Differing Pattern of Sympathoexcitation in Normal-Weight and Obesity-Related Hypertension

Elisabeth Lambert, Nora Straznicky, Markus Schlaich, Murray Esler, Tye Dawood, Elodie Hotchkin, Gavin Lambert

Abstract—Hypertension in normal-weight and obese individuals is characterized by activation of the sympathetic nervous system. Measurement of spillover of the sympathetic transmitter, norepinephrine, to plasma indicates that the regional pattern of sympathetic activation in the 2 “variants” of essential hypertension differs, excluding the heart in obesity-related hypertension. Whether sympathetic nerve firing characteristics also differ is unknown. We studied multiunit and single fiber sympathetic nerve firing properties in patients with normal-weight hypertension and obesity-related hypertension, comparing these with nerve characteristics in normal-weight and obese people with normal blood pressure. Both normal-weight hypertensive (n=10) and obese hypertensive (n=14) patients had increased total multiunit muscle sympathetic nerve activity compared with the normal-weight (n=11) and obese (n=11) people with normal blood pressure (65±4 versus 47±6 bursts per 100 heartbeats, P<0.01 in the normal-weight groups and 68±4 versus 53±3 bursts per 100 beats, P<0.01 in the obese groups). Sympathetic activation in normal-weight hypertension was characterized by increased firing rate of single vasoconstrictor fibers (70±8 versus 28±3 spikes per 100 beats; P<0.001), increased firing probability per heartbeat (39±3% versus 20±3%; P<0.001), and higher incidence of multiple spikes per heartbeat (30±4% versus 17±4%; P<0.05). Sympathetic activation in obesity-related hypertension differed, involving recruitment of previously silent fibers, which fired at a normal rate. The pattern of sympathetic activation in normal-weight and obesity-related hypertension differs in terms of both the firing characteristics of individual sympathetic fibers and the sympathetic outflows involved. The underlying central nervous system mechanism and the adverse consequences of the 2 modes of sympathetic activation may differ. (Hypertension. 2007;50:1-2.)

Key Words: sympathetic nervous system, hypertension ■ essential, hypertension ■ obesity ■ microneurography ■ single unit

A neural basis for hypertension exists both in the setting of obesity and also for hypertension in the nonobese.1-3 However, obese and nonobese hypertensive patients differ in aspects of their pathophysiology and in their clinical course. Normal-weight essential hypertensive subjects have increased arterial stiffness4 and systemic vascular resistance, whereas obese hypertensive subjects have increased cardiac output,5 abnormal lipid profile,6 and increased renal disease.7 Cardiovascular prognosis also differs between the 2 groups of hypertensive subjects with, paradoxically, worse clinical outcome in lean than in obese hypertensive subjects.8

Beyond the presence of an increase in overall sympathetic tone in both normal-weight and obese hypertensive subjects, regional patterns of sympathetic activity, disclosed by measurement of norepinephrine spillover, differ between the 2 groups. In normal-weight essential hypertension, renal and cardiac sympathetic outflows are activated.9 In contrast, in obesity-related hypertension, although the sympathetic outflow to the kidney is increased, sympathetic outflow to the heart is reduced.10 This suggests that the mode and perhaps the central nervous system mechanisms of sympathetic nervous activation present in the 2 “variants” of essential hypertension may differ.

Direct sympathetic nerve recording with clinical microneurography has documented activation of sympathetic efferent in the skeletal muscle vasculature in both normal-weight and obesity-related hypertension.11-13 Previous reports, with some notable exceptions,14-19 have assessed muscle sympathetic nerve activity (MSNA) from recordings of multiunit bursts. Multunit recordings, however, contain a variable and indeterminate number of firing units, which may have different firing frequencies and function. By recording the firing patterns in individual vasoconstrictor sympathetic fibers, a greater discrimination is possible. How sympathetic excitation is achieved can be ascertained,14 possible modes being an increased firing rate of individual nerve fibers and recruitment of additional firing fibers.17 By using single fiber recording methodology, we aimed to examine more specifically the mechanisms of sympathoexcitation in hypertensive individuals with or without obesity.
Methods

Subjects
The study included a total of 46 subjects, ranging in age between 19 and 66 years. All of the patients underwent a clinical examination to screen for underlying illness. Exclusion criteria were composed of a diagnosis of diabetes; secondary hypertension; obstructive sleep apnea; renal, liver, or thyroid disease; and a history of myocardial infarction or stroke. None of the participating subjects were current smokers or had a history of smoking or alcohol abuse. All of the subjects were free of any medication, and hypertensive patients were free of all antihypertensive therapy for ≥3 weeks before the study. No patient was participating in a formal exercise or weight reduction program at the time of the testing, and none of the participating women was taking hormone replacement therapy. Four groups of patients were obtained: normal-weight normotensive (NT; 5 females and 6 males), normal-weight hypertensive (HT; 2 females and 8 males), obese NT (5 females and 6 males), and obese HT (6 females and 8 males).

Hypertension was defined as an average systolic blood pressure (BP) >140 mm Hg or diastolic BP >90 mm Hg on multiple sphygmomanometric measurements in the right arm by a Dinamap monitor (model 1846 SX, Critikon, Inc). Participants were classified as NT if systolic BP was consistently <130 mm Hg and diastolic BP was <80 mm Hg. Normal-weight subjects had a body mass index ≤27 kg/m², and obese ones had a BMI ≥28 kg/m².

The research protocol conformed to the relevant guidelines of the National Health and Medical Research Council of Australia and was approved by the Alfred Hospital Human Research Ethics Committee. Written informed consent was obtained from all of the participants.

MSNA
Multiunit postganglionic sympathetic nerve activity was recorded using microneurography in a muscle fascicle of the peroneal nerve at the fibular head as described previously.20 The needle was adjusted until satisfactory spontaneous MSNA was observed in accordance with previously described criteria.20,21 The nerve signal was amplified (×50 000), filtered (bandpass, 700 to 2000 Hz), and integrated. BP, ECG, and MSNA were digitized with a sampling frequency of 1000 Hz (PowerLab recording system, model ML785/8SP, AD Instruments). After an acceptable nerve-recording site was obtained, resting measurements were performed over a 20-minute period. MSNA was expressed as burst frequency (bursts per minute) and burst incidence (bursts per 100 heartbeats). Relative burst amplitude was calculated by attributing the value of 100 to the largest burst that occurred during the analyzed period and expressing all of the other burst amplitudes as a percentage of the maximum burst. Total MSNA was calculated by multiplying the mean burst amplitude per minute by the burst rate, expressed as units per minute (total MSNA frequency) and units per 100 heartbeats (total MSNA incidence). All of the experiments were performed with subjects in the supine position. BP in the laboratory was measured using radial arterial tonometry (CBM 7000, Colin Corp), and heart rate was determined using a lead III ECG recording.

The microelectrode was then manipulated until large unitary discharges (ie, single-unit MSNAs) appeared out of the multunit sympathetic bursts. Resting measurements for single-unit sympathetic activity were made for ≥3 minutes, as described previously.19 For the analysis of single-unit recordings, we applied similar methods as those developed by Macefield et al,14 which use very stringent criteria for the acceptance of a recording as being truly unitary. The morphology of every candidate spike was carefully analyzed. All of the spikes of similar amplitude (after allowing for the variation induced by the background noise) were selected, and their shape was analyzed using computer software developed in the laboratory that allowed the superimposition of all of the spikes to confirm that the signals originated from a single nerve fiber (Figure 1). Only the units satisfying these criteria were included in the analysis. From a technical point of view, although possible but not probable given the stringency of the selection criteria for unitary spikes, if 2 fibers displayed identical morphology with respect to

Statistics
Data are expressed as the mean ± SEM. Comparisons between data obtained from normal-weight and obese subjects with or without hypertension were made by 2-way ANOVA followed by the Tukey test to allow for pairwise multiple comparisons. A value of P < 0.05 was considered statistically significant.

Results
The clinical characteristics of the 4 groups are shown in Table 1. Obese NT subjects were slightly older than the normal-weight NT ones (P = 0.032). BP in the obese NT subjects was not significantly different to that observed in their normal-weight counterparts (P = 0.128 for systolic BP and P = 0.213 for diastolic BP).

Multiunit MSNA was significantly higher in normal-weight HT subjects compared with the normal-weight NT ones when expressed as burst frequency (40 ± 3 versus 29 ± 3 bursts per minute; P = 0.011), burst incidence (65 ± 4 versus 47 ± 6 bursts per 100 beats; P = 0.01), total MSNA frequency (1770 ± 136 versus 1149 ± 62 U/min; P = 0.005; Figure 2), and total MSNA incidence (2764 ± 265 versus 1743 ± 94 U per

Figure 1. ECG, integrated MSNA, and raw MSNA signals obtained in 1 normal-weight HT subject (A) and in 1 obese HT subject (B). Multiunit MSNA burst incidence was 68 bursts per 100 heartbeats in subject A and 81 bursts per 100 heartbeats in subject B. Firing rate of single vasoconstrictor neuron was 77 spikes per 100 heartbeats in subject A and 28 spikes per 100 heartbeats in subject B. Single vasoconstrictor fiber was identified on each neurogram as indicated by an asterisk. Superimposed spikes show a uniform spike morphology.
100 beats; \(P=0.007\). Similarly, obese HT subjects displayed increased MSNA compared with the obese NT subjects (43±3 versus 32±2 bursts per minute, \(P=0.006\); 68±4 versus 53±4 bursts per 100 beats, \(P=0.01\); 2396±324 versus 1515±118 U/min, \(P=0.01\); 4111±499 versus 2482±230 U per 100 beats, \(P=0.005\)).

Multunit MSNA was elevated in the obese NT group compared with their normal-weight counterparts, but this was only significant when the data were expressed as total MSNA incidence (2484±230 versus 1743±94 U per 100 beats; \(P=0.04\)). Furthermore, there was a further increase in total MSNA incidence in the obese HT subjects compared with the normal-weight HT subjects (4111±499 versus 2482±230 U per 100 beats; \(P=0.044\); see Table 2 and Figure 2).

The firing rate of single vasoconstrictor sympathetic fibers, as assessed by the number of spikes per minute and spikes per 100 beats was significantly greater in normal-weight HT subjects compared with the normal-weight NT ones (42±5 versus 18±2 spikes per minute, \(P<0.001\); 70±8 versus 28±3 per 100 beats, \(P<0.001\)). Normal-weight HT subjects displayed increased firing probability of sympathetic vasoconstrictor fibers compared with the normal-weight NT subjects (39±3% versus 20±3% of heartbeats, \(P<0.001\); 62±5% versus 49±5% of bursts, \(P=0.079\)). Furthermore, the incidence or multiple spikes per burst (and per heartbeat) was elevated in the normal-weight HT subjects compared with the normal-weight NT ones (47±4% versus 31±5% of burst, \(P=0.015\); 30±4% versus 17±4% of heartbeats, \(P=0.017\)). All of the parameters of vasoconstrictor fibers in the obese NT subjects were not significantly different from that observed in the normal-weight NT subjects. When compared with the normal-weight HT groups, obese HT subjects displayed lower firing rate (26±4 versus 42±5 spikes per minute, \(P=0.02\); 42±7 versus 70±8 spikes per 100 heartbeats, \(P=0.003\)), lower firing probability per burst (41±5% versus 62±5%; \(P=0.003\)), and lower incidence of multiple spikes per burst (25±4% versus 47±4%; \(P<0.001\)) or per heartbeat (11±3% versus 30±4%; \(P<0.001\); see Table 2 and Figure 3).

Discussion

Recordings from single-unit muscle vasoconstrictor fibers indicated that the mode of sympathetic excitation in normal-weight essential hypertension differed markedly from that in obesity-related hypertension as illustrated in Figure 4. Results from us and others\textsuperscript{15} indicate that the augmentation of MSNA in normal-weight essential hypertension results from an increase in the firing rate of single vasoconstrictor nerve fibers. Our analysis additionally indicates that this increase in the firing rate of individual fibers involves an increase in the proportion of neural multunit bursts in which a single fiber is active (increased firing probability) and an increase in the number of spikes a fiber generates per burst (increased incidence of multiple spikes or firing “salvos”). These mechanisms constitute the 2 alternatives for increasing the firing rate of individual sympathetic vasoconstrictor fibers.\textsuperscript{17}

In contrast, the sympathetic nervous activation occurring in obese people with normal BP and in obesity-related hypertension occurs via a different mechanism. In obese participants, regardless of their prevailing BP, we found that the firing rate of single vasoconstrictor fibers was normal, despite their total multunit MSNA being elevated. The increase in multunit sympathetic activity present could only have arisen from recruitment of previously silent nerve fibers\textsuperscript{24} and not by any increase in the firing probability of already active vasoconstrictor sympathetic fibers, which our measurements

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Table 1. Characteristics of the 4 Groups

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Normal Weight</th>
<th>Obese</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NT</td>
<td>HT</td>
</tr>
<tr>
<td>No. (men)</td>
<td>11 (6)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Age, mean±SEM, y</td>
<td>37±3</td>
<td>44±4</td>
</tr>
<tr>
<td>Body mass index, mean±SEM, kg/m\textsuperscript{2}</td>
<td>23±0.6</td>
<td>25±0.8</td>
</tr>
<tr>
<td>Heart rate, mean±SEM, bpm</td>
<td>67±2</td>
<td>64±3</td>
</tr>
<tr>
<td>Systolic BP, mean±SEM, mm Hg</td>
<td>120±3</td>
<td>157±3*</td>
</tr>
<tr>
<td>Diastolic BP, mean±SEM, mm Hg</td>
<td>67±2</td>
<td>84±4*</td>
</tr>
</tbody>
</table>

Data are from 2-way ANOVA.

*\(P<0.05\), normal-weight HT vs normal-weight NT.
†\(P<0.05\), obese HT vs obese NT.
‡\(P<0.05\), obese NT vs normal-weight NT.
§\(P<0.05\), obese HT vs normal-weight HT.
excluded. It is unlikely that the increase in multiunit sympathetic activity represented an increased sympathetic innervation of adipose tissue in these subjects. Specific determination of adipose tissue catecholamine spillover in humans has demonstrated that a rise in adipose tissue norepinephrine spillover induced by a 3-day starvation was not accompanied by any changes in muscle and whole-body norepinephrine spillover. This suggests that recordings of activity in the muscle sympathetic branches are unlikely to reflect sympathetic metabolic signals to the adipose tissue.

We noted that increased multiunit MSNA in obese subjects was apparent only when data were expressed as total multiunit MSNA, which is derived from both the multiunit burst frequency and the relative amplitude of the bursts. The amplitude of recorded MSNA bursts is influenced by both the distance between the tip of the recording electrode and the sympathetic fibers and the number of active vasoconstrictor fibers. Our results with single and multiunit MSNA measurements in obesity support the validity of the claim that total MSNA measurements can be used as an indicator of recruitment of vasoconstrictor fibers.

In agreement with others, we found that, when hypertension and obesity coexist, total MSNA incidence is further increased above that present in hypertension or obesity alone. This was not accompanied, however, by any increase in the single-unit vasoconstrictor firing rate. Clearly, when obesity is present, regardless of BP, recruitment of sympathetic fibers is the mechanism by which sympathetic nervous excitation occurs. We cannot exclude that this phenomenon of recruitment of previously silent sympathetic fibers might also be engaged in the generation of high sympathetic tone in the normal-weight hypertensive participants in addition to the higher firing frequency of individual sympathetic fibers that we document. This is because no sampling method for nerve recording exists that can specifically detect the conversion of silent sympathetic fibers to firing fibers. In contrast, in obesity, it is possible to validly infer that recruitment of firing fibers has occurred, because multiunit sympathetic activation occurs in the absence of any increase in single-fiber firing frequency.

Differences in the function of the sympathetic baroreflex may be a factor in influencing sympathetic nervous tone

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Normal Weight, mean ± SEM</th>
<th>Obese, mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multunit recording</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burst frequency, bursts per minute</td>
<td>29 ± 3</td>
<td>40 ± 3*</td>
</tr>
<tr>
<td>Burst incidence, burst per 100 beats</td>
<td>47 ± 6</td>
<td>65 ± 4*</td>
</tr>
<tr>
<td>Total MSNA frequency, U/min</td>
<td>1149 ± 62</td>
<td>1770 ± 136*</td>
</tr>
<tr>
<td>Total MSNA incidence, U per 100 beats</td>
<td>1743 ± 94</td>
<td>2764 ± 265*</td>
</tr>
<tr>
<td>Single-unit recording</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firing rates, spikes per minute</td>
<td>18 ± 2</td>
<td>42 ± 5*</td>
</tr>
<tr>
<td>Firing rate, spikes per 100 beats</td>
<td>28 ± 3</td>
<td>70 ± 8*</td>
</tr>
<tr>
<td>Firing probability per burst, %</td>
<td>49 ± 5</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>Firing probability per beat, %</td>
<td>20 ± 3</td>
<td>39 ± 3*</td>
</tr>
<tr>
<td>Incidence of multiple spikes per burst, %</td>
<td>31 ± 5</td>
<td>47 ± 4*</td>
</tr>
<tr>
<td>Incidence of multiple spikes per beat, %</td>
<td>17 ± 4</td>
<td>30 ± 4*</td>
</tr>
</tbody>
</table>

Data are from 2-way ANOVA.

*P < 0.05, normal-weight HT vs normal-weight NT.
†P < 0.05, obese HT vs obese NT.
‡P < 0.05, obese NT vs normal-weight NT.
§P < 0.05, obese HT vs normal-weight HT.

Figure 3. Left, Number of spikes generated by single vasoconstrictor fibers (expressed per 100 beats); middle, firing probability of single vasoconstrictor fibers (expressed per beat); and right, incidence of multiple spikes (≥2) within a burst (expressed per 100 beats) in normal-weight and obese subjects with or without hypertension. NT indicates normotensive; HT, hypertensive. *P < 0.05 normal-weight HT vs normal-weight NT; §P < 0.05 obese HT vs normal-weight HT.
differently in hypertension and obesity. It has been demonstrated that the reflex sympathetic responses during baroreceptor stimulation and deactivation induced by stepwise intravenous infusions of phenylephrine and nitroprusside are preserved in normal-weight hypertensive subjects but reduced in obese hypertensive subjects,27 perhaps because of a disproportionate reduction in arterial distensibility in the obese subjects.28 It is possible that this reduction in sympathetic baroreflex gain in the obese subjects limits the firing rate of single vasoconstrictor fibers and favors the recruitment of previously silent sympathetic fibers. Such a mechanism has been described in an animal model of nephrotic syndrome where the existing defect in cardiac baroreflex sensitivity involved the number of active renal sympathetic nerve fibers rather than their firing frequency.29

Our results in obesity-related hypertension differ from those of a previous report by Huggett et al,18 who found that, among obese subjects, those with hypertension displayed increased firing rates of single vasoconstrictor fibers, this increase being further augmented if the metabolic syndrome was present. Twelve of 23 of our obese subjects had additional metabolic abnormalities (high level of triglycerides, low high-density lipoprotein, or elevated fasting plasma glucose), but subgroup analysis revealed that these factors did not influence the firing rate of individual fibers (data not shown). The basis for the discrepant results between this previous study and ours remains unknown.

The central nervous system mechanisms of increased sympathetic outflow from the brain must differ between the lean and obese hypertensive subjects. There are clues as to what these 2 different mechanisms might be but as yet no definitive answers. We documented previously that subcortical norepinephrine turnover in the brain is increased in normal-weight patients with essential hypertension.30 These findings suggest an importance of increased firing in brainstem neurons projecting to the hypothalamus and amygdala and underlying mental stress in the sympathetic nervous activation and hypertension pathogenesis. The increase in subcortical forebrain noradrenaline turnover found in normal-weight essential hypertension is absent in obesity-related hypertension.31 The origins of the sympathetic nervous activation must lie elsewhere. The list of possible mechanisms is long, but for none is the supporting evidence totally persuasive. The sympathetic activation may represent an ongoing response to continuing overfeeding, which is suggested by the experimental models,32 or perhaps it is driven by the pathophysiological and clinical changes that accompany obesity once it has developed, including hyperinsulinemia, obstructive sleep apnea (OSA), and high plasma leptin levels.

**Hyperinsulinemia**

The insulin response to increased dietary energy intake was seen as the prime mover in the following cascade: overfeeding–hyperinsulinemia–sympathetic nervous activation–thermogenesis and hypertension.33 This has been a highly influential hypothesis but remains unproven in human obesity.10,34 More recent thinking might shift the emphasis, attributing the hyperinsulinemia in obesity to the accompanying insulin resistance rather than specifically to an overfeeding response.

**OSA**

OSA, common in obesity, has been championed as a cause of the present sympathetic activation. The presence of increased single-fiber firing rates in OSA,16 perhaps argues against this, given that obesity-related hypertension is characterized by recruitment of additional active fibers, not an increase in firing rate. Apneic episodes at night are accompanied by intense sympathetic nervous activation.35 Despite this caveat, it does seem probable that OSA is, in fact, one causal mechanism of sympathetic activation in obesity. An intriguing recent article describes some elevation of sympathetic tone even in lean men with OSA,36 allowing a disentangling of the independent but usually combined influences of obesity and OSA.

**Leptin**

The sympathetic nervous activation of obesity might, perhaps, be driven by high plasma levels of leptin, the “adipocyte hormone.” With intravenous infusion of leptin in rats, activation of the sympathetic outflows to the kidneys and
hindlimb vasculature is seen,37 accompanied by stimulation of epinephrine secretion by the adrenal medulla and an increase in heart rate, suggesting that the cardiac sympathetic nerves are stimulated. These effects have some parallel, although not particularly close, in the pattern of sympathetic nervous change seen in human obesity.1,3,10,18,39 This perhaps suggests that leptin stimulation of the sympathetic nervous system may be the underlying explanation of sympathetic activation, but it should be emphasized that in human obesity epinephrine secretion rates are normal, and the cardiac sympathetic outflow is not stimulated.10,39,40

**Perspectives**

Normal-weight essential hypertension is characterized by activation of sympathetic outflows to the heart, kidneys, and skeletal muscle vasculature and by increased firing rates in individual sympathetic nerve fibers with multiple firings (firing salvos) within a cardiac cycle. The sympathetic activation of obesity-related hypertension differs in excluding the cardiac sympathetic outflow and in the single fiber mechanism of sympathetic activation, which involves an increase in the number of fibers firing (probably by recruitment of previously silent ones), which fire at a normal rate. These differences between lean and obese hypertensive patients may have clinical consequences, which at present are unknown. The high cardiac sympathetic activity in the heart of lean hypertensive patients is probably deleterious, contributing to the development of left ventricular hypertrophy.41

Cardiac clinical end point rates are worse in lean than in obese hypertensive subjects.3 Paradoxically, the hypertensive obese may be spared of this risk burden, because their cardiac sympathetic activity is normal or reduced, and their mode of sympathetic nervous activation involves recruitment of fibers firing at a normal rate. The present study suggests that the central nervous system origins of sympathetic nervous activation differ between obese and normal-weight hypertension. How each condition might be targeted specifically with the mechanism of sympathetic activation, which involves an increase in the number of fibers firing (probably by recruitment of previously silent ones), which fire at a normal rate.

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**Disclosures**

None.

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