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5-Carboxamidotryptamine attenuates the development of deoxycorticosterone acetate-salt hypertension in rats

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Abstract

The effect of chronic i.v. infusion of the 5-HT_1 receptor agonist, 5-carboxamidotryptamine (5-CT), was evaluated during the development of deoxycorticosterone acetate-salt (DOCA-salt) hypertension in rats over 4 weeks. Vehicle-treated ($n = 10$) Sprague-Dawley rats given DOCA (100 mg/kg, s.c.) and 1% saline as drinking fluid developed hypertension with systolic blood pressure reaching 194.6 ± 8.99 mm Hg at 27 days. In DOCA-salt rats treated with 5-CT infusions (15.0 μg/kg per day, $n = 10$) for 4 weeks via osmotic minipumps, systolic blood pressure was significantly lower by 41.7 mm Hg at day 27 when compared to vehicle-treated DOCA-salt rats. Systolic blood pressure values on day 27 in 5-CT-treated DOCA-salt rats were however greater than those in vehicle-treated control rats which were not given DOCA. Systolic blood pressure in 5-CT-treated DOCA-salt rats was significantly lower by day 7 compared to vehicle-treated DOCA-salt rats and remained lowered for the rest of the observation period. Heart rate was significantly greater in 5-CT-treated DOCA-salt rats on day 7 when compared to vehicle-treated DOCA-salt rats. Baroreflex sensitivity on day 28 was significantly greater in 5-CT-treated DOCA-salt rats as compared to vehicle-treated DOCA-salt rats. On day 28, hypotensive responses to hexamethonium (20 mg/kg) in 5-CT-treated DOCA-salt rats were markedly reduced compared to those in vehicle-treated DOCA-salt rats. The data suggest that chronic administration of 5-CT attenuates the development of DOCA-salt hypertension in rats with concomitant attenuation of the dampening of baroreflex sensitivity seen during the development of hypertension. The results also suggest a peripheral sympathoinhibitory action of 5-CT in addition to the known peripheral vasodilatation via 5-HT_1 receptors.

Keywords: 5-Carboxamidotryptamine; DOCA-salt (deoxycorticosterone acetate-salt) hypertensive rat; Blood pressure; Baroreflex sensitivity; (Chronic i.v. infusion)

1. Introduction

5-Carboxamidotryptamine (5-CT) is a prototypical 5-HT_1 receptor agonist which produces hypotension in normotensive and hypertensive animals (Saxena and Lawang, 1985; Dalton et al., 1985). This hypotension is attributed to the activation of vasodilatory 5-HT_1 receptors (Feniuk et al., 1984; Trevethick et al., 1986). In a previous study, chronic 5-CT administration produced a sustained antihypertensive effect in spontaneously hypertensive rats (SHR) (Balasubramaniam et al., 1993).

In conscious DOCA-salt hypertensive rats, 5-CT produced markedly greater acute depressor responses compared to normotensive rats (Dalton et al., 1986). 5-HT_1 receptor involvement was confirmed in these rats since the 5-CT-induced hypotension was susceptible to blockade by a 5-HT_1/5-HT_2 antagonist, methysergide, but not affected by 5-HT_2 receptor blockade with ketanserin or 5-HT_3 receptor blockade with MDL 72222 (Dalton et al., 1985). The data suggest acute antihypertensive properties of 5-HT_1 receptor agonism in DOCA-salt hypertension.

In the present study, the effect of chronic i.v. administration of 5-CT on the development of DOCA-salt hypertension was investigated to see if long-term 5-HT_1 receptor activation could alter the course of hypertension. The pathogenesis of DOCA-salt hypertension is characterised, in part, by hyperactivity of the sympathetic nervous system (De Champlain and Van Ameringen, 1972; Takeda and Bunag, 1980) acccompanied by a dampening of baroreflex responses (Takeda et al., 1988; Nakamura et al., 1988). This dampening of

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baroreflex function seems to contribute to the development and maintenance of hypertension. 5-CT treatment has been shown to improve baroreflex sensitivity in SHR during chronic treatment (Balasubramaniam et al., 1993) Therefore, in this study the effect of long-term 5-CT administration on baroreflex sensitivity was also investigated.

2. Materials and methods

Male Sprague-Dawley rats (Animal Resource Centre, Perth, W. Australia) weighing between 180–200 g were used in all experiments in this study.

2.1. Chronic i.v. administration of 5-carboxamidotryptamine (5-CT) in DOCA-salt rats

Deoxycorticosterone acetate (DOCA; Sigma Chemical Co., St. Louis, MO, USA) was suspended in a silastic elastomer (MDX-4-4210, Dow Corning Corp., Midland, MI, USA). On day 0, pellets delivering a dose of 100 mg/kg were implanted s.c. in rats under pentobarbitone anaesthesia (60 mg/kg, i.p.; Nembutal, Ceva, France). At the same time, a left unilateral nephrectomy was performed. Control rats were prepared in the same way with the exception that the silastic implant contained no DOCA. During the same operation, osmotic minipumps [Alzet 2002 (Alza, Palo Alto, CA, USA)] were implanted s.c. The minipumps were connected to a catheter inserted into the femoral vein. DOCA-treated rats were given 4-week infusions of either vehicle (sterile isotonic saline, 12.0 μl/day, n = 10) or 5-CT (15.0 μg/kg per day, n = 10). Control rats received vehicle (12.0 μl/day, n = 11). Minipumps were renewed on day 14 (after 2 weeks) in rats under light ether anaesthesia. All rats received 1% saline containing 0.2% KCl as drinking fluid and standard laboratory chow ad libitum. Rats were kept in individual cages and systolic blood pressure and heart rate monitored using a tail cuff method (BP recorder 8006, Ugo Basile, Italy). Systolic blood pressure and heart rate readings were taken on day 0, prior to the implantation of DOCA pellets and minipumps, and on days 7 (1 week), 14 (2 weeks), 21 (3 weeks) and 27 thereafter. Saline intake, food intake and body weight were monitored daily.

On day 27, after systolic blood pressure and heart rate readings had been taken, DOCA-salt and control rats were anaesthetised with 60 mg/kg, i.p., pentobarbitone. Chronic indwelling catheters were surgically placed into the right jugular vein and the right femoral artery. All rats were allowed a recovery period of at least 24 h prior to use in experiments. The i.v. catheter was used for the injection of substances while the arterial catheter was connected to a pressure transducer (Statham P23XL, Spectramed, Oxnard, CA, USA) for continuous recording of mean arterial pressure and heart rate (Hellige, Servomed 130-T, Hellige GMBH, Germany).

2.2. Determination of haematocrit and plasma electrolyte concentrations

On day 28, at the start of experiments, 600 μl of blood was collected via the arterial catheter. An equal volume of sterile isotonic saline was injected into the rats immediately after blood collection. 150 μl of blood was retained in EDTA tubes (Microtainer, Becton Dickinson, USA) for determination of haematocrit (Technicon H-1 system, Technicon Instruments Corp., New York, USA). The remainder was transferred into heparinised (Heparin Lithium, Sigma Chemical Co., St. Louis, MO, USA) eppendorf tubes and spun down to collect plasma. Plasma Na^+ concentration (PNa^+) and plasma K^+ concentration (PK^+) were determined using ion-selective electrodes (Kodak Ektachem, Eastman Kodak Co., New York, USA). Plasma osmolality (P_{osm}) was measured using a freezing-point micro-osmometer (Model 3MO plus, Advanced Instruments, MA, USA).

2.3. Assessment of baroreflex sensitivity

After a 1-h rest period following blood collection, increasing doses of phenylephrine (1.0–10.0 μg/kg i.v.) were administered to rats. Peak increases in mean arterial pressure and the concomitant peak decreases in heart rate were recorded after each dose. Pulse interval in ms was calculated from heart rate (beats/min) by the formula: pulse interval = 60000/heart rate. The slope of the regression line (ms/mm Hg) between maximum changes in pulse interval and mean arterial pressure was used to assess the sensitivity of the baroreflex. Blood pressure changes to phenylephrine were also taken as a measure of α_1-adrenoceptor responsiveness in these rats.

2.4. Mean arterial pressure and heart rate responses to hexamethonium

After phenylephrine injections, the rats were rested for at least 30 min following which they were challenged with a single i.v. dose of hexamethonium (20 mg/kg). Maximal changes in mean arterial pressure and heart rate were recorded following hexamethonium injection.

2.5. Determination of heart weight and kidney weight

One day after the end of experiments, rats were killed with i.v. pentobarbitone (Nembutal, Ceva,

France). The heart and kidney were excised and weighed. Heart weight and kidney weight were expressed as a percentage of body weight which was taken prior to the removal of the organs.

2.6. Drugs

The following drugs were used: 5-carboxamidotryptamine maleate (Research Biochem., USA), phenylephrine hydrochloride and hexamethonium chloride (Sigma Chem. Co., USA). All drugs were dissolved in sterile isotonic saline and doses refer to the salts of drugs.

2.7. Statistical analyses

The results are expressed as means ± S.E.M. BRS values were compared using the non-parametric Wilcoxon test for multiple comparisons. All other statistical analyses were performed using Dunnett's test for multiple comparison following one-way analysis of variance (ANOVA). A probability level of 0.05 or less was considered to be statistically significant.

3. Results

3.1. Chronic i.v. administration of 5-carboxamidotryptamine (5-CT) in DOCA-salt rats

Systolic blood pressure increased progressively in vehicle-treated DOCA-salt rats reaching 194.6 ± 8.99 mm Hg at 27 days (Fig. 1). The elevation in systolic blood pressure was significantly different from vehicle-treated control rats from day 7 onwards. Systolic blood pressure increased in 5-CT-treated DOCA-salt rats but was markedly lower compared to vehicle-treated DOCA-salt rats throughout the 4 weeks of treatment. Systolic blood pressure in 5-CT-treated DOCA-salt rats was significantly different from that in vehicle-treated control rats except on day 7 (Fig. 1).

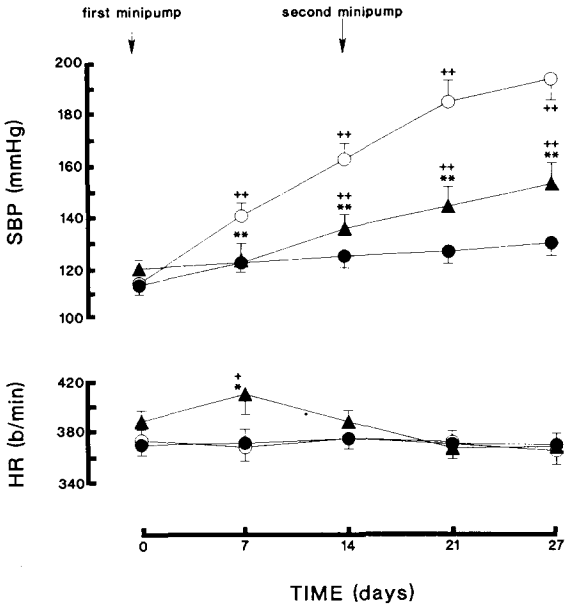

Fig. 1. Systolic blood pressure (SBP) and heart rate (HR) changes in conscious DOCA-salt rats during chronic i.v. infusions of either vehicle (DOCA-salt/vehicle; 12.0 μl/day; open circles, $n = 10$) or 5-carboxamidotryptamine (DOCA-salt/5-CT; 15.0 μg/kg per day; solid triangles, $n = 10$) and in control rats given chronic i.v. infusions of vehicle (control/vehicle; 12.0 μl/day; solid circles, $n = 11$), via osmotic minipumps. $^{*}P < 0.05$; $^{**}P < 0.01$, significant difference compared to DOCA-salt/vehicle group. $^{+}P < 0.05$; $^{++}P < 0.01$, significant difference compared to control/vehicle group.

Heart rate was significantly greater in 5-CT-treated DOCA-salt rats compared to vehicle-treated DOCA-salt rats on day 7. Heart rate changes were not significantly different between vehicle-treated DOCA-salt rats and vehicle-treated controls.

Table 1 shows mean arterial pressure and heart rate values in the three groups of rats on day 28. Mean arterial pressure values in 5-CT-treated DOCA-salt rats were significantly lower compared to vehicle-treated DOCA-salt rats. Mean arterial pressure was significantly greater in 5-CT- and vehicle-treated

Table 1
Mean arterial pressure (MAP), heart rate (HR) and baroreflex sensitivity (BRS) values on day 28 in conscious DOCA-salt rats during chronic i.v. infusions of either vehicle (DOCA-salt/vehicle; 12.0 μl/day) or 5-carboxamidotryptamine (DOCA-salt/5-CT; 15.0 μg/kg per day) and in control rats given chronic i.v. infusions of vehicle (control/vehicle; 12.0 μl/day), via osmotic minipumps

	Groups		
	DOCA-salt/vehicle ($n = 10$)	DOCA-salt/5-CT ($n = 10$)	Control/vehicle ($n = 11$)
MAP (mm Hg)	150.3 ±4.84 [b]	126.8 ±3.57 [a,b]	97.7 ±2.10
HR (b/min)	344.0 ±7.54	342.6 ±8.09	351.5 ±7.01
BRS (ms/mm Hg)	1.87 ± 0.24 [b]	3.59 ± 0.36 [a]	4.05 ± 0.43
r	0.92 ± 0.008	0.87 ± 0.025	0.95 ± 0.007

r, regression coefficient. Values are expressed as means ± S.E.M. [a] $P < 0.01$, significant difference compared to DOCA-salt/vehicle group. [b] $P < 0.01$, significant difference compared to control/vehicle group.

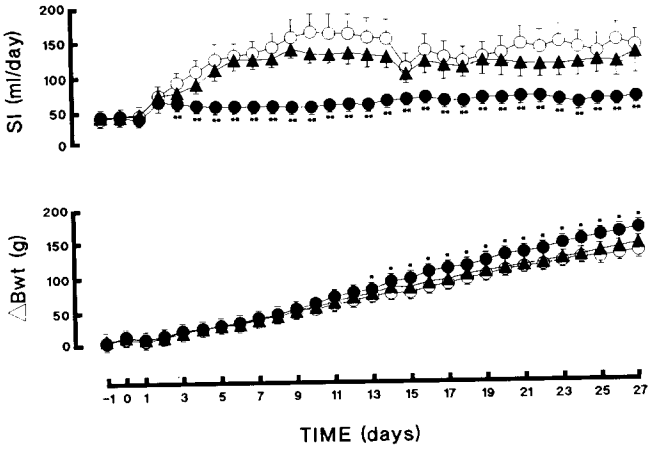

Fig. 2. Saline intake (SI) and body weight (Bwt) changes in conscious DOCA-salt rats during chronic i.v. infusions of either vehicle (DOCA-salt/vehicle; 12.0 μl/day; open circles, $n = 10$) or 5-carboxamidotryptamine (DOCA-salt/5-CT; 15.0 μg/kg per day; solid triangles, $n = 10$) and in control rats given chronic i.v. infusions of vehicle (control/vehicle; 12.0 μl/day; solid circles, $n = 11$), via osmotic minipumps. $^{*}P < 0.05$; $^{**}P < 0.01$, significant difference compared to DOCA-salt/vehicle group.

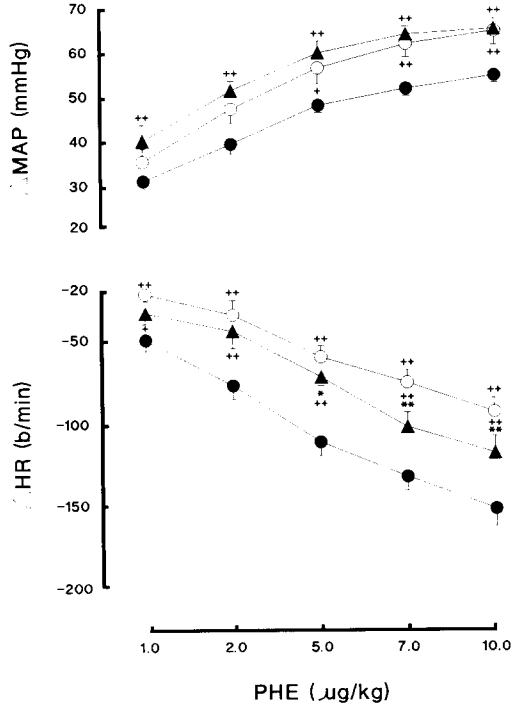

Fig. 3. Changes in mean arterial pressure (MAP) and heart rate (HR) after acute i.v. injections of increasing doses of phenylephrine (PHE; 1.0–10.0 μg/kg) on day 28 in conscious DOCA-salt rats during chronic i.v. infusions of either vehicle (DOCA-salt/vehicle; 12.0 μl/day; open circles, $n = 10$) or 5-carboxamidotryptamine (DOCA-salt/5-CT; 15.0 μg/kg per day; solid triangles, $n = 10$) and in control rats given chronic i.v. infusions of vehicle (control/vehicle; 12.0 μl/day; solid circles, $n = 11$), via osmotic minipumps. $^{*}P < 0.05$; $^{**}P < 0.01$, significant difference compared to DOCA-salt/vehicle group. $^{+}P < 0.05$; $^{++}P < 0.01$, significant difference compared to control/vehicle group.

DOCA-salt rats compared to vehicle-treated control rats. Heart rate was similar in all groups.

Fig. 2 shows daily saline intake and body weight changes in rats. Saline intake was significantly greater in vehicle-treated DOCA-salt rats on day 3 and for the rest of the observation period compared to vehicle-treated control rats (Fig. 2). Saline intake was similar in 5-CT-treated DOCA-salt rats compared to vehicle-treated DOCA-salt rats (Fig. 2). Food intake was similar in all groups. Body weight changes were similar in both groups of DOCA-salt rats. Vehicle-treated control rats, however, showed a small but significantly greater body weight gain compared to DOCA-salt rats (Fig. 2).

3.2. Assessment of baroreflex sensitivity

Table 1 shows baroreflex sensitivity values in the three groups of rats. Baroreflex sensitivity values in vehicle-treated DOCA-salt rats were significantly lower compared to that in vehicle-treated control rats. 5-CT-treated DOCA-salt rats had greater baroreflex sensitivity values compared to vehicle-treated DOCA-salt rats (Table 1). Baroreflex sensitivity values in 5-CT-treated DOCA-salt rats, although slightly lower, were not significantly different compared to vehicle-treated control rats.

Pressor responses to phenylephrine (1.0–10.0 μg/kg) were significantly greater in vehicle-treated DOCA-salt rats compared to vehicle-treated controls (Fig. 3). Pressor responses in 5-CT-treated DOCA-salt rats were significantly enhanced compared to vehicle-treated controls even at the lowest dose of phenylephrine (1.0 μg/kg) (Fig. 3). The concomitant reflex bradycardia following pressor responses to phenylephrine was significantly smaller in 5-CT- and vehicle-treated DOCA-salt rats compared to vehicle-treated controls (Fig. 3).

3.3. Mean arterial pressure and heart rate responses to hexamethonium

Hexamethonium (20 mg/kg, i.v.) produced hypotension with a tachycardia in all groups of rats (Fig. 4). The hexamethonium-induced reduction in mean arterial pressure was significantly smaller in 5-CT-treated DOCA-salt rats compared to vehicle-treated DOCA-salt rats (Fig. 4). The mean arterial pressure response was significantly smaller in vehicle-treated controls when compared to both DOCA-salt groups (Fig. 4).

3.4. Haematocrit and plasma electrolyte concentrations

Haematocrit values in both 5-CT- and vehicle-treated DOCA-salt rats were slightly but significantly lower than those in vehicle-treated control rats.

Table 2
Haematocrit (Hct), plasma Na^+ concentration (P_{Na^+}), plasma osmolality (P_{osm}), plasma K^+ concentration (P_{K^+}), heart weight (Hwt) and kidney weight (Kwt) values on day 28 in conscious DOCA-salt rats during chronic i.v. infusions of either vehicle (DOCA-salt/vehicle; 12.0 μl/day) or 5-carboxamidotryptamine (DOCA-salt/5-CT; 15.0 μg/kg per day) and in control rats given chronic i.v. infusions of vehicle (control/vehicle; 12.0 μl/day), via osmotic minipumps

	Groups		
	DOCA-salt/vehicle ($n = 10$)	DOCA-salt/5-CT ($n = 10$)	Control/vehicle ($n = 11$)
Hct (%)	39.73 ± 0.32 [b]	41.25 ± 0.52 [a,b]	43.30 ± 0.56
P_{Na^+} (mEq/l)	142.7 ± 1.09	143.8 ± 0.71 [b]	140.6 ± 0.31
P_{osm} (mOsm/kg)	295.9 ± 2.24	299.5 ± 2.65	296.8 ± 1.73
P_{K^+} (mEq/l)	3.06 ± 0.12 [c]	2.95 ± 0.12 [c]	4.04 ± 0.07
Hwt (% of Bwt)	0.36 ± 0.009 [c]	0.34 ± 0.005 [c]	0.26 ± 0.0065
Kwt (% of Bwt)	0.79 ± 0.040 [c]	0.63 ± 0.032 [a,c]	0.48 ± 0.013

Values are expressed as means ± S.E.M. [a] $P < 0.05$, significant difference compared to DOCA-salt/vehicle group. [b] $P < 0.05$, [c] $P < 0.01$, significant difference compared to control/vehicle group.

Haematocrit values in 5-CT-treated DOCA-salt rats were significantly greater when compared to vehicle-treated DOCA-salt rats (Table 2). Plasma Na^+ concentration (PNa^+) was not different between vehicle-treated DOCA-salt and control rats. PNa^+ was slightly but significantly greater in 5-CT-treated DOCA-salt rats compared to vehicle-treated controls. PNa^+ was not different between the DOCA-salt rat groups. Plasma osmolality (P_{osm}) was not different in all rat groups (Table 2). Plasma K^+ concentration (PK^+) was significantly lower in both 5-CT- and vehicle-treated DOCA-salt rats compared to vehicle-treated controls (Table 2).

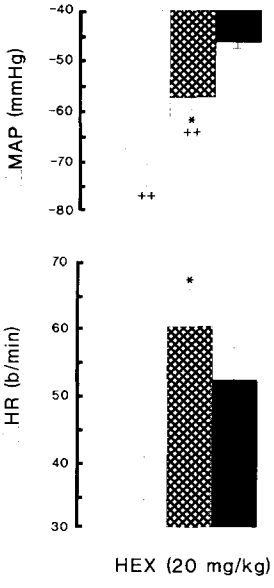

Fig. 4. Changes in mean arterial pressure (MAP) and heart rate (HR) after acute i.v. injections of increasing doses of hexamethonium (HEX; 20 mg/kg) on day 28 in conscious DOCA-salt rats during chronic i.v. infusions of either vehicle (DOCA-salt/vehicle; 12.0 μl/day; open bars, $n = 10$) or 5-carboxamidotryptamine (DOCA-salt/5-CT; 15.0 μg/kg per day; hatched bars, $n = 10$) and in control rats given chronic i.v. infusions of vehicle (control/vehicle; 12.0 μl/day; solid bars, $n = 11$), via osmotic minipumps. * $P < 0.05$, significant difference compared to DOCA-salt/vehicle group. +,+ $P < 0.01$, significant difference compared to control/vehicle group.

3.5. Heart weight and kidney weight

Heart weight was significantly greater in both 5-CT- and vehicle-treated DOCA-salt rats compared to vehicle-treated controls (Table 2). There was however, no difference in heart weight between 5-CT- and vehicle-treated DOCA-salt rats. Kidney weight was markedly greater in vehicle-treated DOCA-salt rats compared to vehicle-treated controls. 5-CT-treated DOCA-salt rats showed a significant reduction in kidney weight when compared to vehicle-treated DOCA-salt rats (Table 2).

4. Discussion

5-HT produces a 5-HT_1-receptor mediated hypotensive response involving peripheral smooth muscle relaxation. This response is mimicked by the prototypical 5-HT_1 receptor agonist, 5-carboxamidotryptamine (5-CT). Acute i.v. administration of 5-CT has antihypertensive effects in DOCA-salt hypertensive rats (Dalton et al., 1986). However, the long-term antihypertensive role of peripheral 5-HT_1 stimulation towards the initiation or development of DOCA-salt hypertension has not been studied. In the present study, the antihypertensive effect of chronic 5-HT_1 receptor activation via 5-CT infusion, was evaluated on the development of DOCA-salt hypertension.

Hypertension was induced in normotensive rats during chronic DOCA-salt treatment with significant increases in blood pressure occurring by 7 days in vehicle-treated DOCA-salt rats compared to vehicle-treated controls. 5-CT markedly attenuated the development of hypertension in DOCA-salt rats with significant changes occurring by day 7 of chronic i.v. infusion. However, 5-CT treatment did not completely prevent

the increase in blood pressure in DOCA-salt rats, when compared to control rats not treated with DOCA.

The hypotensive mechanism of action of 5-CT has been shown to be due to selective activation of peripheral 5-HT_1 receptors although the receptor subtype responsible (i.e. 5-HT_{1A}, 5-HT_{1B} or 5-HT_{1D}) has not been characterised (Feniuk et al., 1984; Trevethick et al., 1986; Dalton et al., 1985; Saxena and Lawang, 1985). It is unlikely that 5-CT has a central hypotensive effect since 5-CT is hypotensive in pithed rats (Dabiré et al., 1988) and in ganglion-blocked animals (Dalton et al., 1985). In addition, i.c.v. administration of 5-CT only produced small reductions in blood pressure compared to i.v. administration (Dalton et al., 1985). Thus, unlike the centrally acting 5-HT_{1A} receptor agonists, flesinoxan and 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) (Dreteler et al., 1990), 5-CT does not seem to possess a central sympathoinhibitory action. This however does not rule out a peripheral sympathoinhibitory action via activation of presynaptic 5-HT_{1A} receptors on postganglionic sympathetic fibres. Indeed, 5-CT has been shown to be a potent prejunctional inhibitor of electrically evoked noradrenaline release from vascular preparations (Charlton et al., 1986; Molderings et al., 1987).

In the present study, systolic blood pressure values at day 7 in 5-CT-treated DOCA-salt rats were not different from those in vehicle-treated controls suggesting that 5-CT dampened the initial rise in blood pressure. The reduction of blood pressure as early as 7 days suggests that 5-CT may have interfered with some of the initial triggering mechanisms of hypertension such as an increase in sympathetic activity. Increase in sympathetic function has been reported as early as 3–7 days following DOCA treatment (Takata et al., 1988) suggesting that sympathetic hyperactivity contributes to the initiation of hypertension. In this study, DOCA-salt hypertensive rats, at 28 days, had significantly greater responses to the sympathetic ganglion blocker, hexamethonium. This supports an increase in sympathetic vascular tone in DOCA-salt hypertensive rats. It is possible that a peripheral sympatholytic action of 5-CT may be responsible for the early blunting of blood pressure rise in addition to vasodilatation. The peripheral sympatholytic action of 5-CT is however, clearly evident at 28 days where the hypotensive responses to hexamethonium, were attenuated in 5-CT-treated DOCA-salt rats compared to vehicle-treated DOCA-salt rats. However, responses to hexamethonium were still greater in 5-CT-treated DOCA-salt rats compared to vehicle-treated controls, suggesting that peripheral sympathoinhibition is only partially responsible for the antihypertensive effects of 5-CT in DOCA-salt rats.

At 28 days, vehicle-treated DOCA-salt hypertensive rats had significantly enhanced α_1-adrenoceptor responses to the higher doses of phenylephrine used. These results are consistent with other studies which show an increase in α_1-adrenoceptor responsiveness in vascular preparations taken from DOCA-salt hypertensive rats (Perry and Webb, 1988; Takata et al., 1989). α_1-Adrenoceptor responses were also enhanced to a greater extent in 5-CT-treated DOCA-salt rats when compared to vehicle-treated controls especially at the lower doses of phenylephrine despite similar baroreflex sensitivity values. This probably indicates postjunctional supersensitivity to prejunctional inhibition of noradrenaline release. Although α_1-adrenoceptor responses seemed to be greater in the 5-CT-treated DOCA-salt rats compared to vehicle-treated DOCA-salt rats there was no statistical difference between the groups. However, vehicle-treated DOCA-salt rats had impaired baroreflex sensitivity making comparison difficult. Thus these results further suggest a prejunctional sympatholytic action of 5-CT.

Baroreflex sensitivity as assessed at 28 days in vehicle-treated DOCA-salt hypertensive rats was significantly reduced compared to vehicle-treated controls. This finding is consistent with other studies which show an impaired baroreflex function in DOCA-salt hypertension (Takeda et al., 1988; Nakamura et al., 1988). 5-CT reduced the baroreflex impairment in DOCA-salt rats and resulted in the restoration of baroreflex sensitivity values to those in control rats. The greater baroreflex sensitivity values in 5-CT-treated DOCA-salt rats may be a consequence of the attenuation of blood pressure rise in DOCA-salt rats. A direct action of 5-CT on central baroreflex pathways is unlikely, but a peripheral sympatholytic effect could also account for the increase in baroreflex sensitivity. It has been suggested that a central impairment of baroreflex sensitivity may precede and contribute to the pathogenesis of hypertension in DOCA-salt rats (Takeda et al., 1988; Nakamura et al., 1988). An increase in baroreflex sensitivity may thus have contributed to the antihypertensive effect of 5-CT in DOCA-salt rats in this study.

DOCA treatment induced a sharp increase in saline intake in both vehicle- and 5-CT-treated rats. 5-CT had no significant effects on saline intake in DOCA-salt rats suggesting a lack of 5-HT_1 receptor involvement in the long-term effects on DOCA-induced saline intake. Therefore this mechanism is unlikely to contribute towards the chronic antihypertensive effects of 5-CT in DOCA-salt hypertension.

In the present study, plasma Na^+ concentration and plasma osmolality were not different in vehicle-treated DOCA-salt rats compared to controls. The results contrast with earlier findings of an increase in plasma Na^+ concentration in DOCA-salt rats (Hofbauer et al., 1984a,b). However, in these previous studies plasma Na^+ concentration was measured in DOCA-salt hypertensive rats at 6 weeks as opposed to 4 weeks in the present study. The reduced haematocrit values in vehi-

cle-treated DOCA-salt hypertensive rats compared to normotensive controls suggest that plasma volume expansion had occurred in DOCA-salt rats to maintain plasma Na^+ concentration within normal physiological limits. However, the greater haematocrit values in 5-CT-treated DOCA-salt rats compared to vehicle-treated DOCA-salt rats suggest that 5-CT had significant effects on reducing plasma volume expansion due to DOCA-salt treatment at the expense of a small increase in plasma Na^+ concentration compared to normotensive controls. Plasma K^+ concentration was significantly reduced in both DOCA-salt-treated groups compared to controls. This is consistent with reports of hypokalemia in DOCA-salt hypertensive rats (Songu-Mize et al., 1987; Bruner, 1992). 5-CT did not prevent the K^+ loss during chronic DOCA-salt treatment. Collectively, the available data suggest that 5-CT may have moderated volume retention leading to DOCA-salt hypertension.

The kidneys play a primary role in the induction of DOCA-salt hypertension. DOCA-salt treatment increases renal mass and tubular hypertrophy (Jeffries et al., 1991) due to an increased demand on fluid and salt handling stimulated by the tubular actions of arginine-vasopressin (AVP) (Hofbauer et al., 1984a). In the present study kidney weight in vehicle-treated DOCA-salt rats was markedly greater compared to that in control rats. 5-CT treatment significantly reduced renal hypertrophy in DOCA-salt rats suggesting an interference with increased renal salt handling. However, 5-CT reduced volume expansion with no significant changes in plasma Na^+ concentration whilst saline intake remained similar to vehicle-treated DOCA-salt hypertensive rats. These results suggest a renal site of action where 5-CT could have increased Na^+ and water excretion probably by influencing renal haemodynamics. In fact, 5-CT has been shown to produce vasodilatation in the rat renal circulation mediated via 5-HT_{1A} receptors (Verbeuren et al., 1991). Another possible mechanism is by attenuation of sympathetic renal nerve activity thereby decreasing Na^+ and water retention by the kidneys. Increased renal sympathetic tone has been shown to facilitate Na^+ retention and is an important contributing factor towards the development of DOCA-salt hypertension (Katholi et al., 1980; Takahashi et al., 1984). In a recent study by Andrzej and Johns (1994), the 5-HT_{1A} receptor agonist, flesinoxan, maintained Na^+ and water excretion despite producing hypotension. The effect was not related to changes in glomerular filtration rate or renal blood flow but likely due to decreased sympathetic outflow to the kidneys. In the present study, 5-CT had peripheral sympathoinhibitory effects which conceivably may have affected renal excretory function. Therefore a renal site of action cannot be precluded.

An increase in heart weight in the present study suggests cardiac hypertrophy during the development of DOCA-salt hypertension. This finding concurs with previous studies showing cardiac hypertrophy in DOCA-salt rats (Tomanek and Barlow, 1990; Huang et al., 1992). The increase in heart weight during DOCA-salt hypertension is associated with an increase in cardiac output which contributes to the development of hypertension (Huang et al., 1992). In the present study, 5-CT had no significant effects on heart weight in DOCA-salt rats.

In summary, the present study shows that chronic 5-CT administration attenuated the development of DOCA-salt hypertension in rats. The attenuation of hypertension could be attributed to peripheral vasodilatation and a reduction of baroreflex impairment as a result of persistent 5-HT_1 receptor stimulation.

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