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EFFECT OF HALLUCINOGENIC DRUGS ON THE ELECTRORETINOGRAM*

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For the past eight years psychiatrists have been interested in certain hallucinogenic drugs. Since these drugs induce visual hallucinations and changes in the personality in normal human subjects, they have been called "psychotomimetic."

Mescaline is one such drug. Its effects have been well described in the published literature.[5] Its property as psychotomimetic was not emphasized at first. Lysergic-acid diethylamine tartrate (LSD-25), however, is another such drug and has been thought to induce a state resembling schizophrenia.[4,10,11,12]

Up till now, neurophysiologists have studied the effects of these drugs on the brain exclusively.[2,7-9] A perusal of the clinical facts, however, indicates that the retina may be involved in the production of the drug-induced visual hallucinations:

Firstly, patients with optic-nerve blindness do not experience the visual hallucinations.[1,3]

Secondly, the character of the hallucinations is best explained on the basis of intraocular structures.

The characteristics common to all drug-induced visual hallucinations are lattices, honeycombs, and blue-red arcs.[5,6,11]

Thirdly, Kluver[6] has shown that this type of visual experience may be produced by rubbing the eyeball and by exposing the eye to flickering or to intensely bright light.

Because of the associated systemic changes, however, these three facts have not suggested to neurophysiologists that the retina should be studied. They have heretofore confined their efforts to studies of the brains of experimental animals.

It should be stressed that these drugs could not be designated as psychotomimetic unless the brain was the site of origin of the visual hallucinations. It is essential, therefore, that the extent to which the retina participates in this drug action be determined. The results obtained from this study directed toward that end is of great interest to ophthalmologists also. This presentation will describe the unique effects the drugs have on the electrical activity of the visual system of cats.

The study is based on the principle that an electrical potential accompanies activity in any nervous element. Action potentials may be detected anywhere on the surface of the eyeball following marked changes in the illumination of the retina.[4] These potentials indicate activity in the retina and indicate that retinal elements are transmitting impulses. It follows, therefore, that such a retinogram would be induced by the hallucinogens when the illumination of the eye remained constant only if the retina were participating in the production of the spontaneous visual experiences. It seemed worthwhile, therefore, to investigate the effects of these drugs on the retinograms of cats.

METHOD

I. Forty-four cats were anesthetized with intraperitoneal pentobarbital (42 mg./kg.). Two nonpolarizable silver-silver chloride electrodes were sutured under the conjunctiva of each cat and served to pick up potentials from the retina through the sclera. A Grass electroencephalograph recorded these potentials. The efficacy of this procedure in demonstrating the activity of the retina

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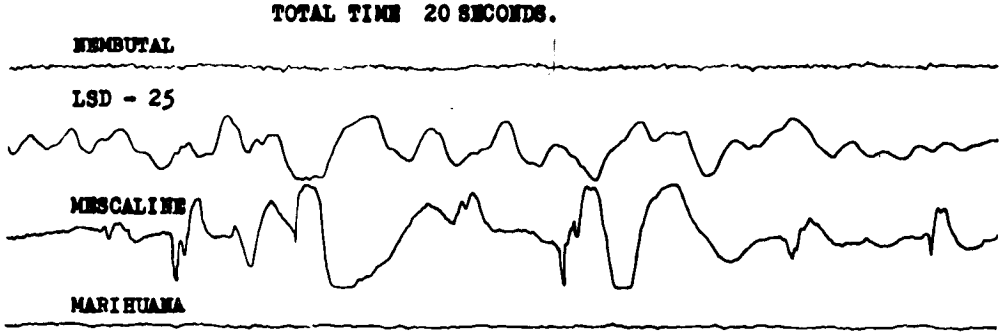

Fig. 1 (Apter and Pfeiffer). Spontaneous potentials from each of four cats, each under the influence of a different drug. (Up is positive.)

was tested by noting the potentials recorded following photic stimulation of the retina. Since evoked potentials appeared consistently at the onset and cessation of this stimulation, this method of pick-up and recording was deemed adequate for this study.

The effects of LSD-25 (25μ/kg.), mescaline (50 mg./kg.), pentobarbital (40 mg./kg.), and dihydrocannabinol (2.0 cc. per cat) on the retinogram and on the resting potentials of the eye were compared in an effort to determine whether the hallucinogenic drugs act directly on the retina.

II. In nine cats, two electrodes were wound around the optic nerve of one eye. In these cases all muscle and nerve connections of that eye were severed to eliminate any contribution nonvisual elements might make to nerve action potentials. The other eye of each of these cats had electrodes applied as in Method I. LSD-25 was injected and its effect on potentials in the optic nerve was studied.

III. In seven cats, two electrodes were placed on each eye as in Method I. Simultaneously a bipolar electrode was placed for pick-up from an exposed area on the occipital visual cortex. The effect of LSD on potentials in this area was noted. Then the effect of section of the optic nerves on the induced LSD-effect was recorded.

IV. In order to ascertain a nontoxic dose of LSD for cats and to determine whether cats experience visual hallucinations with it, 0.10 mg. of LSD-25 was injected into the peritoneal cavity of each of three unanesthetized and unrestrained cats. Their behavior was observed for two hours. In no case were the cats dark adapted.

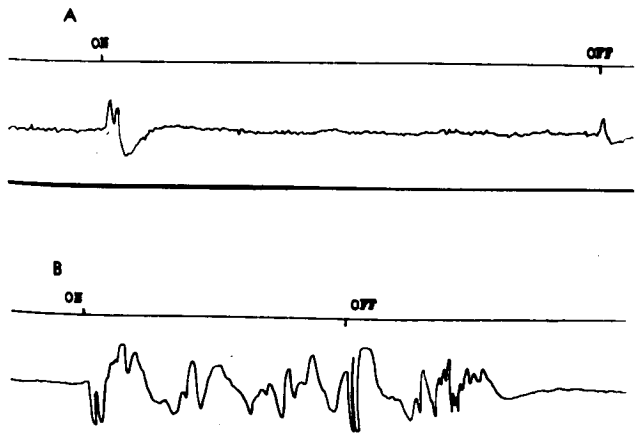

Fig. 2 (Apter and Pfeiffer). (A) Potentials induced by turning a light on and off the cat's retina while anesthetized with Nembutal. (Up is negative.) (B) 15 minutes after administration of 0.10 mg. of LSD-25. (Up is positive.)

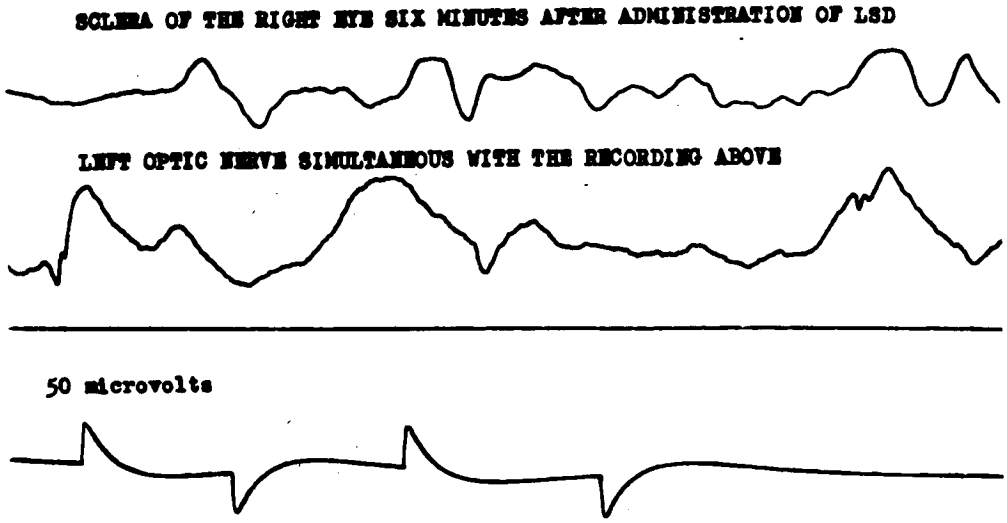

Fig. 3 (Apter and Pfeiffer). Simultaneous pick-up from optic nerve and retina showing spontaneous potentials. (Up is positive.)

Results

I. All 44 cats had a normal resting electroretinogram and a normal response to photic stimulation for about eight minutes. At that time striking changes occurred in the 22 cats that had received LSD or mescaline.

In these cats spontaneous potentials appeared although the illumination to the eyes remained constant. These spontaneous potentials appeared of low amplitude at first (25 microvolts) and increased in amplitude to about 200 microvolts and then gradually decreased in intensity and disappeared.

This build-up and recession of spontaneous potentials was called a "paroxysm." Each paroxysm lasted about 40 seconds and consisted of as many as 50 sharp waves of short duration. Intervening resting periods lasted 60 to 100 seconds. The first or second paroxysm lasted longer and showed higher voltage of potentials than subsequent paroxysms. A single dose of LSD induced about seven to 10 paroxysms of spontaneous potentials.

During the resting periods and for an hour after the paroxysms had ceased, photic

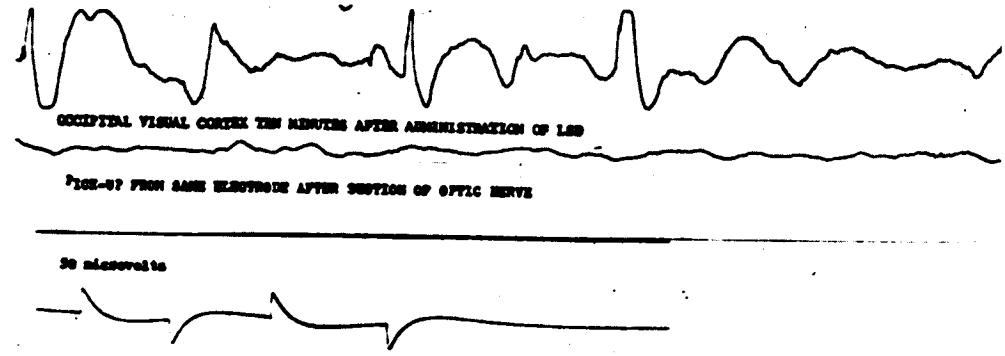

Fig. 4 (Apter and Pfeiffer). Pick-up from occipital visual cortex 10 minutes after the administration of LSD-25 before and after section of the optic nerve. The top record shows spikes induced by LSD; the record below it shows the absence of spikes after section of both optic nerves. (Up is positive.)

stimulation of the retina induced a prolonged evoked electroretinogram. This was characterized by two or three waves (300 microvolts) immediately following the onset of the light and other waves (50 to 150 microvolts) continuing throughout the duration of the photic stimulation. The off-response was of higher voltage than before the drug was administered and was also prolonged.

II. Since the eyes and the animals were immobile during this activity, it did not seem likely that these were motor phenomena. To be certain, however, that these potentials were in the sensory visual pathway, the eye was severed from all muscle and nerve connections except the optic nerve. Pick-up from the optic nerve produced the same picture as the pick-up from the sclera. Section of the optic nerve stopped the potentials in the proximal stump but not in the peripheral stump of the nerve.

III. In four cats pick-up was made from the occipital visual cortex and the sclera simultaneously. Spontaneous spikes appeared on the cortex after ocular paroxysms started. After section of the optic nerves the cortical spikes ceased but the ocular spikes continued for at least four minutes.

IV. In three unanesthetized and unrestrained cats the dose of LSD was administered intraperitoneally and the behavior of the cats was observed. For six minutes the cats rubbed their eyes vigorously. This stopped after four more minutes. Their pupils and lid slits were widely dilated. While the cats rested in a normal crouching position, they moved their heads around in irregular circles as though peering at objects. They moved rapidly backward as though startled by something. They waved a front paw in front of their face as though grasping at some object. This behavior strongly suggested that the cats were having visual hallucinations and it occurred 10 minutes after intraperitoneal administration of LSD. The spontaneous scleral and optic nerve potentials appear 10 minutes after administration of the drug, also.

Conclusions

These experiments demonstrate that a nontoxic dose of LSD-25 induces changes in behavior in cats. This same dose of LSD initiates spontaneous action potentials in the retina of anesthetized cats. The potentials are certainly not induced by muscle activity. Moreover, the cortical activity induced by the drug is dependent upon nervous transmission from the retina and does not appear when the connection with the retina is severed.

These findings are consistent with the clinical data. The objective description of geometric hallucinations induced by LSD in reliable human subjects is best explained on the basis of intraocular structures. In humans with section of the optic nerve, LSD does not induce hallucinations. These facts, coupled with the experimental data, demonstrate that LSD does not induce hallucinations by virtue of an effect on the central nervous system. The facilitation on central synapses produces no effect on the visual pathways unless a visual experience starts in the retina. This facilitation which we have demonstrated in the retina and which Purpura[7] reports in the geniculate body and cortex with mescaline accounts for the complex hallucinations which sometimes appear. They, too, depend on an intact connection from the eye.

These findings lead us to conclude that LSD hallucinations are not similar to psychotic hallucinations. They also introduce a new subject. The study of the effect on the electroretinogram of various hallucinogenic drugs that do not have the undesirable side-effects of LSD and mescaline could prove fruitful in determining the site of pathology in retinal disease.

Summary

1. Spontaneous action potentials appear on the sclera, optic nerves, and occipital visual cortex of cats 10 minutes after systemic administration of lysergic acid diethylamine or mescaline, but not Nembutal or marihuana.

2. Cats seem to experience visual hallucinations 10 minutes after systemic administration of LSD.

3. The optic nerve and cortical potentials cease central to section of the optic nerve.

4. The scleral potentials do not cease after section of the optic nerve.

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References

1. Alema, G.: Rev. Neur., **22**:720, 1952.
2. Evarts, L. W., Freygang, W., Jr., Marshall, W. H.: Effects of lysergic and diethylemine and bufotenine on the electrical activity in the cat's visual system. Am. J. Physiol., **182**:594-598, 1955.
3. Forrer, G. R., and Goldner, R. D.: Arch. Neurol. & Psychiat., **65**: 581-588 (May) 1951.
4. Gastaut, H., Ferrer, S., and Castells, C.: Confinia neurol., **13**:102-120, 1953.
5. Kluver, H.: Mescal, The Divine Plant and Its Psychological Effects. London, Kegan Paul, French, Trubner & Co., Ltd., 1928, p. 109.
6. ———: Mechanisms of hallucinations. In Studies in Personality. New York, McGraw-Hill, 1942, pp. 175-207.
7. Purpura, D. P.: Arch. Neurol. & Psychiat., **75**:122-131, 1956.
8. ———: Arch. Neurol. & Psychiat., **75**:132-141, 1956.
9. Rovetta, P.: EEG and Clin. Neurophysiol., **8**:15-42, 1956.
10. Schwarz, B. E., Bickford, M. B., and Rome, H. P.: Proc. Staff Meet. Mayo Clinic, **30**:407-417, 1955.
11. Stoll, W. A.: Lysergsaure-diethylamid, Schweiz Arch. Neurol. U. Psychiat., **60**:279-323, 1947.
12. Wikler, A.: J. Nerv. & Ment. Dis., **120**:157-175, 1954.

Discussion

Dr. Albert M. Potts (Cleveland): That a study of visual hallucinants might be another lever to pry loose a few more facts about ocular neurophysiology from very resistant bedrock has occurred to a number of us, and Dr. Apter's paper has projected us right into the middle of that particular quarry.

The most striking effect, as far as I was concerned, was the fact that the spontaneous cortical potentials are dependent upon the integrity of the optic nerve under the conditions of these experiments. A fascinating aspect is the suggestion that the geometric nature of the hallucinations may be dependent upon the geometry of the receptor cell mosaic.

There are, however, a number of cautions which should be observed before coming to any final conclusions about the mechanism of action of these drugs. The first of these has to do with the dosage used. Dr. Apter's animals, receiving 100 μg. LSD per cat and 150 mg. of mescaline per kg. of cat, were receiving 10 or more times the customary human dose, and the mescaline dose was an LD^{100} for these animals.

So, we are dealing with a drug effect, at a dosage a whole order of magnitude higher than that used in humans. As a matter of fact, if one assumes a two to four kg. cat and a dose of something like 25 mg. per kg., the customary hallucinogenic dose for humans at 0.5 to 1.0 mg. per kg. is close to one fiftieth of the amount used in these experiments.

The features shown in the electroretinogram are also curious to us in the light of work that we have been conducting, particularly with mescaline, along the same lines. Dr. Wiedenthal and I have been working on the subject for six months now. Our mescaline dosages were approximately 15 mg. per kg., one tenth of that used in the paper reported. We find something that is considerably different.

Instead of a response that is characterized by an unusual spike in the negative deflection, followed by the spontaneous potentials, we find on our doses—which are much lower, to be sure—an apparently nonspecific accentuation of the a-wave compared to the normal and complete abolition of the b-wave.

This, as you may remember, was an effect similar to that observed on the administration of formaldehyde. We have no explanation for its basic physiology, but it seems to bear little relationship to the effect reported in the paper. This certainly is a big area for exploration.

The effect described by Rovetta should also be thought of in connection with the spontaneous potentials, particularly in the cortex, observed here. Rovetta found that local application of strychnine or mescaline to the cortex caused evocation of spontaneous potentials. We might well think of these effects as comparable to those of the photoanaleptic synergism in causing seizures. Here the dosage of analeptic drug itself (ordinarily metrazol) is not at seizure level but, when light stimuli are added, the net result is epileptiform electroencephalograph findings plus epileptic seizures.

It is quite conceivable that in the same way the dosage of hallucinogenic drugs at these high levels causes a lowering of the irradiation threshold so that the light stimulus causes another unusual

thing—spontaneous potentials in the central nervous system.

In the light of this report, and previous ones, there seems to be a considerable amount to be learned about how the visual system works from a study of hallucinants and their antagonists. However, a great deal of this study still lies before us.

DR. WERNER K. NOELL (Buffalo, New York): A year or so ago when it was suggested that Reserpine might exert its action via the serotonin system, we tested in a few experiments on rabbits whether serotonin or lysergic acid would affect the electroretinogram, specifically whether these agents would interfere with the electrically measured function of the pigment epithelium. Dr. Ruedemann, Jr., and I had just found that adrenalin produces specific changes of this function but this effect was rather small with low doses and we wondered whether any other hormone might control the ion transport function of the mammalian pigment epithelium. Moreover, the peripheral circulatory effects of Reserpine are somewhat similar to those of sodium azide and sodium azide has the most powerful action upon the electrical processes which depend upon pigment epithelial functioning.

The experiments to which I referred had negative results, that is, the electroretinogram (a-, b-, and c-waves) were not specifically affected by these agents and the D.C. potential across the eye did not change appreciably nor did the response to azide. I am quite thrilled, therefore, that Dr. Apter's experiments, which differ from ours with respect to animal species and pick-up technique, were so obviously successful. We may have done something wrong. But, it would be interesting to know whether the spontaneous activity which Dr. Apter recorded was associated with an increase in the D.C. potential across the eye. If this were the case, caution should be exercised in the interpretation of A.C. fluctuations because a high D.C. potential across the eye renders the A.C. recording susceptible to all kinds of artefacts; I then also would prefer optic tract recordings to recordings from the optic nerve; changes in neuronal discharge activity I would determine by microelectrode recordings from the retinal ganglion cells.

I would like to mention a further experience of ours. Dr. Petersen and I just completed a study on the retinal effects of trichloroethylene, "Trilene." Trilene is a powerful analgetic and frequently used in neurosurgery. We were interested in its cerebral effects but to our great surprise we found—as it has happened often in our laboratory—outstanding retinal changes. I would like to mention the ability of this agent to increase the amplitudes of the electroretinogram, to transform a photopic electroretinogram into a scotopic one, and to increase the synchronization of certain retinal activities. Here, then, is another agent—known and used for its psychic effects—which affects retinal function and which permits us to analyze phenomena and mechanisms of its action on a much simpler system than the brain. I am certain that once the biologic reality of the phenomena which Dr. Apter recorded have been proven beyond any doubt, it will be possible to pinpoint their anatomic and physiologic origin. I agree with Dr. Potts, that Dr. Apter's studies deserve the most serious consideration.

DR. JERRY HART JACOBSON (New York): After talking to Dr. Apter a few months ago about her interesting findings, I decided to try this on a few humans. We have been able to find only one cooperative individual so far, and unfortunately he did not have hallucinations; so we are in a bit of difficulty.

We did, however, give one human being 50 mg. of LSD, and recorded for a period of two hours his spontaneous reactions and his reactions to light stimuli.

It was impossible to judge any outcome from his spontaneous activity. As any of you who have done any clinical retinography know, the slightest eye motion produces a potential very similar to that which was seen here; and in so far as the reactions to light stimuli were concerned, we could find no effect in this particular individual.

Again I would like to emphasize that he did not suffer hallucinations.

DR. JULIA T. APTER (Manteno, Illinois): I want to thank the discussers. I think their contributions all were most applicable to the problem of the effect of drugs on the electroretinogram.

I do feel that even if these spontaneous potentials in the retina are due (as Dr. Noell says) just to a breakdown of an increase of a drug-induced D.C. potential that has been produced by the A.C. amplifier; even that will stimulate us to find out more about the meaning of action potentials on the retina in other cases, and in normal eyes. Perhaps we do not yet know the full significance of action potentials. This particular drug and others like it may open the field and help us to discover more about that.

However, since the spontaneous potentials induced by LSD in the electroretinogram occur only when the retina is illuminated (they are not present in the dark) this would indicate that these spontaneous potentials are indicative of spontaneous (not evoked) retinal activity. In that case we might assume that the retina participates in the production of visual hallucinations induced by LSD-25.