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Chronic Intraventricular Administration of Lysergic Acid Diethylamide (LSD) Affects the Sensitivity of Cortical Cells to Monocular Deprivation

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In kittens, but not in adult cats, depriving one eye of pattern vision by suturing the lids shut (monocular deprivation or MD) for one week reduces the proportion of binocular units in the visual cortex. A sensitivity of cortical units in adult cats to MD can be produced by infusing exogenous monoamines into the visual cortex[23]. Since LSD interacts with monoamines, we have examined the effects of chronic administration of LSD on the sensitivity to MD for cortical cells in adult cats. Cats were assigned randomly to one of four conditions: MD/LSD, MD/No-LSD, No-MD/LSD, No-MD/No-LSD. An osmotic minipump delivered either LSD or the vehicle solution alone during a one-week period of MD. The animals showed no obvious anomalies during the administration of the drug. After one week the response properties of single units in area 17 of the visual cortex were studied without knowledge of the contents of the individual minipumps.

With the exception of ocular dominance, the response properties of units recorded in all animals did not differ from normal. In the control animals (MD/No-LSD, No-MD/LSD, No-MD/No-LSD) the average proportion of binocular cells was 78%; similar to that observed for normal adult cats. However, in the experimental animals, which received LSD during the period of MD, only 52% of the cells were binocular. Our results suggest that chronic intraventricular administration of LSD affects either directly or indirectly the sensitivity of cortical neurons to MD.

INTRODUCTION

Ingestion of lysergic acid diethylamide (LSD) produces profound behavioral effects, notably hallucinations and other sensory disturbances[8]. We now report that LSD has an additional, previously unsuspected effect: after chronic administration of LSD into the ventricular system of the brain some response properties of cells in the visual cortex of adult animals can be modified by visual deprivation.

Modifications in the response properties of cells in the visual cortex can normally be produced only during a sensitive period while the animals are still very young. Once this sensitive period has ended, the response properties of cells in the adult visual system appear remarkably stable, even in the presence of gross distortions of sensory input such as those produced by suturing shut the lids of one eye[19,36].

In adult animals stability in the response properties of cortical cells, notably the convergence of afferents from the two eyes onto single cells in visual cortex, is reduced by administration of norepinephrine (NE). When NE is administered locally into the visual cortex of adult cats[23] for one week while one eye is deprived of patterned visual stimulation by suturing the eyelids shut (monocular deprivation or MD), then the proportion of neurons in the visual cortex that can be activated through either eye is reduced from its normal level of 80–90% to 30–40%. In normal adult cats receiving no NE, MD has no obvious effect.

Since LSD interacts with monoamines in the central nervous system (for a review see ref. 13), we wanted to determine if it might also disrupt the stability that is characteristic of the response properties of cells in the visual cortex of adult cats. We therefore administered LSD into the ventricular system of the brain of adult cats and investigated the susceptibility of cortical cells to MD. Our results show that when LSD is administered in this manner,

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it influences the stability of cells in the visual cortex of adult cats so that MD reduces the proportion of cells that can be activated equally through either eye.

MATERIALS AND METHODS

Adult cats were assigned randomly to one of four conditions. In the first condition, MD/LSD, cats were monocularly deprived and given 148 μg/kg of LSD intraventricularly over one week. In the second condition, No-MD/LSD, cats were given the same dose of LSD but were not monocularly deprived. In the third and fourth conditions, MD/No-LSD and No-MD/No-LSD, cats received saline intraventricularly while either monocularly deprived or allowed normal visual experience. For all but two preliminary experimental cats, the experimenters did not know the condition to which any animal was assigned until physiological recordings from all animals had been completed.

Drug administration

To administer the LSD (diluted in 170 μl of sterile saline at pH 5.5) or sterile saline alone the cat was anesthetized with Fluothane, placed in a stereotaxic apparatus and a cannula made from a 25 gauge needle was positioned above a hole in the bone and lowered into one lateral ventricle (at Horsley-Clark coordinates AP 11.0, ML 3.5). Proper placement of the cannula was verified by checking for cerebrospinal fluid leakage through the cannula. The cannula was attached by polyvinyl tubing (P.E. 60) to an osmotic minipump (ALZA model 2001) that was filled with drug or saline and placed subcutaneously at the base of the neck. A pedestal made from dental acrylic (Grip, L.D. Caulk Co.) around the cannula assembly helped to protect the system from displacement[22]. For the animals receiving LSD, the pump administered LSD at a rate of 0.88 μg/kg/h.

At the time of the cannula/minipump implantation, the lids of the eye contralateral to the implant were sutured closed for each animal in the MD groups. After completion of the surgical procedures the animals were given intramuscular injections of penicillin and allowed to recover from the anesthesia. The animals were subsequently housed in individual cages and their behavior was observed periodically during the week of administration of the drug or saline. No obvious anomalies were detected. Daily inspections of the sutured lids confirmed that the eyelids remained closed.

Physiological recording

One week after implantation of the cannula/minipump assembly the animal was prepared for electrophysiological recording in a conventional manner[25,26]. The animal was anesthetized with Fluothane and positioned in a stereotaxic apparatus. The cannula/minipump assembly was removed, the integrity of the connections between minipump and cannula verified and the minipump inspected to make certain that its contents had been discharged. Next, a small opening was made in the bone and dura above the striate cortex and a cylindrical chamber positioned over this craniotomy. The skull was affixed to a rigid bar with dental acrylic and the earbars removed. All pressure points and incisions were infiltrated with a long-acting local anesthetic (Anucain). The animal was paralyzed with a mixture of D-tubocurarine (0.7 mg/kg/h) and Flaxedil (7 mg/kg/h) and hyperventilated artificially with a mixture of 70% nitrous oxide, 1–2% carbon dioxide, and 28–29% oxygen. Although nitrous oxide administered at these levels has been reported to be adequate to maintain a pain-free state[5], heart rate was monitored throughout the experiment to verify this and as a check of the animal's state. Fluothane was administered as needed during the remainder of the experiment to maintain a pain-free state, especially during any potentially painful procedures (e.g. opening the sutured eye). The animal's temperature was maintained at 38 °C using a thermistor-controlled heating pad and 5% dextrose in distilled water was administered intravenously at regular intervals throughout the experiment.

Neosynephrine was used to retract the nictitating membrane and atropine was used to dilate the pupils. The eyes were protected from dessication with contact lenses and artificial pupils (3 mm diameter) were mounted as close to the animal's eyes as possible. When necessary, trial lenses were used to focus the eyes on a tangent screen positioned 114 cm in front of the cat. The projections of the optic discs were plotted with the aid of an ophthalmoscope and the position of the area centralis inferred from these

projections[3,11]. Once the animal had been prepared for the physiological recording the sutured eye of the monocularly deprived animals was opened.

We did not begin recording until at least 6 h had elapsed since removal of the cannula/minipump assembly so that the cortex could recover from any resulting trauma. This interval also insured that the levels of LSD in the brain were probably not high enough to cause behavioral disturbances[9,32]. The response of cortical neurons was recorded extracellularly with tungsten-in-glass microelectrodes[27]. The chamber was filled with a 4% agar–saline solution and sealed. A piezoelectric drive (Burleigh Instruments) advanced the electrode through the cortex along an oblique trajectory. The electrode was advanced 75 μm between units to reduce the sampling bias by recording from a large number of ocular dominance columns[18]. Responses of single units were isolated and amplified in a conventional manner. While advancing the electrode we presented a wide range of visual stimuli to minimize the chance of missing units with low spontaneous activity, small receptive fields, and distinct preference for slow stimulus motion[30]. In all but one of the animals (MD/No-LSD No. 2) the recordings were made in the striate cortex (Area 17) contralateral to the deprived eye and ipsilateral to the implant. (The data for MD/No-LSD No 2, in which recordings were made in the striate cortex ipsilateral to the deprived eye and contralateral to the implant, were within the range of the data for other control animals and thus are included with them.)

Measurement of ocular dominance

Each unit was first studied with a manually controlled stimulus to determine the stimulus parameters that were most effective in activating the unit (orientation, length, width, velocity) and to obtain a qualitative measure of ocular dominance. For all but one of the cats a computer-controlled optical system was then used to present to the eye that was most effective in exciting the cell (dominant eye) a stimulus of optimal size and moving at optimal velocity at a series of orientations. From the resulting orientation tuning curve the optimal stimulus orientation was determined. A stimulus at that orientation was moved repeatedly through the receptive field of the cell and a peristimulus time histogram[2] was compiled. The entire procedure was repeated for the second (non-dominant) eye. As a measure of the relative effectiveness of the two eyes in activating the unit, the ratio of the peak response rate activated through the dominant and through the non-dominant eye was computed (ocular dominance ratio). Using this ocular dominance ratio cells were assigned to one of five groups. If the cell had an ocular dominance ratio greater than 10 and it was activated exclusively or predominantly by the contralateral eye, it was assigned to group 1. If the cell had an ocular dominance ratio between 3 and 10 and it was activated by both eyes but dominated by the contralateral eye, it was assigned to group 2. If the cell had an ocular dominance ratio less than 3 and thus was activated in comparable fashion by both eyes, it was assigned to group 3. If the cell had an ocular dominance ratio between 3 and 10 and it was activated by both eyes but dominated by the ipsilateral eye, it was assigned to group 4. If the cell had an ocular dominance ratio greater than 10 and it was activated exclusively or predominantly by the ipsilateral eye, it was assigned to group 5.

Histology

At the termination of the electrophysiological recording session, the animal was given an overdose of anesthetic and then perfused with phosphate buffered saline followed by 10% formalin with 4% sucrose in 0.1 M phosphate buffer. The areas of cortex containing the electrode tracks were frozen and sectioned at 20 μm, mounted on gelatinized slides and stained with cresyl violet. In all cases in which the electrode tracks could be reconstructed we confirmed that the tracks were restricted to area 17.

RESULTS

One hundred and fifty-four units were studied in 5 experimental animals (MD/LSD); 97% of these were responsive to visual stimulation. One hundred and eighty-eight units were studied in 6 control animals (No-MD/LSD; MD/No-LSD; No-MD/No-LSD); 96% of these were responsive to visual stimulation. The response properties of units studied in experimental cats differed from those found in control cats in only one respect: there was a reduction in the proportion of units that could be activa-

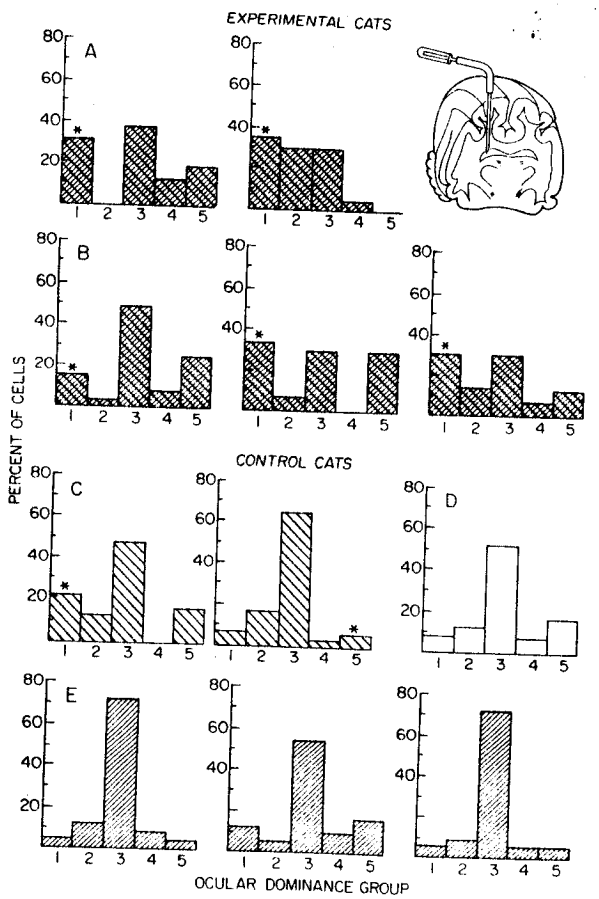

Fig. 1. The ocular dominance histograms for individual experimental (A, B) and control animals (C, D, E). Percent of cells in each ocular dominance group is plotted. Cells were assigned to ocular dominance groups on the basis of the relative effectiveness of the two eyes in activating those cells (see Methods for details). Data from monocularly deprived animals indicated by ▨ -slanting lines; data from animals receiving LSD indicated by ▨ -slanting lines. The deprived eye is identified by an asterisk. Experimental animals in A were part of the preliminary study and were not run using a blind procedure. All other experimental and control animals were run using a blind procedure. The insert (top-right) illustrates schematically the position of the cannula in the lateral ventricle.

ted reliably by either eye in the experimental animals. The ocular dominance distributions of cells recorded from individual experimental and control animals are presented in Fig. 1. Fig. 1A shows the ocular dominance histograms for cats in the MD/LSD group that were recorded in the preliminary study (n = 2) and Fig. 1B shows the ocular dominance histograms for cats in the MD/LSD group that were recorded during the blind procedure (n = 3). Since the data for all these animals are very similar they are combined in Fig. 2A. The data collected from all six control cats (Fig. 1C, D, E), that is those cats which did not receive MD paired with administration of LSD, are also very similar and are combined in Fig. 2B.

The proportion of binocular cells, that is cells that could be activated reliably by either eye (Groups 2–4), was lower (52%) in the MD/LSD animals than it was in any of the control groups (average for all control animals: 78%). Neither the administration of LSD itself (Fig. 1E: No-MD/LSD; 83% binocular cells) nor a one week period of MD during which only saline was injected (Fig. 1C: MD/No-LSD; 74% binocular cells) resulted in an ocular dominance distribution which differed from that of a normal animal subjected to the implanting procedure and saline injection (Fig. 1D: No-MD/No-LSD; 77% binocular cells). For each cat we determined the ratio of the number of monocular cells, that is cells that could be activated exclusively or predominantly by one eye (Groups 1 and 5), to the number of binocular cells. The mean of these ratios for the combined experimental group differed significantly from the mean of these ratios for the combined control group ($t = 3.04$; $df = 9$; $P < 0.02$ two-tailed t-test). Thus, there was a significant change in the proportion of binocular cortical cells when LSD was administered during a one-week period of MD.

We must consider several factors which might have affected the ocular dominance distribution of cells in area 17. First, residual levels of LSD in the brain might have affected ocular dominance in the MD cats. This is unlikely, however, since we waited at least 6 h after removing the cannula/minipump

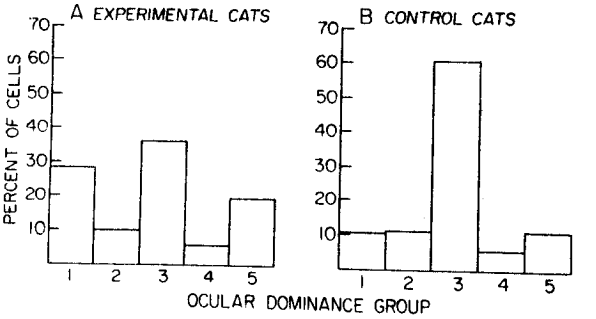

Fig. 2. The averaged histograms for the experimental (A) and control (B) animals for which individual histograms are shown in Fig. 1. Conventions as in Fig. 1.

assembly before beginning data collection[9,23]. Furthermore, the recordings took place over a two day period during which we observed no progressive changes in the ocular dominance distribution of the cells recorded.

Second, unequal sampling of cells from experimental and control cats could produce differences in ocular dominance. If our sample of cells recorded from the MD/LSD group contained relatively more units with receptive fields near the area centralis[1] or with cell bodies located in layer IV[25], then we would expect to obtain a disproportionate number of monocular cells from the MD/LSD animals. However, the receptive fields of cells recorded from our control animals were, in fact, closer on the average to the area centralis (average eccentricities 2.4–4.0°) than were those recorded from the MD/LSD animals (average eccentricities 3.0–8.4°). Thus, the effects of sampling at different eccentricities would not create a difference in ocular dominance between the experimental and the control groups, but rather would cancel some of the differences due to the manipulation. Furthermore, examination of the electrode track reconstructions for the experimental and control animals provided no indication of a disproportionate sampling from layer IV in the MD/LSD group. Thus, we conclude that neither residual levels of LSD in the brain, nor differences in the eccentricities of the receptive fields or in the laminar location of the recording sites can explain the observed differences in ocular dominance between the MD/LSD and control cats.

In summary, no single factor manipulated in this study produced a change in ocular dominance: not the administration of LSD alone (Fig. 1E); not monocular deprivation alone (Fig. 1C); and not the cortical insult which might result from cannula insertion and injection of fluids into the ventricle (Fig. 1D). Thus in our study MD disrupts the binocularity of cortical cells in adult cats only when it is paired with the intraventricular administration of LSD.

DISCUSSION

Our results show that in adult cats the pairing of intraventricular administration of LSD with one week of MD disrupts the binocularity which is characteristic of cells in the striate cortex, even though the deprivation occurs well after the end of the normal sensitive period. The effect of intraventricularly administered LSD is comparable in magnitude to the effect of locally administered NE[23]. On the average in cats administered NE paired with MD there are 2.8 times as many monocular cells as in cats administered NE with no MD[23], whereas in cats administered LSD paired with MD there are 2.7 times as many monocular cells as in cats administered LSD with no MD.

In adult cats the effects of MD, when paired with administration of LSD, differ in several ways from the effects of MD in young kittens. First, in kittens MD produces a change in ocular dominance and virtually all cells can be activated only through the non-deprived eye[19,34,35] whereas in adult cats administered LSD (or NE) MD increases the proportion of cells in both ocular dominance groups 1 and 5. Thus, there is a decrease in the proportion of binocular cells, but each eye can activate comparable numbers of cells. Second, in kittens MD affects response properties of cortical cells other than ocular dominance (e.g. refs 34, 35), whereas in adult cats given LSD MD has no such effects. We measured and analyzed response properties such as orientation and direction selectivity, but found no consistent differences in the pattern for experimental and control animals. Thus, for example, in cats in the MD/LSD group the mean orientation selectivity and direction selectivity for units activated through the eye that had been deprived was comparable to the mean orientation and direction selectivity of units activated through the eye that had not been deprived.

The reasons for these differences between the effects of MD in kittens and in adult cats given LSD are not clear. One possibility is that the extent of the changes produced by MD in adult animals given LSD during a one week period were reduced by the development of a tolerance to the drug. Such a conclusion is suggested by the absence of any marked behavioral effects of the LSD. Single doses of LSD administered by intraperitoneal injections produce a characteristic pattern of behavioral changes[20] which at some dosages last for at least 8 h[33]. Tolerance to the behavioral effects of LSD, even at very low dosages, can develop within 2 h of the injection, and some may last for 3–5 days[33]. Thus,

although our procedure for administering LSD definitely did have an effect on the ocular dominance of cells in the visual cortex, this effect might be different from or less severe than that seen with other schedules of administration, particularly periodic large doses. Our behavioral observations, which were undertaken primarily to insure that the behavior of the cats during administration of LSD did not greatly alter their visual experience (e.g. through excessive sleeping or gross changes in motor behavior that might influence visual input), were begun after the animals had recovered fully from the anesthesia. We would thus have missed early behavioral effects of the drug. Furthermore, our observations were not very extensive and it is quite possible that subtle behavioral effects of the LSD might have been overlooked.

A second possibility is that in adult cats given LSD in combination with one week of MD, competition between geniculocortical afferents might occur at cortical synaptic sites, as is thought to occur in young cats[15,16,35] but that the resulting loss of function might never be as severe as that seen in younger animals. Several experiments have found that a loss of binocularity may be a prelude to the ocular dominance shifts reported following MD in kittens[7,14,19,28]. A third possibility is that administration of LSD produces a drop in responsiveness of binocular cells and that this is aggravated by disruption of normal visual stimulation thereby reducing the likelihood of recording from binocular cells in the cats from the MD/LSD group. In this case, MD may not be the only disruption sufficient to achieve a drop in the proportion of binocular cells recorded. Certainly, in the absence of LSD both dark-rearing and binocular lid-suture have been reported to produce a reduction in the proportion of binocular cells recorded[6,24,26].

In summary, our results do show that a change in the binocularity of cells in the visual cortex occurs, and is associated with the joint occurrence of LSD and MD, but, we cannot determine whether this change in binocularity reflects a change in the ocular dominance of individual cells through 'instruction' or an actual loss of binocular cells through 'selection'. Each of these processes would lead to a reduction in the number of binocular cells recorded (cf. ref. 17).

Although the observed, drug-induced sensitivity to MD for cortical cells in adult cats is not as great as the sensitivity to MD alone for cortical cells in young cats, its existence does have important implications. First, it is possible that an increase in 'plasticity' could be of some benefit in making the nervous system more susceptible to treatments for the effects of early deprivation. To explore this possibility we administered LSD into the ventricular system of adult cats that had been monocularly deprived from birth to adulthood and then had the deprived eye open during drug administration. Using visual acuity as a sensitive assay of the animal's behavioral capabilities with the deprived eye, we could obtain no evidence of any change in performance as a result of chronic administration of LSD (Loop, McCall and Hirsch, unpublished observations). Thus, if recovery from the effects of early deprivation can be facilitated by administration of LSD, it may be limited to damage less severe than that created by long-term monocular deprivation, it may require recovery periods during which the administration of the drug is coupled with the use of procedures to insure balanced, symmetrical visual input to the two eyes (cf. ref. 21), it may require different schedules of drug administration[20], or, in fact, LSD may induce a susceptibility to disruption of existing connectivity without facilitating any of the functional compensation associated with the 'plasticity' that is characteristic of the developing nervous system.

The second implication of our findings is that LSD may be able to affect permanently the human central nervous system. Since monoamine presence affects developmental processes in kittens[22,23], and since LSD crosses the blood-brain barrier[8] and produces changes in brain monoamines when administered systemically[13] the possible effects of LSD on human development, both prenatal and postnatal, must be considered.

The third implication of our findings is that although some of the visual disturbances produced by LSD could be due to a direct effect of the drug on cortical physiology[10,12,31], other behavioral effects may result from the drug-induced plasticity of cortical cells. Normally, in the adult organism cortical cells respond to a given visual stimulus in a constant and predictable manner. Administration of LSD,

however, makes the response properties of cortical cells susceptible to modification by sensory stimulation and, thus, reduces the predictability of a cell's response to an incoming stimulus. For our experiments in adult cats given LSD, MD decreases the proportion of binocular cells in area 17 of visual cortex. Such a drop in the proportion of binocular cells has been shown to be associated with a loss of stereoscopic depth perception in cats[4,29]. Although the loss of binocularity that we have observed is not likely to occur without some form of abnormal visual input, the changes which can be demonstrated with our method may be only one result of a plasticity occurring throughout the visual system. Thus, the relatively persistent disturbances of perception reportedly induced by the use of LSD may involve stimulation-induced changes in the response properties of non-striate, as well as striate cortical cells. Clearly, a sufficient loss of predictability in the responses throughout the visual system must, almost by definition, lead to distortions in perception.

The present experiments do not determine whether LSD acts directly on cells in the visual system or acts indirectly, perhaps through the drug's interaction with the monoamines. Thus, although an understanding of the mechanisms by which LSD affects the nervous system remains as far from our grasp as before, we must add an important, and tangible, sequel to the known effects of this drug.

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