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Short communication

EFFECT OF N,N-DIMETHYL-p-METHOXYPHENYLETHYLAMINE ON BLOOD PRESSURE AND BRAIN CATECHOLAMINES IN DOCA-SALINE HYPERTENSIVE RATS

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Intraperitoneal and intraventricular injections of N,N-dimethyl-p-methoxyphenyl ethylamine (PMPEA) decreased blood pressure in conscious DOCA-saline hypertensive rats. Bilateral injection of this agent into the nucleus tractus solitarii (NTS) of anaesthetized normotensive rats also caused a decrease in blood pressure. The increased turnover of noradrenaline in the dorsal part of the caudal medulla oblongata in DOCA-saline hypertensive rats was found to be restored to normal following treatment with N,N-dimethyl PMPEA. The data indicate a central site of action for the antihypertensive effect of N,N-dimethyl PMPEA.

N,N-Dimethyl-p-methoxyphenylethylamine Nucleus tractus solitarii Hypertension Catecholamine turnover

1. Introduction

Evidence exists that brain catecholamines play a role in cardiovascular control (Chalmers, 1975; De Jong et al., 1975) and the involvement of brain monoamines in hypertension has been suggested. One of the monoamines related to adrenaline is p-methoxyphenylethylamine (PMPEA). This agent has sympathomimetic effects. The hypertensive effect of the i.v. injection of PMPEA in the rat (Cession-Fossion and Michaux, 1963) is well documented. The pressor response is caused by the release of noradrenaline from the sympathetic nerves (Paton and Pasternake, 1974). Substituting methyl groups for a hydrogen in the NH_2 group creates the compound N,N-dimethyl PMPEA. Recent observations indicated that N,N-dimethyl PMPEA could inhibit the development of hypertension in DOCA-saline-treated rats (Shalita and Dikstein, 1981).

In the present study, intraperitoneal (i.p.) and intracerebroventricular (i.c.v.) injections were used to study the effects of N,N-dimethyl PMPEA on the blood pressure and heart rate of DOCA-saline hypertensive rats; microinjections into the A_2 region of the nucleus tractus solitarii (NTS) were used in normotensive rats. Biochemical analysis of catecholamine turnover in the hypothalamus, frontal cortex and the dorsal part of the caudal medulla was performed as well.

2. Materials and methods

2.1. General

Male rats of the inbred Wistar strain weighing 140–160 g (Wi/cpb, TNO, Zeist, The Netherlands) were used in this study. Two pellets of DOCA (20 mg each) were implanted s.c. into rats anaesthetised with pentothal. Food and 0.9% NaCl were available ad libitum. The experiments began 4 weeks after implantation of DOCA (body weight 250–300 g). Blood pressure was measured frequently in the chronic experiments using an indi-

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rect tail-sphygmographic method (Leenen and De Jong, 1971) and direct measurement via a cannula in the femoral artery as described by Zandberg et al. (1979). Plastic cannulas were implanted into the lateral ventricle using the stereotactic coordinates of König and Klippel (1967). N,N-dimethyl PMPEA (in 0.9% NaCl) was injected i.p.; for i.c.v. injections, 300 μg were dissolved in 1 μl. Local microinjections were given in a volume of 0.4 μl (Zandberg et al., 1979).

2.2. Tissue CA

A radioenzymatic method (Van der Gugten et al., 1976) was used to measure catecholamine concentrations in frontal cortex, hypothalamus and dorsal part of the caudal medulla oblongata (containing the NTS) of normotensive and DOCA-saline hypertensive rats which had been treated with α-methyl-p-tyrosine methylester HCl (α-MPT, Labkemi AB, Stockholm, 300 mg/kg i.p.) 4 h prior to decapitation and of non-α-MPT-treated normotensive and hypertensive rats. The decline in catecholamine concentration over a 4 h period was taken as a measure of catecholamine turnover. Student's t-test was used to analyse the data. A P value of less than 0.05 was considered to indicate a significant difference.

3. Results

3.1. The effect of peripheral and central administration of N,N-dimethyl PMPEA on blood pressure over 24 h

The maximum reduction in blood pressure (−37 mmHg; $P < 0.005$) occurred 12 h after i.p. injection and was not accompanied by a change in heart rate (table 1). Table 1 also shows the effect of N,N-dimethyl PMPEA on blood pressure after its administration into a lateral ventricle. The maximum reduction in blood pressure occurred 6 h after injection (−29 mmHg; $P < 0.0005$). This phenomenon remained stable for about 24 h (−28 mmHg; $P < 0.0005$). The blood pressure returned to the baseline value 48 h later. No changes in heart rate were observed.

Bilateral injections of N,N-dimethyl PMPEA into the A_2 region of the NTS also decreased blood pressure. Maximal effects occurred within 10 min and were dose-dependent. Blood pressure returned to the baseline value within 30 min. A dose of 0.1 nmol reduced blood pressure by 19 mmHg in 10 min whereas 0.02 nmol decreased blood pressure by 16 mmHg ($P < 0.05$). The 0.1 nmol dose was still active after 15 min (−15 mmHg; $P < 0.05$) whereas the lower dose was inef-

TABLE 1

The effect of peripheral (i.p.) and central (i.c.v.) administration of N,N-dimethyl PMPEA on blood pressure of DOCA-saline hypertensive rats [a].

Treatment	Dose (mg/kg)	Blood pressure (mmHg)	Δ Blood pressure after		
			8 h	12 h	24 h
Peripheral					
Vehicle (9)	–	191 ± 4	1 ± 2	+ 1 ± 3	+ 1 ± 1
N,N-Dimethyl PMPEA (9)	25	192 ± 5	− 29 ± 4	− 37 ± 3	− 8 ± 3
Treatment	Dose (mg/kg)	Blood pressure (mmHg)	Δ Blood pressure after		
			6 h	24 h	48 h
Central					
Vehicle (6)		184 ± 2	− 2 ± 2	+ 1 ± 2	+ 4 ± 2
N,N-Dimethyl PMPEA (6)	0.1	187 ± 4	− 29 ± 4 [b]	− 28 ± 5 [b]	− 8 ± 1

[a] Data are mean ± S.E.M.; number of animals is given in parentheses.
[b] $P < 0.0005$.

fective (− 12 mmHg, n.s.). A decrease in heart rate (50–60 bpm) was observed with both doses. This bradycardia lasted for about 10 min.

3.2. The effect of N,N-dimethyl PMPEA on the turnover of brain catecholamines

N,N-dimethyl PMPEA (25 mg/kg) was injected i.p. and 12 h later the turnover of catecholamines in the hypothalamus, cortex and the dorsal part of the caudal medulla was determined after treatment with α-MPT (300 mg/kg). The results are summarized in table 2. No significant differences were apparent in the steady state concentration of either noradrenaline and dopamine in the three brain regions studied, or of adrenaline in the hypothalamus of normotensive and DOCA-saline hypertensive rats. Apart from an increase in the turnover of noradrenaline in the dorsal part of the caudal medulla oblongata the turnover of catecholamines in the hypertensive rats was no different from that in the normotensive rats. Treatment with N,N-dimethyl PMPEA did not result in significant alterations in the steady state concentrations of catecholamines in the three brain regions of either normotensive or DOCA-saline hypertensive rats 12 h later. Changes in catecholamine turnover in N,N-dimethyl PMPEA-treated rats were restricted to the dorsal part of the caudal medulla in which region noradrenaline turnover was restored to values similar to that in normotensive rats, and the frontal cortex, where an increased noradrenaline turnover was found.

TABLE 2

Effect of N,N-dimethyl PMPEA (25 mg/kg, i.p.) on catecholamine concentrations and turnover in brain regions of normotensive rats and DOCA-saline hypertensive rats.

Steady state concentration (μg/g tissue)				Concentration 4 h after α-MPT (% of 0 h conc.)			
Normotensive rats		Hypertensive rats		Normotensive rats		Hypertensive rats	
Control [a]	Treated [a]	Control	Treated	Control	Treated	Control	Treated
NORADRENALINE							
Hypothalamus							
2.59 ±0.14 [b]	2.40 ±0.09 [b]	2.39 ±0.10 [c]	2.38 ±0.21 [c]	61±4 [b]	64±3 [b]	69±4 [c]	71±2 [c]
Dors.-caud. medulla							
1.13 ±0.02	1.06 ±0.03	1.08 ±0.05	1.14 ±0.08	52±2	59±3	38±5 [d]	57±2 [e]
Frontal cortex							
0.57 ±0.04	0.57 ±0.04	0.59 ±0.03	0.59 ±0.07	45±4	45±3	55±6	39±3 [e]
DOPAMINE							
Hypothalamus							
0.52 ±0.03	0.48 ±0.02	0.49 ±0.03	0.50 ±0.06	18±1	19±2	15±3	15±1
Dors.-caud. medulla							
0.079±0.006	0.075±0.006	0.070±0.007	0.084±0.012	N.D.	N.D.	N.D.	N.D.
Frontal cortex							
1.20 ±0.08	1.23 ±0.10	0.94 ±0.08	1.24 ±0.18	30±3	36±4	41±8	33±4
ADRENALINE							
Hypothalamus							
0.083±0.005	0.087±0.005	0.076±0.004	0.083±0.013	48±6	42±3	49±8	55±3

[a] Rats were treated with either saline or N,N-dimethyl PMPEA (25 mg/kg, i.p.) either 12 h (steady state concentration) or 16 h (α-MPT-treated rats) prior to decapitation.

[b] Mean ±S.E.M. (n = 8–9); [c] Mean ±S.E.M. (n = 5–6); N.D. = not detectable.

[d] Significantly different from normotensive controls ($P < 0.05$); [e] significantly different from hypertensive controls ($P < 0.05$).

4. Discussion

The present data show that N,N-dimethyl PMPEA had a hypotensive action in DOCA-saline hypertensive rats. There was a slow onset and the effect lasted about 24 h. A much lower dose proved to be effective following i.c.v. administration. It is conceivable that the antihypertensive action of N,N-dimethyl PMPEA is exerted centrally.

That N,N-dimethyl PMPEA affects blood pressure and heart rate after bilateral injection into the A_2 region of the NTS is interesting, since injections of α-methylnoradrenaline were found to be most effective in this region (Zandberg et al., 1979). From the data obtained, it appears that N,N-dimethyl PMPEA is more potent than α-methylnoradrenaline to decrease blood pressure in normotensive rats (Zandberg et al., 1979).

The mechanism of action of N,N-dimethyl PMPEA is not known. It is tempting to implicate the increase in noradrenaline turnover in frontal cortex and in particular, the restoration to normal values of noradrenaline turnover observed in the dorsal part of the caudal medulla oblongata of DOCA-saline hypertensive rats treated with N,N-dimethyl PMPEA. The local bilateral application of noradrenaline, α-methylnoradrenaline or adrenaline into the NTS is known to decrease blood pressure and heart rate (Zandberg et al., 1979). Therefore, the most likely explanation seems to be that which proposes that the changes in noradrenaline turnover in the dorsal part of the caudal medulla oblongata are secondary to the effects of N,N-dimethyl PMPEA on blood pressure rather than a direct result of the action of the drug.

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References

Cession-Fossion, A. and R. Michaux, 1963, Comparison of pharmacodynamic action of tyramine and its O-methyl derivatives, C.R. Soc. Biol. 157, 683.

Chalmers, J.P., 1975, Brain amines and models of hypertension, Circ. Res. 36, 469.

De Jong, W., P. Zandberg and B. Bohus, 1975, Central inhibitory noradrenergic cardiovascular control, in: Hormones, Homeostasis and the Brain, Progr. Brain Res. 42, eds. W.H. Gispen, Tj.B. Van Wimersma Greidanus, B. Bohus and D. De Wied (Elsevier, Amsterdam) p. 285.

König, J.F.R. and R.A. Klippel, 1967, The Rat Brain (R. Kruger Publ. Co., Huntington, N.Y.).

Leenen, F.H.H. and W. De Jong, 1971, A solid silver clip for induction of predictable levels of renal hypertension in the rat, J. Appl. Physiol. 31, 142.

Paton, D.M. and N.L. Pasternak, 1974, Effect of O-methylation on the acceleration of efflux of noradrenaline produced by phenethylamine derivatives, J. Pharm. Pharmacol. 26, 273.

Shalita, B. and S. Dikstein, 1981, The pharmacology of the hypotensive effect of the N,N-dimethyl PMPEA, Res. Commun. Chem. Pathol. Pharmacol. 32, 53.

Van der Gugten, J.M., J.M. Palkovits, H.J.L.M. Wijnen and D.H.G. Versteeg, 1976, Regional distribution of adrenaline in rat brain, Brain Res. 107, 171.

Zandberg, P., W. De Jong and D. De Wied, 1979, Effect of catecholamine-receptor stimulating agents on blood pressure after local application in the nucleus tractus solitarii of the medulla oblongata, European J. Pharmacol. 55, 43.