Sympathetic Nerve Traffic Responses to Surgical Removal of Pheochromocytoma

Guido Grassi, Gino Seravalle, Carlo Turri, Giuseppe Mancia

Abstract—Pheochromocytoma is usually characterized by a marked increase in peripheral catecholamine secretion. Whether this is accompanied by an alteration in central sympathetic drive has not been clarified. In 6 patients with adrenal pheochromocytoma (mean±SEM age, 49.3±7.2 years), we measured systolic and diastolic blood pressure (photoplethysmographic device), heart rate (ECG), venous plasma catecholamines (high-performance liquid chromatography), and postganglionic muscle sympathetic nerve activity (microneurography) before and 78.3±13 days after surgical removal of the tumor. In each experimental session, measurements were performed during (1) a 60-minute resting period to compare several values of sympathetic nerve traffic at similar blood pressures before and after surgery and (2) voluntary end-expiratory apnea, ie, a maneuver inducing sympathetic activation. Tumor removal significantly (P<0.05 at least) reduced plasma catecholamines, blood pressure, and heart rate. In contrast, muscle sympathetic nerve activity was significantly (P<0.01) increased, both when quantified as bursts per minute (from 28.1±5.7 to 54.3±7.5) and as bursts per 100 heartbeats (from 33.4±5.6 to 65.1±6.5). This was also the case when data were evaluated in periods of 2 experimental sessions characterized by similar diastolic blood pressure values. The apnea maneuver induced sympathetic nerve traffic responses that were significantly (P<0.05) greater after surgery than before surgery. These data provide the first direct evidence that in pheochromocytoma central sympathetic outflow is markedly reduced and that this reduction cannot be ascribed to a reflex inhibitory response to elevated blood pressures. It is likely that this sympathoinhibition is rather due to a central depression of sympathetic outflow induced by high circulating catecholamines. (Hypertension. 1999;34:461-465.)

Key Words: nervous system, sympathetic n catecholamines n nervous system, autonomic

The contribution of sympathetic nerve activity to blood pressure (BP) levels in pheochromocytoma is controversial. This is because it has been widely assumed that in this condition the BP elevation and the high level of circulating catecholamines should lead to a depression of sympathetic outflow by reflex mechanisms and direct stimulation of central adrenergic receptors, respectively. It has been reported, however, that in rats harboring a pheochromocytoma, pithing is accompanied by a clear-cut BP reduction,1 pointing toward a sizable neural contribution to the BP elevation characterizing this condition. Furthermore, evidence has been produced that central sympathoinhibition by clonidine causes a similar BP reduction in patients with pheochromocytoma and with essential hypertension,3 suggesting a similar degree of tonic sympathetic activity in both conditions.

We have previously shown that muscle sympathetic nerve traffic as quantified by microneurography is much greater in patients with essential hypertension than in patients with a pheochromocytoma.3 In the present study we report muscle sympathetic nerve activity (MSNA) values in patients with an adrenal pheochromocytoma before and after surgical removal of the tumor. The results indicate that after surgery sympathetic nerve activity markedly increases, documenting for the first time that in this disease there is indeed a central sympathoinhibition.

Methods

Subjects

Our study was performed in 6 subjects (5 men, 1 woman; mean age, 49.3±7.2 years) with a monolateral adrenal pheochromocytoma diagnosed between January 1995 and March 1998. All patients were referred to our hypertension clinic for symptoms compatible with the occurrence of paroxysmal hypertensive crises accompanied by either sustained hypertension (4 patients) or normotension (2 patients). In all patients, the diagnosis of pheochromocytoma was made on the basis of high values of plasma catecholamines (venous sample, high-performance liquid chromatography4) and a positive CT scanning of the adrenal glands. The diagnosis was confirmed by histological examination of tissue removed at surgery.

All patients were in sinus rhythm, and none had a history of smoking, excessive alcohol consumption, or clinical evidence of coronary heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, or diabetes mellitus. Routine laboratory values were all in the normal range. The study protocol was received November 9, 1998; first decision December 24,1998; revision accepted May 3, 1999.

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approved by the ethics committee of our institution. The subjects agreed to participate after being informed of the nature and purpose of the study.

**Measurements**

BP was measured by a mercury sphygmomanometer, with the first and fifth Korotkoff sounds identifying systolic and diastolic values, respectively. BP was also measured by a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values. Heart rate (HR) was monitored beat to beat by a cardiotachometer triggered by the R wave of an ECG lead. Respiration rate was monitored by a strain-gauge pneumograph positioned at the midcheek level. Body mass index was determined before and after tumor removal. In each patient an echocardiogram was obtained in M mode (after identification of the proper measuring section in B mode) to quantify left ventricular end-diastolic diameter and wall thickness (posterior wall plus septum). The echocardiographic data were collected by a single operator before and after surgery. The within-operator coefficients of variation for 2 left ventricular end-diastolic diameter and left ventricular wall thickness measurements obtained at a 2-day interval under standardized conditions were 4% and 7%, respectively.

Multiunit recording of efferent postganglionic MSNA was obtained from a tungsten microelectrode inserted in a peroneal nerve posterior to the fibular head, as previously described. Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with BP, HR, and respiration rate on an ink polygraph (Gould 3800, Gould Instruments). The muscle nature of MSNA was established according to the criteria mentioned in previous studies, and the recording was accepted only if the signal-to-noise ratio exceeded the value of 3. Under baseline conditions, MSNA was quantified both as burst frequency over time (bursts per minute) and as number of bursts corrected for HR values (bursts per 100 heartbeats), ie, by parameters that our group and others have shown to be highly reproducible on both short- and long-term bases. The MSNA response to voluntary apnea (see below) was estimated by calculating both the changes in number of bursts and the percent changes of integrated activity (number of bursts over time×mean burst amplitude, expressed in arbitrary units), with the 5 minutes before the apnea maneuver taken as control value. This integration has been shown to provide reproducible values, ie, to differ only 3.8% when assessed twice in the same session by a single investigator.

**Protocol and Data Analysis**

All 6 patients were studied after a 5- to 7-day hospitalization, during which the diagnosis of pheochromocytoma was made. At hospital admission, 4 patients reported being under drug treatment (α- and β-blockers), while 2 patients reported no previous treatment. Because of the modest degree of sustained BP elevation and the infrequent occurrence of hypertensive crises, 5 individuals were given no treatment for 5 days, and BP values were intermittently measured throughout the 24 hours by a semi-automated device. The remaining individual was given 50 mg of carvedilol daily (a drug blocking α- and β-adrenergic receptors), and this subject’s BP was monitored intermittently by a semi-automated device.

The study was performed in the morning after the subjects had eaten a light breakfast. The protocol of the study was as follows: (1) subjects were placed supine and fitted with devices that allowed sphygmomanometric measurement of BP, finger BP, HR, and respiration rate; (2) BP was also measured 3 times by mercury sphygmomanometer; (3) a microelectrode was inserted into a peroneal nerve to obtain MSNA, which was recorded together with finger BP, HR, and respiration rate for 60 minutes; (4) subjects were asked to hold their breath for at least 30 seconds (voluntary end-expiratory apnea), during which all the aforementioned variables continued to be monitored; (5) the tumor removal was performed 4 to 6 days later; (6) patients were dismissed from the hospital; and (7) after 51 to 94 days, patients were hospitalized again for 3 additional days, after which the study was repeated according to the same procedure outlined from protocol steps 1 to 4. The mean interval between the first and second studies was 78.3±13 days. No patient was receiving antihypertensive drugs at the time of the second study.

Data were analyzed by a single investigator not involved in data collection. In each patient, 3 sphygmomanometric BP values were averaged. Pulse pressure was calculated from the difference between systolic and diastolic values. Finger BP, HR, and MSNA values were averaged every minute of the 60-minute recording period, and the 60 values so obtained were further averaged to determine the mean individual data for the whole recording period. MSNA responses to voluntary apnea were also individually analyzed according to the aforementioned criteria. Data from single patients were averaged to obtain mean values for the group as a whole. Comparisons between data before and after surgery were made by 2-way ANOVA, with the use of the Student’s t test for paired observations to locate the statistical significance of the differences. Data were also calculated as 1-minute averages throughout the 60-minute recording period. This allowed several MSNA values to be compared at times when diastolic BP was superimposable before and after surgery. Correlations between different variables were analyzed by the Spearman method. The level of statistical significance was placed at \( P<0.05 \). The symbol ± refers to SEM.

**Results**

As shown in Figure 1 and the Table, removal of the adrenal pheochromocytoma was accompanied in all patients by a striking fall in plasma venous norepinephrine and epinephrine, a clear-cut reduction in sphygmomanometric and finger systolic and diastolic BP, and a modest reduction in HR, with
Effects of Surgical Removal of Pheochromocytoma on Anthropometric, Hemodynamic, Echocardiographic, Humoral, and Neural Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Surgery</th>
<th>After Surgery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>22.9±0.6</td>
<td>23.3±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg*</td>
<td>164.8±8.8</td>
<td>145.6±9.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg*</td>
<td>104.5±5.0</td>
<td>89.6±5.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg*</td>
<td>60.3±5.6</td>
<td>56.0±5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, finger, mm Hg</td>
<td>166.0±7.7</td>
<td>144.0±9.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic BP, finger, mm Hg</td>
<td>105.0±5.4</td>
<td>88.0±6.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>85.0±4.6</td>
<td>76.1±2.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>18.3±1.2</td>
<td>18.8±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>47.6±1.8</td>
<td>48.8±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVWT, mm</td>
<td>23.3±1.2</td>
<td>22.2±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine, pmol/L</td>
<td>13948.5±1808</td>
<td>1836.2±327</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Epinephrine, pmol/L</td>
<td>2610.6±573</td>
<td>199.8±35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>28.1±5.7</td>
<td>54.7±7.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MSNA, bursts/100 heartbeats</td>
<td>33.4±5.6</td>
<td>65.1±6.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are mean±SEM. BMI indicates body mass index; LVEDD, left ventricular end-diastolic diameter; and LVWT, left ventricular wall thickness. Normal range of norepinephrine values, 300–2800 pmol/L; normal range of epinephrine values, 170–510 pmol/L.

*Mean of 3 sphygmomanometric measurements.

all mean values after surgery significantly different from those recorded before surgery. Surgery did not consistently affect body mass index, pulse pressure, respiration rate, and left ventricular wall thickness and diastolic diameter. However, it significantly increased MSNA, ie, the number of bursts per minute and of bursts per 100 heartbeats over the 60-minute recording period was greater after surgery in each subject (Figure 1). There was no relationship between MSNA increase and BP reduction induced by removal of pheochromocytoma (r=0.59 for systolic and r=0.68 for diastolic BP; P=NS for both). The 1-minute MSNA values were in each patient invariably greater after surgery than before surgery, and this was also the case for values collected at similar diastolic BP (Figure 2).

Before surgery, MSNA increased significantly during voluntary apnea with a mean duration of 33.5±3 seconds. After surgery, apnea with a similar mean duration (37.0±4 seconds; P=NS) caused a much greater increase in MSNA (Figure 3).

Discussion

In our 6 patients with an adrenal pheochromocytoma, MSNA was invariably less before than after surgical removal of the tumor, the difference being so marked as to amount to a mean increase in the number of sympathetic bursts of 103.7±20%. This provides the first direct demonstration that central sympathetic outflow is inhibited in this type of secondary hypertension, in sharp contrast to a condition such as essential hypertension in which the BP elevation has been almost invariably accompanied by a marked central sympathoexcitation.3,9–12

The mechanisms responsible for the sympathoinhibition that characterizes pheochromocytoma are not conclusively clarified by our data, although they allow some mechanistic hypotheses to be excluded and others to be considered. The increased sympathetic nerve traffic that we observed after removal of pheochromocytoma was not accounted for by a reduced inhibitory input from arterial baroreceptors13 because its magnitude was similarly pronounced and was not related to the degree of BP reduction observed after tumor removal. Furthermore, and more importantly, after tumor removal, sympathetic nerve traffic was also markedly increased under conditions in which BP values were very similar to those recorded before the surgical intervention. Increased sympathetic nerve traffic was also probably not accounted for by a reduced inhibitory drive from cardiac receptors14 because removal of pheochromocytoma did not modify several important determinants of this drive in a way that could lead to a reduction in the firing rate of receptors located in ventricles and atria,14 namely, (1) after surgery cardiac volume was slightly although not significantly increased, (2) left ventricular wall thickness was slightly although not significantly decreased, and (3) sympathetic nerve activity was also in-
creased at times when BP was similar to that observed before tumor removal, suggesting that cardiac afterload was not substantially reduced. Thus, other mechanisms must be involved to a great extent in the central sympathoinhibition characterizing pheochromocytoma. One of these mechanisms might be a direct influence of the high levels of circulating catecholamines on adrenergic receptors located in the brain, which can exert, when appropriately stimulated, a marked inhibition of sympathetic outflow.15,16 This is not in agreement with animal data showing that chronic infusions of norepinephrine led to an increased preganglionic cervical sympathetic nerve firing rate.17 It is in agreement, however, with the evidence that surgical removal of pheochromocytoma also led to an enhancement of the sympathoexcitatory response to apnea. It is also compatible with the findings that the blood-brain barrier may be crossed by plasma catecholamines when circulating levels are extremely high and/or at sites where fenestrations of the barrier occur.18,19 This is the case, for example, in brain stem areas where important integrating centers for cardiovascular control are located.

Four additional points should be discussed. First, the MSNA values of our pheochromocytoma patients were less than those reported in studies on essential hypertensive patients,3,9–11 although not clearly less than those reported in normotensive individuals.3,6,9–11 Although external comparisons between data obtained in a limited number of subjects (often demographically unmatched) should be made with caution, this further supports the conclusion of a central sympathoinhibitory state in this form of secondary hypertension. It also may account, however, for the depressor and vasodilatating responses that have been reported in pheochromocytoma after the administration of a centrally acting agent such as clonidine,2,20,21 which, despite the sympathoinhibitory state, may further inhibit residual sympathetic nerve traffic in patients with pheochromocytoma. Second, MSNA provides a sensitive and reproducible measure of central sympathetic outflow that is restricted, however, to the skeletal muscle district. A limitation of our study is that it cannot undisputably allow us to conclude that in pheochromocytoma central sympathetic drive is similarly inhibited throughout the body. Third, previous studies have shown that nocturnal hypotension may be markedly attenuated in patients with a catecholamine-producing tumor.2,22,23 This might be due to the inability of an already inhibited sympathetic nerve activity to further decrease under the influence of the centers that cause depression of adrenergic cardiovascular drive during sleep.24 Fourth, if the central sympathoinhibition that occurs in pheochromocytoma is due to central stimulation by high levels of plasma catecholamines, one might expect this phenomenon to be absent in other causes of secondary hypertension. However, evidence has been obtained that MSNA becomes somewhat greater after successful treatment of a renal artery stenosis by renal artery angioplasty25 or adrenalectomy in primary hyperaldosteronism.26 Thus, whether central sympathoinhibition is specific for pheochromocytoma or it occurs by different mechanisms in other secondary hypertensive states should be the subject of further investigations. Further investigations might also be required to determine the time course of the disinhibition of sympathetic nerve traffic after removal of pheochromocytoma, ie, to assess whether this is an early phenomenon or whether it only characterizes the final stable postsurgical condition.

References


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