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Haemodynamic effects of bromocriptine in the conscious spontaneously hypertensive rat

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The systemic haemodynamic effects of 0·3 mg kg^{-1} bromocriptine s.c. in conscious, chronically instrumented spontaneously hypertensive rats (SHR) has been investigated. Bromocriptine caused a gradual, long-lasting significant fall in mean arterial pressure with a maximum of 26 ± 3 mmHg (−17%). The fall was related to a significant decrease in stroke volume index (−9 ± 2 µl 100 g^{-1}; −10%) and cardiac index (−3·9 ± 0·8 ml min^{-1} 100 g^{-1}; −12%). No significant changes in heart rate or total peripheral resistance index were observed. These data do not support previous suggestions that the antihypertensive effect of bromocriptine is caused by inhibition of the release of vasopressor substances. It is suggested that bromocriptine causes a reduction of venous return of the blood to the heart, possibly related to intrarenal effects.

Recently, attention has been focussed on the antihypertensive actions of dopamine receptor stimulating agents. A decrease in blood pressure was observed in several species, including man, after the administration of different dopamine receptor stimulants, such as bromocriptine (Lewis 1978; Hamilton 1981; Hutchinson et al 1981), lergotrile (Barrett & Lokhandwala 1981), *NN*-di-n-propyldopamine (Cavero et al 1981; Hahn & MacDonald 1982), and pergolide (Yen et al 1979; Hahn 1981). The mechanisms underlying the fall have yet to be elucidated.

A decrease in vascular tone following bromocriptine administration to the conscious spontaneously hypertensive rat (SHR) was proposed, either because of a decrease in circulating vasopressor substances (Hutchinson et al 1981) or β-adrenoceptor mediated vasodilatation following adrenaline release from the adrenal medulla (Hamilton 1981). However, direct haemodynamic measurements to prove such a decrease in vascular tone are so far lacking. We have investigated the haemodynamic effects of bromocriptine in the conscious SHR, using a new technique for the chronic, continuous measurement of drug-induced haemodynamic effects in this species (Smits et al 1982).

Methods

Male, adult (3–4 months old) SHR, 280 and 320 g, were housed individually and had free access to standard rat lab food and tap water before and during the experiments. Minimally 4 days before the start of the experiments, animals were anaesthetized using 60 mg kg^{-1} i.p. pentobarbitone. A Skalar perivascular small animal electromagnetic flowprobe with a diameter of 2·4 or 2·5 mm was implanted on the aorta at a distance of 3–4 mm from the heart, according to Smith & Hutchins (1979) and Smits et al (1982). The probe cable was guided s.c. to the neck, where the connector was secured to the skin.

Two days before the start of the experiments, a polyethylene catheter was implanted under brief ether anaesthesia into the abdominal aorta via the left femoral artery. This catheter was also guided s.c. to the neck, where it was exteriorized. The rats were then allowed 2 days for recovery.

On the experimental days, animals were connected to measuring equipment between 9.00 and 10.00 a.m. Arterial blood pressure was measured from the intra-aortic catheter using a miniature strain gauge transducer (CP-01; Central Technology Company, Ingelwood, Ca). Blood flow through the aorta was measured from the flowprobe, using an electromagnetic flowmeter (Skalar, model 600). Late diastolic flow was taken as zero and mean blood flow was used as an index for cardiac output (cf. Smith & Hutchins 1979). Cardiac output was normalized for body weight (cardiac index, CI) and is expressed as ml min^{-1}/100 g body weight. Heart rate was obtained from the pressure or flow signal which was used to trigger a tachograph. Mean signals were obtained using low-pass filtering. From these variables, the total peripheral resistance index (TPRI) was calculated according to: TPRI = mean arterial pressure × CI^{-1} and is expressed as mmHg min^{-1}/100 g body weight. Stroke volume index (SVI) was calculated as SVI = CI heart rate^{-1} and is expressed as µl/100 g weight.

After the registration equipment had been connected, rats were allowed to adjust to experimental conditions for 1 h. Control values (t = 0 in the results) were obtained as the average of 4 readings with 5 min intervals in the final 20 min before an injection. A group of 10 SHR were injected s.c. with 0·1 ml of a 0·9% NaCl solution containing the mesylate salt of bromocriptine in such a concentration that 0.3 mg^{-1} of the salt was given. Another group of 10 SHR received only 0·1 ml of the vehicle. Haemodynamic variables were then recorded continuously for at least 6 h. Animals were measured again 22–24 h after injection with a 1-h habituation period.

All results are expressed as means ± s.e.m. The effects of bromocriptine were compared with those of vehicle, using Student's *t*-test for unpaired values.

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Results and dicussion

The haemodynamic effects of 0·3 mg kg^{-1} bromocriptine are summarized in Table 1. Bromocriptine caused a gradual fall in blood pressure which reached a maximum decrease of 26 ± 3 mmHg after 4 h. This fall in mean arterial pressure was paralleled by a decrease in CI, which fell maximally by 3·9 ± 0·8 ml min^{-1} 100 g^{-1} at 6 h. The fall in CI was caused primarily by a reduction in SVI, since no significant decrease in heart rate was observed. TPRI, finally, was decreased slightly by bromocriptine, although the effect never reached a statistically significant level. All haemodynamic variables had returned to control values by 22–24 h after the injection of bromocriptine.

The dose of bromocriptine used (0·3 mg kg^{-1} s.c.) was low in comparison to that in previous studies in SHR. Hamilton (1981) studied the effects of 1–30 mg kg^{-1} orally administered bromocriptine, whereas Sowers (1981) and Hutchinson et al (1981) gave a 1-week i.p. dose of approximately 1.2–2 mg kg^{-1} day^{-1}. In a recent abstract, Bucher (1982) showed the dose-response relationship of the blood pressure lowering effect of bromocriptine in conscious SHR, indicating a minimally effective dose of 0·1 mg kg^{-1} s.c. In hypertensive patients, the dose producing a clear fall in blood pressure is 0·1–0·3 mg kg^{-1} day^{-1} when given orally. We thus believe that we have used a clinically relevant dose in our haemodynamic study.

The mechanism of bromocriptine's blood pressure lowering activity in man is not yet understood. Originally, it was claimed that α-adrenoceptor blocking activity is responsible for the hypotensive effect of bromocriptine in patients (Lewis 1978). In-vitro studies using perfused mesenteric blood vessels of the rat confirmed the α-adrenoceptor blocking potential of bromocriptine (Gibson & Samini 1978). More recent clinical studies suggest additional mechanisms for the hypotensive effect of bromocriptine. Thus, bromocriptine reduces plasma catecholamine levels in hypertensives both under basal and stimulated conditions (Kolloch et al 1980; Sowers et al 1982). This effect has been interpreted as indicative for a reduction of sympathetic tone mediated via a central nervous system dopamine receptor (Kolloch et al 1980; Sowers et al 1982). Thus far, however, clinical studies addressing the pharmacological mechanism of action underlying the bromocriptine-induced fall in blood pressure using different antagonists are still lacking.

Our results provide clear evidence that the bromocriptine-induced fall in blood pressure is associated with a decrease in cardiac output rather than peripheral resistance. Thus, our data do not support a mechanism of action whereby vascular tone is reduced as a consequence of a decrease in circulating vasopressor substances (Hutchinson et al 1981) or β-adrenoceptor mediated vasodilatation following adrenaline release from the adrenal medulla (Hamilton 1981). Our data also plead against an α-adrenoceptor blocking activity of bromocriptine in the doses used, since the primary effect of an α-adrenoceptor blocker would be a reduction of peripheral resistance and no change or a reflex increase in cardiac output (Montastruc & Montastruc 1982).

The observed haemodynamic profile of a gradual fall in blood pressure caused by a decrease in cardiac output and stroke volume, points to a reduction in the venous return of blood to the heart. A similar profile is observed after the administration of diuretic agents (Struyker-Boudier et al 1983). A primary effect of bromocriptine on renal control of body fluid excretion was recently implied by several authors (Stier et al 1982; Schmidt et al 1982). According to these authors, stimulation of dopamine receptors by bromocriptine in the kidney would cause renal vasodilatation. It remains to be established by which further mechanisms such a renal vasodilatation leads to a fall in cardiac output and blood pressure.

Bromocriptine was kindly supplied by Sandoz.

Table 1. Effect (mean ± s.e.m.) of bromocriptine (0·3 mg kg^{-1} s.c.) on haemodynamic variables in the conscious spontaneously hypertensive rats ($^{*}P < 0·05$; $^{**}P < 0·01$; $^{***}P < 0·001$, compared with control rats).

	Time (h)					
	0	1	2	4	6	22–24
Mean arterial pressure (mmHg)						
control (n = 10)	147 ± 6	+3 ± 3	+2 ± 3	+3 ± 3	+2 ± 2	+1 ± 4
bromocriptine (n = 10)	154 ± 5	−14 ± 3***	−21 ± 3***	−26 ± 3***	−24 ± 2	−7 ± 6
Cardiac index (ml min^{-1}/100 g)						
control	35·2 ± 1·8	+0·2 ± 0·2	+0·5 ± 0·6	+1·2 ± 1·1	+1·8 ± 0·8	+1·5 ± 1·3
bromocriptine	32·3 ± 3·3	−2·7 ± 0·7**	−2·9 ± 0·6***	−3·2 ± 0·8**	−3·9 ± 0·8***	+0·7 ± 1·0
Heart rate (beats min^{-1})						
control	389 ± 8	+3 ± 4	+4 ± 8	+1 ± 5	+2 ± 9	+2 ± 12
bromocriptine	365 ± 11	−6 ± 8	−1 ± 5	+1 ± 8	−14 ± 9	+18 ± 9
Stroke volume index (μl/100 g)						
control	92 ± 7	0 ± 3	0 ± 2	+2 ± 3	+1 ± 2	+1 ± 5
bromocriptine	89 ± 9	−8 ± 3*	−9 ± 2**	−9 ± 2**	−9 ± 3*	−3 ± 3
Total peripheral resistance index (mmHg min/100 g ml)						
control	4·22 ± 0·28	+0·24 ± 0·21	+0·08 ± 0·21	+0·11 ± 0·24	+0·06 ± 0·19	+0·08 ± 0·15
bromocriptine	5·34 ± 0·53	−0·03 ± 0·17	−0·26 ± 0·12	−0·35 ± 0·23	−0·23 ± 0·17	−0·42 ± 0·31

REFERENCES

Barrett, R. J., Lokhandwala, M. F. (1981) J. Pharmacol. Exp. Ther 217: 660–665

Bucher, T. J. (1982) Naunyn-Schmiedeberg's Arch. Pharmacol. 319 (suppl.): R62

Cavero, I., Lefèvre-Borg, F., Gomeni, R. (1981) J. Pharmacol. Exp. Ther. 219: 510–519

Gibson, A., Samini, M. (1978) J. Pharm. Pharmacol. 30: 314–315

Hahn, R. A. (1981) Life Sci. 29: 2501–2509

Hahn, R. A., MacDonald, B. R. (1982) Naunyn-Schmiedeberg's Arch. Pharmacol. 321: 63–69

Hamilton, T. C. (1981) Br. J. Pharmacol. 72: 419–425

Hutchinson, J. S., Di Nicolantonio, R., Lim, A., Clements, J., Funder, J. W. (1981) Clin. Sci. 61: 343S–345S

Lewis, M. J. (1978) Br. J. Hosp. Med. 20: 661–665

Kolloch, R., Kobayashi, K., DeQuattro, V. (1980) Hypertension 2: 390–394

Montastruc, J. L., Montastruc, P. (1982) Arch. Int. Pharmacodyn. 260: 83–90

Schmidt, M., Imbs, J. L., Giesen, E. M., Schwartz, J. (1982) Eur. J. Pharmacol. 84: 61–70

Smith, T. L., Hutchins, P. M. (1979) Hypertension 1: 508–517

Smits, J. F. M., Coleman, T. G., Smith, T. L., Kasbergen, C. M., Van Essen, H., Struyker-Boudier, H. A. J. (1982) J. Cardiovasc. Pharmacol. 4: 903–914

Sowers, J. R. (1981) Hypertension 3: 544–550

Sowers, J. R., Nyby, M., Jasberg, K. (1982) Ibid. 4: 431–438

Stier, C. T., Cowden, E. A., Allison, M. E. (1982) J. Pharmacol. Exp. Ther. 220: 366–370

Struyker-Boudier, H. A. J., Smits, J. F. M., Kleinjans, J. C. S., Van Essen, H. (1983) Clin. Exp. Hypert. A5: 209–223

Yen, T. T., Stamm, N. B., Clemens, J. A. (1979) Life Sci. 25: 209–216

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Effects of 6-methoxytetrahydro-β-carboline on 5-hydroxytryptamine binding in rat brain

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6-MeOTHBC competes for 5-HT binding sites in rat brain in-vitro and in-vivo. The β-carboline is significantly more active at the type 1 [^{3}H]-5-HT, than the type 2 [^{3}H]spiperone receptors, in-vitro. Following injection, 6-MeOTHBC significantly decreases [^{3}H]-5-HT binding in the cortex. The ineffectiveness on [^{3}H]spiperone binding in-vivo corresponds with the low affinity in-vitro. The effect of 6-MeOTHBC on central 5-HT binding may be a significant aspect of its 5-HT-ergic activity.

A decade ago the compound 6-methoxytetrahydro-β-carboline (6-MeOTHBC) (I) was found in our laboratory to double the 5-hydroxytryptamine (5-HT) concentration in rodent brain without affecting levels of either the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), or noradrenaline (McIsaac et al 1972). Subsequently, 6-MeOTHBC was shown to inhibit MAO, especially type A (Meller et al 1977), and to inhibit 5-HT uptake into synaptosomes (Buckholtz & Boggan 1977); therefore, either of these actions could lead to the observed increase in central 5-HT concentrations.

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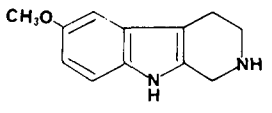

FIG. 1. Chemical structure of 6-methoxytetrahydro-β-carboline.

* Correspondence.

The stimulus properties of 6-MeOTHBC show some similarity to those of lysergic acid diethylamide (LSD) (White et al 1982) which, in turn, are mediated at least in part by activity at 5-HT receptors. Because 6-MeOTHBC selectively affects 5-HT neurotransmission, has an LSD-like behavioural effect, and contains an indole nucleus, it seemed worthwhile to examine its 5-HT receptor binding properties. In the work presented here, we tested the ability of 6-MeOTHBC to compete for 5-HT receptors as defined by [^{3}H]5-HT and [^{3}H]spiperone binding (Peroutka & Snyder 1979).

Methods

Male Sprague-Dawley rats (220–240 g) were used. The hydrochloride form of 6-MeOTHBC was synthesized in our laboratory as previously described (Ho et al 1968). [^{3}H]5-Hydroxytryptamine creatinine sulphate (28·7 Ci mmol^{-1}) and [^{3}H]spiperone (29·9 Ci mmol^{-1}) were obtained from New England Nuclear. Rats were decapitated, the cortex and striatum quickly removed, frozen on dry ice and stored at −80 °C until assayed (within 1–2 weeks). For the in-vivo experiments, groups of 6 rats were injected with 50 mg kg^{-1} i.p. of 6-MeOTHBC or 0·9% NaCl (saline) and killed 2 h later. The cortex was removed and frozen as above.

To measure 5-HT type 1 receptor binding (Peroutka & Snyder 1979), tissues were homogenized in 40 volumes of 0·05 M Tris-HCl buffer, pH 7·7, with a Brinkman Polytron, centrifuged at 48 000*g* for 10 min, and washed once with fresh buffer. Pellets were then