Bromocriptine and dopamine-receptor stimulation

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The ergot derivative bromocriptine (CB 154, 2 Br α-ergocryptine) produces a marked improvement in a number of clinical conditions e.g. galactorrhoea, parkinsonism, acromegaly (Verga, Lutterbeck & others, 1972; Calne, Teychenne & others, 1974; Thorner, Chait & others, 1975). Its effects have been attributed to a direct stimulation of dopamine receptors in the central nervous system (Corrodi, Fuxe & others, 1973; Fuxe, Corrodi & others, 1974).

Much of the evidence for the dopamine receptor stimulant action of bromocriptine has been obtained from rats with unilateral degeneration of the nigro-striatal dopaminergic pathway induced by 6-hydroxydopamine. In these animals, dopamine receptors in the denervated striatium become supersensitive (Ungerstedt, 1971) and the dopamine receptor stimulating drug, apomorphine (Andén, Fuxe & others, 1967; Ernst, 1967) induces turning behaviour away from the denervated side whereas amphetamine, which releases presynaptic dopamine produces turning towards the denervated side. In this preparation bromocriptine produces rotational behaviour in the same direction as that by apomorphine. However the effects of bromocriptine, unlike those of apomorphine, were only apparent after a prolonged latency (Corrodi & others, 1973; Fuxe & others, 1974; Dray, Fowler & others, 1975; Pieri, Pieri & others, 1975; Johnson, Loew & Vigouret, 1976) and moreover were reduced or were not seen when brain dopamine had been depleted by pretreatment with reserpine and a tyrosine hydroxylase inhibitor (Corrodi & others, 1973; Fuxe & others, 1974). These observations suggested to us the possibility that bromocriptine was not acting directly in producing these behavioural effects. In the present report we have explored this possibility further using an animal model in which the nigro-striatal dopaminergic pathway is not destroyed, but its activity is altered by placing small electrolytic lesions in the zona reticulata of the substantia nigra (Dray & others, 1975).

Male albino rats (OLAC, 200–250 g) were anaesthetized with halothane and a unilateral electrolytic lesion was made by passing a current of 500 μA for 20 s through a bipolar electrode (tip separation 0·25 mm placed stereotaxically in the zona reticulata of the substantia nigra (A 2·0–2·4; L 2·0; D −2·5; König & Klippel, 1963). The placement of the electrolytic lesion was confirmed histologically. The animals were studied from 3–21 days after lesioning for their spontaneous and drug-induced rotational behaviour.

Spontaneous head to tail rotation directed away from the lesioned side was occasionally observed when animals were disturbed. However all animals showed tight circling *towards* the lesioned side after injections of apomorphine (2–6 mg kg^{-1}, i.p.), (+)-amphetamine (2–6 mg kg^{-1}, i.p.) or bromocriptine (5–25 mg kg^{-1}, i.p.). No rotation was observed after saline injections. With each drug the intensity of rotation was dose related. Apomorphine-induced rotation began 2–5 min after injection and lasted approximately 60 min with the peak rotation occurring some 30 min after injection (Fig. 1). The mean frequency of rotation was 4·9 ± 0·4 turns min^{-1} after 2 mg kg^{-1} (n = 6); 7·4 ± 0·4 turns min^{-1} after 4 mg kg^{-1} (n = 6) and 8·8 ± 0·5 turns min^{-1} after 6 mg kg^{-1} (n = 6). Amphetamine-induced rotation began 5–10 min after injection, lasted up to 130 min with a peak of rotation between 20–60 min. The frequency of rotation was 1·4 ± 0·2 after 2 mg kg^{-1} (n = 6); 2·9 ± 0·9 turns min^{-1} after 4 mg kg^{-1} (n = 6)

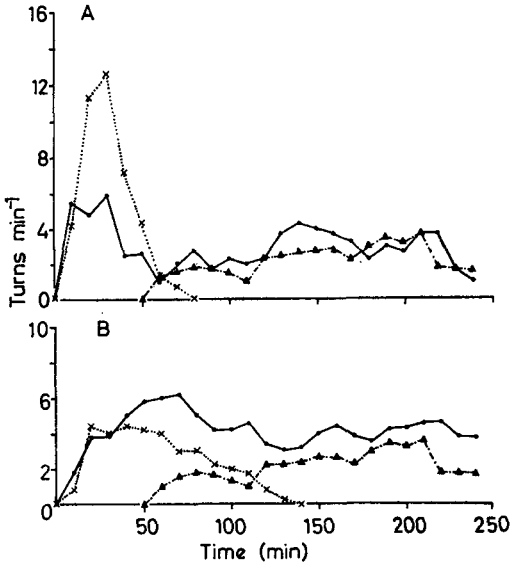

FIG. 1. Rotational behaviour produced by: A ×····× apomorphine alone (4 mg kg^{-1}), ●——● apomorphine (4 mg kg^{-1}) and bromocriptine (10 mg kg^{-1}) or ▲-·-·-▲ bromocriptine alone (10 mg kg^{-1}). B ×····× amphetamine alone (4 mg kg^{-1}), ●——● amphetamine (4 mg kg^{-1}) and bromocriptine (10 mg kg^{-1}) or ▲-·-·-▲ bromocriptine alone (10 mg kg^{-1}).

* Correspondence

and $5{\cdot}2 \pm 0{\cdot}4$ turns min^{-1} after 6 mg kg^{-1} (n = 6) However with bromocriptine, rotation began only after a considerably longer period (50–70 min) and fairly constant rotation persisted for up to 240 min and declined over the next 5–7 h. The mean frequency of rotation was $1{\cdot}1 \pm 0{\cdot}2$ turns min^{-1} at 5 mg kg^{-1} (n = 6); $2{\cdot}6 \pm 0{\cdot}3$ turns min^{-1} at 10 mg kg^{-1} (n = 6) and $3{\cdot}3 \pm 0{\cdot}4$ turns min^{-1} at 25 mg kg^{-1} (n = 6). No turning was observed after 50 mg kg^{-1} of bromocriptine and animals appeared sedated after this dose.

Although each compound also produced stereotyped behaviour, mainly sniffing, no detailed analysis of this was undertaken but its onset and duration was similar to the rotational behaviour. That this stereotyped behaviour did not interfere significantly with rotational behaviour was evident from the dose-dependent increase in rotation observed over the range of concentrations used. Both the rotational and stereotyped behaviour produced by each agent could be reduced or abolished by the injection of haloperidol (0·5 mg kg^{-1}, i.p.) administered either before or after the injection of each agent.

Rotational behaviour was also assessed after combined injections of apomorphine or amphetamine plus bromocriptine. The concentrations chosen for this study, by themselves, produced turning behaviour which was clearly submaximal. When bromocriptine (10 mg kg^{-1}) was administered together with apomorphine (2 or 4 mg kg^{-1}) to animals that had previously been tested with each compound individually, a significant reduction in rotation was observed ($P<0{\cdot}001$, n = 6) during the time that apomorphine had previously been most effective (mean turns min^{-1} apomorphine 2 mg = $0{\cdot}2 \pm 0{\cdot}05$: 4 mg = $3{\cdot}4 \pm 0{\cdot}5$) (Fig. 1A). After 60 min animals circled at the same rate as that observed with bromocriptine alone (Fig. 1A). When apomorphine (2 or 4 mg kg^{-1}) was administered some 60 min after a bromocriptine injection, at a time when bromocriptine-induced rotation had begun, the intensity of apomorphine-induced rotation was reduced as before. Recovery of apomorphine-induced rotation could be observed after some 5 h when the effects of bromocriptine were declining. At each dose combination animals moved freely and no sedation or catatonia, sometimes observed after higher doses of apomorphine (>8 mg kg^{-1}) or bromocriptine (50 mg kg^{-1}), was seen. In addition these combined doses did not produce marked differences in stereotyped behaviour which still consisted mainly of sniffing and this was not of sufficient intensity to interfere with rotational behaviour.

In contrast when bromocriptine (10 mg kg^{-1}) was given together with amphetamine (2 or 4 mg kg^{-1}) an increase in turning was produced which was significantly ($P>0{\cdot}01$, n = 6) greater than that produced by each compound administered individually to the same animals (mean turns amphetamine 2 mg = $4{\cdot}3 \pm 0{\cdot}6$; 4 mg = $4{\cdot}8 \pm 0{\cdot}2$) (Fig. 1B). A similar degree of enhanced amphetamine-induced rotation could also be observed if this compound was administered after bromocriptine-induced rotation had begun.

In the final experiments, amphetamine (2 or 4 mg kg^{-1}) was administered with apomorphine (2 or 4 mg kg^{-1}, n = 6). The intensity of turning behaviour at each dose combination was identical to that observed with apomorphine alone. Animals were tested at weekly intervals (3 weeks) with each drug combination as described previously and similar interactions were observed on each occassion.

These observations confirm previous reports (Corrodi & others, 1973; Fuxe & others, 1974; Dray & others, 1975; Pieri & others, 1975; Johnson & others, 1976) that in appropriate animal models bromocriptine produces similar behaviour to that produced by apomorphine. In addition the effects produced by bromocriptine may be reduced or abolished by the dopamine-receptor antagonists haloperidol or pimozide (Corrodi & others, 1973; Johnson & others, 1976). This evidence is therefore compatible with a direct dopamine-receptor stimulant action by bromocriptine.

The prolonged latency of rotational and stereotyped behaviour observed with bromocriptine has not been satisfactorily explained. However its penetration into the brain cannot be in doubt since in the present experiments bromocriptine was able to reduce apomorphine but enhance amphetamine-induced rotation during this latency. Moreover these interactions with apomorphine or amphetamine cannot be attributable to any observed behaviour induced by bromocriptine though similar interactions may also be seen at times when bromocriptine does produce behaviour changes.

Clearly the difference in the interactions of bromocriptine with apomorphine- or amphetamine-induced rotational behaviour suggests possible complex effects on dopaminergic neurotransmission. These effects may include a partial-agonism at post synaptic sites or an action on presynaptic terminals affecting dopamine release. That bromocriptine does not induce behaviour changes when brain dopamine is depleted (Corrodi & others, 1973; Fuxe & others, 1974) suggests an important involvement of endogenous dopamine. Moreover recent observations suggest that intact granular amine stores are required for bromocriptine to bring about its effects (Johnson & others, 1976).

While the present experiments do not allow a clear cut distinction to be made regarding the precise mode of action of bromocriptine, its ability to stimulate central dopamine receptors certainly appears to differ from that of apomorphine.

This work was supported by an MRC Programme Grant to Professor D. W. Straughan. We would like to thank Dr W. P. Maclay and the late Dr E. R. Evans of Sandoz Products Ltd. for gifts of bromocriptine.

March 17, 1976

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Effects of prostaglandin E_2 methyl analogues on the anti-inflammatory and gastric erosive activity of indomethacin

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The inhibition of prostaglandin synthesis has been proposed as a mechanism for both the anti-inflammatory actions (Vane, 1971) and gastrointestinal side effects (Robert, 1974; Main & Whittle, 1975a) of non-steroid anti-inflammatory drugs. Prostaglandins E_1 and E_2, on local administration, potentiate carrageenan-induced oedema formation in the paw of rats pretreated with indomethacin (Moncada, Ferreira & Vane, 1973). These prostaglandins (PGs), when administered systemically, can also inhibit the formation of rat gastric mucosal erosions induced by indomethacin (Whittle, 1975). In the present study, we have investigated whether the potent gastric-antisecretory methyl analogues of PGE_2 (Robert & Magerlein, 1973; Main & Whittle, 1975b), in doses which inhibit erosion formation, also inhibit the reduction of rat paw oedema by indomethacin.

Oedema formation in the hind paw of male Wistar rats (180–210 g) was induced by injecting 0·1 ml of a carrageenan suspension (Marine Colloids, batch RE 7179; 2% in saline) into the subplantar region. The change in volume of the paw was measured every 45 min with a mercury displacement plethysmograph connected to a transducer-pen recorder system (Van Arman, Begany & others, 1965). Prostaglandins, stored in methanol (—5°) and made up freshly in aqueous solution as required, were injected either locally (0·1 ml) into the hindpaw, or subcutaneously into the flank. Indomethacin (10 mg ml^{-1}) was dissolved in 5% w/v $NaHCO_3$ solution (pH 8) and immediately injected subcutaneously. The formation of gastric erosions following indomethacin administration to fasted (18 h) rats was assessed as described previously (Main & Whittle, 1975a) and expressed as an erosion index.

Administration of carrageenan caused a rapid increase in paw volume (of 660 ± 154 μl after 3h, mean ± s.e.m.; n = 5). In rats pretreated with indomethacin (20 mg kg^{-1}, s.c., 1 h before carrageenan) the increase in paw volume was significantly less (133 ± 31 μl, n = 16; $P<0{\cdot}01$). This oedema formation was maximal after 3 h in rats given carrageenan alone, whereas in those pretreated with indomethacin, plateau values were obtained after 1 h, and remained steady over the next 4 h. Local administration of PGE_2 (0·1–1·0 μg), into the hind paw, 2·25 h after carrageenan administration to indomethacin-pretreated rats caused dose-dependent increases in paw volume (Table 1), whereas there was no significant change following local saline (0·1 ml) administration. These results confirm the finding of previous workers (Moncada & others, 1973; Smith, Ford-Hutchinson & others, 1974; Lewis, Nelson & Sugrue, 1975) that prostaglandins of the E series can increase rat paw oedema.

Similarly, local administration of (15S)-15-methyl PGE_2 methyl ester or 16,16 dimethyl PGE_2 (0·1–1·0 μg) significantly increased rat paw oedema, and appeared to be less potent than PGE_2 in the range investigated. In contrast, systemic administration of the (15S) or 16,16-dimethyl PGE_2 analogues (5–20 μg kg^{-1}, s.c.) had no significant effect on paw oedema (Table 1).

Indomethacin, in the anti-inflammatory doses used in these experiments (20 mg kg^{-1}, s.c.), caused a time-dependent rise in the incidence and severity of gastric mucosal erosions, as reported previously (Main &

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