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STIMULANT PROPERTIES OF BROMOCRIPTINE ON CENTRAL DOPAMINE RECEPTORS IN COMPARISON TO APOMORPHINE, (+)-AMPHETAMINE AND L-DOPA

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1 The activity of bromocriptine has been investigated in tests for the stimulation of central dopaminergic mechanisms. The results obtained have been compared with those of apomorphine, (+)-amphetamine and L-DOPA.

2 Bromocriptine (2.5 to 10 mg/kg) induced stereotyped sniffing and licking in rats. The stereotypy was more intense than that induced by L-DOPA and less intense than that of apomorphine and (+)-amphetamine over the dose ranges studied.

3 In rats lesioned unilaterally in the substantia nigra by local injection of 6-hydroxydopamine, bromocriptine, like apomorphine and L-DOPA, induced turning contralateral to the side of the lesion. The smallest dose of bromocriptine to induce turning was 0.5 mg/kg.

4 Reserpine-induced catalepsy in mice was antagonized by bromocriptine, with an ED_{50} of 1.8 mg/kg. It was intermediate in potency to apomorphine and L-DOPA.

5 Spontaneous locomotor activity in mice was stimulated by bromocriptine in a dose-dependent manner from 2.5 to 10 mg/kg after an initial suppression of activity.

6 In all experiments, bromocriptine was characterized by a prolonged duration of activity after a delay in the onset of effect.

7 The stereotyped behaviour induced by bromocriptine was inhibited by prior administration of pimozide, reserpine or α-methyl-*p*-tyrosine.

8 Bromocriptine-induced turning behaviour was abolished by pretreatment with pimozide, and reduced after α-methyl-*p*-tyrosine pretreatment.

9 The results obtained support the conclusion that bromocriptine acts by stimulating dopamine receptors in the central nervous system and that intact catecholamine synthesis and granular amine storage mechanisms are necessary for it to bring about its effects.

Introduction

Bromocriptine (CB 154), 2-bromo-α-ergocryptine (Figure 1) is an ergot polypeptide derivative comprising a lysergic acid residue with a cyclic polypeptide moiety.

It was originally characterized as a specific inhibitor of prolactin secretion, being active in all vertebrates tested so far, including man (Flückiger, 1972; Del Pozo, Brun Del Re, Vorga & Fiesen, 1972).

Preliminary investigations into the mechanism of action of bromocriptine indicated that it acted directly on prolactin secreting cells of the hypophysis (Marko & Niederer, unpublished results; Pasteels, Danguy, Frerotte & Ectors, 1971). However, Hökfelt & Fuxe (1972) found that, in the rat, bromocriptine also decreased dopamine (DA) turnover in the median eminence and suggested that it might interfere with dopaminergic tuberoinfundibular neurones which allegedly control prolactin secretion. During the course of investigations into the role of these neurones, using bromocriptine as a tool to inhibit prolactin secretion, Corrodi, Fuxe, Hökfelt, Lidbrink & Ungerstedt (1973) discovered that it also decreased DA turnover in the neostriatum, an action attributable to a direct stimulation of DA receptors at this site. This central dopaminergic stimulation is assumed to be responsible for the significant therapeutic action of bromocriptine in patients with idiopathic Parkinsonism (Calne, Leigh, Teychenne, Bamji &

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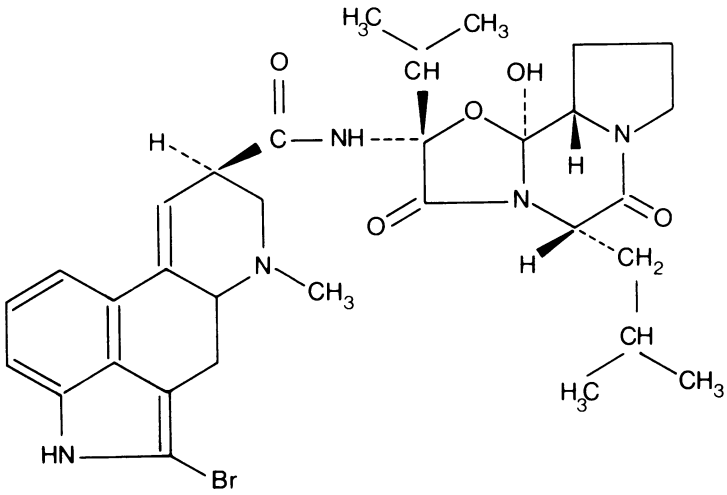

Figure 1 Structure of bromocriptine (2-bromo-α-ergocryptine, CB 154).

Greenacre, 1974a; Calne, Teychenne, Claveria, Eastman, Greenacre & Petrie, 1974b). We have now investigated the activity of bromocriptine in tests sensitive to dopaminergic mechanisms in the central nervous system. Bromocriptine has been compared to L-DOPA, apomorphine and (+)-amphetamine because of their established actions on central dopaminergic mechanisms.

Some preliminary experiments with bromocriptine in comparison to other ergotoxine alkaloids have already been reported (Johnson, Vigouret & Loew, 1973, 1974).

Methods

Production of stereotyped behaviour in rats

Rats, 180–220 g, were placed in perspex cylinders of 30 cm diameter on a wire grid floor. After 30 min acclimatization to the cage, the rats were injected with the compound under investigation. The behaviour of the rats was observed for 2 min at 30 min intervals for 2 h and then at 60 min intervals for a total of up to 7 hours. The degree of stereotyped behaviour observed was assessed using a scoring system based on that described by Costall, Naylor & Olley (1972).

The scores and criteria are as follows: 1 = intermittent sniffing; 2 = persistent sniffing, occasional licking; 3 = licking, occasional biting; 4 = intense and persistent biting. The ratings were carried out by an observer who was unaware of the treatment the rats received. Six rats were investigated at each dose level.

The induction of turning in rats lesioned unilaterally in the substantia nigra by 6-hydroxydopamine

Rats were lesioned by the method described by Ungerstedt (1971), using rats weighing 145–155 g when lesioned.

Four μl of a solution, containing 2 mg/ml of 6-hydroxydopamine hydrochloride, calculated as base, in 0.9% NaCl solution with 0.2 mg/ml ascorbic acid as antioxidant, was slowly injected unilaterally (right) into the medial substantia nigra of rats under sodium pentobarbitone anaesthesia.

One week later, the rats were challenged with 0.25 mg/kg s.c. apomorphine. Rats responding by turning contralaterally to the side of the lesion, i.e. to the left, at not less than 5 turns/min were selected for further experiments. All experiments were carried out in rats that had been lesioned at least 4 weeks previously. After injection, the number of turns occurring in 2 min every 30 min in the case of bromocriptine or every 10 min for other drugs was counted. The direction of the turns was recorded in all instances. Rats were observed until turning stopped or up to 9 h after injection. The total number of turns produced by each treatment was also calculated.

In a preliminary experiment with a group of 6 rats, single doses of bromocriptine (2 mg/kg), apomorphine (0.5 mg/kg), (+)-amphetamine (5 mg/kg) and L-DOPA (100 mg/kg) were investigated. The activity of L-DOPA (25 mg/kg) alone and after pretreatment of the rats with the peripheral DOPA decarboxylase inhibitor, Ro 4-4602, was also tested.

In a second experiment, the effects of 3 doses of

apomorphine and bromocriptine were compared in another group of 6 rats. Treatments were allocated to the rats by means of a Latin square design. The experiments were carried out on alternate days over a period of 2 weeks. Differences between treatments were analysed by means of Student's *t*-test for paired observations.

Antagonism of reserpine-induced catalepsy in mice

Mice (18–25 g) in groups of 10 were injected intraperitoneally with reserpine (5 mg/kg) 17 h before subcutaneous administration of the compounds under investigation. Catalepsy was assessed at 30 min, 1 h, 2 h, 3.5 h and, in the case of bromocriptine, 5 h after administration of the compound using the method of Zetler & Moog (1958). The number of mice showing antagonism of catalepsy, i.e. with the ability to walk off a twine-covered vertical pole in a co-ordinated manner, was recorded. Control animals retain their position when placed on the side of the pole.

The percentage antagonism of catalepsy in the treated groups compared to control was calculated. At least 3 doses of each compound were investigated and the ED_{50} determined graphically at each observation time after compound administration. The standard error of the ED_{50} was determined by the method of Miller & Tainter (1944).

Stimulation of spontaneous locomotor activity in mice

Spontaneous locomotor activity was recorded by means of a conventional light beam cage. The light and sound proof cabinet contained 4 identical cages, each 22 cm × 37 cm, crossed by 6 light beams. Five mice (18–25 g), were placed in each cage 15 min after compound administration and the number of light beam interruptions taking place was recorded at 30 min intervals for 7 hours. Experiments were repeated 6 times, giving a total of 30 mice per treatment. The mean total motility count for 5 mice over the recording period, and the mean, and s.e. mean, of each 30 min count were calculated. Statistical comparisons were carried out by means of Student's *t*-test.

Drug interaction studies

The effects of pimozide, α-methyl-*p*-tyrosine, and reserpine on the stereotyped and turning behaviour in rats were investigated using the method described previously. The schedules of drug treatment are shown in the table and figures.

Materials and drugs

The drugs used were as follows: bromocriptine mesylate (SANDOZ), L-DOPA (Fluka), (+)-amphetamine sulphate (Merck), apomorphine hydrochloride (SANDOZ), Ro 4-4602 (Hoffmann-La Roche), reserpine, α-methyl-*p*-tyrosine methyl ester (Fluka) and pimozide (Janssen). All doses refer to the available form. In all experiments drugs were administered subcutaneously unless otherwise stated.

SANDOZ-bred male OFA-strain rats and male NMRI mice were used.

Results

Production of stereotyped behaviour in rats

Bromocriptine induced dose-dependent stereotyped behaviour over the dose range 1 to 10 mg/kg. The behaviour was of only moderate intensity, with a peak score of 1.4 at 10 mg/kg, and consisted mainly of sniffing. The activity was slow in onset but was more persistent than that of the other treatments. Apomorphine induced dose-dependent stereotyped behaviour of short duration over the dose range, 0.3 to 10 mg/kg. Biting or gnawing (score 3–4) was observed at 10 mg/kg (Figure 2). (+)-Amphetamine induced a stereotyped behaviour over the dose range 1.25 to 10 mg/kg that was intermediate in intensity and duration of action to that of bromocriptin and apomorphine. The administration of L-DOPA (200 mg/kg) produced only slight changes in the behaviour of the rats. However, after pretreatment of the rats with 50 mg/kg of Ro 4-4602, L-DOPA (200 mg/kg) induced stereotyped behaviour of similar intensity to that of apomorphine (2.5 mg/kg).

Induction of turning in rats lesioned unilaterally in the substantia nigra by injection of 6-hydroxydopamine

Apomorphine (0.5 mg/kg), bromocriptine (2 mg/kg), and L-DOPA (25 mg/kg), the latter with and without pretreatment with Ro 4-4602, induced contralateral turning in the lesioned rats (Figure 3). The total number of turns induced by L-DOPA was dose-dependent and pretreatment of the rats with Ro 4-4602 (50 mg/kg i.p.) caused a significant potentiation in the response to L-DOPA (25 mg/kg). In contrast, (+)-amphetamine (5 mg/kg) induced ipsilateral turning. Treatment with drug vehicles resulted in only a small equal total number of turns to both sides. At the doses used, the total number of turns induced by bromocriptine was greater than that produced by any of the other treatments. This was due to the long duration of activity rather than the maximal rate of turning induced, as is clearly illustrated by the results obtained in the second experiment. None of the other treatments induced turning for longer than 4 hours.

In the second experiment, apomorphine induced dose-dependent turning with onset of activity within 10 min of injection. The total number of turns induced

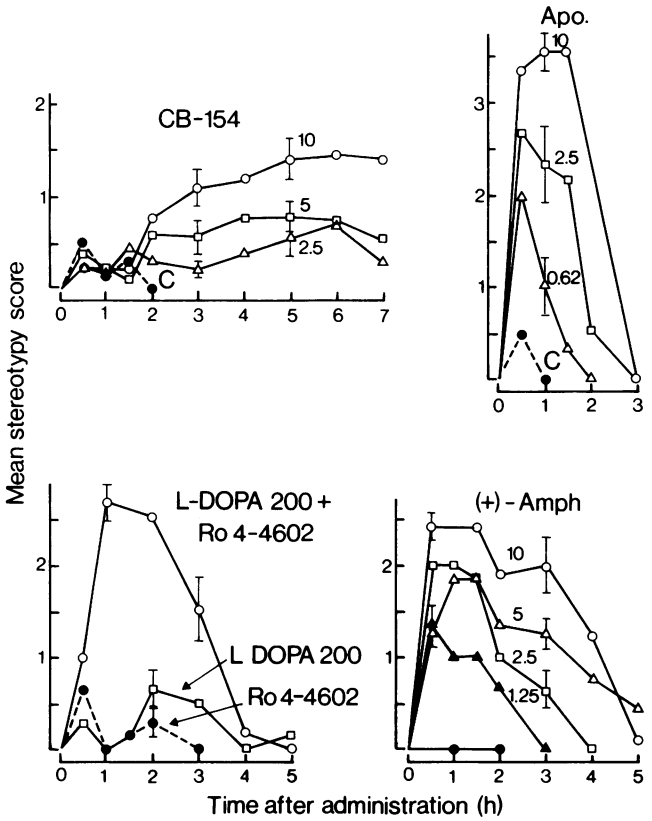

Figure 2 The production of stereotyped behaviour in rats by bromocriptine (CB-154), apomorphine (Apo), L-DOPA before and after intra-peritoneal pretreatment of Ro 4-4602, and by (+)-amphetamine ((+)-Amph). Each point represents the mean sterotypy score of 6 rats. Vertical bars are s.e. mean. The figures on the curve indicate the dose administered in mg/kg. (C) treatment with drug vehicle.

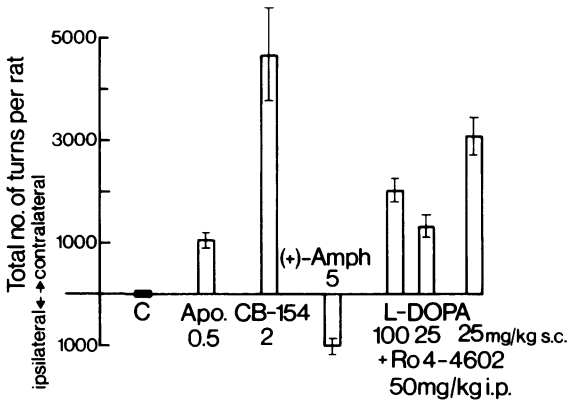

Figure 3 The induction of turning behaviour in rats lesioned unilaterally in the substantia nigra by a local injection of 6-hydroxydopamine after administration of apomorphine (Apo.), bromocriptine (CB-154), (+)-amphetamine ((+)-Amph), and L-DOPA, the latter before and after treatment with Ro 4-4602. Each column represents the mean total number of turns induced by each treatment. The vertical bars indicate the s.e. mean. All treatments were carried out in the same group of 6 rats.

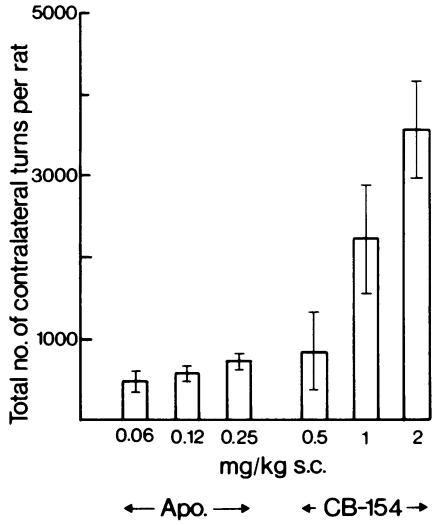

Figure 4 The total number of contralateral turns induced by administration of bromocriptine (CB-154) 0.5, 1 and 2 mg/kg and apomorphine (Apo.) 0.06, 0.12 and 0.25 mg/kg to rats lesioned unilaterally in the substantia nigra by local injection of 6-hydroxydopamine. Vertical bars are the s.e. mean. Turns were recorded for up to a maximum of 9 h after drug administration. A significant difference ($P < 0.05$) between the number of turns induced by each of the doses of apomorphine was observed. The difference between the number of turns induced by 0.5 and 2 mg/kg bromocriptine was statistically significant ($P < 0.05$).

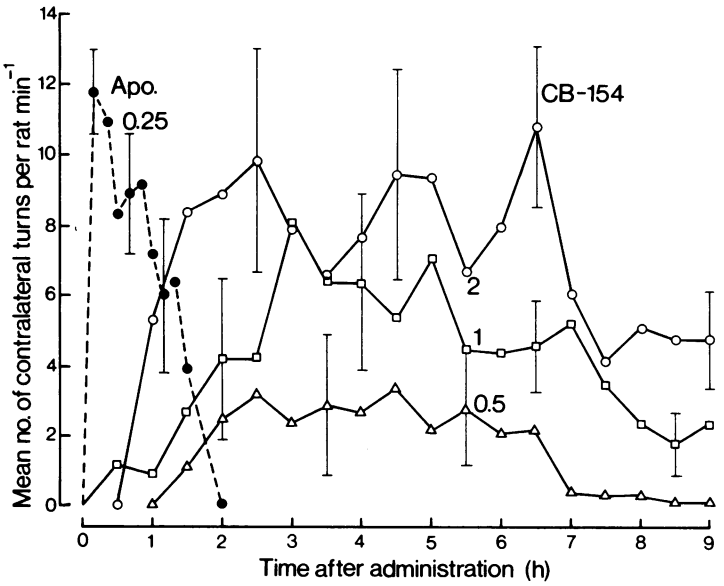

Figure 5 The time course of the induction of turning behaviour in rats lesioned unilaterally in the substantia nigra by a local injection of 6-hydroxydopamine after the administration of bromocriptine (CB-154) 0.5, 1 and 2 mg/kg and apomorphine (Apo.) 0.25 mg/kg. Vertical bars are s.e. mean. The figures on the curve indicate the dose administered in mg/kg. All treatments were administered to the same group of 6 rats. Results obtained in this experiment with apomorphine (0.06 and 0.12 mg/kg) have been omitted for clarity.

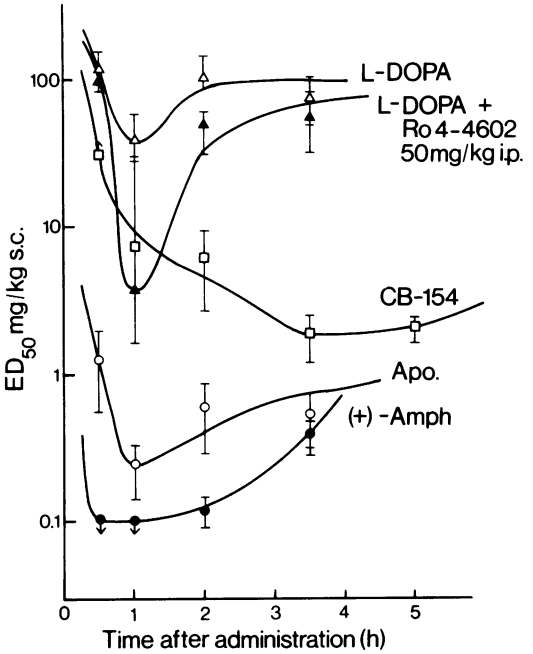

Figure 6 The antagonism of reserpine-induced catalepsy in mice by (+)-amphetamine (+-Amph), apomorphine (Apo), bromocriptine (CB-154) and L-DOPA before and after pretreatment with Ro 4-4602. Results are expressed as the ED_{50} determined at various times after administration of the drugs under investigation. Reserpine (5 mg/kg) was administered by intraperitoneal injection 17 h prior to drug administration. Ten mice per group were used. Vertical bars are s.e. mean.

by a dose of 0.12 mg/kg was significantly ($P < 0.05$) greater than that induced by 0.06 mg/kg and similarly 0.25 mg/kg induced significantly ($P < 0.05$) more turns than 0.12 mg/kg (Figure 4). Maximal rate of turning by 0.25 mg/kg was observed 10 min after injection (Figure 5).

The effects of bromocriptine were dose-dependent with regard to the total number of turns and maximal rate of turning induced. The differences between the number of turns induced by 0.5 and 1 mg/kg, as well as between 1 and 2 mg/kg were not statistically significant; however, the difference between 0.5 mg/kg and 2 mg/kg was significant ($P < 0.05$; Figure 4). Bromocriptine was characterized by a delay in the onset of activity, but turning was still present at 8 h after 1 and 2 mg/kg and from 2 to 6 h after 0.5 mg/kg. In contrast, turning induced by apomorphine (0.25 mg/kg) had ceased 2 h after injection (Figure 5).

Antagonism of reserpine-induced catalepsy in mice

(+)-Amphetamine was the most potent compound tested and had the most rapid onset of action; ED_{50}'s of less than 0.1 mg/kg were recorded at 30 and 60 min after injection (Figure 6). Apomorphine also showed marked activity, a peak ED_{50} of 0.75 mg/kg was recorded 1 h after injection (Figure 6). Bromocriptine was intermediate in potency to apomorphine and L-DOPA. Its maximum activity occurred 3.5 h after administration with an ED_{50} of 1.8 mg/kg. Bromocriptine differed from all the other compounds tested in that its activity was slow in onset and was well maintained.

L-DOPA alone showed only weak activity against reserpine catalepsy (ED_{50} = 38 mg/kg). However, treatment with the peripheral dopa-decarboxylase inhibitor, Ro 4-4602, 1 h before injection of L-DOPA, potentiated its activity, and a peak ED_{50} of 3.7 mg/kg was recorded 1 h after injection.

Stimulation of spontaneous locomotor activity in mice

Bromocriptine caused a dose-dependent stimulation of locomotor activity in doses of 2.5 to 10 mg/kg (Figure 7) after suppression of the initial exploratory phase. Maximum stimulation was observed 3 to 4 h after drug administration and activity after 10 mg/kg was maintained for 7 h after treatment. Apomorphine (10 mg/kg) only weakly stimulated activity in the second 30 min registration period, and the activity was not maintained. The effect was not statistically significant ($P > 0.05$). (+)-Amphetamine stimulated locomotor activity in dose from 1.25 mg/kg in a dose-dependent manner. Increase in activity was observed even in the initial exploratory phase and lasted over 3 hours. L-DOPA (150 mg/kg) both alone and after pretreatment with Ro 4-4602, significantly stimulated locomotor activity after depressing the initial phase. Pretreatment with Ro 4-4602 produced a greater total response although the peak effect was reduced.

Drug interaction studies

The stereotyped behaviour induced by bromocriptine (10 mg/kg) over 7 h after injection was completely blocked by prior administration of pimozide (1 mg/kg). Similarly α-methyl-*p*-tyrosine (200 mg/kg, 60 min previously) and reserpine (5 mg/kg, 16 h previously), abolished the stereotyped behaviour induced by bromocriptine (10 mg/kg; Table 1). In lesioned rats, turning elicited by bromocriptine (20 mg/kg) was abolished by pimozide, and considerably reduced by previous treatment with α-methyl-*p*-tyrosine (Table 2).

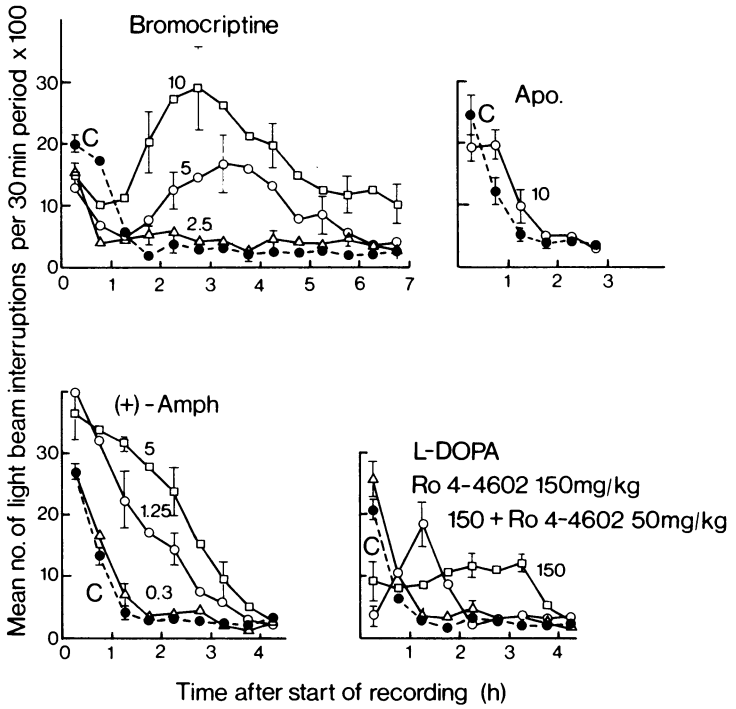

Figure 7 The effect of bromocriptine, apomorphine (Apo), (+)-amphetamine ((+)-Amph) and L-DOPA before and after pretreatment with Ro 4-4602 on the spontaneous locomotor activity of mice. Results are expressed as the mean number of light beam interruptions of a group of 5 mice in 30 min periods. The figures on the curves indicate the dose administered in mg/kg. (C) indicates the effect of vehicle only. Vertical bars are s.e. mean. Six groups of 5 mice were investigated for each treatment and dose level. Experiments commenced 15 min after drug administration.

Table 1 Effect of pimozide, α-methyl-*p*-tyrosine and reserpine pretreatment on bromocriptine-induced stereotyped behaviour in the rat

Group	*Treatment*	*Maximal stereotypy score observed*	*P compared with* (a)
(a)	Bromocriptine	1.4	—
(b)	Bromocriptine + pimozide	0	<0.05
(c)	Bromocriptine + AMPT	0	<0.05
(d)	Bromocriptine + reserpine	0	<0.05

Pimozide (1 mg/kg), α-methyl-*p*-tyrosine (AMPT; 200 mg/kg) and reserpine (5 mg/kg) were administered intraperitoneally 1 h, 1 h and 16 h before bromocriptine, respectively. The maximal stereotypy score for each rat during 7 h observation following the administration of bromocriptine was recorded. Each value is the mean of 6 rats. Statistical analysis by χ^2 test.

Table 2 Effect of pimozide and α-methyl-*p*-tyrosine on bromocriptine-induced rotation in the lesioned rats

Group	*Treatment*	*Total number of turns ± s.e. mean*	*P compared with* (a)
(a)	Bromocriptine	2150 ± 640	—
(b)	Bromocriptine + pimozide	0	<0.05
(c)	Bromocriptine + AMPT	694 ± 502	<0.05

Pimozide (1 mg/kg) and α-methyl-*p*-tyrosine (AMPT; 200 mg/kg) were administered 1 h before bromocriptine. Each value is the mean of 6 rats. Statistical analysis was carried out using Student's *t*-test.

Discussion

It is well established that administration of apomorphine and (+)-amphetamine to rats leads to the production of stereotyped sniffing, licking and biting behaviour (Quinton & Halliwell, 1963; Ernst, 1967; Randrup & Munkvad, 1968), probably due to the stimulation of dopaminergic mechanisms in the striatum (Ernst & Smelik, 1966; Fog, Randrup & Pakkenberg, 1967). The results reported here show that bromocriptine can also induce such behaviour and it may therefore be tentatively concluded that it too activates dopaminergic mechanisms at this site. The stereotyped behaviour induced by bromocriptine was not as intense as that produced by apomorphine or amphetamine; the dose-response curve of bromocriptine was flatter but, after a delay in the onset of action, its duration of action was considerably longer.

The induction of turning by drugs administered to rats with unilateral functional degeneration of the nigro-striatal pathway after the injection of 6-hydroxydopamine into the substantia nigra, has been explained by the suggestion that denervation hypersensitivity develops at striatal DA receptors on the lesioned side (Ungerstedt, 1971). Drugs that mimic the action of DA, e.g. apomorphine (Ernst, 1967; Anden, Rubensson, Fuxe & Hökfelt, 1967), therefore cause a greater stimulation on that side and the rats rotate contralateral to the lesion. Drugs that release DA from neurones, e.g. amphetamine (Ernst, 1967; Fuxe & Ungerstedt, 1968), can do so only on the intact side, causing turning towards this side (ipsilateral turning). Bromocriptine induced turning contralateral to the lesion, indicating that it probably exerts a direct effect at dopamine receptors. These results correspond with those reported by Corrodi *et al.* (1973). The direction of turning observed after administration of apomorphine, (+)-amphetamine and L-DOPA is also in accordance with results reported by Ungerstedt (1971).

The production of catalepsy in animals by neuroleptic drugs is believed to be dependent upon the inhibition of dopaminergic function (van Rossum, Janssen, Boissier, Julou, Loew, Møller-Nielsen, Munkvad, Randrup, Stille & Tedeschi, 1970). Conversely, the neuroleptic-induced cataleptic state is antagonized by administration of drugs known to activate dopaminergic functions, e.g. amphetamine (Morpurgo & Theobald, 1964). In addition, Carlsson, Lindqvist & Magnusson (1957) have reported the antagonism of the tranquillizing action of reserpine by L-DOPA. In the results reported here we have shown that bromocriptine, as well as apomorphine, amphetamine and L-DOPA can antagonize reserpine-induced catalepsy in mice, thus supporting the claim of dopaminergic stimulant properties for this compound. The marked activity of (+)-amphetamine in this test is probably due to the increased sensitivity of reserpinized animals to this compound as reported by Smith (1963), and Morpurgo & Theobald (1966).

Amphetamine and bromocriptine have both been shown to produce dose-dependent stimulation of locomotor activity in mice. In single dose studies, L-DOPA was also effective, the response being modified when mice were pretreated with a dopa-decarboxylase inhibitor. Apomorphine produced only marginal changes in the experimental conditions employed. The stimulation of locomotor activity by amphetamine has been attributed to an action mediated by brain dopamine (Costa, Groppetti & Naimzada, 1972; van Rossum & Hurkmans, 1964; van Rossum, 1970), although noradrenergic mechanism have also been implicated in the action of this class of drugs (Svensson & Waldeck, 1970; Maj, Grobowska & Gajda, 1972; Anden, Strömbom & Svensson, 1973). It is unlikely that noradrenaline is involved in the locomotor stimulant properties of bromocriptin as no pharmacological evidence of the stimulation or facilitation of noradrenaline-dependent processes has yet been obtained (Corrodi *et al.*, 1973). Some reserpine-like activity, i.e. a lowering of cerebral noradrenaline levels has been reported, but this latter effect is more likely to be associated with depression rather than stimulation of spontaneous locomotor

activity. Bromocriptine has been shown to be active in four pharmacological models in which activation of central dopaminergic mechanisms have been implicated and in which drugs known to influence these mechanisms have also been shown to be active.

No attempt was made to rank the potencies of the compounds investigated because the methods used to reveal activity differ. Stereotypy was rated in intact rats but in the other methods normal cerebral function had been modified either by a lesion or by systemic drug administration. In these tests, the potency of a compound will not only depend upon the principal pharmacological effect but also on whether it exerts a direct or indirect action on the mechanisms being investigated. In two tests, mice were used and therefore species differences must also be considered. It may be stated, however, that bromocriptine is at least 4 times less active than apomorphine but more potent than L-DOPA. In all tests it possessed a long duration of action, a property that, if confirmed in clinical investigations, would be a considerable advantage over existing therapy for Parkinson's disease.

Further evidence that the effects of bromocriptine are mediated by stimulation of dopamine receptors is that the induction of stereotyped behaviour and contralateral turning was inhibited by pimozide, a dopamine receptor blocking agent (Anden, Butcher, Corrodi, Fuxe & Ungerstedt, 1970). Corrodi *et al.*, 1973, have also reported that the turning induced by bromocriptine in rats lesioned by the method of Ungerstedt (1971), is inhibited by prior administration of pimozide, as is the stimulation of locomotor activity by bromocriptine in mice (Johnson, Loew & Vigouret, in preparation).

The direction of the turning induced by bromocriptine in the lesioned rats suggests that, like apomorphine, it exerts a direct effect on dopamine receptors. However, when animals were pretreated with α-methyl-*p*-tyrosine, an inhibitor of tyrosine hydroxylase (Spector, Sjoerdsma & Udenfriend, 1965), the turning behaviour and stereotypy are inhibited. This suggests that effects of bromocriptine are dependent upon intact catecholamine synthesis. Similar results have been reported for amphetamine (Weissman, Koe & Tenen, 1966; Hanson, 1966; Dingell, Owens, Norwich & Sulser, 1967; Dominic & Moore, 1969). However, the stereotypy induced by bromocriptine was inhibited in rats pretreated with reserpine, whereas the activity of amphetamine has been reported to be potentiated by this pretreatment (Quinton & Halliwell, 1963; Stolk & Rech, 1968; Dominic & Moore, 1969), and that of apomorphine is not influenced (Ernst, 1967; Maj *et al.*, 1972).

As reserpine blocks the uptake mechanisms in amine storage granules (Carlsson, Hillarp & Waldeck, 1963), bromocriptine appears to require this intact granular amine storage in order to bring about its effects, thus contrasting with both (+)-amphetamine and apomorphine in its mode of action. The inhibition of the bromocriptine-induced locomotor stimulation in mice by prior administration of either α-methyl-*p*-tyrosine or reserpine has also recently been observed (Johnson, Vigouret & Loew, unpublished).

In conclusion, therefore, it may be stated that bromocriptine stimulates central dopamine receptors and differs in its mode of action from both amphetamine and apomorphine.

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