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Psychotomimetics Potentiate Locomotor Hyperactivity Induced by Dopaminergic Drugs

H. FINK, R. MORGENSTERN AND W. OELSSNER

Institute of Pharmacology and Toxicology, Humboldt University, 108 Berlin, Clara-Zetkin-Street 94, German Democratic Republic

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FINK, H., R. MORGENSTERN AND W. OELSSNER. *Psychotomimetics potentiate locomotor hyperactivity induced by dopaminergic drugs*. PHARMAC. BIOCHEM. BEHAV. 11(5)479–482, 1979.—The spontaneous locomotor activity of rats was investigated in an open-field test. Apomorphine and d,l-amphetamine caused a dose dependent increase of locomotor activity. LSD, mescaline, and DMT in low doses were ineffective, when given alone, but caused a strong potentiation of the hypermotility induced by apomorphine and d,l-amphetamine. Cyproheptadine antagonized the potentiating effect of LSD without affecting the hypermotility induced by apomorphine, indicating a causal serotonergic involvement in the potentiation effect.

Amphetamine Apomorphine Cyproheptadine Locomotor activity Open-field Psychotomimetics Rat

VARIOUS difficulties arise in the investigation of locomotor effects of psychotomimetics in laboratory animals. The specifity of locomotor effects induced by high doses of psychotomimetics is doubtful, and the investigation of low doses resulted in contradictory findings. Therefore, because of using different methods for evaluating the locomotor activity in rats or mice a comparison of the results is restrained. But the often used open-field test, also has not provided uniform results. Silva and Calil [17] and Brimblecombe [3] reported that 0.1 and 0.5 mg/kg lysergic acid diethylamide (LSD) were ineffective in changing locomotor activity in rats, whereas Cunha and Masur [6] only under light observed an increase of ambulation by LSD in doses of 0.1 and 0.2 mg/kg. Dandiya *et al.* [7] registered a dose dependent increase of locomotor activity in rats beginning with 2 μg/kg LSD. Lush [13] demonstrated an increase of motility in mice after application of 35 mg/kg mescaline only in five of seven examined strains of mice. Silva and Calil [17] reported a decrease of locomotor activity in rats induced by 20 mg/kg mescaline. In our own experiments we could not find any significant effect of low doses of LSD, dimethyltryptamine (DMT) and mescaline on locomotor activity of rats.

The finding that LSD, DMT, and mescaline inhibit raphe neurons indicates an involvement of the serotonergic transmission system in the central action of these drugs [10]. On the other hand median raphe lesion increases d-amphetamine hypermotility [9, 12, 16] and vice versa intraventricular infusion of serotonin inhibits d-amphetamine induced hypermotility [20]. A serotonergic-dopaminergic interaction in the control of locomotor activity can be assumed. Therefore we suggested that psychotomimetics may alter locomotor effects induced by dopaminergic agents. Consequently, we investigated the influence of psychotomimetics on the increased locomotor activity caused by the dopaminergic agonist apomorphine, and the indirect sympathomimetic drug amphetamine.

METHOD

The experiments were performed on male Wistar rats (VEB Versuchtierproduktion Schönwalde), weighing 150 ± 20 g. The rats were housed in groups of 10 animals per cage under a temperature of 22 ± 2°C and with a 12 hours light/dark schedule (6.00 a.m.–6.00 p.m.). They received food and water ad libitum prior to the experiment. All animals were used only once.

The experiments were carried out between 8.00 a.m. and 11.00 a.m. and between 2.00 p.m. and 4.00 p.m. in a soundproof room. The animals could adapt to this room for two hours. We used a white open-field cage consisting of a 1 m x 1 m area divided into 36 equal squares and surrounded by a 40 cm high wall. The floor was diffusely lighted by a 40 Watt fluorescent tube fixed 2 m above the center of the cage.

After application of the drug the rat was returned to its home cage. At the time of maximum effect of the given drug the animal was transferred to the middle of the open-field cage. The spontaneous locomotor activity of the rat in a new environment was measured by the number of crossed squares counted by the observer for a period of 5 minutes. Changes in the normal behavior of the rat were noted, such as jumps, stereotypies, and tremor.

All drugs (Table 1) were injected intraperitoneally in a volume of 1 ml/kg body weight. The drugs were dissolved in 0.9% NaCl. Controls were treated with saline.

Complete dose response curves were calculated by using nonlinear regression procedures [15]. Each point of the curve represents the mean value of at least 10 animals.

TABLE 1

DOSES AND APPLICATION INTERVAL OF THE DRUGS USED

Drug	Dose (mg/kg)	Application interval (min)
Apomorphine-HCl (SPOFA)	0.125–16	7
d,l-Amphetamine-HCl (Fahlberg-List)	0.125–12	10
Lysergic acid diethylamide tartrat (SPOFA)	0.05 - 0.1	30
Mescaline sulfate (Merck)	50	20
Dimethyltryptamine (Sigma)	1	15
Cyproheptadine-HCl (Sharp & Dohme)	0.1 ; 0.2	20

TABLE 2

EFFECT OF LSD, MESCALINE, AND DMT ON OPEN-FIELD ACTIVITY OF RATS

Drug	Dose (mg/kg)	n	Mean of crossed squares ± SEM*
Saline	—	101	38.5 ± 2.2
LSD	0.05	30	38.5 ± 2.1
LSD	0.1	30	44.6 ± 4.0
Mescaline	50	30	35.8 ± 3.0
DMT	1	10	39.2 ± 5.3

*None of the differences between groups of treated animals and controls were statistically reliable.

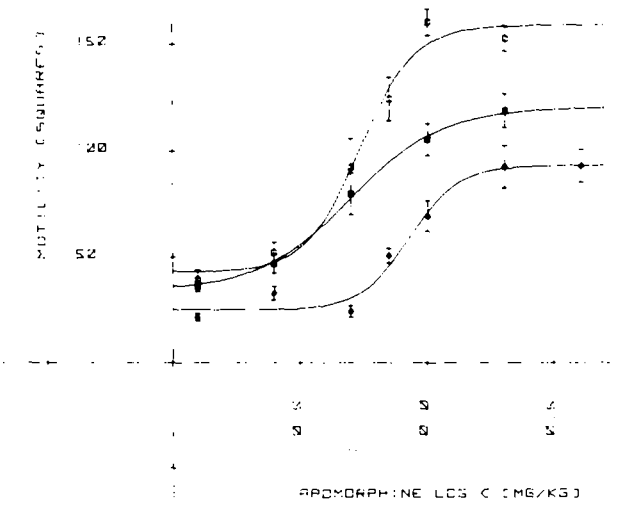

FIG. 1. Effect of LSD on apomorphine induced changes of locomotor activity. The vertical bars indicate the standard error of the mean. ★----★ apomorphine; ■----■ apomorphine + 0.05 mg/kg LSD; ●----● apomorphine + 0.1 mg/kg LSD.

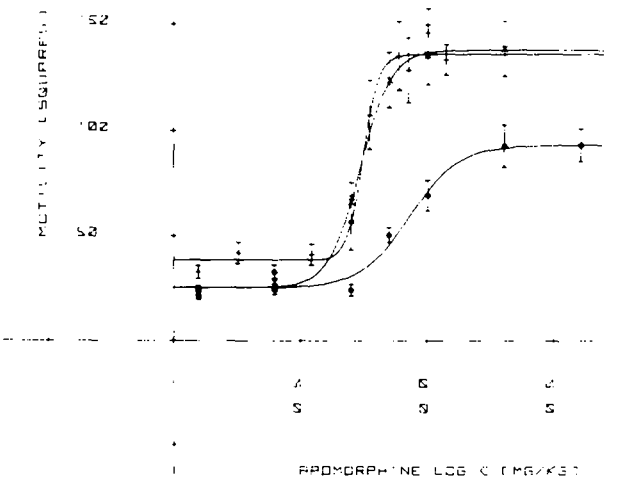

FIG. 2. Effect of Mescaline and DMT on apomorphine induced changes of locomotor activity. The vertical bars represent the standard error of the mean. ★----★ apomorphine; \----\ apomorphine + 50 mg/kg mescaline; +----+ apomorphine + 1 mg/kg DMT.

RESULTS

The saline treated animals crossed 38 squares and sat in a corner of the open-field cage after three or four minutes.

0.1 mg/kg LSD, 50 mg/kg mescaline and DMT in doses up to 1 mg/kg had no significant effect on spontaneous locomotor activity and did not cause aberrant behavior (Table 2.).

Apomorphine in low doses induced a decrease of open-field activity, and in higher doses an increase. Consequently, after high doses of apomorphine the animals moved throughout the observation period except for short interruptions, and crossed a maximum of 93 squares (Fig. 1). The rats showed headweaving and continuous sniffing while moving.

Pretreatment with 0.1 mg/kg LSD, an ineffective dose when given alone, caused a strong potentiation of the hypermotility induced by apomorphine. The maximum value was 160 crossed squares (Fig. 1). Such strong stimulation of locomotor activity was not reached by apomorphine given alone.

Striking symptoms occurred, e.g. straub tail, piloerection, hindlimb abduction, reciprocal forepaw treading, and sometimes tremor, which resembled strongly the behavioral syndrome after treatment with 0.8–1.0 mg/kg LSD as described by Trulson *et al.* [19]. The animals were supersensitive to touch and noise and began to bite or to jump. Besides, 0.1 mg/kg LSD abolished the decrease of spontaneous locomotor activity induced by low doses of apomorphine. 0.05 mg/kg LSD led to a lower increase of apomorphine hypermotility, compared with the effect of 0.1 mg/kg LSD (Fig. 1) and indicates a dose dependency of this potentiation effect.

50 mg/kg mescaline as well as 1 mg/kg DMT, also ineffec-

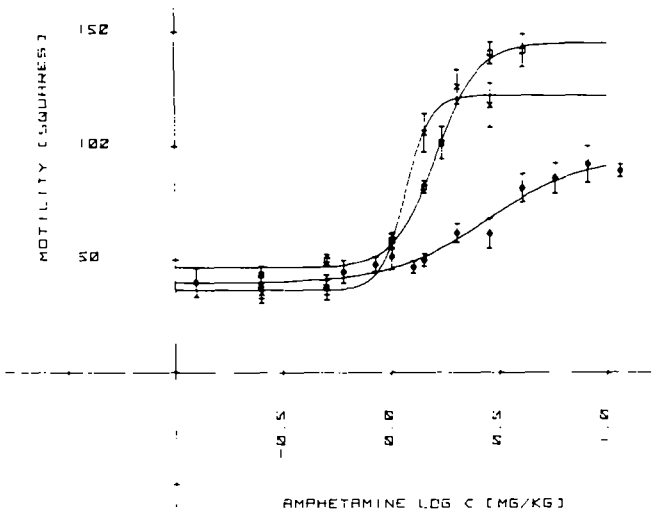

FIG. 3. Effect of LSD and mescaline on locomotor hyperactivity induced by d,l-amphetamine. The vertical bars indicate the standard error of the mean. ★----★ d,l-amphetamine; □----□ d,l-amphetamine + 0.1 mg/kg LSD; X----X d,l-amphetamine + 50 mg/kg mescaline.

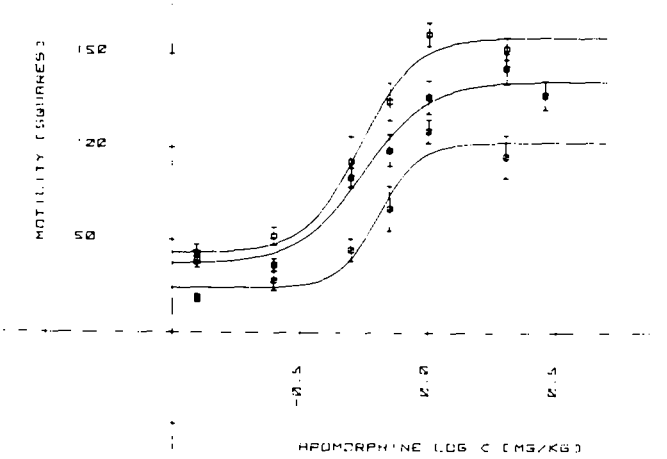

FIG. 4. Effect of cyproheptadine on LSD potentiated locomotor hyperactivity induced by apomorphine. The vertical bars indicate the standard error of the mean. □----□ apomorphine + 0.1 mg/kg LSD; ■----■ apomorphine + 0.1 mg/kg LSD + 0.1 mg/kg cyproheptadine; ◪----◪ apomorphine + 0.1 mg/kg LSD + 0.2 mg/kg cyproheptadine.

tive doses when given alone, potentiated the apomorphine hypermotility like LSD and produced the same aberrant behavior patterns as described above. The maximum effects were 138 and 145 crossed squares, respectively (Fig. 2). Contrary to LSD and DMT, mescaline did not influence the decreased motility after low doses of apomorphine.

Also d,l-amphetamine induced a dose dependent increase of open-field activity. Sterotyped sniffing occurred only after high doses of amphetamine. The hypermotility induced by amphetamine was potentiated by 0.1 mg/kg LSD in the same manner as the effect of apomorphine (Fig. 3). 50 mg/kg mescaline potentiated the amphetamine effect too (Fig. 3). The animals showed abnormal behavioral patterns as described above.

Cyproheptadine in doses of 0.1 and 0.2 mg/kg did not influence the locomotor activity of saline and apomorphine treated rats, but antagonized dose dependently the potentiating effect of LSD (Fig. 4).

DISCUSSION

The open-field test was used to evaluate the spontaneous locomotor activity or rats in the phase of exploration in a novel environment.

In dependence on the time interval after application and the size of the open-field the forward locomotion was not interrupted by stereotypies after high doses of apomorphine or d,l-amphetamine. The observed decrease of locomotor activity by low doses of apomorphine, already described by Strömbom [18], Maj *et al.* [14], and Di Chiara *et al.* [8], confirmed the sensitivity of the method for slight changes of locomotor activity. Nevertheless the psychotomimetics were ineffective in the low doses used. Therefore the potentiation of an increased locomotor activity represents a specific and quantitative measurable effect of the tested psychotomimetics. The potentiation effect occurred independently of the mode of dopaminergic locomotor stimulation. Apomorphine acts as a direct agonist at dopaminergic receptors, and amphetamine works by releasing and inhibiting the reuptake of catecholamines. Moreover, a dopaminergic action of psychotomimetics does not contribute to this potentiation effect, because these drugs were ineffective when given alone. Cyproheptadine antagonized the potentiating effect of LSD without altering the apomorphine induced hypermotility. This finding confirmed the primary and causal involvement of the serotonergic transmission system in the action of the tested psychotomimetics. Furthermore, the relation of equieffective doses of LSD, DMT, and mescaline in our experiments reflected their different inhibitory potencies at raphe neurons [1]. The inhibitory action of psychotomimetics at presynaptic serotonergic receptors seems to be responsible for the potentiating effect, whereas the stimulation of dopaminergic activity is a prerequisite to the realization of this effect.

A serotonergic modulation of the dopaminergic transmission can be assumed as a consequence of this interpretation. Also other evidence indicates that serotonergic fibers have an inhibitory input on dopaminergic transmission system, since median raphe lesion, pretreatment with 5,6-dihydroxytryptamine or p-chlorophenylalanine, and a tryptophan-free diet increase d-amphetamine induced hypermotility [2, 9, 11, 12, 16]. In addition, other studies have found a reduced action of classical neuroleptics after decreasing serotonergic activity [5, 4].

The uniformity of the potentiation by psychotomimetics with probably different mechanisms of action is amazing and indicates a characteristic and common effect of these drugs. In spite of the unique potentiation effect it is possible to differentiate their action by means of the decreased locomotor activity after low doses of apomorphine. Unlike mescaline, LSD and DMT abolished the decreasing effect of apomorphine.

Further investigations are necessary to elucidate the mechanism of action of psychotomimetics. At present this

behavioral test system is a useful tool to demonstrate a quantitative measurable behavioral effect of psychotomimetics in low doses in animals and it is suitable to study the action of other psychotropic drugs.

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