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Further Investigations on the Effects of Ergometrine and Other Ergot Derivatives Following Injection into the Nucleus Accumbens of the Rat

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Abstract—The influence of different pretreatments upon locomotor stimulation, induced by injection of ergometrine into the nucleus accumbens of rats, was investigated. The noradrenergic antagonists phenoxybenzamine and propranolol and the serotonin antagonist methysergide produced no clear changes. Reserpine, alone or in combination with α-MPT, considerably shortened the delay between injection of ergometrine and start of locomotor stimulation. Ro-DOPA, but not Ro-5-HTP, clearly antagonized the locomotor stimulation. The effect of ergometrine was strongly diminished following injection of haloperidol directly into the nucleus accumbens. A strong inhibition was also observed following intracerebral administration of the imidazoline derivative (3,4-dihydroxy-phenylamino)-2-imidazoline (DPI), but not after injection of the structurally related compound clonidine. DPI by itself and also the ergot derivatives ergocornine, bromocryptine, LSD, dihydroergotamine and methysergide in doses 5–10 times as high as that of ergometrine failed to produce locomotor stimulation following injection into the nucleus accumbens. The results are discussed, especially with regard to the role of dopamine.

Introduction

Recently we have reported that bilateral injection of ergometrine into the nucleus accumbens of rats produced a long-lasting stimulation of locomotor activity (1). This effect was similar to that following injection of dopamine into this nucleus after nialamide-pretreatment (2, 3) and could be antagonized by low doses of the neuroleptic drugs haloperidol and pimozide, but not by the

catecholamine synthesis-inhibitor α-methyl-*p*-tyrosine (1). Dopamine-like actions of ergometrine in the rat brain have also been suggested on the basis of studies on circling behaviour following unilateral 6-hydroxydopamine (6-OH-DA) lesions of the substantia nigra (4) and on stimulation of dopamine-sensitive adenylate cyclase (5). Also the inhibition of prolactin release by ergometrine (6, 7) may be caused by a dopamine-like action (8).

However, the mechanism of action of ergometrine may be more complex. Since ergometrine is a potent serotonin antagonist (9) and also has adrenergic stimulant properties (10) the possibility exists that these other monoamines might play an additional role in the above mentioned locomotor stimulant action of ergometrine. Furthermore, it is remarkable that no dopamine-like, but only dopamine blocking actions of ergometrine were found in studies on snail neurones (11–13), on the renal blood flow in the dog (14) and also on the cat brain (Cools, to be published; see also discussion).

The present study was performed, therefore, in order to investigate the role of some other neurotransmitters in the ergometrine-induced locomotor stimulation and to further explore the role of dopamine. Moreover, we wanted to study whether also other ergot derivatives, especially ergocornine and bromocryptine, which have been reported to possess dopamine agonistic properties in the rat brain (16) would produce locomotor stimulation following injection into the nucleus accumbens.

Methods

Intracerebral injections

Male Wistar rats were used, weighing 200 ± 20 g at the time of operation. Under sodium pentobarbital anaesthesia (40 mg/kg, i.p.) double barrelled stainless steel cannulae with an outer and inner diameter of 0.65 and 0.30 mm respectively were stereotaxically implanted into the nucleus accumbens. The injection sites chosen had the following coordinates, according to the atlas of König and Klippel (17): A9.4, L1.2 and H-0.6. Cannulae were brought in from the lateral side at an angle of 10° with the midsagittal plane in order to avoid the ventricular system and fixed on to the skull with acrylic dental cement (Paladur). Following surgery the rats were housed in individual cages with free access to food and water. Illumination was present from 6.00 a.m. to 6.00 p.m.

The experiments were started after a period of at least 10 days. During that period the rats were accustomed to handling and adapted to the activity cages. Intracerebral injections were given bilaterally (without anaesthesia) by means of a 5 μl Hamilton syringe with a 31 gauge needle, which extended into the brain tissue 1.0–1.5 mm below the tip of the permanently implanted cannula. The injection volume was always 0.5 μl on each side. At least 3 days of rest were given between the different treatments.

Measurement of locomotor activity

Locomotor activity of individual rats was measured in activity cages equipped with 3 photoelectric cells 2 cm above a grid floor. The dimensions of the cages were 36 cm × 24 cm × 25 cm. The interruptions of the lightbeams were registered on a cumulative Ralph-Gerbrands recorder. After an adaptation period of about 1 hr to the activity cages locomotor activity was continuously recorded during a period of at least 5 hr following the intracerebral injection.

Drugs

The following drugs were used: ergometrine maleate; 2-Br-α-ergocryptine methanesulphonate (CB 154, bromocryptine); ergocornine hydrogenmaleinate; dihydro-ergotamine mesylate; D-lysergic acid diethylamide (LSD); methysergide bimaleinate; phenoxybenzamine hydrochloride; *l*-propranolol; scopolamine hydrobromide; L-β-3,4-dihydroxyphenylalanine (L-DOPA); DL-5-hydroxytrypt ophan (5-HTP); N-(DL-seryl)-N′-(2,3,4-trihydroxybenzyl) hydrazine hydrochloride (Ro 4-4602); DL-α-methyltyrosine methylester hydrochloride (α-MPT); reserpine (Serpasil®); haloperidol (Serenase®); clonidine hydrochloride; apomorphine hydrochloride; (3,4-dihydroxy-phenylamino)-2-imidazoline (DPI).

The doses used refer to the form indicated above. Drugs were dissolved in saline, except ergocornine and bromocryptine, which were dissolved in 50 % propylene glycol. Since preliminary experiments had excluded a possible effect of the solvents of reserpine and haloperidol, these drugs were used in commercial form.

Histology

At the end of the experiments 0.5 μl of an ink solution was injected to verify the site of injection in the brain. The rats were perfused with saline and a 10 % formalin solution through the left cardiac ventricle under sodium pentobarbital anaesthesia. The brains were removed and kept in a 4 % formalin solution for at least 7 days and were then sectioned for control of the site of injection. In all animals the injection sites were found within the boundaries of the nucleus accumbens as depicted in the atlas of König and Klippel (17). The coordinates of the injection sites varied from 8.9 to 9.6 in anterior direction, from 0.6 to 1.6 laterally and from −0.2 to −1.2 in the depth.

Results

As also previously found (1) bilateral injection of ergometrine into the nucleus accumbens produced a strong stimulation of locomotor activity. When repeated injections of ergometrine were given with an interval of a few days the locomotor

stimulation was in general somewhat stronger at the 2nd or 3rd injection but then remained rather stable. Some rats, when injected with ergometrine a few days earlier, showed a clear locomotor stimulation upon administration of saline into the nucleus accumbens. It is likely that this effect of saline was produced by some residual ergometrine, since neither a 2nd injection of saline nor administration of saline before animals had received ergometrine did result in locomotor stimulation. In the present experiments, therefore, rats received at least 2 injections of ergometrine before the effects of other drugs were tested and between different treatments saline was administered into the nucleus accumbens.

Influence of various drugs upon ergometrine-induced locomotor stimulation

In the following experiments a standard dose of 1 μg of ergometrine was administered bilaterally.

As can be seen from Fig. 1A neither the α-adrenergic antagonist phenoxybenzamine (5 mg/kg, i.p.) nor the β-adrenergic antagonist propranolol (5 mg/kg, i.p.) profoundly influenced the effect of ergometrine. There was perhaps a slight initial depression, which was most clear in the case of propranolol.

Apart from a slight shortening of the duration of locomotor stimulation, also the serotonergic antagonist methysergide (5 mg/kg, i.p.) had no clear influence (Fig. 1B2). Ergometrine, which is by itself also a potent serotonin antagonist (9), does not produce locomotor stimulation when administered peripherally (1). Since one of the reasons might be that an effect upon the nucleus accumbens is masked by actions of ergometrine upon other sites, in another group of rats also the effect of ergometrine administered peripherally (2 mg/kg, i.p.) immediately after the central administration of ergometrine was investigated. Although locomotor stimulation was not inhibited, this combination proved very toxic; 8 of the 9 animals of this group died rather suddenly between 1 and 2 hr after the injection.

The anticholinergic agent scopolamine (1 mg/kg, i.p.) produced an initial enhancement of locomotor activity (Fig. 1B3). This effect was more pronounced with a high dose (15 mg/kg, i.p.) of scopolamine (data not shown).

As reported previously (1) the effect of ergometrine could not be inhibited by pretreatment with the catecholamine synthesis-inhibitor α-MPT. In the present experiments also pretreatment with the storage depleting agent reserpine (2 mg/kg, i.p.) did not inhibit the locomotor stimulation. On the contrary, the effect of ergometrine was rather potentiated and especially the time of latency was clearly reduced, nearly all animals showing strong stimulation of locomotor activity within 5–10 min after injection of ergometrine (Fig. 2A2). This immediate stimulation was also observed when reserpine was given in combination with α-MPT (100 mg/kg, i.p.) (Fig. 2A3). After completion of this experiment 4 animals of this group received further injections of ergometrine at weekly intervals. It was found thereby that the reduced time of latency persisted for at least 3 weeks after the last reserpine administration.

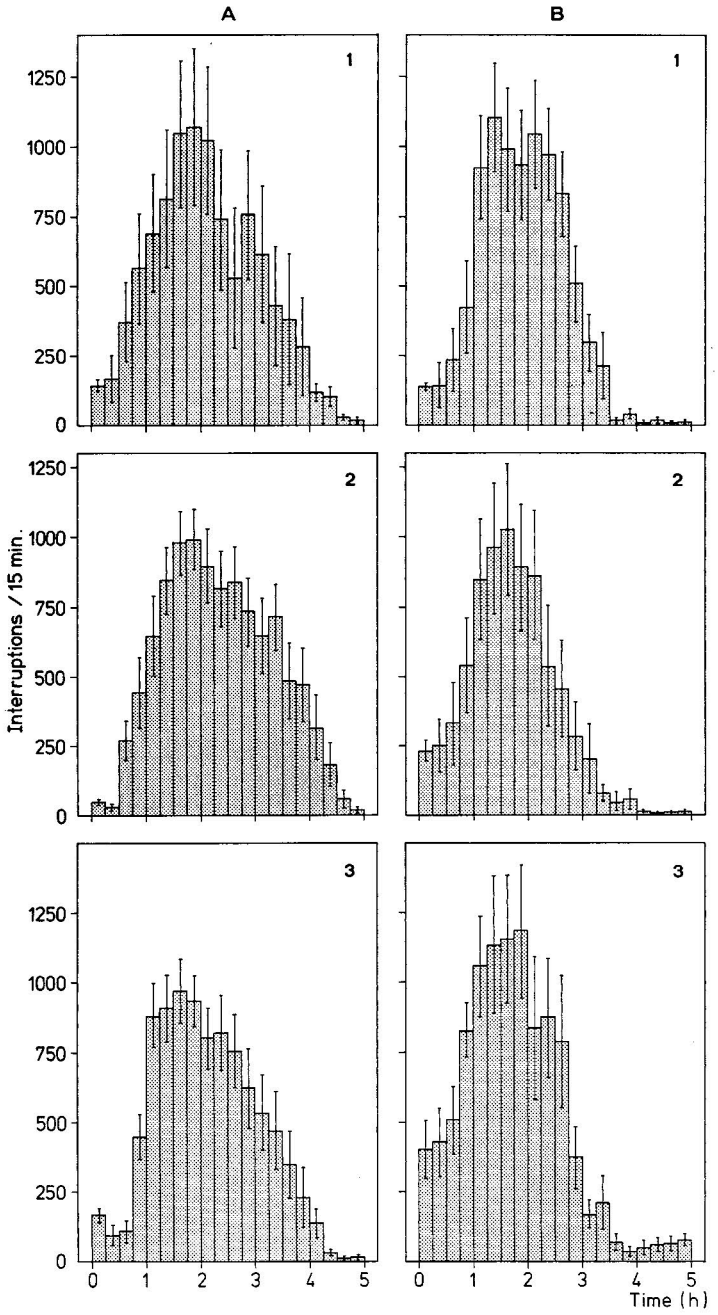

FIG. 1

Mean locomotor activity of rats following bilateral injection of 1 μg of ergometrine into the nucleus accumbens. Vertical bars represent S.E.M.; A and B refer to 2 different groups of rats. Ergometrine was administered at time 0.

A1: without pretreatment (9 rats); A2: 5 min after phenoxybenzamine 5 mg/kg, i.p. (9 rats); A3: 5 min after propranolol 5 mg/kg, i.p. (9 rats); B1: without pretreatment (9 rats); B2: 10 min after methysergide 5 mg/kg, i.p. (9 rats); B3: 10 min after scopolamine 1 mg/kg, i.p. (7 rats).

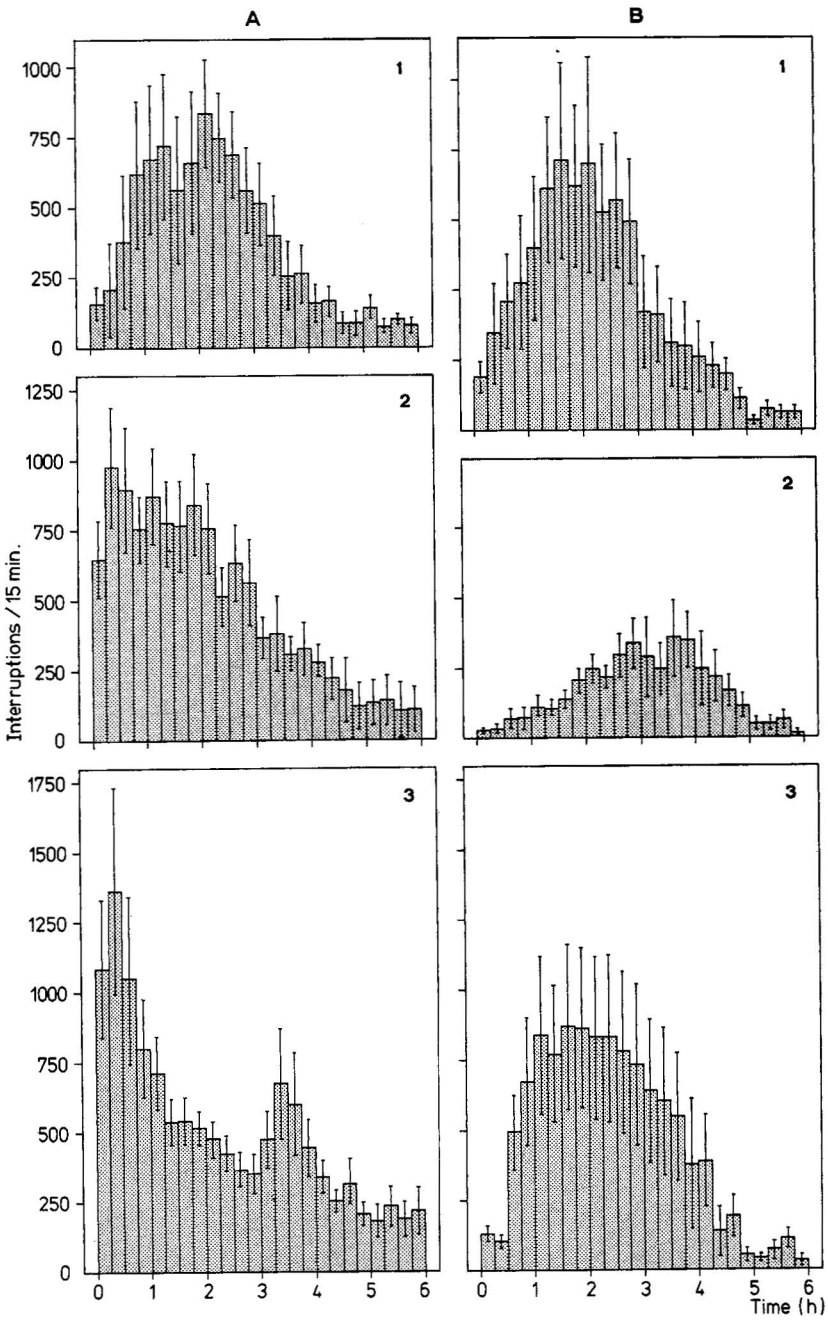

FIG. 2

Mean locomotor activity of rats following bilateral injection of 1 μg of ergometrine into the nucleus accumbens. Vertical bars represent S.E.M.; A and B refer to 2 different groups of rats. Ergometrine was administered at time 0.

A1: without pretreatment (9 rats); A2: 24 hr after reserpine 2 mg/kg, i.p. (8 rats); A3: 24 hr after reserpine 2 mg/kg, i.p. and 6 hr after α-MPT 100 mg/kg, i.p. (9 rats); B1: without pretreatment (4 rats); B2: 50 min after Ro 4-4602 50 mg/kg, i.p. and 20 min after L-DOPA 50 mg/kg, i.p. (4 rats); B3: 50 min after Ro 4-4602 50 mg/kg, i.p. and 20 min after DL-5-HTP 50 mg/kg, i.p. (4 rats).

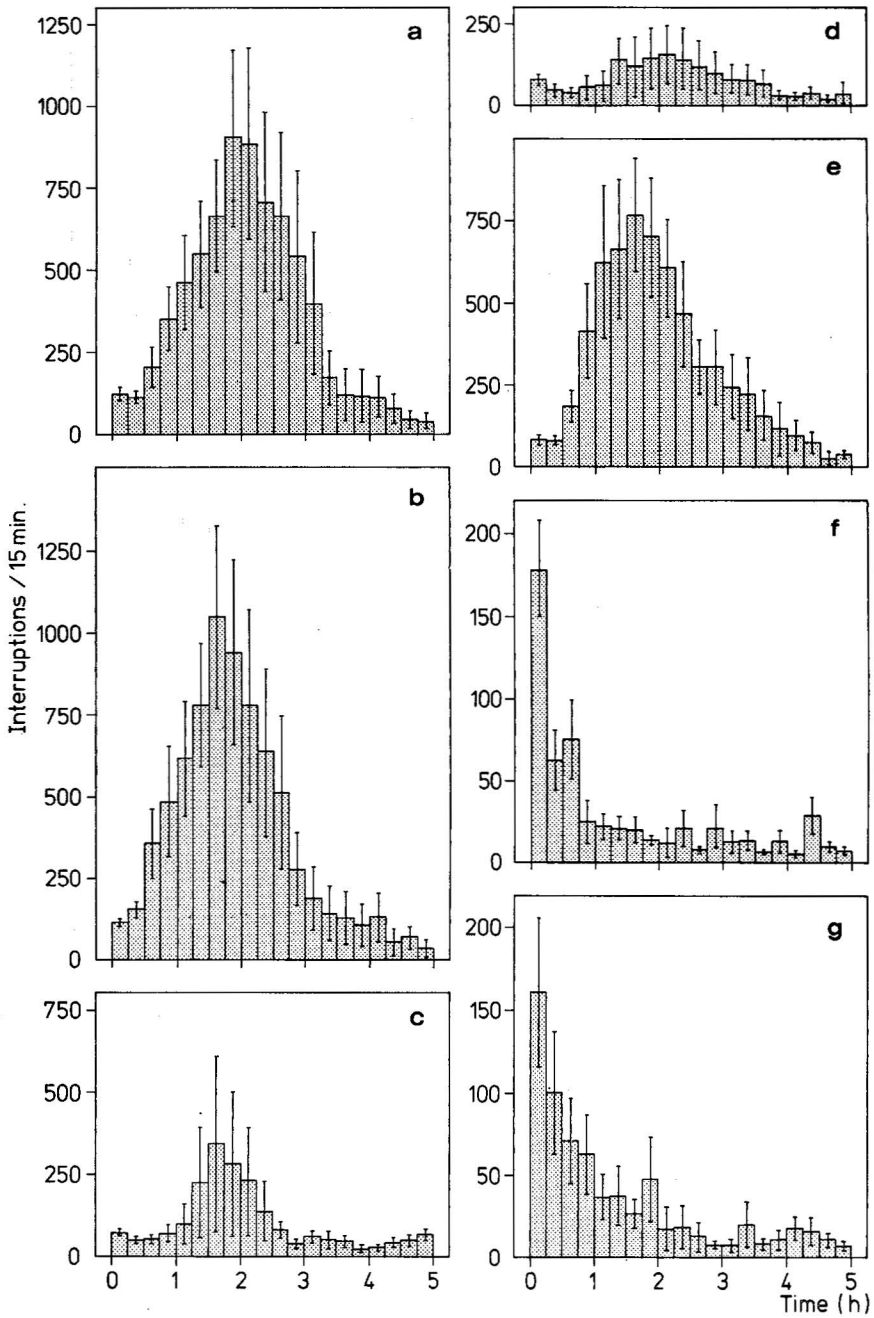

FIG. 3

Mean locomotor activity of rats following bilateral injections into the nucleus accumbens. Vertical bars represent S.E.M.

a) ergometrine, 1 μg (9 rats); b) ergometrine, 1 μg, 20 min after saline 0.5 μl (9 rats); c) ergometrine 1 μg, 20 min after haloperidol 2.5 μg (9 rats); d) ergometrine 1 μg, 20 min after (3,4-dihydroxy-phenylamino)-2-imidazoline (DPI) 5 μg (9 rats); e) ergometrine 1 μg, 20 min after clonidine 5 μg (8 rats); f) saline 0.5 μl (9 rats); g) DPI 5 μg (9 rats). In a)-e) ergometrine was administered at time 0. Note the different ordinate scale in f) and g).

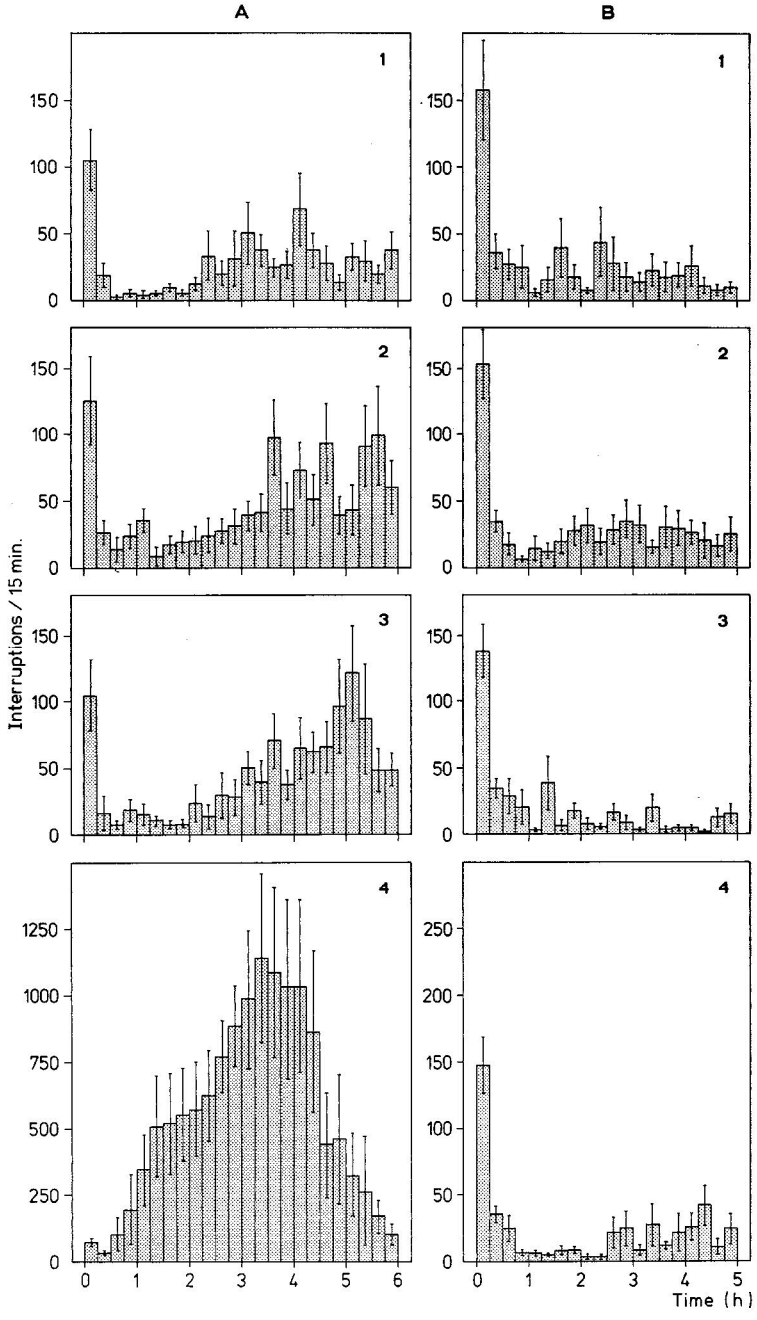

FIG. 4

Mean locomotor activity of rats following injections into the nucleus accumbens. Vertical bars represent S.E.M.; A and B refer to 2 different groups of rats. Injections were given bilaterally at time 0.

A1: 50 % propylene glycol 0.5 μl (9 rats); A2: ergocornine 10 μg (9 rats); A3: bromocryptine 10 μg (9 rats); A4: ergometrine 5 μg (9 rats); B1: saline 0.5 μl (9 rats); B2: LSD 5 μg (8 rats); B3: dihydro-ergotamine 5 μg (9 rats); B4: methysergide 5 μg (9 rats).

In A 50 % propylene glycol was used as solvent, in B saline.

Note the different ordinate scale in A4.

In Fig. 2B the effects of pretreatment with monoamine-precursors are shown. A clear reduction of locomotor stimulation, especially in the beginning phase, was seen when L-DOPA (50 mg/kg, i.p.) in combination with the peripheral DOPA-decarboxylase inhibitor Ro 4-4602 (50 mg/kg, i.p.) was given before ergometrine (Fig. 2B2). In these animals activity was already depressed at the moment of ergometrine injection. Inhibition of locomotor stimulation was not observed after pretreatment with 5-HTP (50 mg/kg, i.p.) in combination with Ro 4-4602 (Fig. 2B3). The influence of apomorphine was investigated in 3 other animals. Administration of apomorphine (2 mg/kg, i.p.) about 10 min after the onset of ergometrine-induced locomotor stimulation produced within 5–10 min stereotyped behaviour, characteristically restricted to the same place of the observation cage. After about 1 hr, when the stereotypy diminished, these animals resumed their enhanced locomotor activity.

We had already previously found that the effect of ergometrine was inhibited by peripheral administration of low doses of haloperidol (1). In the present study we found that the ergometrine-induced locomotor stimulation was also clearly reduced when haloperidol (2.5 μg bilaterally) was administered into the nucleus accumbens (Fig. 3c). Also injection of the imidazoline derivative DPI (5 μg bilaterally) into the nucleus accumbens strongly inhibited the effect of ergometrine (Fig. 3d), whereas this compound by itself had no clear effect upon locomotor activity (Fig. 3g). The structurally related compound clonidine (5 μg bilaterally) produced only a slight reduction of ergometrine-induced activity (Fig. 3e).

Intracerebral injection of other ergot derivatives

Since ergocornine and bromocryptine showed a poor water-solubility, these drugs were dissolved in 50 % propylene glycol. Injection of this solvent into the nucleus accumbens resulted in a depression of activity, followed by a slight stimulation (Fig. 4A1). Administration of 5 and 10 μg doses of ergocornine and bromocryptine hardly produced any locomotor stimulation. The effects of the 10 μg doses are shown in Fig. 4A2 and 4A3 respectively. Ergometrine, however, when dissolved in propylene glycol, produced a strong locomotor stimulation, although a depressant influence of the solvent seemed apparent, especially in the beginning phase. The other ergot derivatives tested were dissolved in saline. Doses of 2 and 5 μg of LSD, dihydroergotamine and methysergide did not produce a clear locomotor stimulation. The effects of the 5 μg doses are shown in Fig. 4B.

Discussion

In agreement with previous findings (1) bilateral injection of ergometrine into the nucleus accumbens resulted in a strong stimulation of locomotor activity. This effect was not or only slightly reduced by pretreatment with noradrenergic

or serotonergic antagonists. Since also pretreatment with Ro-5-HTP or para-chloro-phenylalanine (unpublished observation) did not clearly influence the effect of ergometrine and since also direct injections of noradrenergic agonists and serotonin into the nucleus accumbens did not produce locomotor stimulation in contrast to dopamine (18), it is unlikely that noradrenaline and serotonin play a major role in this effect of ergometrine. Although direct injection of the cholinergic stimulant carbachol produced enhanced activity (18), it is unlikely that the effect of ergometrine is brought about by cholinergic stimulation, since pretreatment with the anticholinergic agent scopolamine did not antagonize this effect.

Locomotor stimulation, which usually started with a delay of 30–60 min following the injection of ergometrine, started much earlier when the animals were pretreated with reserpine. This finding makes it unlikely that the delay is due to diffusion of ergometrine to a site, where it would be active, or due to the time necessary for the formation of an active metabolite. The fact that the ergometrine-induced locomotor stimulation was neither antagonized after depletion of monoamines with reserpine, nor after inhibition of catecholamine synthesis with α-MPT (1) may indicate a postsynaptic action. However, since Ro-DOPA clearly reduced the effect of ergometrine, especially in the beginning phase, and since reserpine shortened the delay, the possibility exists that also the presynaptic state (loaded or depleted stores) in an as yet unexplained way is important. Effects of Ro-DOPA and reserpine upon other brain sites, however, cannot be excluded at the moment. It must be remarked that with respect to the influence of reserpine and L-DOPA, ergometrine resembles apomorphine and also *d*-amphetamine. Reserpine has been reported to reduce the time to peak-activity in *d*-amphetamine-induced locomotor stimulation (19) and to potentiate the apomorphine-induced stereotyped behaviour (20), whereas L-DOPA has been found to reduce stereotyped behaviour, induced by apomorphine and *d*-amphetamine (21). Since, in agreement with our previous finding that the effect of ergometrine could be antagonized by peripheral administration of the dopamine antagonist haloperidol (1), also administration of haloperidol directly into the nucleus accumbens clearly reduced the effect of ergometrine, these results further suggest a dopamine stimulant effect of ergometrine.

It was therefore somewhat unexpected that other ergot derivatives failed to induce locomotor stimulation following injection into the nucleus accumbens. Ergocornine and bromocryptine have been reported to have effects on circling behaviour in rats with unilateral 6-OH-DA-induced lesions of the substantia nigra and on dopamine turnover, which are similar to those produced by the known dopamine agonist apomorphine (16). Also the inhibition of prolactin release produced by ergocornine, bromocryptine and other ergot derivatives (6, 7, 22) resembles that following administration of dopamine or apomorphine (8). Moreover, bromocryptine has been reported to be effective in Parkinson's disease (23, 24). Also LSD, but not BOL-148 and methysergide, produces contralateral turning in animals with unilateral 6-OH-DA lesions (25), whereas

both agonist and antagonist effects of LSD have been reported upon dopamine-stimulated adenylate cyclase (26–28). Although in most of these studies no direct comparison was made, ergocornine, bromocryptine and LSD seemed in general more potent than ergometrine in these models. Since in the present study doses 5–10 times as high as that of ergometrine were used, one would have expected an effect. A possible influence of the solvent propylene glycol upon the effects of ergocornine and bromocryptine cannot be excluded. However, although propylene glycol also suppressed the effect of ergometrine, locomotor stimulation was still produced.

Another finding, which indicates that the mechanism of action of ergometrine may be more complex, is the nearly complete inhibition of ergometrine-induced locomotor stimulation following the injection of the imidazoline derivative DPI into the nucleus accumbens. It is unlikely that the inhibition can be ascribed to the α-adrenergic stimulant properties of DPI (29), since a comparable dosis of the structurally related α-adrenergic agonist clonidine only slightly inhibited the effect of ergometrine. Because injection of DPI into the nucleus accumbens also inhibited locomotor stimulation, induced by peripheral administration of *d*-amphetamine (Cools, to be published) the question arises whether DPI could be considered as a dopamine antagonist. It was found, however, that DPI mimicked actions of dopamine both in the snail and in the cat brain. Studies on snail neurones have revealed the existence of more than one type of dopamine receptor. Excitatory respectively inhibitory actions of dopamine on neurones of the snail Helix aspersa are mimicked selectively by apomorphine respectively DPI, whereas neuroleptic drugs selectively antagonize the excitatory actions of dopamine (13, 30). Ergometrine is a very potent antagonist of the inhibitory actions of dopamine on these snail neurones (11–13) and also inhibits, although less potent, the excitatory actions of dopamine (Struyker Boudier, to be published). Also in the cat brain there is evidence for more than one type of dopamine receptor (15, 31). DPI and ergometrine mimick resp. block the action of dopamine in only one of two functionally distinct dopamine-sensitive areas in the caudate nucleus, whereas apomorphine and neuroleptic drugs have corresponding effects in the other dopamine-sensitive area (Cools, submitted for publication). Both in the snail brain and in the cat brain ergometrine was found to antagonize the actions of DPI. Although other actions of DPI at the moment cannot be excluded, the present results point to the possibility, that also in the rat brain there exist pharmacologically distinct dopamine actions. It must be remarked that DPI by itself did not produce locomotor stimulation following injection into the nucleus accumbens. In contrast, the tetralin derivative 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN), which mimicks not only the inhibitory (32) but also the excitatory (Woodruff, personal communication) actions of dopamine upon snail neurones, has been reported to produce a strong and long-lasting locomotor stimulation following injection into the nucleus accumbens (33).

In conclusion, although the locomotor stimulant effect of ergometrine, which

is similar to that of dopamine in nialamide-pretreated rats and which is inhibited by haloperidol, may suggest a dopamine agonistic action, the inhibition of the ergometrine effect by DPI and also the failure of other ergot derivatives to produce locomotor stimulation indicate that the mechanism of action of ergometrine may be more complex. Further investigations on the way, in which ergot derivatives and DPI interfere with dopaminergic systems in the rat brain, therefore, are needed.

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