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 serotonergic 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,
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 an 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 (Merek), 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.

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