European Journal of Pharmacology, 37 (1976) 295—302

ERGOT ALKALOIDS AS DOPAMINE AGONISTS: COMPARISON IN TWO RODENT MODELS

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Received 18 December 1975, revised MS received 20 February 1976, accepted 26 February 1976

G. ANLEZARK, C. PYCOCK and B. MELDRUM, *Ergot alkaloids as dopamine agonists: comparison in two rodent models*, European J. Pharmacol. 37 (1976) 295—302.

A series of ergot alkaloids, together with the DA agonists apomorphine and piribedil, were tested for protective effects against audiogenic seizures in an inbred strain of mice (DBA/2) and for induction of circling behaviour in mice with unilateral destruction of one nigrostriatal DA pathway. The order of potency against audiogenic seizures was apomorphine > ergocornine > bromocryptine > ergometrine > LSD > methysergide > piribedil while that observed in the rotating mouse model was apomorphine > ergometrine > ergocornine > bromocryptine > piribedil. LSD caused only weak circling behaviour even when administered in high doses (> 1 mg/kg). Methysergide was ineffective. Prior administration of the neuroleptic agent haloperidol blocked the effect of DA agonists and of ergot alkaloids in both animal models. The possible action of ergot alkaloids as DA agonists is discussed.

Ergot alkaloids Audiogenic seizures Dopamine agonists Circling behaviour

1. Introduction

The pharmacology of the ergot alkaloids is complex and not well understood. Peripherally, they act on smooth muscle as 5-hydroxytryptamine (5-HT) antagonists (Goodman and Gilman, 1971) and as α-adrenergic blockers (Nickerson and Hollenberg, 1967). Centrally there is evidence for both agonist and antagonist actions of ergot alkaloids on the 5-HT neurones (Aghajanian, 1972; Hamon et al., 1974; Corrodi et al., 1975). Recently, a possible action of these agents on the catecholamine synapses of the brain has been emphasised (Stolk et al., 1974). Direct dopamine (DA) receptor agonist activity has been suggested for several of these compounds from behavioural (Fog, 1969; Fuxe et al., 1974; Pieri et al., 1974) and biochemical (von Hungen et al., 1974; Da Prada et al., 1975) experiments.

We have therefore studied the activity of a series of ergot derivatives, together with other drugs thought to act as agonists at dopaminergic synapses, in two rodent pharmacological models. The first model studied is 'audiogenic' seizures in genetically susceptible mice. The severity of the seizure responses to auditory stimulation can be modified by a variety of drugs believed to act on monoaminergic transmission in the brain (Lehmann, 1970). We have previously reported that 'audiogenic' seizures can be diminished or blocked by apomorphine and ergocornine (Anlezark and Meldrum, 1975). The second model, contraversive rotation in mice with a unilateral lesion of the nigro-neostriatal tract produced by 6-hydroxydopamine, is widely used to evaluate DA agonist and antagonist activity. Rotational behaviour occurs as the result of an imbalance of activity of the dopaminergic receptors of the two striata. Directly acting DA agonists are believed to stimulate preferentially the presumed supersensitive receptors on the denervated side and thus induce rotational activity away from the side of the lesion (Ungerstedt, 1971).

2. Materials and methods

2.1. DBA/2 mice

DBA/2 mice (Fisons Pharmaceuticals Ltd), 21—28 days old and weighing between 7 and 13 g, were placed under a perspex dome (diameter 58 cm) and 30 sec were allowed for habituation. Auditory stimulation was provided by a bell (Friedland Chimes, 3 inch diameter, generating 109 dB at the level of the mouse) for 60 sec or until tonic extension occurred.

Groups of 5 or 10 mice of either sex were injected i.p. with vehicle or drug solution to give a maximum volume equivalent to 0.1% of the body weight of the mouse. Tests were carried out 20 min after apomorphine (0.08—10 mg/kg), 30 min after LSD-25 (0.15—10 mg/kg) and ergometrine (0.4—20 mg/kg), 45 min after ergocornine (0.5—8 mg/kg) and methysergide (5 and 20 mg/kg) and 60 min after piribedil (0.8—100 mg/kg) and 2-Br-α-ergocryptine (1—25 mg/kg). The times chosen represent the periods when maximal behavioural effects were observed.

The effect of haloperidol (0.5 mg/kg, 40 min before testing) on the responses obtained after apomorphine (1 mg/kg) and ergocornine (2 mg/kg) was also tested.

The maximum seizure response for each animal was recorded according to the following scale: 0 = no response, 1 = wild running, 2 = clonic phase, 3 = tonic phase, 4 = respiratory arrest. The latency in sec to each phase of the seizure was also noted.

Each animal was used in only one experiment. The ED_{50} for each drug was calculated as the dose required to block the clonic phase in 50% of the mice. Statistical comparisons were made using Student's *t*-test or χ^2 where appropriate.

2.2 Unilaterally lesioned mice

Unilateral destruction of nigrostriatal DA terminals was achieved in male Swiss 'S' mice by the direct injection of 16 μg 6-hydroxydopamine (Sigma) dissolved in 4 μl of 0.9% saline containing 0.2 mg/ml ascorbic acid into one striatum as previously described (Von Voigtlander and Moore, 1973). Mice were tested 10 days after operation with 2 mg/kg apomorphine and only animals turning tightly away from the side of the lesion were selected for the following series of experiments.

Groups of 20 randomly selected mice were used to investigate the potencies of a series of systemically administered compounds to induce contraversive circling behaviour. After injection of stimulant or vehicle all mice were placed in individual plastic cages, measuring 12 × 12 cm. The number of complete revolutions made in a 1-min period was recorded 20 min after apomorphine, LSD or methysergide, 30 min after piribedil or ergometrine and 60 min after ergocornine and bromocryptine. The times chosen represent the periods when maximal rates of circling were observed.

An incomplete Latin square design was used to distribute 4—7 doses of each stimulant drug plus one of solvent to 20 lesioned animals. Animals were tested 3 times on alternate days over a 5 day period so that a minimum of 10 observations was made for each dose of drug. Apomorphine was administered in the dose range 0.25—4 mg/kg, ergocornine and ergometrine in the range 2.5—20 mg/kg, bromocryptine (range 2.5—40 mg/kg), piribedil (range 5—40 mg/kg), methysergide (range 0.5—4 mg/kg), and LSD in the dose range 0.025—1.5 mg/kg.

The effect of pretreatment with haloperidol on circling induced by a single dose of stimulant was studied. 10 mice from each group of 20 animals were randomly selected and injected with 0.5 mg/kg haloperidol 15 min prior to the stimulant drug. 10 control animals received saline. All animals then received a single dose of each stimulant agent — apomorphine (2 mg/kg), LSD (1.5 mg/kg), ergocornine and ergometrine (10 mg/kg) and bromocryptine and piribedil (20 mg/kg) — and circling rates were observed after the specific time interval as previously described.

2.3. Drugs

Apomorphine hydrochloride (Evans Medical) and haloperidol (Serenace, Searle) were diluted with 0.9% saline. Piribedil (ET 495; l-3,4-methylene-dioxybenzyl-4-(2-pyrimidinyl)-piperazine-methane sulphonate, Servier Laboratories), d-lysergic acid diethylamide tartrate (Sandoz), methysergide bimaleate (Sandoz), and ergometrine maleate (Sigma) were dissolved in saline. Ergocornine hydrogenmaleinate (Sandoz) and 2-bromo-α-ergocryptine methane sulphonate (CB 154, bromocryptine, Sandoz) were dissolved with an equal amount of tartaric acid crystals in a few drops of 70% ethanol and made up to volume with warm saline. All drug doses were injected i.p. and are expressed as weight of salt.

3. Results

3.1. Audiogenic seizures in DBA/2 mice

The mean latencies in sec (±S.E.) to each phase of the seizure response after saline or vehicle were: wild running 1.1 ± 0.1, clonic phase 7.4 ± 0.6, tonic phase 10.4 ± 0.7 and respiratory arrest 23.2 ± 0.8. The mean seizure response score (±S.E.) was 3.5 ± 0.1.

All the drugs tested, with the exception of piribedil and methysergide, gave a dose-related protection against seizures induced by auditory stimulation (fig. 1). The effects of apomorphine and ergocornine have already been described (Anlezark and Meldrum, 1975) and these two drugs were the most potent, their ED_{50}'s being 0.7 and 1.1 mg/kg respectively (see table 1). Haloperidol (0.5 mg/kg) injected 40 min before testing blocked the protective effects of apomorphine (1 mg/kg) and ergocornine (2 mg/kg) and the stereotyped head movements and sniffing induced by these drugs. Seizure response after apomorphine alone was significantly different from that after saline (χ^2 14.4, $p < 0.05$) or haloperidol plus apomorphine (χ^2 21.5, $p < 0.001$). The seizure responses seen after haloperidol alone and haloperidol plus apomorphine were not significantly different from those seen after saline.

The next most potent drugs in blocking the

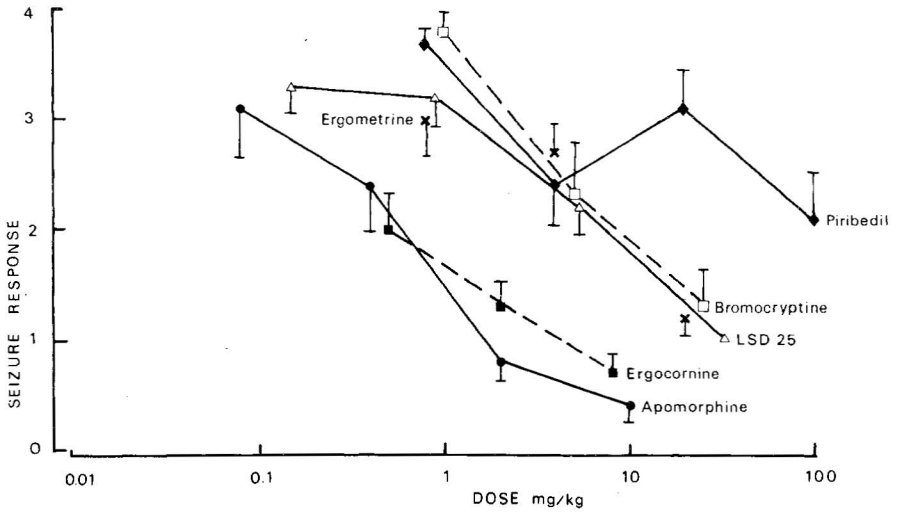

Fig. 1. Effects of apomorphine, piribedil and some ergot alkaloids on audiogenic seizure response score in 21—28 day old DBA/2 mice. Each point is the mean of 5 or 10 animals. Vertical bars represent standard erros.

TABLE 1

ED_{50} of drugs reducing audiogenic seizure response and inducing contraversive circling (rate 4 turns per min) in mice.

Drug	Seizure response		Circling	
	mg/kg	μmoles/kg	mg/kg	μmoles/kg
Apomorphine	0.7	2.2	0.6	1.9
Ergocornine	1.1	1.6	7.5	10.9
Ergometrine	4.0	9.1	6.0	13.6
Bromocryptine	5.0	6.7	25.0	33.3
LSD-25	9.3	28.8	>1.5	4.6
Methysergide	20.0	32.2	>4	6.4
Piribedil	100.0	336.7	>40	134.7

seizure response were ergometrine, bromocryptine and LSD-25, with ED_{50}'s of 4.0, 5.0 and 9.3 mg/kg respectively. Ergometrine (4 and 20 mg/kg) induced piloerection and marked hyperactivity. After the highest dose the seizure response was significantly decreased (χ^2 21.9, $p < 0.001$). Ergometrine significantly delayed the onset of some of the phases of the seizure response at lower doses, (e.g. after 0.8 mg/kg, wild running onset was at 2.8 ± 0.5 sec, $n = 10, p < 0.0025$), but the onset of wild running after 20 mg/kg was not delayed, presumably due to the hyperactivity induced. LSD-25 also induced hyperactivity in the mice beginning only 10—20 sec after injection of 5.4 and 10 mg/kg. Sniffing and stereotyped head movements were also seen. The tonic and clonic phases were significantly delayed after 5.4 mg/kg (tonic phase: 10.2 ± 0.4 sec, $n = 5$, $0.05 < p < 0.1$ and clonic phase: 14.0 ± 4 sec, $n = 2$, $0.05 < p < 0.1$). However, all the mice showed wild running even after 10 mg/kg as they did following ergometrine 20 mg/kg.

Bromocryptine induced ptosis and sedation 30 min after injection of 5 and 20 mg/kg and no stereotyped behaviour was seen. However, all the mice were capable of running and showed spontaneous locomotor activity during the habituation period. The phases of the seizure response were delayed after both these doses, for example, the clonic phase was delayed until 10.6 ± 1 sec, $n = 5$, $p < 0.0005$ after 5 mg/kg, and until 15.0 ± 5 sec, $n = 2$, $p < 0.0005$ after 25 mg/kg. No increases in latency were seen after 1 mg/kg. A significant decrease in seizure response however was observed only after 25 mg/kg (χ^2 22.7, $p < 0.001$).

Only two doses of methysergide were used, 5 and 20 mg/kg. Seizure response scores after these two doses were 2.3 ± 0.3 and 1.7 ± 0.5 respectively (omitted from fig. 1 for clarity). At neither dose did the decrease in seizure response reach significance. As previously described piribedil was not effective in protecting the mice against audiogenic seizures (Anlezark and Meldrum, 1975). An ED_{50} could not be calculated as 50% of the mice showed a tonic phase after 100 mg/kg (the highest dose used).

The order of potency to block seizure activity is shown in table 1.

3.2. Circling behaviour

The mean circling rates produced by various doses of the stimulant drugs are shown in fig. 2. All agents, except methysergide, produced circling away from the side of the lesion in keeping with the concept of preferential stimulation of the presumed supersensitive denervated striatal DA receptors. Injection of vehicle caused no contraversive cir-

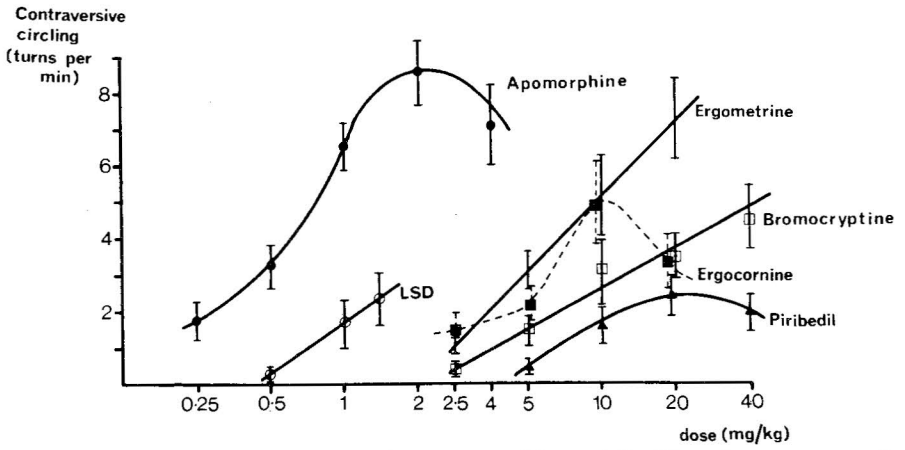

Fig. 2. Log dose—response curves for apomorphine, piribedil and some ergot alkaloids to induce contraversive circling behaviour in mice with unilateral destruction of nigrostriatal DA terminals. Each point represents the mean of at least 10 observations. Vertical bars represent standard errors.

cling: occasionally weak ipsiversive turning was observed. Apomorphine produced circling of highest intensity which decreased slightly at the highest dose (4 mg/kg) when the animals showed more stereotyped behaviour. Methysergide (0.5—4 mg/kg) and the lower range of LSD (0.025—0.2 mg/kg) did not induce any turning behaviour; circling only became apparent after LSD in about 40% of animals at the 1 and 1.5 mg/kg doses. The strong contraversive circling behaviour induced by apomorphine, ergocornine, ergometrine and bromocryptine was also accompanied by a striking body asymmetry away from the side of the lesion: piribedil and LSD produced no such body posture. Piribedil only produced moderate contraversive turning in the order of about 2 turns per min. The order of drug potency in the turning mouse model (to achieve 4 turns per min) was apo-

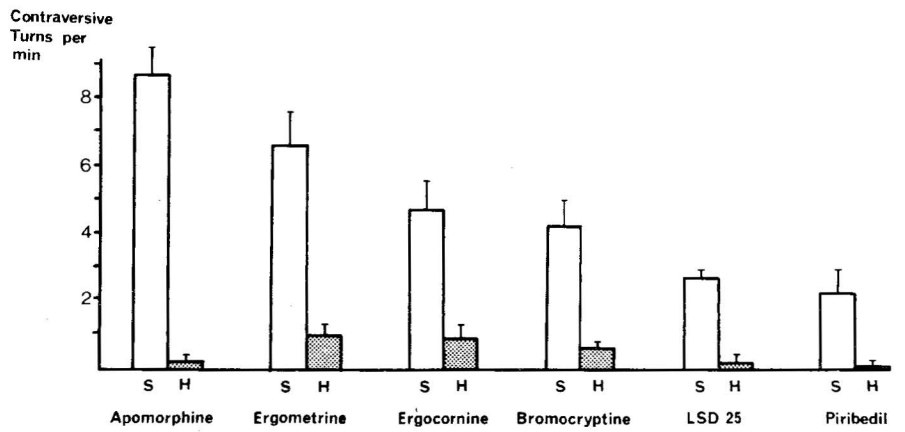

Fig. 3. Inhibition of contraversive circling behaviour induced by apomorphine, piribedil and some ergot alkaloids by pretreatment with haloperidol (0.5 mg/kg, 15 min). Each column represents the mean of 10 observations. Vertical bars represent standard errors. The open columns show the circling response after pretreatment with saline (S); the hatched columns show the response after haloperidol (H).

morphine > ergometrine > ergocornine > bromocryptine (table 1). LSD and piribedil did not achieve this level of activity at the highest doses used.

Pretreatment with haloperidol (0.5 mg/kg) blocked the turning response to all stimulant drugs (fig. 3). In all cases the rate of contralateral circling was reduced to between 5—20% of control values.

4. Discussion

The above experiments show that the ergot alkaloids studied cause contraversive rotation in mice with unilateral destruction of the nigrostriatal DA system and protect DBA/2 mice against audiogenic seizures. Apparently, both behavioural effects can be the result, at least in part, of direct DA receptor stimulation (Ungerstedt, 1971; Anlezark and Meldrum, 1975). This hypothesis is supported by the observation that the neuroleptic agent, haloperidol, a drug known to block central dopaminergic transmission (Andén et al., 1970), reduced the actions of ergot alkaloids and of known DA agonists in both these models.

Biochemical measurements showing a decrease in DA turnover after various ergot alkaloids (Fuxe et al., 1974), and behavioural observations, including increased turning following ergocornine in rats with unilateral substantia nigra lesions (Fuxe et al., 1974), increased locomotor activity following ergometrine (Woodruff et al., 1974) and decreased tremor in monkeys with ventromedial tegmental lesions after bromocryptine (Miyamoto et al., 1974) have all been interpreted as showing a DA agonist action of ergot alkaloids. Support for such activity is provided by the clinical improvement in Parkinson's disease seen after bromocryptine (Calne et al., 1974). Additionally, ergot alkaloids can lower plasma prolactin by stimulating the secretion of prolactin inhibiting factor from the anterior pituitary (Floss et al., 1973), an effect also seen after administration of L-DOPA (Lu and Meites, 1971) and apomorphine (Horowski et al., 1975). Bromocryptine and apomorphine have also been shown to lower the core temperature in rats (Kruk, 1972; Calne et al., 1975). The effect of bromocryptine can be blocked by pimozide.

An interaction of LSD with the DA synapse has only recently been suggested on the basis of a decrease in cerebral homovanillic acid concentration and increased turning behaviour (Pieri et al., 1974; Da Prada et al., 1975). The doses required to cause presumed DA receptor stimulation are high (above 1 mg/kg) and it is difficult to assess the specificity of the reaction. However, LSD has been shown to activate the DA-sensitive adenyl cyclase system (Da Prada et al., 1975; Spano et al., 1975), an enzyme closely associated with the DA receptors (Iversen, 1975).

These data and the work presented here all suggest that the ergot alkaloids possess DA agonist activity. The order of potency obtained in our experiments is apomorphine > LSD-25 > ergometrine > ergocornine > bromocryptine > piribedil for turning and apomorphine ≥ ergocornine > bromocryptine ≥ ergometrine > LSD > methysergide >> piribedil for audiogenic seizures. Apomorphine, therefore, was the most potent drug in both models and piribedil the least potent. In between these two the ergot alkaloids showed varying potencies. A possible explanation for these results lies in the central serotonergic actions of these drugs. In the audiogenic mouse model an increase in cerebral serotonin leads to a decrease in seizure susceptibility and vice versa (Lehmann, 1970; Boggan and Seiden, 1973), whereas in the turning rodent model, rate of turning is increased after inhibition of serotonin synthesis (Baldessarini et al., 1975; Milson and Pycock, 1976). This may explain the difference in potency of ergocornine in the two models as this drug has recently been shown to act as an agonist at central serotonergic synapses (Corrodi et al., 1975). Its potency is almost equal to that of apomorphine in blocking audiogenic seizures, but ten times less potent than apomorphine in

inducing rotation. Its additional potency against seizures may be due to serotonin receptor stimulation. An interaction with serotonergic systems may also explain the position of LSD-25 in table 1. LSD acts as a 5-HT agonist in several areas which receive a serotonergic input and also at serotonin containing cell bodies in the nuclei of the median raphe (where firing is inhibited by both 5-HT and LSD) (Aghajanian, 1972; Haigler and Aghajanian, 1974). That such a pre-synaptic action of LSD (i.e. decreasing firing of 5-HT containing neurones) is significant, is suggested by the greater potency in enhancing turning relative to the prevention of audiogenic seizures.

We have endeavoured to compare a series of potential dopamine agonists in two rodent behavioural models. We are, however, presumably observing a normal dopaminergic synapse in the audiogenic mouse and comparing this with a synapse rendered supersensitive by a previous injection of 6-hydroxydopamine in the circling model. Thus, if these DA agonists possess presynaptic releasing properties this effect will only occur in the audiogenic seizure model. Similarly, if 6-hydroxydopamine pretreatment has in some way altered the reactivity of the effector cells not only to DA agonists but to other receptor agonists this will only be reflected in the circling model. As in the latter case, the 5-HT agonist or antagonist properties of the ergot alkaloids may be non-specifically effective in the denervated striatum, whereas they may be unimportant in the seizure model.

Piribedil displayed only weak activity in these models, although it has been reported as causing moderate circling in rodents (Thornburg and Moore, 1974; Costall and Naylor, 1974). That methysergide was inactive in these models may be the result of its poor capacity to cross the blood—brain barrier (Doepfner, 1962), but there is evidence that it does not stimulate adenyl cyclase activity (Von Hungen et al., 1975).

Action as DA agonists appears to provide part of the explanation for the enhanced turning in mice with unilateral lesions of the nigrostriatal tract and for the reduced susceptibility to audiogenic seizures in DBA/2 mice seen after LSD, bromocryptine, ergocornine and ergometrine.

Acknowledgements

We are grateful for financial support from the Wellcome Trust. Chris Pycock is a Fellow of the Parkinson's Disease Society. We thank Sandoz Ltd. for generous gifts of drugs, and Mr. Colin Brewer for expert technical assistance

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