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The effects of chemical sympathectomy on dopamine, noradrenaline and adrenaline content in some peripheral tissues

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1 Dopamine, noradrenaline (NA) and adrenaline (Ad) depletion by 6-hydroxydopamine (6-OHDA) and pargyline plus 6-OHDA was investigated in the cat left ventricle, mesenteric and renal arteries, renal cortex, renal medulla and adrenal medulla. Catecholamine concentrations in plasma were also analyzed in these two experimental conditions.

2 6-OHDA alone or in combination with pargyline induced parallel decreases of NA and dopamine contents in the left ventricle. In the main trunk and proximal branches of the mesenteric artery and renal artery 6-OHDA selectively reduced NA without a parallel decrease in dopamine content. Previous treatment with pargyline abolished this selectivity.

3 In the kidney of control animals, dopamine content was greater than could be attributed to its presence only in noradrenergic neurones. In the renal cortex 6-OHDA reduced significantly dopamine and NA contents, and in the renal medulla only NA levels were decreased by this drug. Pargyline plus 6-OHDA did not deplete the NA content either in the renal cortex or in the renal medulla, and only reduced significantly the dopamine content in the renal cortex.

4 NA concentrations in plasma were increased by pargyline plus 6-OHDA whilst Ad remained unaffected. In the adrenal medulla only NA content was reduced either by 6-OHDA or pargyline plus 6-OHDA.

5 The present findings suggest a NA-independent dopamine pool in both segments of the mesenteric artery and renal artery but not in the left ventricle.

Introduction

The synthesis of noradrenaline (NA) within the varicosities of adrenergic neurones is associated with the presence of detectable amounts of the precursor, dopamine (Costa *et al.*, 1972; Snider *et al.*, 1973). Since it is accepted that the rate limiting step in the biosynthesis of NA in the peripheral sympathetic nervous system is represented by tyrosine hydroxylase (Udenfriend, 1966) the dopamine/NA ratio should be similar in different tissues endowed with adrenergic innervation, regardless of their NA turnover rate (Levitt *et al.*, 1965; Lacković & Relja, 1983). Thus the presence of high levels of dopamine and a high dopamine/NA ratio point to an independent role of dopamine i.e. to the existence of dopaminergic neurones (Bell & Gillespie, 1981).

Although the two amines (dopamine and NA) are easily distinguished by biochemical techniques, dopamine- and NA-containing neurones have similar spectra with the fluorescent histochemistry technique, which therefore does not readily allow the characterization of hypothetical peripheral dopaminergic neurones.

In the central nervous system (CNS) dopaminergic and noradrenergic neurones have been differentiated due to the fact that they exist within well-defined areas as separate populations and also because they exhibit different sensitivities to 6-hydroxydopamine (6-OHDA); noradrenergic neurones are more apt to be depleted by 6-OHDA than dopaminergic neurones (Bloom *et al.*, 1969). Although the pharmacological mechanism has not been established, previous administration of pargyline has been reported to enhance the neurotoxic effects of 6-OHDA upon brain dopaminergic neurones (Breese & Traylor, 1970).

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The present experiments were designed to investigate the effects of 6-OHDA alone and in combination with pargyline on the dopamine and NA content in the cat heart, mesenteric and renal arteries and kidney, and eventually to seek further evidence in support of an independent dopaminergic innervation in these tissues. Adrenaline (Ad), NA and dopamine content in the adrenal medulla and NA and Ad concentrations in plasma were also analyzed.

Methods

Cats weighing 2.5–3.2 kg were given 6-OHDA hydrobromide 50 mg kg^{-1} by the i.p. route on day 0 plus 50 mg kg^{-1} on day 1 and killed on day 5. 6-OHDA hydrobromide obtained from Sigma Chemical Company (St. Louis, MO) stored in a dessicator at −4°C was dissolved in a vehicle (0.9% NaCl containing 1 mg ml^{-1} of ascorbic acid) and bubbled with nitrogen gas for several minutes. The concentration of 6-OHDA was such that cats received 2.5 ml of this solution. Some animals received 50 mg kg^{-1} of pargyline i.p. 30 min before the first 6-OHDA injection but not before the second dose. All control animals received i.p. injections of vehicle on day 0 and on day 1. Animals were housed individually and had free access to food and water.

The animals were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}) i.v. and blood samples were collected 15 min later by puncture of the femoral artery and plasma obtained by centrifugation (5000 r.p.m., 20 min, 0°C) was frozen at −20°C. Samples of left ventricle, main trunk of the anterior mesenteric artery and its proximal branches, renal artery, renal cortex, renal medulla and adrenal medulla were rinsed in cold 0.9% NaCl solution, blotted with filter paper, weighed, minced with fine scissors and homogenized with a Duall-Kontes homogenizer in 2.0–3.0 ml 0.1 M perchloric acid. The absolute weights of tissue samples used ranged from approximately 20 mg in the case of proximal branches of the anterior mesenteric artery up to approximately 600 mg for some samples of renal cortex or renal medulla and left ventricle. The homogenates were centrifuged (10,000 r.p.m., 15 min 0°C) and the supernatants were decanted. Aliquots of 1 ml supernatant were placed in 5 ml conical glass vials with 50 mg alumina and the pH was adjusted to 8.4. Mechanical shaking for 10 min was followed by centrifugation and the supernatant discarded. In the case of plasma samples, 2 ml was used, but the procedure was the

Table 1 Absolute and relative contents of noradrenaline (NA) and dopamine (DA) (in ng g^{-1}) in some peripheral vascular and non-vascular tissues from control, 6-hydroxydopamine (6-OHDA) or pargyline (Parg) plus 6-OHDA pretreated animals

Tissue	*Treatment*	n	*NA*	*DA*	*DA/NA × 100*
Left ventricle	Control	7	1227 ± 146	70 ± 13	6.2 ± 1.2
	6-OHDA	5	68 ± 6*	3 ± 0.5*	4.4 ± 0.4
	Parg ± 6-OHDA	5	16 ± 1*,**	1 ± 0.4*,**	10.1 ± 1.3**
Mesenteric arteries					
Main trunk	Control	6	2498 ± 222	109 ± 14	4.7 ± 0.9
	6-OHDA	5	300 ± 15*	32 ± 8*	10.4 ± 2.6*
	Parg + 6-OHDA	5	962 ± 178*,**	34 ± 2*	4.0 ± 0.6**
Proximal branches	Control	6	5575 ± 895	151 ± 20	2.8 ± 0.4
	6-OHDA	5	744 ± 113*	105 ± 26	14.4 ± 1.3*
	Parg + 6-OHDA	5	379 ± 53**	24 ± 2*,**	6.8 ± 0.9*,**
Renal artery	Control	6	1970 ± 171	84 ± 13	4.2 ± 0.4
	6-OHDA	5	334 ± 33*	59 ± 16	17.6 ± 4.4*
	Parg + 6-OHDA	5	279 ± 49*	30 ± 6*	11.0 ± 1.4*
Renal cortex	Control	5	113 ± 17	10 ± 1	9.9 ± 1.7
	6-OHDA	5	27 ± 2*	3 ± 0.3*	14.0 ± 0.7
	Parg ± 6-OHDA	5	80 ± 11**	4 ± 0.6*	5.3 ± 0.4**
Renal medulla	Control	5	109 ± 10	7 ± 1	7.1 ± 0.8
	6-OHDA	5	34 ± 6*	4 ± 1	14.6 ± 4.7
	Parg + 6-OHDA	5	92 ± 11**	7 ± 1	8.3 ± 1.7

Values represent means ± s.e.mean
*Values are significantly different from control.
**Values are significantly different from 6-OHDA ($P < 0.01$).

Table 2 Noradrenaline (NA) and adrenaline (Ad) concentrations in plasma and adrenal medulla content of NA, Ad and dopamine (DA) in control conditions and after treatment with 6-hydroxydopamine (6-OHDA) or pargyline plus 6-OHDA

	Amine	*Control*	*6-OHDA*	*Pargyline + 6-OHDA*
Plasma	NA ($ng\,ml^{-1}$)	2.0 ± 0.5 (5)	2.1 ± 0.3 (5)	6.1 ± 0.9*,** (5)
	AD ($ng\,ml^{-1}$)	0.6 ± 0.1 (5)	0.9 ± 0.06 (5)	0.8 ± 0.02 (5)
Adrenal Medulla	NA ($\mu g\,g^{-1}$)	1185 ± 233 (5)	370 ± 31 (5)*	207 ± 34*,** (7)
	AD ($\mu g\,g^{-1}$)	744 ± 121 (5)	666 ± 61 (5)	519 ± 103 (7)
	DA ($\mu g\,g^{-1}$)	9 ± 3 (5)	6 ± 0.3 (5)	9 ± 1 (7)

Numbers in parentheses refer to number of animals.
Values represent means ± s.e.mean (*n*)
*Values are significantly different from control
**Values are significantly different from 6-OHDA ($P < 0.01$)

same. Elution of alumina from Millipore (MF1) microfilters was effected with 300 µl 0.1 M perchloric acid; 200 µl of the eluate was injected into a high performance liquid chromatograph with electrochemical detection (BAS model 304). A 5 µm ODS column of 25 cm length was used. The mobile phase was degassed solution of monochloroacetic acid (0.15 M), sodium octylsulphate (0.3 mM) and EDTA (2 mM), pH 3, pumped at a rate of $1.8\,ml\,min^{-1}$. A carbon paste electrode was used, and the detector potential was +0.65 V. Dihydroxybenzylamine was used as an internal standard and (−)-noradrenaline, (−)-adrenaline and (−)-dopamine injected in different doses. Linearity of peak height versus concentrations of noradrenaline, adrenaline or dopamine was excellent (interassay coefficient of variation was less than 5%). Under our conditions, the limits of detection for noradrenaline, adrenaline and dopamine were 40, 80 and $100\,pg\,ml^{-1}$, respectively. Differences between two means were estimated by Student's *t* test for unpaired data; a probability of less than 0.01 was assumed to denote a significant difference.

Results

Both dopamine and NA were detectable in all tissues examined, even after the administration of 6-OHDA and pargyline plus 6-OHDA. Also, NA and Ad were detectable consistently in the adrenal medulla and plasma samples obtained from control and treated animals. All values presented in the text concerning the left ventricle, blood vessels and kidney are contained in Table 1, and those concerning the adrenal medulla and plasma are listed in Table 2.

In the left ventricle both NA and dopamine, were significantly reduced by 6-OHDA (by 95%). When animals were pretreated with pargyline the dopamine and NA depleting effect of 6-OHDA was significantly enhanced.

After the administration of 6-OHDA the NA contents of the main trunk and proximal branches of the mesenteric artery and renal artery were significantly reduced, reaching values of depletion of 85%. In contrast, dopamine was not affected by 6-OHDA in the proximal branches of the mesenteric artery or renal artery. Only in the main trunk of the mesenteric artery was the dopamine content significantly reduced by 6-OHDA alone, although to a lesser extent than that for NA. In these three vessels dopamine/NA ratios were increased between two and five fold by 6-OHDA.

Previous administration of pargyline significantly enhanced the NA depletion by 6-OHDA in the proximal branches of the mesenteric artery; in the renal artery the pattern of NA depletion was not changed and in the main trunk of the mesenteric artery NA content was increased when compared with the 6-OHDA group values. The extent of dopamine depletion induced by pargyline plus 6-OHDA in the main trunk and proximal branches of the mesenteric artery and renal artery ranged between 64% and 84%. In these three vessels dopamine/NA ratios were decreased when compared with those obtained after 6-OHDA alone; however, only in the main trunk and proximal branches of the mesenteric artery was this reduction found to be significant.

The effects of 6-OHDA alone and after previous pargyline administration on the NA content in the renal cortex and renal medulla were similar. In both tissues a significant reduction of the NA content was obtained after 6-OHDA. However, pargyline plus 6-OHDA was ineffective in depleting the NA content. Dopamine levels in the renal cortex were significantly reduced to a similar level by 6-OHDA alone or in combination with pargyline. In contrast the renal medulla dopamine content was neither reduced by 6-

OHDA nor by pargyline plus 6-OHDA. The dopamine/NA ratios for the renal cortex and renal medulla were not significantly altered after 6-OHDA alone or pargyline plus 6-OHDA, except for the renal cortex where a significant decrease in dopamine/NA ratio was found between the 6-OHDA and pargyline plus 6-OHDA-treated groups.

In all tissues examined (except adrenal medulla) Ad was not detectable consistently, although levels of $10-30\,ng\,g^{-1}$ were found occasionally.

In the adrenal medulla only the NA content was significantly decreased by 6-OHDA (69%) or by pargyline plus 6-OHDA (83%). Adrenal medulla Ad or dopamine content was not affected either by 6-OHDA or by pargyline plus 6-OHDA.

In the 6-OHDA-treated group, NA and Ad concentrations in plasma were not significantly different from those in control animals. However, in pargyline pretreated animals, 6-OHDA increased by three times the NA concentrations in plasma ($P < 0.01$) without a corresponding increase of Ad concentrations.

Discussion

The selective neurotoxic effects of 6-OHDA on dopamine- and NA-containing cells have been used in the study of the presence of dopaminergic neurones in the CNS (for review, see Kostrzewa & Jacobowitz, 1974). One of the methods of this selective approach include previous administration of pargyline, which markedly enhances 6-OHDA-induced dopamine depletion (Breese & Traylor, 1970).

Even though no morphological study was performed to confirm the neurotoxic effects on adrenergic neurones, in our experimental conditions 6-OHDA produced a significant depletion of NA in the left ventricle, mesenteric and renal arteries and kidney. Although in the left ventricle, proximal branches of the mesenteric artery and adrenal medulla, pargyline plus 6-OHDA was found to decrease to a great extent the NA content, in the main trunk of the mesenteric artery, renal artery and kidney (renal cortex and renal medulla) previous administration of pargyline did not enhance the NA depletion induced by 6-OHDA alone. Thus pargyline pretreatment does not appear always to potentiate the neurotoxic effects of 6-OHDA. In addition, Breese & Traylor (1970) have reported no advantage in the 6-OHDA-induced depletion of brain NA by previous administration of pargyline.

The decreases of dopamine content induced by 6-OHDA alone or in combination with pargyline in the left ventricle were parallel to those of NA. These results suggest that in the left ventricle there is no independent dopaminergic innervation.

By contrast, in the proximal branches of the mesenteric artery and renal artery, 6-OHDA selectively reduced the NA content; dopamine content remaining largely unaffected. In the main trunk of the mesenteric artery the dopamine content was significantly reduced by 6-OHDA but dopamine/NA ratios were still significantly increased. The fact that pargyline plus 6-OHDA reduced dopamine/NA ratios in both segments of the mesenteric artery and renal artery, although not significantly for the latter, suggests that dopamine is probably stored in two different neuronal structures which are selectively affected by 6-OHDA. An independent dopaminergic innervation in the main trunk and proximal branches of the mesenteric artery and renal artery is supported also by the studies of Yeh *et al.* (1969), Goldberg (1972); Goldberg *et al.* (1978), Lokhandwala & Buckley, (1977), Lokhandwala & Barrett, (1982), Kullman *et al.* (1983) and Amenta *et al.* (1984) which describe the presence of specific receptors for dopamine in these vascular areas, and by the presence of considerable concentrations of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in mesenteric and renal arteries (Lackoviċ *et al.*, 1982). In addition it has been reported that other vascular and non-vascular peripheral tissues are supplied with nerves where the transmitter substance is dopamine (Bell *et al.*, 1978 a,b; Bell & Rome, 1984; Commissiong *et al.*, 1978; Dinerstein *et al.*, 1979; Lackoviċ & Neff, 1980).

Bell *et al.* (1978a) and Dinerstein *et al.* (1979) have shown the presence in dog kidney of dopamine-containing nerves which predominate in the cortical layer. In cat kidney the dopamine content of the outer cortical layer is greater than would be expected from the presence of only noradrenergic axons (Bell & Gillespie 1981). In the present study the amount of dopamine, either in the renal cortex or in the renal medulla, in control animals was greater than that predicted by the presence of this amine only as a precursor for NA, as can be observed when dopamine/NA ratios in the proximal branches of the mesenteric artery and renal artery are compared with those present in the kidney ($P < 0.01$). However, the chemical sympathectomy technique used in this study did not provide further information concerning the presence of independent dopaminergic neurones in the cat kidney.

Thoenen & Tranzer (1968) have shown that 6-OHDA causes a selective destruction of adrenergic nerve terminals without affecting the chromaffin cells of the adrenal medulla. Two explanations were considered: the lack of an imipramine-sensitive uptake system for 6-OHDA in these cells (Stone *et al.*, 1964) and the different access of 6-OHDA to these tissues, attributed to the presence of permeability barriers or lower rates of blood perfusion. However, Kirpekar *et al.* (1983) have shown that in cultured bovine adrenal chromaffin cells, 6-OHDA induced marked changes in cell morphology and also an irreversible dose-depen-

dent decrease in the catecholamine content. In that study they concluded that 6-OHDA may be taken up inside the chromaffin cell and the difference between the studies *in vivo* and *in vitro* could be due to lower concentrations of 6-OHDA reaching the adrenal medulla *in vivo*. In our experimental conditions we have observed that the Ad and dopamine content in the adrenal medulla was not modified by 6-OHDA or pargyline plus 6-OHDA, whereas the NA content was significantly reduced by 6-OHDA and to a greater extent by pargyline plus 6-OHDA. When the NA content of the adrenal medulla was compared with NA concentrations in plasma, an inverse relationship was evident; an increase in NA concentrations in plasma in the presence of a significant reduction in NA content of the adrenal medulla, which suggests that pargyline plus 6-OHDA affects selectively the NA-containing cells of the adrenal medulla. However, considering that chemical sympathectomy brings about a compensatory increase in catecholamine turnover in the adrenal medulla (Muller, 1971) the present results suggest that NA-containing cells are playing a major role in maintaining homeostasis of the surviving system.

Though an independent peripheral dopaminergic innervation of the mesenteric and renal arteries cannot be concluded, the results obtained in this study suggest the existence of a NA-independent dopamine pool in these vascular beds. Whereas dopamine/NA ratios in the kidney of control animals point to the presence of independent dopaminergic neurones, the chemical sympathectomy technique used was insufficient to enable their characterization, for which further studies will be undertaken.

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