tulated in the lipostatic theory of body-weight set point (42). Leptin acts on its receptor in the arcuate nucleus of the hypothalamus to inhibit food intake and increase energy expenditure through stimulation of SNS activity. Leptin-triggered increases in regional sympathetic traffic promote thermogenesis in brown adipose tissue, lipolysis in white adipose tissue, and an increase in metabolic activities in liver and skeletal muscle, resulting in an increase in energy expenditure (117). As most humans with obesity have elevated plasma leptin concentrations but continue to ingest excess calories, this led to the concept that obesity causes resistance to the anorexogenic effects of leptin. However, it appears that obesity can induce “selective” leptin resistance, with the renal SNS responses to leptin being maintained, while the appetite suppressant effects of leptin are attenuated as indicated in experimental models of obesity (129). The mechanisms underlying the selectivity in leptin resistance are not well understood but could relate to the involvement of different neuronal populations in mediating the metabolic and cardiovascular effects of leptin. Alternatively, this could be due to the divergent intracellular signaling pathways engaged by the leptin receptor differentially regulating the various physiological processes (61). Recently, in normal-fed mice, the circumventricular subfornical organ was identified to play an important role in leptin-induced renal sympathoexcitation; however, this region does not seem to play a role in body weight, food intake, or brown adipose tissue sympathetic thermogenic effects of leptin (182). Experimental studies have identified leptin’s action in the central nervous system as the main driver of increased sympathetic outflow and development of obesity-related hypertension (61, 144). This concept is supported by the high-fat feeding studies by Muntzel et al. (118) and Armitage et al. (7) where leptin levels increased in parallel with sympathetic nerve activity and obesity and the study from Prior et al. (128) in which intracerebroventricular administration of leptin in rabbits increased mean arterial pressure and renal sympathetic nerve activity, with this relationship being further augmented by obesity. The relationship between leptin and sympathetic tone and blood pressure has not been well characterized in humans. Some studies (35, 115), but not all (3, 85), have demonstrated a relationship between leptin and sympathetic tone, as assessed from measures of MSNA or renal norepinephrine spillover. Recently, leptin was acutely infused into healthy human subjects (99) and MSNA was found to increase. However, this acute sympathoexcitation was not accompanied by any change in blood pressure. This is different from the response in rodents where a chronic infusion of leptin elicits hypertension (143). Whereas leptin’s role in obesity-related hypertension in animals has been well characterized, its role in obesity-related hypertension in humans remains to be clarified.

Based on insights from animal studies (53), higher NEFA release was proposed to play a role in the sympathetic nervous activation associated with obesity; however, clinical evidence is conflicting. One study indicated that an acute rise in plasma NEFA levels did not stimulate renal sympathetic activity (54), whereas another showed that acute elevation of plasma NEFA levels induced by lipid infusion led to a rise in MSNA, blood pressure, and heart rate (41). The increase in MSNA was associated with a rise in insulin but not leptin concentration, suggesting that NEFAs’ action on blood pressure and sympathetic tone are independent of leptin. Nevertheless, the role of NEFA in obesity, in particular in causing insulin resistance, was recently reviewed, and this notion is now challenged (78).

Factors Modulating Sympathetic Tone in the Obese State

While there exists a large body of evidence indicating that sympathetic nervous activity is evident in obesity, it is important to recognize that many factors may be involved in the genesis of obesity-related sympathetic activation (see Fig. 1), as previously reviewed (85, 90, 153).

Adiposity. Fat distribution has been known for some time to play an important role in modulating SNS activity, as elevated MSNA is prominent particularly in individuals with increased abdominal visceral fat (4) but not in those with high subcutaneous fat (3). Over recent years it has become clear that the level of sympathetic activation in obesity may be further augmented by physical, clinical, metabolic, or psychological factors. Recently, Brooks et al. (20) highlighted data suggesting that the sympathoexcitatory and hypertensive consequences of obesity that have been well established in men may be muted in women. This can be attributed to sex differences in the distribution of adipose tissue, greater peripheral insulin sensitivity in women compared with men, and greater sympathetically mediated vasoconstriction in men. This is consistent with our earlier data where we showed that in women, MSNA was predominantly linked to the level of blood pressure but not to BMI, whereas in men, BMI constituted a major determinant for the level of MSNA independent of blood pressure and age (85).

Obstructive sleep apnea. OSA is commonly associated with obesity, and recent data confirmed that MSNA is markedly elevated in individuals with the condition, both when it is present in individuals who are lean or associated with subjects with obesity (47). However, the precise mechanism whereby OSA leads to persistent sympathetic nervous activation remains unclear. The SNS activation associated with OSA may occur as a result of chronic peripheral chemoreceptor stimulation induced by the frequent hypopneic-apneic episodes (150). Interestingly, it was reported that the apnea-hypopnea index improved in 8 of 10 patients 6 mo after renal denervation for the treatment of uncontrolled hypertension, thereby suggesting a link between OSA and renal sympathetic activation (178).

Metabolic syndrome components. Obese individuals with the metabolic syndrome have been shown to display higher MSNA compared with those individuals free of metabolic abnormalities, with the additional presence of hypertension further intensifying this hyperactivity (70). More recently, individual metabolic dysregulation such as insulin resistance (161), impaired insulin clearance (156), early stage diabetes (157), and mild dyslipidemia (86) has been shown to independently contribute to activated sympathetic nervous tone.

Stress. In agreement with a link between stress, obesity, and the SNS, many studies have noted that participants with obesity present with significantly higher levels of anxiety than participants who are lean (44). In addition, Skilton et al. (147)
found that the prevalence of depression was tightly linked with the number of metabolic syndrome components (147). We noticed that the underlying degree of anxiety reported by individuals with obesity was higher than in those who were lean, and those with higher anxiety also had increased SNS activity (87). Analysis of single-unit MSNA indicated that in hypertensive subjects with obesity, the sympathetic nerve-firing pattern was significantly associated with anxiety state and trait and the affective symptoms of depression, suggesting that chronic mental stress modulates the pattern of firing of sympathetic nerves (83).

SNS in Obesity and End-Organ Damage

Hypertension. It is well established that obesity is one of the major determinants in the development of hypertension in the general population (77). Epidemiological studies have clearly demonstrated that being overweight or obese predicts the future development of hypertension, and the relationship between BMI and blood pressure appears to be linear in different populations (58). According to a 2011 National Health Service survey in England, high blood pressure was recorded in 48% of men and 46% of women in the obese group, compared with around 30% of those in the overweight and 15% of those in the normal weight category (63a). Obesity-related hypertension is a multifactorial and polygenic trait (2). The mechanisms contributing to the development of higher blood pressure in humans with obesity include many factors such as hyperinsulinemia, activation of the renin-angiotensin-aldosterone system, abnormal levels of certain adipokines such as leptin, and an altered spectrum of cytokines acting at the vascular endothelial level (59). Sympathetic nervous stimulation is certainly a key factor in the development of hypertension. Earlier studies have shown that neurogenic abnormalities during various stress tests can be detected by recording MSNA in adolescents with borderline hypertension (114), and MSNA is already elevated in adults with borderline hypertension (108) and in those with mild essential hypertension (40). Nevertheless, one study found that resting MSNA was not important in the early developmental phase of essential hypertension (140), and our data indicated that differences in MSNA between patients with hypertension and normotension were more prominent in women than men (85). When hypertension develops as a consequence of obesity, data clearly indicate that SNS activation is a key determinant. It was demonstrated that when weight gain develops in young men, increased MSNA occurs early, together with increased blood pressure (45). Recently, it was shown that sympathetic activation to the kidneys occurs as early as 1 wk after exposure to a high-fat diet in rabbits (7), and this early sympathoexcitation appears integral to the development of obesity-related hypertension. To investigate the precise mechanisms whereby the SNS mediates obesity-induced hypertension, the effects of global and renal-specific suppression of sympathetic activity (prolonged baroreflex activation vs. bilateral renal denervation) were compared in dogs with a 50% increase in body weight after 4 wk of feeding a high-fat diet (98). The antihypertensive effects of global reduction in sympathetic activity by prolonged baroreflex activation was attributed to suppression of renal sympathetic nervous activity, clearly demonstrating that the renal nerves play a critical role in maintaining obesity-related hypertension. Given that renal denervation did not reduce the high-circulating levels of norepinephrine associated with weight gain, the authors suggested that sensory afferent signals from the kidneys do not importantly contribute to chronic sympathetic overactivity in obesity hypertension.

Recent experimental studies support a strong link between circulating leptin, secreted primarily from adipocytes, and the initiation and maintenance of obesity-related hypertension (130). However, a recent study (7) also suggested that increased plasma leptin and insulin may contribute to the initiation of hypertension but are not required for maintenance of mean arterial pressure. Leptin is considered a critical signal in activating the renal sympathetic nerves in obese animal models by activating the brain renin-angiotensin system, hypothalamic phosphatidylinositol 3-kinase, and melanocortin receptors (60). Recently, it was shown that intracerebroventricular injection of a leptin antagonist decreased the elevated levels of renal sympathetic nervous activity in conscious obese hypertensive rabbits, thereby providing direct evidence of a causal relationship, with central leptin signaling accounting for increased renal sympathetic outflow (94). Activation of the brain pro-opiomelanocortin neurones with subsequent stimulation of melanocortin-4 receptors (MC4Rs) has recently been documented to be a key factor playing a crucial role in the increased SNS activity and elevated blood pressure (30). The link between melanocortin signaling in obesity and hypertension has been studied in humans with MC4R mutations. A recent investigation provided evidence for a role of neuronal melanocortins in the modulation of blood pressure in humans (51). Blood pressure, heart rate, urinary catecholamines, and heart rate variability were examined in human subjects who were overweight and obese with loss-of-function mutations in MC4Rs. Results indicated that the prevalence of hypertension in the subjects with MC4R deficiency was approximately half that compared with controls, and blood pressure was lower in humans with MC4R deficiency (51).

Cardiac function. Cardiac hypertrophy. Many studies have demonstrated the impact of obesity on cardiac structure and function. Studies using radionuclide angiography indicated the presence of subclinical impairment of left ventricular systolic and diastolic function at rest and during exercise in subjects with asymptomatic, severe obesity but otherwise healthy (39). Assessment by tissue Doppler, in addition, showed that increasing BMI was associated with increasing severity of left ventricular dysfunction in subjects who were overweight and obese and in whom there was no evidence of overt heart disease (179). While in patients with essential hypertension, cardiac sympathetic nervous activation is recognized to exert detrimental effects on cardiac structure and function (152), its role in the development of ventricular dysfunction and hypertrophy in individuals who are obese is unclear given that cardiac sympathetic nervous activation may not necessarily be evident in individuals with obesity (171). In a cohort of young individuals ranging from lean to obese, a direct relationship, independent of BMI and sex, was found between MSNA and left ventricular mass index, supporting a link between the level of cardiac sympathetic drive and the development of early cardiac remodeling (84). A link between sympathetic tone and cardiac dysfunction was previously shown in subjects with hypertension using measures of cardiac norepinephrine spillover (139) and MSNA (22). The best evidence for a role of...
sympathetic activation in left ventricular hypertrophy in individuals who are overweight comes from a recent study indicating that the magnitude of left ventricular hypertrophy regression achieved by inhibiting the renin-angiotensin system and SNS neuroendocrine pathways was greater than that produced by comparable blood pressure reduction using bendroflumethiazide and amlodipine (21). Furthermore, the reduction in left ventricular mass following renal denervation in patients with hypertension who are overweight resistant also supports the concept that sympathetic nervous activation may confer detrimental effects on cardiac structure and function in individuals with obesity (17).

TACHYCARDIA AND CARDIAC ARHYTHMIAS. Clinical studies have identified obesity as an important risk factor for the development of cardiac arrhythmias, with a positive correlation between BMI and an increased risk of atrial and ventricular arrhythmias having been reported (126). This observation may, at least in part, underlie the increased cardiac morbidity and mortality in subjects who are obese. The mechanisms underlying proarhythrogenic effects of obesity have received little attention. Despite the recognized role of increased activation of the SNS in mediating obesity hypertension, studies in dogs and humans using adrenergic and muscarinic blockers showed that the obesity-induced tachycardia was primarily attributable to inhibition of the parasympathetic nervous system (170). These findings of decreased basal parasympathetic tone are consistent with observations of normal cardiac norepinephrine spillover in patients with obesity-related hypertension, despite impaired baroreflex control and increases in sympathetic activity to the kidneys and skeletal muscular vasculature (171). Recently, it was found that the consumption of a high-fat diet in rats, even in the absence of overt obesity, stimulates sympathetic outflow because the glomerular filtration rate and renal blood flow, and glomerular filtration rate and activity of the renin-angiotensin-aldosterone system. A common occurrence in obesity is glomerular hyperfiltration, most likely reflecting a compensatory response to achieve sodium balance (122). In human subjects with obesity, impaired pressure natriuresis is initially due to neurally mediated sodium resorption because the glomerular filtration rate and renal blood flow are increased. In a cohort of young individuals who were lean and overweight, we reported that creatinine clearance was higher in subjects who were overweight or obese compared with their counterparts who were lean, and increased creatinine clearance was directly correlated with increased MSNA (84). Increases in glomerular filtration rate early in the pathogenesis of obesity-related hypertension provide further evidence that neurally mediated increases in tubular sodium resorption play a causal role in the initiation of obesity-related hypertension. The glomerular hyperfiltration was shown to lead to increased postglomerular oncotic pressure and enhanced proximal tubular sodium resorption, suggesting that it may promote the development of hypertension in individuals who are obese (24).

**Interventions to Treat Obesity and Their Role in Modulating Sympathetic Tone**

Diet and exercise. The mainstay of obesity treatment remains lifestyle modification aimed at reducing calorie intake and increasing physical activity (95). Nevertheless, prolonged lifestyle modification to overcome obesity has often proved disappointing as many patients with obesity do not achieve or maintain sufficient weight loss with diet and exercise alone (33).

A number of studies have demonstrated the importance of calorie-restricted weight loss in improving sympathetic tone in normosensitive individuals with obesity (49) or in those with the
metabolic syndrome (159) (Table 1). The reduction in sympathetic activity in response to weight loss may be due to improved insulin sensitivity, a restoration of the baroreflex control of the cardiovascular system, or subjects being in negative energy balance at the time of retesting. One study investigating the effects of diet and exercise on blood pressure in Japanese individuals with hypertension who are overweight demonstrated a substantial decrease in weight following an exercise program, and this was associated with a significant reduction in plasma norepinephrine concentrations, similar to that observed in the group on calorie restriction (106). Whether exercise would reduce sympathetic tone in the absence of weight reduction has not been reported in individuals who are obese. Considering the large reduction in sympathetic tone following a moderate exercise program in patients with a history of heart failure who are of normal weight (6), it seems likely that a similar response would be observed in individuals with obesity as moderate exercise, which had minimal effect on weight and was shown to improve blood pressure and plasma glucose in middle-aged women who were overweight (46). The comparison of the effect of adding an exercise program to a calorie-restricted diet on sympathetic nervous activity was investigated in two previous studies. Adding a moderate-intensity, aerobic exercise training to a weight-loss program did not lead to additional benefits on resting sympathetic nervous activity as assessed from measures of MSNA (160, 166) and whole body norepinephrine spillover (160). Metabolic and blood pressure parameters significantly improved similarly between the two study groups. This seems to indicate that weight loss, independent of exercise, is the main determinant of sympathetic inhibition. This is supported by the results of longitudinal study of Masuo and colleagues (106) who observed that calorie restriction results in a reduction in plasma norepinephrine followed by improvement of insulin sensitivity, whereas exercise was associated with an initial improvement in insulin sensitivity with subsequent sympa-

Table 1. Studies investigating the effects of weight loss interventions in individuals with obesity in whom sympathetic tone was assessed

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Weight Loss Achieved</th>
<th>Reference</th>
<th>Patients</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>−14.8 kg (13%)</td>
<td>49</td>
<td>20 subjects, obese normotensive</td>
<td>↓ MSNA, ↓ plasma norepinephrine, ↓ BP, ↑ IS, ↑ sensitivity of the baroreceptor heart rate.</td>
</tr>
<tr>
<td>D + E</td>
<td>−9.3 kg (10%)</td>
<td>154</td>
<td>18 subjects, obese with metabolic syndrome</td>
<td>↓ MSNA at the end of active weight loss but rebounded following weight maintenance. Total body norepinephrine spillover reduced from baseline, ↓ BP, improvement in all metabolic syndrome components. Weight loss was associated with a reduction in albuminuria and an improvement in estimated glomerular filtration rate, which was augmented by exercise counterintervention.</td>
</tr>
<tr>
<td>D</td>
<td>−6.3 kg (7%)</td>
<td>159</td>
<td>23 subjects, obese with metabolic syndrome</td>
<td>↓ Plasma norepinephrine, ↓ BP, ↑ creatinine clearance.</td>
</tr>
<tr>
<td>D + E</td>
<td>−12.6 kg (14.4%)</td>
<td>105</td>
<td>154 Japanese men, overweight or obese</td>
<td>↓ MSNA, ↑ IS in both groups, but BP did not change. D + E increased forearm vascular conductance at rest and during exercise.</td>
</tr>
<tr>
<td>D + E</td>
<td>D: −8.9 kg (10%)</td>
<td>168</td>
<td>49 women, normotensive obese</td>
<td>↓ Plasma norepinephrine, ↓ BP, ↑ IS from both D alone and E alone and D + E.</td>
</tr>
<tr>
<td>D + E</td>
<td>D: −16.2 kg (16.5%)</td>
<td>106</td>
<td>90 subjects, overweight or obese with grade I hypertension</td>
<td>↓ Plasma norepinephrine, ↓ BP, ↑ IS from both D alone and E alone and D + E.</td>
</tr>
<tr>
<td>D + E</td>
<td>D: −8 kg (9%)</td>
<td>166</td>
<td>53 women, obese</td>
<td>↓ MSNA in D alone and D + E, ↑ forearm blood flow only in D + E group. Small effects on BP in both groups.</td>
</tr>
<tr>
<td>D + E</td>
<td>D: −10 kg (11.7%)</td>
<td>160</td>
<td>59 subjects, obese with metabolic syndrome</td>
<td>↓ MSNA, ↓ norepinephrine spillover, ↓ BP, ↑ all metabolic syndrome components, ↑ sensitivity of the baroreceptor heart rate.</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>Weight: 36%</td>
<td>29</td>
<td>17 subjects, gastric bypass surgery</td>
<td>No additive effects of exercise to the diet. MSNA and plasma norepinephrine concentrations were lower in subjects with gastric bypass compared with individuals with obesity. No change in resting energy expenditure after systemic β-blockade in gastric bypass subjects.</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>BMI: −10.8 kg/m²</td>
<td>142</td>
<td>10 subjects, severe obese hypertension before and after vertical sleeve gastrectomy</td>
<td>↓ MSNA, ↓ BP, ↑ IS at 6 but not at 12 mo, baroreflex control of sympathetic nerve traffic improved.</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>−11.4 kg (10%)</td>
<td>88</td>
<td>23 subjects, severely obese and nondiabetic before and after laparoscopic adjustable gastric band surgery</td>
<td>↓ MSNA, ↓ BP, ↓ total cholesterol, ↑ IS, ↑ creatinine clearance.</td>
</tr>
</tbody>
</table>

BP, blood pressure; MSNA, muscle sympathetic nerve activity; D, diet; E, exercise; IS, insulin sensitivity; BMI, body mass index.
of serotonin and norepinephrine, mainly acts to increase satiety and was shown to profoundly and selectively reduce MSNA at rest and to attenuate the responsiveness to sympathetic stimuli after 5 days of treatment (67). Although the increase in heart rate associated with sibutramine may be due to its peripheral blockade of the norepinephrine transporter in the heart, the reduction in MSNA and sympathetic responsiveness indicates a central sympathetic suppression by the drug (67). Tricyclic antidepressant medications such as desipramine, which block the norepinephrine transporter, also exert a central effect resulting in reduction in MSNA (36). Adverse events such as hypertension, tachycardia, arrhythmias, and myocardial infarction have been reported in sibutramine-treated patients (138) and have resulted in the suspension of the marketing authorization for sibutramine by the European Medicines Agency.

Rimonabant, an endocannabinoid receptor antagonist, was shown to induce more weight loss than in those taking placebo. The average weight loss was 3.9 kg. Rimonabant significantly reduced blood pressure and triglyceride concentrations and increased high-density lipoprotein cholesterol, fasting glucose, and hemoglobin A1C levels. However, the most worrying adverse effect was an increased incidence of psychiatric disorders including depression, anxiety, irritability, and aggression, leading to its removal from the European market in 2009. While there are no data in humans as to whether the decrease in blood pressure by rimonabant involved sympathetic inhibition, experimental studies suggested that cannabinoid receptors are involved in central blood pressure control (124) and that rimonabant-treated obese Zucker rats display decreased urinary excretion of norepinephrine (112). A recent study in mice indicated that the food intake effects of rimonabant as well as the anxiety response involved modulation of SNS activity (11).

Orlistat is a reversible intestinal lipase inhibitor that blocks about 30% of dietary fat absorption, reducing weight by 3% and blood pressure by 2 mmHg, in addition to what is achieved with lifestyle intervention. Orlistat has particular benefits on low-density lipoprotein cholesterol and glycemia (10 and 7% reductions) and reduces the risk of developing diabetes (133). Observations in a small cohort of patients indicated that orlistat decreased sympathetic nerve traffic by 20% in patients who were obese normotensive and by 26% in those who were obese hypertensive (28).

Glucagon-like peptide 1 (GLP1) analogs are promising new treatment options for patients with type 2 diabetes, but as well as having potentially beneficial effects, some of the cardiovascular effects could be harmful. GLP-1 analogs such as exenatide and liraglutide are associated with a small increase in heart rate and modest reductions in body weight and blood pressure (132). Experimental studies of GLP-1 analogs have reported that the direct effects on blood pressure could possibly involve an interaction with the autonomic nervous system (132), and a small study reported that acute GLP-1 increased MSNA in humans (14); however, the longer-term effects on sympathetic function are unknown.

Interventions to Treat Hypertension and Their Potential Beneficial Role in Obesity

Antihypertensive drugs. There is no specific guidance with regard to the use of antihypertensive drugs in the treatment of obesity-related hypertension. Antihypertensive agents such as angiotensin-II antagonists and centrally acting sympatholytic...
agents including the imidazoline-I1 agonists, moxonidine or rilmenidine, may have beneficial effects on the metabolic profile in patients with obesity-related hypertension. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have renal and cardiac protection properties (18). Preclinical studies indicated that ACE inhibition selectively reduced body fat (107) and protected against the development of diet-induced obesity and improved glucose control (31). It is unclear if these effects are mediated through interaction between the renin-angiotensin system and SNS because ARBs such as losartan and eprosartan were found to exert no effect on MSNA (82).

Imidazoline-I1 agonists cause a marked inhibition of sympathetic drive in patients with hypertension (52) and in those with end-stage renal disease (62), which leads to blood pressure reduction and possibly improves various aspects of the metabolic profile and its sequelae. However, some but not all clinical studies using moxonidine indicated an improved cardiovascular risk profile. For example, in patients with hypertension, moxonidine improved left ventricular mass and capillary blood flow (38). In patients with high blood pressure already treated with an ACE inhibitor or ARB, the decline of renal function appeared to be significantly slower in patients in the moxonidine group than in patients treated with a dihydropyridine calcium channel blocker (175). Moreover, moxonidine improved endothelial dysfunction in patients with mild to moderate hypertension (81) and in obese and insulin-resistant patients with the metabolic syndrome and was associated with improved insulin sensitivity, fasting plasma glucose, low-density lipoprotein cholesterol, and leptin levels (38). A recent study indicated that in addition to lowering blood pressure, in subjects who are hypertensive with the metabolic syndrome, moxonidine was associated with 2.1-kg weight loss and improved fasting plasma glucose and triglyceride levels (26) (Table 2). On the other hand, in a randomized crossover study, the effects of inhibition of the renin-angiotensin system, inhibition of the SNS (moxonidine), and a thiazide-type diuretic were compared in patients with obesity-related hypertension; it was found that renin-angiotensin system inhibition was the only treatment resulting in an improvement of the endothelial function. Insulin sensitivity was not improved by any of the treatments (34). Likewise, in patients who were insulin resistant with hypertension, moxonidine was found to have no effects on insulin resistance despite having beneficial effects on weight, high-density lipoprotein cholesterol, and triglycerides (102).

The use of β-adrenergic blocking drugs in the obese population has often been seen as problematic because older agents had an adverse effect on several components of the metabolic syndrome, resulting in weight gain due to reduced diet-induced thermogenesis, fat oxidation, and physical activity (92). Several studies have confirmed an increased risk for new-onset type 2 diabetes mellitus in patients with hypertension who are treated with β-blocking drugs such as atenolol and metoprolol (9, 121); therefore, such antihypertensive drugs are not considered first-line therapy in the metabolic syndrome.

Newer β-blockers such as carvedilol and nebivolol seem to have overcome these problems and have been shown to improve the lipid profile and insulin resistance and not to increase weight gain (10). The vasodilating action of carvedilol and nebivolol may explain the lack of adverse metabolic effects. These findings may be of clinical relevance as these antihypertensive drugs could be a valuable aid for subjects with metabolic syndrome.

Renal denervation. Given the important role that renal nerves play in regulating blood pressure, a percutaneous approach to ablate the renal sympathetic nervous system has been developed to control blood pressure in patients who are refractory to pharmacological treatment. Of note, the majority of patients with resistant hypertension are either overweight or obese (23).

A number of clinical trials (66, 163, 164, 180) have shown favorable long-term effects by reducing blood pressure, although this effect was recently disputed (15). The consequences of renal ablation may be due to blockade of both afferent and efferent neural pathways. One study (65) showed that ablation of afferent renal nerve activity leads to decreased circulating levels of both sympathetic and parasympathetic activity in the kidneys and that indices of renal perfusion and function were negatively affected. The findings of these studies indicate that renal denervation may be a promising treatment for resistant hypertension.

### Table 2. Studies showing various beneficial effects of decreasing sympathetic tone in individuals with hypertension

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reference</th>
<th>Patients</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal denervation</td>
<td>100</td>
<td>50 patients with therapy-resistant hypertension</td>
<td>↓ BP, glucose metabolism and IS improved significantly.</td>
</tr>
<tr>
<td>Renal denervation</td>
<td>17</td>
<td>46 patients with resistant hypertension</td>
<td>↓ BP, left ventricular mass and diastolic function improved.</td>
</tr>
<tr>
<td>Renal denervation</td>
<td>64</td>
<td>40 patients with resistant hypertension</td>
<td>↓ BP, augmentation index improved.</td>
</tr>
<tr>
<td>Renal denervation</td>
<td>89</td>
<td>40 patients with resistant hypertension</td>
<td>↓ BP, quality of life improved.</td>
</tr>
<tr>
<td>Renal denervation</td>
<td>178</td>
<td>10 patients with resistant hypertension and sleep apnea</td>
<td>↓ BP, plasma glucose concentration at 2 h post-glucose improved, decrease in apnea-hypopnea index.</td>
</tr>
<tr>
<td>Baroreflex activation therapy</td>
<td>176</td>
<td>25 patients with resistant hypertension</td>
<td>↓ BP, augmentation index and pulse wave velocity improved.</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>81</td>
<td>58 patients who were not obese but with hypertension</td>
<td>Improvement of endothelial function in those who achieved BP control.</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>175</td>
<td>89 patients with hypertension and advanced renal failure</td>
<td>Decline of creatinine clearance was slower in moxonidine group than in nitrendipine group.</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>26</td>
<td>5,603 patients with hypertension and metabolic syndrome</td>
<td>↓ BP, weight loss of 2.1 kg. Improved fasting plasma glucose and triglycerides.</td>
</tr>
<tr>
<td>Valsartan and moxonidine</td>
<td>21</td>
<td>42 patients with hypertension and left ventricular hypertrophy</td>
<td>Magnitude of left ventricular hypertrophy regression achieved by the combination of valsartan and moxonidine was greater than that produced by comparable BP reduction alone.</td>
</tr>
<tr>
<td>Carvedilol and metoprolol</td>
<td>10</td>
<td>1,235 participants with type 2 diabetes and hypertension who were receiving renin-angiotensin system blockers</td>
<td>Addition of carvedilol for BP control resulted in a significant decrease in triglyceride, TC, and non-HDL cholesterol levels compared with that for metoprolol.</td>
</tr>
</tbody>
</table>
MSNA, indicating a suppression of overall sympathetic vasoconstrictor drive that contributes to the antihypertensive actions; however, two recent reports (19, 173) are inconsistent with this possibility. Likewise, in dogs with obesity-related hypertension, renal denervation did not decrease global sympathetic nervous activity (98). Besides the known effect on blood pressure, renal denervation may have potential beneficial effects on the cardiometabolic risk profile (Table 2). It was shown that the procedure was associated with improvement in glucose metabolism (100), diastolic function (17), health-related quality of life (89) and arterial stiffness (64), and a reduction in left ventricular mass (17) in those with resistant hypertension. On the other hand, a recent study (173) showed no improvement in insulin sensitivity after one year following renal denervation in hypertensive patients with the metabolic syndrome despite a reduction in blood pressure.

**Chronic baroreflex activation.** Cardiac baroreflex sensitivity is depressed in human subjects after several weeks of weight gain or in subjects with long-standing obesity (13). Chronic electrical stimulation of the carotid sinus activates the carotid baroreflex and lowers arterial pressure by suppressing central sympathetic outflow (68, 97) and decreases heart rate by mechanisms that may include activation of the parasympathetic nervous system (68, 97). Electrical activation of the carotid sinus has been shown to increase the sensitivity of the spontaneous baroreflex control of heart rate, while lowering blood pressure in normotensive animals (97). A recent study in dogs with hypertension induced by a high-fat diet indicated that 7 days of chronic baroreflex activation decreased plasma renin activity and abolished the hypertension (98). In addition, it also suppressed sympathetic activity and tachycardia and reduced glomerular hyperfiltration while increasing fractional sodium excretion. This indicated that suppression of global sympathetic activity by baroreflex activation may exert beneficial effects in obesity in addition to attenuating hypertension (98). Current clinical trials using baroreflex activation for blood pressure reduction in drug-resistant patients hold promise (8, 16). One recent study reported that baroreflex activation therapy exerted a favorable effect on arterial properties by improving the augmentation index and pulse wave velocity (176).

**Interventions to Treat Metabolic Disturbances and Their Potential Beneficial Role in Obesity**

**Statins.** Statins or 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors competitively act on the mevalonate pathway to reduce endogenous production of cholesterol. It has been recently acknowledged that a “pleiotropic” property of statins is their effect on the autonomic nervous system. This is in addition to their effect on blood lipids, endothelium-dependent vasodilation, inflammation, and oxidative stress. In fact, several studies have consistently documented that statin therapy decreased MSNA from 10 to 30% in a variety of patient groups (111). Large-scale trials have demonstrated that statins reduce cardiovascular morbidity and mortality in high-risk populations (69) and the risk of major vascular events in low-risk populations (27). Whether the benefit is principally due to their effects on plasma cholesterol or could also be attributed in part to the lowering of SNS activity is uncertain but raises the issue that in conditions characterized by exaggerated sympathoexcitation and elevated oxidative stress, such as obesity, statin therapies may be of benefit.

**Insulin sensitizers.** In addition to improving insulin resistance, pioglitazone decreased MSNA in patients with type 2 diabetes (80) and in those with type 2 diabetes following a recent myocardial infarction (181), which indicated that the sympathoinhibitory effects of pioglitazone may, at least in part, have contributed to the beneficial effects of pioglitazone. Our recent study using pioglitazone in individuals who were insulin resistant and obese, however, showed only a marginal reduction in MSNA and no effect on whole body norepinephrine spillover but was associated with improvement of diastolic function (158). Likewise, metformin, which is widely used in patients with insulin resistance, was found not to alter sympathetic nerve traffic in individuals who are obese (55). While many studies suggest that hyperinsulinemia strongly contributes to sympathetic activation in patients who are obese with metabolic syndrome (90); surprisingly, improving insulin sensitivity may only exert minor effects on sympathetic tone.

**Conclusions and Future Considerations**

The high prevalence of cardiovascular and noncardiovascular comorbidities in individuals who are obese emphasizes the importance of elucidating the underlying pathophysiology of obesity and obesity-related illness to develop and implement the best possible evidence-based treatment strategies. A large raft of evidence supports the view that sympathetic nerve activation is a hallmark of obesity and its associated metabolic disorders. Both experimental and clinical data have indicated that sympathetic activation occurs early in the development of obesity and may play a role in the development of metabolic disturbance or complications of hypertension and renal, cardiac, and endothelial dysfunction in subjects who are obese. Experimental studies recently revealed the importance of leptin as a crucial mediator of sympathetic activation, yet leptin’s role in sympathetic regulation in human obesity remains largely unknown and requires further clarification. Of particular importance are the identification of how adipokines centrally act to influence sympathetic regulation.

With the continued and growing burden of obesity, a number of challenges lay ahead. While the detrimental effect of obesity on health is acknowledged, perhaps surprising is the observation that the obesity-related relative risk of death from stroke and all cardiovascular diseases combined is stronger in younger than in older subjects (12). This raises the important issue that excess adiposity must have deleterious effects on the cardiovascular system at an early age, well before the clinical manifestations of disease are evident. Lifestyle modification such as weight loss and exercise remains the first line of treatment of excess adiposity. Given the lack of success in sustaining long-term weight loss, the development of interventions and strategies that optimize weight loss but also limit obesity-related cardiometabolic disease development and progression is vital. Importantly, the degree of sympathetic nervous activation influences the development of obesity-related illnesses, such that interventions directly targeting the SNS are likely to be of benefit. Indeed, targeting the SNS is at the forefront of cardiometabolic medicine, first in human trials currently underway in New Zealand examining the safely and effectiveness of radiofrequency sympathetic denervation of the
liver in patients whose type 2 diabetes is not well controlled despite treatment with multiple medications (ClinicalTrials.gov Identifier: NCT02278068). Reduction in sympathetic activity following renal denervation has been associated with improvement in glucose control. Whether this occurred in response to afferent or efferent sympathetic denervation remains unknown but is important to clarify. Pharmacologically targeting the SNS with sympatholytic agents such as imidazoline-II agonists hold promise and may exert a beneficial effect on the metabolic profile and end-organ damage. It remains to be determined whether the addition of a sympatholytic agent to a diet could confer further beneficial metabolic and cardiovascular effects in individuals who are obese compared with those on a diet alone and whether this could be an option in patients who do not achieve target weight loss. Further research and appropriately controlled randomized trials are clearly needed to establish whether sympathetic inhibition should be considered a priority to prevent and/or reverse the cardiovascular and metabolic consequences of obesity.

DISCLOSURE

J. B. Dixon is a consultant for Apollo Endosurgery, Bariatric Advantage, and Nova Nordisk and is a member of the Optifast Medical Advisory Board for Nestle Health, Australia. He has been supported to provide educational programs for iNova Pharmaceuticals and has developed educational material for Novartis and iNova Pharmaceuticals. G. W. Lambert has acted as a consultant for Medtronic and has received honoraria from Medtronic, Pfizer, and Wyeth Pharmaceuticals for presentations. The laboratories of J. B. Dixon and G. W. Lambert currently receive research funding from Medtronic, Abbott, and Servier Australia.

AUTHOR CONTRIBUTIONS

E.A.L. conception and design of research; E.A.L. drafted manuscript; E.A.L. and G.W.L. edited and revised manuscript; E.A.L., N.E.S., J.B.D., and G.W.L. approved final version of manuscript.

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