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PROLONGED EFFECTS OF *p*-CHLOROPHENYLALANINE ON THE BLOOD PRESSURE OF CONSCIOUS NORMOTENSIVE AND DOCA/SALINE HYPERTENSIVE RATS

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1 In deoxycorticosterone acetate (DOCA) saline hypertensive rats a single dose of *p*-chlorophenylalanine methylester (PCPAME) (400 mg/kg i.p.) produced a significant fall in blood pressure (20–43 mmHg) which lasted for at least 8 days and was accompanied by a parallel depletion of brain stem 5-hydroxytryptamine (5-HT) but not of noradrenaline (NA).

2 In normotensive rats single doses of PCPAME (200 and 400 mg/kg i.p.) produced a significant hypotension (15–20 mmHg) after a latent period of 5 days. An initial pressor response (12 mmHg) was observed at the higher dose level only on day 3.

3 The hypotensive response to PCPAME (200 mg/kg i.p.) in normotensive rats was not modified by pretreatment with 5,6-dihydroxytryptamine (5,6-DHT; 50 μg i.c.v.) or 6-hydroxydopamine (6-OHDA; 3 × 250 μg intracerebroventricularly).

4 It is concluded that the hypotensive response to PCPAME in normotensive rats is independent of brain stem depletion of 5-HT and is probably not mediated by the formation of a false transmitter substance acting via central noradrenergic inhibitory pathways. The mechanism involved in the antihypertensive response to PCPAME in DOCA/saline hypertensive rats has yet to be defined.

Introduction

Serotoninergic neurones have been identified in various vasomotor regions of the central nervous system (Dahlström & Fuxe, 1965; Fuxe, Hökfelt & Ungerstedt, 1968) but their rôle in cardiovascular regulation is poorly understood. Central serotoninergic mechanisms in circulatory control have been investigated in only a few studies with conflicting results. Intracisternal administration of 5,6-dihydroxytryptamine (5,6-DHT), which produces a selective destruction of central 5-hydroxytryptamine (5-HT) secreting nerve terminals (Baumgarten, Lachenmayer & Schlossberger, 1972) causes a fall in blood pressure in normal and in neurogenically hypertensive rabbits, and prevents the development of neurogenic, but not of renal hypertension in this species (Wing & Chalmers, 1974a). The development and maintenance of deoxycorticosterone acetate (DOCA)/saline hypertension in the rat were unaffected by intracisternal injections of 5,6-DHT (Myers, Reid & Lewis, 1974) but the rate of development of hypertension in genetically hypertensive rats was retarded by the intracerebroventricular (i.c.v.) injection of 5,6-DHT to 6 week old animals (Buckingham, Hamilton & Robson, unpublished results). Parachlorophenylalanine (PCPA) depletes 5-HT stores by inhibition of tryptophan hydroxylase (Koe & Weissman, 1966; Jéquier, Lovenberg & Sjoerdsma, 1967) and although it does not prevent the onset of neurogenic hypertension in the rabbit, it lowers blood pressure in the normotensive rabbit (Wing & Chalmers, 1974b) and in the genetically hypertensive rat (Jarrot, McQueen and Louis, 1975). In contrast, PCPA raises blood pressure in the normotensive rat (Ito and Schanberg, 1972) and is without effect in the normotensive dog (Dunkley, Sanghvi, Friedman & Gershon, 1972).

In conscious dogs, moderate to high doses of 5-hydroxytryptophan (5-HTP) produce an elevation of blood pressure (Bogdanski, Weissbach & Udenfriend, 1958; Sanghvi & Gershon, 1970) whereas a hypotensive response is produced in conscious rats (Henning & Rubenson, 1971) and anaesthetized, intact monoamine oxidase inhibited cats (Florez & Armijo, 1974) and anaesthetized monoamine oxidase inhibited dogs (Antonaccio & Robson, 1973). In the present studies, the effects of DL-*p*-chlorophenylalanine methyl ester hydrochloride (PCPAME) on resting blood pressure have been investigated in

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conscious normotensive and DOCA/saline hypertensive rats.

Methods

Induction of experimental hypertension

Experimental hypertension was induced in male Sprague-Dawley rats, 120–150 g, by unilateral nephrectomy under ether anaesthesia and subcutaneous implantation of 2 compressed tablets each containing 25 mg deoxycorticosterone acetate (DOCA). The drinking water was replaced by 0.9% w/v saline. Studies were begun 5–6 weeks later. Animals with a systolic blood pressure of less than 180 mmHg (measured indirectly: see below) were not included in the study.

Indirect measurement of systolic blood pressure

Rats were placed in an incubator (32–34°C) for 30 min to 1 hour. Systolic blood pressure (1 mmHg 133 Pa) was then measured indirectly using a tail cuff strain gauge detector coupled to a W & W 8002 recorder.

Intra-cerebroventricular (i.c.v.) administration of drugs

Some normotensive animals received i.c.v. injections via a cannula implanted in the lateral cerebral ventricle according to the method of Hayden, Johnson & Maickel (1966). Cannulae were implanted approximately 1 week before studies commenced.

Drug administrations

a. The effects of single doses of PCPAME (200 and 400 mg/kg), administered intraperitoneally (i.p.), were studied in normotensive and DOCA/saline hypertensive rats. Systolic blood pressure was monitored 6, 4, 2 days and immediately before dosing (day 0) and 1,3, 5, 8, 11 and, in some experiments, 16 days after dosing.

b. In a separate experiment, 5-HT and noradrenaline (NA) levels in medulla-pons were determined 1, 3, 5, 8 and 11 days after PCPAME (400 mg/kg i.p.), administered to DOCA/saline hypertensive rats.

c. Normotensive rats were pretreated with 5,6-DHT (50 μg i.c.v.), or vehicle, 4 days before PCPAME (200 mg/kg i.p.). Systolic blood pressure was monitored as described in *a*.

d. Normotensive rats were pretreated with 6-hydroxydopamine (6-OHDA; 250 μg i.c.v.), or vehicle, 6, 4 and 2 days before PCPAME (200 mg/kg i.p.). Systolic blood pressure was monitored as described in *a*.

Biochemical determination of 5-HT and noradrenaline (NA) in medulla-pons

Rats were killed by decapitation. Brains were removed and placed on a cooled glass plate. The medulla-oblongata-pons region was dissected out according to the method of Miller, Cox, Snodgrass & Maickel (1970). This procedure took less than 2 min to perform. The brain samples were frozen in polythene bags at −20°C until analyses were performed, usually within 1 day. The brain samples were pooled in groups of 4 or 5 and homogenized in 7 ml of cold 0.4 N perchloric acid containing EDTA (0.1%), and ascorbic acid (0.2 mg/ml). The extraction procedure for NA and 5-HT was essentially that of Uretsky & Iversen (1970). After the potassium hydroxide neutralization step, the supernatant and precipitate washings were combined, shaken and divided into 2 equal parts, one for NA determination and the other for 5-HT. Column chromatography was employed to purify and concentrate the extracts. Noradrenaline was adsorbed on Amberlite CG 120 Na^+ form cation exchange resin, and eluted with 10 ml of 1 N HCl (Uretsky & Iversen, 1970) whilst 5-HT was adsorbed on Amberlite CG 50 Na^+ form resin, and eluted with 3 ml of 1 N HCl (Anden & Magnusson, 1967). Aliquots of the eluates were estimated for NA by the method of Laverty and Taylor (1968). The fluorescence technique of Anden & Magnusson (1967) was used to measure 5-HT. Results were corrected for loss of amines during the isolation procedure by inclusion of internal standards. Average recoveries for NA and 5-HT were 80% and 65% respectively.

Drugs

For intraperitoneal injection: DL-*p*-chlorophenylalanine methyl ester hydrochloride (PCPAME) (Koch-Light) dissolved in 0.9% saline. Doses are expressed as the salt.

For i.c.v. injection: 6-hydroxydopamine hydrobromide (6-OHDA) dissolved in nitrogen bubbled N/100 hydrochloric acid; 5,6-dihydroxytryptamine creatinine sulphate (5,6-DHT) dissolved in 0.1 mg/ml ascorbic acid. Both drugs were kindly supplied by Dr Langemann (F. Hoffmann La Roche Limited, Basel). Doses of these drugs are expressed as the base.

Statistical analysis

Changes in systolic blood pressure for each animal at each time interval were related to values recorded on day 0. Group mean changes were calculated together

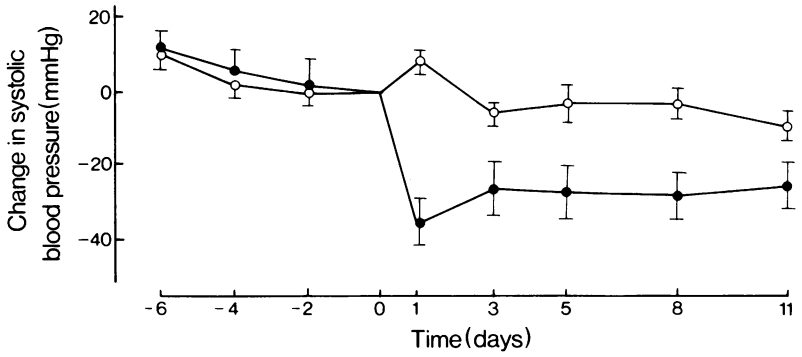

Figure 1 Time course (days) of change in systolic blood pressure (mmHg) produced by (●) PCPAME, 400 mg/kg i.p. and by (○) vehicle, injected at day 0, in DOCA/saline hypertensive rats. At day 0 the resting systolic blood pressure of the treated ($n=22$) and control ($n=18$) groups were, respectively, 216 ± 5 and 217 ± 4 mmHg.
n is the number of animals per group; vertical bars extend to s.e. mean.

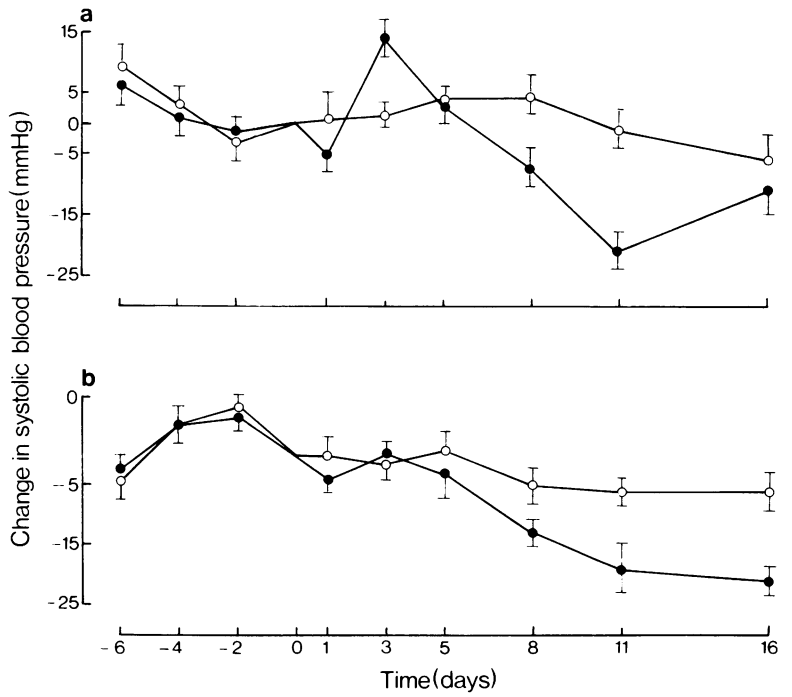

Figure 2 Time-course (days) of change in systolic blood pressure (mmHg) produced (a) by PCPAME, 400 mg/kg i.p. (●), and vehicle (○) and (b) by PCPAME, 200 mg/kg i.p. (●), and vehicle (○) injected at day 0 in normotensive rats. At day 0 the resting systolic blood pressure of treated and control groups were (a) 142 ± 3 ($n=16$) and 144 ± 3 ($n=12$) mmHg respectively and (b) 144 ± 1 ($n=15$) and 145 ± 2 ($n=15$) mmHg respectively.
n is the number of animals per group; vertical bars extend to s.e. mean.

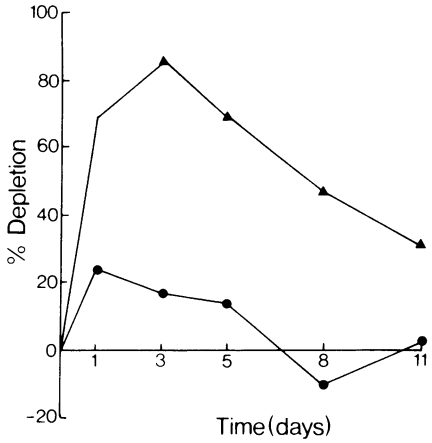

Figure 3 Time-course (days) of percentage depletion of NA (●) and 5-HT (▲) from the medulla-pons region of DOCA/saline hypertensive rats treated at day 0 with PCPAME (400 mg/kg i.p.). Each point represents the mean of determinations carried out in groups of 4 or 5 rats at each time interval.

with standard error of the mean. Differences between groups were assessed by Student's 't' test.

Results

Effects of single doses of PCPAME on the blood pressure of DOCA/saline hypertensive and normotensive rats

In DOCA/saline hypertensive rats PCPAME (400 mg/kg i.p.) produced a significant fall in systolic blood pressure (20–43 mmHg) which was maintained for at least 8 days after drug administration (Figure 1). In other experiments PCPAME (200 mg/kg i.p.) produced no significant changes in systolic blood pressure.

In normotensive rats single doses of PCPAME (200 and 400 mg/kg i.p.) also produced significant falls in systolic blood pressure though only after a latent period of 5 days (Figures 2a and 2b). During this initial period, PCPAME (400 mg/kg, but not 200 mg/kg i.p.) produced a significant rise in systolic blood pressure on day 3 (12 mmHg); the hypotensive response following the higher dose reached a maximum on day 11 (20 mmHg) and the blood pressure was not significantly different from that of the control group by day 16. The hypotensive response evoked by PCPAME (200 mg/kg i.p.) was greatest on day 16 (15 mmHg) when the study was terminated.

Effect of a single dose of PCPAME (400 mg/kg i.p.) on 5-HT and NA levels in medulla-pons region of the brain of DOCA/saline hypertensive rats

PCPAME, 400 mg/kg i.p., in DOCA/saline hypertensive rats produced a rapid depletion of 5-HT in the medulla-pons region (Figure 3). Maximal depletion (85%) was achieved by day 3 and thereafter 5-HT levels gradually returned towards control levels, though 5-HT levels were still 30% depleted by day 11. PCPAME also slightly decreased NA levels (24% on day 1) but by day 8 NA levels in PCPAME-treated rats were slightly higher (10%) than those observed in control animals.

Effect of pretreatment with 5,6-DHT (50 μg i.c.v.) on the delayed hypotensive response to PCPAME (200 mg/kg i.p.) in normotensive rats

Pretreatment of a group of normotensive rats with 5,6-DHT (50 μg i.c.v.) produced no significant change in systolic blood pressure when compared to a group pretreated with vehicle only (Figure 4). Four days

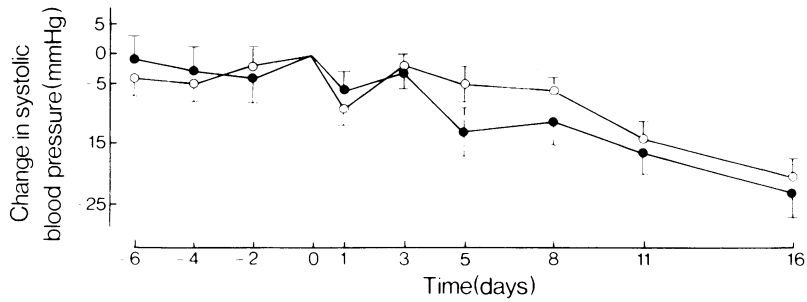

Figure 4 Time-course (days) of change in systolic blood pressure (mmHg) produced by PCPAME (200 mg/kg i.p.), injected at day 0, in normotensive rats pretreated with i.c.v. 5,6-DHT (50 μg ●) or vehicle (○) at day-4. At day 0, the resting systolic blood pressure of 5,6-DHT treated rats ($n=22$) and control rats ($n=23$) were, respectively, 139 ± 3 and 138 ± 2 mmHg.
n is the number of animals per group; vertical bars extend to s.e. mean.

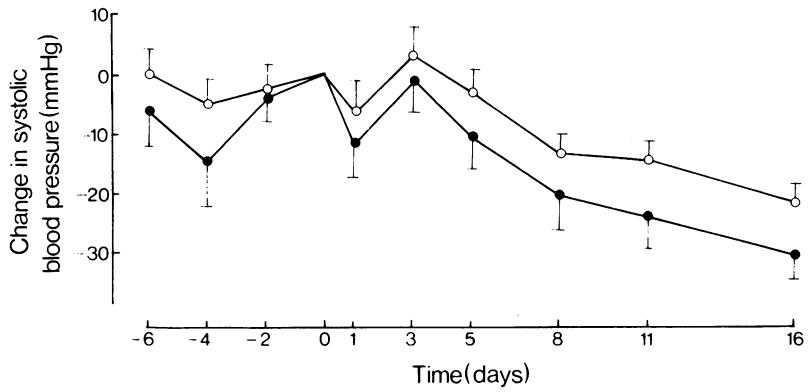

Figure 5 Time-course (days) of change in systolic blood pressure (mmHg) produced by PCPAME (200 mg/kg i.p.), injected at day 0, in normotensive rats pretreated with i.c.v. 6-OHDA (250 μg; ●) or vehicle (○) on days −6, −4 and −2. At day 0, the resting systolic blood pressure of 6-OHDA-treated rats ($n=13$) and control rats ($n=15$) were, respectively, 151 ± 5 and 146 ± 3 mmHg.
n is the number of animals per group; vertical bars extend to s.e. mean.

after pretreatment all rats received PCPAME (200 mg/kg i.p.). The pattern of the blood pressure response to PCPAME was similar in both groups though in the 5,6-DHT-pretreated group the onset of the hypotensive response preceded that in the control group. The magnitude of the hypotensive response recorded on days 11 (14–17 mmHg) and 16 (20–23 mmHg) were very similar.

Effect of pretreatment with 6-OHDA (3 × 250 μg) on the delayed hypotensive response to PCPAME (200 mg/kg i.p.) in normotensive rats

Pretreatment of a group of normotensive rats with 6-OHDA (3 × 250 μg i.c.v.) produced a slight fall in systolic blood pressure following the first dose but subsequent recovery to resting levels on day 0. Pretreatment with vehicle (i.c.v.) produced little effect on systolic blood pressure. Following pretreatment with 6-OHDA, rats developed characteristic symptoms of aggression. The pattern of the blood pressure response to PCPAME was similar in both groups (Figure 5), and at no time interval were the blood pressure changes of the 2 groups significantly different.

Discussion

These investigations have shown that single doses of PCPAME produced a prolonged hypotensive response in both conscious normotensive and DOCA/saline hypertensive rats; in addition a small pressor response was recorded after PCPAME (400 mg/kg), in normotensive rats. Reductions in arterial blood pressure have also been observed in the normotensive rabbit (Wing & Chalmers, 1974b) and genetically hypertensive rat (Jarrot *et al.*, 1975) when PCPA was administered in repeated dose studies. Ito & Schanberg (1972) have previously demonstrated that the elevation of blood pressure produced by PCPA in normotensive rats was prevented, or could be reversed, by treatment with 5-HTP; in addition a hypotensive phase was observed 5 days after the administration of PCPA (200 mg/kg), but the effect was short-lived. Ito & Schanberg (1972) also found that the hypertensive response to PCPA in normotensive rats was accompanied by marked parallel depletion of brain 5-HT levels. In the present study the antihypertensive response produced by PCPAME (400 mg/kg) in DOCA/saline hypertensive rats was accompanied by a parallel depletion of 5-HT, but not of NA, from the brain stem and followed a similar time course to that described by Miller *et al.* (1970) during studies with PCPA (400 mg/kg) in normotensive rats. It appears therefore that in normotensive rats the significant rise in blood pressure observed on day 3 in our experiments, coincided with the maximal degree of 5-HT depletion in the medulla-pons and is thereby in agreement with the observations of Ito & Schanberg (1972).

In separate experiments 5-HTP (150–200 mg/kg) subcutaneously, was administered to DOCA/saline hypertensive rats, both in the presence and absence of the peripheral decarboxylase inhibitor, Ro 04-4602 (50 mg/kg i.p.) in an attempt to restore 5-HT levels depleted by PCPAME. The experiments, however, were inconclusive since 5-HTP *per se* produced an antihypertensive response.

We are unable, at present, to demonstrate if the antihypertensive response in DOCA/saline hypertensive rats produced by PCPAME is a function of brain 5-HT depletion.

In contrast to the studies of Ito & Schanberg (1972) the elevation of systolic blood pressure produced in normotensive rats by PCPAME in our experiments was transient and small relative to the ensuing hypotensive phase; a smaller dose of PCPAME (200 mg/kg i.p.) did not produce an elevation of systolic blood pressure. The dominant hypotensive phase produced by both doses of PCPAME would appear, from the biochemical study, to be independent of depletion of 5-HT in the brain stem. This conclusion is supported by the finding that in rats pretreated with 5,6-DHT (50 μg) the hypotensive response to PCPAME (200 mg/kg i.p.) was not significantly modified. Baumgarten, Björkland, Lachenmayer, Nobin & Stenevi (1971) showed that 5,6-DHT (25–75 μg) injected into the lateral cerebral ventricle of the rat produced a marked and persistent depletion of brain 5-HT; whilst depletion of 5-HT was lowest in medulla-pons, other areas and especially spinal cord were markedly depleted. Baumgarten *et al.* (1972) later showed that 5,6-DHT (75 μg) not only depletes 5-HT stores but also causes degeneration of serotoninergic nerve endings. If the hypotensive response to PCPAME in normotensive animals was a consequence of central 5-HT depletion, then treatment with 5,6-DHT itself might have been expected to produce a hypotensive response.

In our experiments 5,6-DHT did not produce any detectable change in systolic blood pressure. Similar observations have been made in DOCA/saline hypertensive rats when 5,6-DHT was administered intracisternally (Myers *et al.*, 1974), and when administered intracerebroventricularly to adult genetically hypertensive rats (Buckingham, Hamilton & Robson, unpublished results). It is possible that bundles of central serotoninergic neurones which may mediate the response to PCPA may be insensitive to this regimen of 5,6-DHT treatment.

Stark & Fuller (1972) suggested that some of the effects of PCPA on blood pressure may be mediated by a metabolite, *m*-chlorotyrosine, which may in turn be converted to a false transmitter, *m*-chloro-octopamine. King & Caldwell (1974) showed that, in the cat, *m*-chlorotyrosine induced, after a brief latent period, an elevation of blood pressure. This interesting observation raised the possibility that the prolonged hypotensive response to PCPAME in normotensive rats may be due to the release of an, as yet unidentified, false transmitter substance which acts centrally. The persistence of the response to PCPAME after destruction of central noradrenergic inhibitory pathways by 6-OHDA, suggests that a false transmitter acting through central noradrenergic inhibitory pathways is unlikely to mediate the hypotensive response to PCPAME in normotensive rats. The same pretreatment regimen has been shown in other studies to produce a widespread destruction of the nerve terminals of central noradrenergic neurones (Uretsky & Iversen, 1970) and to inhibit the antihypertensive response to α-methyldopa in genetically hypertensive rats (Finch & Hauesler, 1973). There remains the possibility that bundles of noradrenergic neurones involved in such a mediated response could be insensitive to this pretreatment regimen of 6-OHDA. At present we are unable to define the mechanism by which PCPAME produces prolonged hypotension in normotensive rats. The evidence so far accumulated suggests that this response is independent of brain stem 5-HT depletion.

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