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THE EFFECTS OF LSD AND SOME ANALOGUES ON THE RESPONSES OF SINGLE CORTICAL NEURONS OF THE CAT TO OPTICAL STIMULATION

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SUMMARY

The effects of lysergic acid diethylamide (LSD) and its analogues, 2-bromo-LSD (BOL) and methysergide, have been investigated on the responses to photic stimulation of single neurons in the striate cortex of the paralyzed, anesthetized cat. Systemic LSD (0.1–50 μg/kg, i.v.) produced: (a) enhancement or depression of evoked activity, the former being common with low, the latter with high doses; (b) changes in directional selectivity; and (c) changes in unstimulated background discharges. The effectiveness of the drug was reduced by repeated administration. Both BOL (10–75 μg/kg) and methysergide (100–700 μg/kg) produced effects qualitatively similar to LSD, but were considerably less potent. Microelectrophoretic administrations of LSD to single cortical neurons had actions similar to those caused by intravenous administration. BOL and methysergide required much larger currents to produce any effect and sometimes no effect could be induced by iontophoresis. It was concluded that these drugs influence visually evoked neuronal responses mainly by acting directly on cortical cells or synapses; and that the interference with visual cortical function could account for the distortion of visual perception caused by lysergic acid analogues; but that the hallucinogenic and psychotomimetic actions of LSD probably require additional, subcortical effects.

INTRODUCTION

Sensory disturbances are a common and well described feature of D-lysergic acid diethylamide (LSD) intoxication in both man and other mammals[26,36,42,43,51]. Distor-

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tion of visual perception is an early symptom in which, for example, changes in the outline of patterns, alterations in perspective and the perception of straight lines as zigzags, have been reported. The mechanisms by which LSD produces visual distortions is poorly understood though this substance is known to alter the electrical activity and propagation of information at several levels of the visual system; in the retina[6,7,44] optic tract,[10,15,55,65] and lateral geniculate nucleus[10,15,22,25,58]. In many of the earlier experiments on the visual system relatively high doses of LSD were used, and the visual pathway was activated by undifferentiated optical or electrical stimuli. In the studies where LGN or visual cortical neurons were activated by adequate, patterned optical stimuli, a variety of effects were reported[38,55,61]. The relationship of the changes of neuronal responses produced by LSD to its hallucinogenic properties remained however uncertain, since no control agents were tested. Furthermore, with systemic administration it was not clear whether the drug acted in the cortex, or indirectly through modification of subcortical mechanisms. We have confirmed and extended these previous findings concerning the effects of LSD on neurons in the striate cortex, and also investigated the effects of related analogues (2-bromo-LSD, and methysergide) administered both systemically (at doses which produce visual disturbances in behavioral studies[43]) and by microelectrophoresis. Some of our findings have appeared in abstract or preliminary form[24,28,35].

METHODS

Experiments were performed on adult cats (male or female) prepared for surgery under pentobarbitone (35 mg/kg, i.p.) or ether anesthesia. All wound edges were infiltrated with a long acting local anesthetic agent (Anucaine, Calvin Chemicals) and anesthesia was maintained during recording with a mixture of 75% nitrous oxide, 25% oxygen (v/v) and supplemented by intravenous thiopentone (2–5 mg/kg). A unilateral pneumothorax was performed, the animal paralyzed with gallamine (infused i.v. at 10 mg/kg/h.) and artificially ventilated. End-expiratory CO_2 concentration was kept between 3.5 and 4%, rectal temperature was maintained at 37 °C by means of a heated water blanket and arterial blood pressure was monitored. The head was stabilized by means of a steel rod screwed and cemented to the temporal bone. Drainage of CSF from the cisterna magna minimized cerebral pulsations.

Topically applied phenylephrine and atropine were used to cause the nictitating membrane to contract and to dilate the pupils. Contact lenses, corrected for refraction errors, were placed over the eyes. Photic stimuli, projected from an electromechanical system were usually presented at 0.1 Hz and consisted of a bright bar ($5 \times 0.6°$, 80 cd/sq.m) projected onto a white tangential screen (illuminated at 40 cd/sq.m) moving (7°/sec) repeatedly across the receptive field of a given cell. The dwell time on either side of the receptive field was equal for both directions of motion. Neuron receptive fields were plotted on tracing paper attached to the tangential screen by moving a projector's beam by hand, and marking the boundaries of the zone within which a cell's firing was influenced. All cells were classified from their visual response fields according to the criteria of Hubel and Wiesel[39]. Thus, simple cells were recognized by clearly defined

'on' and 'off' subdivisions in their receptive field and/or spatial summation within a subdivision. Complex cells generally have wider receptive fields than simple cells and give clear 'on–off' responses to stationary flashing stimuli throughout their receptive field. Hypercomplex cells exhibit length preference, giving little or no response if the bar of light extends beyond the boundaries of a central excitatory region.

Recordings of extracellular activity were made from single neurons in cortical area 17, using either a glass-coated tungsten electrode (tip diameter 2–5 μm), an electrolyte filled micropipette (2 M NaCl), or one barrel of a multibarrelled micropipette containing 3 M NaCl (combined tip diameter 6–8 μm). Stimulus–time histograms of single cell responses were electronically computed for 8–32 stimulus presentations usually at the optimal orientation and direction. Invariably, stimuli were presented to the preferred eye. 'Tuning-curves' were constructed for some neurons by presenting stimuli at varying angles of tilt and direction of motion.

Multibarrelled micropipettes were used to administer drugs locally by electrophoresis. NaCl (165 mM) served as a pharmacologically inert control. The remaining barrels contained LSD-tartrate, 2-bromo-LSD (BOL) and methysergide maleate, all at 1 mM, pH 4.0; all in 165 mM NaCl, so that drugs were ejected mainly by electroosmotic flow, with Na^+.

Drug effects were tested only after a stable, reproducible baseline of visually evoked responses had been established. The electrode placement was verified histologically in some experiments; in others cortical depth was read from the micromanipulator.

RESULTS

Intravenous administration

LSD. The effects of LSD (0.1–50 μg/kg) were tested on 43 cortical neurons of which 24 had simple, 14 had complex and 5 had hypercomplex receptive fields. Cells were located at depths from 0.25 to 2.25 mm below the cortical surface. Injections of LSD were made slowly over 2–4 min periods and produced no significant changes in blood pressure. Only one cell was studied in each animal to avoid desensitization invalidating quantitative comparisons. No changes in spike configuration were noted following LSD administration.

Two kinds of gross effects were produced by LSD on visually evoked firing: enhancement or depression. These effects did not appear to be related to the type of neuron studied or the depth location in the visual cortex. Drug-induced changes in evoked responses were considered to be genuine when they were 40% or more of the predrug control values, and then partial or complete recovery of responses was observed.

In 22 cells (9 simple, 9 complex, 4 hypercomplex) a single injection of LSD produced an enhancement (up to 300%) of visually evoked activity (Fig. 1) whereas in 19 cells, (13 simple, 5 complex, 1 hypercomplex) activity was depressed (up to 100%). Though the sensitivity of the cells was variable, the nature of the effects in a qualitative sense was dose related, enhanced activity being observed more commonly with small doses, and depression at higher ones (Figs. 2 and 3). Biphasic responses were seen in 3

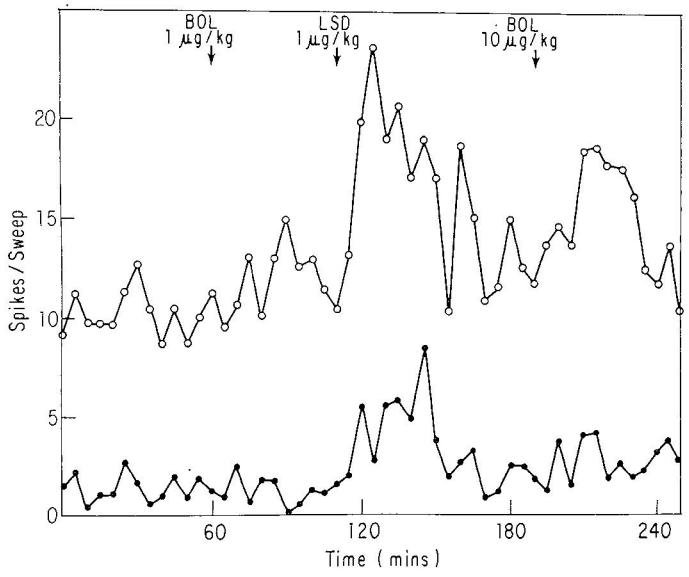

Fig. 1. Effects of intravenously administered LSD on visually evoked responses in the striate cortex. Continuous plot of the responses (spikes per sweep) of a simple cell to stimulation by a moving bar of light, during the course of an experiment (minutes), showing responses to the optimal (open circles) and null (filled circles) directions of stimulus movement. Arrows mark the intravenous administration of drugs. Note that the effect of the lower dose of LSD was of greater magnitude and duration than the effect of a higher dose of BOL.

cells; either enhancement was followed by depression of evoked activity (dose level 25 μg/kg), or the reverse (at dose of 1 μg/kg).

The effect of LSD was first noticeable 2–15 min (mean 7 min) after the injection and reached a peak 12–80 min (mean 24 min) later, with a protracted recovery which appeared to be dose related. Recovery from the enhancing effects occurred 40–230 min (mean 77.5 min) after injection, probably reflecting the smaller doses required to produce this effect. Complete recovery from the depressant effects of LSD was rare within the period of observation of 6 h following higher doses (25–50 μg/kg), but ranged from 48 to 180 min (mean 87 min) with relatively small doses (1.0–10 μg/kg). Statistical analysis (Student's *t*-test) of the time course of LSD effects on simple versus complex cells showed no significant differences.

Accompanying the changes in visually evoked responses, unstimulated background neuronal discharges were also affected by LSD. An increase in firing (seen in 3 simple, 3 complex, 2 hypercomplex cells, Fig. 2b) was particularly conspicuous since most cells were quiescent or discharged at a low rate when not stimulated. In 3 simple cells depression of background discharges accompanied the depression of evoked activity; whereas in one complex cell background discharges were increased even though evoked activity was depressed.

In 49 % of the cells tested, LSD also altered the degree of selectivity of the response to the direction of light-movement (Fig. 4). In these cases the responses evoked by sti-

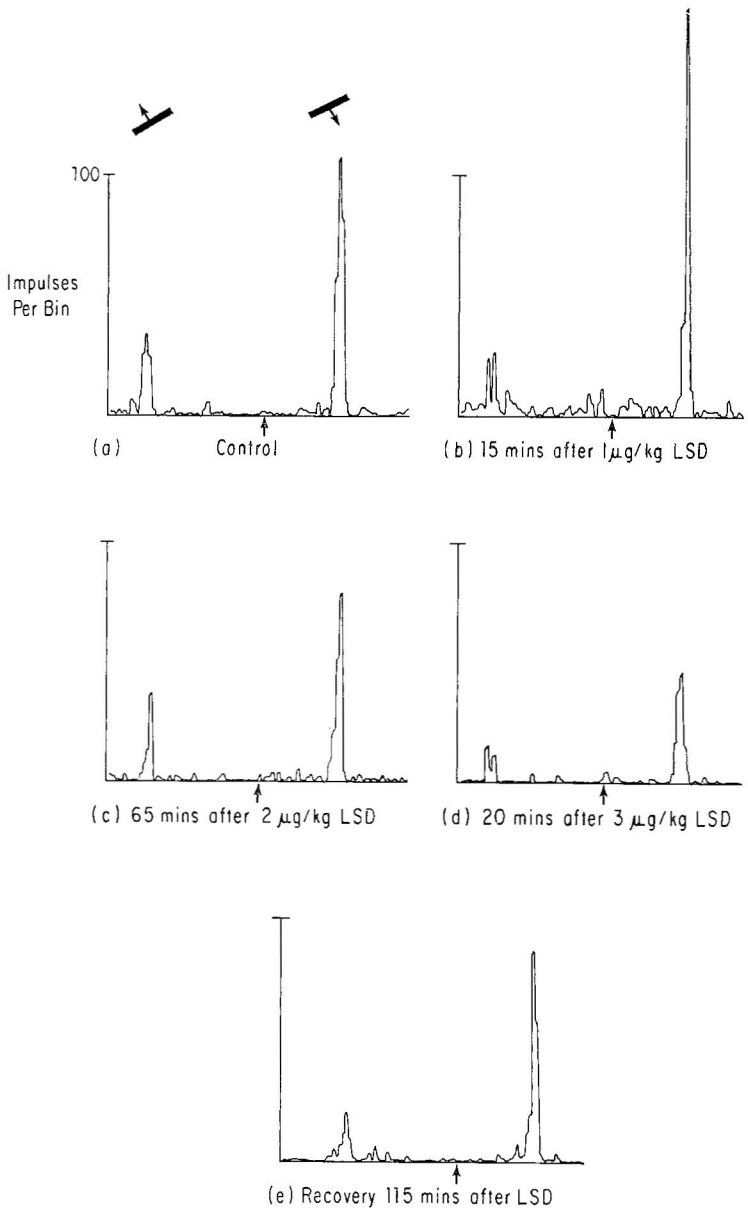

Fig. 2. Cumulated spike-count histograms (8 stimulus presentations) from a simple cell showing the responses to optimal and null directions of stimulus movement. The bars above the histogram indicate the direction of stimulus movement and the arrows under the abscissa show the moment at which the direction of movement was reversed. Note increase of unstimulated 'background' discharge after first i.v. administration of LSD (b), with increased response evoked by preferred stimulus direction; whereas in c and d further injections of LSD reduced the responses. Calibration: 100 impulses per bin.

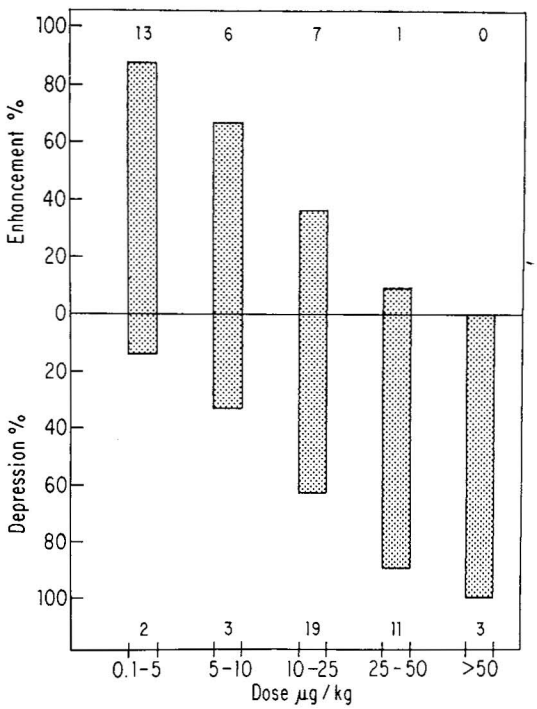

Fig. 3. Statistical incidence of the effects of LSD at varying dose levels. Ordinates: percentage of cells studied, in which evoked responses were either enhanced or depressed; at different doses of intravenously administered LSD. The numbers above and below each bar refer to the number of cells in each category. Dose levels indicate cumulated totals, in cases where more than one injection preceded the effect.

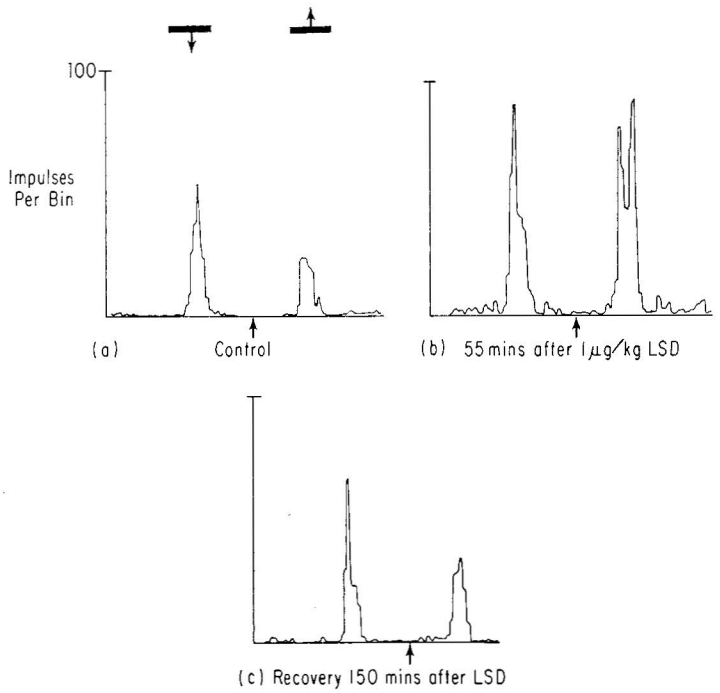

Fig. 4. Changes in directional selectivity produced by i.v. LSD. a: control responses (16 sweeps) from a complex cell showing preference for downward movement of stimulus. b: enhancement of responsiveness caused by LSD, with loss of directional preference, and increased unstimulated background activity. c: almost complete recovery.

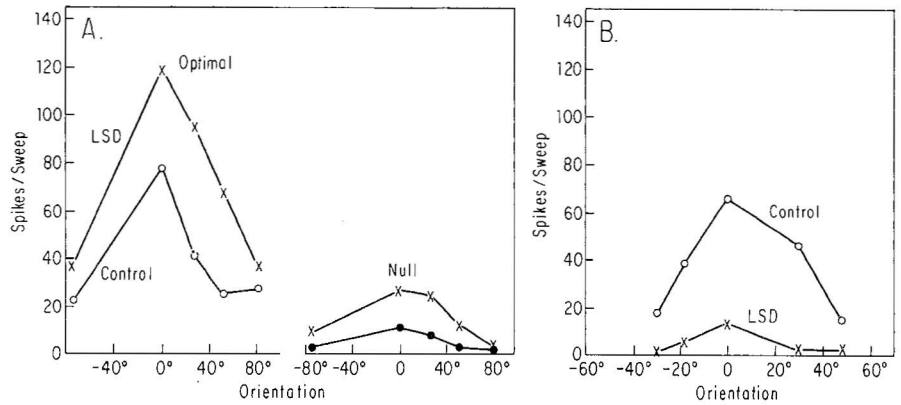

Fig. 5. The effect of i.v. LSD on orientation 'tuning curves' of two neurons determined in the control state and during the peak of the LSD effect. The net responses (mean of 3 stimulus cycles, 16 sweeps per cycle in A and 8 in B are plotted, after subtracting the mean number of spikes recorded during unstimulated 'blank' sweeps. The abscissae show the orientations of the light bar stimulus, relative to the optimal angle (0°). A: 10 μg/kg of LSD (simple cell) produced an overall enhancement of responses to optimal and null directions of movement (control: circles; LSD: crosses) and also enhanced the responses to non-optimal angles of stimulus orientation. B: 25 μg/kg of LSD depressed the responses to all angles in this complex cell. This cell responded only to one direction of stimulus movement.

muli moving in optimal and non-optimal directions were affected to a different degree. The ratio of optimal to non-optimal direction responses was either decreased (12 cells, 40–90%) or increased (8 cells, 90–240%). The probability of this effect appeared to be unrelated to the dose of LSD. Directional selectivity could deteriorate either when evoked responses were depressed, or when overall disproportionate enhancement of evoked responses occurred (Fig. 4). In two cells (one simple, one complex) directional selectivity was actually reversed.

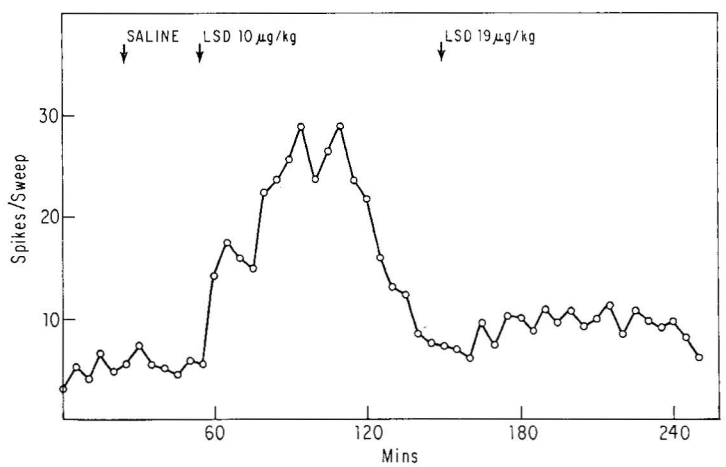

Fig. 6. Reduced effectiveness of repeated administration of LSD. Cell responded to only one direction of stimulus movement.

In 8 neurons (six simple, one complex, one hypercomplex) responses were tested to orientation of the light-bar at various angles ($\pm$ 80° from optimal) before and after LSD (10–50 μg/kg). Responses to non-optimal orientations were affected similarly to those at the optimal angle. In this sample 7 cells were depressed and the eighth, a simple cell was enhanced (Fig. 5).

In a number of cells, where partial or complete recovery from the effects of LSD occurred, additional injections were tested (3–50 μg/kg). Where initial enhancement had occurred (7 cells) a further dose produced either no change in evoked activity (1 cell), a similar response (2 cells) or depression (4 cells) (Fig. 2). Where initial depression

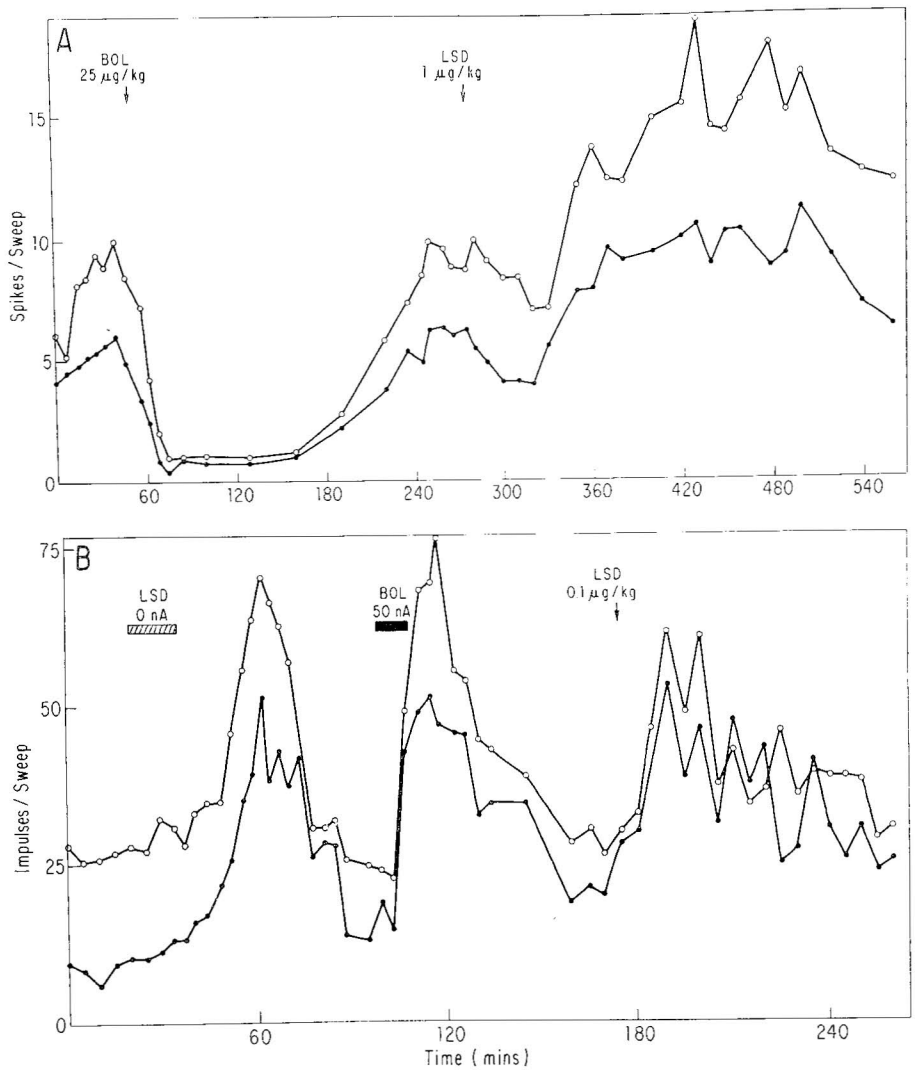

Fig. 7. The effects of BOL and LSD compared on two neurons. A: intravenous administration at arrows. B: microelectrophoretic administration at bars, with current strength indicated; intravenous injection at arrow.

of evoked responses occurred, subsequent doses also produced depression (5 cells) or no effect (1 cell). Whenever the effect of a second administration was qualitatively similar to the first, the second effect was either weaker (Fig. 6), or it lasted for a shorter period.

BOL and methysergide. BOL (10–75 μg/kg) produced either depression or enhancement of visually evoked activity when tested on 10 neurons (3 simple, 7 complex), 8 of which were also tested with LSD. Enhancement by BOL (10–25 μg/kg) was observed in 6 cells (Fig. 1) and depression (25–75 μg/kg) in the remainder (Fig. 7A). As with LSD, the overall effect on evoked activity appeared to be dose related, enhancement being more common with lower doses and depression with higher ones. The time of the onset (5–20 min; mean 7.9) and of the peak of the effects (15–50 min; mean 26) of BOL were similar to those of LSD, but its duration was shorter, recovery being observed in each case 50–190 min after the injection. The brevity of the BOL effect could not be attributed to cross-tolerance, since in most cases BOL was administered prior to LSD.

Accurate quantitative comparisons of dose–effect curves of BOL and LSD on the same neurons was not possible (see Discussion) (Figs. 1 and 7A). However, higher doses of BOL were always required to produce significant effects. A crude estimate of the

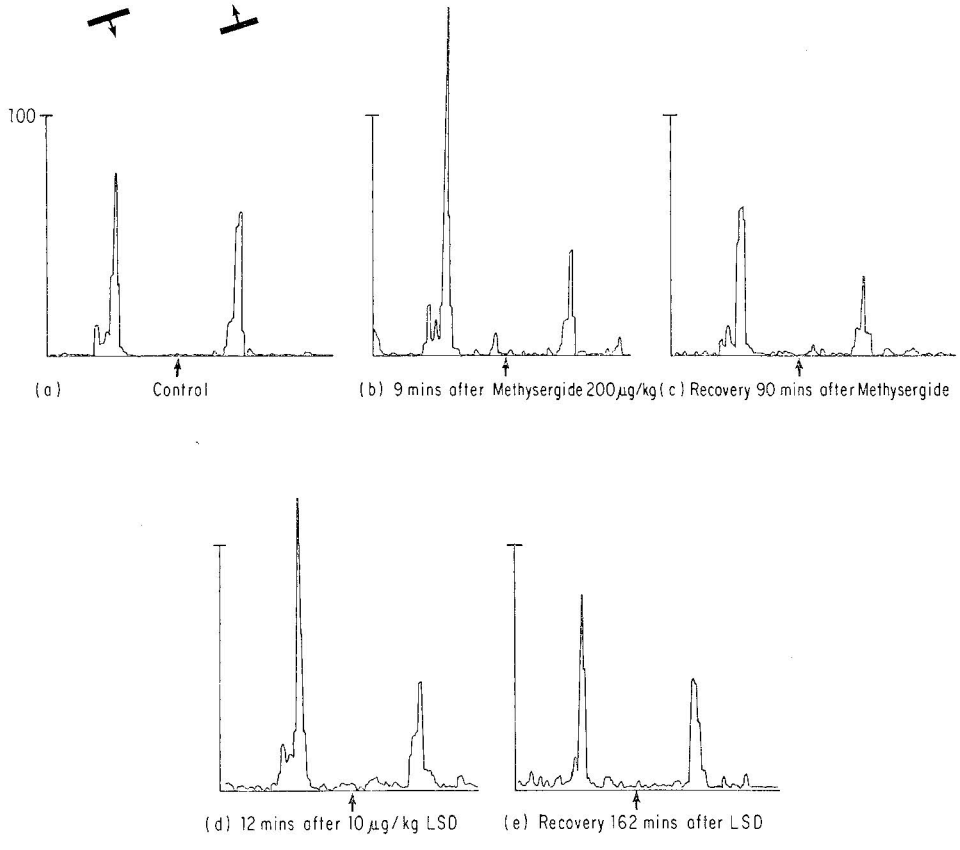

Fig. 8. Effects of i.v. administration of methysergide and LSD on the same neuron. Each histogram is the result of 16 stimulus presentations to a simple cell. Calibration: 100 impulses per bin.

potency difference of BOL compared with LSD based on those cells that were affected in the same way, shows it to be 20–100 times less potent in producing enhancement, and about 5 times less potent in producing depression.

BOL and LSD were similar also in the manner in which they affected directional selectivity (4 of 10 cells). In two cells, BOL impaired directional selectivity. In two other cells, BOL reversed directional selectivity.

Methysergide (100–700 μg/kg) was tested on 5 simple cells, 3 of which were also tested with LSD. Both depression and enhancement (Fig. 8) of visually evoked activity was seen, but only at significantly higher doses than with BOL or LSD. Thus, an initial dose of 100–200 μg/kg methysergide enhanced activity in 3 cells, but depressed it in another: one cell was unaffected. In 2 out of 3 of the enhanced cells, LSD (10 μg/kg) also enhanced visually evoked activity but it produced depression in the third. An additional dose of methysergide (200–500 μg/kg) produced depression in each case. The effects of methysergide were weaker and more short-lived than those of LSD, ranging from 20–180 min (mean 90.8 min), recovery being observed in each cell tested. Methysergide also influenced directional selectivity, accentuating it in two cells (Fig. 8), and reducing it in two others.

Microelectrophoretic administration

The evoked activity of all the cells tested (16 simple, 13 complex, 7 hypercomplex) was affected by LSD. The dug's effect was considered genuine when: (a) the visually evoked responses were changed 60% or more; (b) partial (>50%) or complete recovery was observed; (c) the effect was reproducible, and (d) not mimicked by the ejection of Na^+.

Evoked activity was enhanced by LSD in 19 neurons (10 simple, 7 complex, 2 hypercomplex) (Fig. 7B), and depressed in the others (6 simple, 6 complex, 5 hypercomplex). The effect was related to the dose: less LSD was required to produce enhancement, and switching off the drug retaining current was often sufficient. The mean effective dose was 3.5 nA for 7.1 min for enhancement and 10.5 nA for 8.5 min for depression. Where enhancement was the initial effect, the subsequent administrations of larger amounts invariably produced a depression of the evoked activity. No changes in spike configuration were noted during the electrophoresis of LSD. Unstimulated background activity was enhanced in 5 cells (3 simple, 2 hypercomplex) (Fig. 9A).

The time courses of the two kinds of LSD effects were similar in mean onset (3.8 and 3.9 min) and peak times of activity (10.7 and 11.1 min respectively). However, enhancement of evoked activity was of shorter duration (24.9 min) than depression (35.4 min), possibly reflecting the larger doses used to induce depression. But, unlike the trials with intravenous administration, recovery from the effects of iontophoretically administered LSD was observed in all cells tested.

In 20 cells, LSD also produced a change in degree of preference to the direction of stimulus movement (Fig. 9B). Thus directional selectivity deteriorated (46–81%) in 15 cells, in 10 of which evoked activity was depressed, but in 5 others it was enhanced. Five cells had accentuated directional selectivity, in 4 of these evoked activity was enhanced, but it was depressed in the fifth.

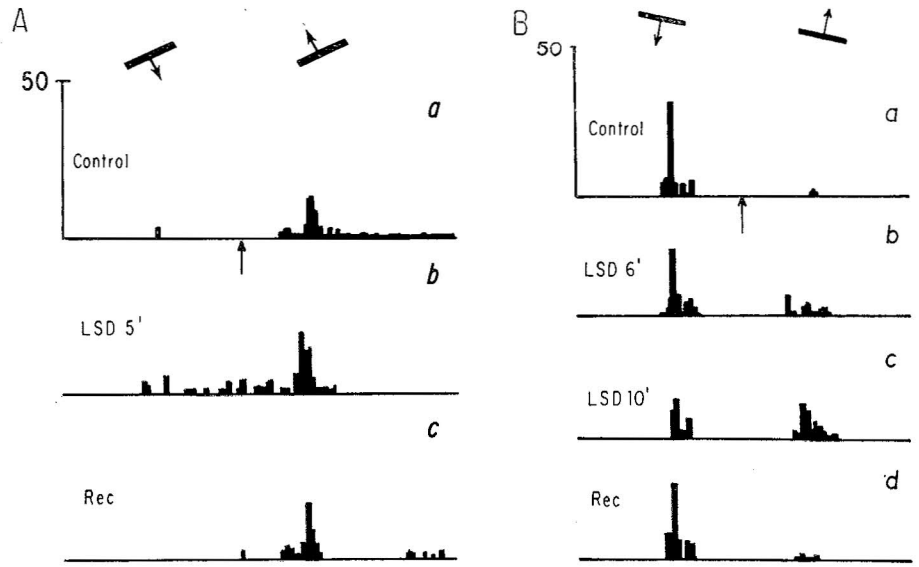

Fig. 9. The effects of microelectrophoretic administrations of LSD on optically evoked responses of two cortical neurons. A: responses of a complex cell (8 sweeps each histogram) before (a), during (b) and after (c) the administration of LSD by 10 nA current for 5 min. Note small increase in the optimal response, and a significant increase in unstimulated background discharges. B: records from a hypercomplex cell (16 sweeps each histogram) before, during and after administration of LSD by diffusional release (0 nA). Note clear reversal of directional preference in c. Recovery of responses (d), occurred 25 min after the end of the LSD ejection.

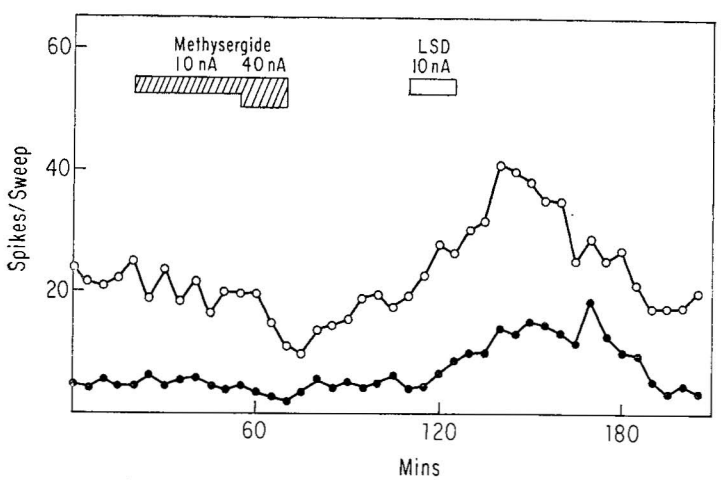

Fig. 10. The microelectrophoretic administration of methysergide and of LSD to a neuron: open circles, responses to preferred direction of movement; filled circles, responses to 'null' direction.

Repeated administration of LSD on the same neurons often resulted in a reduced sensitivity either to LSD-induced enhancement or LSD-induced depression. Thus either a larger dose was required to produce a similar magnitude of effect, or a shorter lasting change was produced for a similar administration.

On 19 neurons either BOL (2 simple, 7 complex, 4 hypercomplex) or methysergide (4 simple, 2 complex cells) were also tested besides LSD. BOL, administered in amounts similar to LSD, had no effect on any of the cells studied. Significantly higher doses (30 nA for 12.3 min) produced depression in 3, and enhancement in a fourth cell (Fig. 7B). Two of these cells were depressed by LSD while the others were enhanced (two complex) (Fig. 7B). Dose for dose BOL was weaker then LSD and did not produce changes in directional selectivity though, LSD impaired this in 3 cases.

Methysergide had no discernible effect on visually evoked responses when administered in amounts similar to LSD. In 2 out of 6 cells weak and short-lived depression was produced by ejections of 20 and 40 nA for 11 and 15 min respectively (Fig. 10). Both these cells' responses were enhanced by small amounts of LSD. No changes in directional selectivity were observed with methysergide.

On 4 neurons (1 simple, 3 complex) the effects of electrophoretic LSD were compared with those of systemic administration. All 4 cells were enhanced by small electrophoretic administration of LSD and 3 were also enhanced by a small (0.1–10 μg/kg) i.v. dose (Fig. 7B). The fourth was depressed by 15 μg/kg of LSD i.v.

DISCUSSION

Confirming a previous study[61], systemically administered LSD produced a variety of changes in the physiologically evoked activity of single cells in the cat's primary visual cortex. These effects were obtained at dose levels which produce behavior changes in the cat[42,43]. That enhancement of stimulus-evoked discharge was common with low and depression with higher doses of LSD, may be related to the fact that certain behavior also shows dose related changes following LSD administration[43]. Enhancement and depression by LSD can be produced on the same neurons at different dose levels. It seems that both these phenomena can occur simultaneously to varying degrees in different cells; the balance depending on the concentration of LSD. In the intermediate dosage range (10–25 μg/kg) the evoked responses of the majority of neurons were depressed. This is in keeping with the effects of LSD gauged on the dominant activity of mixed populations of neurons[17].

Significant changes in responsiveness were obtained in some cells even at the lowest dose administered (0.1 μg/kg). There appeared to be little relationship between the sensitivity, or effect of LSD, and neurons type-classified by their receptive field properties, though Rose and Horn[61] suggested that the effects of LSD appeared earlier in complex cells than in simple cells. The marked changes in directional selectivity observed in many cells contrasts somewhat the report of Rose and Horn who found few cells where directional responses were impaired by LSD. The reasons for such differences are not apparent, though conceivably differences in experimental protocol (e.g. our control predrug analysis periods were significantly longer; and only one cell was

tested in each of our animals) and methods of data analysis (we measured total evoked responses whereas they measured peak response) could be contributing factors. In agreement with their[61] observations, in our sample LSD did not produce marked differences in orientational selectivity.

Since we found no correlation between qualitative (enhancing or depressing) and quantitative susceptibility to LSD and receptive field type (single, complex, hypercomplex), the variability of the response at the intermediate dosage range must be attributed to differences other than receptive field organization. In an earlier study a similar independence was noted of the receptive field organization and susceptibility to excitatory and inhibitory effects of iontophoretically applied acetylcholine[72].

BOL and methysergide also produced changes in the activity of visual neurons which were similar to those of LSD. Accurate quantitative comparison of dose–effect functions was precluded by dose dependent differences in qualitative effects, the development of tolerance, and differences in the time course of the effect of different drugs. Nevertheless BOL and methysergide were considerably less potent than LSD. Correspondingly, high doses of methysergide are needed to produce hallucinations in man[2,51]. BOL, even though it is not considered to be hallucinogenic[16,37,62,63,68], certainly reproduces many of the sensory disturbances seen with smaller amounts of LSD[9,40,45,59,64]. The present findings suggest that these compounds also disturb visual sensory processing in the cat.

The local administration of LSD near visual cortical neurons by electrophoresis produced effects similar to those seen following intravenous administration. BOL and methysergide were ineffective when administered in amounts similar to LSD, but both agents produced changes in some cells when administered in larger quantities. Our results suggest, therefore, that both BOL and methysergide were considerably less active in the cortex than LSD. Release of LSD by iontophoresis is low[14], yet evoked activity was often dramatically changed merely by allowing this substance to be released by diffusion (e.g. Figs. 7B, and 9). Thus, synaptic activity in the visual cortex must be extremely sensitive to LSD. No direct comparisons were made in this study of the effects of LSD on neural responses evoked by other types of sensory input to different cortical areas. In other studies of extravisual cortical areas the larger quantities of LSD administered produced non-specific depression of cell firing and reduction in spike amplitude[48,50,60] which are not comparable to our observations.

The effectiveness of electrophoretically administered LSD makes it likely that the visual cortex is at least one of the important sites for the actions of the systemically administered compound. Indeed in our limited number of trials both electrophoretic and systemic LSD tested on the same neurons often, though not always, produced parallel effects. Rigorous comparisons were difficult, as the direction of the effect was dose dependent, and not entirely predictable.

In common with repeated systemic administration, the effect of electrophoretic LSD on the same cell diminished with repetition. This may be related to the tolerance observed in humans[1,18,41] and animals and is in keeping with the rapid onset of tolerance to behavioral effects following a single dose[69]. Human studies indicate that high doses of BOL may prevent the hallucinogenic effects of small doses of LSD, even before cross-

tolerance is seen[9,31,39]. This might be explained from our observations as being a consequence of opposing pharmacological actions, BOL in appropriate dose depressing synaptically driven activity, while LSD tending to enhance it.

Our observations offer merely a descriptive rather than a mechanistic account for the visual distortions produced by LSD. The comprehensive pharmacological studies (see ref. 29) revealing complex interactions of LSD with central serotonin[3–5,11,12,19,53,60], dopamine and histamine[20,23,24,57,71] systems might have a bearing on its mechanism of action in the visual cortex. However, information regarding the chemical identity of synaptic transmitters in the visual cortex is limited, though an intricate system of noradrenergic fibers originating from the locus coeruleus has been described[54,56]. These may be involved in visual plasticity[46,47]. Furthermore, a cortical serotonin innervation seems likely[13,30,49,52].

Following systemic administration, LSD might act at many sites. Changes in synaptic activity appear to occur at all levels of the visual system (see refs in Introduction) and it could be envisaged that if the effects were similar, they might amplify the cortical changes. In addition, activity in the visual cortex could be influenced by extravisual inputs, for example from the brain stem[8,27]. Indeed the serotonin neurons of the brain stem appear to be particularly sensitive to LSD and the hypothesis that the action of hallucinogenic drugs is mediated by interactions at these sites is compelling[4,29] though controversial[70]. That local administration of LSD to visual cortical neurons reproduces the spectrum of changes observed following systemic administration indicates that LSD does in fact interact within the cortex with geniculocortical synapses, with other input, or with intrinsic cortical mechanisms. The directional specificity of some types of cortical neurons is determined by intracortical inhibitory, possibly GABA-mediated, mechanisms modifying geniculate inputs[21,32,33,66,67]. Changes in direction selectivity produced by LSD suggest the need to explore the additional involvement of monoaminergic mechanisms.

It seems quite plausible that the observed changes in cortical neuronal responsiveness cause a distortion of visual perception. It is less likely that the neocortical effects could, by themselves, explain the occurrence of visual hallucinations and other psychotic changes for which additional effects, probably on subcortical structures, seem required.

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