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Participation of the Hypothalamus-Hypophysis Axis in the Sympathetic Activation of Human Obesity

Guido Grassi, Gino Seravalle, Raffaella Dell’Oro, Carlo Turri, Lucia Pasqualinotto, Manuela Colombo, Giuseppe Mancia

Abstract—Previous studies have shown that hypothalamic and hypophyseal factors are involved in the acute sympathoexcitation induced by a variety of laboratory stimuli. Whether a chronic condition of sympathetic activation, such as that characterizing human obesity, is also dependent on these factors has never been investigated. In 40 normotensive obese subjects (mean±SEM age, 39.1±0.8 years) we measured blood pressure (Finapres), heart rate (ECG), and postganglionic muscle sympathetic nerve activity (MSNA) (microneurography). In 20 subjects measurements were repeated, according to a double-blind randomized sequence, after a midnight oral dose of dexamethasone (1 mg) (n=10) or placebo (n=10), while in the remaining subjects they were performed again after 1 week of a daily evening oral administration of 1 mg of dexamethasone (n=10) or placebo (n=10). The same protocol was performed in 16 age-matched lean normotensives. In both groups acute dexamethasone administration markedly reduced plasma cortisol (radioimmunoassay), without affecting hemodynamic and neural variables. In contrast to the acute administration, in obese subjects prolonged dexamethasone administration, although not affecting blood pressure and heart rate, significantly reduced both plasma cortisol (from 16.0±1.3 to 0.7±0.1 μg/dL; P<0.01) and MSNA (from 59.5±2.8 to 39.6±2.9 bursts per 100 heartbeats; P<0.02; -33.1±4.1%). This was not the case in lean subjects, in which the dexamethasone-induced reduction in plasma cortisol was associated with a slight and nonsignificant MSNA decrease. In both lean and obese subjects, placebo administration caused no change in any variable. Thus, prolonged dexamethasone administration exerts in obese subjects marked sympatoinhibitory effects that are not detectable in lean individuals. This suggests that hypothalamic and hypophyseal factors substantially contribute to the sympathoexcitation of obesity. (Hypertension. 2001;38:1316-1320.)

Key Words: obesity □ sympathetic nervous system □ hypothalamus □ hormones

In anesthetized rats or dogs, intracerebroventricular administration of corticotropin-releasing hormone (CRH) increases plasma levels of norepinephrine and elicits a sudden rise in blood pressure (BP) that is abolished by ganglionic blockade, thereby indicating origination from sympathoexcitation.1,2 Furthermore, in conscious rats the sympathetic activation induced by stress is suppressed by acute blockade of CRH release by dexamethasone.3 Finally, the acute increase in muscle sympathetic nerve activity (MSNA) that occurs in humans by administering alcohol intravenously or by increasing plasma insulin through a euglycemic clamp is also suppressed by a dose of dexamethasone capable of blocking corticotropin.4,5 Thus, the activation of the sympathetic nervous system (as well as the related cardiovascular effects) acutely occurring in response to a number of laboratory stimuli appears to be mediated at least in part by centrally secreted peptides and possibly also by the intervention of the hypothalamus-hypophysis axis.

Whether the dependence of the sympathetic activation on the aforementioned mechanisms is confined to acute conditions naturally characterized by chronic sympathetic activation has never been assessed. We addressed this issue by studying the effect of acute and prolonged dexamethasone administration on MSNA, directly recorded in a peroneal nerve via microneurography, in subjects with a marked degree of obesity, ie, a condition almost invariably characterized by adrenergic hyperactivity.6–11 The results were compared with those obtained in age-matched lean normotensives.

Methods

The study population consisted of 56 subjects of both genders (40 men, 16 women) with age ranging from 20 to 57 years, classified as obese (n=40) or lean (n=16) according to a body mass index value >27 kg/m² (range, 30 to 40 kg/m²) or <27 kg/m² (range, 21 to 26 kg/m²), respectively. The subjects selected had (1) BP values <140/90 mm Hg at repeated sphygmomanometric measurements performed on 2 visits in the outpatient clinics; (2) no diabetes mellitus and no history or physical or laboratory evidence of cardiovascular or noncardiovascular diseases; and (3) no history of short-lived experimental stimuli or also occurs in conditions naturally characterized by chronic sympathetic activation has never been assessed. We addressed this issue by studying the effect of acute and prolonged dexamethasone administration on MSNA, directly recorded in a peroneal nerve via microneurography, in subjects with a marked degree of obesity, ie, a condition almost invariably characterized by adrenergic hyperactivity.6–11 The results were compared with those obtained in age-matched lean normotensives.

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cigarette smoking and/or excessive alcohol consumption. All subjects gave written informed consent to participate in the study; the protocol was approved by the Ethics Committee of our institution.

**Measurements**

The methodological details of the procedures we used to assess sphygmonanometric and beat-to-beat (Finapres 2300, Ohmeda) BP, heart rate (HR, by use of ECG), respiration rate (pneumotachograph), and MSNA (microneurography) have been described in previous reports.9,10,12,13 With the exception of sphygmonanometric BP, all measurements were displayed on thermic paper by an ink polygraph (Gould 3800). Plasma cortisol was assayed by radioimmunoassay* on a venous blood sample withdrawn between 7:30 and 8:30 AM.

**Protocol and Data Analysis**

All subjects were studied in the morning after a light breakfast and an overnight abstinence from alcohol and coffee consumption. They were placed supine and fitted for the intravenous cannula, the microelectrodes for MSNA recording, and the other measuring devices. After the withdrawal of a blood sample for cortisol assessment, 3 sphygmonanometric BP measurements were performed. All measuring devices were then set, and after 30 minutes BP, HR, respiration rate, and MSNA were continuously measured during a 30-minute period. In 20 obese subjects the procedure was repeated the following morning after instructions to take an oral dose of dexamethasone (1 mg, n=10) or placebo (n=10) at midnight. In the remaining 20 obese subjects the procedure was repeated after 1 week, during which the subjects were instructed to take a daily evening oral dose of 1 mg dexamethasone (n=10) or placebo (n=10). The 16 lean subjects were studied (1) in the baseline state; (2) after an acute midnight oral dose of dexamethasone (1 mg, n=8) or placebo (n=8); and (3) after 1 week of a daily evening oral dose of dexamethasone (1 mg, n=8) or placebo (n=8). In all subjects dexamethasone or placebo administration was performed according to a randomized, double-blind sequence. Adherence to treatment was verified by counting of pills.

Data were analyzed by a single independent observer unaware of the study design and of whether subjects belonged to the dexamethasone or placebo group. Values from individual subjects were averaged for each group and expressed as mean ± SEM. Comparisons between data obtained before and after dexamethasone or placebo or in lean and obese subjects were made by 2-way ANOVA. The 2-tailed Student’s t test for paired and unpaired observations was used to locate the statistical differences between (1) the condition preceding and following dexamethasone or placebo and (2) the data obtained in lean and obese subjects, respectively. The Bonferroni correction for multiple comparisons was used. A value of P<0.05 was taken as the level of statistical significance.

**Results**

As shown in Table 1, in both obese and lean subjects a single oral dose of dexamethasone did not alter sphygmonanometric BP, finger BP, HR, and respiration rate, but it reduced plasma cortisol to almost undetectable values. As shown in Figure 1, in the obese subjects baseline MSNA averaged 39.6 ± 2.2 bursts per minute and 57.4 ± 3.0 bursts per 100 heartbeats, ie, it showed values almost double those found in lean subjects. In both obese and lean subjects, MSNA did not show any change after the single dose of dexamethasone either when quantified as burst incidence over time (bursts per minute) or when quantified as number of bursts corrected for HR values (bursts per 100 heartbeats). No hemodynamic, respiratory, hormonal, or neural changes were seen in the 2 groups after placebo administration (Table 1 and Figure 1).

Table 2 and Figure 2 show the effects of prolonged administration of dexamethasone. In both obese and lean subjects this intervention also did not alter BP and HR, while it strikingly reduced plasma cortisol levels. In contrast to the single-dose administration, however, in obese subjects the prolonged administration of dexamethasone significantly and markedly reduced both the number of sympathetic bursts per minute (−35.8 ± 4.2%; P<0.01) and the number of sympathetic bursts per 100 heart beats (−33.1 ± 4.1%). This was not the case in lean individuals, in whom the prolonged dexamethasone administration caused a slight and nonsignificant reduction in MSNA, expressed as either burst incidence over time (−10.9 ± 3.0%; P=NS) or burst number per 100 heartbeats (−9.1 ± 2.5%; P=NS). Again, no change was seen in obese and lean subjects followed for 1 week with placebo administration.

**Discussion**

In our normotensive obese subjects, MSNA was markedly greater than in age-matched lean individuals, thus confirming

### TABLE 1. Effects of Acute Administration of Dexamethasone or Placebo on Anthropometric, Hemodynamic, and Plasma Cortisol Levels in Obese and in Lean Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obese Subjects</th>
<th>Lean Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DXM</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>36.2 ± 1.6</td>
<td>36.2 ± 1.6</td>
</tr>
<tr>
<td>Sphygmonanometric SBP, mm Hg*</td>
<td>124.6 ± 2.9</td>
<td>122.7 ± 2.5</td>
</tr>
<tr>
<td>Sphygmonanometric DBP, mm Hg*</td>
<td>76.9 ± 2.5</td>
<td>77.4 ± 2.3</td>
</tr>
<tr>
<td>Finapres SBP, mm Hg</td>
<td>122.8 ± 2.5</td>
<td>120.4 ± 2.6</td>
</tr>
<tr>
<td>Finapres DBP, mm Hg</td>
<td>74.1 ± 2.4</td>
<td>74.5 ± 2.7</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69.2 ± 3.1</td>
<td>68.8 ± 3.3</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>18.2 ± 0.8</td>
<td>18.5 ± 0.9</td>
</tr>
<tr>
<td>Cortisol, μg/dL</td>
<td>16.2 ± 1.4</td>
<td>16.0 ± 1.1</td>
</tr>
</tbody>
</table>

*BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; and DXM, acute dexamethasone (1 mg/d) administration. Values are mean ± SEM. Mean age of the obese subjects in the DXM (n=10) and placebo (n=10) groups was 37.5 ± 3.1 and 38.3 ± 2.9 years, respectively. The corresponding age in the lean subjects was 38.8 ± 2.8 (n=8) and 39.4 ± 3.2 years (n=8), respectively.

*Average of 3 measurements.
previous evidence that a marked increase in body weight is associated with central sympathetic activation.9,10 The new evidence that a marked increase in body weight is unaffected by acute administration of dexamethasone at a dose capable of virtually suppressing plasma cortisol (and presumably corticotropin) levels, but it was clearly reduced when this suppression was maintained for 1 week by the repeated drug administration. Thus, prolonged dexamethasone administration has an effect on the central sympathetic hyperactivity of obese subjects similar to the effect of a single dose of the drug on the acute central adrenergic activation induced by alcohol or insulin infusion.4,5 This is compatible with the possibility that the chronic sympathetic overactivity of the obese state depends at least in part on substances and/or structures whose release and/or function are altered by dexamethasone administration.

Our study does not clarify which substances and/or structures are responsible for the obesity-related sympathoexcitatory effect seen after prolonged administration of dexamethasone could not be artifically determined by the drug per se because exogenous

**TABLE 2. Effects of Prolonged Administration of Dexamethasone or Placebo on Anthropometric, Hemodynamic, and Plasma Cortisol Levels in Obese and in Lean Normotensive Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obese Subjects</th>
<th>Lean Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>D XM</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>38.1±1.4</td>
<td>38.0±1.4</td>
</tr>
<tr>
<td>Sphygmomanometric SBP, mm Hg*</td>
<td>123.8±3.1</td>
<td>122.1±3.0</td>
</tr>
<tr>
<td>Sphygmomanometric DBP, mm Hg*</td>
<td>77.4±2.8</td>
<td>76.7±2.6</td>
</tr>
<tr>
<td>Finapres SBP, mm Hg</td>
<td>122.0±2.6</td>
<td>120.9±2.7</td>
</tr>
<tr>
<td>Finapres DBP, mm Hg</td>
<td>74.7±2.5</td>
<td>74.0±2.7</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73.0±3.3</td>
<td>74.7±3.2</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>19.3±0.9</td>
<td>18.8±1.0</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>16.0±1.3</td>
<td>0.7±0.1</td>
</tr>
</tbody>
</table>

DXM indicates values after 1 week of dexamethasone (1 mg/d) administration; placebo, values after 1 week of placebo administration. Other abbreviations are as defined in Table 1. Values are mean±SEM. Mean age of the obese subjects in the DXM (n=10) and in the placebo (n=10) groups was 40.7±3.1 and 41.1±3.2 years, respectively. The corresponding age in the lean subjects was 38.8±2.9 (n=8) and 39.4±3.2 years (n=8), respectively.

*Average of 3 measurements.
Glucocorticoids have been shown to have effects, eg, insulin resistance and thus hyperinsulinemia, which may favor rather than restrain central sympathetic outflow. It is also important to emphasize that the sympathetic activation of human obesity is unlikely to be due to endogenous glucocorticoids, because cortisol infusion in humans has been shown, if anything, to inhibit MSNA. This leads to the possibility of major involvement of substances released from the hypothalamus and/or the hypothalamus. There is indeed evidence that in humans acute administration of corticotropin triggers a sympathetic activation. There is also evidence that, in animals, CRH and neuropeptide Y (ie, peptides released by the hypothalamus) stimulate central sympathetic nerve traffic through (1) hormonal effects (corticotropin release) that increase circulating insulin levels; (2) activation of pathways descending from the hypothalamus to the medulla and spinal sympathetic neurons; and (3) determination of insulin resistance (and thus a further increase in insulin levels) through sympathetic vasoconstriction in the skeletal muscle circulation. This implies the intervention of substances that act through but also independently of the hypothalamus-hypophysis adrenal axis.

Our study raises the question of whether the involvement of the aforementioned mechanisms in the sympathetic overactivity seen in obesity is specific to this condition or can also be seen in the absence of any increase in body weight, thereby representing a more generalized participation of hypothalamic and hypophyseal factors in any degree of sympathetic activity. The latter possibility is supported by the report of Dodt and coworkers that in lean subjects an intravenous infusion of hydrocortisone was accompanied by some MSNA reduction. It is also supported by the finding of Macefield et al that in lean individuals MSNA was significantly reduced by a 5-day dexamethasone administration. However, other considerations and data speak against a substantial participation of the hypothalamic and hypophyseal factors in the determination of the level of sympathetic activity characterizing lean subjects. First, in the study of Macefield and coworkers, inhibition of MSNA would be alternatively explained by the fact that the dose of dexamethasone used was high enough to increase BP and thus cause sympathoinhibition through a reflex mechanism. Furthermore, Scherrer and coworkers observed no change in MSNA after acute dexamethasone administration in lean individuals. Finally, in our lean subjects, either acute or chronic dexamethasone administration, at a dose that did not alter BP, failed to consistently affect MSNA, although admittedly the average individual change was qualitatively similar to that seen in obese individuals. It would thus seem that the sympathoexciting effect of hypothalamic and hypophyseal factors is, if not specific to the obese state, at least more evident when there is a pathological increase in body weight. This may originate from a hyperfunction or dysfunction of the hypothalamus-hypophysis axis in obesity, as suggested by the evidence that (1) in our obese individuals cortisol levels were greater than in controls, (2) greater baseline cortisol levels have been reported in the metabolic syndrome X, and (3) CRH not only exerts sympathoexcitatory effects but also regulates diet-induced thermogenesis in a fashion that alters body weight.

Several other points deserve to be discussed. First, in our study acute dexamethasone administration had no effect on sympathetic outflow, which is at variance from previous studies in which the sympathoexcitation induced by increased...
insulin levels or alcohol administration quickly vanished after a single dose of the drug.4–5 This may imply that different central mechanisms are involved. It is also possible, however, that the mechanisms are the same but that it is more difficult to reduce a chronic sympathoexcitatory state, as in obesity, by sympathoinhibitory interventions. Second, in our obese patients prolonged dexamethasone administration did not allow MSNA to return to values entirely comparable to those found in age-matched lean individuals. Thus, mechanisms other than the hypothalamic and hypophyseal mechanisms are likely to participate in the central sympathetic overactivity associated with obesity. Third, in our study neither acute nor prolonged dexamethasone administration caused any increase in BP, HR, or body weight, which makes it unlikely that the reduction in MSNA was due in part to a stimulation of arterial and cardiopulmonary volume receptors.27 However, a reflex contribution to the sympathetic effects we observed cannot be entirely excluded because (1) lack of central blood volume and pressure measurement does not allow us to rule out an increase in cardiopulmonary receptor activity27 and (2) a baroreflex activation may have counterbalanced the direct effects of dexamethasone.27

Finally, it may seem surprising that in our obese patients the MSNA reduction after prolonged dexamethasone administration was not paralleled by a reduction in BP. We can speculate that this depends on the fact that in obesity the sympathetic hyperactivity is not generalized to the whole cardiovascular system,28 and that only in the limited number of districts where there is an increased sympathetic outflow do hypothalamic and hypophysal factors play a role. It is also possible, however, that although the sympathoinhibitory effect of dexamethasone was diffused, a clear-cut fall was prevented by direct peripheral pressor mechanisms at the neuroeffector junctions or at receptor level.29 This has been shown to occur for insulin infusion with no change in BP because of a concomitant peripheral vasodilatation.5,16 It has also been shown to occur for cigarette smoking, which acutely inhibits central sympathetic outflow to muscle with an increase in BP due to a concomitant increase in peripheral norepinephrine secretion leading to systemic vasoconstriction.30

References