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Dual Actions of Lysergic Acid Diethylamide Tartrate (LSD), 2-Bromo-D-Lysergic Acid Diethylamide Bitartrate (BOL) and Methysergide on Dorsal Root Potentials Evoked by Stimulation of Raphe Nuclei[1]

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ABSTRACT

Larson, Alice A., Chung Chinn, Herbert K. Proudfit and Edmund G. Anderson: Dual actions of lysergic acid diethylamide tartrate (LSD), 2-bromo-D-lysergic acid diethylamide bitartrate (BOL) and methysergide on dorsal root potentials evoked by stimulation of raphe nuclei. J. Pharmacol. Exp. Ther. **217:** 99-104, 1981.

A variety of drugs reported to antagonize serotonin were found to affect spinal cord potentials evoked by electrical stimulation of the caudal raphe nuclei of the cat. These brain stem-evoked dorsal root potentials (DRPs) consisted of a short latency depolarization (DRP-1), which was evoked by stimulation of a wide variety of sites in the medial brain stem and a long latency potential (DRP-2), which was elicited only when stimuli were applied near the raphe. The ability of serotonergic antagonists to increase or decrease these DRPs was dependent on the dose of the drug administered. High doses of lysergic acid diethylamide tartrate (LSD), 2-bromo-D-lysergic acid diethylamide bitartrate (BOL), methysergide and cinanserin each produced an immediate inhibition of DRP-2 and a simultaneous enhancement of DRP-1, both of which recovered by approximately 30 min. Each of the drugs produced a dose-related inhibition of DRP-2 at high doses, with LSD being the most potent and cinanserin the least potent. In contrast, low doses of LSD, BOL and methysergide elicited little or no immediate change in either DRP-2 or DRP-1, but produced an enhancement of DRP-2 which developed slowly over a period of 60 to 90 min. This increase in DRP-2 was most dramatic after administration of LSD and was not accompanied by changes in DRP-1. The inhibition of DRP-2 by high doses of LSD, BOL, methysergide and cinanserin may result primarily from inhibition of postsynaptic serotonergic receptors located on the primary afferent terminals. The increase in DRP-2 produced by low doses of LSD, BOL and methysergide is postulated to result from an interaction with receptors distinct from those which produced the inhibition of DRP-2 at higher doses.

We have previously reported that stimulation of sites within the inferior central nucleus (ICN) of the cat evokes depolarizing potentials which can be recorded from dorsal roots of the lumbar and sacral spinal cord (Proudfit and Anderson, 1974; Proudfit *et al.*, 1980). Stimulation at these sites evokes two negative dorsal root potentials (DRPs), designated DRP-1 and DRP-2. While DRP-1 can be elicited from many sites in the brain stem (Carpenter *et al.*, 1966; Lundberg and Vylicky, 1966; Proudfit and Anderson, 1973), only stimulation at sites near the ICN can evoke DRP-1 followed by a DRP with a longer latency (DRP-2). DRP-1 and DRP-2 are also carried in two different populations of primary afferent fibers (Proudfit *et al.*, 1980). The long-latency DRP (DRP-2) has been postulated to be mediated by 5-hydroxytryptamine (serotonin; 5-HT). The evidence supporting this conclusion is: 1) this potential is evoked only from brain stem areas containing serotonergic neurons which project to the spinal cord; 2) the long latency of DRP-2 is consistent with the slow conduction velocity expected for the small diameter serotonergic axons; and 3) DRP-2 is selectively blocked by several putative 5-HT antagonists, including methysergide and cinanserin (Proudfit and Anderson, 1974; Proudfit *et al.*, 1980).

Although antagonists of 5-HT are potentially useful tools in the study of serotonergic neurons in the brain, a major limitation in the use of these agents has been the disagreement in the literature over the specificity and effectiveness of these drugs when used in the central nervous system (CNS) (Haigler and Aghajanian, 1977). Lysergic acid diethylamide tartrate (LSD), methysergide, 2-bromo-D-lysergic acid diethylamide bitartrate (BOL), cinanserin, cyproheptadine and methergoline have all been shown to antagonize serotonergically mediated motor reflexes or complex behaviors (Banna and Anderson, 1968; Clineschmidt and Lotti, 1974; Ferrini and Glasser, 1965; Rubin *et al.*, 1964). However, none of the putative antagonists of 5-HT blocked the inhibitory effects of 5-HT microiontophoreti-

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cally applied to neurons receiving strong serotonergic input (Haigler and Aghajanian, 1974a; DeMortigny and Aghajanian, 1977; Aghajanian, 1976). In contrast, the excitatory effects of 5-HT on neurons in the reticular formation, which lack documented serotonergic input, were antagonized by most 5-HT antagonists (Boakes *et al.*, 1970; Bradley and Briggs, 1974; Bramwell and Gonye, 1976; Haigler and Aghajanian, 1974b).

In addition to its antagonistic actions in certain test systems, LSD has also been found to act as an agonist in specific behavioral tests (Horita and Gogerty, 1958; Andén *et al.*, 1968) as well as when applied microiontophoretically to serotonergic neurons (Aghajanian, 1976). However, the existence of a postulated serotonergic autoreceptor on raphe neurons could not be demonstrated by LSD-receptor binding assays (Bennett and Aghajanian, 1976; Bennett and Snyder, 1976).

These discrepancies have previously been attributed to the wide variety of test systems used for evaluating the actions of these drugs and the lack of complete dose-response data for most antagonists. It was, therefore, of particular interest that, during the course of our studies of DRP-2, we noted two qualitatively different effects of some of these drugs within the same test system. LSD, BOL and methysergide were found to either inhibit or enhance DRP-2, depending on the dose of the drug administered. The present study describes the dose- and time-response relationships of the dual actions of certain 5-HT antagonists on DRP-2.

Methods

Surgical preparation. Cats were pretreated with atropine methyl nitrate (0.1 mg/kg) and anesthetized with ether. The brain rostral to the pons-medulla was rendered anoxic by using the anemic decerebration method of Pollock and Davis (1922). Ether anesthesia was discontinued and the cats were artifically respired with room air after administration of gallamine triethiodide (Flaxedil) to immobilize the animals. Blood pressure was continuously monitored from a cannula placed in the carotid artery.

After exposure of the spinal cord from the fourth lumbar to the second sacral segment, the seventh lumbar dorsal root was dissected free and mounted on platinum recording electrodes. A radiant heat source and a heating pad placed under the animal were electronically regulated to maintain the temperatures of the body and the mineral oil bath covering the cord at 37 ± 0.5°C.

Drug administration. All drugs and solutions were administered i.v. through an indwelling catheter placed in the antecubital vein. All drugs were made up in saline except gallamine triethiodide, which was purchased as an injectable solution.

BOL and methysergide bimaleate were gifts from Sandoz Pharmaceuticals (Hanover, NJ). LSD and cinanserin hydrochloride were obtained from the National Institute of Mental Health (Bethesda, MD) and E. R. Squibb & Sons, (New Brunswick, NJ), respectively.

Electrical stimulation and recording. The raphe nuclei of the caudal brain stem were electrically stimulated by using a concentric bipolar stainless-steel electrode (model NE-100; David Kopf Instruments, Tujunga, CA), having an inner shaft diameter of 0.2 and 0.5 mm separation between the inner and outer barrel. The electrode was lowered into the brain stem by using the stereotaxic coordinates of the ICN according to the atlas of Berman (1968). The ICN of the cat includes the nucleus raphe magnus and nucleus raphe obscurus, both of which contain serotonergic cell bodies whose axonal processes project to the spinal cord.

Thirty millisecond trains of nine pulses (0.5 msec duration; 0.08–1.0 mA) were used to evoke each DRP. Recorded signals were amplified by Grass P5 preamplifiers and viewed on a Tektronics 502 oscilloscope. Eight to 12 consecutive DRPs elicited at 3-sec intervals were summed by a Mnemotron Computer of Average Transients (Cat 1000) and the resulting analog waveforms were plotted by using a Grass Polygraph (model 5). The waveform was divided into DRP-1 and DRP-2 at the time of the peak negative wave between the two potentials. The area beneath the waveforms was then measured by planimetry.

Histological verification of electrode placement. The majority of brain stem electrode placements were verified histologically. At the end of the experiment, a brief d.c. was passed across the bipolar electrode to deposit iron at the tip which was detected in brain sections by using the Prussian Blue technique (Adrian and Moruzzi, 1939).

Results

Alterations in DRPs after high doses of 5-HT antagonists. The antagonists selected for study included cinanserin, methysergide, LSD and BOL. Each of these agents produced a rapid and selective inhibition of DRP-2 after i.v. administration. The inhibition produced by doses ranging from 0.05 to 4.0 mg/kg was usually maximal within 5 to 10 min and recovered progressively over the next hour. Dose-response curves of this inhibitory action were constructed for LSD, methysergide and cinanserin (fig. 1). The effect of each dose was allowed to wear off before additional injections were made. These inhibitory responses to subsequent doses were not altered by prior administration of these drugs. Of these three agents, LSD was clearly the most potent (ED_{50}, 0.1 mg/kg) in antagonizing DRP-2; methysergide (ED_{50}, 0.23 mg/kg) was less so and cinanserin (ED_{50}, 2 mg/kg) was the least potent. At sufficiently high doses, all three agents were capable of producing a total blockade of DRP-2.

Cinanserin and methysergide were studied further to assess the selectivity and time course of their effects on DRP-1 and DRP-2. When administered in doses which produced a near maximal inhibition of DRP-2 (cinanserin, 4 mg/kg; methysergide, 1 mg/kg), both agents caused a significant increase in the size of DRP-1 (figs. 2 and 3). Thus, DRP-1 and DRP-2 were affected in a reciprocal fashion over the same time period. Although the magnitude of effect on the two potentials differed, the time course of the alterations in the two potentials were near mirror images.

Although complete time course curves for LSD and BOL were not constructed, LSD (0.25 mg/kg) and BOL (1 mg/kg) also increased DRP-1 while simultaneously producing a total blockade of DRP-2. Both of these agents were also maximally effective within 5 min of i.v. injection and recovery occurred within 60 min. Thus, the effects and time course of these antagonists were qualitatively indistinguishable from those of cinanserin and methysergide.

Alterations in DRPs after low doses of 5-HT antagonists. In contrast to the depression of DRP-2 produced by high doses of the 5-HT antagonists, very low doses of methysergide, BOL and LSD increased the size of DRP-2. However, this increase usually occurred only after a latency of 30 to 50 min, it was maximal at 50 to 90 min and it slowly recovered from 90 to 120 min. This slowly developing facilitation of DRP-2 was only observed at doses which were too small to induce any initial depression of DRP-2.

Figure 4 illustrates the response to either 0.05 mg/kg of methysergide or of BOL. Because of the long time course of this effect, these results were compared to those from a group of saline-treated animals by using a two-way analysis of variance and Dunn's test for multiple *post hoc* comparisons (Keppel, 1973). This low dose of methysergide was found to significantly increase DRP-2 at 60 and 90 min, whereas the same dose

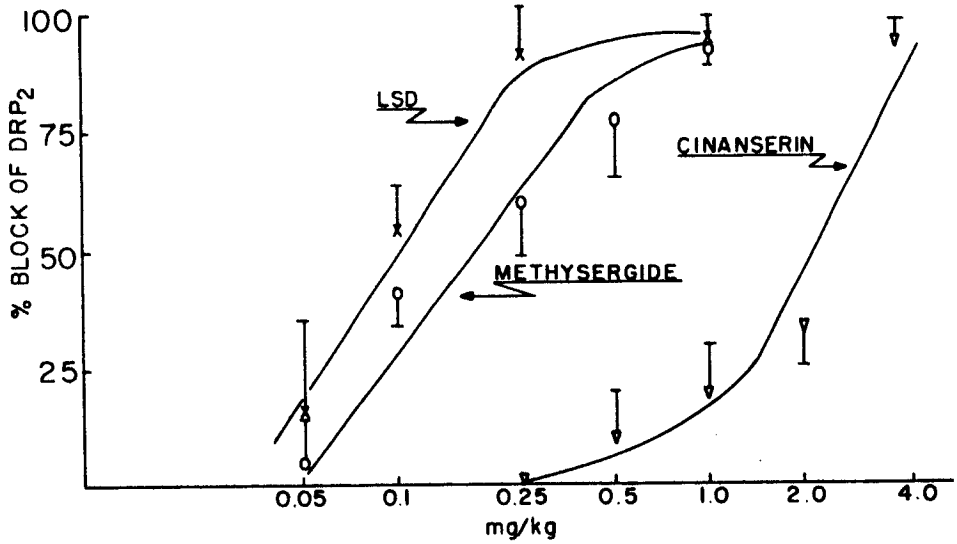

Fig. 1. Dose-response curves of the inhibition of DRP-2 by relatively high doses of LSD, methysergide and cinanserin. Each point represents the average percentage of control DRP (±S.E.) for five to six cats at 5 min after drug injection.

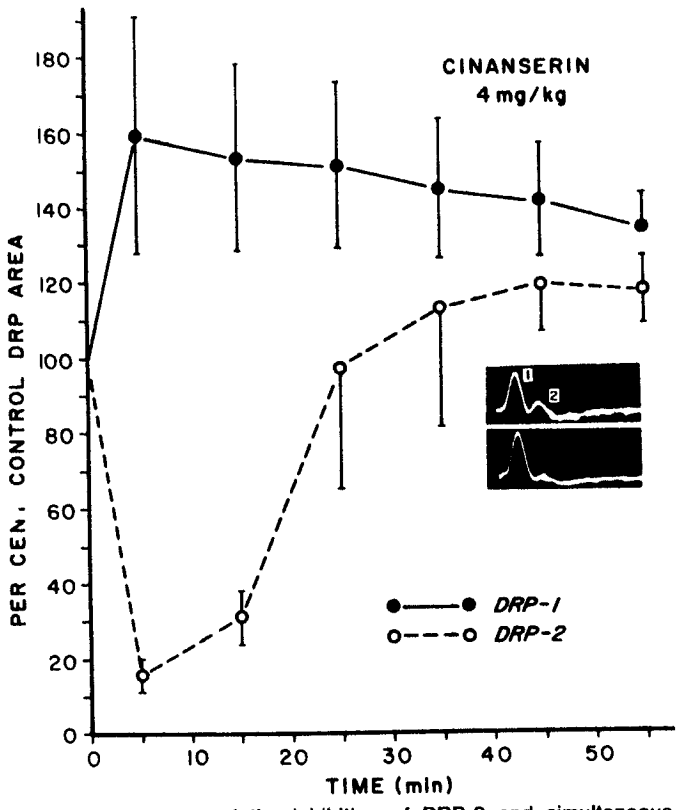

Fig. 2. Time course of the inhibition of DRP-2 and simultaneous enhancement of DRP-1 by 4 mg/kg of cinanserin i.v. Each point represents the average values (±S.E.) obtained from 11 cats. Upper 400-msec insert indicates control DRP-1 and DRP-2. Lower insert illustrates DRP-1 and DRP-2 at 5 min after drug administration.

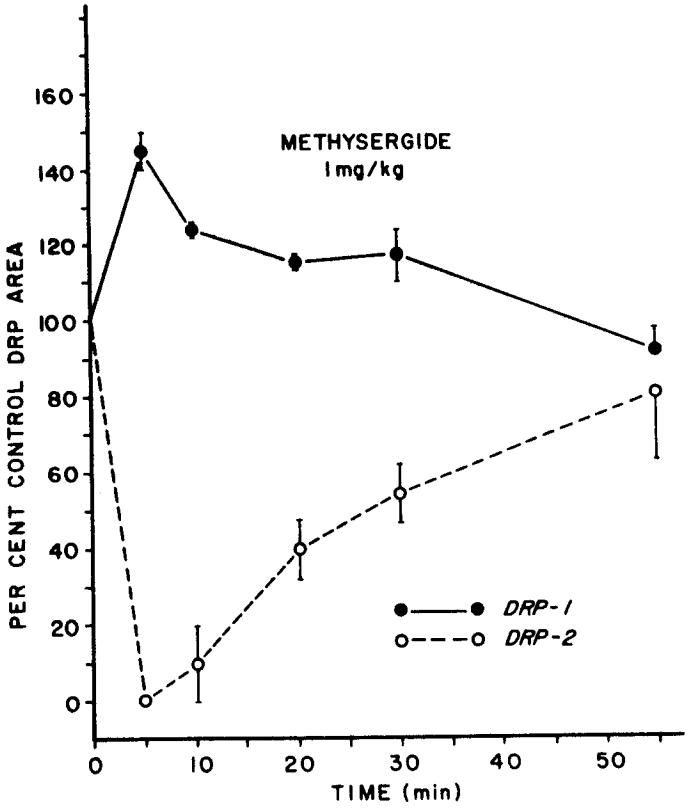

Fig. 3. Time course of the inhibition of DRP-2 and simultaneous enhancement of DRP-1 by 1 mg/kg of methysergide i.v. Each point represents the average value (±S.E.) obtained from four cats.

of BOL caused a similar increase in DRP-2 which was statistically significant at 90 min after its injection. DRP-1 was unaffected by this dose of either agent. The facilitation of DRP-2 produced by this dose of either BOL or methysergide was maximal at 90 min. Similar effects were seen after the i.v. administration of 0.05 mg/kg of LSD, except that the facilitatory effect on DRP-2 was of much greater magnitude and was already statistically significant and clearly apparent by 10 min after administration of LSD (fig. 5). Thus, the effects of low doses of these 5-HT antagonists differed from those of high doses of these agents both in the direction of their effects on the DRPs and in their time course.

Cinanserin differed from the other serotonin antagonists in that it failed to show a facilitatory action on bulbospinal DRPs in doses ranging from 0.05 to 0.25 mg/kg. Thus, it is possible that the slow facilitatory action of the 5-HT antagonists on

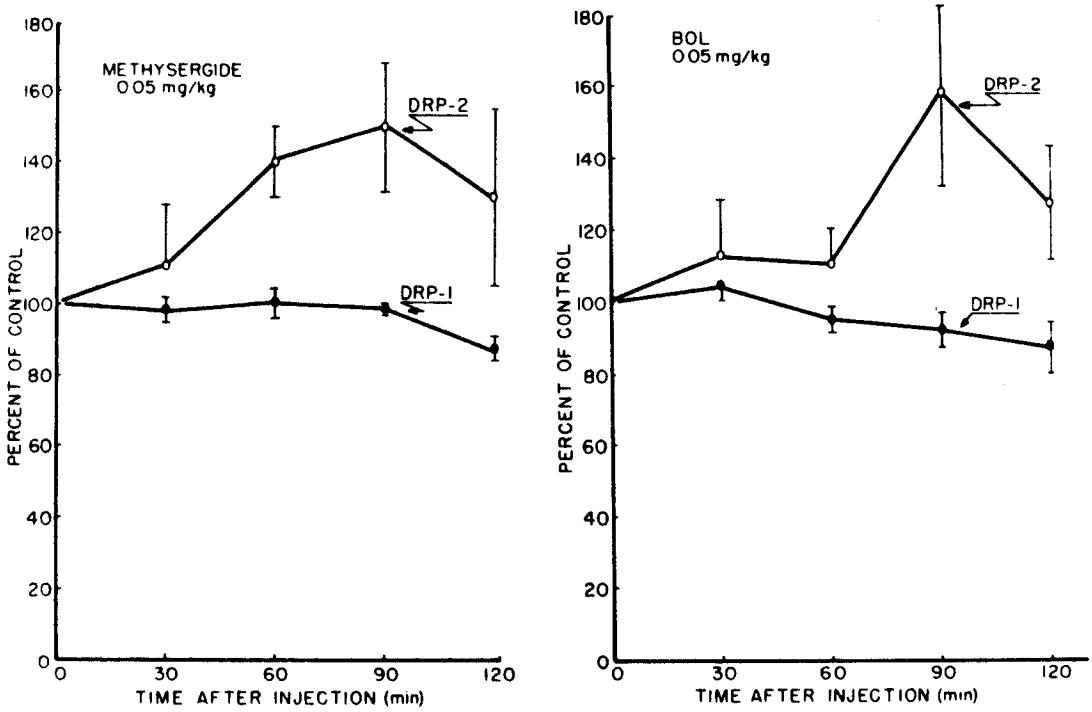

Fig. 4. Effect of low doses of methysergide (left) and BOL (right) on DRP-1 and DRP-2 after i.v. administration. Each point represents the mean area beneath each DRP, expressed as percentage of control (±S.E.), at varous times after injection (five cats).

DRP-2 is prominent only in those 5-HT antagonists which contain an indoleamine nucleus.

Discussion

The effects of high doses of LSD, BOL, methysergide and cinanserin observed in the present experiments support the hypothesis that DRP-2 results from activation of a serotonergic pathway. Previously published evidence supporting this assumption is: DRP-2 only occurs when the stimulation site includes those areas in which the cell bodies of the bulbospinal serotonergic neurons are located; the long latency of DRP-2 is consistent with the slow conduction velocity expected for the small diameter serotonergic axons; and DRP-2 is selectively blocked by some antagonists of 5-HT (Proudfit and Anderson, 1974; Proudfit *et al.*, 1980).

The high binding affinity of LSD, BOL and methysergide for postsynaptic serotonergic receptors has been clearly demonstrated (Bennett and Snyder, 1976). In addition, several reports indicate that these and other 5-HT antagonists will block the excitatory effects of iontophoretically applied 5-HT on neurons in the CNS (Boakes *et al.*, 1970; Roberts and Straughn, 1967; Bradley and Briggs, 1974; Haigler and Aghajanian, 1974b; Couch, 1976). However, these compounds are either ineffective (Haigler and Aghajanian, 1974a,b; Krnjevic and Phillis, 1963; Curtis and Davis, 1962) or marginally effective (Segal, 1976) in blocking the inhibitory actions of 5-HT. Although the DRP-2 signals presynaptic inhibition, it is generated by a depolarizing or excitatory event on the primary afferent terminals apparently induced *via* serotonergic neurons. Thus, the blockade of this potential by the 5-HT antagonists is consistent with the iontophoretic data, indicating preferential blockade of the excitatory events mediated by 5-HT.

The blockade of DRP-2 by the antagonists of 5-HT may result from antagonism at serotonergic receptors located either on an interneuron or directly on the primary afferent fibers. However, the failure of the γ-aminobutyric acid-depleting agent, semicarbazide, to block DRP-2 (Proudfit *et al.*, 1980) and the evidence of a direct depolarizing action of 5-HT on afferent fibers (Tebēcis and Phillis, 1967) are consistent with a serotonergic synapse on afferent terminals.

The augmentation of DRP-1 by 5-HT antagonists occurs over the same dose range and initial time course as the blockade of DRP-2, which suggests that similar pharmacodynamics are involved. As DRP-1 can be evoked by stimulation of numerous areas of the brain stem, it was not anticipated that the 5-HT antagonists would block DRP-1. The increase in DRP-1 by administration of 5-HT antagonists may be explained by assuming that in the decerebrate cat the smaller primary afferent terminals, in which DRP-1 is generated (Proudfit *et al.*, 1980), are under a tonic depolarizing influence from serotonergic pathways. Inhibition of this depolarizing influence by the 5-HT antagonists would thus allow a greater depolarization in response to brain stem stimulation. Thus, receptor blockade can account for both the inhibition of DRP-2 and the augmentation of DRP-1.

The slowly developing facilitation of DRP-2 produced by low doses of some 5-HT antagonists appears to differ qualitatively from the inhibition of DRP-2 produced by higher doses. Its apparent restriction to antagonists containing an indole nucleus, its prolonged onset and the lower effective dose range suggest receptor mechanisms different from those responsible for the blockade of DRP-2.

The time course and doses of 5-HT antagonists necessary to produce facilitation of DRP-2 in the present experiments are similar to those reported by others. For example, LSD potentiates the 5-HT-induced facilitation of facial motorneurons (McCall and Aghajanian, 1979) and facilitates flexor and C-fiber reflexes (Martin and Eades, 1970; Bell and Martin, 1974). The character of the receptors involved in these responses remains to be clearly defined. However, there is some evidence that this facilitatory action of LSD and methysergide is me-

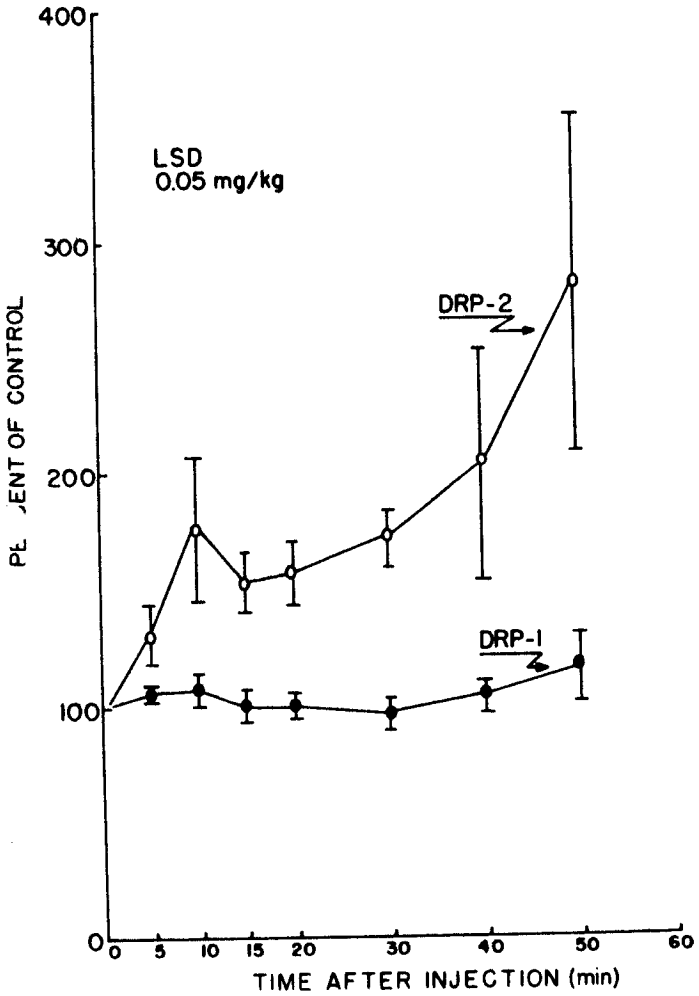

Fig. 5. Effect of a low dose of LSD i.v. on DRP-1 and DRP-2. Each point represents the mean area beneath each DRP, expressed as percentage of control (±S.E.), at various times after injection (four cats).

diated by stimulation of tryptamine receptors (Nozaki *et al.*, 1977; Bell and Martin, 1974; Bell *et al.*, 1976).

There are also several striking similarities between the enhancement of DRP-2 by low doses of LSD and the effects of LSD on spontaneous raphe unit activity (Trulson and Jacobs, 1979a) and on certain behavioral effects specific to LSD and related hallucinogens (Jacobs *et al.*, 1976; Trulson and Jacobs, 1977); depression of raphe unit activity and production of several LSD-related behavioral phenomena occur at doses of LSD which enhance DRP-2; maximal enhancement of DRP-2 occurs at the same time (60 min) as peak behavioral and raphe unit changes are observed; and just as LSD produced a greater enhancement of DRP-2 than either BOL or methysergide at equal doses, inhibition of raphe unit activity and changes in behavior by LSD have not been duplicated by BOL.

Although the time course of facilitation of DRP-2 is similar to that of the inhibition of raphe unit activity (recovery by 3 hr), the effects of LSD on both of these parameters are of much shorter duration than on the behavioral effects. The temporal discrepancy between behavioral and electrophysiologic events has been suggested to reflect changes in the sensitivity of serotonergic receptors on those neurons receiving serotonergic projections from the raphe. Such alterations, as indicated by changes in the binding of LSD and 5-HT, have recently been reported (Trulson and Jacobs, 1979b). However, the present data allow no conclusions regarding the nature of the receptors involved in the facilitatory response to low doses of the indole containing 5-HT antagonists, except to suggest that the receptors involved are distinct from those which inhibit DRP-2 at higher doses.

The differential effects of high and low doses of the indole-containing antagonists cannot be explained in terms of their partial agonist properties. Such an explanation would assume that the same drug-receptor complex is involved in the agonist and antagonist actions of the drug. Thus, the affinity of the drug for the receptor would remain the same, but the efficacy or intrinsic activity would change with the dose. Accordingly, the time of onset of either the agonist or antagonist action would be comparable. This conclusion is supported by the fact that one of the best documented agonistic actions of LSD, the inhibition of dorsal raphe neuronal discharge, occurs over the same time course (Aghajanian *et al.*, 1970) as do the antagonist actions of LSD (Banna and Anderson, 1968). However, the onset of the low-dose effects of the 5-HT antagonists in the present study differed greatly from that of high doses. This is again suggestive that the facilitation of DRP-2 produced by low doses of 5-HT antagonists is mediated by a different receptor from that involved in the inhibition of DRP-2 by high doses.

The slow development of the low-dose facilitatory action of the indolamines on DRP-2 suggests that a metabolic mechanism may be involved. LSD will increase the concentration of 5-HT while decreasing that of 5-hydroxyindole-acetic acid in the brain (Rosecrans *et al.*, 1967). However, these changes only occur at higher doses (0.5 mg/kg), are too transient (dissipate within 90 min) and are in the wrong direction to explain the facilitatory action of LSD on DRP-2. Furthermore, the effects of LSD on 5-HT-release (Hamon *et al.*, 1974) and methysergide on 5-HT-turnover (D'Amico *et al.*, 1976) do not occur in the same dose range or with the same time course as the facilitatory action on DRP-2. Thus, the effects of these indole-containing antagonists on the metabolism of 5-HT do not account for their facilitatory action on DRP-2.

In conclusion, we have shown that relatively high doses of several reported antagonists of 5-HT produce a dose-related inhibition of DRP-2, a potential evoked by electrical stimulation of the raphe nuclei. In contrast, very small doses of certain of these compounds, LSD being the most potent, cause facilitation of this same potential. The effect of low doses of LSD on DRP-2 correlates in dose range and time course with the inhibition of spontaneous raphe unit activity and behavioral effects produced by LSD in the cat. Although the effect of high doses of these drugs on both DRP-1 and DRP-2 appears to result from a direct antagonism at serotonergic receptors, the mechanism by which DRP-2 is enhanced by low doses of LSD, and to a lesser degree BOL and methysergide, appears to differ from that of high doses of those same drugs.

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References

Adrian, E. D. and Moruzzi, G.: Impulses in the pyramidal tract. J. Physiol. (Lond.) **97**: 153-199, 1939.

Aghajanian, G. K.: LSD and 2-bromo-LSD: Comparison of effects on serotonergic neurones and on neurones in two serotonergic projection areas, the ventral lateral geniculate and amygdala. Neuropharmacology **15**: 521-528, 1976.

Aghajanian, G. K., Foote, W. E. and Sheard, M. H.: Action of psychotogenic

drugs on single midbrain raphe neurons. J. Pharmacol. Exp. Ther. **171:** 178–187, 1970.

ANDÉN, N.-E., CORRODI, H., FUXE, K. AND HÖKFELT, T.: Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. Br. J. Pharmacol. **34:** 1–7, 1968.

BANNA, N. AND ANDERSON, E. G.: The effects of 5-hydroxytryptamine antagonists on spinal neuronal activity. J. Pharmacol. Exp. Ther. **162:** 319–325, 1968.

BELL, J. A. AND MARTIN, W. R.: Studies of tryptamine and lysergic acid diethylamide (LSD) on cutaneous C-fiber and polysynaptic reflexes in the cat. J. Pharmacol. Exp. Ther. **190:** 492–500, 1974.

BELL, J. A., MARTIN, W. R., SLOAN, J. W. AND BUCHWALD, W. F.: The effect of L-tryptophan on spinal cord C-fiber reflexes. J. Pharmacol. Exp. Ther. **196:** 373–379, 1976.

BENNETT, J. L. AND AGHAJANIAN, G. K.: Response of single raphe neurons to (+)-LSD: Correlation with (+)-LSD binding in brain. J. Pharm. Pharmacol. **28:** 516–518, 1976.

BENNETT, J. P. AND SNYDER, S. H.: Serotonin and lysergic acid diethylamide binding in rat brain membranes. Relationship to postsynaptic serotonin receptors. Mol. Pharmacol. **12:** 373–389, 1976.

BERMAN, A. L.: The brain stem of the cat, University of Wisconsin Press, Madison, WI, 1968.

BOAKES, R. J., BRADLEY, P. B., BRIGGS, I. AND DRAY, A.: Antagonism of 5-hydroxytryptamine by LSD 25 in the central nervous system: A possible neuronal basis for the actions of LSD 25. Br. J. Pharmacol. **40:** 202–218, 1970.

BRADLEY, P. B. AND BRIGGS, I.: Further studies on the mode of action of psychotomimetic drugs: Antagonism of the excitatory actions of 5-hydroxytryptamine by methylated derivatives of tryptamine. Br. J. Pharmacol. **50:** 345–354, 1974.

BRAMWELL, G. J. AND GONYE, T.: Responses of midbrain neurones to microiontophoretically applied 5-hydroxytryptamine: Comparison with the response to intravenously administered lysergic acid diethlamide. Neuropharmacology **15:** 457–461, 1976.

CARPENTER, D., ENGBERG, I. AND LUNDBERG, A.: Primary afferent depolarization evoked from the brain stem and the cerebellum. Arch. Ital. Biol. **104:** 50–72, 1966.

CLINESCHMIDT, B. V. AND LOTTI, V. J.: Indoleamine antagonists: Relative potencies as inhibitors of tryptamine and 5-hydroxytryptophan-evoked responses. Br. J. Pharmacol. **50:** 311–313, 1974.

COUCH, J. R.: Action of LSD on raphe neurons and effect on presumed serotonergic raphe synapses. Brain Res. **110:** 417–424, 1976.

CURTIS, D. R. AND DAVIS, R.: Pharmacological studies upon neurons of the lateral geniculate nucleus of the cat. Br. J. Pharmacol. **18:** 217–246, 1962.

D'AMICO, D. J., PATEL, B. C. AND KLAWANS, H. L.: The effect of methysergide on 5-hydroxytryptamine turnover in whole brain. J. Pharm. Pharmacol. **28:** 454–455, 1976.

DEMORTIGNY, C. AND AGHAJANIAN, G. K.: Preferential action of 5-methoxytryptamine and 5-methoxydimethyltryptamine on presynaptic serotonin receptors: A comparative iontophoretic study with LSD and serotonin. Neuropharmacology **16:** 811–818, 1977.

FERRINI, R. AND GLASSER, A.: Antagonism of central effects of tryptamine and 5-hydroxytryptophan by 1,6-dimethyl-8 -carbobenzyloxy-aminomethyl-10-ergoline. Psychopharmacologia **8:** 271–276, 1965.

HAIGLER, H. J. AND AGHAJANIAN, G. K.: Lysergic acid diethylaminde and serotonin: A comparison of effects on serotonergic neurons and neurons receiving a serotonergic input. J. Pharmacol. Exp. Ther. **188:** 688–699, 1974a.

HAIGLER, H. J. AND AGHAJANIAN, G. K.: Peripheral serotonin antagonists: Failure to antagonize serotonin in brain areas receiving a prominent serotonergic input. J. Neural Transm. **35:** 257–273, 1974b.

HAIGLER, H. J. AND AGHAJANIAN, G. K.: Serotonin receptors in the brain. Fed. Proc. **36:** 2159–2164, 1977.

HAMON, M., BOURGOIN, S., JAGGER, J. AND GLOWINSKI, J.: Effects of LSD on synthesis and release of 5-HT in rat brain slices. Brain Res. **69:** 265–280, 1974.

HORITA, A. AND GOGERTY, J.: The pyretogenic effect of 5-hydroxytryptophan and its comparison with that of LSD. J. Pharmacol. Exp. Ther. **122:** 195–200, 1958.

JACOBS, B. L., TRULSON, M. E. AND STERN, W. C.: An animal model for studying the actions of LSD and related hallucinogens. Science (Wash., DC) **194:** 741–743, 1976.

KEPPEL, G.: Design and Analysis: A Researcher's Handbook, Prentice Hall, New Jersey, 1973.

KRNJEVIC, K. AND PHILLIS, J. W.: Actions of certain amines on cerebral cortical neurons. Br. J. Pharamcol. **20:** 471–490, 1963.

LUNDBERG, A. AND VYKLICKY, L.: Inhibition of transmission to primary afferents by electrical stimulation of the brain stem. Arch. Ital. Biol. **104:** 86–97, 1966.

MARTIN, W. R. AND EADES, C. G.: The action of tryptamine on the dog spinal cord and its relationship to the agonistic actions of LSD-like psychotogens. Psychopharmacologia **17:** 242–257, 1970.

MCCALL, R. B. AND AGHAJANIAN, G. K.: Serotonergic facilitation of facial motoneuron excitation. Brain Res. **169:** 11–27, 1979.

NOZAKI, M., BELL, J. A., VAUPEL, D. B. AND MARTIN, W. R.: Responses of the flexor reflex to LSD, tryptamine, 5-hydroxytryptophan, methoxamine, and *d*-Amphetamine in acute and chronic spinal rats. Psychopharmacology **55:** 13–18, 1977.

POLLOCK, L. J. AND DAVIS, L.: The influence of the cerebellum upon reflex activities of the decerebrate animal. Brain **50:** 277–312, 1922.

PROUDFIT, H. K. AND ANDERSON, E. G.: Influence of serotonin antagonists on bulbospinal systems. Brain Res. **61:** 331–341, 1973.

PROUDFIT, H. K. AND ANDERSON, E. G.: New long latency bulbospinal evoked potentials blocked by serotonin antagonists. Brain Res. **65:** 542–546, 1974.

PROUDFIT, H. K., LARSON, A. A. AND ANDERSON, E. G.: The role of serotonin and GABA in the mediation of raphe-evoked spinal cord dorsal root potentials. Brain Res. **195:** 149–165, 1980.

ROBERTS, M. H. T. AND STRAUGHN, D. W.: Excitation and depression of cortical neurons by 5-hydroxytryptamine. J. Physiol. (Lond.) **193:** 269–294, 1967.

ROSECRANS, J. A., LOVELL, R. A. AND FREEDMAN, D. X.: Effects of lysergic acid diethylamide on the metabolism of brain 5-hydroxytryptamine. Biochem. Pharmacol. **16:** 2011–2021, 1967.

RUBIN, B., PIALA, J., BURKE, J. AND CRAVER, B.: A new specific serotonin inhibitor (Sq 10,643)2'(3 dimethylaminopropylthio) cinnamanlide hydrochloride. Arch. Int. Pharmacodyn. Ther. **152:** 132–143, 1964.

SEGAL, M.: 5-HT antagonists in rat hippocampus. Brain Res. **103:** 161–166, 1976.

Tebēcis, A. K. and Phillis, J. W.: The effects of topically applied biogenic monamines on the isolated toad spinal cord. Comp. Biochem. Physiol. **23:** 553–563, 1967.

TRULSON, M. E. AND JACOBS, B. L.: Usefulness of an animal behavioral model in studying the duration of action of LSD and the onset and duration of tolerance to LSD in the cat. Brain Res. **132:** 315–326, 1977.

TRULSON, M. E. AND JACOBS, B. L.: Dissociations between the effects of LSD on behavior and raphe unit activity in freely moving cats. Science (Wash., DC) **205:** 515–518, 1979a.

TRULSON, M. E. AND JACOBS, B. L.: Alterations of serotonin and LSD receptor binding following repeated administration of LSD. Life Sci. **24:** 2053–2062, 1979b.

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