Obesity

Autonomic Contribution to Blood Pressure and Metabolism in Obesity

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Abstract—Obesity is associated with alterations in the autonomic nervous system that may contribute to the increase in blood pressure and resting energy expenditure present in this condition. To test this hypothesis, we induced autonomic withdrawal with the ganglionic blocker trimethaphan in 10 lean (32±3 years) and 10 obese (35±3 years) subjects. Systolic blood pressure fell more in obese compared with lean subjects (−17±3 versus −11±1 mm Hg; P=0.019) because of a greater decrease in total peripheral resistance (−310±41 versus 33±78 dynes/sec/cm²; P=0.002). In contrast, resting energy expenditure decreased less in obese than in lean subjects, (−26±21 versus −86±15 kcal per day adjusted by fat-free mass; P=0.035). We confirmed that the autonomic contribution to blood pressure was greater in obesity after including additional subjects with a wider range of blood pressures. Systolic blood pressure decreased −28±4 mm Hg (95% CI: −38 to −18.0; n=8) in obese hypertensive subjects compared with lean (−9±1 mm Hg; 95% CI: −11 to −6; n=22) or obese normotensive subjects (−14±2 mm Hg; 95% CI: −18 to −10; n=20). After removal of autonomic influences, systolic blood pressure remained higher in obese hypertensive subjects (109±3 versus 98±2 mm Hg in lean and 103±2 mm Hg in obese normotensive subjects; P=0.004) suggesting a role for additional factors in obesity-associated hypertension. In conclusion, sympathetic activation induced by obesity is an important determinant to the blood pressure elevation associated with this condition but is not effective in increasing resting energy expenditure. These results suggest that the sympathetic nervous system could be targeted in the treatment of obesity-associated hypertension. (Hypertension. 2007;49:27-33.)

Key Words: obesity □ hypertension □ autonomic nervous system □ sympathetic nervous system □ vascular resistance □ metabolism

Obesity affects >30% of the US population and is associated with increased mortality, mostly related to diabetes and cardiovascular events,1 which translates to a reduction in life expectancy estimated to be 5 to 20 years.2 Obesity is a precursor of hypertension, insulin resistance, dyslipidemia, and subclinical inflammation, a cluster known as the metabolic syndrome. The incidence of this disorder has increased dramatically in the past 2 decades with an age-adjusted prevalence of 27% among adults in the United States.3 The mechanisms underlying hypertension in obesity are not completely understood. One of the prevailing theories, proposed by Landsberg,4 states that obesity results in a compensatory sympathetic activation to drive thermogenesis and increase energy expenditure. In this scenario, obesity-associated hypertension may be an adverse result of sympathetic activation in an attempt to maintain energy balance. Indeed, there is increasing evidence that sympathetic nervous system activity is augmented in obesity. Sympathetic traffic to skeletal muscle reflecting baroreflex-modulated vasoconstrictive function is consistently increased in obesity and positively correlated with all indices of adiposity.5–7

In the present study, we induced complete autonomic withdrawal by blocking ganglionic transmission with trimethaphan to gauge the contribution of the autonomic nervous system to blood pressure regulation and resting energy expenditure (REE) in obesity. We have previously validated this approach to determine the short-term contribution of the autonomic nervous system to blood pressure regulation.8

Methods

Protocol 1: Autonomic Contribution to Blood Pressure and Energy Expenditure in Obesity

Study Subjects
We studied 10 lean (age: 32±3 years) and 10 obese (age: 35±3 years) healthy normotensive (≤140/90 mm Hg) subjects matched by age and gender. Obese subjects had both ≥30 kg/m² body mass index (BMI) and ≥35% body fat, and lean subjects had both <25 kg/m² BMI and <35% body fat. We excluded highly trained athletes,
subjects with significant (>5%) weight change in the past 3 months, and subjects taking medications known to affect energy expenditure or autonomic function. Women of childbearing potential had a negative pregnancy test. Food containing methylxanthines were prohibited for ≥72 hours before study. All of the studies were approved by Vanderbilt’s Institutional Review Board, all of the participants gave informed consent, and procedures were in accordance with institutional guidelines.

**Experimental Design**

Subjects were studied on 3 different occasions. The initial screening visit included a medical history, physical examination, ECG, and routine laboratory analysis. Body composition, fat mass (FM), and fat-free mass (FFM) were determined by dual energy x-ray absorptiometry (Lunar DPA software 3.6, GE Medical System). Waist circumference was measured at the level of the umbilicus while supine. A certified diettian contacted the participant to remind subjects not to change their eating or physical activity pattern.

During the second visit we determined the effect of ganglionic blockade on REE, which accounts for 60% to 80% of 24-hour energy expenditure. Blood samples were taken at baseline and during autonomic withdrawal in the supine position to determine plasma catecholamines and metabolic hormones. Blood pressure was measured at 2-minute intervals using an automated sphygmomanometer and continuously by finger plethysmography for spectral analysis of blood pressure variability. ECG and heart rate were monitored throughout the study. Relative changes in cardiac output were estimated using impedance cardiography.9 During a third visit, basal muscle sympathetic nerve activity was measured in 14 subjects who consented to the procedure (7 lean and 7 obese), as described previously.10

**Protocol 2. Autonomic Contribution to Obesity-Associated Hypertension**

To determine the autonomic contribution to blood pressure in a larger number of subjects with a wider range of blood pressure, we studied 30 additional patients: 12 lean normotensive subjects (age: 31±3 years; BMI: 22±1 kg/m²), 10 obese normotensive subjects (age: 35±2 years; BMI: 34±1 kg/m²), 8 obese hypertensive subjects (age: 41±2 years; BMI: 34±1 kg/m²). 10 patients with autonomic failure and sympathetic-dependent supine hypertension (multiple system atrophy [MSA], “positive controls”; age: 67±2 years; BMI: 25±1 kg/m²), and 10 patients with autonomic failure and sympathetic-independent supine hypertension (pure autonomic failure [PAF] “negative controls”; age: 72±4 years; BMI: 24±1 kg/m²).11 All of the obese hypertensive patients were treated for ≥1 year with antihypertensive medications. All antihypertensive medications were withheld for ≥5 half-lives before the study day. The studies were performed as described under protocol 1 to determine the effect of ganglionic blockade on blood pressure.

**Specific Procedures**

**Ganglionic Blockade**

Ganglionic blockade was induced by trimethaphan (Cambridge Labs), at a starting dose of 1 mg/min and increased up to 5 mg/min, until no change in heart rate to a 25 mm Hg increase in blood pressure produced by phenylephrine was observed. Autonomic withdrawal was documented by the abolition of spontaneous baroreflex function and heart rate and blood pressure variability.8

**Spectral Analysis of Blood Pressure and Heart Rate**

All of the physiological data were recorded using a data acquisition system (14 Bit, 500 Hz) and processed using custom written software as described previously,8 following task force recommendations for heart rate variability.12

**REE**

Subjects were studied after 12-hour fasting, and only clear fluids were allowed after 8:00 PM the night before. Intense physical activity was not permitted the day before. Women were studied in the follicular phase of their menstrual cycle (days 1 to 12). Subject rested quietly supine at an ambient temperature of 21°C for 30 minutes before testing. REE was assessed by an open-circuit indirect calorimeter with a ventilated canopy or a face tent device (CPX/D system, Medical Graphics Corporation). Only the last 20 minutes of a 40-minute measurement period were analyzed.13 The respiratory quotient was used for quality control.14 Basal REE was measured between 7:00 and 8:00 AM and between 11:00 and 12:00 AM during ganglionic blockade. This sequential design was selected to use each subject as their own control. The main comparison was between lean and obese subjects, making a time effect less relevant. A single operator performed all of the studies.

**Hormone Determinations**

Catecholamine, insulin, glucose, nonesterified fatty acids (NEFAs), lactate, and leptin were determined at baseline and during ganglionic blockade through an intravenous catheter placed ≥30 minutes before sampling using previously described assays.15,16

**Data Analysis and Statistics**

In protocol 1, our primary end point was the change in systolic blood pressure (SBP) before and after complete ganglionic blockade (∆SBP), and we used a nonparametric Mann–Whitney U test to determine the difference between lean and obese groups. Our sample size calculation was based on our preliminary data in 9 subjects; ∆SBP after autonomic withdrawal was −10.4±4.3 and −18.1±5.8 mm Hg (mean±SD) in lean and obese subjects, respectively. A sample size of 10 in each group had a 90% power to detect a difference in means of 7.8 assuming that the common SD was 5 using a 2-group t test with a 0.05 two-sided significance level.

The secondary end point was the change in REE before and after complete ganglionic blockade (∆REE) between lean and obese subjects matched by gender and age. Because there is a linear relationship between REE and FFM, absolute values of energy expenditure were first adjusted for FFM.17 The primary statistical analysis was a nonparametric Mann–Whitney U test. In addition, we determined whether the linear relationship between REE and FFM was different before and after ganglionic blockade using a mixed-effect model.

Additional end points of interest included changes in metabolic parameters, such as glucose, insulin, NEFA, and lactate, and other cardiovascular parameters (cardiac output and total peripheral resistance) in lean and obese subjects. To test for differences before and after trimethaphan, we used a nonparametric Wilcoxon signed rank test.

In protocol 2, our primary end point was the ∆SBP induced by ganglionic blockade among lean, obese, and obese hypertensive subjects. The primary analysis was a nonparametric Kruskal–Wallis test. All of the values are reported as mean±SEM unless otherwise specified. A 2-tailed P value <0.05 was considered significant. The analyses were performed using SPSS for Windows (version 13.0, SPSS).

**Results**

**Protocol 1**

**Subject Characteristics**

Supine SBP and diastolic blood pressure were significantly elevated in obese subjects (P=0.03 and 0.01, respectively; Table 1). Heart rate and cardiac output were similar between groups, but total peripheral resistance was significantly higher in obese subjects (P=0.006). As expected, obese subjects have higher percentage of body fat, FM, FFMI, and REE (P<0.001). Serum lipids levels were similar between groups.

**Basal Autonomic Parameters**

Muscle sympathetic nerve activity was greatly increased in obese compared with lean subjects (33±4 versus 19±2 bursts

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TABLE 1. Baseline Parameters in Lean and Obese Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lean</th>
<th>Obese</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, male/female</td>
<td>5/5</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>32 ± 3.0</td>
<td>35 ± 3.0</td>
<td>0.256</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23 ± 0.4</td>
<td>36 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting energy expenditure, kcal/day</td>
<td>1426 ± 58.5</td>
<td>1858 ± 126.0</td>
<td>0.009</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>27 ± 2.0</td>
<td>45 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>66 ± 2.9</td>
<td>109 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>50 ± 3.0</td>
<td>62 ± 4.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Total lean mass, kg</td>
<td>17 ± 1.0</td>
<td>47 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>76 ± 1.7</td>
<td>107 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>92 ± 3.0</td>
<td>120 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.82 ± 0.02</td>
<td>0.89 ± 0.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>168 ± 5.7</td>
<td>184 ± 15.0</td>
<td>0.50</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>55 ± 4.5</td>
<td>51 ± 3.1</td>
<td>0.88</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>92 ± 3.9</td>
<td>107 ± 13.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>104 ± 17.3</td>
<td>126 ± 19.3</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

\(P^*\) values were calculated by Mann–Whitney U test.

per min; \(P=0.007\); Table 2). Obese subjects had greater SBP variability in the low frequency band compared with lean subjects (9.3 ± 1.9 versus 4.0 ± 0.8 mm Hg\(^2\); \(P=0.04\)), consistent with their higher sympathetic tone.8,18 Obese subjects had decreased baroreflex gain and lower heart rate variability in the high frequency band, but these did not reach significance. Spectral analysis could not be obtained in 2 obese subjects because of premature atrial contractions. No difference was observed in supine plasma norepinephrine levels between lean and obese subjects (Table 2).

**Effect of Ganglionic Blockade on Cardiovascular and Spectral Parameters**

As expected, all of the indices of heart rate variability were greatly reduced during ganglionic blockade. The low frequency heart rate variability decreased from 874 ± 278 and 1262 ± 359 ms\(^2\) to 2 ± 1 and 2 ± 0.4 ms\(^2\) in lean and obese subjects, respectively. The high frequency of heart rate variability decreased from 1361 ± 845 and 863 ± 314 to 7 ± 2 and 4 ± 1 ms\(^2\) in lean and obese subjects, respectively. There was also a significant reduction in low frequency variability of blood pressure and in baroreflex gain during trimethaphan infusion (Table 2). The decrease in SBP and diastolic blood pressure induced by trimethaphan was significantly greater in obese compared with lean subjects (\(-17 ± 3\) versus \(-11 ± 1\) mm Hg; \(P=0.019\); and \(-13 ± 2\) versus \(-7 ± 1\) mm Hg; \(P=0.007\), respectively; Figure 1A), and the intrinsic SBP in the absence of autonomic modulation was similar between groups (102 ± 4 versus 96 ± 2 mm Hg; \(P=0.25\)). The increase in heart rate in response to trimethaphan was not significantly different between lean and obese subjects matched for age (23 ± 2.1 versus 19 ± 2.8 bpm, respectively; \(P=0.39\)). Cardiac output did not change with trimethaphan. The increased total peripheral resistance observed at baseline in the obese was significantly reduced by trimethaphan to values that were no longer different from the lean group.

**TABLE 2. Cardiovascular, Autonomic, Neuroendocrine, and Metabolic Changes Induced by Ganglionic Blockade**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Ganglionic Blockade</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>107 ± 1</td>
<td>120 ± 2</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>62 ± 2</td>
<td>68 ± 2</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>60 ± 3</td>
<td>65 ± 3</td>
<td>0.31</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>7.3 ± 0.4</td>
<td>7.0 ± 0.3</td>
<td>0.16</td>
</tr>
<tr>
<td>TPR, dynes/s cm(^{-1})</td>
<td>893 ± 41</td>
<td>1171 ± 72</td>
<td>0.006</td>
</tr>
<tr>
<td>LF SBP, mm Hg(^2)</td>
<td>4 ± 0.8</td>
<td>9.3 ± 1.9</td>
<td>0.04</td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>14.6 ± 1.5</td>
<td>11.9 ± 1.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>274 ± 32</td>
<td>257 ± 35</td>
<td>0.84</td>
</tr>
<tr>
<td>MSNA, burst/min</td>
<td>19 ± 1.9</td>
<td>33 ± 3.9</td>
<td>0.007</td>
</tr>
<tr>
<td>MSNA, burst/100 bpm</td>
<td>32 ± 3.4</td>
<td>50 ± 4.8</td>
<td>0.017</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>88.5 ± 2.4</td>
<td>91.8 ± 3.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Insulin, mm/mL</td>
<td>5.3 ± 0.9</td>
<td>8.5 ± 0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>5.4 ± 1.2</td>
<td>17.6 ± 2.7</td>
<td>0.002</td>
</tr>
<tr>
<td>NEFA, mmol/L</td>
<td>232.4 ± 55.2</td>
<td>387.3 ± 70</td>
<td>0.14</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>1.1 ± 0.1</td>
<td>1.5 ± 0.2</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Ganglionic Blockade**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lean</th>
<th>Obese</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>96 ± 2</td>
<td>102 ± 4</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>55 ± 2</td>
<td>56 ± 2</td>
<td>0.38</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>83 ± 4</td>
<td>84 ± 2</td>
<td>0.97</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.5 ± 0.6</td>
<td>8 ± 0.5</td>
<td>0.51</td>
</tr>
<tr>
<td>TPR, dynes/s cm(^{-1})</td>
<td>926 ± 85</td>
<td>861 ± 61</td>
<td>0.80</td>
</tr>
<tr>
<td>LF SBP, mm Hg(^2)</td>
<td>0.5 ± 0.2</td>
<td>1 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>1.6 ± 0.3</td>
<td>2 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>69 ± 12</td>
<td>67 ± 9</td>
<td></td>
</tr>
<tr>
<td>MSNA, burst/min</td>
<td>1.9 ± 1.9</td>
<td>33 ± 3.9</td>
<td></td>
</tr>
<tr>
<td>MSNA, burst/100 bpm</td>
<td>32 ± 3.4</td>
<td>50 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>89 ± 1.5</td>
<td>87 ± 2.6</td>
<td>0.44</td>
</tr>
<tr>
<td>Insulin, mm/mL</td>
<td>5.5 ± 0.8</td>
<td>8.9 ± 1.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>4.5 ± 0.9</td>
<td>17.3 ± 2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>NEFA, mmol/L</td>
<td>166.2 ± 50.6</td>
<td>358.6 ± 74</td>
<td>0.05</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0.9 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Plus–minus values are expressed as mean ± SE. To convert values of norepinephrine to nanomoles per liter multiply by 0.0059, glucose to millimoles per liter multiply by 0.056, and insulin to picomoles per liter multiply by 6. RRI indicates R-R interval; LFSBP, low frequency of SBP variability; TPR, total peripheral resistance; BRS, baroreflex slope; and MSNA, muscle sympathetic nerve activity.

\(P^*\) values were calculated by Mann–Whitney U test.
Effect of Ganglionic Blockade on REE

In contrast to the greater decrease in blood pressure induced by trimethaphan in obese subjects, REE adjusted by FFM decreased less after ganglionic blockade in obese compared with lean subjects (−26±21 versus −86±15 kcal per day, respectively; \( P=0.035 \); Figure 1A). If REE was analyzed in absolute values, uncorrected to FFM, no significant difference between groups was observed (−59±36 versus −52±41 kcal per day in obese and lean subjects, respectively), and absolute REE remained higher in obese versus lean subjects during trimethaphan infusion (1799±140 versus 1373±78 kcal per day, respectively; \( P=0.04 \)). The slope of the linear relationship between REE and FFM was steeper during ganglionic blockade (\( P=0.01 \)), and the Y intercept was lower (\( P=0.004 \)) and no longer different from 0 (Figure 1B).

Effect of Ganglionic Blockade on Metabolism

Plasma NEFA levels decreased during trimethaphan administration in lean subjects (Table 2), suggesting regulation by the sympathetic nervous system. Basal plasma NEFA levels were higher in obese subjects and failed to decrease significantly with trimethaphan. Ganglionic blockade produced a small but significant decrease in plasma leptin in lean but not in obese subjects. Plasma lactate decreased significantly in both groups. No changes in insulin or glucose were induced by trimethaphan in either group.

Protocol 2

To further explore the contribution of the autonomic nervous system to blood pressure we combined the subjects studied in protocol 1 (\( n=20 \)) with the additional subjects studied in protocol 2 (\( n=30 \)), which included obese hypertensive subjects. REE was not measured in these additional subjects because of results in protocol 1. Baseline supine SBP was 106±1, 117±2, 138±4, 200±9, and 188±5 mm Hg in lean, obese, obese hypertensive, MSA, and PAF patients, respectively. SBP decreased more during trimethaphan administration in the obese hypertensive group (−28±4 mm Hg; 95% CI: −38 to −18.0; Figure 2) compared with normotensive lean (−9±1 mm Hg; 95% CI: −11 to −5.6) or obese (−14±2 mm Hg; 95% CI: −18 to −10.0) subjects. By comparison, blood pressure decreased by −94±10 mm Hg (95% CI: −116 to −73) in MSA patients known to have hypertension mediated by residual sympathetic activity (“positive controls”), whereas it decreased only −15±4 mm Hg (95% CI: −24 to −6) in PAF patients known to have sympathetically independent hypertension (“negative controls”; Figure 2A). After removal of autonomic influences, intrinsic SBP remained higher in obese hypertensive subjects (109±3 mm Hg) compared with lean and obese normotensive subjects (98±2 and 103±2 mm Hg, respectively; \( P=0.004 \); Figure 2B). As expected, SBP was normalized by ganglionic blockade in MSA (96±9 mm Hg), but it remained elevated in PAF patients (164±6 mm Hg).

Baseline heart rate in lean, obese, and obese hypertensive patients was 61±2, 64±3, and 68±2 mm Hg, respectively. Heart rate tended to increase less during autonomic blockade in obese hypertensive subjects compared with obese and lean normotensive subjects (16±3, 20±2, and 23±1 bpm, respectively; \( P=0.153 \)).

Discussion

Our results indicate that sympathetic activation determines the increase in blood pressure associated with obesity. Previous studies had already shown an association between these 2 conditions, but our observation that acute autonomic withdrawal reduced and even normalized blood pressure and peripheral vascular resistance in the obese state provides...
strong evidence for a causal relationship. In contrast, the increases in REE and plasma NEFAs associated with obesity were not significantly decreased by ganglionic blockade, suggesting resistance to the metabolic effects of sympathetic activity in this condition. The relevance of these findings lies in the fact that obesity-associated hypertension could be treated by targeting the sympathetic nervous system.

Two “competing” theories are put forward to explain the relationship between the autonomic nervous system and obesity. According to Landsberg, obesity causes sympathetic activation as a compensatory mechanism to increase energy expenditure. Conversely, the MONA LISA hypothesis (most obesities known are low in sympathetic activity) proposes a decreased sympathetic activity as the primary event predisposing to obesity. The preponderance of evidence supports the hypothesis by Landsberg. Sympathetic activity to skeletal muscle (muscle sympathetic nerve activity), which is tightly coupled to blood pressure control, has been consistently shown to be positively correlated with various indices of adiposity, including BMI, percentage of body fat, and visceral fat, and it is increased in obese hypertensive subjects. This association, however, has been studied mostly in white populations and may not necessarily apply to all ethnic groups. Pima Indians from Arizona, for example, have a high incidence of obesity but lower sympathetic activity compared with whites. Thus, the MONA LISA and Landsberg hypotheses are not necessarily exclusionary and may be applicable to different ethnic groups.

Of note, Pima Indians have a high incidence of diabetes but not hypertension, consistent with their lower sympathetic activity and with the concept that sympathetic activation contributes to hypertension in obesity. In accordance, we found increased sympathetic activity in our obese subjects as measured directly by the microneurography technique and noninvasively by the power of the low-frequency band of blood pressure variability.

Several abnormalities associated with obesity have been implicated in the pathogenesis of sympathetic activation, including central activation by insulin, leptin, and other hormones. Obstructive sleep apnea, commonly observed in obesity, also seems to play an important role; obese subjects with obstructive sleep apnea seem to have higher sympathetic nerve activity and a greater risk for developing hypertension. In the present study, we did not explore these important pathophysiological mechanisms but instead focused on the potential role of the sympathetic nervous system in supporting the increase of blood pressure in obesity.

Previous studies have reported a positive association between sympathetic activity and increased blood pressure in obesity. Furthermore, a causal relationship has been suggested in animal and human studies showing that blockade of sympathetic activity prevents the increase in blood pressure.
in obesity. The approach we used to gauge the autonomic contribution to obesity-associated hypertension was to determine the effect of ganglionic blockade on blood pressure. Autonomic withdrawal induced by ganglionic blockade with trimethaphan had little effect on blood pressure in normal subjects while supine; this is to be expected given that sympathetic tone is low under these conditions. It also has a small effect in PAF patients, in whom autonomic function is virtually absent, despite severe supine hypertension, whereas it has a dramatic lowering effect in blood pressure in MSA patients who have residual sympathetic tone. The fact that intrinsic blood pressure, in the absence of autonomic influences, remains elevated in PAF patients demonstrates that trimethaphan does not simply lower blood pressure in the obese group because of their higher baseline values but that the reduction in blood pressure induced by this ganglionic blocker reflects the autonomic support to blood pressure.

A limitation of using ganglionic blockade with trimethaphan is that it eliminates both sympathetic and parasympathetic activities. The magnitude of the decrease in blood pressure induced by trimethaphan, therefore, may not only reflect tonic sympathetic influence on the heart and blood vessels. Subjects with reduced vagal tone at baseline (eg, the elderly) have a greater reduction in blood pressure with trimethaphan in part because of lessened increase in heart rate. This phenomenon cannot account for the results presented in Figure 1, because these groups were matched by age and gender, and their increase in heart rate was similar. It is also important to note that blood pressure in healthy subjects is regulated by a balance between cardiac output and peripheral resistance modulated by changes in sympathetic nerve activity. In this regard, in our obese subjects, the normalization in blood pressure induced by autonomic withdrawal was related to a greater decrease in vascular resistance.

We conclude, therefore, that sympathetic activity exerts tonic vasoconstriction that contributes to the increased blood pressure found in obesity. We do not imply that acute sympathetic support of blood pressure is the sole determinant of obesity-mediated hypertension. Blood pressure decreased by 28 mm Hg in obese hypertensive subjects, but remained significantly higher (by 11 mm Hg) compared with lean normotensive control subjects. It is possible that nonautonomic factors contribute to hypertension in obese individuals and account for this difference. Also, studies in animal models and humans have documented an increased sympathetic tone to the kidneys in obesity. This will result in stimulation of the renin–angiotensin–aldosterone system and promotion of sodium and fluid reabsorption. Our experimental approach does not allow us to determine the contribution of these long-term sympathetic mechanisms to obesity-associated hypertension. However, this, if anything, would lead to an underestimation of the contribution of the autonomic nervous system to the hypertension of obesity.

The sympathetic nervous system plays a role in energy balance through the regulation of REE, which accounts for 60% to 80% of total energy expenditure in humans and is increased in obesity. The autonomic nervous system regulates REE mostly through stimulation of β adrenoreceptors. It has been proposed that the obesity-induced sympathetic activation increases REE as a way to counteract the excessive energy intake. Our results do not support this hypothesis. On the contrary, we found that autonomic modulation of REE is relatively modest. Both REE and sympathetic activity were increased in our obese subjects, but REE decreased less in obese subjects compared with lean subjects when sympathetic activity is removed. This was true if REE was expressed in absolute terms or if it was adjusted for FFM. This finding suggests that the autonomic nervous system does not contribute to the increase in REE observed in the obese group. Normal aging provides a precedent of a condition characterized by an increase in body fat and sympathetic activity as measured by muscle sympathetic nerve activity but with a reduced sympathetic support to REE. A similar phenomenon was observed with nonesterified FFAs. Plasma NEFAs were increased in obese individuals, likely because of an increase in fat mass, but autonomic withdrawal decreased plasma NEFAs in lean but not in obese subjects, suggesting impairment in sympathetic-mediated lipolysis in the obese state. A potential explanation for these paradoxical findings is that sympathetic stimulation may produce β-adrenoceptor downregulation, thus reducing its importance in regulating thermogenesis. This concept is supported by the observations that the sensitivity to the thermogenic and lipolytic effects of β-agonists and the lipolytic effects of direct stimulation of sympathetic nerves are reduced in obesity.

If sympathetic activation does not explain the increase in the REE characteristic of obesity, then what is the mechanism underlying this phenomenon? FFM is the most important contributor of REE and lean body mass, not just fat mass, is increased in obesity. In our cohort, FFM was 12 kg greater in obese subjects compared with lean control subjects, and FFM accounted for 83% of the variability in REE in the absence of autonomic influences. Thus, the increase in REE observed in obesity is likely attributable in large part to the increase in FFM. We conclude, therefore, that the increase in sympathetic activity that occurs in obesity is an important contributor to blood pressure elevation but provides no metabolic benefit and is ineffective in increasing REE.

Perspectives

Obesity is a major risk factor for the development of hypertension, and its incidence is increasing. This “obesity epidemic” puts at risk the successful reduction in morbidity that we have so far achieved in hypertensive populations. Despite evidence that sympathetic activation contributes to obesity-associated hypertension, medications that reduce sympathetic tone are not included in current guidelines for the treatment of hypertension, perhaps because effective antihypertensive drugs with a better adverse effect profile are available. However, commonly used antihypertensive treatment is ineffective in reducing sympathetic activation. We argue that increased sympathetic activity can be targeted in the treatment of obesity-associated hypertension and that drug development should be directed toward this end.
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References
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