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EFFECT OF LSD ON THE TONIC ACTIVITY OF THE VISUAL PATHWAYS OF THE CAT*

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The hallucinatory effects of such substances as lysergic acid diethylamide (LSD) have been partially attributed to their direct action on the retina (1, 2). This retinal action was inferred from the effects of LSD on the spontaneous electroretinogram (ERG) activity in cats (1) and from changes in evoked ERG in humans (2). The ERG is a gross measure of retinal activity and tells very little about the underlying neuroelectric phenomena which may accompany drug administration.

Further, Apter and Pfeiffer (1) reported spontaneous ERG changes in the light-adapted eye only; this was subsequently confirmed by Short (3). However, the data of Krill et al., (3) suggest that changes in amplitude of the ERG, together with the report of hallucinations, occur in the dark-adapted human. We have sought to extend the above findings by examining the average massed unit or tonic activity level of the optic tract and lateral

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geniculate body of the cat after administration of LSD, and to relate these levels to those produced by various forms of visual stimulation.

Methods

Ten acute anesthetized (sodium pentobarbital, 40 mg/kg) and eight chronically implanted, unanesthetized cats were used for this study. Bipolar, stainless steel electrodes were placed in the optic tract and lateral geniculate body, usually on opposite sides. Recordings were made on magnetic tape (direct record, bandpass 50-12,500 cps) after suitable amplification.

To measure the average number of unit impulses we have adopted the method described by Arduini and Pinneo (1962). The tonic activity of a system of all-or-none units is measured by a Ballantine True RMS volt meter whose output is a DC voltage proportional to the mean square, _i.e._, power of the voltage at the input. They have demonstrated mathematically that the mean square (or average power) is proportional to the number of nerve impulses per unit time. In the present experiment, the signal from the tape was first led through an RC high-pass filter (500-12,500 cps) then into the Ballantine RMS meter. The DC output from the latter was connected to a DC amplifier which drove an Acromag electrical integrator with a continuous dial readout. A timer switch in series between the driver amplifier and the integrator provided a 10 second constant integration time of the output of the RMS meter. The bandpasses of the recording system insured that only the all-or-none unit activity of the optic tract and lateral geniculate nucleus would be measured by the RMS meter. Ten integration samples were taken at various intervals during each experimental condition. Several chronic cats were tested more than once, always with at least an intervening two-week period.

"Light-adapted" records were taken after 5-15 minutes exposure to room light. Average illumination for the chronic cats was 3 candles per sq. ft.; for the acute cats, illumination at eye level was 10 candles per sq. ft., determined with a photometer. "Dark-adapted" records were taken after ½-1½ hours in total darkness. Under both conditions it was found necessary to wait until the background activity level had stabilized for at least 10 minutes before a final reading was obtained.

Intraperitoneal injections of LSD ranged from 0.1 to 0.25 mg. total dose. Scopolamine hydrobromide (1%) was placed in each eye of several cats. This procedure did not appear to affect our results.

All the chronic and most of the acute experiments were carried out in a soundproof, light-proof chamber. In addition, chronic, unanesthetized animals were kept in a wooden box 17" wide, 17" deep and 22" high, with a plastic transparent door on one side facing a one-way window of the soundproof chamber. No attempt was made to limit the visual environment otherwise.

In several cats, both acute and chronic, the effects of flickering light or changing visual patterns was noted. The former was accomplished with a glow modulator tube (Sylvania R1131C) flashing from 8 to 50 cps; the latter by recording during head and eye movements in the light or by moving black and white patterned cards before their eyes.

Histological verification of the electrode placements has been completed on the acute cats only. The chronic animals are being used for further experiments.

Results

In 18 out of 20 experiments, LSD resulted in an increase in the tonic activity level of the optic tract and lateral geniculate body. These increases, both in the light and the dark, ranged from less than 1% to 125%, with a mean of 37% and a median of 22%. These percentages were derived by comparing the average post-injection RMS reading with the average pre-injection reading under the same adaptation conditions. Applying the Wilcoxon matched pairs signed-ranks test to these data showed that the total difference is significant beyond the .01 level of probability (two-tailed test) (5). In the two exceptional cases (chronic) the geniculate showed a decrease in the dark after drug injection. LSD effects (electrical and behavioral in the chronic, electrical in the acute) were first seen about 5 to 10 minutes after i.p. injection and reached a peak within 15 minutes. Increased tonic levels remained for as long as 50 minutes with these doses, then often declined to levels below the equivalent control condition. That these increased tonic levels were not entirely due to increased head movements resulting from the hyperactivity produced by LSD in the chronic preparations or to changing visual patterns (see below), is shown by the similar results obtained in the acute experiments and by recordings made in absolute darkness. We observed no eye movements in the anesthetized cats either before or after LSD.

Arduini and Pinneo (6) have shown that the tonic activity this phenomenon to the unanesthetized, unrestrained cat in light and dark. Conceivably, the paroxysms of spontaneous ERG activity noted by Apter and Pfeiffer and the increased tonic activity levels noted by us, are due to the same retinal mechanisms. Since the ERG paroxysms were not eliminated after section of the optic nerve, Apter and Pfeiffer suggested that LSD had a direct retinal effect, and that these effects may be contributory to the simple hallucinatory experiences reported by humans. Although we have no direct proof as yet that the increased activity levels found in our cats are due to retinal activity and not to centrifugal fibers, there are two reasons to believe the former situation is more likely: (1) Arduini and Pinneo (6) have shown that all the impulses recorded at the optic chiasma disappear after reversible ischemia of the eye. The resulting level of activity is equal to the noise level manifest after the death of the animal. (2) Brindley and Hamasaki have demonstrated that sectioning the optic nerve, before or after anesthesia, has no effect on retinal activity and concluded that the physiological evidence for central innervation of the retina is questionable (7).

The LSD effect reported here may be compared with the consequence of retinal stimulation with changing geometric patterns and flashing lights. Both result in increased tonic activity levels, so that there is some justification for the notion that LSD produces retinal effects equivalent to that produced by visual stimulation with honeycombs, lattices, flashing lights, as reported by humans and possibly experienced by cats. Such a conclusion is questionable, however, for the following reasons: (1) Patients with non-functioning retinas report simple hallucinations after LSD (8). (2) Preliminary observations in our laboratory show that the cat with enucleated orbits behaves in the same manner as normals after LSD. That is, the peripherally blinded cat demonstrates head movements and paw flicking indistinguishable from the behavior exhibited by the non-enucleated cat. (3) The time course of the drug-induced retinal and optic pathway effects is different (i.e., shorter) than the behavioral effects. Our data support the notion that LSD affects the retina in a manner which may result in the experience of simple hallucinations, but the overt behavior of the cat consequent to drug administration may be independent of the changes produced in the visual system.

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