Spontaneous Retinal Electrical Potentials

JERRY HART JACOBSON, M.D., and GIDON F. GESTRING, New York

Recent interest in psychopharmacology has led to extensive investigation of a number of types of drugs. The derivative of ergot known as D-lysergic diethylamide, or LSD-25, is one of the most thoroughly studied. This substance has been known to have pronounced effects upon the uterus, vagina, and bronchi and to cause mydriasis, tachycardia, rise in temperature, and other autonomic effects.[1] Hoffman,[2] in 1943, was the first to report psychic effects of the drug, after he had accidentally ingested a small quantity of it. These have been found to include mood changes, schizoid states, and, most important from the ophthalmological standpoint, visual hallucinations.

The doses required for production of hallucinations in man are extremely minute, as little as 0.5μg. to 1.0μg. per kilogram of body weight being effective.[3] Larger doses are required in schizophrenic patients.[4]

Recently Apter and Pfeiffer[5] reported their observation that upon administration of LSD-25 to cats, the animals behaved as though they were having visual hallucinations and that spontaneous electrical activity occurred in the eyeball of the cat when the drug was administered. The conclusion was drawn that, contrary to the opinion generally held that the visual disturbances of the drug were due solely to central nervous system effects, the peripheral action of the drug upon the retina must be considered as a participant in the production of the hallucination. Our study was undertaken in an attempt to determine the characteristics of this phenomenon.

Methods

Forty-five adult cats were utilized in this study. The majority of the studies were performed by recording from the surface of the eyeball. In these experiments a chlorided silver electrode, 1 mm. in diameter, was sutured against the corneal surface about 1 mm. inside of the limbus. The animals were anesthetized with pentobarbital sodium, about 30 mg per kilogram, and artificially ventilated. The subclavian vein and femoral artery were cannulated, and remote control syringes were so arranged within a shielded chamber as to allow simultaneous systemic administration of drugs and recording of the blood pressure without disturbing the shield or the state of dark-adaptation. Bilateral recording was usually performed, and the outer canthus or the nose served as reference leads.

In another group of cats, the cornea, lens-iris diaphragm, and vitreous were removed. Micromanipulators were used to position and hold electrodes against the retinal surface.

Monkey and human excised retina was studied, with use of the technique which has been described elsewhere.[6]

A Grass polygraph unit was used for ink-writer recordings and a DuMont Type 333 dual-beam oscilloscope and Grass Kymograph camera for photographic records. Section of the optic nerve, when performed, was accomplished acutely by sharp traction on a silk suture which had been previously looped about the nerve at the chiasm. In chronic studies the nerve was sectioned at

Submitted for publication March 24, 1959.

Mr. Richard Dowling gave technical assistance.

From the Division of Electrophysiology, Department of Research, New York Ear and Eye Infirmary and Albert Einstein College of Medicine.

Supported by Grant B-1194, National Institute of Neurological Diseases and Blindness, U. S. Public Health Service, The Ophthalmological Foundation, and The National Council to Combat Blindness, Inc.

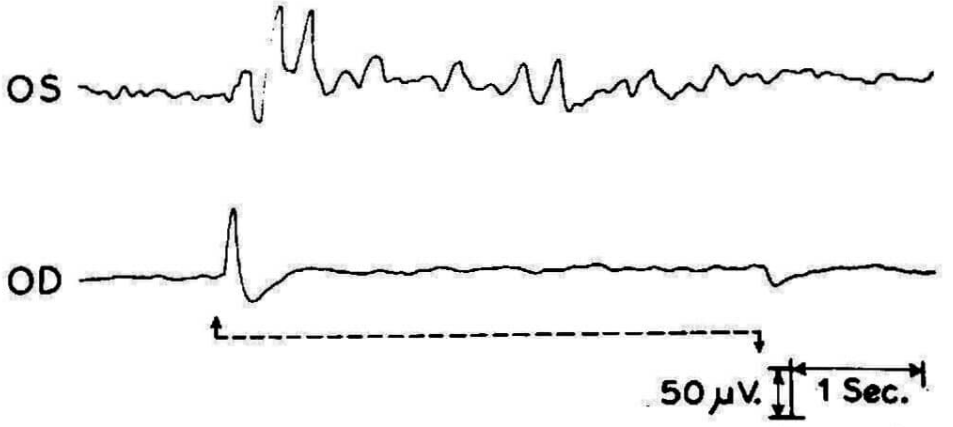

Fig. 1.—Effect of 100μg. of LSD-25 per kilogram on the ERG of the cat. "Spontaneous" potentials developing in cat eye after administration of LSD-25. Arrows indicate light stimuli. Tracing of right eye is after section of the optic nerve.

the chiasm after gentle retraction of the frontal lobes. In all "optic-nerve-sectioned animals" the central retinal circulation was kept intact and verified by ophthalmoscopic examination. All animals were adapted to total darkness for 20 minutes prior to recordings.

Results

In 40% of all animals given injections intravenously with LSD-25 at a dosage level of about 50μg. per kilogram of body weight, spontaneous potentials were recorded from the eyelall, sometimes triggered by light stimuli (Fig. 1).

Section of the optic nerve at the chiasm abolished these potentials. If the section was unilateral the spontaneous activity disappeared in the sectioned eye and persisted in the intact eye (Fig. 2).

Similar potentials can be shown to develop in animals which have suffered heavy blood loss or have had a large dose of barbiturate (Fig. 3).

Figure 4 shows a series of ERG's recorded from the surface of a cat eye. In the left column the topmost record is the response of a cat lightly anesthetized with pentobarbital. Additional doses of pentobarbital causes an increase in the *b*-wave amplitude until a maximum is attained (3d tracing). Added drug causes diminution of response until the original amplitude of response is reached (5th tracing). From

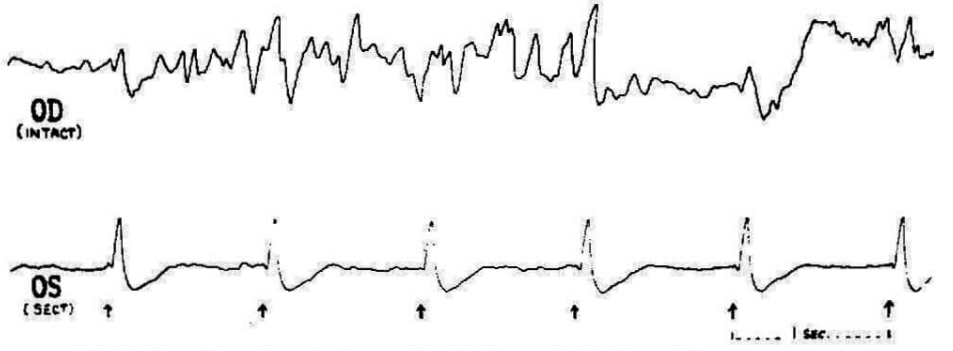

Fig. 2.—Recordings from both eyes of a deeply anesthetized cat with unilateral optic nerve section, showing "spontaneous" activity only in eye with intact nerve. Arrows indicate light stimulation. Normal ERG's in eye with sectioned nerve.

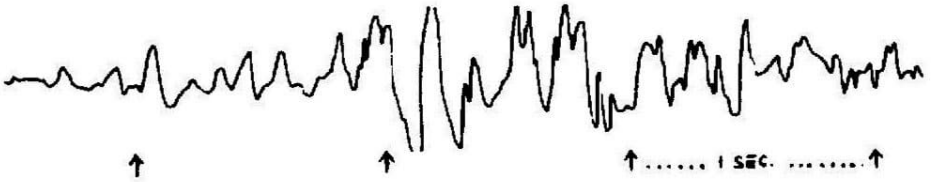

Fig. 3. "Spontaneous" activity in eye of cat after heavy blood loss. Arrows indicate light stimulation.

this point on if one administers more barbiturate or LSD-25 or bleeds the animal, a sequence of changes as shown in the right hand column is induced. This reversal of sign is typical of deeply depressed animals. Most animals recover under artifical respiration and regain a normal response to light stimuli.

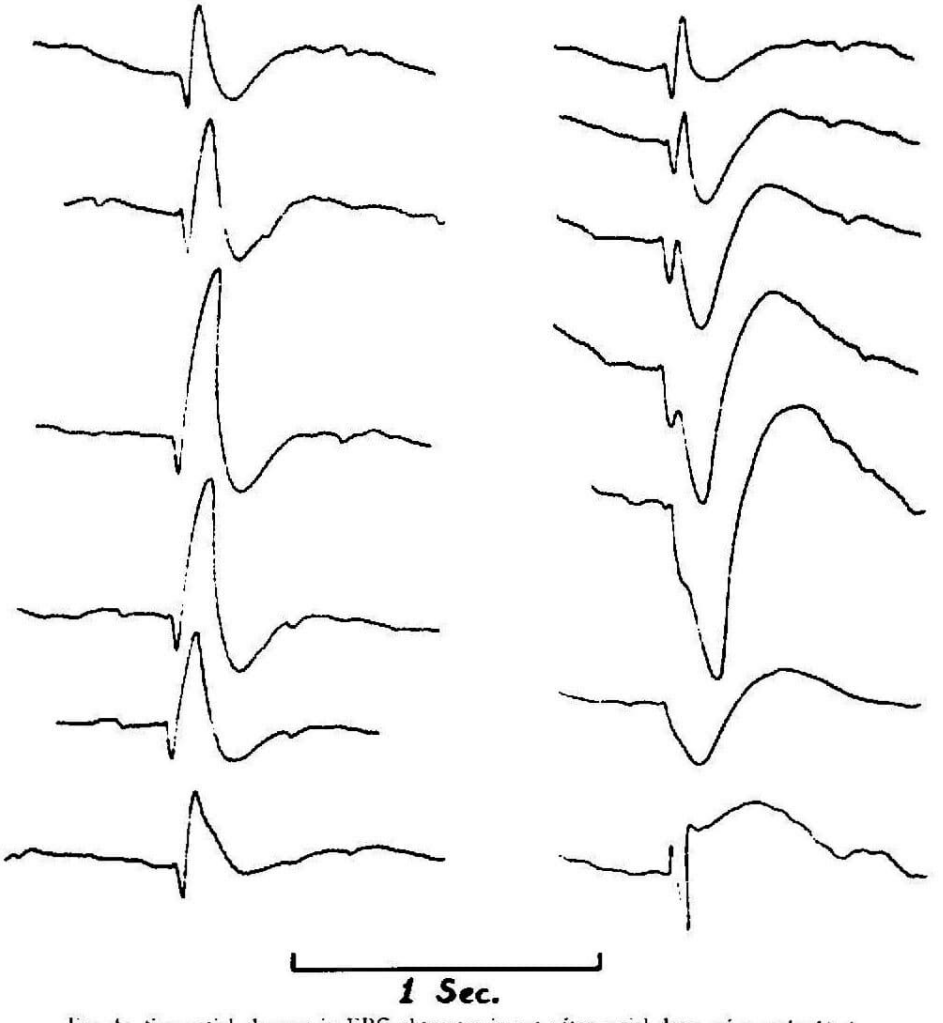

Fig. 4. Sequential changes in ERG character in cat after serial doses of pentobarbital

Samples of human, cat, and monkey retina were excised, and records were made of the tissue to light. No alteration in the character of the responses of such tissue was obtained when LSD was added to the medium in which the tissue was suspended.

Comment

The electrical activity of the retina may be modified by a variety of factors. A number of drugs, including barbiturates,[7,8] hexamethonium,[9] iodoacetate,[10] trichloroethylene,[11] ethyl alcohol,[12] and LSD-25, affect the characteristics of the response to light. Variations in the effects noted with some of these agents were striking.[13] This difference in character of response is noted[11] not only in the retina but in cerebral neurophysiology as well.

Increase in amplitude of the *a*- and *b*-wave components of the ERG due to administration of one toxic agent, trilene, thought by Noell to be due to an inhibition "of the ability of certain parts of the ERG system to shift from scotopic operation to the photopic one."[13]

In a recent report[9] we presented a hypothesis which projected the existence of an inhibitory center at a higher level than the retina affecting the electrical activity of the retina through centrifugal fibers. We feel that this is a possible explanation for the inhibition suggested by Noell. Clinical findings with the afterimage test also show that there is a marked cerebral influence upon what had been thought to be the purely retinal function of persistence of images.[15,16]

The matter of dosage must be carefully considered in this work. The amount needed to produce visual hallucinations in normal man, as reported, among others, by Mayer-Gross, McAdam, and Walker,[3] is as little as 0.5μg. per kilogram of body weight. Apter and Pfeiffer[5] used doses of 100μg. in their cats, or, assuming a normal 3 kg. cat, 33μg. per kilogram. The effect of pentobarbital must also be considered, since it too[17] has an interaction with the effect of LSD-25. Complexity is added to this already confused picture by the fact that blindness has been found to occur in monkeys[17] given doses of LSD-25 not much higher than that used by Apter and Pfeiffer.

All of this causes us to approach with great caution the drawing of conclusions from any given set of observations. We feel, for example, that the evidence of cats rubbing their eyes, peering into their cages, and grasping the air with their paws, as reported,[5] is rather tenuous evidence for the conclusion that "cats are capable of having hallucinations."[18] Similar effects can be seen upon the administration of drugs, for example, pentobarbital, before the animal loses consciousness.

With due caution, therefore, we should like to suggest the possibility that many of the electrophysiological variations in retinal activity noted as a result of administration of drugs are not entirely due directly to the action of the drugs on the retinal elements themselves but rather are due to effects upon a hypothetical "feedback" type of control, in the form of an inhibitory center in the brain. We feel that many of the observed phenomena can be best explained in this manner.

It is our concept that the purpose of this center is to stabilize the level of retinal impulses at the retinal level. An intense light stimulus, for example, will activate the center which in turn will inhibit the retinal activity level, thus decreasing the visual signal to an interpretable level. A weak signal, on the other hand, will reach the higher levels of the brain uninhibited because the inhibitory center is not stimulated to activity.

External interference with this delicate system by either depression (anesthesia or blood loss) or stimulation (electrical or pharmacological) will then cause an absence of appropriate inhibitory potentials at intense illumination levels or sporadic, uncoordinated bursts of inhibitory potentials in the dark. This is, in our opinion, the source of the spontaneous potentials observed.

A wide variety of drugs at certain dosage levels will probably produce effects similar to those described above. However, in all cases, spontaneous activity of this type is abolished by cephaloretinal interruption, such as optic nerve section.

Summary

Doses of D-lysergic diethylamide (LSD-25) (below 25μg. per kilogram) administered to cats systemically show no effect on the electrical potential of the eye.

Higher doses of LSD-25 (50μg.-100μg. per kilogram) sometimes produce spontaneous potential fluctuations in the intact eyeball of the cat.

Similar potentials can also be observed in animals which have suffered heavy blood loss or overdose of anesthesia (pentobarbital, sodium amobarbital [amytal], or ether).

Those potentials are abolished by section of the optic nerve, increase of anesthesia, or CNS stimulants.

The effect of large quantities of LSD-25 (over 200μg. per kilogram) on the ERG is identical to that observed upon administration of large quantities of pentobarbital.

LSD-25 has no effect upon the ERG of the excised retina of the human, cat, or monkey.

A hypothetical explanation of these phenomena is presented.

880 5th Ave. (21).

REFERENCES

1. Rothlin, E.: Lysergic Acid Diethylamide and Related Substances, Ann. New York Acad. Sc. 66:668, 1957.

2. Hoffman, cited by Rothlin.[1]

3. Mayer-Gross, W.; McAdam, W., and Walker, T.: Psychological and Biochemical Effects of LSD, Nature, Lond. 168:827, 1951.

4. Mayer-Gross, W.; McAdam, W., and Walker, T.: Further Observations on the Effects of LSD, J. Mental Sc. 99:804, 1953.

5. Apter, J. T., and Pfeiffer, C. C.: The Effect of the Hallucinogenic Drugs LSD-25 and Mescaline on the Electroretinogram, Ann. New York Acad. Sc. 66:508, 1957.

6. Jacobson, J. H.; Stephens, G.; Basar, D., and Gestring, G.: Electrical Response of Human Excised Retina, A. M. A. Arch. Ophth. 60:23, 1958.

7. Wohlzogen, F. X.: Beeinflussung des Sauger-ERG durch Zentral Nervos Wirksame Substanzen, Ztschr. Biolog. 108:217, 1956.

8. Noell, W. K.: Differentiation of Visual Cell, A. M. A. Arch. Ophth. 60:702, 1958.

9. Jacobson, J. H., and Gestring, G.: Centrifugal Influence upon the Electroretinogram, A. M. A. Arch. Ophth. 60:295, 1958.

10. Noell, W. K.: The Effects of Iodoacetate on the Vertebrate Retina, J. Cell. & Comp. Physiol. 37:283, 1951.

11. Noell, W. K., and Petersen, P. N.: Retinal Effects of Trichloroethylene, Am. J. Physiol. 187:619, 1956.

12. Granit, R.: Sensory Mechanism of the Retina, London, Oxford University Press, 1947.

13. Noell,[8] p. 722.

14. Purpura, D.: Experimental Analysis of the Inhibitory Action of Lysergic Acid Diethylamide on Cortical Dendritic Activity, Ann. New York Acad. Sc. 66:515, 1957.

15. Urist, M. J.: Afterimages and Ocular Muscle Proprioception, A. M. A. Arch. Ophth. 61:230, 1959.

16. Brock, F. W., and Givner, I.: Fixation Anomalies in Amblyopia, Arch. Ophth. 47:775, 1952.

17. Evarts, E. V.: A Review of the Neurophysiological Effects of Lysergic Acid Diethylamide (LSD) and Other Psychotomimetic Agents, Ann. New York Acad. Sc. 66:479, 1957.

18. Apter and Pfeiffer,[5] p. 512.