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Locomotor Hypokinesia in the Reserpine-Treated Rat: Drug Effects From the Corpus Striatum and Nucleus Accumbens

BO JOHNELS

Department of Neurology, University of Göteborg, Götebors, Sweden

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JOHNELS, B. *Locomotor hypokinesia in the reserpine-treated rat: Drug effects from the corpus striatum and nucleus accumbens.* PHARMAC. BIOCHEM. BEHAV. 17(2) 283–289, 1982.—A mechanographic method was used to assess the locomotor performance induced by apomorphine or other dopaminergic drugs in reserpine-treated rats. Reserpine was found to induce locomotor hypokinesia. The hypokinesia was dose-dependently reversed by apomorphine (APO), bromocriptine and pergolide. Locomotion was induced by microinjection of APO into the nucleus accumbens. No locomotor effect was found after injection into corpus striatum. Injection into both nuclei was not superior to accumbens only. Intra-striatal or intraaccumbens injections of trifluoperazine blocked the effect on locomotion by systematic apomorphine. The results confirmed that reserpine-induced locomotor hypokinesia is reversed by dopaminergic stimulation in the nucleus accumbens. There were indications that blockade of striatal or accumbens' dopamine receptors counteracts apomorphine-induced locomotion presumably by interaction with postural motor control. Evidence was found for separate dopaminergic control of locomotion and muscletone. This may be of importance for the development of new antiparkinson drugs.

Locomotion Hypokinesia Reserpine Corpus striatum Nucleus accumbens

PARKINSON's disease causes severe locomotor disturbances. There is a general slowness of movement (hypokinesia) that may progress to total immobility (akinesia) and there are difficulties to initiate and to stop walking. The pattern of gait is radically changed with a "shuffling" movement of the feet. The patients also have disturbances of postural regulation with a forward-bent attitude and loss of balance [20]. The striking effect of treatment with l-dopa or dopamine receptor agonists such as apomorphine, bromocriptine or pergolide with a change of these symptoms towards normal movements strongly indicate an important role of dopamine in the regulation of locomotion [14,19]. It has also been suspected that loss of noradrenergic and serotoninergic transmission might be of importance in the syndrome since the levels of these transmitters are reduced in parkinsonian brains [9]. Therapeutic trials with agonist drugs have, however, failed to give additional benefit to the dopaminergic treatment [4,18].

In the advanced stages of the disease, new problems often appear in the treatment of these motor dysfunctions. Episodes of "transient freezing" of the gait with total immobility of the feet become more frequent and protracted. They may exist concomitant with involuntary movements of the trunk and the arms (hyperkinesia).

The many motor symptoms are incompletely understood and there is a need for specific therapeutic measures against them. In research aimed at developing new treatments, there is a need for animal models relevant to the different symptoms. In the present study, reserpine-treated rats have been used since these animals display symptoms similar to those of Parkinsonian patients [3, 6, 10, 18, 25]. Their motor symptoms could be abolished by treatment with l-dopa indicating a pathophysiologic mechanism that was analogous to that of Parkinson's disease [6, 11, 18, 24].

In this study, locomotor performance was measured by a simple tread-mill apparatus. Local microinjection of drugs to the brain was used as a method to stimulate or block dopamine receptors in corpus striatum and nucleus accumbens bilaterally. These nuclei are innervated by the two major projections to the forebrain of the ascending dopamine system, the nigro-striatal and mesolimbic pathways [17,26]. The basic hypothesis for this work is that the dopaminergic transmission in the nucleus accumbens region controls locomotion whereas that of corpus striatum controls muscle tone and posture [3]. Akinesia is thought to depend on insufficient dopamine release in the mesolimbic part and rigidity on lack of transmission in the nigrostriatal part of these pathways. Thus, it has been shown that injection of dopaminomimetic substances into nucleus accumbens causes hyperlocomotion [12, 23, 28], while injection of apomorphine into corpus striatum reduces the rigidity of reserpine-treated rats [2]. The aim of this study was to provide a basis for further studies of the pathophysiologic mechanisms for hypokinesia and for the evaluation of new

drugs. The effects on reserpine-induced locomotor hypokinesia by a) systemic treatment with apomorphine, bromocriptine and pergolide, and b) microinjection of apomorphine into the corpus striatum and nucleus accumbens were studied. Finally, trifluoperazine was microinjected into these nuclei to find out if receptor blockade would prevent the hyperlocomotion induced by systemically given apomorphine.

METHOD

Three hundred and ten male Sprague-Dawley rats (200–300 g) were used. They were given food and water ad lib and were subjected to a 12 hr light/darkness scheme. After drug treatment, their rectal temperature was controlled to within 36–38°C by assisted heating or cooling. Stereotaxic operations were performed on the day before the experiments under pentobarbital anesthesia. Stereotaxically directed guide cannulas (i.d. 0.5 mm) were placed in boreholes through the skull with their tips on the dura mater and fixed to the bone with dental cement. During the experiments, injections cannulas (o.d. 0.4 mm) were introduced through the guide cannulas to the brain. The microinjections into the corpus striatum (2 μl) and into the nucleus accumbens (1 μl) were performed with a Unimetrics 10 μl syringe at an injection rate of 1 μl/min. The injection cannulas were then left in place for another minute. Coordinates: corpus striatum, AP=2.0, Lat. ± 2.5 mm, V=4 mm (from the cortical surface), nucleus accumbens, AP ± 4.0, Lat. ± 1.5, V=7.0, according to the atlas of Pellegrino and Cushman [22].

Drugs

Reserpine (Serpasil, CIBA-Geigy, 2.5 mg/ml) was taken from commercial ampoules. Apomorphine (Apomorfin, ACO) was dissolved in sterile water during cautious heating and used immediately. Trifluoperazine (Terfluzin, Leo-Rhodia) and pergolide (Lilly) were dissolved in 0.9% saline. Bromocriptine mesylate (Sandoz) and prazosin (Pfizer) were dissolved in a few drops of concentrated acetic acid and diluted with 5.5 percent glucose and titrated to pH = 4.0 with NaOH.

Mechanography

Locomotor performance was measured in a simple treadmill outfit, designed to permit drug injections as well and electrophysiological recording and stimulation during the experiments (Fig. 1). The "locometer" unit consisted of a drum made from a lightweight bicycle wheel and mounted vertically projecting somewhat up through a slit in a table top. An 8 inch wide running track was arranged on the periphery of the wheel by application of a thin steel band dressed with a rubber cloth. The rat was held in place on top of the drum by a pivot arm from behind and a harness around the belly. The drum was brought to rotate by the stepping activity of the rat. Normally the rats were placed with their heads and forelegs in a narrow plastic tube. This procedure protected the rats from disturbances during the recordings and was found to increase the spontaneous running by 10–20 percent (unpublished results). The rotation of five such drums arranged in the same table was measured by cogwheels and optoelectronic counters fed into a small computer (ABC 80, Luxor). The accumulated distance performed by the rats on the drum for a selected period of time was displayed as shown in the graphs.

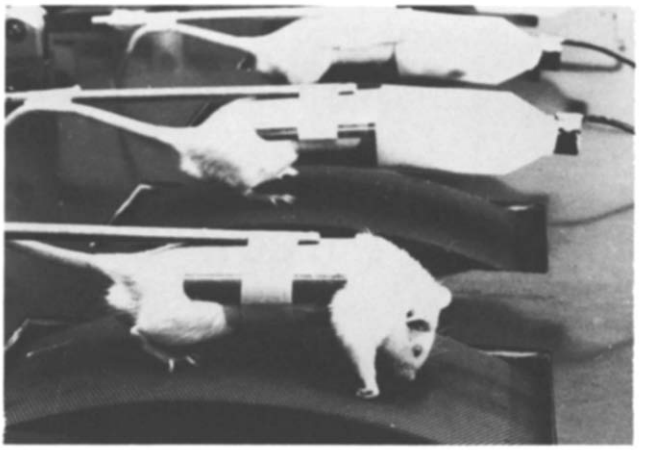

FIG. 1. Locomotor activity was recorded by a simple treadmill arrangement. The rats were kept in place on top of drums, brought to rotate by their stepping. The rotation was recorded by means of optoelectronic counters and a small computer. Five drums were arranged in the same table.

Statistical significances of the differences in locomotor activity during different times and between different groups of animals were calculated with two way variance analysis: pxq factorial experiments for unequal cell frequencies [29] unless otherwise noted.

RESULTS

Reserpine-Treatment, Observations on General Behaviour

When a high dose of reserpine (10 mg/kg IP) was given to the rats their spontaneous motor activity gradually ceased and after one hour they were lying still in a corner of the cage. The legs were flexed and adducted, drawn in under the body. A sudden strong light or a sharp noise did not give rise to any motor activity, but after a pinch of the tail the animal took a few apparently normal steps forward and then returned to tranquil immobility. If a rat was held upside down and then released from a low height, it quickly turned around and landed with normal righting reaction on the table. Such quick and apparently normal reactions were elicited after a variety of equilibrium perturbations, and it seemed that reflex motor reactions were preserved while spontaneous behaviour had ceased. The body had a hunchback appearance with flexion of the head and a characteristic parkinsonism-like flexion of forepaw digits (Fig. 1).

Spontaneous Locomotion

Spontaneous locomotion was very sparse when recorded during the morning hours. No significant differences were therefore found between controls and reserpine-treated rats (Fig. 2). On the other hand, when the recording was performed in the evening and night with only little light in the laboratory, significantly ($p<0.05$) more spontaneous locomotion was found (Fig. 3). Reserpine-treated rats now displayed a depressed locomotor activity within 2 hours compared to the saline treated control group, but 5–6 hours later there was a new slowly increasing activity.

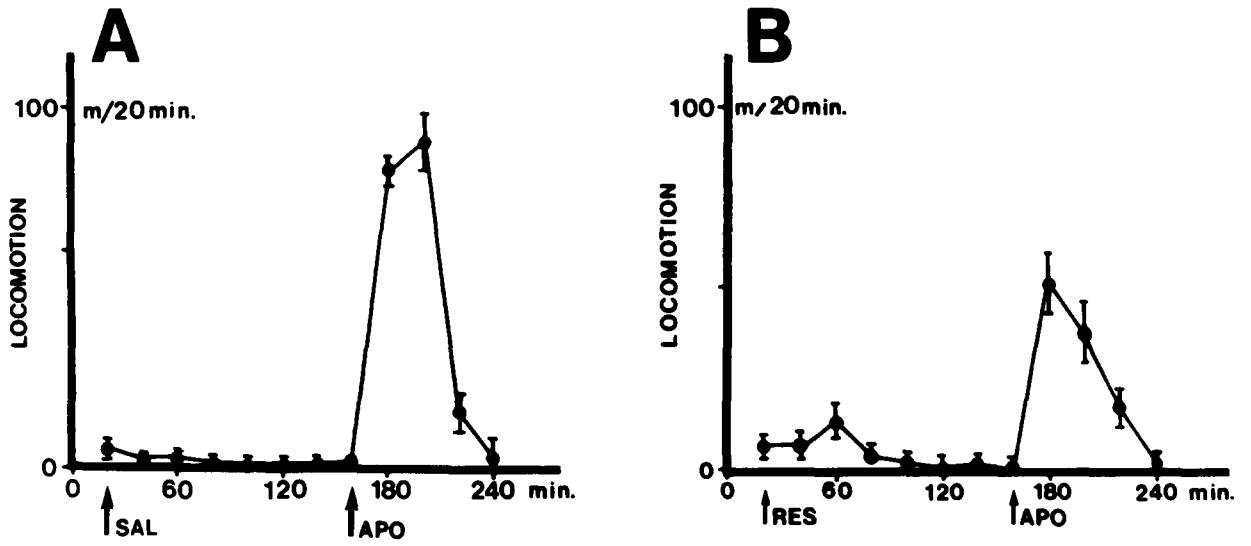

FIG. 2. Spontaneous and induced locomotion. Twenty rats were treated with either saline (SAL/1 ml, IP A) or reserpine (RES/10 mg/kg IP B) 20 minutes after the start of recording (9 a.m.). Two hours later apomorphine (APO) (0.5 mg/kg, SC) was given to induce locomotion. Mean±S.E.M. for the locomotion (in meters on the drum) accumulated during each successive 20 min period.

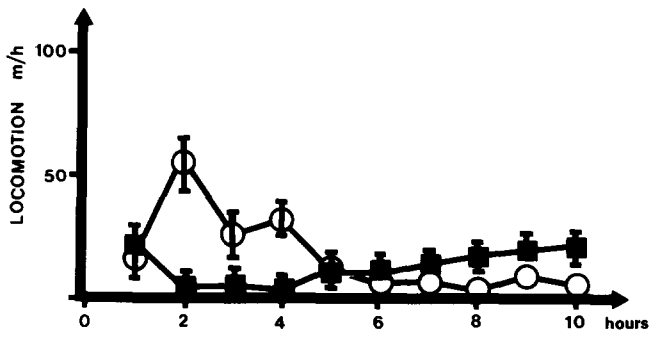

FIG. 3. Spontaneous locomotion of rats treated with saline (circles) or reserpine (squares) 20 minutes after start of recording (5 p.m.). 10 rats in each group. Mean±S.E.M. for the accumulated locomotion (meters on the drum during each hour).

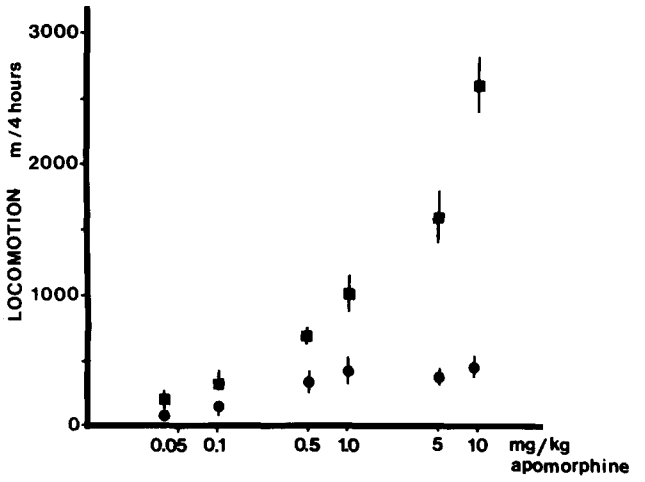

FIG. 4. Apomorphine-induced locomotion. The rats were either previously untreated (squares) or given reserpine (10 mg/kg, IP) one hour before the recording (circles). After 20 minutes of recording, different doses of apomorphine were given. Accumulated locomotion during 4 hours (mean±S.E.M., n=6).

Induced Locomotion

A subsequent injection of apomorphine (0.5 mg/kg, SC) caused a period of intense running (Fig. 2A) and a reversal of the reserpine hypokinesia (Fig. 2B). Apomorphine also induced a short period of stereotyped behaviour (sniffing, licking and gnawing on the cylinder). This effect was most pronounced in the reserpine-treated rats. The amount of locomotion induced was clearly dose related and strongly attenuated by previous treatment with reserpine (Fig. 4). It was thought to be of interest to see if the more long-acting dopamine agonist drugs with known antiparkinson efficacy showed a similar pattern. This was, in fact, found for bromocriptine (Fig. 5A and B). The drug induced comparatively little locomotor activity in the dose-range tested (1–20 mg/kg). The locomotor response appeared with a latency of about one hour (A) and it was clearly attenuated by reserpine pre-treatment (B). Higher doses than 10 mg/kg IP did not further enhance locomotion.

In contrast, pergolide (0.1–2.0 mg/kg) was more potent at efficacious (as seen in Fig. 5C). Previous reserpine-treatment caused a slightly attenuated total amount of locomotion in the higher doses tested but an increase in the low doses. This increase was especially prominent during the first hour after the injection of pergolide (Fig. 5D). Experi-

TABLE 1

EFFECTS OF PERGOLIDE AND VARIOUS PRETREATMENTS ON LOCOMOTOR ACTIVITY

Treatments mg/kg/hours before recording	Accumulated Locomotion (meters) during 1st hour	during 6 hours	Number of rats
A. Pergolide *0.5	68 ± 13	400 ± 59	10
B. Reserpine 10/1+Pergolide* 0.5	141 ± 19†	311 ± 39	10
C. Reserpine 10/18+Pergolide* 0.5	393 ± 36‡	460 ± 61	6
D. Reserpine 10/1+H44/68 200/2 + Pergolide* 0.5	154 ± 20	279 ± 55	6
E. Reserpine 10/1+Prazosin 10/1+Pergolide* 0.5	206 ± 38§	355 ± 39	10

*Pergolide 0.5 mg/kg was given at the start of recording. All treatments were given intraperitoneally. Reserpine and Prazosin (treatments B, D and E) were given 10 mg/kg, IP one hour before the start of recording. In C, Reserpine 10 mg/kg IP was given 18 hours in advance.

Statistical significances for the differences between the treatments were as follows: †, A–B $p<0.005$, ‡, B–C: $p<0.001$, §, B–E unsignificant ($p>0.05$). Student's t-test.

ments were made to see whether this first period of increased locomotion was due to a dopamine-releasing effect of pergolide or to a concomitant activation of α_1-adrenergic receptors (Table 1). When the time interval between the injections of reserpine and pergolide was increased from 1 to 18 hours to allow for a further decrease of the endogenous monoamine content in the brain, there was a further potentiation of the locomotor effect of perfolide (Table 1, treatment C). Addition of the catecholamine synthesis inhibitor α-methylparathyrosine (H 44/68, treatment D) did not reduce the effect of pergolide. Finally, the α_1-adrenergic receptor blocking drug prazosin [5] was given in a high dose together with reserpine to see if pergolide had noradrenergic receptor stimulating qualities (treatment E), but no reduction of pergolide-induced locomotion was found in comparison to reserpine alone (treatment B).

Locomotor Induction from Nucleus Accumbens and Corpus Striatum

Six groups of rats (n=10, each) were placed in the locometer. Three of the groups were treated with reserpine

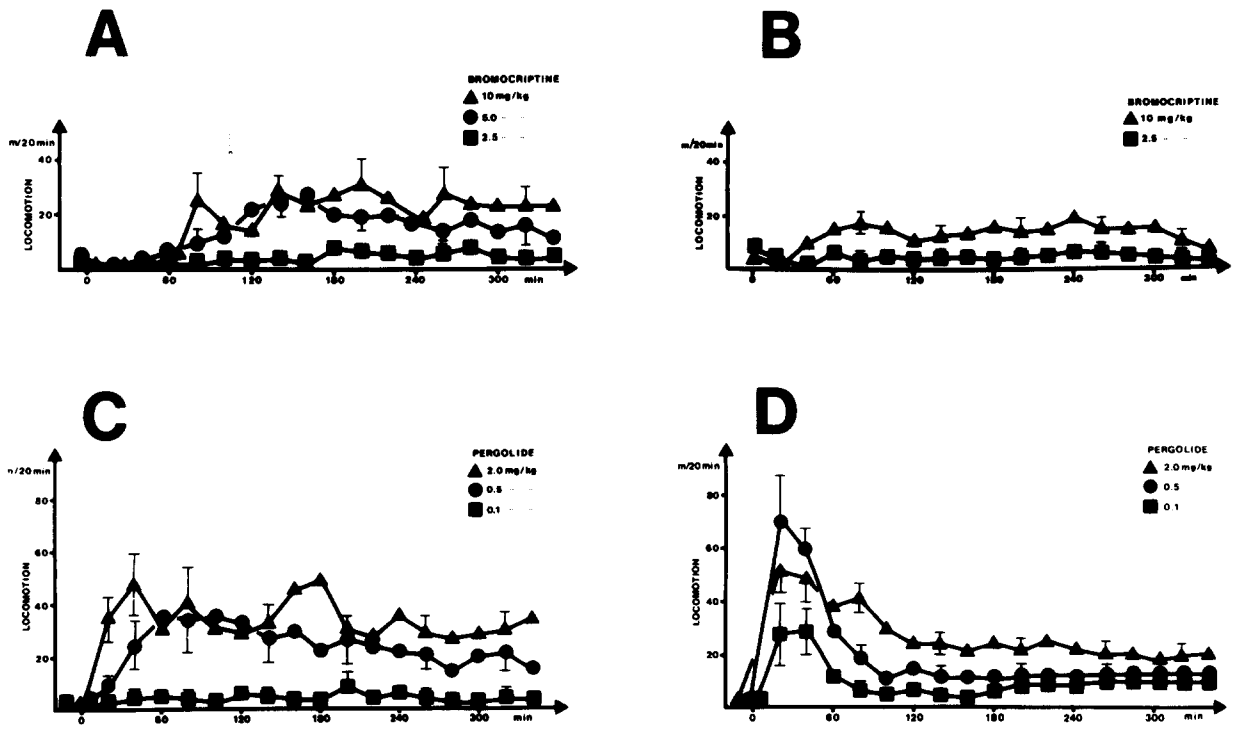

FIG. 5. The effect of some long acting dopamine agonist drugs on locomotion in previously untreated rats (A and C) or rats injected with reserpine (10 mg/kg, IP) one hour before recording (B and D). Mean accumulated locomotion (20 min) ±S.E.M. (n=6 for each dose).

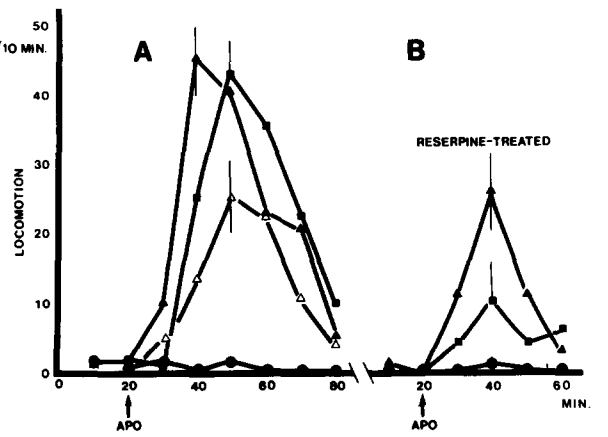

FIG. 6. Locomotor stimulating effect of bilateral microinjections of apomorphine to corpus striatum (2 μl/side, circles), nucleus accumbens (1 μl/side, triangles) or both (squares). Filled symbols 10 μg/side, open symbols: 3μg/side. Mean values. The maximal standard error is indicated with vertical lines. A: previously untreated rats. B: reserpine (10 mg/kg, IP) one hour in advance.

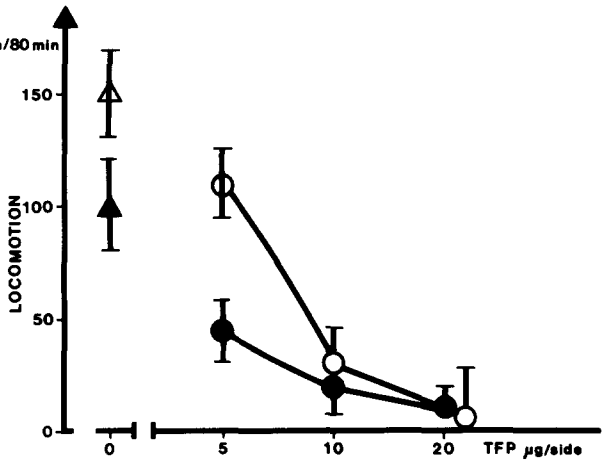

FIG. 7. The antagonistic effect by intrastriatal (filled signs) or intra-accumbens (open signs) injection of trifluoperazine (TFP) on apomorphine-induced locomotor activity. The triangles represent the control groups injected with saline (+ascorbic acid). Mean ±S.E.M.(n=8).

(10 mg/kg IP, 1 hour in advance) to induce hypokinesia (Fig. 6B). The rats were then subjected to bilateral microinjection of apomorphine into nucleus accumbens (3–10 μg/1 μl, per side), corpus striatum (10 μg/1–4 μl, per side) or both nuclei 20 min after start of recording. Injections into nucleus accumbens (Fig. 6, triangles) induced a brief period of increased locomotion ($p<0.001$), while injection into corpus striatum (filled circles) did not evoke any significant locomotor activity. Concomitant bilateral injection of apomorphine to both nuclei (open circles) did not produce a further increase of locomotion. Reserpine-pretreatment clearly attenuated the response to apomorphine as seen in Fig. 6B. Injection to both nuclei did not enhance the locomotor response. Stereotyped hyperkinetic behaviour (sniffing, licking and gnawing) was observed after the intrastriatal injections.

Effect on Apomorphine-Induced Locomotion by Local Receptor Blockade in Corpus Striatum and Nucleus Accumbens

Locomotion was induced by treatment with apomorphine (0.5 mg/kg, SC). In the control rats, saline was injected into corpus striatum (closed triangle, 2 μl) or into nucleus accumbens (open triangle, 1 μl) 30 min in advance (Fig. 7). There seemed to be a slightly reduced effect of apomorphine in the striatal rats as compared to those injected into the nucleus accumbens although the difference in accumulated locomotion between these two groups did not reach statistical significance. When the rats had been given trifluoperazine into the brain (to block the dopamine receptors locally) 30 minutes before start of recording, there was a dose-dependent reduction of the apomorphine-induced locomotion from both nuclei. In those experiments, reserpine was not given.

DISCUSSION

The present study is an investigation of the reserpine-treated rat as an animal model of the locomotor hypokinesia in Parkinson's disease. The quantitative method used for the assessment of motor performance is similar to tread-mill methods that may be used for clinical determination of gait. Reference data is given of the effect of reserpine on spontaneous and apomorphine-induced locomotion.

Two dopamine receptor agonists, bromocriptine and pergolide are compared regarding their effect on the reserpine-induced hypokinesia. They showed interesting differences pointing to the possibility that they may activate different receptor populations in the brain. Finally microinjections of dopamine agonist and antagonist drugs were given into the terminal area of the two main branches of the ascending dopamine system [17,26] to test the hypothesis that a dysfunction of the nigro-striatal and mesolimbic pathways may be responsible for different symptoms.

With the present method, little spontaneous locomotor activity was recorded during daylight as seen in Fig. 2. During the dark hours locomotion increased, and in Fig. 3 it is demonstrated that a high dose of reserpine transiently attenuated spontaneous running. Subcutaneous injection of apomorphine induced hyperlocomotion and reversed reserpine-akinesia. Figure 4 shows the dose dependency of apomorphine-induced locomotion. Previous treatment of the rats with reserpine considerably attenuated the locomotor response to apomorphine during the first day as found by other [27]. This effect is thought to depend, at least partly, on the concomitant loss of endogenous noradrenergic stimulation caused by reserpine [1]. Such effects may indicate a functional difference between the animal model and the disease as there is yet little indication on that α_1-adrenergic stimulant drugs would favorably influence the hypokinesia in man [18]. There are, however, several reports that some of the new, ergot-derived dopamine agonist drugs such as bromocriptine and pergolide reduce the "on-off" hypokinetic phenomenon in patients treated with l-dopa [8, 15, 16, 19]. When these drugs were tested, significant differences ap-

peared. Bromocriptine induced hyperlocomotion after a latency of one hour (Fig. 5A). Reserpine-pretreatment attenuated the response (Fig. 5B). Pergolide was more potent and efficacious as the drug could induce much higher levels of locomotor activity (Fig. 5C). In the reserpine-treated rats, on the other hand, pergolide differed from bromocriptine in that there was an augmentation of the induced locomotion which was most significant at the lowest doses (Fig. 5D). The mechanism behind this phenomenon is not known. It is probably not caused by an amphetamine-like effect of pergolide or stimulation of noradrenergic receptors as the early potentiation of locomotion was not counteracted by the addition of the dopamine synthesis blocker α-methyl-p-tyrosine (H44/68) or of prazosin which blocks α-adrenergic receptors [5] as seen in Table 1. These differences between bromocriptine and pergolide indicate different mechanisms of action in these drugs. Speculatively, this might make pergolide favourably suited for the treatment of akinetic symptoms in parkinsonism. Pergolide has been reported to have an effect on hypokinetic symptoms in patients that did not respond well to bromocriptine [16].

These similarities between the findings in the animal model and clinical experience motivated more detailed studies of the reserpine-treated rat. Fig. 6 shows the effects of microinjection of apomorphine into the corpus striatum, the nucleus accumbens or both. The findings were in accordance with earlier studies. Dopaminergic stimulation in the nucleus accumbens caused a dose dependent hyperlocomotion but no such effect was seen when apomorphine was injected to the corpus striatum [12,28]. To test a presumed interaction between the mesolimbic (locomotor regulating) and the nigro-striatal (tone-regulating) pathways, apomorphine was injected to both nuclei simultaneously. The induced hyperlocomotion was not significantly different from that after injection to the nucleus accumbens only. Pretreatment with reserpine attenuated the motor-stimulant response (Fig. 6B) in analogy with systemic treatment (Fig. 2).

Finally, the effects of a localized blockage of dopamine receptors was studies by injections of the catecholamine receptor blocking drug trifluoperazine [13]. From Fig. 7, it can be seen that a dose-dependent block of apomorphine-induced locomotion was caused by both corpus striatum and nucleus accumbens injections.

The dose dependent antagonism found after intra-accumbens injection of trifluoperazine on the apomorphine induced locomotion strengthens the assumption that the initiation and quantitation of locomotion is related to the level of dopamine transmission in the nucleus accumbens. The antagonistic effect produced by trifluoperazine when injected into the corpus striatum is difficult to explain, as no locomotor activity could be evoked on stimulation of the striatal dopamine receptors with apomorphine (Fig. 6A). Locomotion could also be elicited from nucleus accumben when the striatal dopamine transmission must have been reduced by the pretreatment with reserpine as seen in Fig. 6B. One possible explanation is that diffusion of trifluoperazine had occurred, blocking nucleus accumbens receptors. In recent experiments on reserpine-induced rigidity, however, no blockage of the striatal receptors was found on injection of trifluoperazine (10 μg/1 μl) bilaterally to nucleus accumbens. Admittedly, the somewhat greater injection volume to the striatum (2 μl) might make some difference. The present findings that the blockage was more pronounced from injections of trifluoperazine to the corpus striatum than from nucleus accumbens in the lowest dose (2×5 μg) does not favour the idea of an effect by diffusion. A speculative explanation could be that the injection of trifluoperazine to corpus striatum interacted with the regulation of muscle tone in such a way that this caused unfavourable circumstances for the release of locomotor activity from subordinated nervous centers [21].

Conclusion

It was confirmed with the present method that the dopamine receptor agonist drugs apomorphine, bromocriptine and pergolide all induced hyperlocomotion in rats. In reserpine-treated animals, these drugs counteracted the akinesia. Pergolide was most potent in this respect, and the effect on locomotion was enhanced in the low doses in contrast to treatment with apomorphine and bromocriptine. As bromocriptine was found to be more effective than pergolide in reducing reserpine-induced rigidity (unpublished observations), there are interesting differences between these drugs in the proposed animal model of Parkinson's disease. The findings in the experiments with local application to the brain of apomorphine and trifluoperazine strengthen the hypothesis of a differential regulation of locomotor activity and muscle tone from the nucleus accumbens and corpus striatum respectively. If there are different properties of the dopaminergic effects on motor control from the nigro-striatal and mesolimbic (mesocortical) pathways, this would have important implications for selection of antiparkinson drugs with more specific activity against the different motor symptoms. In this work, the reserpine-treated rat might prove to be a valuable tool. It was indeed this model that gave the incitement to l-dopa therapy of Parkinson's disease [6,7].

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