EXPERIMENTAL NEUROLOGY **13**, 273-282 (1965)

Retinal Effects of High Doses of LSD in the Cat

ARTHUR S. SCHWARTZ AND CARL CHENEY[1]

Laboratory of Physiological Psychology, Barrow Neurological Institute, Phoenix, Arizona; and Department of Psychology, Arizona State University, Tempe, Arizona

Received June 7, 1965

Low doses of LSD previously have been shown to produce a retinal effect similar to stimulation with low frequency flashing lights or moving visual patterns. The present study extended these findings to high LSD doses, which resulted in retinal effects similar to stimulation with high frequency or constant, steady illumination. Retinal activity was derived from measurements of the average tonic discharge levels per unit time of the optic tract. Although high doses of LSD produce retinal changes in association with behavioral visual unresponsivity, no alteration in this tonic activity appears upon stimulation with changing visual stimuli. The data indicate a direct retinal action of LSD. However, the resultant behavioral visual unresponsivity does not appear to be due to retinal changes alone.

Introduction

Lysergic acid diethylamide (LSD) produces many effects in the body, not the least interesting of which are its effects on the visual system. It is well known that one of the psychotomimetic effects of this drug is the production of so-called visual hallucinations which in the human often consist of the experience of patterned lights, flashes, honeycombs and lattices. The possibility that these psychological effects may be due to the retinal action of LSD has been raised by Apter and Pfeiffer (2) who found that the electroretinogram (ERG) in the cat showed spontaneous electrical activity after suitable doses of this drug. These authors seem to have ruled out muscle artifacts or efferent feedback systems.

We extended these findings to the optic tract and lateral geniculate body of the cat, and recently have shown that the tonic activity levels of these

[1] Supported in part by NIMH Grant 7997 and NINDB Grant B-3528, and a NIMH Traineeship to C. Cheney. We acknowledge with thanks the technical assistance of Mr. William Bullock, and the supplies of LSD from Mr. Harry Althouse of Sandoz Pharmaceuticals.

structures increase after low doses of LSD (14). Similar increases were produced by stimulation with flickering light or changing visual patterns. Arduini and Pinneo (5) originally observed that the tonic discharge level in the optic chiasma during steady light illumination is less than the discharge in total darkness, and that low flicker rates cause an increase while high flicker rates produce a decrease of this tonic activity (6). We have confirmed these findings in our laboratory. From these data we have derived the hypothesis that if low doses of LSD induce a low-flicker effect, high doses should produce an effect resembling that resulting from stimulation with high flicker rates or steady, constant illumination. In this case we would expect high doses of LSD to *decrease* the tonic discharge level of the optic tract and lateral geniculate, in contrast to low doses.

We were also concerned with finding an explanation for the lack of behavioral response to visual stimuli, exhibited by animals treated with high LSD doses (10). That this lack of response is related to changes in the visual system and its connections and not the result of nonspecific toxic effects is supported by the fact that such subjects are extremely responsive to auditory stimuli and manifest no motor weakness. Conceivably, one explanation might be that the retina is in a state resembling continuous light adaptation and is less excitable by visual stimulation. This may be analogous to the blurring and disappearance of contours which occurs when retinal units become adapted to fixed images (12). However, as one of us has reported (13), enhanced cortical evoked potentials to light flash occurred after high doses of LSD. This suggests that the visual system is still functional and that the behavioral "blindness" results from altered perceptual and integrative mechanisms. In this respect we wanted to determine whether or not the retina, as well as the cortex, retains an ability to react quantitatively to visual stimuli while the animal is behaviorally unresponsive. The data we will present indicate that a high dose of LSD induces a retinal state analogous to stimulation with high flicker rates, as well as a lack of behavioral response to visual stimuli, but without a concomitant loss in retinal responsivity, measured in terms of tonic discharge activity.

Method

To measure the tonic activity levels of the optic tract and lateral geniculate body during various conditions of this experiment, the technique described by Arduini and Pinneo was used (4). Bipolar electrodes were placed in the optic tract and lateral geniculate nucleus of twenty cats—twelve acute and eight chronic experiments. The amplified signal was then

led through a band-pass filter (500–10 000 cycle/sec band width) into a Ballantine RMS meter. The d-c voltage output of this meter is directly proportional to the root mean square voltage of the input signal which in turn has been related by Arduini and Pinneo to the average number of unit impulses per unit time (4). Assuming an all-or-none discharge system around our electrodes, since slow activity was filtered out, the voltage output of the meter is directly proportional to the average impulse rate in the optic tract and geniculate nucleus. This RMS output was then fed to a driver amplifier which in turn operated an Acromag electromechanical integrator. A timer in series with the driver and integrator allowed setting of a constant integration time of 10 sec.

All subjects were placed in a sound-insulated, light-proof chamber. A tungsten 200-watt overhead lamp provided about 60 foot-candles illumination as measured from a white card at the cat's eye level. Flicker stimulation and moving or changing visual patterns were supplied, respectively, by a Sylvania R1131C glow modulator tube and striped cards, waved manually in front of the eyes.

The usual procedure was as follows: (*i*) The light-adapted control readings were obtained after 5 min in the light. (*ii*) Changing visual stimulation was presented. (*iii*) Dark tonic discharge was measured after at least 30 min in complete darkness. (*iv*) LSD (0.25–1.0 mg/kg, ip) was injected under subdued red light to minimize visual stimulation. (*v*) Post-drug measurements in the dark started 10 min after injection. (*vi*) Post-drug light measurements were made after 5 min light adaptation. (*vii*) Finally, the effects of changing visual stimulation were again determined.

In one cat radio-frequency lesions were made in the optic tract bilaterally about 3 mm posterior to the optic chiasma in order to interrupt any centrifugal fibers. Recordings from this cat were obtained from the optic chiasma.

Sodium pentobarbital (40 mg/kg, supplemented when necessary) was administered to the anesthetized cats at least 1.5 hours before recording. Electrode placements and lesions were verified histologically afterwards.

Results

Our first objective was to measure the tonic activity levels of the optic tract and lateral geniculate bodies under light and dark conditions in twelve anesthetized acute preparations. Figure 1 shows the comparison between those levels before and after LSD. The combined RMS readings in the dark control are considered as 100% and the tonic discharge levels under all

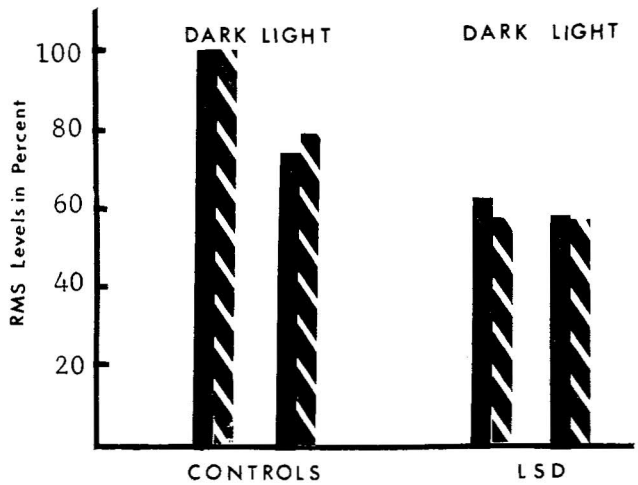

FIG. 1. Combined tonic discharge levels of twelve anesthetized cats under various experimental conditions. Solid bar = optic tract; striped bar = lateral geniculate body.

other conditions are expressed as a percentage of this baseline level. In nine of the twelve preparations, the optic tract tonic discharge decreased in the steady light. Combining the data of all twelve cats shows a total decrease of 25% as compared with their dark discharge levels (left side of figure). This decrease is significant at the 0.05 level according to the Wilcoxon Paired Signed-Ranks Test (15) and confirms the finding of Arduini and Pinneo (5), although we found more variability than they reported. The same relationship was obtained in the lateral geniculate body. Steady light decreased the tonic activity level by 20% in ten of the twelve preparations, also significant at the 0.05 level of probability. In one animal the activity level of the geniculate decreased while the tract activity increased slightly. With this exception, both tract and geniculate showed changes in the same direction as a result of steady light conditions.

After administration of LSD (0.25–0.75 mg/kg, ip) the tonic activity of the tract decreased by a statistically significant 38% in the dark ($p < 0.05$, two-tailed test). Light adaptation did not reduce this level further, although it was significantly less than the light-adapted control level (75 vs. 59%, ($p < 0.05$). Thus both stimulation with steady light and administration of high doses of LSD reduced the tonic discharge activity of the tract. Also, after LSD, light stimulation was relatively ineffective in producing the typical reduction in discharge activity. The same situation

applies to the geniculate, in which tonic activity decreased by 42% from its dark control level but showed no further decrease in the light after drug injection.

Our original hypothesis concerning high doses was also tested in eight unanesthetized cats with electrodes chronically implanted in the same structures. Figure 2 shows the decrease in RMS levels after LSD, in both dark and steady light. There is, however, one interesting difference between the chronic and acute preparation. In the pre-drug control the light tonic discharge level was *not* decreased, compared to the dark, in the unanesthetized animals. We attributed this to the fact that in our initial runs these cats were unrestrained in a nonuniform visual field. The head and eye movements could then result in changing visual patterns impinging upon the retina, and thus result in increased tonic discharge levels, similar to the effect of stimulation with low flicker rates. This was checked by lining our observation cage with white cardboard. Under these conditions of minimized pattern stimulation the tonic levels of all three cats tested decreased in the light as in the restrained, acute preparations. However, because of the small samples in each group (five in the unlined cage, three in the uniform field) we have combined all the unanesthetized cat data

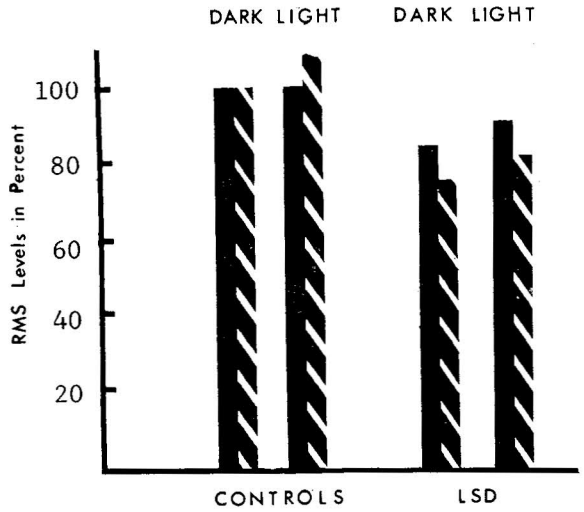

FIG. 2. Combined tonic discharge levels of eight chronically implanted, unanesthetized cats under various experimental conditions. See text. Solid bar = optic tract; striped bar = lateral geniculate body.

into one group. Consequently Fig. 2 shows no decrease in the tonic discharge under conditions of steady light. The same situation applies to the post-LSD light data. Comparing the LSD dark and light levels with their respective dark and light control levels shows that the LSD decreased activity in all eight cats in both optic tract and lateral geniculate in the dark condition, while under conditions of steady light there were two instances of slight increases. This total decrease, with the two exceptions included in the signed-rank test, was statistically significant ($p < 0.05$).

Bilateral section of the optic tract at the level of the nucleus entopeduncularis did not affect the results; LSD produced a decrease in the tonic discharge activity from the optic chiasm well within the range found in the optic tract of the anesthetized group.

The effect of low flicker rates and moving, striped patterns is shown in Fig. 3. The combined tonic activity levels of twelve cats (six anesthetized and six unanesthetized) in steady, constant light is represented as 100%, both before and after LSD, while the tonic activity levels during changing

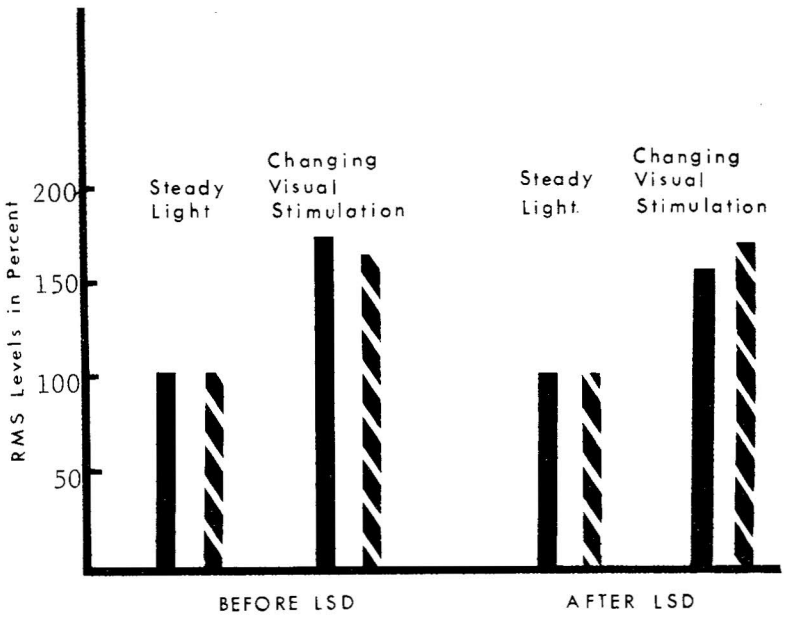

FIG. 3. Effect of changing visual stimulation on combined tonic discharge levels of six anesthetized and six unanesthetized cats. Steady light conditions are considered as 100%. Solid bar = optic tract; striped bar = lateral geniculate body.

visual stimulation is depicted as a percentage of these respective measures. As indicated above, changing visual stimulation prior to LSD increases the tonic impulse activity in both optic tract and lateral geniculate body. These increases amounted to 175% in the former and 166% in the latter. After LSD, changing visual stimulation also increased the tonic activity levels in these structures, in this case amounting to 156% in the optic tract and 170% in the geniculate body. Again, these increases over their respective steady light control were statistically significant ($p < 0.05$). Although the optic tract shows less of an increase in tonic activity after LSD, applying the matched-pairs signed-ranks test to the two groups of data under changing visual stimulation conditions demonstrates no significant difference. As Fig. 3 indicates, LSD exerted little if any effect on the ability of changing visual stimulation to increase the tonic activity levels of the cat's optic pathways.

Discussion

Although there is little doubt that LSD affects other neural systems (1, 9, 13), it is probable that our results, as well as those of Apter and Pfeiffer (2), represent retinal changes. The LSD-induced changes in the ERG observed by these authors persisted after section of the optic nerves and ocular muscles (2). Brindley and Hamasaki reported no evidence of centrifugal influences on the ERG (7), and as we have shown above, high LSD doses reduced the tonic activity levels in the optic chiasm after section of the optic tract, which presumably interrupted most if not all centrifugal fibers that may exist.

The data illustrated in Fig. 1 suggest that high doses of LSD affect the cat's retina in a manner similar (but not necessarily identical) to stimulation with high flicker rates or constant, steady illumination. Both of these manipulations decrease the tonic discharge levels of the optic tract and lateral geniculate body. These data supplement those of earlier studies which showed that low doses of LSD produce an optic effect, as indicated by tonic activity changes, similar to that produced by low flicker rates (14). The relative decrease produced by steady light appears to be comparable in magnitude to that reported by Arduini and Pinneo (5), and might have decreased even further in our study if a more intense light source had been used. Whether it would be possible to increase light intensity or adjust dosage levels so that equivalent retinal effects are obtained cannot be stated at present. In several cases LSD reduced the tonic activity levels to a value very close to the effect of light alone, but

the variability in tonic activity levels and the small sample used here precludes any demonstration of dose-response relationships.

In order to obtain measurements of tonic activity under conditions of dark and steady light in unanesthetized cats, Arduini and Pinneo had to restrain their animals in a head-holder to avoid the effects of changing visual stimulation (6). We found it too difficult to restrain our cats after LSD, but careful observation during those periods when the cat's head was still, especially in a uniform-field box, showed that in those instances steady illumination also reduced the tonic activity levels. Figure 2 combines the readings obtained from all unanesthetized cats and consequently shows no decrease under light conditions due to changing visual stimulation. However, based on the findings of Arduini and Pinneo (5, 6) and our own observations under the special circumstances outlined above, i.e., the three cats in the lined cage, we conclude that steady light or high flicker rates reduce the tonic activity levels in unanesthetized cats as it does in anesthetized subjects. Again, LSD results in decreased tonic discharge, while at the same time the cat is behaviorally unresponsive to visual stimuli.

Although we seem to have a possible explanation for this visual unresponsivity by suggesting that LSD drives the retinal elements into a state equivalent to steady light-adaptation, and therefore unreceptive to brightness gradients (12), the data illustrated by Fig. 2 and 3 are against this interpretation. Changing visual stimulation, whether produced by shifting the gaze in a nonuniform field (Fig. 2) or in the form of flicker or patterned moving cards (Fig. 3), is about as effective after LSD as before in increasing retinal activity.

Similarly, the finding by Evarts that LSD alters synaptic transmission in the lateral geniculate (10), determined by the use of single electrical shocks to the optic nerve, cannot be invoked as an explanation for the lack of behavioral response. One of us (13) has shown that cortical and geniculate evoked responses to light flash are enhanced in unanesthetized, visually unresponsive cats after high doses of LSD. This enhancement effect not only suggests a viable visual pathway, but also is in line with Arduini and Hirao's (3) view that the tonic discharge activity from the retina represents an inhibitory influence on the cortex and that reduction of this activity level (as with steady light illumination or high LSD doses) results in enhanced cortical evoked potentials (8).

Two possible explanations of the behavioral "blindness" may be offered. (*i*) The lack of visual response is a consequence of retinal effects of LSD,

but our measuring technique is inadequate to detect the relevant changes. (*ii*) Central factors, with or without retinal interaction, are responsible for the visual behavior deficit. Substantial evidence exists which demonstrates that LSD affects the limbic system (1, 9), and that a syndrome described as "sensory agnosia" results from lesions in this system (11). The fact that our cats were still responsive to auditory and tactile stimulation may not be against this possibility since such reactions were also altered. Thus a sudden sound evoked an exaggerated startle reaction but without clear localization or orientation responses, while a tactile stimulus evoked hissing and snarling, withdrawal or defense reactions resembling "sham rage." Despite the evidence presented in this paper for retinal effects of LSD, these considerations indicate that a more central site of action, possibly in the limbic system, must still be invoked in any explanation for the behavioral visual unresponsivity.

References

1. ADEY, W. R., F. R. BELL, and B. J. DENNIS. 1962. Effects of LSD-25, psilocybin, and psilocin on temporal lobe EEG patterns and learned behavior in the cat. *Neurology* **12**: 591-602.
2. APTER, J. T., and C. C. PFEIFFER. 1960. Some effects of hallucinogenic drugs on the electrical activity of the visual pathways of cats. *Am. J. Ophthalmol.* **42**: 206-211.
3. ARDUINI, A., and T. HIRAO. 1960. Enhancement of evoked responses in the visual system during reversible retinal inactivation. *Arch. Ital. Biol.* **98**: 182-205.
4. ARDUINI, A., and L. R. PINNEO. 1962a. A method for the quantification of tonic activity in the nervous system. *Arch. Ital. Biol.* **100**: 415-424.
5. ARDUINI, A., and L. R. PINNEO. 1962b. Properties of the retina in response to steady illumination. *Arch. Ital. Biol.* **100**: 425-448.
6. ARDUINI, A., and L. R. PINNEO. 1963. The effects of flicker and steady illumination on the activity of the cat visual system. *Arch. Ital. Biol.* **101**: 508-529.
7. BRINDLEY, G. S., and D. I. HAMASAKI. 1962. Evidence that the cat's electroretinogram is not influenced by impulses passing to the eye along the optic nerve. *J. Physiol. London* **163**: 558-565.
8. EECKEN, H. V., and J. FAUTREZ. 1965. Cellular modifications in the rabbit's visual system after unilateral ocular enucleation. *Nature* **206**: 423-424.
9. EIDELBERG, E., M. K. MILLER, and M. LONG. 1965. Spectrum analysis of EEG changes induced by psychomomimetic agents. *Intern. J. Neuropharmacol.* **4**: 255-264.
10. EVARTS, E. V. 1958. Neurophysiological correlates of pharmacologically-induced behavioral disturbances, pp. 347-380. *In* "Brain and Human Behavior." Williams and Wilkins, Baltimore, Maryland.

11. KLUVER, H., and P. C. BUCY. 1939. Preliminary analysis of functions of the temporal lobes in monkeys. *A.M.A. Arch. Neurol. Psychiat.* **42**: 979-1000.
12. RIGGS, L. A., F. RATLIFF, J. C. CORNSWEET, and T. N. CORNSWEET. 1953. The disappearance of steadily fixated visual test objects. *J. Opt. Soc. Am.* **43**: 495-501.
13. SCHWARTZ, A. S. 1963. Effects of LSD on evoked potentials and behavior in the conscious cat. *Federation Proc.* **22**: 627.
14. SCHWARTZ, A. S., and C. CHENEY. 1965. Effect of LSD on the tonic activity of the visual pathways of the cat. *Life Sci.* **4**: 771-778.
15. SIEGEL, S. 1956. "Nonparametric Statistics." McGraw Hill, New York.