Secretion of Dopa in Pheochromocytoma

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Summary

In a series of 11 cases with pheochromocytoma, two patients were found in whom the tumour secreted dopa in addition to dopamine, noradrenaline, and adrenaline. These two patients were normotensive in spite of high plasma and urinary levels of noradrenaline and adrenaline. This raises the possibility that dopa may be able to protect against the hypertensive action of noradrenaline. Such a mechanism would also explain the absence of hypertension in many cases of neuroblastoma.

Introduction

Although cases of pheochromocytoma are relatively rare, studies of patients with this condition have clarified some aspects of the pharmacology of noradrenaline and adrenaline in man (Sjoerdsma, 1959, 1968). The hypertension in patients with pheochromocytoma is due to an overproduction of catecholamines, and removal of the tumour or inhibition of noradrenaline synthesis results in the blood pressure falling to normal levels (Sjoerdsma, 1968). However, not all patients with pheochromocytoma have sustained hypertension, and non-chromaffin sympathetic tumours, particularly neuroblastoma, commonly produce a large excess of noradrenaline without evidence of hypertension. The reason for the relative lack of symptoms of excess noradrenaline production in patients with neuroblastoma is not clear (Von Studnitz *et al.*, 1963; Voorhess, 1966).

We report two unusual cases of pheochromocytoma in which there was a high urinary excretion of dihydroxyphenylalanine (dopa) and dopamine in addition to noradrenaline and adrenaline. Neither of these two patients had sustained hypertension. Catecholamine levels in urine and in the tumours in these two patients are compared with nine typical cases of pheochromocytoma studied at the Austin Hospital. We suggest that the excess of the noradrenaline precursor dopa, may have prevented a rise in blood pressure in the two patients with atypical pheochromocytoma, and that a similar antihypertensive effect occurs in patients with neuroblastoma.

Case 1

A girl aged 14 years presented with an influenza-like illness. This was slow to resolve, and over the next three months she remained lethargic, tired, anorexic, and lost 12 kg in weight. Investigations showed nothing abnormal except that the intravenous pyelogram showed the right kidney to be much lower than the left, both kidneys being of normal size. In view of these findings an aortogram was performed and showed a large tumour mass in the region of the adrenal gland. Urinary catecholamine data are summarized in Table I.

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TABLE I—Urinary Excretion of Noradrenaline, Adrenaline, Dopamine, and Dopa in Patients with Pheochromocytoma

Case No.	Noradrenaline (μg/24 hr)	Adrenaline (μg/24 hr)	Dopamine (μg/24 hr)	Dopa (μg/24 hr)	Blood Pressure
1	173	77	1,340	620	Normotensive
2	200	340	627	380	Normotensive
3	3,900	N.S.	214	<10	raised
4	4,200	N.S.	108	"	raised
5	5,700	1,400	171	"	raised
6	440	N.S.	144	"	raised
7	110	170	92	"	raised
8	90	140	185	"	raised
9	200	130	220	"	raised
10	258	235	110	"	raised
11	1,300	N.S.	149	"	raised
N.R.	10-60	0-15	90-250	0-10	

N.S. = Not significant (see methods section in text). N.R. = Normal range.

After localization of this tumour blood pressure measurements were taken every four hours over the next two weeks. During the whole of this preoperative period she remained normotensive.

Laparotomy showed a large, firm, and well-encapsulated tumour in the right adrenal gland. It did not appear to be infiltrating adjacent tissues but was adherent medially to the inferior vena cava and it displaced the right kidney downwards. Operative removal was rather difficult because of its size, and at one stage a small tear in the inferior vena cava led to much blood loss. During operation no rise in blood pressure occurred at any stage. After removal of the tumour the patient remained hypotensive but eventually responded to blood transfusion and noradrenaline infusion.

The tumour weighed 39 g and consisted of firm yellow tissue with a brown edge. Microscopically the greater part of the tumour was necrotic, but at the periphery there were clumps of polyhedral cells with "cobweb" cytoplasm and somewhat irregular large vesicular nuclei. The appearance was that of a pheochromocytoma. Catecholamine levels in the tumour are summarized in Table II.

TABLE II—Adrenal Content of Catecholamines and Dopa in Pheochromocytoma

Tumours Patient Case No.	Noradrenaline (mg/g)	Adrenaline (mg/g)	Dopamine (mg/g)	Dopa (mg/g)
1	8.3	1.0	0.23	0.16
2	1.9	1.5	0.20	0.09
5	7.4	1.9	N.D.	N.D.
9	2.4	1.4	N.D.	N.D.
10	5.2	3.1	N.D.	N.D.
11	1.1	N.D.	N.D.	N.D.
Normal adrenal values	0.034 ± 0.014	0.224 ± 0.080	0.00	0.00

N.D. = Not detected.

The subsequent course was uneventful. Her blood pressure remained steady at 120/70 mm Hg and she gained 6 kg in weight in the first three months postoperatively.

Case 2

A man had six episodes of flushing, diarrhoea, and vomiting during the eight years before admission. The attacks started suddenly with diarrhoea, followed shortly afterwards by vomiting. After two to three days this settled and was followed by polyuria and flushing which would persist for two to three weeks. He did not notice any headache or sweating during the episodes, and no rise in blood pressure was recorded. During these episodes he became quite weak, at times being unable to wash himself, would lose 4-7 kg in weight, and on one occasion was found to have a mildly diabetic glucose tolerance curve.

Examination showed nothing abnormal. For six weeks before operation he was an inpatient, and his blood pressure was recorded regularly. He was not given treatment and remained

normotensive, his blood pressure ranging from 100-120 mm Hg systolic and 70-80 mm Hg diastolic. Investigations were: serum electrolytes, normal except that the serum K^+ fell to 3.0 during the episodes of weakness; glucose tolerance test, fasting 93 mg/100 ml, 1 hr 220 mg/100 ml, 2 hr 165 mg/100 ml; 5-hydroxyindole acetic acid levels, less than 10 mg/24 hr on three occasions and did not increase with reserpine; Vanillylmandelic acid levels, 8.8, 11.9, 18.5, and 19.5 on four separate occasions; and serum thyroxine, 4.6 μ g/24 hr. Urinary catecholamine data are summarized in Table I. A prerenal air insufflation showed a right adrenal tumour.

At operation a right adrenal tumour was removed under cover of phentolamine, propranolol, and noradrenaline. During the initial skin incision the blood pressure rose, and numerous extrasystoles were noted. The blood pressure rose again when the tumour was being manipulated. It fell when the tumour was removed but was readily raised with noradrenaline and fluid replacement. The tumour weighed 48 g and histologically was a pheochromocytoma. Catecholamine levels in the tumours are summarized in Table II.

CHEMICAL METHODS

Eleven patients with pheochromocytoma had 24-hour specimens of urine collected in plastic bottles containing 10-15 ml of 6N hydrochloric acid and stored at 0°. Free urine catecholamines were determined by a modification of the trihydroxyindole procedure (Crout, 1960) using tritiated noradrenaline as an internal recovery marker. The results were then corrected for 100% recovery. Adrenaline values were regarded as lacking quantitative significance when they were less than 5% of the noradrenaline figure.

After passage over alumina, urinary dopa and dopamine were separated by passage over an amberlite column (100-200 mesh) at pH 6.0. Dopamine was then eluted with 1N acetic acid. Dopa which was contained in the effluent of the amberlite columns was further purified by adsorption on alumina at pH 8.4 and eluted with 0.2N acetic acid. Dopa and dopamine were then assayed by a modification of the method of Carlsson and Waldek (1958).

An aliquot of the tumours (about 300 mg) was homogenized in 10 ml 0.4N perchloric acid centrifuged at 4° in a Sorval Centrifuge at 27 000 g for 10 min. The supernatant was then treated in a similar fashion to the urines, being passed over amberlite and the eluate and effluent being assayed for dopamine and dopa respectively.

Results

The urinary excretion of "free" noradrenaline, adrenaline, dopamine, and dopa in 11 patients with pheochromocytoma is summarized in Table I. All patients had raised urinary noradrenaline excretion, and seven of the 11 also had raised adrenaline excretion. Two patients (Cases 1 and 2) had raised urinary dopamine levels (>250 μ g/24 hr). They also had raised levels of urinary dopa (620 and 380 μ g/24 hr respectively) and urinary adrenaline.

The tumour concentrations of noradrenaline, adrenaline, dopa, and dopamine in six of the 11 cases shown in Table I are given in Table II. Dopa and dopamine were detected only in the tumours of the patients who had been shown to have an excess of these two noradrenaline precursors in the urine (Cases 1 and 2, Table I).

Discussion

In a series of 11 cases with pheochromocytoma, two patients were found in whom the tumour secreted dopa in addition to noradrenaline and adrenaline. Although dopa is a precursor of noradrenaline it usually cannot be found in normal human adrenal glands or in most cases of pheochromocytoma (Shepherd and West, 1953). The mere finding of dopa and dopamine in these tumours provides evidence that in man these compounds are intermediates in the formation of noradrenaline and adrenaline by chromaffin tissue. Presumably in these two cases enzyme relations differed sufficiently to produce these findings, there

being some alteration in either dopamine beta-oxidase activity or granular uptake of dopamine into noradrenaline-secreting granules (Sjoerdsma, 1968).

In contrast to pheochromocytoma, hypersecretion of dopa is characteristic of non-chromaffin sympathetic tumours such as neuroblastoma (Von Studnitz *et al.*, 1963; Voorhess, 1966). These tumours also secrete dopamine and noradrenaline but do not secrete adrenaline, as sympathetic nervous tissue lacks the N-methyl transferase necessary to methylate noradrenaline to adrenaline (Wurtman, 1965). The presence of adrenaline together with the typical histological features serve to separate the cases reported here from neuroblastoma.

There is only one other case in the literature of a pheochromocytoma producing dopa. No clinical features are available except for a statement that the patient was normotensive with episodes of paroxysmal hypertension (Weil-Malherbe, 1956). In the present series one patient was normotensive during the whole period of observation and the other was normotensive except during the operation. This patient had other clinical evidence of catecholamine hypersecretion such as paroxysmal weakness, gastrointestinal symptoms, polyuria, and a mildly diabetic glucose tolerance curve. During most of the period of observation, however, there was a relative lack of symptoms, and he remained normotensive in spite of a continuous hypersecretion of noradrenaline as shown by a persistently raised 24-hour urinary noradrenaline excretion.

As the two patients in this series and the case reported by Weil-Malherbe (1956) all had raised noradrenaline excretion it is not easy to understand why they were usually normotensive. Other patients with similar urinary levels of catecholamines had substantial rises in systolic and diastolic pressure (Cases 7, 8, 9, and 10 in Table I). A common feature of the "normotensive" pheochromocytomas was the presence of dopa in the urine and in the tumour. In this respect they clinically resemble patients with neuroblastoma. It seems significant that in these unusual cases of pheochromocytoma and in neuroblastoma there is a hypersecretion of dopa and dopamine in addition to noradrenaline.

It is possible that the secretion of dopa may be responsible for the relative absence of symptoms of sympathetic overactivity in neuroblastoma and atypical pheochromocytoma. The amino-acid dopa has been shown to be hypotensive in man (Watanabe *et al.*, 1970) and animals (Henning and Rubenson, 1970). Unlike the amines noradrenaline and dopamine it crosses the blood-brain barrier where it is decarboxylated to dopamine and noradrenaline, and there is much evidence that the hypotensive action of levodopa is related to the accumulation of these two amines in the central nervous system (Tabei *et al.*, 1969; Henning and Rubenson, 1970; Watanabe *et al.*, 1970; Louis, 1972). Peripheral metabolic products of dopa, dopamine (Burn and Rand, 1958; Holmes and Fowler, 1962), and tetrahydropapaveroline, (Holtz *et al.*, 1964) also possess hypotensive properties.

It is clear that dopa can antagonize at least in part the peripheral action of its product noradrenaline. Cases of pheochromocytoma which secrete dopa therefore could erroneously be termed "non-functioning," and this may lead to errors in diagnosis and even failure to suspect pheochromocytoma.

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Familial Acute Myeloid Leukaemia with Acquired Pelger-Huët Anomaly and Aneuploidy of C Group

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Summary

All five members of one generation in an Icelandic family were affected by acute myeloid leukaemia or preleukaemia. Two sibs died of acute myeloid leukaemia and another of myelofibrosis associated with leukaemic changes. The other two sibs are alive; one of them (the proband) has haematological features consistent with preleukaemia; both of them have evidence of an abnormal cytogenetic clone in the bone marrow with 47 chromosomes, an extra chromosome in the C group. The finding of the acquired Pelger-Huët anomaly in the neutrophils of the five affected sibs suggests that a specific genetic cell defect has been transmitted with autosomal dominant characteristics. The presence of immunological deficiencies and an undue susceptibility to oncogenic viruses, as suggested by warts affecting three family members, may have played a part in the pathogenesis of the leukaemic process.

Introduction

Current concepts of the pathogenesis of leukaemia suggest the interaction of genetic, environmental, and immunological factors (Gibson *et al.*, 1968; Zuelzer and Cox, 1969; Gunz, 1970; Galton and Spiers, 1971). The demonstration of genetic factors in human leukaemia relies on the study of familial clusters of the disease, as genetic manipulations are possible only in animal leukaemias. Many families have been described in which two or more cases of leukaemia have occurred in the same or successive generations (Videback, 1947; Hayhoe, 1960; Heath and Moloney, 1965; McPhedran *et al.*, 1969; Snyder *et al.*, 1970). In adults this has been adequately shown in chronic lymphocytic leukaemia (Fraumeni *et al.*, 1969; Gunz and Veale, 1969) but it is rare in acute myeloid leukaemia (Snyder *et al.*, 1970). We have studied an Icelandic family in which all five members of a sibship were affected, two with acute myeloid leukaemia, one with myelofibrosis and leukaemic changes, and two with preleukaemia as evidenced by an abnormal bone marrow clone.

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Transmission of a genetic defect with autosomal dominant characteristics was suggested by the findings of the acquired form of Pelger-Huët anomaly in the neutrophils of all the siblings and by the demonstration of aneuploidy of the C group of chromosomes in the bone marrow of two sibs. In addition immunological deficiencies and an increased susceptibility to virus infection were present in this family. The family pedigree is shown in Fig. 1.

FIG. 1—Family pedigree.

Case Reports

Subject II 2.—This patient, the proband, was referred to Hammett Hospital for investigation in March 1971 at the age of 37. In 1959 he developed a chest infection affecting the left lower lobe. As the lesion did not resolve completely despite treatment a thoracotomy and decortication was performed five months later. Since that time he had suffered from chronic oral moniliasis. In 1966 he developed thrombophlebitis and in 1968 a perianal abscess. A necrotic granulomatous lesion developed subsequently which grew *Candida albicans* and led to the collapse of the bridge of his nose. In February 1969 he developed a right lower lobe pneumonia. The only physical signs at presentation were multiple warts affecting hands, feet, and neck, present for 15 years. The haemoglobin was 15.2 g/100 ml, the P.C.V. 45%, platelets were 81,000/mm³, and the W.B.C. was 7,800/mm³. Blood films showed a shift to the left with 1% of promyelocytes (Fig. 2 A), 15% of myelocytes, and 52% of neutrophils. One-third of the neutrophils were found to have only two nuclear segments and some (including eosinophils) had a round nucleus (Pelger-Huët