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Inhibition of *d*-Amphetamine-Induced Locomotor Activity by Injection of Haloperidol into the Nucleus Accumbens of the Rat

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Abstract. The effect of intracerebral administration of antagonists of dopamine and noradrenaline upon the locomotor stimulation induced by intraperitoneal injection of *d*-amphetamine sulfate in rats was investigated. Injection of low doses of the dopamine antagonist haloperidol (2.5 μg and 5 μg) bilaterally into the nucleus accumbens antagonized the locomotor stimulation following *d*-amphetamine. No significant inhibition was observed following administration of the alpha-adrenergic antagonist phentolamine or the beta-adrenergic antagonist propranolol into the nucleus accumbens. Injection of the same doses of haloperidol into the caudate nucleus did not inhibit the *d*-amphetamine induced locomotor activity, in contrast to the effects seen following injection into the nucleus accumbens.

The results confirm the significance of dopaminergic mechanisms for the locomotor stimulant effect of *d*-amphetamine and indicate that the mesolimbic dopamine system plays an important role in this respect.

Key words: *d*-Amphetamine Sulfate – Dopamine Antagonist – Noradrenaline Antagonist – Nucleus Accumbens – Caudate Nucleus – Locomotor Activity – Haloperidol – Phentolamine – Propranolol.

Introduction

Pharmacological and biochemical studies have shown that brain catecholamines are involved in the central stimulant actions of amphetamine (Fuxe and Ungerstedt, 1970; Glowinski, 1970). At the moment there is still some controversy regarding the individual role of dopamine and noradrenaline.

The actions of *d*-amphetamine can be inhibited by the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine, which inhibits the synthesis of both dopamine and noradrenaline (Weissman and Koe, 1965; Weissman *et al.*, 1966; Randrup and Munkvad, 1966; Dominic and Moore, 1969; Scheel-Krüger, 1971). Inhibition of the synthesis of noradrenaline but not of dopamine by diethyldithiocarbamate or disulfiram reduces the locomotor stimulant effect of *d*-amphetamine, but does not antagonize the stereotyped behaviour (Randrup and Scheel-Krüger, 1966; Pfeifer *et al.*, 1966; Maj and Przegalinski, 1967). From these studies it was concluded that the locomotor stimulant effect of amphetamine is mediated by noradrenaline, while the stereotyped behaviour after amphetamine is mediated by dopamine. Carlsson (1970), however, suggested that diethyldithiocarbamate has a central depressant action with rapid onset which may not be related to noradrenaline depletion. Experiments with more specific dopamine-β-hydroxylase inhibitors like U-14,624 or FLA-63 in rats and mice did not or only moderately reduce the locomotor stimulation following amphetamine (Johnson *et al.*, 1970; Svensson, 1970; Thornburg and Moore, 1973b; Hollister *et al.*, 1974).

The relative effect of *d*- and *l*-amphetamine on the accumulation of exogenous dopamine and noradrenaline in different brain regions and on behaviour led Taylor and Snyder (1971) to suggest that noradrenaline is selectively involved in amphetamine-induced locomotor stimulation, whereas the compulsive gnawing syndrome is mediated by dopamine. The relative potencies of *d*- and *l*-amphetamine on catecholamine uptake and on motor activity, reported in their study, however, are not consistent with those reported in other biochemical and behavioural studies (Ferris *et al.*, 1972; Scheel-Krüger, 1972; Svensson, 1971; Harris and Baldessarini, 1973; Chiueh and Moore, 1974; Thornburg and Moore, 1973a). Costa

et al. (1972) found that a dose of *d*-amphetamine which enhanced motor activity in rats increased the turnover of brain dopamine but not of brain noradrenaline.

Furthermore, it was shown that dopamine antagonists were more potent in blocking amphetamine-induced locomotor activity in rats and mice than noradrenaline antagonists (Rolinski and Scheel-Krüger, 1973). Other studies also suggest that dopamine is not only involved in stereotyped behaviour but plays an important role in locomotor activity as well (Carlsson, 1970; Creese and Iversen, 1973; Fibiger *et al.*, 1973; van Rossum, 1970).

Until now much less attention has been paid to the different dopaminergic systems in the brain with regard to the action of amphetamine. In the present work, the respective role of the nigro-neostriatal dopamine system and the mesolimbic dopamine system with cell bodies in the A-10 group (classification according to Dahlström and Fuxe, 1965) and nerve terminals mainly in the nucleus accumbens and tuberculum olfactorium (Andén *et al.*, 1966; Arbuthnott *et al.*, 1970; Ungerstedt, 1971) have been studied with respect to the locomotor stimulant action of *d*-amphetamine by means of intracerebral injections of the dopamine antagonist haloperidol.

Methods

Surgery

Male Wistar rats were used, weighing 200 ± 20 g at the time of operation. Under sodium pentobarbital anesthesia (40 mg/kg i.p.) double barrelled stainless steel cannulae were stereotaxically implanted into the caudate nucleus (caudate-putamen complex) and into the nucleus accumbens. The injection sites chosen had the following coordinates, according to the atlas of König and Klippel (1963): caudate nucleus: A 8.0, L 2.5, H 0.5 and nucleus accumbens: A 9.4, L 1.2, H −0.6. Preliminary experiments had revealed that slight modifications of these coordinates were necessary to reach the intended injection sites, probably because these rats were larger than those used in the atlas. The cannulae placed in the nucleus accumbens were brought in from the lateral side at an angle of 10° with the midline in order to avoid the ventricular system. The cannulae, which had an outer and inner diameter of 0.65 mm and 0.30 mm respectively were fixed on to the skull with acrylic dental cement (Paladur). Following surgery the animals received oxytetracycline (Terramycine) in their drinking water for a period of 5 days.

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 10 days, during which time the rats were accustomed to handling and to the injection procedure and during which time they were adapted to the activity cages.

Apparatus

Locomotor activity was measured in activity cages equipped with 3 light sources and opposite to them 3 photoelectric cells 2 cm above a grid floor. The dimensions of the cages were 36 cm × 24 cm × 25 cm. The cages were situated in a ventilated soundproof box. The interruptions of the light beams were registered on a cumulative Ralph-Gerbrands recorder.

Procedure

All experiments were started at the same time of the day (9.00 a.m.). After an adaptation period of 1 hr for each experiment in the activity cages locomotor activity was measured during 3 hrs (6 periods of 30 min) following the injection of *d*-amphetamine. *d*-Amphetamine was injected intraperitoneally. The standard dose of 1.0 mg/kg was chosen because this dose reliably induces stimulation of locomotor activity without stereotyped gnawing or licking behaviour.

Intracerebral injections of different drugs were given bilaterally 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. Injections into the brain were given immediately before the injection of *d*-amphetamine and in the case of haloperidol 15 min earlier too. The injection volume was 0.5 or 1.0 µl on each side. Treatments were given in a randomized sequence. At least two days of rest were given between the different treatments.

Drugs

The following drugs were used: *d*-amphetamine sulfate; haloperidol (Serenase); phentolamine methanesulfonate (Regitine); *l*-propranolol. All drugs, except the commercial preparations, were dissolved in a 0.9% saline solution. Saline was used as a control.

Statistics

Statistical comparison between different treatments was made using Students *t*-test. Two-tailed probability values are reported.

Histology

At the end of the experiments 1.0 µl of an ink solution was injected to verify the site of injection. The rats were perfused with saline and a 10% formalin solution through the left cardiac ventricle under sodium pentobarbital anesthesia. 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. Animals in which the injection sites were incorrect were discarded from the results.

Results

The Effect of Injections into the Nucleus Accumbens upon *d*-Amphetamine Sulfate-Induced Locomotor Activity

Intraperitoneal injection of *d*-amphetamine sulfate (1 mg/kg) caused a significant enhancement of loco-

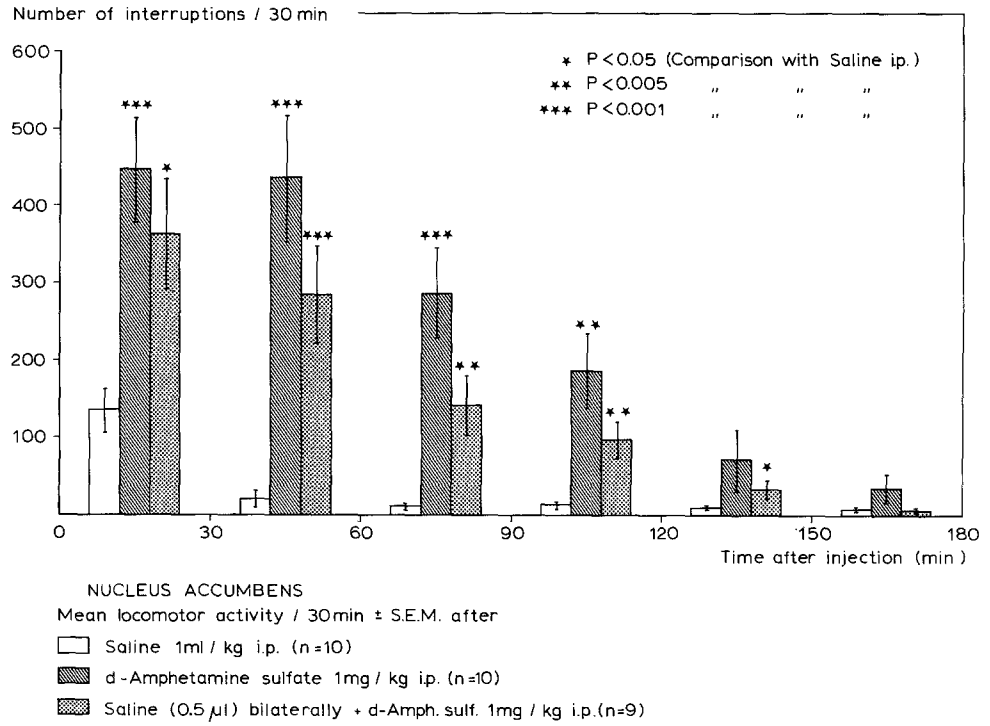

Fig. 1. Locomotor activity of rats during six successive 30-min periods following drug administration. Mean values ± S.E.M. are given. n = number of experiments

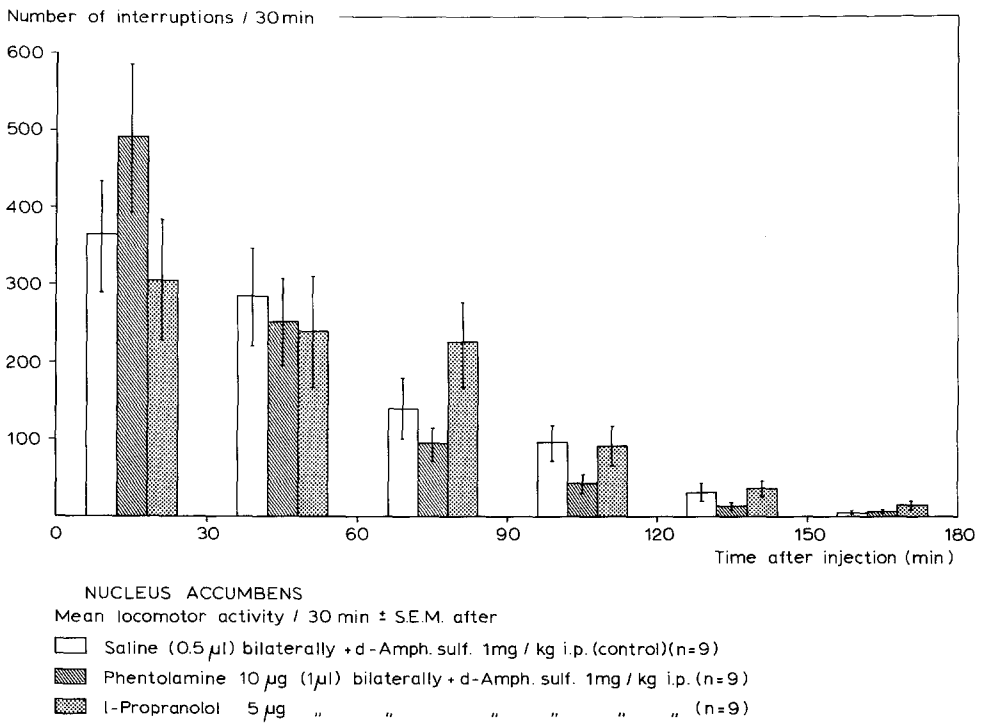

Fig. 2. Locomotor activity of rats during six successive 30-min periods following injections into the nucleus accumbens immediately before *d*-amphetamine sulfate 1 mg/kg i.p. Mean values ± S.E.M. are given. n = number of experiments

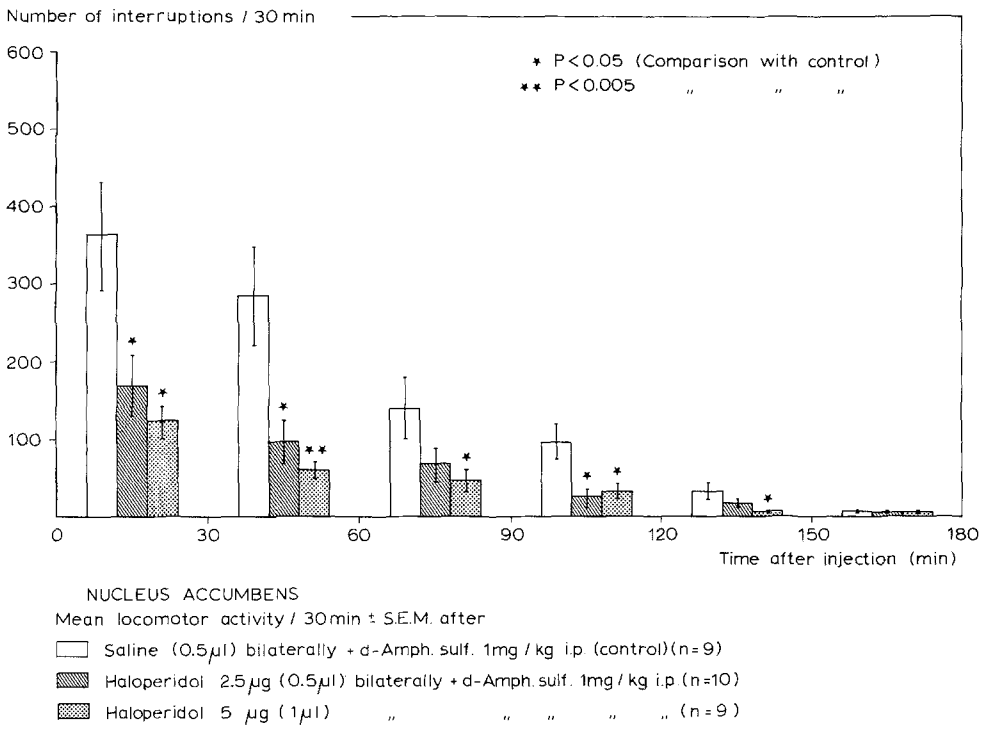

Fig. 3. Locomotor activity of rats during six successive 30-min periods following injections into the nucleus accumbens immediately before *d*-amphetamine sulfate 1 mg/kg i.p. Mean values ± S.E.M. are given. *n* = number of experiments

motor activity during the first four 30-min periods compared to the intraperitoneal injection of saline in the same volume of 1 ml/kg (Fig. 1). During the first 30-min period after saline injection locomotor activity was stronger than during the following periods because the animals showed exploratory behaviour following the manipulation and replacement in the cage. The effect of *d*-amphetamine was diminished during all periods when saline was injected into the nucleus accumbens, immediately before the injection of *d*-amphetamine (Fig. 1). The differences, however, were not significant, although in the third 30-min period there was a considerable diminishment of activity ($P < 0.10$). It is possible that the intracerebral injection disturbs the integrity of the nucleus in such a way that it influences the effect of *d*-amphetamine. Since in preliminary experiments it was found that the solvent of the commercial preparations used in this study also produced a reduction of activity comparable with saline, the effect of intracerebral injections of other substances was compared with the effect of saline. Injection of the alpha-adrenergic antagonist phentolamine (10 µg bilaterally) did not significantly change the effect of *d*-amphetamine as compared to the injection of saline during any period (Fig. 2). The beta-adrenergic antagonist propranolol (5 µg bilaterally) also had no clearcut influence (Fig. 2).

In contrast to these noradrenergic antagonists, injection of the dopamine antagonist haloperidol in doses of 2.5 and 5 µg bilaterally given both immediately (Fig. 3) and 15 min before (not shown) injection of *d*-amphetamine resulted in an inhibition of the *d*-amphetamine-induced locomotor activity. This inhibition was significant during the first, second and fourth 30-min period for both doses of haloperidol. During the third period the inhibition was only significant for the 5 µg dose of haloperidol.

The Effect of Injections into the Caudate Nucleus upon *d*-Amphetamine Sulfate-Induced Locomotor Activity

In animals with cannulae in the caudate nucleus intraperitoneal injection of *d*-amphetamine sulfate (1 mg/kg) resulted in a stimulation of locomotor activity which was significant during the first five 30-min periods compared to intraperitoneal saline injection (Fig. 4). Injection of saline bilaterally into the caudate nucleus resulted, just as in the nucleus accumbens experiments, in a non-significant reduction of the effect of *d*-amphetamine (Fig. 4).

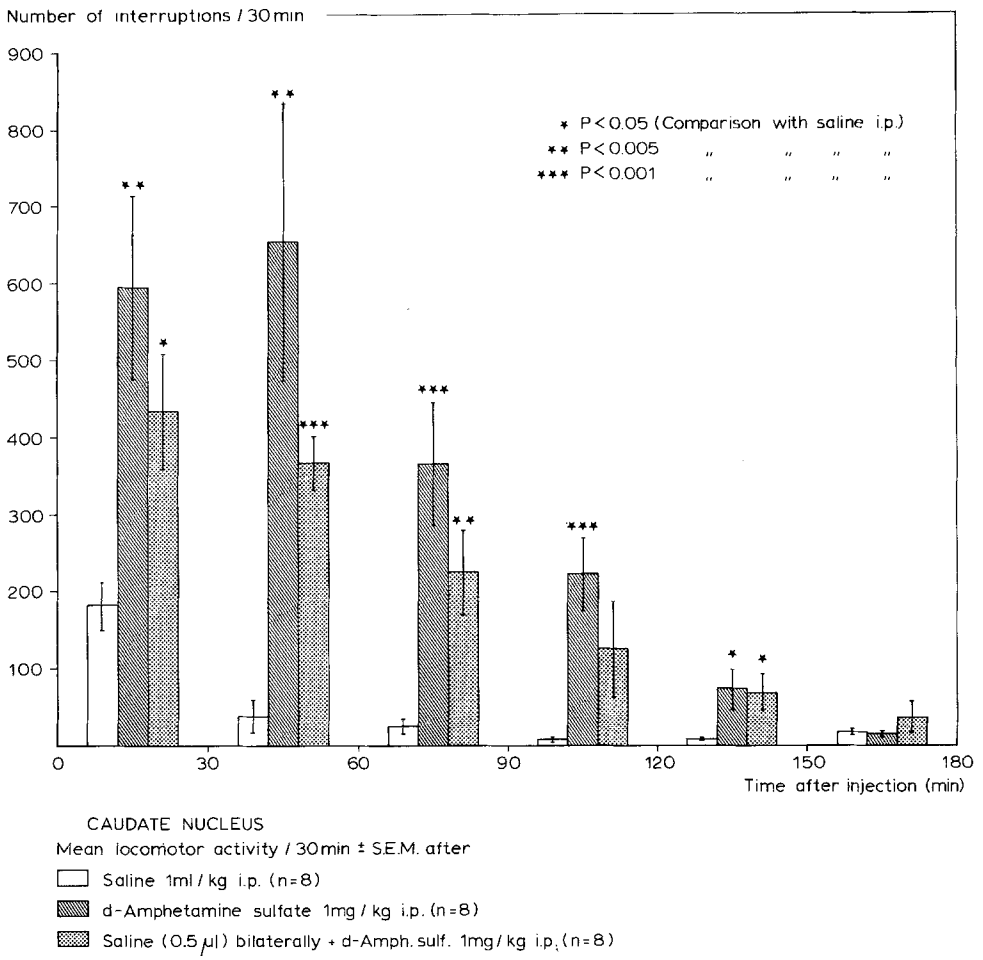

Fig. 4. Locomotor activity of rats during six successive 30-min periods following drug administration. Mean values ± S.E.M. are given. n = number of experiments

Administration of the alpha-adrenergic antagonist phentolamine (10 µg bilaterally) had no significant influence as compared to the intracaudate saline injection (Fig. 5). In contrast to the effects seen in the nucleus accumbens group, injection of haloperidol in doses of 2.5 and 5 µg bilaterally into the caudate nucleus both immediately before (Fig. 6) and 15 min before (not shown) the *d*-amphetamine administration did not result in a significant lowering of the *d*-amphetamine effect during any of the 30-min periods. Due to the fact that two animals showed a rather high activity following injection of the 5 µg dose of haloperidol immediately before the *d*-amphetamine injection a stronger locomotor activity was found in this experiment (Fig. 6).

Discussion

The present study shows that injections of haloperidol bilaterally into the nucleus accumbens strongly antagonize the stimulation of locomotor activity following intraperitoneal injection of *d*-amphetamine. Haloperidol is considered as a relatively specific dopamine antagonist (Andén *et al.*, 1970a; Janssen *et al.*, 1965; van Rossum, 1966). This result therefore suggests an important role for the mesolimbic dopamine system in *d*-amphetamine-induced locomotor stimulation, although in the present study only the nucleus accumbens was investigated because in the rat this nucleus is better suited for the intracerebral injection technique than the other terminal areas of the mesolimbic dopamine system. The doses used in this study (2.5 and 5 µg bilaterally) for inhibition of the locomotor stimulant action of *d*-amphetamine are relatively low when compared to the doses, administered into the caudate nucleus or globus pallidus (20–100 µg bilaterally) which seem necessary to antagonize the stereotyped behaviour induced by amphetamine (Fog *et al.*, 1971; Costall *et al.*, 1972).

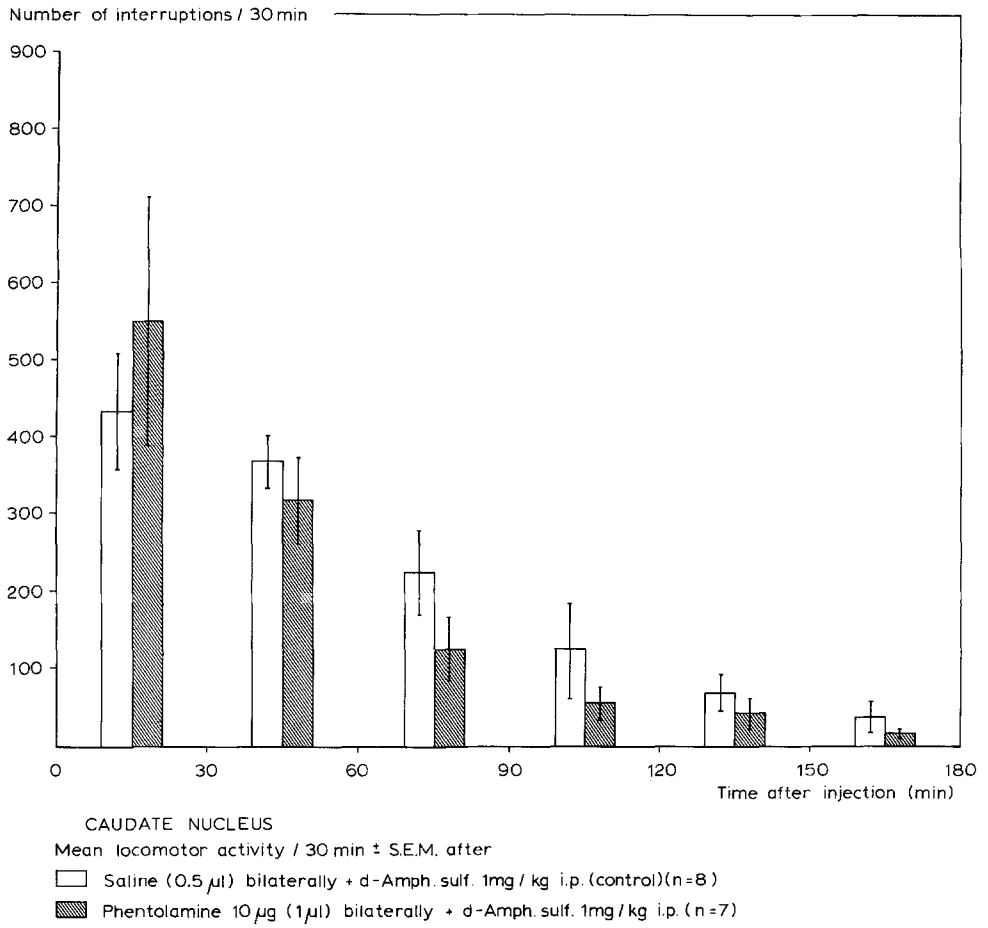

Fig. 5. Locomotor activity of rats during six successive 30-min periods following injections into the caudate nucleus immediately before *d*-amphetamine sulfate 1 mg/kg i.p. Mean values ± S.E.M. are given. *n* = number of experiments

Injection of the alpha-adrenergic antagonist phentolamine and the beta-adrenergic antagonist propranolol into the nucleus accumbens did not result in a significant inhibition of the *d*-amphetamine effect. Although the main catecholamine in the nucleus accumbens is dopamine (Andén *et al.*, 1966; Ungerstedt, 1971; Lidbrink *et al.*, 1974), the occurrence of noradrenaline in this nucleus is also described (Jacobowitz, 1973; Koob *et al.*, 1974). The noradrenergic system in this nucleus is probably not of major importance for stimulation of locomotor activity by *d*-amphetamine. This system, however, forms only a small part of the noradrenergic systems in the brain and therefore the role of noradrenaline cannot be excluded. Several authors assume that both dopamine and noradrenaline are involved in the regulation of locomotor activity, but that dopamine is of primary significance. As already mentioned in the introduction, Rolinski *et al.* (1973) found that low doses of neuroleptic agents completely blocked *d*-amphetamine-induced locomotor activity, whereas noradrenaline antagonists produced only partial inhibition. Furthermore, stimulation of dopamine receptors by apomorphine enhances locomotor activity, whereas activation of central noradrenaline receptors by clonidine is ineffective in this respect. Combined stimulation of both dopamine and noradrenaline receptors, however, results in a marked potentiation of the effect of apomorphine alone (Andén *et al.*, 1970b; Maj *et al.*, 1972; Andén *et al.*, 1973).

In contrast to the effects in the nucleus accumbens, injection of haloperidol into the caudate nucleus did not inhibit the *d*-amphetamine-induced locomotor activity. It is possible that the injection-volume or doses used are too small to reach the whole nucleus and that there remain enough free dopamine receptors. However, Creese and Iversen (1972) found that bilateral lesions of the substantia nigra with 6-hydroxy-

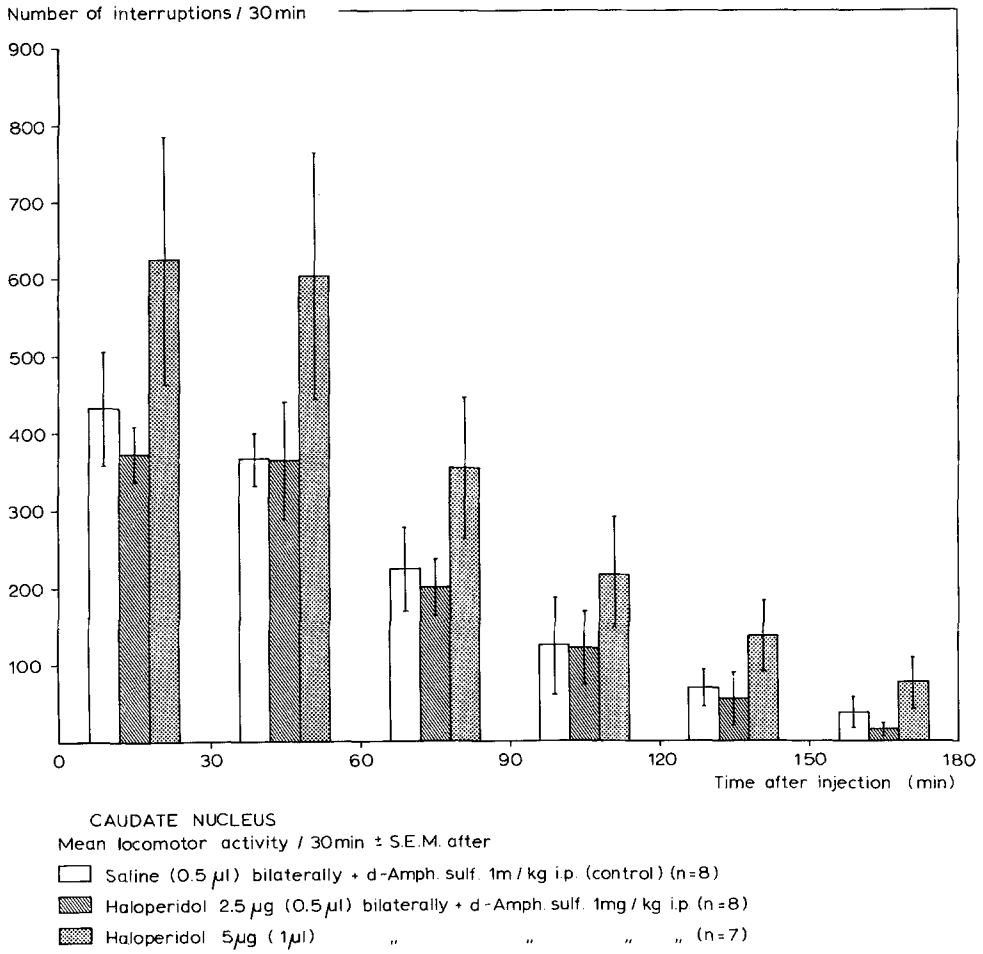

Fig. 6. Locomotor activity of rats during six successive 30-min periods following injections into the caudate nucleus immediately before *d*-amphetamine sulfate 1 mg/kg i.p. Mean values ± S.E.M. are given. *n* = number of experiments

dopamine did not reduce locomotor activity following amphetamine, whereas stereotyped behaviour was abolished. In contrast, Fibiger *et al.* (1973) reported that amphetamine-induced locomotor stimulation was significantly reduced following bilateral injection of 6-hydroxydopamine into the substantia nigra, but not completely abolished as following intraventricular injection of 6-hydroxydopamine in tranylcypromine pretreated rats. The role of the nigro-neostriatal dopamine system can therefore not be excluded with certainty.

Several data suggest that the mesolimbic dopamine system may play a role in states of hyperactivity. Electrical stimulation of the A-10 group in rats causes a syndrome of hyperactivity characterized by continuous exploration and sniffing (Miliaressis, 1973; Broekkamp, personal communication). Injection of ergometrine bilaterally into the nucleus accumbens (Pijnenburg *et al.*, 1973) and injection of dopamine in nialamide pretreated rats (Pijnenburg and van Rossum, 1973) results in a strong and long lasting stimulation of locomotor activity in contrast to injection of these substances into the caudate nucleus. In non-pretreated rats injection of *d*-amphetamine and also of dopamine into the nucleus accumbens causes a strong but shorter lasting enhancement of locomotor activity, whereas noradrenaline causes a depression (Pijnenburg, in preparation). It was found that bilateral lesions of the nucleus accumbens and antero-medioventral region of the caudate nucleus in cats prevented the increased locomotor activity induced by L-Dopa (Harik and Morris, 1973).

The fact that injection of haloperidol into the nucleus accumbens antagonizes the locomotor activity induced by amphetamine does not necessarily imply that the locomotor stimulant action of amphetamine is brought about by release of dopamine or inhibition of uptake mechanisms (Horn *et al.*, 1974) in this nu-

cleus, although it may play a role in its effects. It is found for instance that amphetamine can provoke stimulation of locomotor activity and elements of stereotyped behaviour in the thalamic rat with extensive lesions of the whole forebrain and striatum (Huston and Borbély, 1974). It is likely that amphetamine acts on different levels of the brain and that the resultant stimulation of activity is not a simple, but a complex response, which can be brought about by different mechanisms. The inhibition of the locomotor stimulation following *d*-amphetamine by administration of haloperidol into the nucleus accumbens can be explained by assuming that inhibition of the dopaminergic activity in this nucleus results in changes in the functional state of this nucleus and other brain structures, which are in some way involved in the achievement of the response. Inhibition by haloperidol of the effects of amphetamine upon the nucleus accumbens itself may play an additional role.

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