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Psychopharmacology 65, 233 – 237 (1979)

Psychopharmacology

Psychopharmacology (Berl.) 65, 233-237 (1979). DES 1584

Lisuride and LSD: Dopaminergic and Serotonergic Interactions in the "Serotonin Syndrome"

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Abstract. A characteristic behavioral syndrome has been associated with stimulation of central serotonin receptors in rats. This behavior can be produced by inhibition of monoamine oxidase and administration of 5-hydroxytryptophan as well as by direct acting serotonergic agonists. LSD and the novel ergot derivative lisuride produced this syndrome in rats. These drugs possess both serotonergic and dopaminergic properties. Since changes in dopaminergic function have also been reported to affect the so-called serotonin syndrome, it was not clear how the two ergot drugs acted to produce this syndrome. The syndrome produced by pargyline and 5-hydroxytryptophan methyl ester was blocked by haloperidol, methysergide, para-chlorophenylalanine, and alpha-methylparatyrosine; these treatments failed to block the effects of lisuride. Metoclopramide did not block the syndrome produced by either lisuride or pargyline plus 5-hydroxytryptophan methyl ester. Methysergide partially blocked the behavioral effects of LSD; pretreatment with either haloperidol or metoclopramide potentiated and prolonged the behavioral effects of LSD. The results suggest that dopaminergic modulation of the serotonin syndrome occurs before the serotonin receptor involved in this behavior. Also, the differences between LSD and lisuride may be relevant to their different psychopharmacological properties.

Key words: Serotonin – Behavior – LSD – Lisuride – Dopamine – Ergots

Increased activation of central serotonergic neurons has been associated with the behavioral expression of hyperactivity and a distinct set of stereotyped activities in the rat (Grahame-Smith, 1971; Green and Grahame-Smith, 1976; Jacobs, 1976; Sloviter et al., 1978). This behavior is distinguishable from the stereotypy associated with apomorphine (and other drugs that increase stimulation of dopamine receptors) by the appearance of the following signs: A rapid resting tremor, particularly of the body; rigidity of the body musculature; raised or rigid tail; kneading of the forepaws; abducted position of the hindlimbs; and head twitches. This behavior, referred to here as the serotonin syndrome, can be produced by inhibition of monoamine oxidase (MAO) and by the administration of tryptophan or 5-hydroxytryptophan (5-HTP), the metabolic precursors of serotonin (5-hydroxytryptamine) (5-HT). In addition, administration of tryptophan, 5-HTP, 5-HT, or 5-methoxy-N,N-dimethyltryptamine, or *d*-lysergic acid diethylamide (LSD) also produces signs of the serotonin syndrome (Jacobs, 1976). On this basis, Jacobs (1976) has suggested that the syndrome can be used as a behavioral assay for compounds thought to possess central serotonergic activity.

However, there are two problems associated with the direct equation of these behavioral signs with central serotonergic stimulation. First, there is not a good correlation between motor responses and neurochemical measurements of increased serotonergic function, such as levels of 5-HT, its synthesis or accumulation (Foldes and Costa, 1975). Second, the serotonin syndrome is significantly influenced by drugs that act primarily on dopaminergic neurotransmission. The syndrome as produced by MAO inhibition and 5-HTP administration, can be blocked by pretreatment with the dopamine (DA) antagonists spiroperidol, alpha-flupenthixol, or haloperidol (Jacobs et al., 1974; Green and Grahame-Smith, 1976), as well as by the serotonin receptor blockers methysergide or cinanserin (Jacobs, 1974). It can also be blocked by inhibition of DA synthesis by alpha-methylparatyrosine (Green and Grahame-Smith, 1974), as well as by inhibition of 5-HT synthesis by para-chlorophenylalanine (PCPA) (Jacobs,

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0033-3158/79/0065/0233/$01.00

1976). Thus, although production of the syndrome appears to require 5-HT receptor stimulation, expression of the syndrome can be significantly modulated by manipulations of dopaminergic function. The nature of this interaction between DA and 5-HT in producing the syndrome is not well understood (Jacobs, 1976; Green and Grahame-Smith, 1976).

Lisuride and LSD are ergot derivatives which, on the basis of neurochemical and behavioral studies, are reported to act as potent agonists at both serotonergic and dopaminergic receptors in the central nervous system (CNS) (Horowski and Wachtel, 1976; Kehr, 1977; Silbergeld et al., 1979). However, unlike LSD, lisuride is reported to be nonhallucinogenic (Pieri et al., 1978). Because of their similar neurochemical properties but dissimilar psychotropic nature, it was of interest to investigate further their behavioral effects, particularly as these were related to 5-HT function. In addition, experiments were performed with these two ergots to investigate the nature of the dopaminergic regulation of the serotonin syndrome.

Materials and Methods

All studies used male Sprague-Dawley rats (Taconic Farms) (150–300 g). Each animal was used in only one drug trial. Drugs were dissolved in saline, and injected IP in a concentration such that the volume administered was 0.1 or 0.2 ml/100 g body weight. When drugs were dissolved in media other than saline, control rats were injected on a equivalent volume/body weight basis with the media used for solution. The following compounds (and suppliers) were used: LSD bitartrate (Sandoz), haloperidol (injectable, McNeil), apomorphine (Merck), para-chlorophenylalanine (PCPA; Sigma), alpha-methylparatyrosine (AMPT; Sigma), methysergide (Sandoz), pimozide (Janssen), metoclopramide (Beecham), 5-HTP methyl ester (Sigma), lisuride (Schering, A.G.), and pargyline (Sigma). Doses used in these studies are based on the salts. All drug solutions were made immediately before use.

The serotonin syndrome was produced by IP administration of either the MAO inhibitor pargyline, followed 25 min later by the soluble salt of 5-HTP, 5-HTP methyl ester, or by the ergot drugs lisuride or LSD. Rats were caged in groups of four and at 10- or 15-min intervals each animal was observed by at least two observers (whose scores were averaged) for the presence of the following signs: Tremor, body rigidity, forepaw kneading, abducted hindlimbs, raised or rigid tail, or head twitches. Behavioral scores were based only on the number of signs present (0–6); the scores do not reflect intensity of behavioral signs. Other behaviors were noted as these occurred. For all drugs, mean scores were determined for each dose and treatment category and the groups compared by *t*-test of sample means.

Results

The number of signs of the serotonin syndrome present was related to the dose of 5-HTP methyl ester (Fig. 1). At doses of 50, 100, or 150 mg/kg, more than half of the rats died within 60 min after drug administration; thus these high doses were not used in further studies. Rats given doses of 25 mg/kg or less appeared behaviorally normal within 4 h after drug administration.

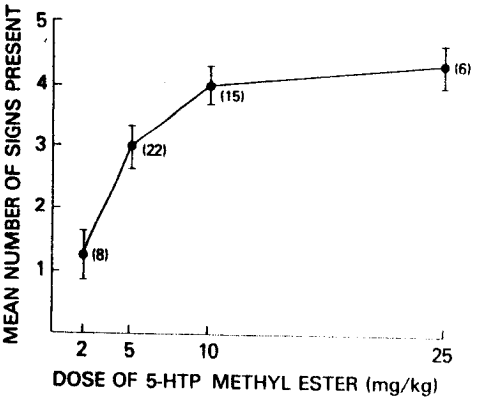

Fig. 1. Dose-response curve of 5-HTP methyl ester administered to rats pretreated with pargyline (50 mg/kg). Number of signs present was determined 90 min after the injection of 5-HTP methyl ester; each point is the mean ± SEM for the number of animals indicated in parentheses

LSD and lisuride both produced the serotonin syndrome when administered alone, without prior MAO inhibition or 5-HTP administration. The syndrome associated with these two drugs was indistinguishable. For lisuride, the maximum mean score was related to dose; at 0.1 mg/kg the maximum mean score was 2.75, at 0.25 mg/kg it was 3.75, at 1.0 mg/kg it was 4, and at 1.5 mg/kg it was 5. However, the initial score (10 min after drug administration) or the duration of scores greater than 1.0 was not directly related to the dose of lisuride. At doses greater than 0.1 mg/kg, the duration was at least 90 min. The lack of a clear dose-response relationship for lisuride may result from the induction of other behaviors at doses greater than 0.25 mg/kg. These behaviors included male-to-male mounting behavior and stereotyped fighting. For LSD, doses of 1.0 mg/kg or less did not produce scores greater than 2, and in most cases the only sign present was body rigidity. At doses of 1.5 or 2.0 mg/kg, signs of the serotonin syndrome (five of six) appeared within 2 min after administration of LSD, and the number of signs was maximal at 10 min after administration. At 40 min a mean of only two signs or less was present at all doses.

The serotonin syndrome produced by pargyline and 5-HTP methyl ester can be blocked by haloperidol, AMPT, methysergide, or PCPA (Table 1). However, these treatments did not block the syndrome produced by lisuride. Metoclopramide or apomorphine did not affect the syndrome produced by either lisuride or pargyline and 5-HTP methyl ester (Table 1). The interactions of these drugs with LSD was more complex. Methysergide (1 mg/kg) given 15 min before LSD

Table 1. Effect of drugs on the serotonin syndrome produced by pargyline and 5-HTP methyl ester or by lisuride

Drug	Dose (mg/kg)	Time before treatment (h)	Treatment	
			Pargyline (50 mg/kg) and 5-HTP methyl ester (5 mg/kg)	Lisuride (0.5 mg/kg)
PCPA	3 × 100	49, 25, 1	Blocks	No effect
Methysergide	1	0.25	Blocks	No effect
AMPT	100	1	Blocks	No effect
Haloperidol	2	0.25	Blocks	No effect
Metoclopramide	20	0.25	No effect	No effect
Apomorphine	2	0.25	No effect	No effect

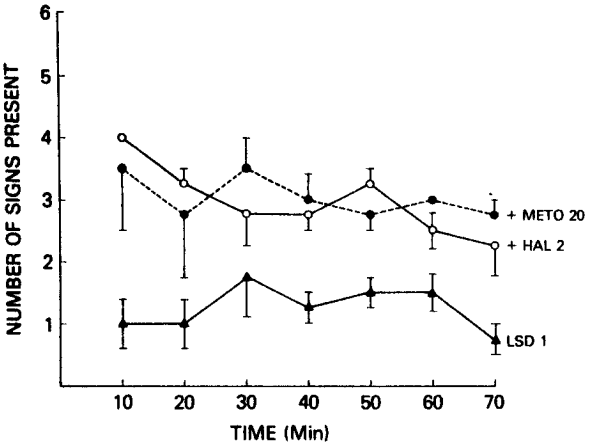

Fig. 2a. Effect, over time, of metoclopramide (METO) (20 mg/kg) and haloperidol (HAL) (2 mg/kg) on the number of signs of the serotonin syndrome produced by LSD (1 mg/kg). Each point is the mean ± SEM of four rats; METO pretreatment significantly increased the number of signs present (except at 20 min); HAL significantly increased the number of signs present (except at 30 min)

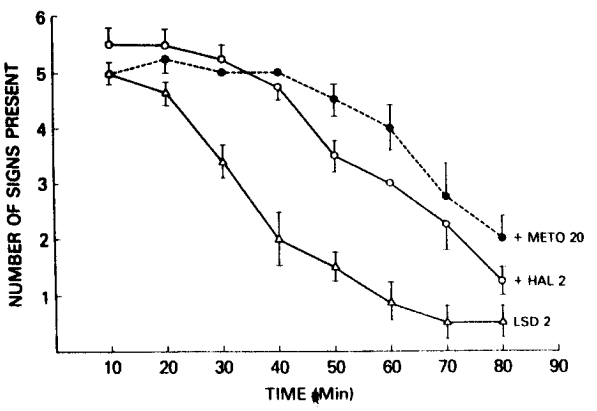

Fig. 2b. Effect, over time, of METO and HAL (same doses as Fig. 2a) on the number of signs of the serotonin syndrome produced by LSD (2 mg/kg): Each point is the mean ± SEM of four rats: Both METO and HAL significantly increased the number of signs present 30–80 min after treatment with LSD

(1 mg/kg) reduced the number of signs observed to 14% of control at 30 min. However, the same dose of methysergide had less effect on the higher dose of LSD (2 mg/kg), reducing the number of signs observed to 75% of control at 40 min. This may suggest a direct interaction between the two drugs. Pretreatment with haloperidol or metoclopramide 15 min before LSD administration, significantly potentiated and prolonged the serotonin syndrome (Fig. 2).

Discussion

A characteristic behavior can be produced by inhibition of MAO with pargyline and increasing the substrate available for 5-HT synthesis by administration of 5-HTP. The use of the soluble salt of 5-HTP (5-HTP methyl ester) permits considerably lower doses of 5-HTP than those reported in the literature (Green and Grahame-Smith, 1974, 1976; Jacobs, 1976; Sloviter et al., 1978) and, additionally, may avoid the lethality observed after high doses of 5-HTP. The use of 5-HTP methyl ester produces a dose-related response (Fig. 1).

It has been reported that LSD can also produce signs of the serotonin syndrome (Jacobs, 1976; Trulson et al., 1976). Another ergot derivative, lisuride, which has great structural similarity to LSD, also produced the syndrome when administered to rats without prior inhibition of MAO or 5-HT precursor administration. The serotonin syndrome was apparently identical when produced by pargyline and 5-HTP methyl ester, lisuride, or LSD. However, lisuride and LSD in the doses used also produced other behavioral signs (male-to-male mounting, stereotyped fighting, and excitability), which may have interfered with the observation of the signs characteristic of the serotonin syndrome and thus lowered the scores. The induction of male-to-male mounting by lisuride has been reported previously and is thought to relate to the 5-HT agonist properties of lisuride (Da Prada et al., 1977).

In agreement with other studies (Green and Grahame-Smith, 1976; Jacobs, 1976), we found that the serotonin syndrome produced by pargyline and 5-HTP methyl ester can be blocked completely by treatment with antidopaminergic as well as by antiserotonergic compounds. However, direct DA receptor stimulation with apomorphine does not potentiate or affect the syndrome. Thus the serotonin syndrome produced by 5-HT precursor administration appears to be regulated only negatively by a dopaminergic receptor. The location and nature of this regulatory receptor in the neuronal circuits producing the serotonin syndrome is unclear. The DA receptor involved does not appear to recognize the new neuroleptic metoclopramide, since this drug does not block the serotonin syndrome produced by either lisuride or pargyline and 5-HTP.

Antagonism of DA function with AMPT does not block the serotonin syndrome produced by lisuride (Table 1). This suggests that the DA synapse involved in the serotonin syndrome occurs before the 5-HT synapse.

The serotonin syndrome produced by lisuride or LSD is not blocked by inhibition of 5-HT synthesis by PCPA (Table 1). This has been previously reported for LSD (Trulson et al., 1976). This would indicate that the ergot drugs are acting directly on 5-HT receptors and, unlike the treatment with pargyline and 5-HTP, do not depend upon the functional integrity of 5-HT neurons. This is in agreement with other studies which suggest that lisuride acts directly on 5-HT receptors (Kehr, 1977; Pieri et al., 1978). The ability of methysergide to reduce the behavior produced by LSD also indicates that LSD acts on serotonin receptors. The failure of methysergide to reduce the syndrome produced by lisuride or completely block the syndrome produced by LSD may reflect the relatively weak 5-HT blocking actions of methysergide (Haigler and Aghajanian, 1974; Sofia and Vassar, 1975).

Further pharmacological studies with LSD and lisuride indicate that the two drugs act differently. While haloperidol and metoclopramide are without effect on lisuride-induced behavior (Table 1), the effects of LSD are significantly potentiated (in terms of number of signs present as well as duration) by haloperidol or metoclopramide pretreatment (Fig. 2a and 2b). This may reflect differences between the actions of LSD and lisuride on serotonergic receptors, or their relative potency of action on DA receptors. With regard to the first hypothesis, it has been suggested that lisuride, in contrast to LSD, stimulates the presynaptic 5-HT autoreceptor preferentially (Da Prada et al., 1977; Kehr, 1977; Pieri et al., 1978).

An alternative hypothesis suggests that drugs like LSD and lisuride have both serotonergic and dopaminergic actions (Horowski and Wachtel, 1976; Kehr, 1977; Pieri et al., 1978; Kehr and Speckenbach, 1978; Silbergeld et al., 1979). Behaviorally, these mixed actions may be correlated with stereotypy (dopaminergic) and the serotonin syndrome (serotonergic). When dopaminergic actions are blocked, then serotonergically related behaviors may be more clearly expressed. This hypothesis is supported by the report that stereotypy produced by amphetamine is potentiated by PCPA, presumably by suppression of amphetamine effects on serotonergic systems (Hollister et al., 1976; Simon et al., 1975). Therefore, blockade of the dopaminergic properties of LSD by haloperidol or metoclopramide allows expression of more observable serotonergic properties. The failure to observe this interaction with lisuride may be related to the greater potency of lisuride for both DA and 5-HT receptors (Pieri et al., 1978; Walters et al., 1979). Finally, the implications of these different effects in the serotonin syndrome between lisuride and LSD may have relevance to their neuropharmacological and psychopharmacological applications. The lack of hallucinogenic properties for lisuride (Pieri et al., 1978) may be related to these differences.

References

Da Prada, M., Bonetti, E. P., Keller, H. H.: Induction of mounting behavior in female and male rats by lisuride. Neurosci. Letters **6**, 349–353 (1977)

Foldes, A., Costa, E.: Relationship of brain monoamine and locomotor activity in rats. Biochem. Pharmacol. **24**, 1617–1621 (1975)

Grahame-Smith, D. C.: Studies in vivo on the relationship between brain tryptophan, brain 5-HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor and L-tryptophan. J. Neurochem. **18**, 1053–1066 (1971)

Green, A. R., Grahame-Smith, D. G.: The role of brain dopamine in the hyperactivity syndrome produced by increased 5-hydroxytryptamine synthesis in rats. Neuropharmacology **13**, 949–959 (1974)

Green, A. R., Grahame-Smith, D. G.: Effects of drugs on the processes regulating the functional activity of brain 5-hydroxytryptamine. Nature **260**, 487–491 (1976)

Haigler, H., Aghajanian, G. K.: Peripheral serotonin antagonists: Failure to antagonize serotonin in brain areas receiving a prominent serotonergic input. J. Neural. Transm. **35**, 257–273 (1974)

Hollister, A. S., Breese, G. R., Kuhn, C. M., Cooper, B. R., Schanburg, S. M.: An inhibitory role for brain serotonin-containing systems in the locomotor effects of *d*-amphetamine. J. Pharmacol. Exp. Ther. **198**, 12–22 (1976)

Horowski, R., Wachtel, H.: Direct dopaminergic action of lisuride hydrogen maleate, an ergot derivative, in mice. Eur. J. Pharmacol. **36**, 373–383 (1976)

Jacobs, B. L.: Evidence for the functional interaction of two central neurotransmitters. Psychopharmacology **39**, 81–86 (1974)

Jacobs, B. L.: An animal behavior model for studying central serotonergic synapses. Life Sci. **19**, 777–786 (1976)

Jacobs, B. L., Eubanks, E. E., Wise, W. D.: Effect of indolealkylamine manipulations on locomotor activity in rats. Neuropharmacology **13**, 575–583 (1974)

Kehr, W.: Effect of lisuride and other ergot derivatives on monoaminergic mechanisms in rat brain. Eur. J. Pharmacol. **41**, 261–273 (1977)

Kehr, W., Speckenbach, W.: Effect of lisuride and LSD on monoamine synthesis after axotomy or reserpine treatment in rat brain. Naunyn Schmiedebergs Arch. Pharmacol. **301**, 163–169 (1978)

Pieri, L., Keller, H. H., Burkard, W., Da Prada, M.: Effects of lisuride and LSD on cerebral monoamines systems and hallocinosis. Nature **272**, 278–280 (1978)

Silbergeld, E. K., Hruska, R. E., Weir, R., Kennedy, S. W.: In: Dopaminergic ergot derivatives and motor function. K. Fuxe, D. B. Calne, eds., pp. 223–235. Oxford: Pergamon 1979

Simon, P., Puech, A. J., Chermat, R., Boissier, J. R.: Stereotyped behavior induced in rats by apomorphine and amphetamine. An approach to better utilization. In: Neuropsychopharmacology, J. R. Boissier, H. Hippius, P. Pichot, eds., pp. 517–523. New York: Elsevier 1975

Sloviter, R. S., Drust, E. G., Connor, J. D.: Specificity of a rat behavioral model for serotonin receptor activation. J. Pharmacol. Exp. Ther. **206**, 339–347 (1978)

Sofia, R. E., Vassar, H. B.: The effect of ergotamine and methysergide on serotonin metabolism in the rat brain. Arch. Int. Pharmacodyn. Ther. **216**, 40–50 (1975)

Trulson, M. E., Ross, C. A., Jacobs, B. L.: Behavioral evidence for the stimulation of CNS serotonin receptors by high doses of LSD. Psychopharmacol. Commun. **2**, 149–164 (1976)

Walters, J. R., Baring, M. D., Lakoski, J. M.: Effects of ergolines on dopaminergic and serotonergic single unit activity. In Dopaminergic ergot derivatives and motor function. K. Fuxe, D. B. Calne, eds., pp. 207–221. Oxford: Pergamon 1979

Received November 6, 1978; Final Version March 19, 1979