LSD AND CNS TRANSMISSION

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The dominant assumption underlying much research on the central actions of D-lysergic acid diethylamide (LSD) is that it is involved in the facilitation or inhibition of synaptic transmission. The beginnings of this concept can be traced back to the early 1950s when it was hypothesized that LSD may produce its effects by interfering with the function of serotonin (5-hydroxytryptamine) in the brain (1–4). This speculation was initially based upon the following observations: (*a*) LSD was found to antagonize the excitant effect of serotonin in smooth muscle preparations (e.g., isolated rat uterus); (*b*) both LSD and serotonin were known to contain an indole nucleus; and (*c*) serotonin was shown to be present in the brain (5, 6). Serotonin came to be regarded as a possible neurohumoral or neurotransmitter substance in the CNS (3, 4, 6, 7) and through this association it followed that LSD might also affect synaptic transmission, at least where serotonin was involved. Thus, in neurophysiological and even biochemical studies there tended to be the implicit if not explicit assumption that the effects of LSD could ultimately be traced to an alteration in synaptic transmission.

It has obviously been enormously difficult to study directly the effects of drugs on synaptic transmission in the CNS. There have been two very different strategies employed to approach the problem of where and in what manner LSD might affect CNS transmission. One approach has been to examine familiar brain systems that would appear to have some relevance to the observed behavioral or psychological effects of LSD. For example, since LSD is known to induce hallucinations, the visual system formed a natural target for the study of the neurophysiological actions of the drug. A second strategy has been to examine neuronal systems on the basis of their presumed chemical relationship to LSD. The latter approach was given new impetus by the discovery of Dahlstrom & Fuxe (8) in 1965 that serotonin in brain is located within a specific set of neurons whose perikarya are situated in the brain stem raphe nuclei. The localization of serotonin to a neuronal system has given greater weight to the hypothesis that this amine functions as a transmitter substance. Interest was thus reawakened in the notion that LSD may have its actions at "serotonergic" synapses (9, 10).

One way of classifying research on LSD and CNS transmission would be according to whether it precedes or antedates the discovery of serotonin-containing neurons in brain. Another means of classification could be in terms of methodological approach. In many of the earlier studies, the influence of LSD on evoked potentials was observed in a variety of sensory and other pathways. Information derived from studies on gross, evoked potentials was often interpreted as providing an indication as to overall changes in synaptic transmission. This approach has largely been supplanted by the analysis of LSD actions at a cellular level by means of single unit recording and microiontophoretic techniques. In accordance with this temporal sequence the first section of this review will be concerned with work on evoked potentials, the second will deal with the microiontophoretic studies, and the last will consider these and other results in the light of recent findings on the effects of LSD on the serotonin-containing neurons of the raphe nuclei.

LSD and Evoked Potentials

In 1955, just shortly after the initial flurry of interest in the possible relationship between LSD and brain serotonin, the first studies on the effects of LSD on evoked potentials were published. Marazzi & Hart examined the influence of LSD and serotonin on transcallosal evoked responses (11). These investigators found that as little as 8 μg/Kg of LSD or 1 μg/Kg of serotonin injected into the carotid artery could suppress evoked responses in this system. They concluded that both of these compounds were cerebral synaptic inhibitors, and did not observe the occurrence of mutually antagonistic effects. The interpretation of these results in terms of CNS transmission is somewhat uncertain because the brain is relatively impermeable to serotonin (12). Obviously, it is possible that serotonin could alter transcallosal responses indirectly via some peripheral action such as by an effect on cerebral blood flow. In another early study, Evarts and associates (13) looked for effects of LSD in the visual system based on the rationale that LSD was known to produce perceptual changes in experimental animals. They found that 30 μg/Kg of LSD (13), but not serotonin (14), administered via the carotid artery, depressed the postsynaptic response in the lateral geniculate of cats with no decrease in the visual cortex. Following upon these initial studies there were a number of other attempts at determining the influence of LSD on evoked responses in various areas of the brain and spinal cord. The results of some representative studies are summarized in Table 1. It may be noted that there is an extraordinary degree of variation in experimental conditions (e.g., anesthesia, dosage, route of administration) which leads to some difficulty in making meaningful generalizations about this work. It is clear, however, that LSD does not consistently have a depressant effect on evoked responses as might have been concluded from the early studies. In fact, with few exceptions, in unanesthetized animals LSD generally enhances or has no effect on evoked responses

TABLE 1. EFFECT OF LSD ON EVOKED POTENTIALS

Authors	Animal	Site of Recording	Anesthesia	Response	
Marrazzi & Hart 1955 (11)	cat	transcallosal (optic cortex)	pentobarbital	↓	8 μg/Kg (carotid artery)
Evarts, et al. 1955 (13)	cat	visual system	pentobarbital		
		a. optic tract		↓	2–5 μg/Kg (carotid artery)
		b. lateral geniculate		↓	30 μg/Kg (carotid artery)
		c. visual cortex		↑	1.5 mg/Kg (carotid artery)
Purpura, 1956 (15)	cat	auditory & visual cortex	none (succinyl choline)	↑	2–3 μg/Kg
Rovetta, 1956 (16)	cat	visual cortex	chloralose-urethane	0	40 μg/Kg i.v.
Bishop et al. 1958 (17)	cat	lateral geniculate	Dial	↓	25 μg/Kg (lingual artery)
Geiger & Cervoni, 1958 (18)	cat	spinal cord neutral root	none (spinal section)	↑	200 μg/Kg i.v.
Evarts, 1958 (14)	cat	lateral geniculate	none	↓	1 mg/Kg i.v. or i.p.
Key, 1965 (19)	cat	cochlear nucleus	encephalé isolé	↑	5–10μg/Kg i.v.
Revzin & Armstrong 1966 (20)	cat	amygdala-hippocampal	none	↑	100–25 μg/Kg i.v.
Bond & Guth 1968 (21)	cat	transcallosal (visual cortex)	pentobarbital	↓	6–100 μg/Kg (lingual artery)
Banna & Anderson 1968 (22)	cat	ventral root, spinal cord	none (spinal section)	↑	300 μg/Kg i.v.
Mouriz-Garcia 1969 (23)	cat	visual cortex	none (gallamine)	0	50–100 μg/Kg i.v.

(15, 18, 19, 22, 23). Interestingly, in terms of the serotonin hypothesis, experiments in spinal animals have shown that monosynaptic potentials evoked by dorsal root stimulation are facilitated both by LSD and loading doses of serotonin precursors (22, 24). In this preparation, methylsergide and 2-brom-LSD blocked the effects of serotonin precursors but LSD itself had no blocking action except at extremely high doses (1.5 mg/Kg). Evarts (14) found that LSD given by the intravenous route could depress evoked potentials in the lateral geniculate nucleus, but a dose of approximately 1 mg/Kg was required. This exceeds an effective dose for psychotomimetic effects in humans by a factor of almost 1,000. Key has commented that "these effects in the visual system, although providing an explanation for the behavioral blindness observed in cats and monkeys . . . when high doses of LSD25 (1 mg/Kg intraperitoneally) are used, are difficult to correlate with the alerting and increased responsiveness to sensory stimuli occurring after the administration of smaller doses (5–30 μg/Kg)" (19). On the basis of studies in the auditory pathway, Key concludes that alterations in the amplitudes of evoked potentials after small doses of LSD "do not appear to be due to the direct effect of the drug on this pathway or on the inhibitory and facilitatory synapses capable of controlling the flow of information through the subcortical relays." Instead, it has been postulated that LSD at low doses in the waking animals acts primarily upon the afferent collateral system of the brain-stem and that alterations in sensory evoked responses are essentially secondary phenomena (25, 26). The validity of these intriguing concepts remains to be thoroughly tested.

In summary, as can be seen from Table 1, the presence or absence of anesthesia and the dosage range of the drug can significantly alter the nature of the effect of LSD on evoked potentials. At lower doses and in the absence of anesthesia, LSD tends to enhance rather than depress evoked potentials. However, because of the fact that the LSD is being administered by the systemic route, the primary site of action of the drug cannot readily be localized to transmission at a particular synapse.

Neuronal Responses to LSD: Microiontophoretic Studies

In an effort to avoid uncertainties inherent in the systemic route of administration about such matters as site of action or degree of penetration, the technique of microiontophoresis via multibarreled micropipettes has come into use increasingly in neuropharmacological studies. This technique was first applied to the study of the cellular actions of LSD, serotonin, and other substances in brain by Curtis & Davis (27). These investigators studied responses of units in the lateral geniculate nucleus of cats anesthetized with pentobarbital. In these studies both LSD and serotonin were found to have primarily depressant effects on the orthodromically evoked firing of cells in this nucleus. In addition to serotonin, the 4, 6, and 7-hydroxytryptamines were found to have a potent depressant effect on unit responses in the lateral geniculate nucleus. None of the compounds tested blocked the excita-

TABLE 2. MICROIONTOPHORETIC EFFECTS OF LSD

Authors	Animal	Anesthesia	Site of Recording	Unit Discharge Rate Response to LSD	Unit Discharge Rate Response to 5HT	Effect of LSD on 5HT Response
Curtis & Davis 1962 (27)		pentobarbital	lateral geniculate	↓	↓	no antagonism
Krnjevic & Phillis 1963 (28)	cat, rabbit, rhesus monkey	Dial or "cerveau isole"	cerebral cortex	↓	↓	—
Krnjevic & Phillis 1963 (29)	cat	Dial	cerebral cortex	↓	↓	no antagonism
Bloom et al. 1964 (30)	cat	none (decerebrate)	olfactory bulb	↓	↓	antagonism of 5HT
Bradley & Wolstencroft 1965 (31)	cat	none (decerebrate)	brain stem	↓	↓, ↑	—
Legge et al. 1966 (32)	cat	Dial	pyriform cortex	↓	↓	no antagonism
Phillis & Tebecis 1967 (33)	cat	nitrous oxide & halothane	thalamus	↓	↓, ↑	no antagonism
Roberts & Straughan 1967 (34)	cat	none (encephalé isolé)	cerebral cortex	↓	↓, ↑	antagonism of 5HT
Johnson, Roberts & Straughan 1969 (35)	cat	a. anesthetic			↓	—
		b. none (cerveau isolé)	cerebral cortex		↑	—
Boakes, et al. 1970 (36)	cat	none (decerebrate)	brain stem	↓	↓, ↑	antagonism of 5HT

tory effects of either L-glutamate or antidromic stimulation. The fact that LSD applied microiontophoretically can depress geniculate units correlates with the previous finding that LSD can depress evoked potentials in this nucleus (see above). However, Curtis & Davis cautioned that "the psychotomimetic action of lysergic acid and of related compounds in the human subject, is produced by doses which are much lower than those necessary to depress geniculate responses in the cat." Furthermore, "the depression of potentials generated by many cells, or even the prevention of firing of one cell, are relatively crude methods of assessing alterations in neuronal function." Curtis & Davis conclude that with "smaller doses of these compounds subtle alterations in the responses of certain neurons produced by the same mechanism by which large doses block these responses, may be sufficient to cause psychic disturbances."

Since this initial study there have been a number of microiontophoretic investigations on the effects of LSD on neurons in various regions of the brain (Table 2). Again, as in the case of studies on evoked potentials, a great variety of experimental conditions were employed, making difficult any attempt at generalization. However, one consistent feature of the microiontophoretic studies is that LSD has a depressant effect on neuronal firing in all regions of the brain tested both in the presence and absence of anesthesia. This overall finding is somewhat puzzling in view of the fact that with the exception of cells in the raphe nuclei, small doses of LSD given parenterally usually increase or do not alter unit activity in the brain stem (37, 38) and lateral geniculate (23). A possible explanation for this discrepancy could be that concentrations of LSD in the vicinity of the micropipette tip might be high enough to have a local anesthetic effect (39, 40). As can be seen from Table 2, serotonin, like LSD, had a depressant effect on some cells. However, in contrast to LSD, excitatory responses to serotonin were also seen, particularly in unanesthetized preparations (35). In unanesthetized animals Bloom et al (30) found that in some cases the depressant effect of serotonin could be blocked by LSD. However, in all cases norepinephrine responses were also blocked under these conditions. In unanesthetized animals, Roberts & Straughan (34) and Boakes et al (36) found that LSD was consistently effective in blocking the excitatory action of serotonin. In both of these studies it was shown that methylsergide and 2-brom-LSD, analogs with little or no psychotomimetic action, were less effective than LSD in antagonizing the excitatory responses to serotonin. Curiously, LSD applied iontophoretically has also been found to block glutamate excitation (29, 33, 36). Boakes et al (36) analyzed the specificity of this effect and found that LSD antagonizes the excitatory action of glutamate only in the case of cells that were also excited by serotonin. These authors comment that this "connexion between the excitatory actions of glutamate is difficult to account for, especially as glutamate can excite many neurons which are either unaffected or inhibited by 5HT." They speculate that this overlapping effect of LSD might result from "steric occlusion if

the two receptors [i.e., serotonin and glutamate] are adjacent, or by some form of allosteric inactivation." However, it remains to be determined if such blocking actions of LSD are due to a partial local anesthetic effect of abnormally high drug concentrations in the vicinity of the micropipette tip. Bradley & Wolstencroft (31) point out with regard to studies on amphetamine that the parenteral administration of this drug had an excitatory effect on some cells that were inhibited after iontophoretic application. It may be necessary to have side-by-side comparisons of the effects of LSD given parenterally versus iontophoretically to settle the question as to whether there is any overall consistency between the effects of this drug given by these different routes. A further issue raised by the iontophoretic studies concerns the interactions found between LSD and serotonin. In assessing the meaning of these results it will be important to know if the cells under study are actually innervated by "serotonergic" neurons. Obviously, LSD and serotonin applied iontophoretically to cells for which serotonin is not normally a transmitter may have little bearing upon relevant biological actions of these substances. The studies of Cottrell (41, 42) in *Helix pomatia* are of interest in this respect because follower cells of identified serotonin-containing neurons were studied. In this preparation, the follower cells were activated by stimulation of the serotonergic neuron. High concentrations of LSD blocked (41) but low concentrations mimicked (42) this activation. In the mammalian brain, the histochemical mapping of serotonin-containing neurons opens the way for similar kinds of studies on "follower" cells of identified serotonergic neurons.

LSD AND SEROTONIN-CONTAINING NEURONS IN THE CNS

Although serotonin has long been suspected of being a neurohumoral or neurotransmitter substance in the CNS, hard evidence for this thesis has been late in coming. Initially, it was shown by means of density gradient analyses of brain homogenates that serotonin was concentrated in the pinched-off nerve ending or "synaptosome" fraction (43). Soon afterwards it was found that a selective lesion in the lateral hypothalamus led to a depletion of brain serotonin, particularly in the neocortex and limbic areas, suggesting that neuronal pathways were intimately involved in the maintenance of serotonin levels in brain (44, 45). Although the above findings are consistent with a neuronal localization of serotonin, the most direct and graphic evidence for the existence of serotonin-containing neurons came from the work of Dahlstrom & Fuxe in 1965 (8). These workers showed by means of the formaldehyde-condensation histochemical fluorescence method of Falck et al (46) that serotonin was present only within a small, select group of neurons. The perikarya of these neurons were located in the raphe nuclei of the brainstem. Axons originating from the raphe neurons were shown to project to the various regions of the forebrain (47, 48). By means of electron microscopic autoradiography, the uptake of radioactive serotonin was shown to occur selectively in nerve endings in areas that were

found by histochemical fluorescence to be rich in endogenous serotonin (49). Taken together, these studies on the identification and mapping of the "serotonergic" neuronal system provided a basis for the direct investigation on a cellular level of the interaction between LSD and serotonin in brain.

Based on the observations that LSD reduced the turnover of brain serotonin (50, 51) and that electrical stimulation of the serotonin-containing neurons of the midbrain raphe nuclei increased turnover, it was suggested that LSD might depress the firing of raphe neurons (9). Independently, a similar suggestion was made based on the fact that LSD slowed the rate of depletion of serotonin which occurs after inhibition of synthesis (10). By means of direct microelectrode recording from single raphe neurons in rats, it was demonstrated that extremely small doses of LSD (10 μg/Kg, intravenously) produced a total but reversible inhibition of firing (37, 38). This was an invariable finding and occurred both in anesthetized (37, 38) and unanesthetized animals (52). This inhibitory effect of LSD was exceedingly selective and the firing of units outside the raphe nucleus was either unaffected or increased. The nonpsychotomimetic analog of LSD, 2-brom-LSD, which is even more potent in blocking the actions of serotonin in smooth muscle preparations (53), was found to have less than 1% of the activity of LSD in depressing raphe neurons. Taken together these results reinforce the original hypothesis that LSD might act in the brain by interacting somehow with serotonin.

There are a number of possible mechanisms that might account for the observed inhibition by LSD of serotonin-containing (i.e. raphe) neurons. First, LSD might have a direct inhibitory action. The microiontophoretic approach would obviously be very useful in exploring this possibility. One difficulty, however, is the fact that LSD given microiontophoretically has been found to inhibit a substantial proportion of neurons in the brain whereas by the "normal" parenteral route small doses of the drug inhibit only raphe units (see above). Nevertheless, in preliminary studies, using extremely dilute solutions of LSD (100 μg/ml of 0.9% saline), raphe but not other nearby neurons were inhibited by microiontophoretic administration (54). LSD was also found to reverse L-glutamate excitation of raphe neurons. The fact that raphe neurons may be inhibited directly by LSD does not exclude the possibility that the drug also acts at postsynaptic sites. A rich network of raphe terminals is clearly demonstrated by histochemical fluorescence in the linearis caudalis nucleus (dorsal to interpeduncular nucleus) in the rat (47, 55). Single unit recording from cells in this area shows a marked increase in firing rate after small doses (10 μg/Kg) of LSD (55). It remains to be seen whether excitatory effects would also occur after microiontophoretic administration and if the same or opposite effect would result from raphe stimulation or the application of serotonin. Terminals of raphe cells are also clearly seen in the suprachiasmatic nucleus (47). In preliminary studies (56) inhibitory responses were found in suprachiasmatic cells, both to microiontophoretically applied serotonin and

stimulation of the raphe nucleus. However, no effects of LSD were seen when it was given iontophoretically or parenterally. The above studies represent only beginning efforts toward clarifying the interrelationship between the effects of LSD, serotonin, and raphe neurons on postsynaptic neurons, and further studies are obviously needed. The key to future work in this area will be establishment of close correlations between the sites of electrophysiological recordings and identification by histochemical fluorescence of raphe terminal input to various cells under study.

Conclusions

As is apparent from the foregoing review, the assumption that LSD produces its effects by altering synaptic transmission in the CNS has received much experimental support in recent years. Moreover, the fact that serotonin-containing neurons of the raphe nuclei are so exquisitely and selectively sensitive to small parenteral doses of LSD (see above) suggests that the drug has its primary effects on specific neurons and synapses linked to the raphe neuronal system rather than on synaptic transmission in general. It is evident, therefore, that a specific problem for future research in this area is the testing of the hypothesis that the raphe neurons and their afferent and efferent connections represent the primary site of action of LSD in the CNS. A corollary of this general question is whether LSD acts by mimicking or blocking the effects of the transmitter substance of raphe neurons. Although it is generally assumed that serotonin is the likely transmitter of raphe neurons, recent studies suggest that other indoleamines may also be present in these neurons (63). The original hypothesis that LSD either blocks (1-4) or mimics (57, 58) serotonin can now be restated to encompass any transmitter substance of raphe neurons, whether it be serotonin or another indoleamine. This hypothesis has undergone a series of vicissitudes (9), beginning with the finding that 2-brom-LSD was even more potent than LSD in blocking serotonin in the rat uterus but had little psychotomimetic activity (53). Furthermore, there is a general lack of correlation between peripheral antiserotonin activity and psychotomimetic potency (59). However, contrary to general belief, in many peripheral tissues LSD but not 2-brom-LSD tends to have a serotonin-like (i.e., excitatory) effect at low doses and is inhibitory only at high doses (57, 58, 60, 61). In any event such studies in peripheral tissues obviously cannot settle the issue of whether LSD blocks or facilitates serotonin in the CNS. Boakes et al (36) have recently summarized the evidence from CNS studies on this point. They believe the preponderance of evidence favors the view that LSD blocks rather than mimics serotonin. They place particular weight on the finding that LSD blocks excitatory responses to iontophoretically applied serotonin in unanesthetized animals. However, the fact that under these same conditions LSD also antagonizes the excitatory action of glutamate remains rather puzzling. On the other hand, combined histochemical observations and single cell recordings on raphe neurons suggest a similarity in

the action of LSD and serotonin. This is shown in part by the fact that monoamine oxidase inhibitors, which block the degradation of serotonin and L-tryptophan, which increases serotonin synthesis, have in common the ability to raise serotonin levels in brain, increase the intensity of raphe fluorescence, and depress the rate of firing of raphe neurons (55, 62, 63). Thus, there is a reciprocal relationship between serotonin level and raphe firing rate which is consistent with the concept of a negative feedback action due to an excess of transmitter substance. It is therefore significant that the effect of LSD, at least upon raphe neurons, resembles that of an excess of serotonin. The latter results, along with the findings of Banna & Anderson (22) in the spinal cord, seem to indicate that LSD can mimic the central actions of serotonin. Nonetheless, there are plausible arguments on both sides of the issue as to whether LSD blocks or mimics serotonin in the CNS and this matter requires further experimental study. In any event, the elucidation of the mechanism of action of LSD will require more than simply isolated observations on the effects of LSD or serotonin on raphe or other individual neurons. Ultimately it will be necessary to integrate data from the unit level with knowledge about the interconnections and physiological role of the neuronal systems within which these units function.

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