3313

LSD

Brain Research, 161 (1979) 167–172
© Elsevier/North-Holland Biomedical Press

Iontophoresis of LSD: effects on responses of single cortical neurones to visual stimulation

P. C. FOX and A. DRAY

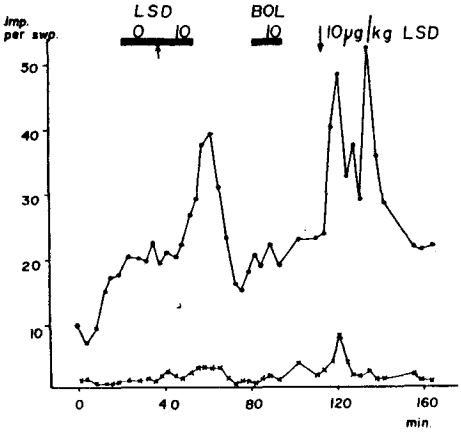
Department of Physiology, Duke University Medical Center, Durham, N.C. 27710 (U.S.A.)

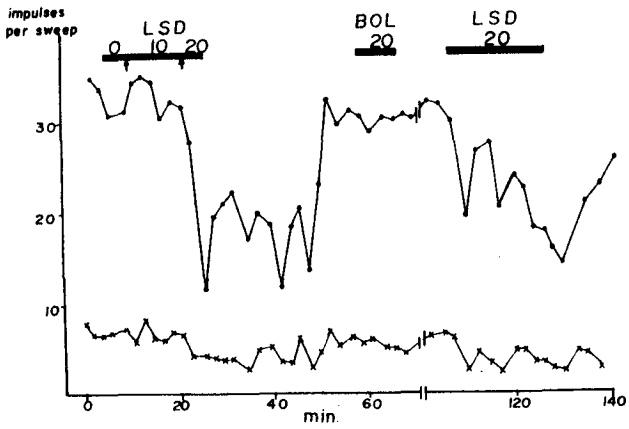
(Accepted October 12th, 1978)

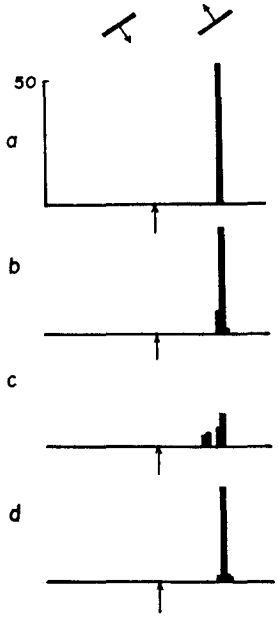
The mechanisms by which LSD produces sensory disturbances in man and other mammals[14,17] are poorly understood though LSD alters nervous activity in the visual system at several levels[3,6,10,15,18]. In particular systemic LSD may enhance or depress the activity of neurones in the visual cortex when these cells are activated by physiological optical stimulation[12,13,19]. However the lack of suitable control agents and the route of administration employed in these latter studies makes it uncertain whether these changes were mediated directly or were related to the hallucinogenic properties of LSD. The present report describes the effects of LSD and structurally related analogues administered by microelectrophoresis onto visual cortical neurones.

Experiments were performed on adult cats anaesthetized with pentobarbitone (35 mg/kg i.p. and supplemented with thiopentone i.v. as required) during surgery. Wound edges were infiltrated with local anaesthetic (Anucaine, Calvin Chemical Corp.) and anaesthesia was maintained during recording with nitrous oxide (75%) supplemented by intravenous thiopentone. A unilateral pneumothorax was performed, the animal paralysed with gallamine and artifically ventilated. End-tidal CO_2 concentration was kept within physiological limits: rectal temperature was maintained at 37 °C, blood pressure and heart rate were continuously monitored. Substances were administered systemically via a femoral cannula. Phenylephrine was used to contract the nictitating membrane and atropine to dilate the pupils. Contact lenses, corrected for refraction errors were placed over the eyes. Stimuli were usually presented at 0.1 HZ and consisted of a moving (7°/sec) bright bar (5 × 0.6°, 80 cd/sq.m) projected onto a screen (illuminated at 40 cd/sq.m) such that stimulus excursions started and stopped outside the receptive field.

Recordings of extracellular activity were made from single cells in cortical area 17 using one barrel (3 M sodium chloride) of a five-barelled micropipette (tip diam. 6–8 um). Another barrel, filled with 165 M sodium chloride, was used to eject Na^+ to test for any effects of electrophoretic current. The remaining barrels contained LSD tartrate, methysergide maleate, 2-bromo-LSD (BOL), all at 1 mM, pH 4.0 in 165 mM sodium chloride. Substances were made up in this way to obtain a more valid comparison of electrophoretic potency. Histograms of single cell responses were


Imp. per swp.
LSD
0 10
BOL
10
10µg/kg LSD
50
40
30
20
10
0
40
80
120
160
min.


impulses per sweep
LSD
0 10 20
BOL
20
LSD
20
30
20
10
0
20
40
60
120
140
min.


50
a
b
c
d

collected during visual stimulation at optimal orientation and direction. All cells were classified from their visual response fields[16].

The evoked activity of each cell tested (11 simple, 5 complex, 5 hypercomplex) was affected by LSD. An effect was considered genuine when the evoked responses were (a) changed by 40% or more from the pre-LSD values, (b) partial or complete recovery was observed following the LSD ejection and (c) the effect was reproducible.

LSD produced enhancement (6 simple, 4 complex) and reduction (10 simple, 3 complex, 5 hypercomplex) of evoked firing (Fig. 1). Smaller administrations were required to produce enhancement (mean 2.5 nA for 6.2 min) than depression (mean 12.7 nA for 8.5 min) and evoked activity of several neurones was dramatically changed merely by turning off the LSD retaining current for 2–3 min. These changes were occasionally accompanied by changes in unstimulated background firing. This in 3 simple cells (2 enhanced, 1 depressed) background activity was increased during the administration of LSD. LSD-induced changes were not accompanied by depression of spike amplitude nor did they result from electrophoretic current flow since they were not mimicked by the administration of Na^+.

The mean time course of the effect, whether enhancement or depression, was similar (onset from start of ejection 3.6 min, peak 11.0 min, recovery 25.4 min).

On 13 cells LSD produced an impairment of their response to the preferred direction of light movement (Fig. 1b). The ratio of non-optimal to optimal direction responses, indicated that in 4 simple cells directional selectivity was enhanced (66–117%) while in 11 cells (6 simple, 3 complex, 2 hypercomplex) it was depressed (46–78%). The changes in directional selectivity were often related to the overall effect of LSD on evoked responses. Thus were directional selectivity was enhanced, evoked responses were also enhanced (3 cells) but reduced in another cell. Also where directional selectivity was reduced, evoked responses were also reduced (10 cells) but enhanced in one complex cell. These directional changes usually involved a more

Fig. 1. a: graph of visually evoked responses (impulses/sweep) plotted against time (mins) of a complex cell responding to a light-bar stimulus moving in the optimal (dots) and null direction (crosses). The electrophoretic administration of LSD (bar above the graph) at OnA produced little change but increasing the expelling current to 10 nA produced a marked enhancement of evoked responses particularly to the optimal direction. BOL administered at the same current for a similar period produced no significant change. A subsequent intravenous injection of 10 μg/kg of LSD also produced a significant enhancement of evoked responses in this neurone. b: in this cell activity was only depressed when the LSD expelling current was increased to 20 nA. Note the prolonged recovery of responses following the period of ejection. A second administration of LSD at 20 nA required a significantly longer period of expulsion in order to depress evoked response to the same extent as before. BOL administered at 20 nA produced no significant changes. Also note that the degree of depression of the optimal response was affected to a greater extent than the null direction response, indicating an impairment of directional selectivity. c: individual histograms of the responses of a tightly tuned hypercomplex cell (16 sweeps); (a) control response, (b) response following a 10 min administration of LSD at 5nA. The magnitude of the response was reduced and the receptive field was broader, (c) further deterioration of the fine tuning of this cell after 15 min of LSD at 5nA and (d) partial recovery from LSD some 20 min after the termination of the electrophoretic ejection. The bars above the histogram indicate the direction of stimulus movement and the arrow below the histogram shows that position at which the direction of stimulus movement was reversed. Calibration, 50 impulses/bin.

significant effect on the optimal directional responses though in 2 cells (1 simple, 1 complex) the null direction responses were affected to a greater extent.

No consistent changes in the dimensions of the receptive field of neurones were observed whether their evoked responses were enhanced or depressed by LSD. However on 2 tightly-tuned hypercomplex cells LSD produced a significant broadening of the receptive field which accompanied depression of evoked activity (Fig. 1c).

Repeated ejections of LSD, tested on 13 neurones, often resulted in a reduced effectiveness. Thus either a shorter lasting change was produced for a similar administration (1st dose 32 mins, 2nd dose 17 mins) or a larger administration was required to produce a similar effect (1st dose mean 6.2 nA at 8.2 min; 2nd dose 14.4 nA for 11.7 min). This reduced responsiveness was observed both for LSD-induced enhancement (3 simple cells out of 4 simple and 1 complex) and for LSD-induced depression (1 simple, 1 complex, 3 hypercomplex out of 4 simple, 1 complex, 3 hypercomplex tested; Fig. 1b).

Methysergide administered in similar amounts to LSD produced no significant effect on visually evoked firing of 4 simple cells which were depressed by LSD. However larger administrations (mean current 32.5 nA for 9.5 min) produced weak depression in 3 or these cells. The time course of depression by methysergide was similar to that of LSD. No significant changes in directional selectivity were observed on any of these cells during methysergide administration. 2-Bromo-LSD (mean current 7.5 nA for 11.2 min) produced no significant effects on 8 neurones tested (1 simple, 3 complex, 4 hypercomplex), 7 of which had been depressed by LSD and one enhanced (complex cell; Fig. 1).

The local administration of LSD onto visual cortical neurones produced variable effects on their responses to visual stimulation. Enhancement or reduction of evoked activity did not appear to be related to the neurone type for simple or complex cells but appeared to be related to the amount of LSD administered. Thus enhancement was seen more commonly with lower administrations of LSD than depression. Similar differences have been noted in the responses of visual cortical neurones following the systemic administration of LSD where there was a tending towards enhancement of evoked activity at lower doses but depression at higher ones[12,13,19]. It was noteworthy that none of the hypercomplex cells studied were enhanced even by low (OnA) ejections of LSD. Whether this reflects a real difference in the responses of this type of cell to LSD requires further study.

Repeated administration of LSD onto the same neurones often produced a smaller effect. A reduction in the sensitivity of visual cortical neurones is also seen following the systemic administration of LSD[12] and may be due to the occurrence of tolerance which is commonly observed in humans and in animal studies[14,17]. LSD also impaired the ability of cells to discriminate between the direction of stimulus movement. In some cells directional selectivity was enhanced but in others it was depressed. These changes also occur following systemic LSD[12,19] and are suggestive of an impairment of intracortical inhibitory mechanism which may control directional selectivity of visual neurones[9,20].

The observation that some of the effects of LSD could be mimicked by larger

administrations of methysergide, a hallucinogen when administered in high systemic doses[1], but not by BOL, the inactive analogue of LSD[7] suggest that effects produced by LSD were related to its hallucinogenic properties. Moreover, the facts that the release of LSD by microelectrophoresis is very low[5] and that evoked activity in each of visual cortical neurones tested was affected by LSD, often merely by turning off the retaining current, suggest that visual cortical neurones exhibit exquisite sensitivity to this compound. It is likely that the changes produced by LSD resulted from interactions with central synaptic neurotransmitters, for example serotonin[2,4] and dopamine[8,11]. The possibility that similar interactions occur on visual neurones is being investigated.

It would seem that the distortion of visual perception produced by systemic LSD may result from a multiplicity of actions on synaptic activity at a number of stages of visual information processing[6]. The present experiments clearly implicate the visual cortex as an important locus for this action.

Supported by NIDA grant DA 01458 and Training Awards from NIEHS, 5-T32-E5007002 (PCF) and NIMH, 5-T01-MH-08394-13 (AD). We are grateful to Dr. G. G. Somjen for initiating this project and for his enthusiastic support.

1 Abramson, H. A. and Rolo, A., Comparison of LSD with methysergide and psilocybin on test subjects. In H. A. Abramsom (Ed.), *The uses of LSD in Psychotherapy and Alcoholism*, Bobbs-Merrill, New York, 1967, p. 53–73.
2 Aghajanian, G. K., Haigler, H. J. and Bloom, F. E., Lysergic acid diethylamide and serotonin: direct actions on serotonin-containing neurons, *Life Sci.*, 11 (1972) 615–622.
3 Bishop, P. O., Field, G., Hennessey, B. L. and Smith, J. R., Actions of D-lysergic acid diethylamide on lateral geniculate synapses, *J. Neurophysiol.*, 21 (1958) 529–548.
4 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, *Brit. J. Pharmacol.*, 40 (1970) 202–218.
5 Bradley, P. B. and Candy, J. M., Iontophoretic release of acetylcholine, noradrenaline, 5-hydroxytryptamine and D-lysergic acid diethylamide from micropipettes, *Brit. J. Pharmacol.*, 40 (1970) 194–201.
6 Brawley, P. and Duffield, J. C., The pharmacology of hallucinogens, *Pharmacol. Rev.*, 24 (1972) 31–66.
7 Cerletti, A. and Rothlin, E., Role of 5-hydroxytryptamine in mental diseases and its antagonism to lysergic acid derivatives, *Nature (Lond.)*, 176 (1955) 785–786.
8 Creese, I., Burt, D. R. and Snyder, S. H., The dopamine receptor: differential binding of D-LSD and related agents to agonist and antagonist states, *Life Sci.*, 17 (1975) 1715–1720.
9 Creutzfeldt, O. D., Kuhnt, U. and Benevento, L. A., An intracellular analysis of visual cortical neurones to moving stimuli: responses in a co-operative neuronal network, *Exp. Brain Res.*, 21 (1974) 251–274.
10 Curtis, D. R. and Davis, R., Pharmacological studies upon neurones of the lateral geniculate nucleus of the cat, *Brit. J. Pharmacol.*, 18 (1962) 217–246.
11 Da Prada, M., Saner, A., Burkard, W. P., Bartholini, G. and Pletscher, A., Lysergic acid diethylamide: evidence for stimulation of cerebral dopamine receptors, *Brain Research*, 94 (1975) 67–73.
12 Dray, A., Connors, B., Fox, P. C., Hilmy, M., Moore, C. and Somjen, G. G., Effects of LSD on unit activity and extracellular potassium responses in cat cortex during visual stimulation, *Fed. Proc.*, 37 (1978) 612.
13 Hilmy, M., Connors, B., Fox, P. and Somjen, G., Effects of LSD on neurons in visual cortex, *Neurosci. Abst.*, 3 (1977) 562.
14 Hoffer, A. and Osmond, H., *The Hallucinogens*, Academic Press, New York, 1967.

15 Horn, G. and McKay, J. M., Effects of lysergic acid diethylamide on the spontaneous activity and visual receptive fields of cells in the lateral geniculate nucleus of the cat, *Exp. Brain Res.*, 17 (1973) 271–284.
16 Hubel, D. H. and Wiesel, T. N., Receptive fields, binocular interaction and functional architecture in the cat's visual cortex, *J. Physiol. (Lond.)*, 160 (1962) 106–154.
17 Jacobs, B. L., Trulson, M. E. and Stern, W. C., An animal behavior model for studying the actions of LSD and related hallucinogens, *Science*, 194 (1976) 741–743.
18 Mouriz-Garcia, A., Schmidt, R. and Arlazoroff, A., Effects of LSD on the spontaneous and evoked activity of retinal and geniculate ganglion cells, *Psychopharmacologia*, 15 (1969) 382–391.
19 Rose, D. and Horn, G., Effects of LSD on the responses of single units in cat visual cortex, *Exp. Brain Res.*, 27 (1977) 71–80.
20 Sillito, A. M., Inhibitory processes underlying the directional specificity of simple, complex and hypercomplex cells in the cat's visual cortex., *J. Physiol. (Lond.)*, 271 (1977) 699–720.