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INVOLVEMENT OF THE ADRENAL GLANDS IN THE HYPOTENSIVE RESPONSE TO BROMOCRIPTINE IN SPONTANEOUSLY HYPERTENSIVE RATS

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1 The dopamine agonist, bromocriptine, produced a hypotensive response following oral administration to conscious normotensive and spontaneously hypertensive (SH-) rats.

2 In SH-rats the dose-related falls in blood pressure to bromocriptine, 3 to 30 mg/kg orally or intraperitoneally, were biphasic, an initial fall at 1 h being followed by some recovery at 2 h and a subsequent fall in blood pressure at 4 and 6 h.

3 The dopamine antagonists, metoclopramide, sulpiride, haloperidol and pimozide, had little or no effect on the hypotensive response to bromocriptine, 10 mg/kg orally, in SH-rats.

4 Pretreatment with α-methyl-*p*-tyrosine augmented the hypotensive response to bromocriptine, 10 mg/kg orally, in SH-rats.

5 In adrenal demedullated SH-rats, the hypotensive response to bromocriptine, 3 to 30 mg/kg orally, was abolished.

6 In SH-rats the hypotensive response to bromocriptine, 10 mg/kg orally, was prevented by the β-adrenoceptor blocking drugs, propranolol and oxprenolol, but was unaffected by (+)-propranolol and by the cardio-selective β-adrenoceptor blocking drug, atenolol.

7 In SH-rats pretreated with bromocriptine, 10 mg/kg orally, and then anaesthetized, the pressor responses to low doses of intravenous adrenaline were reversed to depressor, indicating that bromocriptine possesses α-adrenoceptor blocking activity.

8 The results suggest that the hypotensive response to bromocriptine in conscious SH-rats is mediated by adrenaline released from the adrenal medullae which, in the presence of α-adrenoceptor blockade, stimulates vascular β-adrenoceptors producing vasodilatation.

Introduction

Postural hypotension is one side effect of the clinical use of the dopamine agonist, bromocriptine, in the treatment of parkinsonism, acromegaly and infertility (O'Mullane, Davis, Hipkin & Walker, 1976; Greenacre, Teychenn, Petrie, Calne, Leigh & Reid, 1976; Brosens, 1977; Linch, Shaw, Muhlemann & Ross, 1978; Price, Debono, Parkes, Marsden & Rosenthaler, 1978). In the treatment of hypertension, bromocriptine has been used successfully either alone (Stumpe, Kollock, Higuchi, Krück & Vetter, 1977) or in combination with other antihypertensive drugs (Kaye, Shaw & Ross, 1976; Lewis, Henderson & Fisher, 1976). Examination of the effect of bromocriptine on the blood pressure of animals is limited to a few studies: bromocriptine reduces blood pressure after intravenous and central administration to anaesthetized cats (Flückiger, 1976; Leighton & Parmeter, 1979) and is also hypotensive after intravenous administration to anaesthetized dogs (Clark, 1977; Lokhandawala, 1979). In the present study, in conscious spontaneously hypertensive rats, bromocriptine reduced blood pressure after acute dosing and the mechanism of this response has been investigated.

Methods

Male spontaneously hypertensive (SH) rats (14 to 24 weeks old), derived from the Japanese strain (Okamoto & Aoki, 1963), and male Sprague-Dawley rats were used for these studies.

Some SH-rats were anaesthetized with methohexitone sodium, 45 mg/kg intraperitoneally, and subjected to unilateral adrenalectomy and contralateral adrenal demedullation (SHAD-rats). SHAD-rats were used in experiments 4 to 8 weeks postoperatively.

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Indirect measurement of blood pressure and heart rate in conscious rats

Rats were placed in an incubator (32°C) for 20 to 30 min. Systolic blood pressure (1 mmHg ≈ 133 Pa) and heart rate were then measured indirectly in restrained conscious rats with a W+W blood pressure recorder, model 8002 (Kontron Intertechnique, St Albans, Herts); each determination was the mean of at least 6 readings. Groups of 6 animals were usually used, measurements being made pre-dose (zero), 1, 2, 4, 6 and, usually, 24 h after dosing.

In drug-interaction studies with, for example, dopamine antagonists and β-adrenoceptor blocking drugs, these drugs were given intraperitoneally (i.p.) immediately before bromocriptine orally. In the case of α-methyl-*p*-tyrosine, SH-rats were pretreated intraperitoneally according to the relevant pretreatment schedule (see Results) before the oral administration of bromocriptine.

Adrenaline reversal in anaesthetized SH-rats

Groups of 6 SH-rats were dosed orally with bromocriptine, 10 mg/kg, or vehicle, 1 or 6 h before being anaesthetized with pentobarbitone sodium (75 mg/kg i.p.). Changes in blood pressure produced by intravenous doses of adrenaline were recorded from the carotid artery with a Bell and Howell physiological pressure transducer (1 mmHg ≈ 133 Pa) connected to a chart recorder.

Measurement of plasma prolactin levels

Plasma prolactin levels were determined in groups of 6 SH-rats 1 and 6 h after oral dosing with bromocriptine, 10 mg/kg or vehicle. At the appropriate time, the animals were rapidly anaesthetized with ether and blood quickly removed from the abdominal aorta with heparinized syringes. After centrifugation of the whole blood, the plasma prolactin was measured using the NIAMID rat prolactin radioimmunoassay kit supplied by the NIAMID-NIH pituitary hormone programme.

Statistical analysis

Student's *t* test was used to evaluate the significance of differences between vehicle- and bromocriptine-treated rats in the plasma prolactin and adrenaline reversal tests and for significance of differences in changes in blood pressure between rats receiving bromocriptine alone and those receiving bromocriptine together with an antagonist. Values of $P<0.05$ were considered to be significant.

Drugs

The following drugs were used: adrenaline bitartrate (Sigma), atenolol (ICI), bromocriptine mesylate (Sandoz), haloperidol (Janssen), α-methyl-*p*-tyrosine methyl ester hydrochloride (Sigma), metoclopramide (Beecham), oxprenolol hydrochloride (Ciba), pimozide (Janssen), propranolol and (+)-propranolol hydrochloride (ICI), sulpiride (Delagrange). Doses are expressed as base. Bromocriptine, pimozide and sulpiride were dissolved in water with the aid of tartaric acid. Haloperidol was used from the commercially available ampoules. Other drugs were dissolved in water or saline (0.9% w/v NaCl solution).

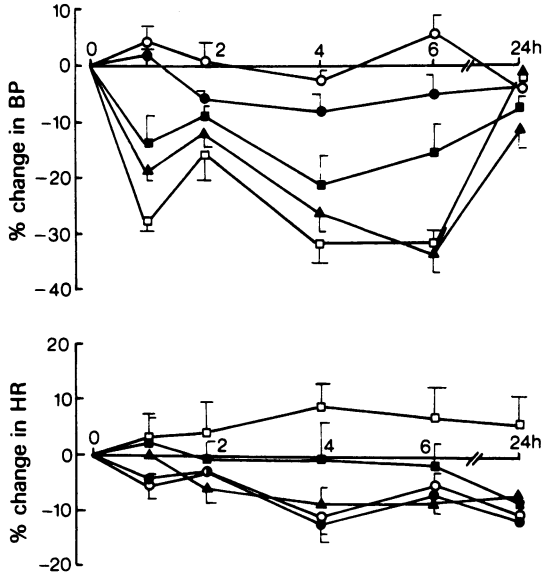

Figure 1 Percentage change in systolic blood pressure (BP) and heart rate (HR) produced by bromocriptine 1 (●), 3 (■), 10 (▲), 30 (□) mg/kg orally or control vehicle (○) in groups of 6 SH-rats. Vertical bars show s.e. mean. The basal BP and HR of each group were, respectively, for bromocriptine 1 mg/kg, 213 ± 3 mmHg and 412 ± 19 beats/min; for 3 mg/kg, 199 ± 7 mmHg and 427 ± 20 beats/min; for 10 mg/kg. 213 ± 4 mmHg and 418 ± 15 beats/min; for 30 mg/kg, 200 ± 1 mmHg and 443 ± 15 beats/min and for the control group, 209 ± 5 mmHg and 419 ± 18 beats/min. Abscissa scale shows time (h).

Results

Effect of bromocriptine on the blood pressure and heart rate of conscious SH- and normotensive rats

Bromocriptine, 3 to 30 mg/kg, caused similar dose-related falls in blood pressure, with little change in heart rate, whether administered intraperitoneally or orally to SH-rats. Figure 1 shows that the oral administration of bromocriptine, 1 mg/kg, had little effect on blood pressure whilst 3, 10 and 30 mg/kg

Table 1 Effect of bromocriptine (10 mg/kg orally) on plasma prolactin levels in SH-rats

Treatment	*Plasma prolactin* (ng/ml)
None	52 ± 7
Vehicle 1 h previously	44 ± 8
Bromocriptine 1 h previously	13 ± 2 ($P<0.001$)
Vehicle 6 h previously	89 ± 10*
Bromocriptine 6 h previously	14 ± 1 ($P<0.001$)

Values are mean ± s.e. mean from 6 rats/group apart from * for which 5 animals were used. Age-matched SH-rats were used.

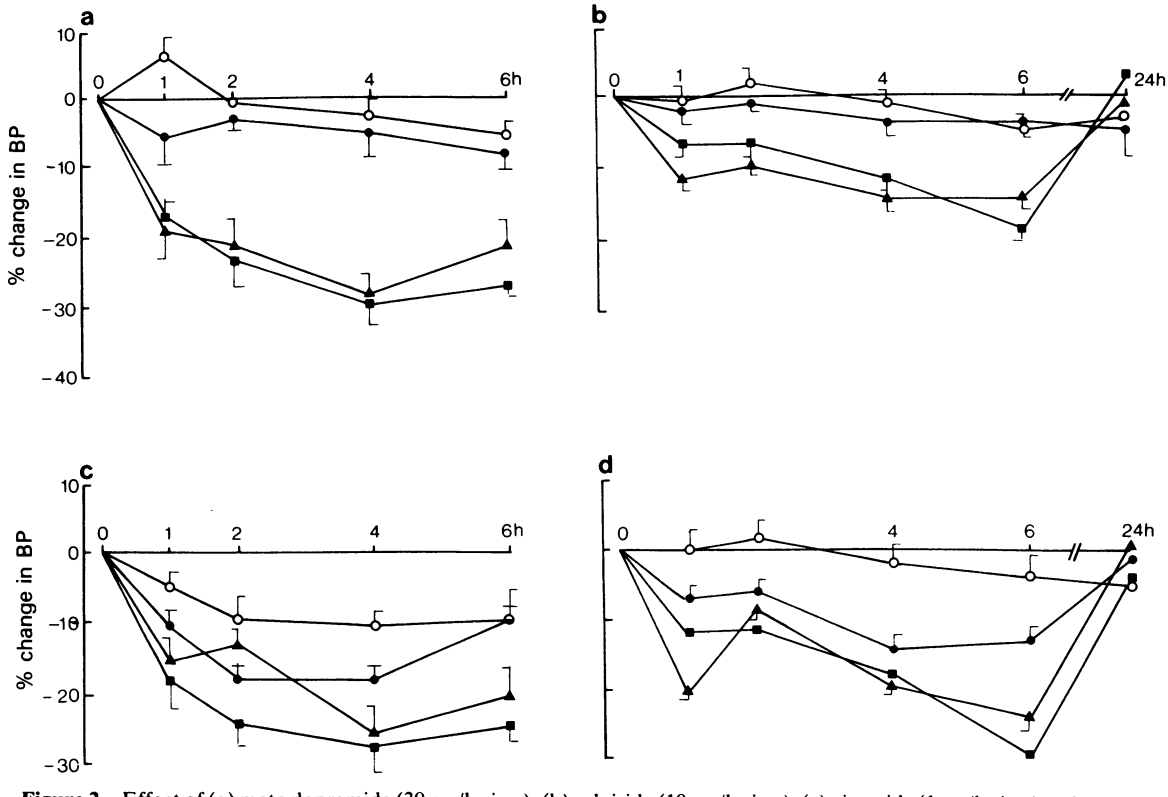

Figure 2 Effect of (a) metoclopramide (30 mg/kg i.p.), (b) sulpiride (10 mg/kg i.p.), (c) pimozide (1 mg/kg i.p.) and (d) haloperidol (0.5 mg/kg i.p.) on the change in systolic blood pressure (BP) produced by bromocriptine 10 mg/kg orally or control vehicle in SH-rats; (■) represents animals receiving bromocriptine and an antagonist, (▲), (●), (○) animals receiving, respectively, bromocriptine, an antagonist or control vehicle alone. Vertical bars show s.e. mean. Groups of 6 rats were used apart from those in the sulpiride experiment for which groups of 9–11 rats were used. The basal BP of each group was in (a) for bromocriptine, metoclopramide, the combination and the control groups respectively, 211 ± 5, 207 ± 6, 220 ± 6 and 199 ± 7 mmHg; (b) for bromocriptine, sulpiride, the combination and the control groups respectively 231 ± 7, 233 ±7, 228 ± 5, 230 ± 7 mmHg; (c) for bromocriptine, pimozide, the combination and the control groups respectively, 206 ± 4, 205 ± 4, 212 ± 6 and 207 ± 2 mmHg; (d) for bromocriptine, haloperidol, the combination and the control groups respectively 199 ± 3, 200 ± 1, 202 ± 2, 198 ± 5 mmHg. Abscissa scale shows time (h).

caused dose-related biphasic reductions in blood pressure: an initial fall in blood pressure at 1 h was followed by partial recovery at 2 h and then further decreases at 4 and 6 h.

In most subsequent experiments bromocriptine caused a biphasic fall in blood pressure but in a few experiments (see Figure 2a) blood pressure continued to fall at 2 h.

In normotensive rats, bromocriptine, 10 and 30 mg/kg orally, caused falls in blood pressure similar in magnitude and time course to those described for these doses in SH-rats.

Effect of bromocriptine on plasma prolactin levels in conscious SH-rats

Bromocriptine, 10 mg/kg orally, significantly reduced plasma prolactin levels in SH-rats both 1 and 6 h after dosing (Table 1).

Effect of dopamine antagonists on the blood pressure response to bromocriptine in conscious SH-rats

The fall in blood pressure produced by bromocriptine was unaffected by metoclopramide (10 and 30 mg/kg i.p.) (Figure 2a) and slightly but significantly, reduced at 1 h only ($P<0.05$), by sulpiride (10 mg/kg i.p.) (Figure 2b).

Interpretation of the effects of pimozide (1 mg/kg), and haloperidol (0.5 mg/kg), both intraperitoneally, on the blood pressure response to bromocriptine is complicated by the reductions in blood pressure caused by pimozide and haloperidol *per se* (Figures 2c and d). However, in animals receiving both pimozide and bromocriptine the fall in blood pressure was slightly greater (at 2 h significantly different from that of bromocriptine alone $P<0.02$) than that in animals receiving either drug alone (Figure 2c). Haloperidol reduced the fall in blood pressure to bromocriptine, but only at 1 h ($P<0.001$) (Figure 2d). In these experiments there were no significant changes in heart rate in any group of animals.

Effect of inhibition of catecholamine synthesis on the blood pressure response to bromocriptine in conscious SH-rats

In SH-rats that received α-methyl-*p*-tyrosine (200 mg/kg i.p.) 1 h previously, the fall in blood pressure to bromocriptine (10 mg/kg orally) was augmented compared to the response in animals receiving bromocriptine alone (Figure 3); the bromocriptine response was significantly ($P<0.05$) increased at 1 h after α-methyl-*p*-tyrosine. α-Methyl-*p*-tyrosine *per se* caused a gradual decline in blood pressure between 2 and 6 h after dosing without any change in heart rate.

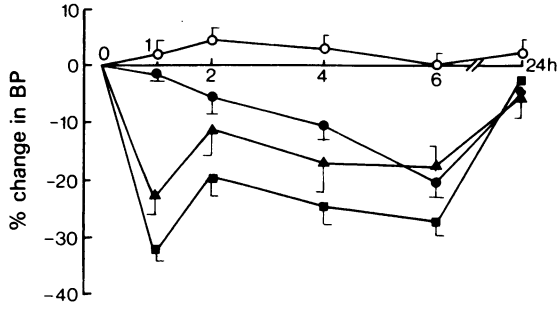

Figure 3 Effect of pretreatment with α-methyl-*p*-tyrosine (200 mg/kg i.p.) on the change in systolic blood pressure (BP) produced by bromocriptine, (10 mg/kg orally) or control vehicle in SH-rats. Vertical bars show s.e. mean. Groups of 6 rats were used. The basal BP of each group was for bromocriptine, 228 ± 6 mmHg (▲); for α-methyl-*p*-tyrosine, 206 ± 4 mmHg (●); for the combination group 219 ± 6 mmHg (■), and for the control group 226 ± 5 mmHg (○). Abscissa scales shows time (h).

Effect of adrenal demedullation on the blood pressure response to bromocriptine in conscious SH-rats

In SH-rats previously subjected to unilateral adrenal demedullation and contralateral adrenalectomy (SHAD-rats), the fall in blood pressure to bromocriptine (10 mg/kg orally), was almost abolished whereas in intact SH-rats the same dose of bromocriptine produced a marked, biphasic fall in blood pressure (Figure 4). Similarly, at 3 and 30 mg/kg orally, bromocriptine produced little or no fall in blood pressure in SHAD-rats.

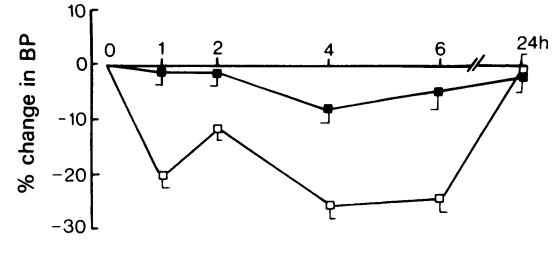

Figure 4 Comparison of percentage change in systolic blood pressure (BP) produced by bromocriptine (10 mg/kg orally) in SH-rats (□) and SHAD-rats (■) (6/group). Vertical bars show s.e. mean. The basal BP of each group was, respectively, for SH-rats, 200 ± 5 mmHg, and for SHAD-rats, 237 ± 7 mmHg. Abscissa scale shows time (h).

Effect of β-adrenoceptor blocking drugs, and of (+)-propranolol, on the blood pressure response to bromocriptine in conscious SH-rats

The non-selective β-adrenoceptor blocking drugs, propranolol and oxprenolol (1 mg/kg i.p.) reduced or abolished the fall in blood pressure to bromocriptine (10 mg/kg orally) in SH-rats (Figures 5a and b) whereas (+)-propranolol, and the cardio-selective β-adrenoceptor blocking drug, atenolol (both 1 mg/kg i.p.) had no effect on the bromocriptine response (Figure 5c and d).

The β-adrenoceptor blocking drugs, and (+)-propranolol, had little effect on the basal blood pressure of SH-rats though propranolol, oxprenolol and atenolol caused bradycardia; bradycardia also occurred in animals that received both bromocriptine and a β-adrenoceptor blocking drug.

Adrenaline reversal in anaesthetized SH-rats

In SH-rats that had received vehicle 1 or 6 h beforehand, adrenaline, (0.3 to 300 μg/kg i.v.) caused dose-dependent pressor responses whereas, in animals dosed 1 or 6 h previously with bromocriptine (10 mg/kg orally) low doses of adrenaline (0.3 and 1 μg/kg) were depressor and the pressor responses to higher doses of adrenaline were reduced (Figure 6).

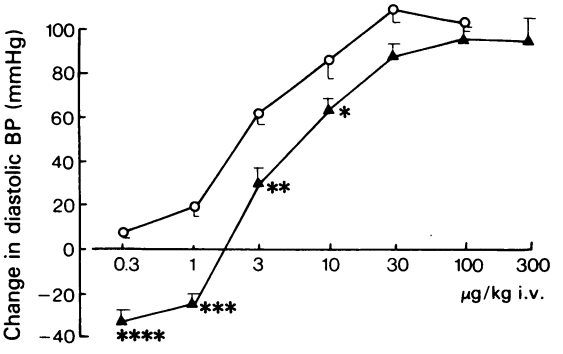

Figure 6 Effect of pretreatment 1 h previously with bromocriptine (10 mg/kg) orally (▲) or control vehicle (○) on the change in diastolic blood pressure evoked by intravenous adrenaline (0.3 to 300 μg/kg) in groups of 6 SH-rats anaesthetized with pentobarbitone sodium (75 mg/kg i.p.). *, **, ***, **** indicate $P<0.05, 0.02, 0.01, 0.001$ respectively.

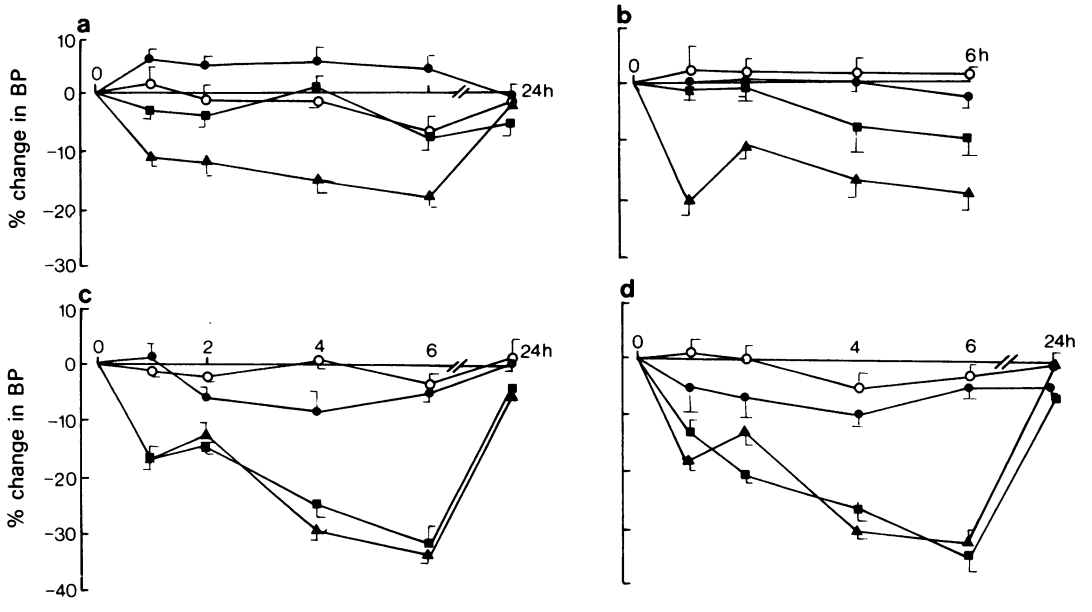

Figure 5 Effect of (a) propranolol, (b) oxprenolol, (c) (+)-propranolol and (d) atenolol (each at 1 mg/kg i.p.) on the change in systolic blood pressure (BP) produced by bromocriptine (10 mg/kg orally) or control vehicle in SH-rats; (■) represents animals receiving bromocriptine and an antagonist; (▲), (●), (○) animals receiving, respectively, bromocriptine, an antagonist or control vehicle alone. Vertical bars show s.e. mean. Groups of 6 rats were used. The basal BP of each group was in (a) for bromocriptine, propranolol, the combination and the control group respectively, 229 ± 8, 223 ± 4, 230 ± 5, 222 ± 9 mmHg (b) for bromocriptine, oxprenolol, the combination and the control groups respectively, 215 ± 4, 232 ± 5, 222 ± 2, 212 ± 7 mmHg; (c) for bromocriptine, (+)-propranolol, the combination and the control groups respectively 212 ± 4, 210 ± 4, 214 ±6 and 205 ± 4 mmHg and (d) for bromocriptine, atenolol, the combination and the control groups respectively 204 ± 4, 206 ± 3, 212 ± 4, 207 ± 4 mmHg. Abscissa scale shows time (h).

Discussion

In conscious SH-rats the acute oral or intraperitoneal administration of bromocriptine caused a dose-related fall in blood pressure without affecting heart rate. A fall in blood pressure also occurred in normotensive rats treated with bromocriptine orally suggesting that the drug's activity is hypotensive in nature and independent of any aetiological factor(s) specific to SH-rats. The hypotensive response to bromocriptine in rats was biphasic, an initial fall in blood pressure at 1 h being followed by recovery towards pre-dose levels at 2 h and then a further fall in blood pressure over the next 4 h. Two other dopamine agonists, lergotrile and pergolide, also cause a biphasic reduction in blood pressure in SH-rats (Yen, Stamm & Clemens, 1979).

That the bromocriptine-induced hypotensive response in SH-rats is mediated by stimulation of dopamine receptors seems unlikely since, of the four dopamine antagonists (pimozide, metoclopramide, sulpiride and haloperidol) used, only sulpiride and haloperidol caused a slight reduction in the bromocriptine response at a single time interval (1 h). Similarly, haloperidol reduced only the initial hypotensive response to lergotrile whereas the hypotensive response to pergolide was prevented over its entire time course (4 h) (Yen *et al.*, 1979). In contrast to the findings in the present study, vascular dopamine receptors have been implicated in the hypotensive response to intravenous bromocriptine in the anaesthetized dog (Clark, 1977).

The elevation of plasma prolactin levels in some hypertensive patients may indicate a reduction in the activity of central dopamine receptors involved in the regulation of blood pressure: moreover in these patients bromocriptine reduced blood pressure and plasma prolactin levels (Stumpe *et al.*, 1977). In the SH-rat, a hypertensive model in which plasma prolactin levels do not differ from those in normotensive rats (Flack, Hamilton, McClelland & Poyser, 1979), bromocriptine reduced plasma prolactin levels at times when blood pressure was reduced. However, it seems unlikely that this is a causal relationship since the hypotensive response was not prevented by dopamine antagonists. Others (e.g. Flückiger, 1976) have shown that the reduction in prolactin levels by bromocriptine is due to the dopamine stimulant properties of the drug.

The mechanism of the hypotensive response to bromocriptine in the rat differs from that causing its behavioural actions in this species: the latter effects are prevented for several hours by pimozide (Johnson, Loew & Vigovret, 1976) at the dose which failed to prevent the hypotensive response to bromocriptine. Using a pretreatment schedule for α-methyl-*p*-tyrosine which decreases brain levels of catecholamines but has little effect on those in the adrenal glands (Snider, Hutt, Stein, Prasad & Fahn, 1976), the hypotensive response to bromocriptine was augmented compared to that in animals receiving bromocriptine alone. Therefore, in contrast to the behavioural actions of bromocriptine which are reduced by pretreatment with α-methyl-*p*-tyrosine (Johnston *et al.*, 1976; Jenner, Marsden & Reavill, 1979), the hypotensive activity of the drug is not dependent on intact catecholamine synthesis in the brain.

The time course of the behavioural actions of bromocriptine is characterized by prolonged duration after a slow onset (Johnson *et al.*, 1976; Jenner *et al.*, 1979) and is therefore similar to the second phase of the blood pressure response to bromocriptine. The possibility that each phase of the hypotensive response to bromocriptine is due to a different mechanism is an attractive one but is not supported by the abolition of the response, over its entire time course, by adrenal demedullation. The present study in SH-rats provides no satisfactory explanation for the biphasic nature of the time-course of the hypotensive response to bromocriptine: the initial response may be due to the parent drug, the subsequent recovery and delayed fall in blood pressure representing respectively, the time for metabolism of bromocriptine and the onset of pharmacological activity of the metabolites. From studies in the rat, Silbergeld, Adler, Kennedy & Calne (1977) and Jenner *et al.* (1979) have suggested that bromocriptine-induced hypothermia and circling behaviour respectively may be mediated by active metabolites.

That the biphasic hypotensive response to bromocriptine is abolished by adrenal demedullation indicates the involvement of adrenal medullary catecholamines in the response. The persistence of the response to bromocriptine after α-methyl-*p*-tyrosine may seem contradictory to this evidence but α-methyl-*p*-tyrosine has little effect on adrenal medullary catecholamines (Snider *et al.*, 1976). Furthermore, since the non-selective β-adrenoceptor blocking drugs, oxprenolol and propranolol, but not (+)-propranolol, antagonize the biphasic hypotensive response to bromocriptine in intact SH-rats, a mechanism involving stimulation of β-adrenoceptors is implicated. These data suggest that stimulation of vascular β_2-adrenoceptors by adrenaline released from the adrenal medulla by bromocriptine and/or metabolites produces vasodilatation and hence the hypotensive response. Further evidence supporting this hypothesis is provided by the failure of the cardioselective β-adrenoceptor blocking drug, atenolol, to affect the biphasic hypotensive action of bromocriptine.

Bromocriptine possesses α-adrenoceptor blocking activity *in vitro* (Gibson & Samini, 1978; Buylaert & Bogaert, 1978) and this has been confirmed *in vivo* since, in SH-rats, pretreatment with bromocriptine

caused reversal. However, the α-adrenoceptor blocking activity of bromocriptine *per se* is not solely responsible for the hypotensive action of bromocriptine since the drug is inactive as a hypotensive in the SHAD-rat while prazosin, another α-adrenoceptor blocking drug, is equally effective as a hypotensive in the SHAD- and SH-rat (unpublished observations). However, the α-adrenoceptor blocking activity of bromocriptine is necessary for the drug's hypotensive action since, as shown by reversal of the response of low doses of injected adrenaline from pressor to depressor, this activity of bromocriptine will allow adrenaline released from the adrenal medulla to exert a vasodilator action by stimulation of vascular β_2-adrenoceptors.

In conclusion, this study has shown that both phases of the hypotensive response to bromocriptine in SH-rats are mediated by adrenaline released from the adrenal medulla which causes vasodilatation by stimulation of β_2-adrenoceptors in the presence of α-adrenoceptor blockade induced by bromocriptine. The clinical relevance of these findings in the rat is not known. Certainly the α-adrenoceptor blocking properties of bromocriptine may contribute to the postural nature of the fall in blood pressure in some patients; the role of the adrenal glands is less clear. However, as in the rat, there is some evidence that in man, bromocriptine-induced hypotension is not mediated by stimulation of dopamine receptors since the response persists after metoclopramide (Price *et al.*, 1978) and was evident after domperidone, a peripherally-acting dopamine antagonist (Agid, Bonnet, Pollack, Signoret & Lhermitte, 1979).

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References

AGID, Y., BONNET, A.M., POLLAK, P., SIGNORET, J.L. & LHERMITTE, F. (1979). Bromocriptine associated with a peripheral dopamine blocking agent in treatment of Parkinson's disease. *Lancet*, **i**, 570–572.

BROSENS, I.A. (1977). Fainting and bromocriptine: danger when smoking. *Lancet*, **ii**, 244–245.

CLARK, B. (1977). Dopamine receptor stimulants in hypertension. *Acta. med. scand.*, Suppl., **606**, 95–100.

FLACK, J.D., HAMILTON, T.C. McCLELLAND, C. & POYSER, R.H. (1979). Plasma prolactin concentrations in hypertensive rats. *J. Pharm. Pharmac.*, **31**, 61.

FLÜCKIGER, E. (1976). The pharmacology of bromocriptine. In *Pharmacological and Clinical Aspects of Bromocriptine (Parlodel)*, ed. Bayliss, R.I.S., Turner, P. & Maclay, W.P., pp. 12–26. Tunbridge Wells: MCS Consultants.

GIBSON, A. & SAMINI, M. (1978). Bromocriptine is a potent α-adrenoceptor antagonist in the perfused mesenteric blood vessels of the rat. *J. Pharm. Pharmac.*, **30**, 314–315.

GREENACRE, J.K., TEYCHENNE, P.F., PETRIE, A., CALNE, D.B., LEIGH, P.N. & REID, J.L. (1976). The cardiovascular effects of bromocriptine in Parkinsonism. *Br. J. clin. Pharmac.*, **3**, 571–574.

JENNER, P., MARSDEN, C.D. & REAVILL, C. (1979). Evidence for metabolite involvement in bromocriptine-induced circling behaviour. *Br. J. Pharmac.*, 103–104P.

JOHNSON, A.M., LOEW, D.M. & VIGOURET, J.M. (1976). Stimulant properties of bromocriptine on central dopamine receptors in comparison to apomorphine, (+)-amphetamine and L-DOPA. *Br. J. Pharmac.*, **56**, 59–68.

KAYE, S.B., SHAW, K.M. & ROSS, E.J. (1976). Bromocriptine and hypertension. *Lancet*, **ii**, 1176–1177.

LEIGHTON, H.J. & PARMETER, L.L. (1979). Hypotensive effects of bromocriptine in anaesthetised cats. *Pharmacologist*, **21**, 178.

LEWIS, M.J., HENDERSON, A.H. & FISHER, D. (1976). Bromocriptine in methyldopa treated hypertension. In *Pharmacological and Clinical Aspects of Bromocriptine (Parlodel)*, ed. Bayliss, R.I.S., Turner, P. & Maclay, W.P., pp. 92–95. Tunbridge Wells: MCS Consultants.

LINCH, D.C., SHAW, K.M., MUHLEMANN, M.F. & ROSS, E.J. (1978). Bromocriptine-induced postural hypotension in acromegaly. *Lancet*, **i**, 320–321.

LOKHANDAWALA, M.F. (1979). Analysis of the effects of bromocriptine on blood pressure and sympathetic nerve function. *Eur. J. Pharmac.*, **56**, 253–256.

OKAMOTO, K., & AOKI, K. (1963). Development of a strain of spontaneously hypertensive rats. *Japanese Circ. J.*, **27**, 282–293.

O'MULLANE, N.M., DAVIS, J.C., HIPKIN, L.J. & WALKER, B.A. (1976). Hypotension and bromocriptine. *Lancet*, **ii**, 1358.

PRICE, P., DEBONO, A., PARKES, J.D., MARSDEN, C.D. & ROSENTHALER, J. (1978). Plasma bromocriptine levels, clinical and growth hormone responses in Parkinsonism. *Br. J. clin. Pharmac.*, **6**, 303–309.

SILBERGELD, E.K., ADLER, H., KENNEDY, S. & CALNE, D.B. (1977). The roles of pre-synaptic function and hepatic drug metabolism in the hypothermic actions of two novel dopaminergic agonists. *J. Pharm. Pharmac.*, **29**, 632–635.

SIMONIC, A., BUYLAERT, W.A. & BOGEART, M.G. (1978). Does bromocriptine possess α-lytic properties? *Archs int. Pharmacodyn. Ther.*, **236**, 323–324.

SNIDER, S.R., HUTT, C., STEIN, B., PRASAD, A.L.N. & FAHN, S. (1976). Correlation of behavioural inhibition or excitation produced by bromocriptine with changes in brain catecholamine turnover. *J. Pharm. Pharmac.*, **28**, 563–566.

STUMPE, K.O., KOLLOCH, R., HIGUCHI, M., KRÜCH, F. & VETTER, H. (1977). Hyperprolactinaemia and antihypertensive effect of bromocriptine in essential hypertension. *Lancet*, **ii**, 211–214.

YEN, T.T., STAMM, NANCY B. & CLEMENS, J.A. (1979). Pergolide, a potent dopaminergic anti-hypertensive. *Life Sci.*, **25**, 209–216.

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