Pharmacology Biochemistry & Behavior, Vol. 18, pp. 13–17, 1983. Printed in the U.S.A.

LSD-Potentiated Apomorphine Hypermotility: A Model for Differentiating Antipsychotic Drugs

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Received 28 May 1982

MORGENSTERN, R., H. FINK AND W. OELSSNER. *LSD-potentiated apomorphine hypermotility: A model for differentiating antipsychotic drugs.* PHARMACOL BIOCHEM BEHAV **18**(1) 13–17, 1983.—The model of LSD-potentiated apomorphine hypermotility (LPAH) in rats in comparison to apomorphine-induced hypermotility (AH) was used to investigate typical and atypical neuroleptics by analyzing complete dose response curves. Haloperidol (0.06 mg/kg) induced a parallel shift to the right of both the AH and LPAH dose response curves indicating dopaminolytic properties without any serotonolytic effect. Chlorpromazine (0.5 mg/kg) caused a mixed inhibitory effect on the LPAH, whereas the AH was not affected, probably due to the variety of actions at different transmission systems. Clozapine (0.125 mg/kg) anatagonized the LSD effect indicating serotonolytic properties, whereas an additive influence on the AH might be caused by its cholinolytic properties. Sulpiride (10 mg/kg) potentiated both the AH and the LPAH, probably due to presynaptic dopaminergic mechanisms. Two conclusions can be drawn: (1) The results agree with and support the idea of a serotonergic modulation of the (predominant) mesolimbic dopaminergic system in the induction of locomotor effects. (2) The model of LPAH is useful to clearly differentiate typical from atypical neuroleptics, and to obtain information whether there is a primary involvement of dopaminergic or serotonergic mechanisms.

Locomotor activity Apomorphine Lysergic acid diethylamide (LSD) Haloperidol Chlorpromazine Clozapine Sulpiride

THE mesolimbic-mesocortical dopaminergic system [16,47] has been shown to be an important site for both the actions of neuroleptics and dopaminergic drugs [6, 31, 43]. Although there is much evidence for a role of this system in the control of locomotor activity [11, 12, 25, 39] its relevance to an antipsychotic action is only purely understood [23]. However, the current opinion would favor a mesolimbic-mesocortical involvement in the antipsychotic action of neuroleptics [1, 3, 10, 15, 24], and there is an extensive literature dealing with the influence of neuroleptics on locomotor activity as the most typical behavioral effect representing the activity level of the mesolimbic dopaminergic system [11, 12, 25, 30, 35, 39, 40].

Much work has been done to elucidate the pharmacological mechanisms of action of antipsychotic drugs; however, the results obtained with the atypical neuroleptics have been rather confusing [4, 5, 9, 35, 41, 42, 45].

In the last few years, it was established that changes of serotonergic activity may alter dopaminergic effects [7, 13, 14, 20, 22, 26, 36]. Recently, we could demonstrate that different psychotomimetics like LSD, mescaline, and DMT in low doses potentiate locomotor hyperactivity induced by dopaminergic drugs [18], and that this potentiating effect can be antagonized by 5-HT antagonists like cyproheptadine, danitracen, mianserin, and pizotifen [18,21], in a very specific manner. More recently, we could show that the potentiating effect of LSD on dopaminergic-induced locomotor hyperactivity can be evoked and antagonized by microinjection of LSD and methysergide, respectively, into the median but not the dorsal raphe nucleus [19,37].

Thus, we produced further evidence in support of the hypothesis that LSD potentiates dopaminergic-induced locomotor activity by its inhibitory action upon serotonergic neurons. The present study uses the model of LPAH as it was introduced by us [18,38] three years ago. In view of our previous results it seemed highly interesting to test whether different types of neuroleptic drugs having different clinical profiles would differ in their capability of influencing the LPAH. In this paper we now report that the model is quite advantageous to differentiate neuroleptics as to their possible influence on various synaptic mechanisms. Furthermore, regarding the dopaminergic-serotonergic interaction in mesolimbic areas the results favor a predominant role of a dopaminergic system, which is modulated by a serotonergic one.

METHOD

The experiments were carried out on male Wistar rats weighing 150±20 g. The animals were housed in groups of 10 per cage under a room temperature of 22±2°C and with a 12 hours light/dark schedule (6:00 a.m.–6:00 p.m.). They re-

TABLE 1
DOSES AND APPLICATION INTERVAL OF THE DRUGS USED

Drug	Dose (mg/kg)	Application interval (min)
Apomorphine-HCl (Spofa)	0.125–16.0	7
Lysergic acid diethyl-amide tartrate (Spofa)	0.1	30
Haloperidol (Orion)	0.03 - 4.0	30
Chlorpromazine-HCl (Rodleben)	0.125–16.0	30
Clozapine (Sandoz)	0.015–16.0	30
Sulpiride (Schürholz)	0.25 -64.0	30

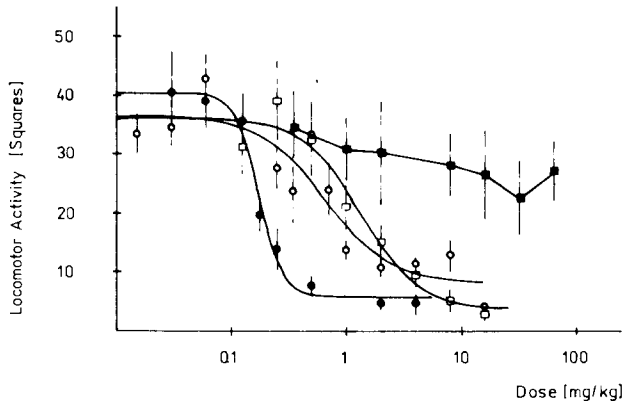

FIG. 1. Dose response curves of spontaneous locomtor activity influenced by increasing doses of neuroleptic drugs. The points represent the mean value (±standard error of the mean) of at least ten animals. ● haloperidol; ○ clozapine; ■ sulpiride; □ chlorpromazine.

ceived food and water ad lib 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. Prior to the experiment the animals were allowed to adapt to that room for two hours.

A white wooden open field cage was used consisting of a 1×1 mm 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 the administration of the drug the rat was returned to its home cage. At the time of the maximum response to the drug administered the animal was put to the middle of the open field cage. Immediately starting the spontaneous locomotor activity of the rat was measured by the number of crossed squares counted by an observer for a period of 5 minutes. All drugs (Table 1) were injected intraperitoneally in a volume of 1 ml/100 g body weight. The drugs were dissolved in minor amounts of tartaric acid (clozapine), acetic acid (haloperidol, sulpiride) and diluted with water or in 0.9% NaCl (chlorpromazine, apomorphine, LSD). Controls were treated with the corresponding amount of saline. Complete dose response curves were fitted by using a nonlinear regression procedure [34]. Each point of the curves represents the mean value of at least 10 animals.

RESULTS

Dose Response Curves of the Neuroleptics

The saline treated animals crossed about 38 squares. Haloperidol, chlorpromazine, and clozapine induced a dose dependent depression of spontaneous locomotor activity whereas sulpiride up to a dose of as high as 64 mg/kg was without any significant locomotor effect. The dose response curves of haloperidol, chlorpromazine, and clozapine differed markedly in slope and ED_{50} value.

The slope of the dose response curve of haloperidol was found to be the steepest one; the slope of the clozapine dose response curve was rather flat; and the chlorpromazine dose response curve had a medium steep slope (Fig. 1).

These dose response curves were used to select the following "subeffective" doses for the next experiments: haloperidol 0.06 mg/kg, chlorpromazine 0.5 mg/kg, and clozapine 0.125 mg/kg. For sulpiride a dose of 10 mg/kg was chosen.

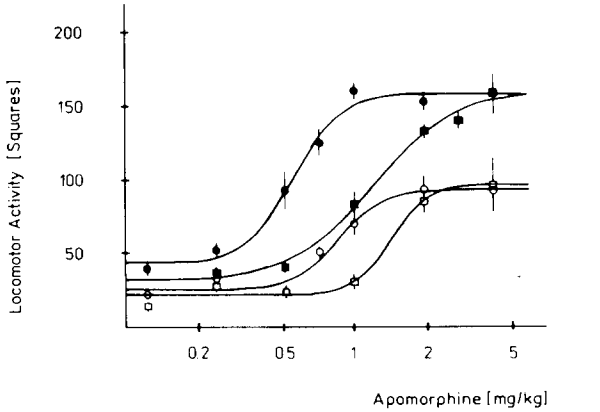

FIG. 2. Effect of haloperidol (0.06 mg/kg) on apomorphine and LSD-potentiated apomorphine hypermotility. The points represent the mean vlaue (±standard error of the mean) of at least ten animals. ○ apomorphine; □ apomorphine + haloperidol; ● apomorphine + LSD; ■ apomorphine + LSD + haloperidol.

Effects of the Neuroleptics on Apomorphine Hypermotility

It is demonstrated in Fig. 2 that the dose response curve of apomorphine is shifted to the right by haloperidol (increase of ED_{50} from 0.85 mg/kg to 1.45 mg/kg; see Table 2). In the given low dose, chlorpromazine was without any significant effect on the AH (Fig. 3). Contrary to haloperidol, clozapine induced a parallel shift of the apomorphine dose response curve to the left (Fig. 4). Sulpiride strongly potentiated AH, i.e., the locomotor effect of apomorphine was increased at each dose level by a fixed dose of sulpiride (Fig. 5). The ED_{50} values of apomorphine to produce locomotor hyperactivity at fixed doses of the neuroleptics in comparison to that of saline treatment provide a measure of the neuroleptic-induced shift of the dose response curve (Table 2).

TABLE 2

ED_{50} VALUES (mg/kg) OF APOMORPHINE (WITHOUT AND WITH 0.1 mg/kg LSD) HYPERMOTILITY AT FIXED DOSES OF NEUROLEPTICS

Drug (mg/kg)		Locomotor hyperactivity APO	APO+LSD
Saline		0.85	0.54
Haloperidol	0.06	1.45	1.21
Chlorpromazine	0.5	0.82	0.63
Clozapine	0.125	0.64	0.57
Sulpiride	10.0	0.69	0.64

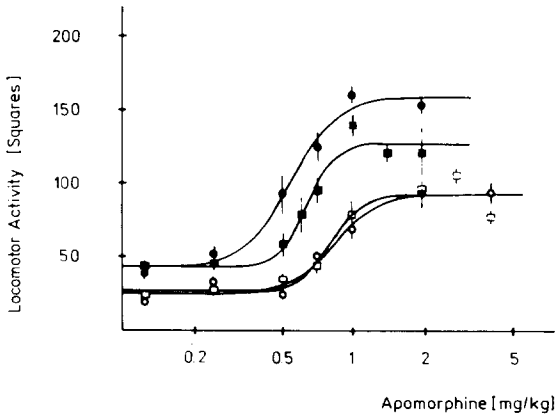

FIG. 3. Effect of chlorpromazine (0.5 mg/kg) on apomorphine and LSD-potentiated apomorphine hypermotility. The points represent the mean value (±standard error of the mean) of at least ten animals. ○ apomorphine; □ apomorphine + chlorpromazine; ● apomorphine + LSD; ■ apomorphine + LSD + chlorpromazine.

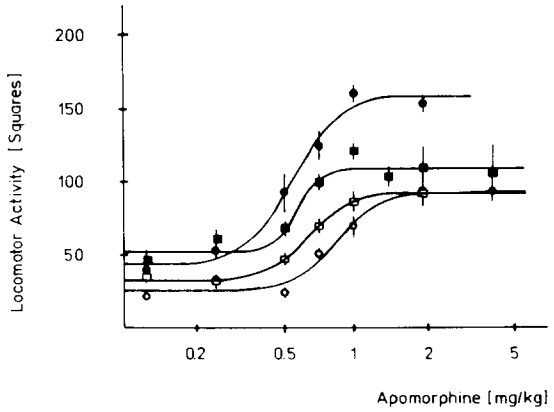

FIG. 4. Effect of clozapine (0.125 mg/kg) on apomorphine and LSD-potentiated apomorphine hypermotility. The points represent the mean vlaue (±standard error of the mean) of at least ten animals. ○ apomorphine; □ apomorphine + clozapine; ● apomorphine + LSD; ■ apomorphine + LSD + clozapine.

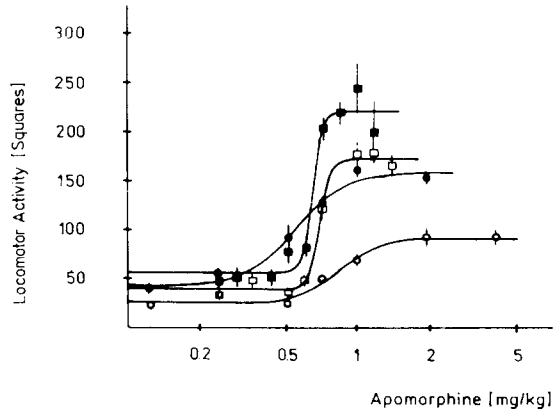

FIG. 5. Effect of sulpiride (10 mg/kg) on apomorphine and LSD-potentiated apomorphine hypermotility. The points represent the mean value (±standard error of the mean) of at least ten animals. ○ apomorphine; □ apomorphine + sulpiride; ● apomorphine + LSD; ■ apomorphine + LSD + sulpiride.

Effects of the Neuroleptics on LSD-Potentiated Apomorphine Hypermotility

The LPAH was inhibited by haloperidol in the same way as was the AH, i.e., the dose response curve was shifted to the right (Fig. 2). Chlorpromazine produced both a slight parallel shift and a significant depression of the maximum response (Fig. 3).

After clozapine, the dose response curve of the LPAH was strongly suppressed, without any parallel shift (Fig. 4). Sulpiride was found to further increase the LPAH (Fig. 5). The ED_{50} values of LPAH at fixed doses of the neuroleptics are given in Table 2.

DISCUSSION

The dopaminergic-induced locomotor hyperactivity and the neuroleptic-induced locomotor hypoactivity are generally assumed to be closely related to functions of the mesolimbic dopaminergic system [11–14, 25, 28, 30, 39]. Classical neuroleptics strongly block postsynaptic dopamine receptors, thus antagonizing the effects of dopaminergic agonists or, when given alone, prevent the effects of physiologically liberated dopamine [41].

This is the usual explanation of their locomotor inhibitory effect. Atypical neuroleptics were suggested to influence rather mesolimbic than nigrostriatal dopaminergic mechanisms [2,6]. Therefore, it seems somewhat contradictory that the dose response curve of the clozapine-induced locomotor inhibition (Fig. 1) is very flat. Moreover, sulpiride even in very high doses did not suppress spontaneous locomotor activity, a behavior closely related to the activity of the mesolimbic dopaminergic system [11, 12, 25, 30, 39]. Therefore, major non-postsynaptic dopamine receptor blocking properties of clozapine and sulpiride must be taken into account (see below) [12,29].

The potentiating effect of LSD (or mescaline) on dopaminergic-induced locomotor hyperactivity was estab-

lished to be a serotonergic inhibitory effect on the serotonergic cells within the median raphe nucleus and it was concluded that the mesolimbic dopaminergic system is modulated by this serotonergic one [18, 19, 21, 37, 38]. Therefore, "competitive" parallel shifts of the dose response curves of both AH and LPAH, are not surprising and can be explained as the result of the dopaminolytic effect of haloperidol. A serotonolytic effect of haloperidol was not seen in our experiments. Chlorpromazine is well known to exhibit a variety of actions on different transmission systems (see e.g., [41]). In the dose used it had no effect on AH whereas the LSD-potentiated dose response curve was slightly shifted to the right while already depressed. These findings confirm the broad spectrum of actions upon a variety of receptors [24]. Clozapine, an atypical neuroleptic [45] lacking antidopaminergic activity in several animal tests [4, 5, 41, 45], differed clearly from the classical neuroleptic haloperidol. The slight parallel shift of the AH dose response curve to the left may be explained by the rather strong central cholinolytic action of clozapine [5, 24, 33, 44] since dopaminergic and cholinolytic drugs act additive in the induction of locomotor hyperactivity [17]. The LPAH was inhibited by clozapine in the same way as it was influenced by 5-HT antagonists [18,21]: It is only the LSD potentiation that is abolished by clozapine whereas the apomorphine-induced hyperlocomotion itself is not inhibited. To explain this phenomenon, we could produce some experimental (behavioral and neurochemical) evidence that this serotonolytic effect of clozapine [29] is induced within the median raphe nucleus (in preparation). Sulpiride, a substituted benzamide drug [32,46] produced locomotor effects which are not necessarily adequate to predict an antipsychotic activity [27] since the AH and the LPAH were potentiated. In further studies with sulpiride we found that it potentiates the scopolamine-induced hypermotility, induces a dose dependent locomotor hyperactivity when given together with a subeffective dose of LSD, and has some activity to antagonize the sedative apomorphine effect (in preparation). In agreement with the literature on sulpiride [8, 9, 42, 46] we assume that presynaptic dopaminergic mechanisms are involved in these effects.

It can be summarized that the results of the present study are in support of the idea of a serotonergic modulation of the mesolimbic dopaminergic system. The model of LPAH [18, 37, 38] could be demonstrated to be useful for differentiating typical and atypical neuroleptic drugs. Furthermore, the model permits a preclassification of psychotropic drugs into preferential dopaminolytic and preferential serotonolytic drugs.

ACKNOWLEDGEMENT

The Authors wish to thank Miss G. Baunack, Mrs. C. Tanneberger and Mrs. R. Winter for their excellent technical assistance.

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