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The Role of Epinephrine, Norepinephrine, and Dopamine in Blood Pressure Disturbances in Patients with Pheochromocytoma

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Fifty-six patients with pheochromocytoma underwent surgery during the 9-year period from 1981 to 1990. These patients were divided into two groups according to whether the dominant plasma concentration was of epinephrine or norepinephrine. Plasma levels of the catecholamines were stratified into three grades at 5 and 10 times the normal upper limit. Pre-operative disturbances of blood pressure, sustained or paroxysmal, and normal blood pressure were highly correlated with the dominantly secreted catecholamine and its plasma concentration. Thirteen patients with high plasma norepinephrine levels (≥10 times normal) had sustained hypertension while 18 patients with moderate to high plasma epinephrine levels (≥5 times normal) had paroxysmal hypertension. In the majority of normotensive patients (12 of 14), plasma catecholamine levels were <10 times the upper normal limit. Urinary excretion of dopamine and size of the tumor were analyzed according to these patient groups. In the norepinephrine dominant group, urinary dopamine excretion tended to be proportional to the plasma epinephrine levels and when the patients were normotensive, urinary dopamine excretion decreased. In norepinephrine-secreting patients, urinary dopamine tended to be inversely correlated with the plasma norepinephrine level; however dopamine did not prevent the hypertensive action of norepinephrine. Tumor size showed no correlation with the plasma levels of catecholamine in the moderate to high plasma catecholamine groups. We conclude that the plasma catecholamine type and its level are the most important factors in determining the patterns of blood pressure disturbances of patients with pheochromocytoma.

The hypertension that accompanies pheochromocytoma has generally been ascribed to the excessive circulating catecholamines released from the tumor. Epinephrine and norepinephrine are the main catecholamines released and cause sustained or paroxysmal hypertension [1, 2]. Some tumors have been reported to release dopamine or dopa, but rarely, and when these are released predominantly, the patients show no hypertensive disturbances [3–5]. However, a marked discrepancy between the elevation of arterial blood pressure and the prevailing plasma catecholamine concentration has also been demonstrated [6, 7].

In order to clarify the role of each catecholamine in the blood pressure disturbances of patients with pheochromocytoma, we analyzed 56 patients in whom pheochromocytoma was proved by surgery. The size of the tumor was also evaluated as a possible determining factor of catecholamine release from tumors.

Material and Methods

From April 1981 to December 1990, a total of 56 patients were diagnosed as having pheochromocytoma and were treated by surgery. Except for 1 patient who had 2 recurrent abdominal masses due to malignant adrenal pheochromocytoma, all the operations were primary. The location and pathological features of these tumors are shown in Table 1. Pre-operative plasma epinephrine concentration, plasma norepinephrine concentration, and urinary excretion of dopamine were measured by high performance liquid chromatography. The normal range of each is as follows: plasma epinephrine ≤0.1 ng/ml, plasma norepinephrine 0.05–0.4 ng/ml, urinary dopamine 0.1–1 mg/day. In all patients plasma and urinary catecholamines were measured repeatedly pre-operatively. The values analyzed were the highest in each patient; consequently these were levels under the conditions of severe attack or sustained hypertension in symptomatic patients.

The 56 patients were divided into 2 groups according to the dominantly secreted catecholamine, epinephrine or norepinephrine, which was defined by comparing each value expressed as a multiple of the upper limit of normal in each patient. The plasma epinephrine and norepinephrine levels were stratified into 3 grades at 5 and 10 times the maximal normal level.

Patients in these groups were further divided into 3 subgroups according to the pattern of pre-operative blood pressure disturbance: sustained hypertension, paroxysmal hypertension, or normotension. Patients classified as normotensive had no history of proven hypertension or had not suffered an attack of headache, sweating, nausea, or pallor; however, some of them showed diabetic metabolic abnormalities.

Urinary excretion of dopamine in each subgroup was measured to determine whether massive dopamine release correlated with blood pressure disturbances.

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Table 1. Clinical features of patients with pheochromocytoma.

Clinical feature	No. of pts.
Adrenal	50
Unilateral	38
Benign	37
Malignant	1
Bilateral	2
Familial	1
Sporadic (malignant)	1
MEN-2	10
Extraadrenal	6
Single	3
Multiple	3
Benign	1
Malignant	2

MEN-2: Multiple endocrine neoplasia type 2.

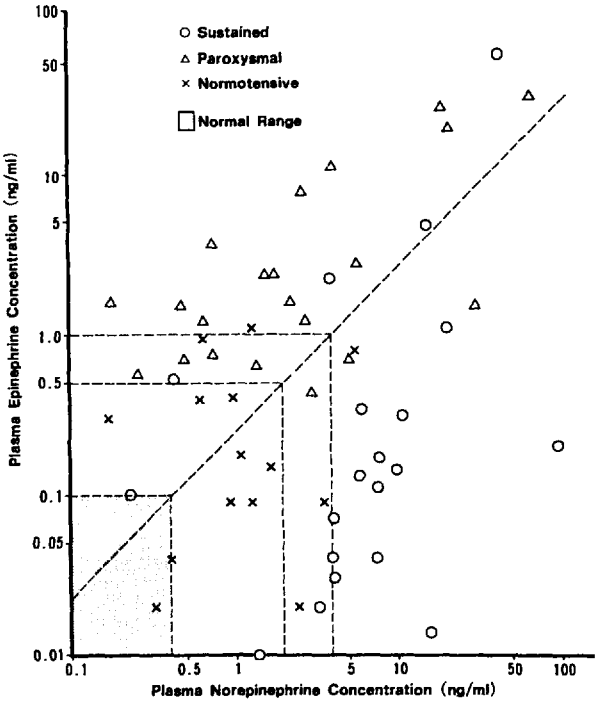

Fig. 1. Scatter plot of plasma epinephrine and norepinephrine concentrations. The diagonal dotted line divides the epinephrine-secreting from the norepinephrine-secreting patients. Lines at right angles mark the borders of 5 and 10 times the upper normal limit.

The size of the tumor was also evaluated as a determining factor in blood pressure disturbances or catecholamine release.

Results

Catecholamine Type and Blood Pressure

Figure 1 shows that 53 patients released excess catecholamines, the majority of them both epinephrine and norepinephrine. However, either epinephrine or norepinephrine was predominant in each patient when relative superiority was calculated as described above. As a result, 29 patients secreted primarily epinephrine and 27 patients secreted primarily norepinephrine. Nineteen epinephrine-secreting patients had paroxysmal hypertension, 5 patients had sustained hypertension, and 5 patients had been normotensive throughout the pre-operative course. In contrast, the majority of norepinephrine-secreting patients (15 of 27 patients) had sustained hypertension and 9 patients were normotensive. Only 3 patients who secreted primarily norepinephrine had paroxysmal hypertension. This difference in distribution was statistically significant ($p < 0.005$).

Table 2. Plasma catecholamine levels and blood pressure disturbances in patients primarily secreting epinephrine or primarily secreting norepinephrine.

Blood pressure disturbance	Catecholamine level (n)[a]		
	<5	≤5 < 10	≤10
Epinephrine-secreting			
Sustained	1	1	3
Paroxysmal	1	4	14
Normotensive	2	2	1
Norepinephrine-secreting			
Sustained	1	1	13
Paroxysmal	0	1	2
Normotensive	6	2	1

[a]Multiple of the upper limit of normal.
n: Number of patients.

Plasma Catecholamine Level and Blood Pressure

In the patients secreting primarily epinephrine, 14 of the 19 patients who had paroxysmal hypertension had a plasma epinephrine level ≥10 times the normal upper limit. When the plasma epinephrine level was <5 times normal, 2 patients remained normotensive but 2 patients were symptomatic. In the norepinephrine-secreting patients, 13 patients with sustained hypertension showed markedly high plasma norepinephrine levels, whereas 8 of the 11 patients with plasma norepinephrine levels <10 times the normal upper limit remained normotensive. These differences were also highly significant ($p = 0.005$). These results are shown in Table 2.

Urinary Dopamine and Blood Pressure

Urinary excretion of dopamine was plotted against plasma epinephrine or norepinephrine concentration in each group. In the hypertensive patients who secreted epinephrine (Fig. 2), urinary dopamine tended to increase according to increase in plasma epinephrine levels. However, in the 5 normotensive patients urinary dopamine excretion was very low. In the norepinephrine-secreting patients (Fig. 3), dopamine excretion tended to be inversely correlated with the plasma norepinephrine level in hypertensive patients whereas in 4 normotensive patients urinary dopamine was increased. However another 5 normotensive patients in this group showed the same range of plasma norepinephrine levels but urinary dopamine excretion was normal. In addition, even if urinary dopamine excretion was excessive, patients were hypertensive when plasma norepinephrine levels were also elevated. Therefore, we conclude that excessive dopamine did not prevent hypertensive conditions in the majority of patients with pheochromocytoma.

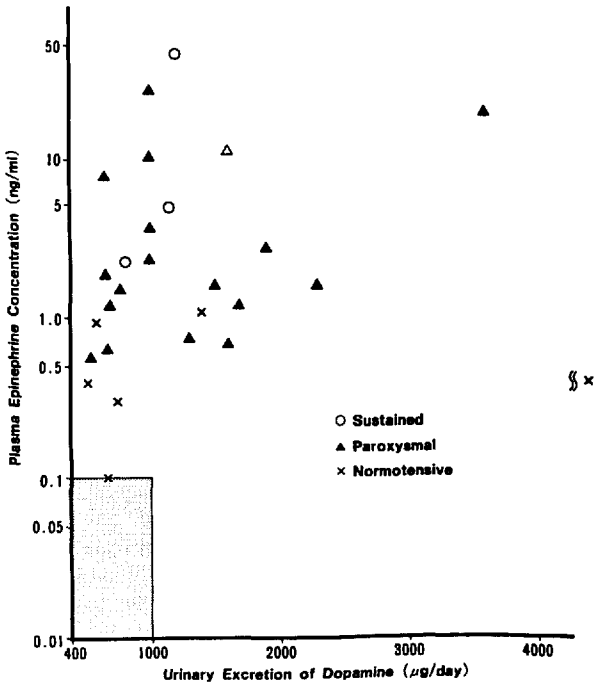

Fig. 2. Scatter plot of plasma epinephrine concentrations and urinary dopamine excretion in the patients secreting epinephrine. Symbols are the same as in Fig. 1.

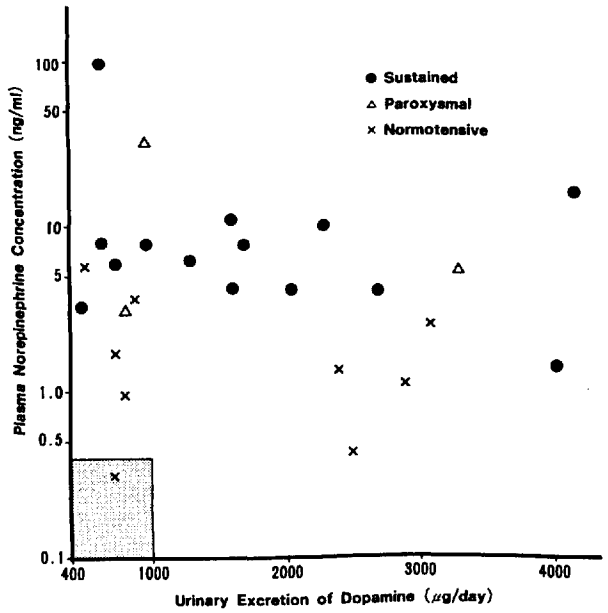

Fig. 3. Scatter plot of plasma norepinephrine concentrations and urinary dopamine excretion in the patients secreting norepinephrine. Symbols are the same as in Fig. 1.

Size of Tumor and Catecholamines

The mean maximal diameter of the tumors are shown in Table 3. The largest mean tumor size was in patients with low plasma norepinephrine secretion and the smallest tumor size was in patients with low epinephrine secretion. Among the other patients there was not much difference in tumor size. The group

Table 3. Mean tumor size (cm) and plasma catecholamine levels in patients primarily secreting epinephrine or primarily secreting norepinephrine.

	Mean tumor size (cm)		
	Catecholamine level[a]		
Catecholamine secreted	<5	≤5 < 10	≤10
Epinephrine	3.1 + 1.2	7.8 + 2.5	6.3 + 2.6
Norepinephrine	8.3 + 1.9	6.3 + 2.9	6.9 + 3.7

[a]Multiple of the upper limit of normal.

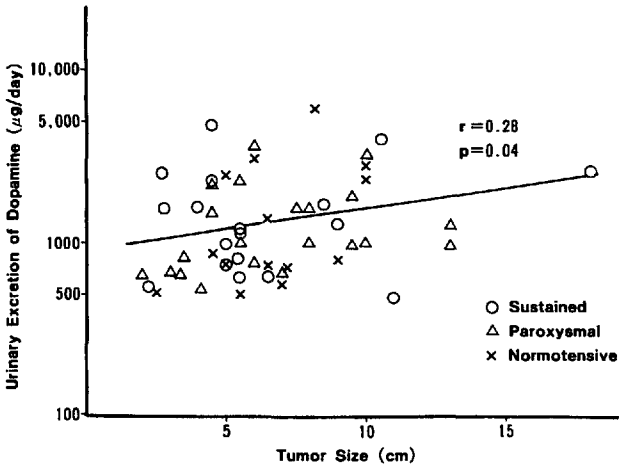

Fig. 4. Scatter plot of urinary dopamine excretion and maximum tumor diameters. Symbols are the same as in Fig. 1.

with the smallest tumors were primarily patients with multiple endocrine neoplasia type 2 and their diagnosis and surgery were accomplished relatively early; consequently the tumors were small and plasma epinephrine levels were very low. In contrast, the patients with low norepinephrine secretion consisted of patients who had an incidentally discovered adrenal mass which was diagnosed as pheochromocytoma because of excessive excretion of metabolites of catecholamines even if the plasma and catecholamine levels were low.

Urinary dopamine excretion was weakly but significantly correlated with the tumor diameter (Fig. 4). However in the majority of hypertensive patients, the size of the tumor had no significant role in determining the type of catecholamine secreted or the pattern of blood pressure disturbances.

Discussion

It is well known that pheochromocytomas produce and release a variety of catecholamines which cause hypertensive disturbances. However, secretion from the pheochromocytoma varies considerably and the effects of the secreted catecholamines also vary significantly. Epinephrine is usually thought to cause systolic hypertension, tachycardia, sweating, flushing, and anxiety whereas norepinephrine produces both diastolic and systolic hypertension, less tachycardia, and less anxiety or palpitation. Dopamine has the dual actions of vasodilatation and vasoconstriction according to its plasma concentration. The effective plasma concentration or potency of hormonal action also differs between epinephrine and norepinephrine. Epineph-

rine is reported to be about 10 times more potent than norepinephrine in humans [8]. We think therefore that it is important to classify patients with pheochromocytoma according to the relative potency of the secreted hormones, epinephrine and norepinephrine.

In our present study, relatively increased concentration of plasma epinephrine produced paroxysmal hypertension, in particular when the plasma epinephrine concentration was ≥5 times the normal upper limit. Sustained hypertension was strongly correlated with a high plasma norepinephrine concentration which was ≥10 times the normal upper limit. These results agree well with experimental studies. In one study, Clutter and coworkers [9] demonstrated that the cardiac chronotropic effect of epinephrine occurs at plasma epinephrine levels only 2-fold to 3-fold basal values. In a norepinephrine infusion study, Silverberg and colleagues [10] showed that the minimum biologically effective synaptic cleft norepinephrine concentration is roughly 8 times basal levels. These catecholamine infusion studies explain why a relatively smaller excess of epinephrine than of norepinephrine causes hypertension. However, they do not explain why epinephrine causes chiefly paroxysmal hypertension and norepinephrine induces sustained hypertension. Epinephrine is chiefly a hormone and norepinephrine is primarily a neutrotransmitter. When norepinephrine is released from a pheochromocytoma, it is taken up by sympathetic nerve endings and stored. The excess norepinephrine stored in a nerve ending is easily released by many sympathetic nervous system stimuli, thereby causing continuous vasoconstriction and sustained hypertension [11, 12]. In contrast to norepinephrine, epinephrine may be rapidly metabolized in the general circulation after being released, consequently causing only episodic attacks of hypertension, tachycardia or other symptoms. Another reason may be that an epinephrine-secreting pheochromocytoma is well differentiated; therefore the hormone-storing and metabolizing ability of the tumor is high compared to the less differentiated norepinephrine-producing pheochromocytoma. As a result, epinephrine is episodically released whereas norepinephrine is continuously released or spilled over from the tumor and causes sustained hypertension.

The role of dopa or dopamine in pheochromocytoma is controversial. In several previous reports, it is documented that excessive dopa or dopamine release is associated with normal blood pressure in patients with pheochromocytoma [3–5, 13]. Our present study revealed that high urinary excretion of dopamine was associated with normal blood pressure in 4 patients with norepinephrine-secreting pheochromocytoma. However, in all 4 patients the plasma norepinephrine levels were <10 times the normal upper limit, which was the range of the normotensive patients in this group. In epinephrine-secreting patients, normotensive patients showed both low plasma epinephrine concentration and low urinary dopamine excretion. Therefore we conclude that urinary dopamine concentration has no role in altering patient blood pressure when the plasma catecholamine level is significantly elevated.

The size of the tumor is reported to be important in the pathophysiological behavior of pheochromocytoma. In 1964, Crout and Sjoerdsma [14] demonstrated 2 types of pheochromocytoma. In some tumors (<50 g) the catecholamine store is replaced at a rapid rate, and a relatively pure infusion of norepinephrine (and sometimes epinephrine) is secreted into the host, whereas in other tumors (>50 g) the catecholamine store is turned over more slowly, and a considerable portion of the norepinephrine and epinephrine synthesized is apparently metabolized directly in the tumor. The latter observation is very important. Recently detection of incidental adrenal masses has been increasing and many such tumors are asymptomatic pheochromocytoma [15, 16]. Our present study also included these incidentally found adrenal masses and the majority of them were in norepinephrine-secreting normotensive patients. These tumors were generally large (mean diameter 8.3 cm) and secreted large quantities of metabolites of catecholamines in the urine, but plasma norepinephrine concentrations of these patients were in the range of normotensive patients. However, as Crout and Sjoerdsma [14] also stated, tumor size is not the sole decisive factor of the biological behavior of a pheochromocytoma.

Morphological analysis revealed no correlation between the clinical symptomatology and the electron micrographic fine structure, the latter being similar in the pheochromocytoma of patients with or without paroxysmal or sustained hypertension [17]. Probably not a morphological but a functional biological study is necessary to clarify these symptomatological differences in patients with pheochromocytoma.

In conclusion we believe that the type of plasma catecholamine and its level are most important in determining the pattern of blood pressure disturbance in patients with pheochromocytoma.

Résumé

Cinquante six patients ayant un phéochromocytome ont été opérés en 9 ans (1981–1990). Ces patients ont été répartis en deux groupes en fonction des concentrations plasmatiques prédominantes de norépinéphrine ou d'épinéphrine. Les taux plasmatiques de cathécolamines ont été stratifiés en 3 classes par rapport aux niveaux de 5 fois et 10 fois la limite supérieure de la normale. Des anomalies préopératoires de la pression artérielle, permanentes ou paroxystiques, ainsi que des chiffres normaux de pression artérielle étaient étroitement corrélés au type de cathécholamine prédominante et sa concentration plasmatique. Treize patients ayant des concentrations plasmatiques élevées de norépinéphrine (10 fois la normale ou plus) avaient une hypertension permanente alors que 18 patients avec des concentrations modérées ou élevées d'épinéphrine (5 fois la normale ou plus) avaient une hypertension paroxystique. Chez la majorité des patients normotendus (12 sur 14), les concentrations plasmatiques de cathécolamine étaient inférieures à 10 fois la limite supérieure de la normale. L'excrétion urinaire de Dopamine et la taille de la tumeur ont été analysées pour ces groupes de patients. Dans le groupe à épinéphrine dominante, l'excrétion urinaire de Dopamine semblait propotionnelle aux concentrations plasmatiques d'épinéphrine. En cas de normalisation tensionnelle, il existait une diminution de l'excrétion urinaire de Dopamine. Dans le groupe sécréteur de norépinéphrine, l'excrétion urinaire de Dopamine semblait corrélée de façon inverse aux concentrations plasmatiques de norépinéphrine; toutefois la Dopamine ne prévenait pas l'action hypertensive de la norépinéphrine. Il n'y avait aucune corrélation entre la taille de la tumeur et les concentrations plasmatiques de

cathécholamine, qu'elles soient modérées ou élevées. Nous pensons que le type de cathécholamine et son taux plasmatique sonf les facteurs principaux déterminant les profils tensionnels des patients ayant un phéochromocytome.

Resumen

Cincuenta y seis pacientes con feocromocitoma operados en un período de 9 años (1981–1990) fueron divididos en dos grupos según la concentración plasmática dominante fuera epinefrina o norepinefrina. Se estratificaron los niveles plasmáticos de catecolaminas en tres grados a niveles de 5 y 10 veces el límite normal superior. Las alteraciones preoperatoria de la presión arterial, sostenidas o paroxísticas, así como la presión arterial normal, aparecieron notoriamente correlacionadas con la catecolamina dominante y con su concentración plasmática. Trece pacientes con elevados niveles plasmáticos de norepinefrina (10 veces lo normal o más) exhibieron hipertensión sostenida, en tanto que 18 pacientes con niveles moderados o altos de epinefrina (5 veces lo normal o más) exhibieron hipertension paroxística. En la mayoría de los pacientes normotensos (12 de 14) los niveles plasmáticos de catecolamina fueron inferiores a 10 veces el límite superior de lo normal. La excreción urinaria de dopamina y el tamaño del tumor fueron analizados en tales grupos de pacientes. En el grupo con norepinefrina dominante la excreción urinaria de dopamina exhibió tendencia a ser proporcional a los niveles plasmáticos de epinefrina y en los pacientes normotensos la excreción urinaria de dopamina apareció disminuída. En los pacientes secretores de norepinefrina la excreción urinaria de dopamina demostró tendencia a correlacionarse en forma inversa con el nivel plasmático de norepinefrina; sin embargo, la dopamina no impidió la acción hipertensora de la norepinefrina. El tamaño del tumor no demostró correlación con los niveles plasmáticos de catecolamina en los grupos con niveles moderados o altos de catecolamina plamática. Creemos que el tipo de catecolamina plasmática y sus niveles son los factores más importantes para determinar los patrones de alteración de la presión arterial en pacientes con feocromocitoma.

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Invited Commentary

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The present paper by Ito and coworkers is an interesting analysis of catecholamine secreting tumors. The authors have made several determinations of plasma catecholamines and analyzed the maximal plasma levels in relation to blood pressure. It is an important contribution to stress that most patients with symptomatic paroxysmal hypertension have an epinephrine secreting tumor. The reason for this difference is not obvious and further studies will be needed to elucidate why epinephrine, in comparison with norepinephrine, is secreted in this way.

It is evident that the authors have more data as they have analyzed numerous samples from their patients. It is probably not only the level of plasma catecholamines but also the secretory pattern that determines whether the patient has paroxysmal or sustained hypertension or even is normotensive.

In an earlier study [1] we found that patients with a continuous release of even high levels of catecholamine could be normotensive, probably due to downregulation of alpha adrenergic receptors. It would be interesting if the authors continued to analyze their data not only to use the highest level but also the secretory pattern in comparison with blood pressure which