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Metabolite involvement in bromocriptine-induced circling behaviour in rodents

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Bromocriptine and apomorphine produced identical circling responses in rodents with medial forebrain bundle lesions. Rotation induced by bromocriptine, but not by apomorphine, was inhibited by prior treatment with reserpine or α-methyl-*p*-tyrosine suggesting a requirement for intact presynaptic events. Bromocriptine-induced circling also was inhibited by the catecholamine re-uptake blockers nomifensine and desmethylimipramine, supporting the role of presynaptic mechanisms. Bromocriptine-induced circling, but not apomorphine circling, was reduced by pre-treatment with SKF 525A, an inhibitor of monooxygenase enzymes, suggesting metabolite involvement in the turning response. This compound prolonged hexobarbitone sleeping times and zoxazolamine paralysis times in mice. These indices of drug metabolizing activity also were prolonged by pre-treatment with desmethylimipramine while nomifensine prolonged only hexobarbitone sleeping times and α-methyl-*p*-tyrosine had no effect on either index. The data suggest that a metabolite of bromocriptine may be of importance in causing circling and that uptake of bromocriptine (or a metabolite) into presynaptic catecholamine terminals may be necessary.

Bromocriptine (2-bromo-α-ergocryptine; CB 154) is an ergot alkaloid possessing dopamine agonist properties. Bromocriptine decreases serum prolactin concentrations (Fluckiger et al 1976), induces stereotypy (Fuxe et al 1974; Silbergeld & Pfeiffer 1977), increases locomotor activity (Johnson et al 1976) and reduces cerebral dopamine turnover in rodents (Corrodi et al 1973; Fuxe et al 1974). In all these respects it resembles the postsynaptic dopamine receptor agonist apomorphine and both drugs cause contralateral turning in rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion in one nigrostriatal pathway (Fuxe et al 1974). Contralateral turning in this animal model suggests a postsynaptic site of action for bromocriptine as well as apomorphine.

However, some findings are against the hypothesis that bromocriptine acts solely as a postsynaptic dopamine receptor agonist. For example, turning induced by bromocriptine in rats with a unilateral 6-OHDA lesion of the nigrostriatal pathway is abolished by pretreatment with α-methyl-*p*-tyrosine (AMPT) or reserpine (Fuxe et al 1974), and locomotor activity induced by bromocriptine in mice also is reduced by these drugs (Johnson et al 1976; Dolphin et al 1977). AMPT prevents dopamine synthesis while reserpine prevents dopamine storage, so although bromocriptine appears to act postsynaptically in the turning model, it appears also to require intact presynaptic mechanisms.

Drug-induced circling involves stimulation of both striatal and mesolimbic dopamine receptors (Kelly & Moore 1976; Pycock & Marsden 1978). Thus, while denervation of one striatum causes drugs to induce a postural asymmetry, stimulation of mesolimbic structures is required to produce strong locomotion which converts a postural deviation into active circling. In the classical 6-OHDA circling rodent, only one striatum and mesolimbic area is denervated, leaving the opposite sites intact. So it is possible that a a drug with both presynaptic and postsynaptic dopamine actions might mimic the effect of a pure post-synaptic agonist such as apomorphine, yet still be susceptible to disruption of presynaptic mechanisms.

We have examined, therefore, bromocriptine's actions both in animals with a unilateral 6-OHDA-induced lesion of one striatum and one mesolimbic area and in animals with 6-OHDA-induced denervation of dopamine receptors in one striatum and both mesolimbic areas (see Pycock & Marsden 1978) in order to distinguish between pre- and post-synaptic actions of this compound. In addition we have investigated whether uptake into presynaptic terminals is of importance for the activity of bromocriptine and whether this involves the parent molecule or an active metabolite.

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MATERIALS AND METHODS

6-Hydroxydopamine lesions of the medial forebrain bundle in rats

Male Wistar rats (190–230 g; Olac International Ltd.) were anaesthetized with chloral hydrate (300 mg kg^{-1} i.p.) and immobilized in a Kopf stereotaxic frame. Intracerebral injections of 6-hydroxydopamine hydrobromide (6-OHDA 8 μg in 3 μl ice cold sterile 0·9% w/v NaCl (saline) containing 2 μg ascorbic acid; Sigma Chemical Co.) were delivered through a Hamilton syringe (5 μl capacity) with Luer type needle (outer diameter 0·33 mm; inner diameter 0·18 mm) at a rate of 1 μl min^{-1}. The syringe was left in situ for a further minute following drug injection. The lesion sites and co-ordinates used were as follows: (i) 6-OHDA into the left ascending medial forebrain bundle (MFB) at the level of the lateral hypothalamus (A 4·6; L 1·9; V−1·9; De Groot 1959), and into the right MFB at the level of the rostral hypothalamus (A 6·6; L 2·3; V−1·0). (ii) 6-OHDA into the left ascending MFB at the level of the lateral hypothalamus (A 4·6; L 1·9; V−1·9). Control vehicle injections of saline were made into the same areas in other rats.

Determination of striatal and mesolimbic dopamine concentrations

At least 2 weeks after behavioural testing rats with 6-OHDA induced destruction of the medial forebrain bundle(s) or saline control animals were killed by cervical dislocation, the brains removed, cooled on ice, and divided into left and right hemispheres. A slice of limbic forebrain (including the nucleus accumbens septi, tuberculum olfactorium and the anterior amygdaloid complex) and the striatum were dissected and frozen at −20 °C. Dopamine content of the samples was then determined according to the fluorimetric technique of Laverty & Sharman (1965).

Rats which had received left lateral hypothalamic lesions showed an ipsilateral depletion of mesolimbic dopamine from 2275 ± 250 ng g^{-1} to 590 ± 310 ng g^{-1} (down 74%; $P < 0·05$) and striatal dopamine of 3250 ± 325 ng g^{-1} to 1075 ± 290 ng g^{-1} (down 68%; $P < 0·05$). Dopamine concentrations in the contralateral forebrain were not different from those of control animals (control striatum 3690 ● 275 ng g^{-1}, contralateral striatum 3150 ± 260 ng g^{-1}; control mesolimbic area 2000 ± 350 ng g^{-1}, contralateral mesolimbic area 1860 ± 230 ng g^{-1}; in both areas $P > 0·05$).

Animals with left lateral and right rostral hypothalamic lesions showed a dopamine depletion from 2275 ± 250 ng g^{-1} to 460 ± 150 ng g^{-1} (down 80%; $P < 0·05$) in the left mesolimbic area and a dopamine depletion from 2000 ± 350 ng g^{-1} (down 72%; $P < 0·05$) in the right mesolimbic area and a left striatal dopamine depletion from 3350 ± 325 ng g^{-1} to 900 ± 150 ng g^{-1} (down 73%; $P < 0·05$) when compared to control animals.

The dopamine content of the right striatum was not different from that of control animals (control striatum 3690 ± 275 ng g^{-1}; right (contralateral striatum) 3100 ± 410 ng g^{-1}; $P > 0·05$).

Circling behaviour

Circling behaviour was tested at 4 or more days following surgery. Circling rates (as turns min^{-1}) were counted over a 5 min period at the time of maximal drug effect, 30 min after administration of (+)-amphetamine sulphate (3 mg kg^{-1} i.p. in distilled water; Smith, Kline & French Ltd.), 15 min after apomorphine hydrochloride (0·5 mg kg^{-1} s.c. in 0·1% sodium metabisulphite; Evans Medical Ltd.) or 60 min after bromocriptine mesylate (10 mg kg^{-1} i.p.; Sandoz Products Ltd.). Bromocriptine together with the same weight of tartaric acid was dissolved in a minimum volume of 70% ethanol and made up to volume with distilled water. Results are presented as the mean (±1 s.e.m.) circling rate for at least 6 animals.

The effect of depleting granular dopamine stores or inhibiting dopamine synthesis on circling behaviour was investigated by pretreatment with reserpine (10 mg kg^{-1} i.p. 24 h previously; Halewood Chemical Co.) or α-methyl-*p*-tyrosine methyl ester hydrochloride (200 mg kg^{-1} i.p. 1 h previously; Sigma Chemical Co.).

In order to analyse the effects of inhibiting microsomal drug metabolizing enzyme systems on drug-induced circling, rats were pre-treated with SKF 525A (β-diethylaminoethyl-2,2-diphenylpentanoate; proadifen hydrochloride, 75 mg kg^{-1} i.p.; Smith, Kline & French Ltd.) 30 min before the administration of bromocriptine or apomorphine.

In some experiments designed to study the role of uptake of drugs into presynaptic terminals, rats were pre-treated with the dopamine re-uptake blocker, nomifensine hydrogen maleate (25 mg kg^{-1} i.p.; Hoechst Pharmaceuticals Ltd.) or the noradrenaline re-uptake blocker desmethylimipramine hydrochloride (desipramine, 25 mg kg^{-1} i.p.; Geigy Pharmaceuticals Ltd.) either singly or together 30 min before the injection of bromocriptine or apomorphine.

Determination of hexobarbitone sleeping times and zoxazolamine paralysis times in mice

In order to determine the effect of AMPT, SKF 525A, nomifensine or desmethylimipramine on drug metabolizing activity, hexobarbitone sleeping times or zoxazolamine paralysis times were studied. Groups of 17–20 female P strain mice (25–33 g; Animal Suppliers Ltd.) received AMPT (200 mg kg^{-1} i.p.) or SKF 525A (75 mg kg^{-1} i.p.) or nomifensine hydrogen maleate (25 mg kg^{-1} i.p.) or desipramine hydrochloride (25 mg kg^{-1} i.p.). All drugs were given 1 h before study, except SKF 525A which was given 30 min beforehand.

Animals were subsequently injected with hexobarbitone (100 mg kg^{-1} i.p. in equimolar sodium hydroxide) or zoxazolamine (150 mg kg^{-1} dissolved in a minimum volume of 0·1 M HCl and made up to volume with water; Sigma Chemical Co. Ltd.). Sleeping or paralysis time was defined as the interval between loss and recovery of the righting reflex. The mice were considered to have recovered after righting themselves twice in quick succession.

Statistical analysis

The data was analysed using Student's *t*-test for grouped data.

RESULTS

Circling behaviour

Unilateral lesions of MFB (Fig. 1)

Rats 4 days after unilateral 6-OHDA lesions of the MFB turned away from the side of the denervated striatum following administration of apomorphine (0·5 mg kg^{-1} s.c.; 15 min previously) (mean rate of circling 18·9 ± 9·1 turns min^{-1}) but towards the denervated striatum following amphetamine (3 mg kg^{-1}; 30 min previously) administration (mean rate of circling 6·0 ± 2·0 turns min^{-1}). Circling 21 days following surgery to apomorphine (mean rate of circling 26·6 ± 6·3 turns min^{-1}) or amphetamine (mean rate of circling 8·3 ● 1·3 turns min^{-1}) was similar. At this time bromocriptine (10 mg kg^{-1}; 1 h previously) induced marked circling away from the side of the denervated striatum (mean rate of rotation 15·3 ± 9·1 turns min^{-1}).

Pre-treatment of animals with unilateral MFB lesions with reserpine (10 mg kg^{-1} i.p.; 24 h beforehand) or AMPT (200 mg kg^{-1} i.p.; 1 h beforehand) abolished amphetamine induced turning. Turning in response to apomorphine was unaffected by reserpine or AMPT pre-treatment. Bromocriptine-induced circling was reduced, but not abolished, following either reserpine or AMPT pre-treatment ($P < 0·05$).

Bilateral lesions of MFB (Fig. 2)

Rats with bilateral lesions of the MFB 4 days after surgery turned away from the side of the denervated striatum following administration of apomorphine (0·5 mg kg^{-1} s.c.; 15 min previously) (mean rate of circling 9·4 ± 2·0 turns min^{-1}) but towards the denervated striatum following amphetamine (3 mg kg^{-1} i.p.; 30 min previously) administration (mean

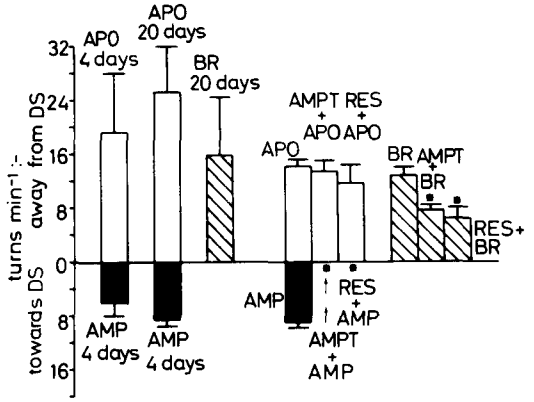

FIG. 1. Circling behaviour induced in rats with unilateral 6-OHDA lesions of the medial forebrain bundle by apomorphine hydrochloride (APO, 0·5 mg kg^{-1} s.c., 15 min previously), (+)-amphetamine sulphate (AMP, 3 mg kg^{-1} i.p., 30 min previously) or bromocriptine mesylate (BR, 10 mg kg^{-1} i.p., 60 min previously) and the effect of pre-treatment with reserpine (RES, 10 mg kg^{-1} i.p., 24 h prior) or AMPT (200 mg kg^{-1} i.p. 1 h prior). ■ $P < 0·05$. DS = denervated striatum.

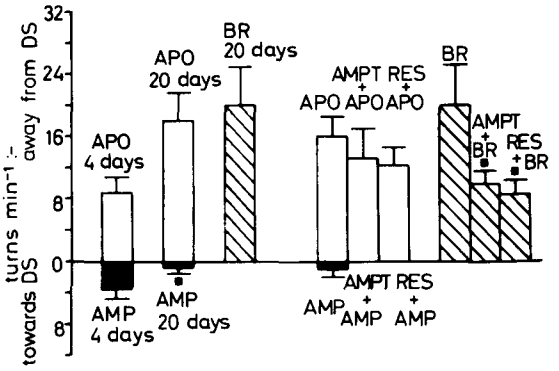

FIG. 2. Circling behaviour induced in rats with bilateral 6-OHDA lesions of the medial forebrain bundle by apomorphine hydrochloride (APO, 0·5 mg kg^{-1} s.c., 15 min previously), (+)-amphetamine sulphate (AMP, 3 mg kg^{-1} i.p., 30 min previously) or bromocriptine mesylate (BR, 10 mg kg^{-1} i.p., 60 min previously) and the effect of pre-treatment with reserpine (RES, 10 mg kg^{-1} i.p., 24 h prior) or AMPT (200 mg kg^{-1} i.p., 1 h prior). ■ $P < 0·05$. DS = denervated striatum.

rate of circling 3·5 ± 2·4 turns min^{-1}). Circling 21 days after surgery in response to apomorphine had increased (mean rate of circling 17·1 ± 4·4 turns min^{-1}; $P < 0.05$) whereas circling in response to amphetamine virtually had disappeared (mean rate of circling 1·0 ± 0·5 turns min^{-1}). At this time bromocriptine (10 mg kg^{-1} i.p.; 1 h previously) produced brisk circling away from the side of the denervated striatum (mean rate of circling 15·3 ± 9·1 turns min^{-1}).

Pre-treatment of animals with bilateral MFB lesions with reserpine (10 mg kg^{-1} i.p.; 24 h) or AMPT (200 mg kg^{-1} i.p.; 1 h) abolished residual amphetamine-induced circling. Turning in response to apomorphine was unaffected by reserpine or AMPT pre-treatment. Bromocriptine induced circling was reduced following either reserpine or AMPT pretreatment ($P < 0.05$) but was not abolished.

Effect of inhibition of drug metabolism on circling behaviour (Fig. 3)

Pre-treatment of rats with bilateral lesions of the MFB with SKF 525A (75 mg kg^{-1}; 30 min previously) had no effect on circling behaviour induced by apomorphine (0·5 mg kg^{-1}; 15 min previously) (mean rates of circling: apomorphine 20·4 ± 6·2 turns min^{-1}; apomorphine + SKF 525A 19·8 ± 8·1 turns min^{-1}; $P > 0.05$). However, pre-treatment with SKF 525A produced a marked reduction (67%) in bromocriptine (10 mg kg^{-1} i.p.; 1 h previously) induced circling in these animals (mean rate of circling: bromocriptine 14·8 ± 3·9 turns min^{-1}; bromocriptine + SKF 525A 4·9 ± 2·2 turns min^{-1}; $P < 0.05$).

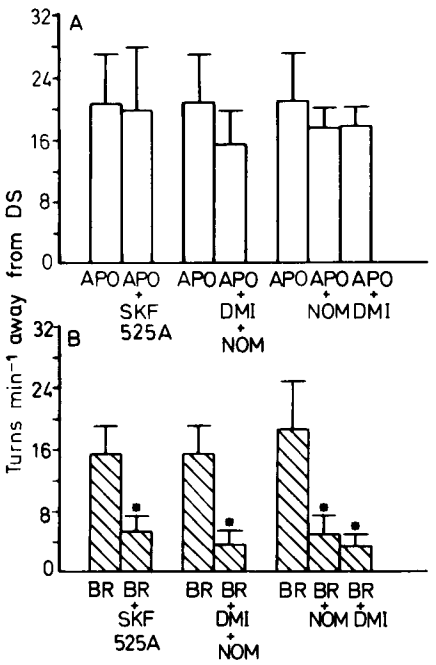

FIG. 3. The effect of pre-treatment with SKF 525A (75 mg kg^{-1}, 30 min prior) or nomifensine hydrogen maleate (NOM, 25 mg kg^{-1}, 30 min prior) or desipramine hydrochloride (DMI, 25 mg kg^{-1} 30 min prior) alone or in combination on turning behaviour induced by A) apomorphine hydrochloride (APO, 0·5 mg kg^{-1} s.c., 15 min previously) or B bromocriptine mesylate (BR, 10 mg kg^{-1} i.p., 1 h previously) in rats with bilateral 6-OHDA induced lesions of the medial forebrain bundle. ■ $P < 0.05$. DS = denervated striatum.

Effect of blockade of neuronal re-uptake mechanisms on circling behaviour (Fig. 3)

Pre-treatment of rats with bilateral lesions of the MFB with nomifensine (25 mg kg^{-1} i.p.; 0·5 h previously) and desmethylimipramine (25 mg kg^{-1} i.p.; 0·5 h previously) alone or in combination caused no circling and had no effect on circling behaviour induced by apomorphine (0·5 mg kg^{-1}; 15 min previously) (mean rates of circling: apomorphine 20·4 ± 6·2 turns min^{-1}; apomorphine + nomifensine 17·2 ± 1·9 turns min^{-1}; $P > 0.05$; apomorphine + desipramine 17·5 ± 1·5 turns min^{-1}; $P > 0.05$). However, pre-treatment with desipramine or nomifensine produced a marked reduction (83 and 74% respectively) in bromocriptine (10 mg kg^{-1} i.p.; 1 h previously) induced circling in these animals (mean rates of circling: bromocriptine 18·4 ± 6·3 turns min^{-1}; bromocriptine + nomifensine 5·1 ± 2·5 turns min^{-1}; $P < 0.05$; bromocriptine + desipramine 3·2 ± 1·9 turns min^{-1}; $P < 0.05$).

Determination of hexobarbitone sleeping times and zoxazolamine paralysis times in mice (Fig. 4)

Normal female mice (25–35 g) receiving either hexobarbitone (100 mg kg^{-1} i.p.) or zoxazolamine (150 mg kg^{-1} i.p.) remained asleep or paralysed for approximately 55 min and 45 min respectively. Some variation between batches of animals was apparent so each experiment involving drug pre-treatment was carried out in parallel with control animals receiving hexobarbitone or zoxazolamine alone.

Pre-treatment of mice with nomifensine (25 mg kg^{-1} i.p.; 1 h previously) or desipramine (25 mg kg^{-1} i.p.; 1 h previously) prolonged hexobarbitone induced sleeping time ($P < 0.05$). Zoxazolamine paralysis times also were prolonged by desipramine pre-treatment ($P < 0.05$) but were unaffected by the prior administration of nomifensine. AMPT (200 mg kg^{-1} i.p.; 1 h previously) had no effect on either hexobarbitone sleeping times or zoxazolamine paralysis times ($P > 0.05$). SKF 525A (75 mg kg^{-1}

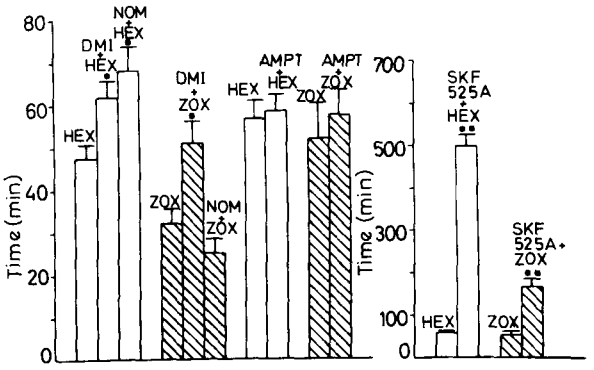

FIG. 4. The effect of pre-treatment with desipramine hydrochloride (DMI, 25 mg kg^{-1} i.p., 1 h previously), nomifensine hydrogen maleate (NOM, 25 mg kg^{-1} i.p., 1 h previously), AMPT (200 mg kg^{-1} i.p., 1 h previously) or SKF 525A (75 mg kg^{-1} i.p., 30 min previously) on hexobarbitone (HEX, 100 mg kg^{-1} i.p.)-induced sleeping times and zoxazolamine (ZOX, 150 mg kg^{-1} i.p.)-induced paralysis times in mice. ■ $P < 0.05$. ** $P < 0.005$.

i.p.; 30 min previously) caused a marked prolongation of both hexobarbitone sleeping times and zoxazolamine paralysis times ($P < 0.05$).

DISCUSSION

Bromocriptine acts as a dopamine agonist in, for example, reducing serum prolactin concentrations (Fluckiger et al 1976), and cerebral dopamine turnover (Corrodi et al 1973). Bromocriptine is believed to act on postsynaptic dopamine receptors since on administration to rats with a unilateral 6-OHDA lesion of the nigrostriatal pathway (Ungerstedt 1971) it mimicked apomorphine in causing animals to circle away from the side of the denervated striatum (Fuxe et al 1974, and this study). However, doubt exists about the purity of its postsynaptic action because pre-treatment of such rats with AMPT or reserpine inhibited bromocriptine-induced circling (Fuxe et al 1974, and this study). The disruption of presynaptic events by AMPT or reserpine is difficult to reconcile with a postsynaptic action of bromocriptine. The identical contraversive circling produced by the dopamine postsynaptic agonist apomorphine is unaffected by disruption of dopamine synthesis by AMPT or storage in presynaptic terminals by reserpine (see Johnson et al 1976).

Bromocriptine may possess both pre- and postsynaptic actions on cerebral dopamine pathways. Dray & Oakley (1976) also tried to distinguish between pre- and post-synaptic actions of this drug in the rotating rat. They found that bromocriptine reduced apomorphine-induced circling, possibly indicating a partial agonist action at dopamine receptors, while bromocriptine enhanced amphetamine-induced turning, suggesting a facilitatory presynaptic action. To investigate this further we employed the two component rotating rat model of Pycock & Marsden (1978). This model differs from that of Ungerstedt (1971) in that not only are the nigrostriatal and tegmento-accumbens dopamine pathways lesioned unilaterally with 6-OHDA, but also the tegmento-accumbens pathway is lesioned with 6-OHDA in the opposite hemisphere. The principal advantage of this model is that it should differentiate completely between pre- and postsynaptic dopamine agonists. Postsynaptic agonists cause contraversive rotation and presynaptically acting compounds cause ipsiversive rotation in the Ungerstedt (1971) model but it is still possible for a compound with both pre- and post-synaptic actions to cause contraversive circling. This would involve a preferential postsynaptic action on the denervated striatal receptors producing a contraversive posture accompanied by a bilateral locomotor component generated to some extent by a presynaptic action on the intact nucleus accumbens. In the model of Pycock & Marsden (1978), however, the input to both nuclei accumbens has been removed. Apomorphine will therefore cause circling away from the denervated striatum due to preferential stimulation of the supersensitive dopamine receptors on this side and a bilateral action on dopamine receptors in the nuclei accumbens. Drugs such as amphetamine, although causing posturing towards the denervated striatum due to a presynaptic action on the intact striatum, do not cause circling since no presynaptic locomotor action on nucleus accumbens receptors is possible (see Fig. 1).

In this later model bromocriptine mimicked apomorphine, suggesting that it is indeed a pure postsynaptic dopamine agonist, but such turning caused by bromocriptine was still suppressed by pretreatment with AMPT or reserpine. Indeed the requirement for intact presynaptic events in catecholamine-containing neurons in the turning behaviour induced by bromocriptine was confirmed by the ability of the re-uptake blockers desipramine and nomifensine (Horn et al 1971; Kruse et al 1977) to inhibit this behaviour while not affecting rotation in response to apomorphine. These data might indicate an action of bromocriptine in altering neuronal activity at the presynaptic level. Alternatively, they may suggest a need for bromocriptine to be taken up into catecholamine terminals and there be converted

to the metabolite responsible for postsynaptic activation. Indeed, there is some evidence to suggest that the action of bromocriptine might be due to the in vivo metabolism to an active moiety. Thus, the locomotor activity produced by bromocriptine is only apparent after a considerable lag period, the length of which is dependent on dose (0·5–5·0 h), which may represent the time necessary to produce the active moiety (Dolphin et al 1977). Further, bromocriptine, unlike other postsynaptic dopamine agonists, does not stimulate basal striatal adenylate cyclase activity in vitro and may depress the stimulation caused by dopamine (Trabucchi et al 1976; Markstein et al 1978; Fuxe et al 1978). Bromocriptine administered intraperitoneally caused only a short lived increase in striatal cAMP concentrations (Trabucchi et al 1976) and this occurred at a time when locomotor function was not enhanced.

To examine the possible involvement of an active metabolite of bromocriptine in the circling response, we investigated the action of SKF 525A, an inhibitor of monooxygenase drug metabolizing enzymes (Anders 1971). SKF 525A reduced bromocriptine-induced circling by 60% but had no effect on that produced by apomorphine. The possibility that some central action of SKF 525A was responsible for the inhibition of bromocriptine-induced circling seems unlikely. It may act as a monoamine oxidase inhibitor and indeed accentuates the effects of amphetamine (Carrano & Malone 1966) but this is uncertain (see Keller & Da Prada 1979) and would not explain a decrease in bromocriptine-induced circling. The conclusion therefore must be that at least a part of the circling produced by bromocriptine is due to the formation of an active metabolite.

Could the ability of AMPT, nomifensine and desipramine to attenuate circling to bromocriptine, but not that to apomorphine, be due to these drugs affecting the metabolism of bromocriptine? We found that desipramine, like SKF 525A, potentiated both hexobarbitone sleeping times and zoxazolamine paralysis times indicating that desipramine might also inhibit the metabolism of bromocriptine. This was not unexpected since desipramine has been suggested also to impair the metabolism of amphetamine (Consolo et al 1967). The action of nomifensine was more difficult to interpret for it enhanced hexobarbitone sleeping times but did not affect zoxazolamine paralysis times. However, AMPT had no effect on hexobarbitone sleeping times or zoxazolamine paralysis times.

The evidence suggests that metabolism of bromocriptine is necessary, at least partially, to induce its effects on central monoamine pathways. In addition, the uptake of bromocriptine or its metabolite(s) into intact presynaptic catecholamine terminals appears fundamental to its mechanism of action. It is possible that these facts may be connected since the brain contains drug metabolizing monooxygenase enzymes (Marietta et al 1979) and has some limited ability to metabolize drugs. Which catecholamine terminals are involved and why remains an open question.

These findings support the proposal that a metabolite of bromocriptine may be involved in the hypothermic actions of this drug in cold acclimatized rats (Silbergeld et al 1977). Thus SKF 525A is claimed to inhibit the hypothermic response although the difference appears slight. However, in direct contrast to these data and to the present study, Keller & Da Prada (1979) have demonstrated that SKF 525A does not reduce, and indeed may potentiate, the hypothermic action of bromocriptine and its action in reducing cerebral HVA concentrations. There is no obvious explanation for this discrepancy. However, the bromocriptine molecule is complex and it is conceivable that different aspects of its pharmacological profile are due to different moieties derived from bromocriptine either individually or in combination. Further studies of the metabolites of bromocriptine therefore may help to unravel this paradox.

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REFERENCES

Anders, M. W. (1971) Annu. Rev. Pharmacol. 11: 37–56

Carrano, R. A., Malone, M. H. (1966) J. Pharm. Sci. 55: 563–567

Consolo, S., Dolfini, E., Garattini, S., Valzelli, L. (1967) J. Pharm. Pharmacol. 19: 253–256

Corrodi, H., Fuxe, K., Hokfelt, T., Lidbrink, P., Ungerstedt, U. (1973) J. Pharm. Pharmacol. 25: 409–412

De Groot, J. (1959) Verh. K. Ned. Akad. Wet. 52: 11–40

Dolphin, A. C., Jenner, P., Sawaya, M. C. B., Marsden, C. D., Testa, B. (1977) J. Pharm. Pharmacol. 29: 727–734

Dray, A., Oakley, N. R. (1976) Ibid. 28: 586–588

Fluckiger, E., Doepfner, W., Marks, M., Niederer, W. (1976) Postgrad. Med. J. 52: (Suppl. 1) 57–63

Fuxe, K., Corrodi, H., Hokfelt, T., Lidbrink, P., Ungerstedt, U. (1974) Med. Biol. 52: 121–132

Fuxe, K., Fredholm, B. B., Agnati, L. F., Ogren, S-O., Everitt, B. J., Johnsson, G., Gustafsson, J-Å. (1978) Pharmacology 16 (Suppl. 1) 99–134

Horn, A. S., Coyle, J. T., Snyder, S. H. (1971) Mol. Pharmacol. 7: 66–80

Johnson, A. M., Loew, D. M., Vigouret, J. M. (1976) Br. J. Pharmacol. 56: 59–68

Keller, H. H., Da Prada, M. (1979) Life Sci. 24: 1211–1222

Kelly, P. H., Moore, K. E. (1976) Nature (London) 263: 695–696

Kruse, H., Hoffman, I., Gerhards, H. J., Leven, M., Schacht, V. (1977) Psychopharmacologia 51: 117–123

Laverty, R., Sharman, D. F. (1965) Br. J. Pharmacol. 24: 538–548

Marietta, M. P., Vesell, E. S., Hartman, R. D., Weisz, J., Dvorchik, B. H. (1979) J. Pharmacol. Exp. Ther. 208: 271–279

Markstein, R., Herrling, P. L., Burki, H. R., Asper, H., Ruch, W. (1978) J. Neurochem. 31: 1163–1172

Pycock, C. J., Marsden, C. D. (1978) Eur. J. Pharmacol. 47: 167–175

Silbergeld, E. K., Adler, H., Kennedy, S., Calne, D. B. (1977) J. Pharm. Pharmacol. 29: 632–635

Silbergeld, E. K., Pfeiffer, R. F. (1977) J. Neurochem. 28: 1323–1326

Trabucchi, M., Spano, P. F., Tonon, G. C., Frattola, L. (1976) Life Sci. 19: 225–231

Ungerstedt, U. (1971) Acta Physiol. Scand. Suppl. 367: 69–93