Psychopharmacology (1985) 85: 464–468

Locomotor effects of lisuride: A consequence of dopaminergic and serotonergic actions

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Abstract. The open-field test was used to study the involvement of serotonergic and dopaminergic mechanisms in the action of lisuride on locomotor activity in the rat. Lisuride produced a biphasic locomotor effect. The maximum locomotor stimulatory response of lisuride was stronger than that of apomorphine and comparable with that of apomorphine and LSD combined. Hypermotility induced by high doses of lisuride was partially suppressed by the serotonin antagonist cyproheptadine and not further enhanced by LSD. A moderate dose of lisuride potentiated apomorphine-induced hypermotility in the same manner as has been shown for LSD. Lesion of dopaminergic structures within the median raphe nucleus by 6-OHDA produced a potentiation of lisuride-induced hypermotility. This effect was suppressed by cyproheptadine. The locomotor inhibitory effect of low doses of lisuride may be related to a stimulation of presynaptic mesolimbic dopamine receptors. It is concluded that the locomotor stimulant effect of higher doses of lisuride may depend on stimulation of postsynaptic dopamine receptors and a serotonergic action and that the locomotor effects of lisuride reflect a complex interaction at dopaminergic and serotonergic transmission systems.

Key words: Dopamine agonist – Lisuride – Apomorphine – Locomotor activity – Serotonin agonist – Rat

A large number of studies have demonstrated that the ergot derivative lisuride interacts with the central dopaminergic, serotonergic and noradrenergic transmitter systems (Cote et al. 1979; Kehr 1977; Keller et al. 1983; Loew et al. 1979; Pieri et al. 1978, 1983).

In electrophysiological and neurochemical studies lisuride has been reported to act as a potent agonist at both dopaminergic and serotonergic receptors (Kehr 1977; Rogawski and Aghajanian 1979; Rosenfeld and Makman 1981; Tissari et al. 1983; Walters et al. 1979; Weir et al. 1981; White and Wang 1983).

In behavioural studies lisuride has been shown to induce locomotor inhibition and sedation in low doses, and locomotor stimulation, stereotypies, mounting behaviour and signs of the "serotonergic syndrome" in higher doses (Carruba et al. 1980; Carruba and Mantegazza 1983; Horowski and Wachtel 1976; Keller et al. 1983; Marini et al. 1981; Silbergeld et al. 1979; Silbergeld and Hruska 1979; Wachtel 1978).

At present, there are many open questions regarding the mechanisms underlying these behavioural effects. Thus, it is not clear which brain structures are involved in the expression of the "serotonergic syndrome" and how lisuride induces mounting behaviour. The mesolimbic-mesocortical dopaminergic transmission system has been accepted to play an important role in the control of locomotor activity. In previous papers we were able to demonstrate that locomotor activity is a suitable parameter to reflect interactions between the serotonergic system and the mesolimbic dopaminergic system and to characterize psychotropic drugs with respect to the transmission system primarily involved in their actions (Fink et al. 1979; Fink and Oelssner 1981; Fink et al. 1984; Morgenstern et al. 1983).

In the literature, the locomotor effects of lisuride were considered to be solely linked to the dopamine agonist properties without taking into account the action of lisuride on the central serotonergic system (Carruba and Mantegazza 1983; Wachtel 1978; Wachtel 1983; Wachtel and Schlangen 1979). Therefore, it was of interest to investigate lisuride-induced locomotor effects, in particular regarding the complex involvement of both serotonergic and dopaminergic functions.

Material and methods

Animals. The experiments were performed on male Wistar rats (VEB Versuchstierproduktion Schönwalde) weighing 140–160 g. They were housed in groups of 10 animals per cage at a room temperature of 22 ± 2° C and a 12-h light-dark schedule. The rats received food and water as required.

Measurement of locomotor activity. 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 sound proof room. Prior to the experiment the animals were adapted to that room for at least 2 h.

Locomotor activity of rats in a new environment was measured in an open-field, consisting of a 1-m × 1-m area surrounded by a 40 cm high wall. An array of 10 infrared light beams divided this area into 36 equal squares. The detector signals, produced by interrupting these photobeams, were fed into a digital logic providing a selective automatic counting of squares, crossed by the animal during a 5-min observation period. Repetitive interruptions

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of one photobeam induced by stereotyped behaviour, e.g., sniffing, rearing, or rotations were not registered.

Mounting behaviour was assessed in groups of animals prior to the open-field.

Rats were used only once.

Values are presented as the mean ± standard error of the mean (SEM). Drug effects were assessed using one-way analysis of variance; individual treatment groups were compared with *t*-test.

Drugs. The following drugs were used: Apomorphine hydrochloride (SPOFA), Cyproheptadine hydrochloride (Sharp & Dohme), Desipramine hydrochloride (AWD), 5,7-Dihydroxytryptamine creatinine sulfate (5,7-DHT) (Sigma), 6-Hydroxydopamine hydrochloride (6-OHDA) (Fluka), Lisuride hydrogenmaleate (Schering), Lysergic acid diethylamide tartrate (LSD) (SPOFA), Pargyline hydrochloride (Fahlberg-List), Sulpiride (Schürholz).

Lisuride, sulpiride, and cyproheptadine were generous gifts from the respective drug companies. All drugs were dissolved in 0.9% NaCl, except 6-OHDA, which was dissolved in 0.1% ascorbic acid.

All doses were calculated as the salt. The injection volume of intraperitoneally (IP) administered drugs was 10 ml/kg body weight. The interval between the injection of drug and the commencement of testing was 7 min for apomorphine, and 30 min for the other drugs.

6-OHDA and 5,7-DHT administration. Rats were anesthetized with sodium hexobarbital (120 mg/kg IP) and positioned in a stereotactic apparatus after pretreatment with desipramine (25 mg/kg IP); for 6-OHDA lesion the rats were additionally pretreated with pargyline (50 mg/kg IP). The neurotoxins 6-OHDA and 5,7-DHT or 0.9% NaCl were administered by means of a Hamilton µl syringe (CR 700-20) in a volume of 0.5 µl over a period of 2 min. The injection cannula had an outer diameter of 0.23 mm. The coordinates of the cannula tip were, according to König and Klippel for the median raphe nucleus A = 0.35; L = 0; V = 2.6. One week after surgery the behavioural experiments were carried out. Rats were killed after the experiment for histological examination. Data were discarded if the lesion was not in the raphe nucleus.

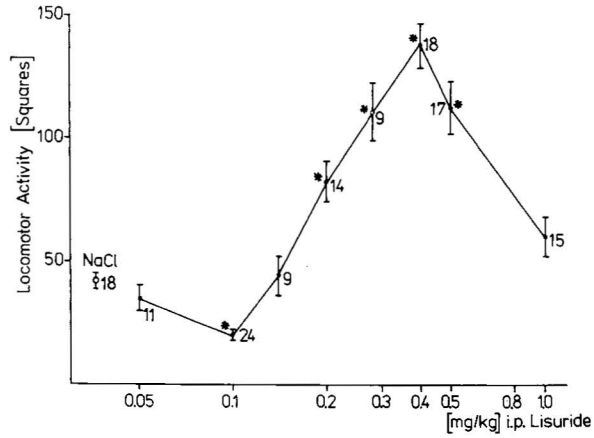

Fig. 1. Dose-response curve for lisuride effects (●) on locomotor activity. Crossed squares of an open-field were counted for 5 min. *Vertical bars* represent SEM. Numbers of rats used are shown in the figure. * $P < 0.001$ versus control (○)

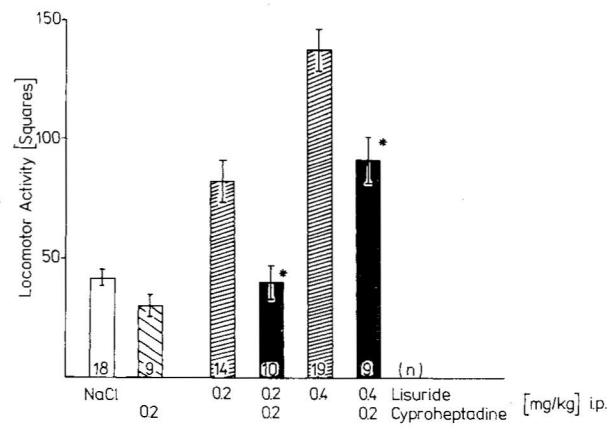

Fig. 2. Effect of cyproheptadine (0.2 mg/kg) on lisuride-induced hypermotility. Crossed squares of an open-field were counted for 5 min. *Columns* represent means ± SEM, *n* = number of rats. * $P < 0.005$ versus lisuride alone (0.2 mg/kg and 0.4 mg/kg, respectively)

Results

Figure 1 shows that lisuride induced a biphasic effect on locomotor activity of rats: a low dose (0.1 mg/kg IP) decreased and higher doses (0.2–0.4 mg/kg IP) increased motility dose dependently ($F_{7,116} = 31.3$, $P < 0.001$). A dose of 0.4 mg/kg lisuride produced the maximum stimulant response. Following higher doses of lisuride (0.4 mg/kg and higher) signs of the behavioural "serotonin syndrome", e.g., Straub tail, hindlimb abduction, head weaving, tremor, vocalisation, stereotypies, and mounting were observed.

Figure 2 shows that cyproheptadine at a dose which did not alter spontaneous locomotor activity significantly but which has been shown to antagonize serotonergic-induced locomotor effects (Gold et al. 1980) attenuated lisuride-induced hyperlocomotion. Additionally, lisuride-induced mounting behaviour was suppressed by cyproheptadine.

LSD, given in a low dose, which was ineffective by itself, but has been shown to produce a serotonergic locomotor effect in combination with dopaminergic drugs (Fink et al. 1979), abolished the locomotor inhibitory effect of lisuride and actually induced locomotor hyperactivity.

Figure 3 shows that the potentiating effect of LSD on lisuride-induced locomotor hyperactivity disappeared with increasing doses of lisuride.

Figure 4 shows that destruction of serotonergic neurons within the median raphe nucleus by 5,7-DHT, which has been demonstrated to produce degenerations at polygonal raphe neurons and dendritic structures of fusiform ones (Hölzel et al. 1984), potentiated slightly hypermotility induced by 0.2 mg/kg lisuride. Mounting behaviour was induced by the combination of LSD with a dose of lisuride (0.2 mg/kg), which did not produce this behavioural effect by itself.

Figure 5 shows that apomorphine also induced a biphasic locomotor effect ($F_{4,66} = 12.75$, $P < 0.001$). However, the maximum stimulatory effect was significantly

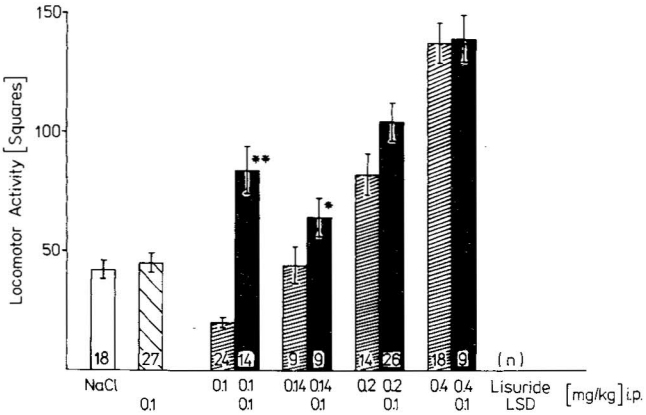

Fig. 3. Influence of LSD (0.1 mg/kg) on lisuride-induced locomotor effects. Crossed squares of an open-field were counted for 5 min. *Columns* represent means ± SEM, n = number of rats. ** $P < 0.005$ versus lisuride (0.1 mg/kg) and LSD (0.1 mg/kg), respectively, * $P < 0.02$ versus lisuride (0.14 mg/kg) and LSD (0.1 mg/kg), respectively

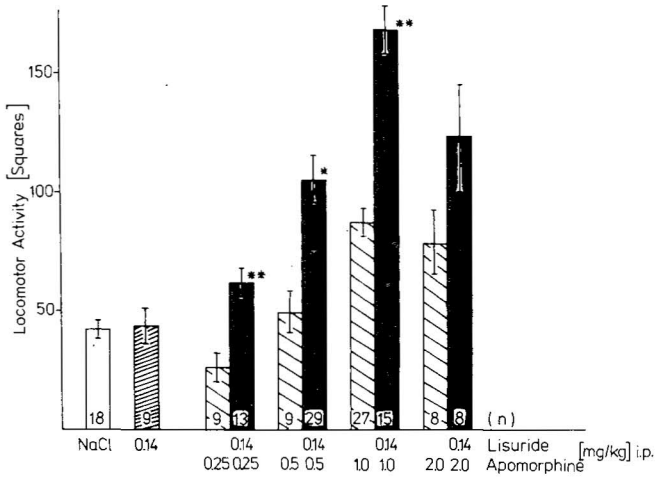

Fig. 5. Influence of increasing doses of apomorphine on locomotor effect induced by 0.14 mg/kg lisuride. Crossed squares of an open-field were counted for 5 min. *Columns* represent means ± SEM, n = number of rats. ** $P < 0.002$, * $P < 0.01$ versus corresponding apomorphine control

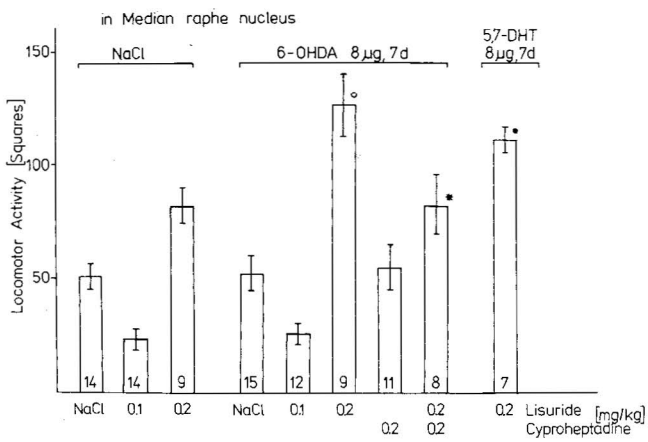

Fig. 4. Influence of lesion of the median raphe nucleus by 6-OHDA or 5,7-DHT on lisuride-induced locomotor effects. Crossed squares of an open-field were counted for 5 min. *Columns* represent means ± SEM, n = number of rats. ○ $P < 0.002$, • $P < 0.05$ versus lisuride (0.2 mg/kg) in unlesioned rats, * $P < 0.02$ lisuride (0.2 mg/kg) in 6-OHDA lesioned rats

Table 1. Effect of apomorphine and sulpiride on lisuride-induced locomotor inhibition

Drug	Dose (mg/kg)	Locomotor activity (Mean of crossed squares ± SEM)	Number of rats
NaCl		42.6 ± 4.2	18
Lisuride	0.1	20.9 ± 2.2*	24
Apomorphine	0.25	19.6 ± 4.3*	18
Lisuride + Apomorphine	0.1 0.25	40.9 ± 12.3**	8
Sulpiride +	4.0	38.3 ± 4.4	24
Lisuride + Sulpiride	0.1 4.0	37.9 ± 5.9***	10

* $P < 0.002$ versus NaCl
** $P < 0.05$ versus apomorphine and lisuride
*** $P < 0.005$ versus lisuride

lower ($P < 0.001$) than that of lisuride. The apomorphine-induced hypermotility was potentiated by pretreatment with lisuride in a dose of 0.14 mg/kg. The locomotor depressant effect of apomorphine was abolished by this and a lower dose of lisuride (Fig. 5, Table 1).

Sulpiride did not induce any locomotor effect when given alone, but antagonized the sedative lisuride effect (Table 1). After 6-OHDA injection into the median raphe nucleus [^{3}H]-dopamine uptake (1×10^{-7} M [^{3}H]-dopamine) in a crude synaptosomal fraction prepared from punches of the median raphe nucleus was decreased to 54 ± 7% ($n = 8$), indicating lesion of dopaminergic terminals (K. Drescher, personal communication).

In Fig. 4 it is shown that after 6-OHDA injection into the median raphe nucleus lisuride-induced locomotor inhibition was not affected, whereas locomotor stimulation produced by a high dose of lisuride was potentiated. This potentiating effect was suppressed by cyproheptadine.

Discussion

Lisuride and the dopamine agonist apomorphine produced very similar locomotor dose-response curves following systemic administration: both curves are biphasic, with low doses reducing and high doses increasing locomotor activity (Figs. 1, 5). The curves are similar in slope, whereas the maximum stimulant effect of lisuride was considerably higher than that of apomorphine. On a molar base, lisuride was three times more potent than apomorphine in respect of induction of locomotor effects.

The reduction in spontaneous locomotor activity by a low dose of lisuride seems to be compatible with a stimulation of presynaptic dopamine receptors in the mesolimbic system as has been demonstrated in neurochemical experiments (Kehr 1977; Tissari et al. 1983;

Tissari and Gessa 1983). In accordance with the finding of Wachtel (1978) it was shown that the presynaptic dopamine antagonist sulpiride prevented the inhibitory locomotor effect of lisuride (Table 1). After combined injection of locomotor depressant doses of lisuride and apomorphine, the locomotor inhibition was not augmented, but abolished, indicating that the total dose of dopamine agonists is large enough to stimulate postsynaptic dopamine receptors (Table 1).

LSD in a low dose, ineffective when given alone, abolished the sedative effect of lisuride and produced locomotor stimulation (Fig. 3). This is in accordance with our previous findings that LSD also prevents the inhibitory apomorphine effect, and that LSD induced this effect by a serotonin agonist action (Fink and Morgenstern 1984b). Thus, serotonergic mechanisms do not seem to be involved in the sedative effect of lisuride. Therefore, this lisuride effect is compatible with a stimulation of presynaptic dopamine receptors.

However, the locomotor stimulant effect of higher doses of lisuride is not satisfactorily explained solely by stimulation of postsynaptic dopamine receptors in the mesolimbic system, since the maximum locomotor response of lisuride is higher than that of dopamine agonists, e.g., apomorphine (Fig. 5) and amphetamine (Fink et al. 1979). Electrophysiological and neurochemical studies revealed a marked central serotonin agonist property of lisuride in addition to its dopamine agonist action (Kehr 1977; Rogawski and Aghajanian 1979; Rosenfeld and Makman 1981; Tissari et al. 1983; Walters et al. 1979; Weir et al. 1981; White and Wang 1983). Considering these findings, an attempt will now be made to compare the locomotor stimulant effect of lisuride with that of the drug combination of apomorphine and LSD. LSD has been previously demonstrated to act in a low dose as a serotonin agonist preferentially at presynaptic receptors on serotonergic raphe neurons, resulting in a reduced activity of the serotonergic system. It is well established that changes of serotonergic activity may alter dopaminergic effects (See Fink and Oelssner 1981).

Whereas low doses of LSD failed to alter spontaneous locomotor activity, hypermotility induced by dopamine receptor stimulation was potentiated (Fink et al. 1979). The maximum locomotor response induced by apomorphine plus LSD was comparable to that induced by lisuride.

The LSD-induced potentiation effect has been shown to be suppressed by serotonin antagonists (Gold et al. 1980).

In parallel, lisuride-induced locomotor hyperactivity was strongly inhibited by the serotonin antagonist cyproheptadine. This corresponds to the finding that LSD failed to potentiate hyperactivity induced by a high dose of lisuride (Fig. 3). Furthermore, the locomotor effect of increasing doses of apomorphine was potentiated by lisuride (Figs. 1, 5). The maximum response produced by this combined drug treatment was similar to that of high doses of lisuride alone and that of apomorphine plus LSD, respectively (Fink et al. 1979). These findings are in line with the hypothesis that in addition to the dopaminergic action, a serotonergic component, which is comparable with the serotonergic action of LSD, may also contribute to hypermotility induced by high doses of lisuride.

Lisuride produced signs of the "serotonergic syndrome", which has been observed also after combined injection of apomorphine and LSD or after injection of higher doses of LSD alone (Fink et al. 1979; Silbergeld and Hruska 1979). Besides that, lisuride-induced mounting behaviour was influenced by cyproheptadine and by LSD. Thus, our results support those findings in the literature, which indicate a serotonergic involvement in the induction of these behavioural effects (Horowski 1983; Keller et al. 1983; Silbergeld and Hruska 1979).

Recently, we found that the potentiating effect of sulpiride on apomorphine hypermotility was prevented by 6-OHDA lesion of the median raphe nucleus, suggesting that dopaminergic terminals in this nucleus may play a role in the mediation of locomotor effects (Fink and Morgenstern 1984a). The lisuride-induced hypermotility was potentiated by 6-OHDA lesion of the median raphe nucleus (Fig. 4). It is likely, therefore, that this potentiation effect is produced by an action of lisuride at supersensitive postsynaptic dopamine receptors on raphe neurons. Since cyproheptadine abolished the potentiation effect, it is conceivable that the potentiation effect is mediated by the serotonergic system. It is suggested that both serotonin and dopamine receptor stimulation by lisuride contributes to an inhibition of serotonergic activity, facilitating hypermotility. The sedative lisuride effect is not influenced by 6-OHDA lesion of the median raphe nucleus, indicating that dopamine receptors in the median raphe nucleus do not play a role in lisuride-induced sedation.

In conclusion, our results suggest that the locomotor effects of lisuride can be related to a complex action involving both dopaminergic and serotonergic mechanisms.

Acknowledgement. We thank Mrs. Cornelia Tanneberger for excellent technical assistance.

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Received June 6, 1984; Final version October 30, 1984