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Electrophysiological Studies of d-Lysergic Acid Diethylamide in the Visual System[1]

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FOOTE, W. E. *Electrophysiological studies of d-lysergic acid diethylamide in the visual system.* NEUROSCI. BIOBEHAV. REV. 6(4) 503–507, 1982.—Experiments involving the use of LSD and observing its effects on neurons involved in the processing of visual information are reviewed. These studies typically involved either intravenous or iontophoretic application of the compound. Both modes of application appeared to block the optic afferent synapse at the level of the dorsal lateral geniculate nucleus and to alter the evoked activity of visual cortical neurons. Increasing the dose of LSD regardless of the manner in which it was applied tended to produce depression of both spontaneous and visually driven activity. The receptive field properties of the neurons at all levels of the visual system appear to remain intact after LSD despite changes in spontaneous activity. The effect of LSD on non-specific afferents to the dorsal lateral geniculate nucleus is depicted in relationship to two of the different kind of relay cells located in this structure. Data on LSD interaction with the effects of midbrain stimulation on "X" and "Y" neurons is presented.

Electrophysiology LSD Visual cortical neurons

ATTEMPTS to understand the action of d-lysergic acid diethylamide (LSD) on the neural substrate for vision began in the mid-fifties. Evarts *et al.* [9] had noted that large doses of LSD (1 mg/kg) given intravenously produced abnormal visual reactions in cats and monkeys and began a series of studies to determine the neural basis for LSD's effects. In the anesthetized, paralyzed cat these investigators observed the effects of LSD and Bufotenine on evoked responses recorded from the optic tract, the dorsal lateral geniculate nucleus and the visual cortex. At the levels of the optic tract and visual cortex they found that large doses of LSD (greater than 1 mg/kg) altered both visual and electrical responses recorded from these structures. Bufotenine in doses 2 to 6 times greater than LSD produced little or no effect. However, the evoked response from the dorsal lateral geniculate nucleus (dLGN) was shown to be much more sensitive to both agents with 30 μmg/kg LSD resulting in a 30 to 100% decrease in the postsynaptic response to optic nerve stimulation. Bufotenine produced similar results but only at greater dosage. Parallel findings were obtained from cats decerebrated at the intercollicular level, ruling out anesthetic effects. These initial observations indicated that on the basis of dosage the dLGN was the visual area most sensitive to the effects of LSD. Subsequent to this initial work, Bishop *et al.* [3] studied the effects of varying doses of LSD on the pre- and postsynaptic components of the dLGN evoked response. Using broken micropipettes, Bishop *et al.* [3] recorded potentials reflecting the different conduction velocities of optic tract fibers and their corresponding postsynaptic responses to shocks of the optic nerve. LSD was given in doses of 5 μg/cat to 1 mg/cat and depressed postsynaptic activity, leaving the presynaptic potentials unchanged, implying that the drug was interfering with optic afferent synapses. The extent of depressed activity and time to recovery were dose-dependent with 10 μg/cat reducing the response by 25% to 50% and 50 to 75 μg/cat producing a 90% reduction. Larger doses produced only slightly greater depression of activity but were correlated with longer recovery times which ranged from 5 to 30 minutes depending on the dose employed. In addition, Bishop *et al.* [3] noted the effects of LSD on the awake, behaving cat and reported that 1 mg/kg IV produced pupillary dilation,, piloerection, marked ataxia of the hind limbs and inability to avoid objects in their paths. The animals appeared functionally blind but recovered in 90 minutes to two hours, which corresponded roughly to the half-life of LSD in cat as determined by Axelrod [2].

In parallel with these preliminary studies of LSD and visual system function were observations of LSD's interaction with the reticular formation. Purpura [18] noted the effects of tegmental reticular formation stimulation on slow dendritic potentials evoked by stimulation of the cortical surface. He found that moderate doses (40 to 50 μg/kg) reduced the size of the slow potentials in a fashion similar to that seen with reticular formation stimulation. He suggested that LSD enhanced synaptic inhibition on cortical dendrites and appeared to mimic the effect of reticular formation stimulation.

The work of Bradley and Key [4] indicated that an intact neuraxis was important for LSD to produce behavioral and cortical arousal in the cat. Small doses (1–20 μg/kg) of LSD

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decreased auditory thresholds and antagonized habituation responses in normal and encephale isolé cats. However, in cerveau isolé animals much larger doses of LSD were required to produce either a neural or behavioral change. Although these studies did not directly test the role of the reticular formation in mediating the effects of LSD, they implied that it made a significant contribution to them.

All of these early studies utilized gross potential recordings for acquiring neural data. With advances in refined electronics and microelectrode technology, it became possible to record from single neurons and observe the effects of LSD upon them. One of the first studies to investigate the effects of LSD and related compounds on individual cells in the cat visual system was performed by Curtis and Davis [5]. These investigators iontophoresed LSD, serotonin (5-HT) and glutamate onto neurons in the dorsal lateral geniculate nucleus. They observed that both LSD and 5-HT blocked orthodromic activation but did not affect antidromic activation of dLGN neurons, suggesting that these compounds were probably acting at synaptic receptors. This suggestion was further supported by the observation that neither LSD nor 5-HT could depress the non-specific excitatory effect of glutamate on dLGN cells. Subsequent studies by Curtis and Davis [6] confirmed their previous results and in addition implicated acetylcholine as an excitatory transmitter affecting dLGN activity that operated at neuronal sites other than those sensitive to 5-HT.

With the publication of the work of Dahlström and Fuxe [7] indicating the presence of monoaminergic terminals in the dLGN, interest in the role of possible transmitters in this structure was rekindled. Phillis *et al.* [17] replicated the work of Curtis and Davis [5] and in addition to using 5-HT and LSD observed the effects of iontophoretic application of dopamine (DA) and noradrenaline (NE) on dLGN neurons. Orthodromic activation, induced by either visual or optic nerve stimulation, was blocked when either LSD, 5-HT, DA, or NE was applied to dLGN cells. In addition Phillis *et al.* [17] also found blockade of antidromic activation when the above compounds were iontophoresed by currents larger than those used to suppress orthodromic responses. These results implied that LSD and the 3 amines could possibly have postsynaptic effects and was supported by the findings that they could also reduce the excitatory effects of glutamic acid. Differences between these observations and those of Curtis and Davis [5] regarding antidromic activation and depression of glutamate excitation was ascribed to the use of barbiturate anesthesia by Curtis and Davis [5]. In an attempt to reconcile this issue Tebecis and DiMaria [22] reinvestigated the problem using anesthetized and unanesthetized animals. They concluded that the differences between results of Curtis and Davis [5] and Phillis *et al.* [17] was not due to anesthesia but to the amount of electrophoretic injection current used. That is, 5-HT and LSD were found to block both ortho- and antidromic activations at high currents (100 nA), whereas at low currents (20–40 nA) only orthodromic activity was affected. Dopamine and noradrenaline were capable of depressing both orthodromic and glutamate induced activations but only at high phoretic currents.

Additional information regarding the effects of putative transmitters on dLGN neurons came from the work of Satinsky [21]. In unanesthetized decerebrate cats, he studied the effects of 5-HT, ACh and NE applied iontophoretically onto units identified by antidromic invasion from visual cortex. In all cases 5-HT depressed whereas NE and ACh enhanced spontaneous activity. However, with a small number of unidentified cells the reverse was found, 5-HT was excitatory and NE and ACh inhibitory. The author suggested that this reversal might be associated with recording from interneurons. LSD was not tested in this study.

In summary, then, the effects of iontophoretic application of LSD on single units in the dorsal LGN indicated that LSD altered the optic afferent synapse by either interfering with release of transmitter or blockade of the postsynaptic receptor. When applied in greater concentration it caused depression of the postsynaptic neuron. Iontophoresis of 5-HT appeared to produce similar results and was occasionally noted to require less current for its effects than LSD. These findings are consistent across a number of experiments, if one assumes that Satinsky's [21] data showing excitation following 5-HT was associated with recording from interneurons and not relay cells.

When LSD was given intravenously and activity in the LGN was monitored, a somewhat different picture emerged. While it had generally been concluded on the basis of gross potential recording (Evarts [9], Bishop *et al.* [3]) that LSD did not affect retinal afferents to the LGN, Moruiz-Garcia *et al.* [16] found that doses of 40–50 μg/kg given intravenously altered the spontaneous activity of 21 optic tract axons and a small number of dorsal lateral geniculate neurons. Fourteen of the axons increased their activity whereas the remainder were depressed up to 50% of control levels. Repeated doses of LSD did not produce additional activation of axons previously excited by this drug. Four neurons in the dLGN were excited and the remainder did not show any clear response. There was no alteration of receptive field organization in the units studied beyond that indicated by changes in spontaneous activity. The authors also noted that the electroretinogram and the visual cortical evoked response remained normal.

Moruiz-Garcia *et al.* [16] concluded that due to its time of onset, 2–3 minutes for initial effect, 10 minutes for peak effect, that LSD probably did not affect the nerve membranes directly but may have acted via monoamines. However, in a study of in vitro activity of retinal ganglion cells, Ames and Pollen [1] noted that both LSD and 5-HT in micromolar concentrations increased the spontaneous activity of both the on and off center ganglion cells, and that the effects of LSD were still apparent 24 minutes after several washes in control medium, suggesting that LSD was adhering to cell membranes.

Several years later Horn and McKay [13] observed the effects of varying doses of LSD on the spontaneous and light driven activity in dLGN. Cats were given total doses of 25, 100, 200 or 300 μg, and it was noted that spontaneous activity decreased with increasing dose. At the highest dose every unit studied decreased its spontaneous activity and this effect is probably correlated with the functional blindness seen with large doses. However, with administration of 100 μg/cat some units displayed increased activity while others showed decreases. This dose seemed to produce the greatest variability in firing rate, although as mentioned earlier the net effect of increasing dosage was depression. This trend also held for stimulation of visual receptive fields; that is, with increasing dose of LSD the effectiveness of spots of light or annuli was also depressed relative to control. However, it should be noted that there was no correlation between changes in spontaneous activity and receptive field activation. Some LGN neurons whose spontaneous rate had been increased by the drug displayed diminished response to light shown on their receptive fields. This finding suggested that

the mechanisms underlying spontaneous and visually driven activity were differentially affected by LSD. A diminished response to visual stimuli supports the hypotheses that the drug interferes with the optic afferent synapse. Brom-lysergic acid (BOL) in doses of 100 μg/kg had no effect in this experiment. The main difference between intravenous studies and iontophoretic work is that increases in spontaneous activity were not found when LSD was ionotophoresed onto LGN neurons.

More recently, Haigler and Aghajanian [12] observed the effects of iontophoretic and intravenous doses of LSD in the ventral lateral geniculate nucleus of the rat. This structure was selected rather than the dorsal portion of the nucleus since prior work, Kuhar *et al.* [14], indicated the presence of dense 5-HT terminals in the ventral LGN. 5-HT blocked both spontaneous and light driven activity in this structure but iontophoretic application of LSD at currents capable of suppressing raphé neurons were ineffective in the nucleus. Larger iontophoretic currents greater than 40 nA were capable of depressing neuronal activity in much the same fashion as indicated in earlier reports. Intravenous injections of LSD (20 μg/kg) produced a slight transient increase in spontaneous activity.

While all the preceding studies have generated some consistent data regarding 5-HT and LSD they do not reveal much about possible mechanisms involved in hallucinations. When such studies are extended to the visual cortex the results are somewhat similar.

Rose and Horn [19] observed the effects of intravenous doses of 200 μg/cat of LSD on simple and complex cells in area 17. The units peak response to an optimally oriented bar of light was noted before and after LSD. In some cases responsiveness was increased and in other instances decreased after the drug. This finding applied to both simple and complex cells. The orientation specificity of the cell was not distorted. Direction selectivity was maintained after injection of the drug, with some cells displaying greater activity to the non-preferred direction over control values. However, in general, receptive field integrity was preserved suggesting that hallucinatory phenomena were not based on receptive field changes. Spontaneous activity was either unaffected or displayed variable increases and decreases after LSD.

Additional information about the effects of LSD on visual cortical neurons was obtained by Dray *et al.* [8]. These investigators noted the effects of LSD and BOL administered both intravenously and iontophoretically on simple, complex and hypercomplex cells in the cat. Intravenous doses of LSD ranged from 0.1 to 50 μg/kg and the general result was that there was enhancement of visual evoked responses in the dose range of 0.1 to 10 μg/kg. With progressively larger doses depression of evoked activity was observed. The response to an optimally oriented stimulus could be increased or decreased depending upon the dose given but the orientation properties of cells remained unchanged. Direction selectivity was altered more in this study than had previously been reported. It was reversed in 2 cells and response to the non-preferred direction enhanced in other cells. While BOL produced effects similar to LSD, it was noted that this drug was 20–100 times less effective than LSD in producing enhanced responses and 5 times less potent in producing depressions. Comparison of results obtained with iontophoresis were similar to that seen with intravenous injections in that the amount of drug given was critical to producing a given effect.

Changes in evoked activity were related to the quantity of current used to eject LSD or BOL. Often the switching off of the retaining current on the LSD pipette, permitting diffusion of the drug, was sufficient to increase neuronal activity. With larger currents (an average of 10 nA) depression was noted. Iontophoresis of LSD could produce changes in direction selectivity either by accentuating, depressing, and, in some cells, reversing the response to movement of an optimally oriented stimulus. BOL had no effect on cells with currents up to 10 nA, but with currents of 30 nA or larger changes similar to those seen with LSD occurred with the exception of changes in direction selectivity.

As in the preceding cortical work [19] the receptive field properties of cortical neurons remained intact after administration of LSD. This finding coupled with receptive field data noted at other stages in the visual system [13,16] indicates that LSD induced visual abnormalities occur despite receptive field constancy. Consequently, it is difficult to account for subjective phenomena such as enhancement of colors or perception of vertical lines as bent or bowed that occur with ingestion of LSD by observing changes in visual neuronal activity. However, as research in vision progresses it may be possible to gain further insight into the mechanisms underlying LSD's effects.

Recently there have been described three different types of neurons in the dLGN that receive input from three functionally and morphologically distinct kinds of retinal ganglion cells. These dLGN cells have been called "X", "Y" and "W" or "sustained," "transient" and "sluggish sustained and transient" (see Rowe and Stone [20] for review). A variety of operational criteria have been used to distinguish among these cell types. They have different receptive field properties, and differ in the conduction velocity of their axons.

In an early study Foote *et al.* [10] observed the effects of electrical stimulation of the midbrain raphé nuclei, reported to innervate the dLGN, on identified neurons in that structure. The overall effects observed when single shocks were delivered to the midbrain is depicted in Fig. 1. The poststimulus time histograms depict the two types of effects observed, i.e., facilitations and suppressions. The time course of the effects differed with the facilitations occurring with latencies that varied from 15–25 msec and the suppressions developing within a more restricted range of 7–10 msec. The occurrence of a suppression with this latency was interesting in view of the fact that iontophoreses of 5-HT in dLGN, produced a cessation of activity. If one assumed a distance of 10 mm from the raphé to the dLGN, an effect with a latency of 10 msec suggested a conduction time of 1 m/sec, which could be a function of small diameter axons emanating from the raphé. Furthermore, the use of conditioning-test procecures indicated that raphé stimulation depressed the excitatory effect of optic nerve stimulation by either visual or electrical means.

When the effect of midbrain stimulation was correlated with "X" and "Y" cells a significant relationship was noted (Foote *et al.* [11]). The majority of "Y" cells were suppressed and the "X" cells facilitated. The addition of LSD to this paradigm produced the effects shown in Fig. 2. The series of histograms displayed in Fig. 2 represents the response of an "X" cell before and after intravenous injection of 100 μg/cat of LSD. This dose results in variability of spontaneous activity as noted by Horn and McKay [13]. However, the drug produced a dramatic increase in the facilitatory responses to midbrain stimulation. This increased responsiveness occurred despite the fact that LSD successfully depressed the

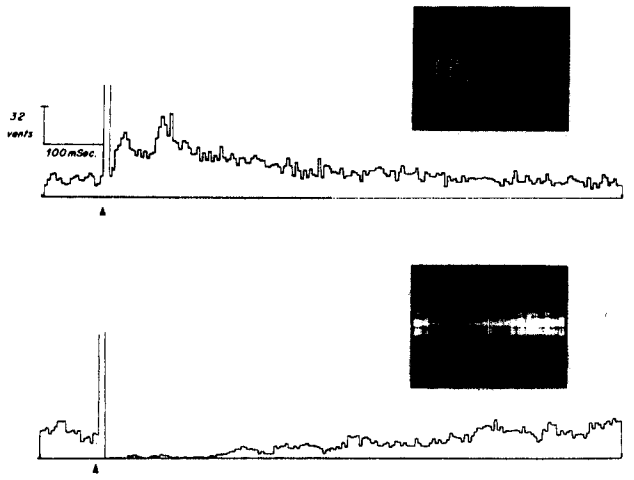

FIG. 1. Histograms reflecting the effects of midbrain stimulation on dorsal lateral geniculate neurons. Each histogram is based on 128 trials and is 1 second in duration. Arrowheads indicate onset of single shocks delivered to the midbrain. Oscillographic records displaying the unitary activity comprising each histogram are also shown. Each record is 100 msec in duration and the leading edge of the 10 msec square pulse indicates stimulus onset. The top portion of the figure depicts a neuron that was facilitated by midbrain stimulation; the bottom half a neuron that was suppressed.

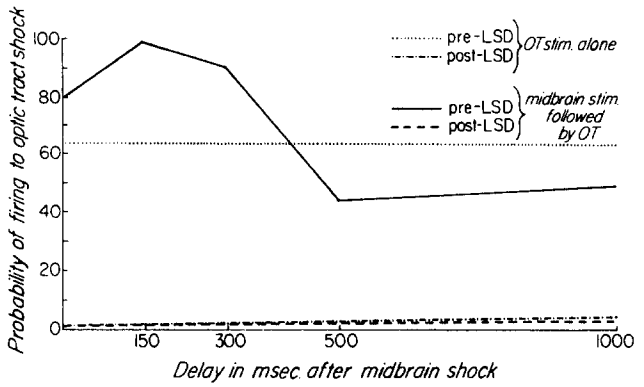

FIG. 3. Response of a facilitated cell to optic tract shock alone and optic tract shock after a conditioning pulse to the midbrain. Following injection of 100 μg/cat LSD the response to optic tract shock alone and in combination with the conditioning pulse is depressed.

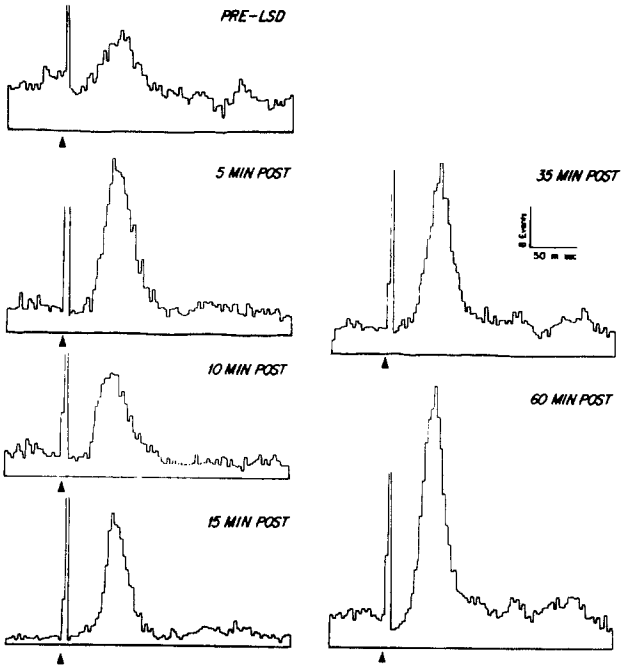

FIG. 2. Peristimulus time histogram of a facilitated "X" cell in the dorsal lateral geniculate nucleus. Arrowheads indicate onset of electrical stimulation; truncated vertical lines represent stimulus artifact. Each histogram is based on 128 trials with 100 msec of spontaneous activity (left of arrow) and 400 msec of poststimulation activity. Note changes in spontaneous activity that appear independent of the effect of LSD on poststimulation activity.

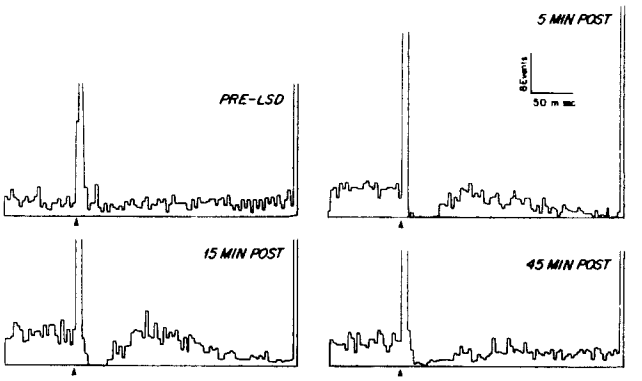

FIG. 4. Peristimulus time histograms of a geniculate relay cell which showed no effect to midbrain stimulation prior to LSD. Arrowheads mark the onset of stimulation; truncated lines represent stimulus artifacts. As in Fig. 2 each histogram is based on 128 trials with 100 msec of spontaneous and 400 msec of poststimulus activity. This is a record of a presumptive "Y" cell from an enucleated animal.

neuron's response to optic tract stimulation as can be seen in Fig. 3. The conditioning test procedure depicted in Fig. 3 indicates that midbrain stimulation can facilitate the effect of threshold pulses to the optic nerve prior to LSD administration. Once the drug has been given this effect is eliminated, suggesting that the enhanced activity seen in the histograms of Fig. 2 is unrelated to optic nerve activity. In order to confirm this contention 5 cats were binocularly enucleated and tested four to five days postsurgery in order to ensure optic nerve degeneration. Lateral geniculate neurons in these animals were identified by means of antidromic invasions from visual cortex. The combination of LSD plus midbrain stimulation produced enhancement of "X" cells similar to those seen in Fig. 2. This finding confirms the fact that

LSD can alter non-specific inputs to the visual system. The extent to which such enhancement of midbrain stimulation underlies hallucinatory images is unclear, but since "X" cells are known to respond to colors and patterns [20] one might postulate that LSD enhancement of midbrain input coupled with decreased effectiveness of retinal input could lead to visual distortions.

When similar studies were conducted on "Y" cells a different picture emerged. Although LSD can produce changes in spontaneous activity, the combination of the drug plus electrical stimulation did not appear to increase the duration or affect the latency of onset of the suppression of activity. However, on several occasions the results depicted in Fig. 4 could be observed. "Y" cells that were unaffected by midbrain stimulation prior to LSD manifested a suppression after the drug was given, suggesting that LSD was capable of lowering the threshold for electrical stimulation. Whether or not this represents potentiation of serotonergic input to "Y" cells remains to be determined. These findings suggest that LSD can differentially alter non-visual input to the dorsal lateral geniculate nucleus. The neurochemical mechanisms underlying its effects are unknown. However, it is worth noting that, in addition to LSD's interactions with serotonin, it may also affect cholinergic transmission, as the facilitatory effect of midbrain stimulation on dLGN neurons can be blocked by scopolamine [15].

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