Ethnic Differences in Insulinemia and Sympathetic Tone as Links Between Obesity and Blood Pressure

Christian Weyer, Richard E. Pratley, Soren Snitker, Maximilian Spraul, Eric Ravussin, P. Antonio Tataranni

Abstract—Hyperinsulinemia and increased sympathetic nervous system (SNS) activity are thought to be pathophysiological links between obesity and hypertension. In the present study, we examined the relation among heart rate (HR), blood pressure (BP), and percent body fat (hydrodensitometry or DEXA), fasting plasma insulin concentration, and muscle sympathetic nerve activity (MSNA, microneurography) in male, normotensive whites (n=42) and Pima Indians (n=77). Pima Indians have a high prevalence of obesity and hyperinsulinemia but a relatively low prevalence of hypertension. Compared with whites, Pima Indian men had a higher percent body fat (28% versus 21%) and higher fasting insulin concentrations (210 versus 132 pmol/L) but lower MSNA (27 versus 33 bursts/min) (all P<0.001). In both ethnic groups, HR and BP were positively related to percent body fat and MSNA, and both were significant independent determinants of HR and BP in multiple regression analyses. However, MSNA was positively related to percent body fat and the fasting insulin concentration in whites (r=0.60 and r=0.47, both P<0.01) but not in Pima Indians (r=0.15 and r=0.03, NS) (P<0.01 for ethnic differences in the slope of the regression lines). These results confirm the physiological importance of the SNS in normal BP regulation but indicate that the roles of hyperinsulinemia and increased SNS activity as mediators for the relation between obesity and hypertension can differ between different ethnic groups. The lack of an increase in SNS activity with increasing adiposity and insulinemia in Pima Indians may contribute to the low prevalence of hypertension in this population. (Hypertension. 2000;36:531-537.)

Key Words: adipose tissue ■ hyperinsulinism ■ autonomic nervous system ■ hypertension, obesity ■ ethnic groups

Obesity is associated with an increased risk of cardiovascular diseases including hypertension, stroke, and coronary artery disease. The pathophysiological mechanisms predisposing obese individuals to hypertension are not fully understood, but hyperinsulinemia and increased sympathetic nervous system (SNS) activity have been suggested to play a role. Almost 15 years ago, Landsberg proposed that the hyperinsulinemia associated with obesity-related insulin resistance leads to increased SNS activity, which in turn contributes to increased blood pressure (BP) through chronotropic, vasoconstrictive, and antinatriuretic effects. Although there is both epidemiological and experimental evidence to support the links between obesity/hyperinsulinemia and increased SNS activity and between hyperinsulinemia/increased SNS activity and hypertension, some studies provide conflicting results. Thus, the potential role of hyperinsulinemia and increased SNS activity in the pathogenesis of obesity-related hypertension remains controversial.

Ethnicity may be an important factor to consider since insulinemia, SNS activity, and the propensity for obesity and hypertension all differ substantially among different populations. The Pima Indians of Arizona are interesting in this respect because they have the highest reported prevalence of obesity in the world but a relatively low prevalence of hypertension and atherosclerotic disease. Compared with whites, Pima Indians have, on average, a higher percentage of body fat and higher fasting plasma insulin concentrations, even after controlling for body size and the degree of insulin resistance, but lower SNS activity. On the basis of these findings, it appears that the interrelation between adiposity, insulinemia, SNS activity, and BP may differ between Pima Indians and whites. To further examine these relations and to revisit Landsberg's hypothesis, we analyzed data from a large number of normotensive Pima Indian and white men characterized for body composition, glucose tolerance, fasting plasma insulin concentration, resting heart rate (HR) and BP, and in whom postganglionic efferent sympathetic discharge rates to skeletal muscle (MSNA, muscle sympathetic nerve activity) were recorded directly by microneurography as a measure of SNS activity.
Physical, Metabolic, and Cardiovascular Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whites</th>
<th>Pima Indians</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>42</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>30 ± 1</td>
<td>28 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177 ± 1</td>
<td>172 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>87.1 ± 3.1</td>
<td>96.0 ± 3.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8 ± 1.0</td>
<td>32.2 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>21 ± 1</td>
<td>28 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>20.0 ± 1.9</td>
<td>28.2 ± 1.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>67.1 ± 1.4</td>
<td>67.8 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Waist-to-thigh ratio</td>
<td>1.55 ± 0.02</td>
<td>1.62 ± 0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>4.6 ± 0.4</td>
<td>4.6 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>2-h plasma glucose, mmol/L</td>
<td>6.4 ± 0.3</td>
<td>6.1 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma insulin, pmol/L</td>
<td>132 ± 30</td>
<td>210 ± 36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting MSNA, bursts/min</td>
<td>33 ± 2</td>
<td>27 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>62 ± 1</td>
<td>62 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>113 ± 2</td>
<td>117 ± 1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Resting DBP, mm Hg</td>
<td>64 ± 2</td>
<td>68 ± 1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Methods

Subjects

Since 1992, Pima Indian and white subjects have been admitted to the Clinical Diabetes and Nutrition Section of the NIH in Phoenix, Arizona, for studies of SNS activity as measured by microneurography. For the present analysis, we included all male subjects from our database who had complete measurements of body composition, glucose tolerance and fasting plasma insulin concentration, resting HR and BP, and resting MSNA (42 whites, 77 Pima Indians, Table). All subjects were between 18 and 50 years of age, nondiabetic (75 g oral glucose tolerance test), normotensive [resting systolic (SBP) and diastolic (DBP) BP <140 and <90 mm Hg, respectively], nonsmokers at the time of the study, and healthy according to a physical examination and routine laboratory tests. None of the subjects had a personal history of hypertension or cardiovascular disease and none was taking any medication. All subjects were admitted to the National Institutes of Health Clinical Research Unit, where they were fed a weight-maintaining diet (50% of calories as carbohydrate, 30% as fat, and 20% as protein) and abstained from strenuous exercise for at least 3 days before testing. The study was approved by the Tribal Council of the Gila River Indian Community and by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases, and all subjects provided written informed consent before participation.

Anthropometric Measurements

Body composition was estimated by either underwater weighing with simultaneous determination of residual lung volume with helium dilution or by total-body dual-energy x-ray absorptiometry (DPX-L; Lunar Corp.). A conversion equation was used to make measurements comparable between the two methods.24 The waist-to-thigh ratio was assessed as an index of body fat distribution.

Oral Glucose Tolerance Test

After a 12-hour overnight fast, subjects underwent a 75-g oral glucose tolerance test. Plasma glucose and insulin concentrations were determined by the glucose oxidase method (Beckman Instruments) and radioimmunoassay, respectively.24

Measurement of Resting MSNA, HR, and BP

On a separate day after a 12-hour overnight fast, resting MSNA was measured by microneurography as previously described.19 In brief, a tungsten microelectrode was inserted into the peroneal nerve posterior to the fibular head and a reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. The electrical signal was amplified, filtered, full-wave rectified, and integrated to obtain a full-voltage neurogram. HR, SBP, and DBP were continuously monitored with an automated sphygmomanometer (Escort 100, Medical Data Electronics). When a successful neurogram was obtained (for criteria, see Reference 19), subjects rested quietly for 20 minutes to allow physiological measures to return to baseline. Then, subjects remained supine with their eyes open for a 10-minute baseline period, during which HR and BP were measured each minute and MSNA was recorded continuously with a physiological recorder (Windograph, model 40-8474, Gould). Mean resting HR, SBP, and DBP were calculated as the average of the 10 baseline measurements. MSNA was identified visually and expressed as the mean number of bursts per minute averaged over the 10-minute baseline period.19

Statistical Analysis

Statistical analyses were performed with the software of the SAS Institute. Measurements were compared between Pima Indians and whites by the use of general linear regression models with and without simultaneous adjustment for age and percent body fat. Simple correlation analyses were used to assess the relations among percent body fat, fasting insulin, MSNA, HR, and BP within each ethnic group. Partial correlation analyses and multiple regression analyses were used to examine the relation between different measures after adjustment for covariates and to assess whether the relations differ between Pima Indians and whites. Results are given as mean ± SEM.

Results

The characteristics of the study population are given in the Table. On average, Pima Indians were shorter and heavier than whites and had a higher percent body fat. There were no ethnic differences in mean fasting and 2-hour plasma glucose concentrations, but the mean fasting plasma insulin concentration was higher in Pima Indians, a difference that remained significant (P<0.01) after adjustment for percent body fat. Pima Indians had lower MSNA, similar HR, and higher SBP and DBP as compared with whites. After adjustment for percent body fat, the ethnic difference in MSNA increased from 5 bursts/min (P<0.001) to 9 bursts/min (P<0.0001), whereas SBP and DBP were no longer different between the two groups.

Correlation Analyses

Adiposity

HR, SBP, and DBP were all positively related to percent body fat in both whites (HR: r=0.27, P<0.05; SBP: r=0.49, P<0.005; DBP: r=0.39, P<0.05) and Pima Indians (HR: r=0.25, P<0.05; SBP: r=0.30, P<0.01; DBP: r=0.22, P<0.07), as was the fasting insulin concentration (Figure 1). In contrast, MSNA was positively related to percent body fat in whites but not in Pima Indians (Figure 1, P<0.01 for an ethnic difference in the slopes of the regression lines). In whites, SBP and DBP but not HR remained significantly related to percent body fat after adjustment for MSNA (partial r=0.31, P<0.06; r=0.36, P<0.05; and r=0.14, NS, respectively). In Pima Indians, HR and SBP but not DBP...
remained significantly related to percent body fat after adjustment for MSNA (partial \( r = 0.28, P < 0.05; r = 0.31, P < 0.01; \) and \( r = 0.18, \) NS, respectively).

**Insulinemia**

MSNA was positively related to fasting insulin concentration in whites but not in Pima Indians (Figure 1, \( P < 0.01 \) for an ethnic difference in the slopes of the regression lines). In whites, the relation between MSNA and fasting insulin concentration remained significant after adjustment for percent body fat (partial \( r = 0.34, P < 0.05 \)). Neither HR nor SBP and DBP were related to fasting insulin concentration in whites (Figure 2). In Pima Indians, SBP but neither HR nor DBP was positively related to fasting insulin concentration (Figure 2). The relation between SBP and fasting insulin concentration in Pima Indians was no longer significant after adjustment for percent body fat.

**MSNA**

HR and SBP were positively related to MSNA in both whites and Pima Indians (Figure 3). DBP was positively related to MSNA in Pima Indians but not in whites.

In multiple regression analyses with adjustment for age and ethnicity, percent body fat and MSNA were significant independent determinants of HR, SBP, and DBP. Together, these four factors explained 17%, 24%, and 25% of the variance (\( R^2 \)) in HR, SBP, and DBP, respectively. Fasting insulin concentration was not a significant determinant of either measure.

The ethnic differences in mean MSNA as well as in the relation between MSNA and percent body fat and insulinemia remained significant when MSNA was expressed as bursts/100 heartbeats, whereas SBP and DBP were no longer significantly related to MSNA in either ethnic group after the latter had been normalized for heart rate.

**Discussion**

The results of the present study in normotensive white and Pima Indian men confirm the physiological importance of the SNS in normal BP regulation but indicate that the roles of hyperinsulinemia and increased SNS activity as links between obesity and BP can differ between different ethnic
groups. The lack of increase in MSNA with increasing adiposity and insulinemia in Pima Indians may explain, in part, why this population has a low propensity for hypertension despite the high prevalence of obesity and hyperinsulinemia.

Our results in whites seem to support Landsberg’s hypothesis,2 because increased adiposity and elevated fasting plasma insulin concentrations were associated with increased MSNA and because MSNA in turn was positively correlated with HR and BP. The former observation agrees with findings from 2 previous microneurography studies,8,9 which also showed increased MSNA in obese whites. Other studies, however, have found conflicting results,13–16,27 bringing into question whether increased SNS activity is, in fact, a hallmark of human obesity.17,18 The finding that the fasting plasma insulin concentration was an additional determinant of MSNA in whites, independent of percent body fat, agrees with the study by Scherrer et al9 and is in keeping with experimental evidence that hyperinsulinemia may lead to increased SNS activity.10 However, our results also confirm the previous assumption2 that hyperinsulinemia-induced SNS activation may not be the only link between obesity and elevated BP. First, MSNA remained significantly related to percent body fat after adjustment for the fasting insulin concentration, indicating that hyperinsulinemia is not the only and probably not the primary mechanism responsible for increased SNS activity in obese whites. Second, BP remained related to percent body fat after adjustment for MSNA, indicating that mechanisms other than hyperinsulinemia and increased SNS activity must be in place to mediate the association between obesity and BP. As recently reviewed,28 these mechanisms might include obesity-related alterations in the structure and function of the cardiovascular system, in glomerular morphology and renal sodium excretion, and/or in leptin secretion and signaling.

Several previous studies have reported increased SNS activity in individuals with hypertension.29,30 Our results indicate that MSNA is positively correlated with HR and BP even within the normotensive range, confirming the physiological importance of SNS activity in normal BP regulation. Although the observed positive association between MSNA and HR agrees with findings by others,31 it is noteworthy that the positive association between MSNA and BP in the present study disappeared when MSNA was normalized for HR. This seems to support recent findings indicating that MSNA and HR have
interactive effects on BP. As with SNS activity, we and others have previously shown that BP increases with increasing insulinemia in whites. The fact that these findings could not be confirmed in the present study is probably due to the small number of subjects. Mechanisms other than increased SNS activity that could account for the association between insulinemia and BP include the effect of insulin on renal sodium excretion and the resistance of vascular smooth muscle cells to the vasodilatory effect of insulin.

Our results in Pima Indians provide further interesting insights into the relation between adiposity, insulinemia, SNS activity, and BP. In agreement with previous findings, Pima Indian men were more obese and had markedly higher fasting plasma insulin concentrations than white men but had lower MSNA. This ethnic difference in MSNA appears to be largely attributable to the fact that MSNA does not increase with increasing adiposity in Pima Indians as it does in whites. Thus, low MSNA in Pima Indians does not seem to be an inherent characteristic but rather the result of a different SNS response to weight gain. This might be due, at least in part, to the dissociation between insulinemia and MSNA. Although insulinemia increases with increasing adiposity in Pima Indians, this is not accompanied by an increase in MSNA, as is the case in whites. Our findings in Pima Indians, therefore, indicate that hyperinsulinemia is not invariably associated with increased SNS activity, thus challenging Landsberg’s hypothesis. It is possible that obese Pima Indians, who manifest resistance to the action of insulin on peripheral glucose uptake, also become resistant to the central effects of insulin to stimulate sympathetic outflow. However, MSNA does increase acutely in response to insulin infusion in Pima Indians, suggesting that central SNS activation can be provoked. It has recently been suggested that MSNA may be increased primarily in those obese individuals who have obstructive sleep apnea. Although we did not test for the presence of sleep apnea in the present study, our clinical experience is that this condition is not less prevalent in obese Pima Indians than in obese whites. We have previously reported that in addition to having lower MSNA, Pima Indian men may

**Whites**

**Pima Indians**

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Figure 3. Relations between resting HR, systolic and diastolic BP, and resting MSNA in male normotensive whites (left panels) and Pima Indians (right panels).
also have lower β-adrenergic sensitivity than whites. In the present study, however, MSNA was positively related to HR and BP in Pima Indians and in whites, indicating that the low prevalence of hypertension in Pima Indians is probably not due to a resistance of the cardiovascular system to the stimulatory effect of the SNS. Rather, it appears that the lack of increase in MSNA with increasing adiposity and insulinemia in Pima Indians may contribute to their low propensity for hypertension. However, our data in normotensive subjects cannot ultimately prove this hypothesis.

While the direct measurement of MSNA by microneurography is highly reproducible and offers several advantages over indirect methods, it only assesses postganglionic efferent sympathetic discharge rates to skeletal muscle and therefore does not allow for the determination of regional differences in SNS activity. These could be important, however, because recent evidence suggests that sympathetic overactivity in human obesity might be restricted to certain organs such as the kidneys. Furthermore, our conclusions are based on associative findings and warrant confirmation by intervention studies.

In summary, the present study indicates that in both whites and Pima Indians, HR and BP are positively and independently related to percent body fat and MSNA. However, MSNA is positively and independently related to percent body fat and insulinemia only in whites but not in Pima Indians. These results confirm the physiological importance of the SNS in normal BP regulation but indicate that the roles of hyperinsulinemia and increased SNS activity as mediators of the relation between obesity and BP can differ between different ethnic groups. The lack of increase in SNS activity with increasing adiposity and insulinemia in Pima Indians may contribute to the low prevalence of hypertension in this population.

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References


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