The Effect of Two Hallucinogenic Agents on Human Retinal Function

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It has been shown in previous studies that visual hallucinations are part of the total response to both *d*-lysergic acid diethylamide (LSD-25)[1,2,3] and *n*-ethyl-3-piperidyl benzilate hydrochloride (JB 318).[4,5] It has never been demonstrated, however, where these drugs act to induce this phenomenon. Since visual hallucinations can arise from any level of the visual pathways (i.e., retina to the cerebral cortex),[6] the problem of defining the hallucinogenic mechanism is quite complex. Various workers have attempted to gain insight into this problem by studying the effects of hallucinogenic drugs on different levels of the visual pathways. The objective techniques used have been primarily electrophysiological and most of the studies have been done on animals. Drug effects have been noted on (1) cortical potentials, both spontaneous and evoked, (2) synaptic transmission at different levels of the visual system, and (3) optic tract responses to photic stimuli. Retinal function evaluation has included both electroretinographic and visual threshold studies.

Purpura[7,8] found that doses of LSD up to 60μg. per kilogram caused facilitation of cortical responses to photic stimulation in unanesthetized paralyzed cats. Inhibition of these induced potentials occurred at doses of 70μg.-100μg. per kilogram.[9] Purpura also found that the visual cortical response to lateral geniculate body stimulation was facilitated with LSD while the response to suprasylvian stimulation was inhibited. Various workers have observed changes in the electroencephalogram (EEG) after LSD in both man and animals.[10] The changes usually observed involved the loss of alpha waves and the occurrence of the "arousal" pattern, i.e., low amplitude fast activity. Rinkel et al.[11] and Gastaut et al.[12] found slight increases in the frequency of the alpha rhythm in most human subjects.

Evarts et al.[13] studied the effects of LSD (1 mg. per kilogram) on synaptic transmission in the visual system of the cat. They found a pronounced decrease in the amplitude of the geniculate postsynaptic response to optic nerve stimulation, while certain synapses—those of the retina and those between the lateral geniculate radiations and visual cortex cells—proved to be extremely resistant to any blocking effects of this drug. They also noted that large doses of LSD (2.5 mg. per kilogram) caused a decrease in the amplitude of the optic nerve response to photic stimulation of the retina.

The electroretinogram (ERG) has been evaluated primarily in animals.[14-19] Apter and Pfeiffer[14,15] gave 0.10 mg. of LSD (33μg. per kilogram) to anesthetized cats and found that spontaneous retinal potentials occurred about 10 minutes later. At the same time spontaneous potentials from the optic nerve and large spikes from the visual cortex were also recorded. If the optic nerve was sectioned while spontaneous potentials were recorded the spikes in the occipital cortex and the potentials in the proximal stump of the optic nerve disappeared whereas those in the distal stump of the optic nerve and retina persisted. After the spontaneous retinal potentials disappeared, the entire ERG complex was in-

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creased in amplitude and prolonged in duration.

In other reports [16,17] Apter noted the same ERG findings in cats after administration of mescaline, strychnine, and atropine. In addition, all drugs used were found to prolong the presence of a detectable ERG in enucleated cat eyes. LSD prolonged this response to 5 to 12 minutes as against the usual duration of 2 to 4 minutes in controls.

Evans, Jacobson, and Gestring [18] studied the effect of LSD (50μg.-75μg. per kilogram) on the ERG in the opossum and noted, in most records, "spike-like activity" which disappeared within 24 hours. Jacobson and Gestring [19] found that doses of LSD smaller than 25μg. per kilogram had no effect on the ERG of the cat, but doses greater than 50μg. per kilogram sometimes produced spontaneous potentials. The authors noted no effects of LSD on the excised retina of man, cat, or monkey.

Only one electroretinographic study with a human subject has been previously reported. This subject, studied by Jacobson,[14] received 50μg. of LSD and did not report hallucinations. No changes were noted in the ERG.

Visual threshold studies have been reported both in animals [20] and in man.[21] Blough studied the effect of LSD on the absolute visual threshold of the pigeon [20] and found a substantial elevation of this threshold. The largest rise was about 1.8 log units and the elevations had diminished considerably in 5 hours. Within 24 hours all thresholds were back to normal levels.

Carlson [21] studied the effect of LSD on the absolute visual threshold in man. He tested 9 normal subjects and varied the pupillary control by using a 2 mm. artificial pupil in 4 subjects, homatropine dilatation in 2 subjects, and a natural pupil in 3 subjects. The drug was given intravenously one hour before testing. A dose of 50μg. was used in 3 subjects and 100μg. in 6 subjects. He found that threshold values for the entire adaptation curve were raised a small but definite amount. The cone portion was elevated more than the rod portion of the curve. No effect was noted on the rate of adaptation. Because of the consistency of subject responses the author did not feel that inattention, impaired ability to concentrate, or possible interfering visual hallucinatory effects caused the elevation of threshold.

In the previously cited studies, LSD and mescaline, drugs with similar central and autonomic nervous system effects and chemical structure, were the hallucinogens employed. In the present study, the two drugs used, LSD and JB 318, are similar in hallucinogenic properties but differ in chemical structure and in certain autonomic and somatomotor effects. LSD is an indole amine with adrenergic autonomic effects; JB 318 is a piperidyl derivative with anticholinergic properties. The hallucinogenic effects of the two drugs overlap but differ in some respects. LSD is more likely to induce brightly colored, vivid, but simply structured hallucinations such as mosaics, rings, dots, and clouds; after JB 318 images are more likely to be gray, white, or black and include people, faces, landscapes, and animals.

It is evident that hallucinogenic properties of drugs can be studied only in conscious and cooperative man. The purpose of the present study therefore was twofold: (1) to evaluate the effects of two hallucinogenic drugs on retinal function in man, and (2) to relate possible retinal effects to the occurrence of hallucinations.

Method

Retinal function was studied with the ERG and the dark-adaptation curve. Color vision testing was also done in 7 subjects. A total of 40 experiments was carried out on 19 medical students. Twelve were males, all were between 21 and 30, and all were trained subjects, having participated in drug studies previously. All had normal ophthalmological findings and were free of psychotic or major neurotic disorders. The subjects were informed that they would receive either a hallucinogenic or nonhallucinogenic drug

and were instructed to report all bodily and mental changes in detail. Drugs were administered by the oral route with subjects in the fasting state.

Three kinds of drug experiments were carried out. 1. Ten subjects on 13 occasions received large hallucinogenic doses of LSD or JB 318; i.e., 75μg. to 100μg. LSD or 7.5 to 15.0 mg. JB 318. 2. To determine if retinal effects of these agents were dose dependent, 5 subjects on 5 occasions received smaller nonhallucinogenic doses, i.e., 2.5 to 5 mg. JB 318 or 25μg. LSD. 3. Four subjects received one nonhallucinogenic analogue of LSD or JB 318. These analogues, 1 methyl-d-lysergic acid butanolamide tartrate (UML-491) and N-ethyl-3-piperidyl diphenyl acetate (JB 808), in the doses employed herein, exhibited no psychotomimetic properties in preliminary studies but induced autonomic effects qualitatively similar to the hallucinogenic agents.[23] The rationale for employing the analogues was as follows. If retinal effects occurred with both hallucinogenic and nonhallucinogenic agents they probably were not related to the hallucinogenic properties but to some other effect that each drug and its analogue have in common. On the other hand, if only the hallucinogenic drugs induced retinal effects, these effects are probably intimately related to the hallucinogenic properties.

Approximately half the subjects received a drug on the first trial and no drug at the second trial, thus serving as their own controls; the other half served as controls first and received the drugs on a later trial. Fourteen subjects participated in one drug trial, and 5 subjects participated in at least two drug trials. The frequency distribution of drugs and doses is shown in Table 1. For both the control and the drug trials the subjects reported to the laboratory in the fasting state; their pupils were dilated; and an initial ERG and dark-adaptation curve were obtained. In the control trial the studies were repeated after one hour. In the drug trial the agent was administered orally and the ERG and dark adaptation studies were repeated after the subjects

TABLE 1.—*Distribution of Drug and Control Trials*

Drug	Dose	No. of Drug Trials	Subjects Reporting Visual Changes	No. of Control Trials
LSD	25.0 μg.	2	0	
	75.0 μg.	7	7	7
JB318	2.5 mg.	1	0	
	5.0 mg.	2	0	
	7.5 mg.	1	1	1
	10.0 mg.	6	5	6
	12.5 mg.	1	1	1
	15.0 mg.	1	1	
UML	2.0 mg.	1	0	
	4.0 mg.	1	0	
JB808	5.0 mg.	1	0	
	10.0 mg.	1	0	

reported illusions and/or hallucinations; if these effects were not reported, the studies were repeated in about an hour. When retinal functions were not being measured dim illumination was maintained in the room. Brief interviews were carried out at intervals of 5 to 10 minutes to determine the occurrence of psychological effects. Simple hallucinations were defined as those consisting of circles, dots, clouds, mosaics, etc. Complex hallucinations were defined as those consisting of faces, people, animals, landscapes, etc.

In all subjects one eye was used for adaptation studies and the other for ERG testing; the untested eye was always patched. Both eyes were dilated with cyclopentolate hydrochloride (Cyclogyl); the testing was begun 30 to 45 minutes after the last application, at which time the pupillary size usually measured between 8 and 8.5 mm. The patient was first placed in complete darkness for 3 minutes and then exposed to a preadapting illumination of 2,400 lux for 7 minutes. Dark-adaptation threshold measurements were begun immediately at the completion of preadaptation; scotopic electroretinographic testing was started 10 minutes later.

Adaptometry was done with the Goldmann-Weekers adaptometer. Prior to experimental trials all subjects received one training session in which the full test was

carried out. The purpose of the test was explained at that time. The subject fixated on a 2 mm. red light of variable brightness located about 10 degrees above the center of the test object, which was an opal disc of 5.6 cm. in diameter subtending a visual angle of about 11 degrees. The stimulus was presented in the form of light flashes of one second in duration, the dark interval also being one second. The test light was calibrated at a maximum intensity of 6 lux and at the onset was presented at an intensity of 0.6 lux with the subsequent direction of change dependent on the response of the subject. An attempt was made to maintain a constant rate of change of stimulus intensity. Both the "on" and "off" thresholds were noted and the approximate true absolute threshold was calculated as an average of these values according to the method of Gunkel and Bornschein.[24] Each subject was tested for a total of 30 minutes with the responses being charted continuously during the first 3 minutes, at half-minute intervals during the next 7 minutes, and every minute for the remainder of the test. The subject was always notified immediately before the test light was presented and before a rest period. Between each rest period 4 "on" and 4 "off" responses were charted, and the consistency of these responses gave a good indication of the reliability of the subject.

The evaluation of the dark-adaptation curve was based on measurement of (1) the times of the final cone threshold, rod-cone break, and final rod threshold; (2) the value of the final cone threshold, and (3) the value of the rod threshold at 8, 10, 15, 20, 25, and 30 minutes.

The electroretinographic examination included an evaluation of scotopic single flash responses at 4 or more intensities and scotopic single flash responses at the lowest intensity with a blue filter. The subject was at rest on a bed and the lamp, a Grass PS-1 photic stimulator, was centered 24 in. above the tested eye. A 1.5 mm. red fixation light was placed below the center of this lamp. The active electrode, a Burian-Allen contact lens, was placed on the cornea of the eye to be tested and the indifferent electrode on the bridge of the nose. The ground electrodes were placed either on the forehead or on both ears. The stimulus intensity was varied by using the different intensity settings on the photic stimulator. At each intensity an attempt was made to obtain at least 3 good responses in terms of steadiness of baseline and consistency of response. A time interval of at least one-half minute between the lower intensity stimuli and one minute between the higher intensity stimuli usually sufficed to prevent a change in amplitude in succeeding scotopic responses. A blue stimulus was obtained by the use of a Grass Wratten filter which had a peak transmission of about 55% at 450 mμ with less than 1% transmission at 570 mμ. Recordings were obtained with the direct ink-writing Grass electroencephalograph. The pens were calibrated so that a deflection of 4 mm. equaled 100μv.; a second channel with a calibration of 4 mm. for 200μv. was also used with large amplitude responses.

The evaluation of the ERG included 3 measurements, on a millimeter ruler, of the a- and b-wave amplitudes at each intensity. Two observers made measurements to offset possible errors.

Color testing was done with Hardy-Rand-Rittler (H-R-R) pseudoisochromatic plates. Seven subjects were color tested before and after the administration of a drug.

Results

Fifteen subjects experienced visual hallucinations after the larger doses of LSD or JB 318. Only 2 subjects of this group described complex hallucinations (both with JB 318), and all of this group described simple hallucinations. In addition, 2 subjects receiving LSD and 4 subjects receiving JB 318 reported auditory hallucinations. In all 15 subjects illusions were also noted. Six subjects who received the lowest dosage of these drugs did not report hallucinations

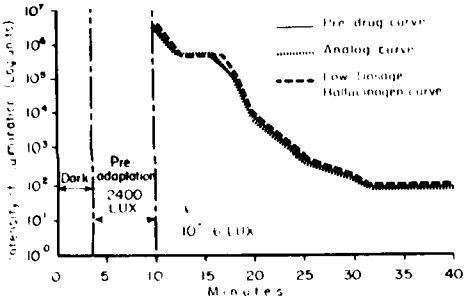

Fig. 1.—Dark-adaptation curves for trials with nonhallucinogenic analogues and low-dosage hallucinogens. Values of each curve were plotted from averages of all trials.

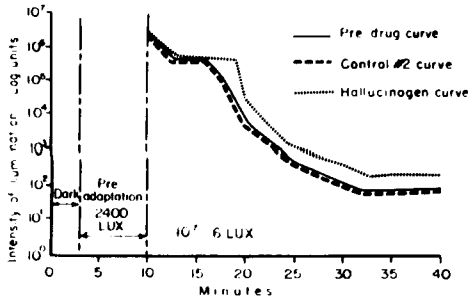

Fig. 2.—Dark-adaptation curves for trials with hallucinogens and with no drug (control). Values of each curve were plotted from averages of all trials.

(Table 1); 5 of these 6 subjects received a larger dose of drug at a different trial and at that time did report hallucinations. One subject did not hallucinate at an expected hallucinogenic dose (10 mg. of JB 318).

Dark-adaptation studies revealed essentially similar findings for control, nonhallucinogenic analogue, and low-dosage hallucinogen trials (Figs. 1 and 2). The average differences between the threshold values of the first curve (first control or predrug curve) and those of the second curve (second control or postdrug curve) were always less than 0.2 log unit—most often less than 0.1 log unit. All values of the second curve tended to be slightly lower than those of the first. The time values were almost the same for first and second curves—the largest difference being about one minute. The dark-adaptation curves during the period when hallucinations were reported (Fig. 2) showed a different pattern. All the rod threshold values of this curve were noticeably higher than the predrug curve, and the rod-cone break usually occurred later. The average rod threshold differences between predrug and postdrug curves ranged from 0.4 to 0.7 log units and the average rod-cone break was delayed about three minutes in the postdrug curves.

An example of the findings in one subject is shown in Table 2. This subject experienced some peripheral autonomic effects with the 5 mg. dosage of JB 318, but re-

TABLE 2.—*Dark Adaptation Findings in One Subject*

	Control #1	Trial #2	JB 318 5 Mg. Before	JB 318 5 Mg. After	JB 318 10 Mg. Before	JB 318 10 Mg. After	Changes: Control Trial	Changes: JB 318 5 Mg.	Changes: JB 318 10 Mg.
Time of Final Cone Threshold	2.5	2	3.5	4	2	2.5	−0.5	+0.5	+0.5
of Rod-Cone Break	8	6.5	8	7.5	6	8.5	−1.5	−0.5	+2.5
of Final Rod Threshold	23	23	26	26	26.5	26.5	0	0.5	0
Value at Final Cone Threshold	4.3	4.3	4.2	4.1	4.3	4.5	0	0.1	+0.2
Rod-Threshold at 8 minutes	4.2	4.1	4	3.7	3.8	4.5	−0.1	0.3	+0.7
at 10 minutes	3.7	3.6	3.3	3.3	3.3	4.1	0.1	0	+0.8
at 15 minutes	2.3	2.4	2.1	2.3	2.2	2.4	+0.1	0.1	+0.2
at 20 minutes	1.8	1.8	2.2	2	1.6	2.1	0	0.2	+0.5
at 25 minutes	1.7	1.6	1.8	1.8	1.5	2.0	0.1	0	+0.5
at 30 minutes	1.3	1.4	1.6	1.5	1.3	1.9	+0.1	−0.1	+0.6

Time in minutes 10⁷=6 Lux Values in Log Units

TABLE 3.—*Changes in Second ERG (Microvol s)*

	Control Trials (15)			Analogue Trials (4)			Low-Dosage Hallucinogen Trials (6)			Hallucinogen Trials (15)		
	$\Delta\bar{A}$	$\Delta\bar{B}$	R ΔB	$\Delta\bar{A}$	$\Delta\bar{B}$	R ΔB	$\Delta\bar{A}$	$\Delta\bar{B}$	R ΔB	$\Delta\bar{A}$	$\Delta\bar{B}$	R ΔB
Intensity 1	−10	−22	0 to −75	− 6	−31	−25 to −50	− 6	−28	−25 to −37.5	+11	+37	+25 to +75
Intensity 2	−14	−25	0 to −50	+ 6	−19	0 to −25	− 6	−25	0 to −75	+16	+27	0 to +50
Intensity 4	−21	−25	0 to −50				− 4	− 4	0 to −12.5	+14	+34	+12.5 to +75
Intensity 8	−20	−31	0 to −75	−13	−25	0 to −50	0	− 7	0 to −25	+ 8	+41	+25 to +100
Intensity 16	−16	−23	0 to −50	−13	−25	0 to −50	−20	−24	0 to −67.5	+15	+32	0 to +100
Blue Filter Intensity 1		−15	0 to −25		−31	0 to −75		−25	0 to −67.5		+37	+25 to +75

$\Delta\bar{A}$ = Average change of A-wave.
$\Delta\bar{B}$ = Average change of B-wave.
R ΔB = Range of average B-wave change.

ported hallucinations only after the 10 mg. dose.

Three subjects showed a slight variability of response during the first five minutes of postdrug testing not noted in the predrug trial; however, in no other instances did the reliability of performance appear to be affected by the presence of hallucinations or other effects. This reliability was estimated by the consistency of the responses, evenness of the curves, and spread between the "on" and "off" thresholds.

The ERG changes are summarized in Table 3. The effect of the retest on a- and b-wave amplitudes was similar in control, nonhallucinogenic analogue and low-dosage trials. The a-wave usually remained about the same or showed a slight decrease in amplitude whereas the b-wave usually decreased in amplitude on repeat testing.

In contrast to these results, records obtained after subjects reported hallucinations almost always revealed an increase in the b-wave amplitude and very frequently the a-wave amplitude. The average amplitude increase for the b-wave was 27 to 41μv. (Table 3); that for the a-wave was from 8 to 16μv. The range of b-wave amplitude changes included increases up to 100μv. The changes in amplitude at 4 intensities are shown in 1 subject at a 10 mg. dose of

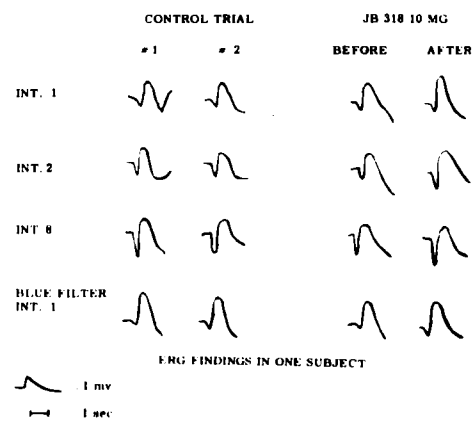

Fig. 3.—ERG findings in one subject showing a control trial and a hallucinogen trial (JB 318). Note decrease in amplitudes in second column (control No. 2 record) and increase in amplitude in fourth column (postdrug record).

JB 318 (Fig. 3). In this subject the second record in the control trial shows a slight decrease in a- and b-wave amplitudes whereas an increase in amplitudes is seen at all intensities after JB 318.

Color testing of 7 subjects with the H-R-R pseudoisochromatic plates did not reveal any differences before and after either hallucinogenic drug at the larger doses.

A statistical analysis was made of the changes in the ERG and in dark adaptation. The ERG data analyzed included the a-wave and b-wave amplitude changes at all intensities for all experiments. The adaptation data evaluated included the change in time of the rod-cone break and the change in the rod threshold values in every experiment.

The question asked of the data was: Is there a significant change in pertinent aspects of the electroretinograms and dark-adaptation curves after second control trials, smaller doses of hallucinogenic drugs, nonhallucinogenic analogues, and larger doses of hallucinogenic drugs? No assumptions were made about the form of the distribution of the data and the direction of results was not predicted in advance. Therefore, a two-tailed nonparametric test, the Wilcoxon matched-pairs signed-ranks test, was employed.[25]

There was no major difference in any aspect of the data between the first and second control measurements, and between the predrug and postdrug measurements for the smaller doses of JB 318 and LSD and for the nonhallucinogenic analogues. In general, there was a tendency for both a- and b-waves to diminish slightly in size during the second control measurements as compared to the first. The same minor decrease on retesting was also apparent in those experiments in which a smaller dosage of the hallucinogenic agents or nonhallucinogenic analogues were administered.

The analysis for the larger doses of LSD and JB 318 was done both for each drug separately and for the two drugs together. The only essential difference between the two analyses was in the significance of the a-wave changes.

The calculations for the two drugs together are shown in Tables 4 and 5. Significant changes ($p<0.01$) include (1) delay in the rod-cone break, (2) elevation of the rod thresholds at each time period, and (3) increase in the amplitude of the b-waves at every intensity. The changes in the a-wave amplitude were not uniformly significant. For the analysis involving both drugs together the changes in the a-wave were significant ($p<0.05$) at intensities 1,

TABLE 4.—*Statistical Evaluation of Adaptometry Differences by Wilcoxon Matched-Pairs Signed-Ranks Test*

Drug Dose	Differences Rod-Cone Break Time *	Differences Rod-Threshold 10 Minutes †	Differences Rod-Threshold 20 Minutes †	Differences Rod-Threshold 30 Minutes †
LSD-75 μg.	+2.0	+0.6	+0.3	+0.1
-75 μg.	+3.0	+0.6	+0.2	+0.3
-75 μg.	+3.0	+1.0	+0.3	+0.6
-75 μg.	+1.5	+1.0	+0.5	+0.1
-75 μg.	+2.0	+0.9	+0.6	+0.6
-75 μg.	+7.5	+1.4	+1.0	+0.6
-75 μg.	+1.5	+0.6	+0.2	0
JB318-15 mg.	+3.0	+0.6	+0.2	0
-12.5 mg.	+3.0	+0.9	+0.5	+0.7
-10 mg.	0	0	0	0
-10 mg.	+2.5	+0.8	+0.5	+0.6
-10 mg.	+1.5	+0.1	0	+0.1
-10 mg.	+2.5	+0.3	+0.1	+0.7
-10 mg.	+2.5	+0.3	+0.3	+0.1
-7.5 mg.	0	0.1	0	+0.3
* In minutes	N = 13	N = 14	N = 12	N = 12
† In log units	T = 0	T = 1.5	T = 0	T = 0
	P < .01	P < .01	P < .01	P < .01

TABLE 5.—*Statistical Evaluation of ERG Differences* by Wilcoxon Matched-Pairs Signed-Ranks Test*

	Differences Int. 1		Differences Int. 2		Differences Int. 4		Differences Int. 8		Differences Int. 16		Differences Blue Filter
Drug Dose	A	B	A	B	A	B	A	B	A	B	B
LSD-75 μg.	+25	+25	+25	+25	0	+25	+25	+25	0	+50	+25
-75 μg.	+50	+25	+25	+25	0	+25	0	+25	0	+25	+25
-75 μg.	0	+25	0	+25	+25	+25	0	+25	+25	+25	+25
-75 μg.	0	+50	0	+50	+50	+50	+50	+100	+50	+100	+50
-75 μg.	0	+25	0	+25	+25	+50	+25	+50	+50	+50	+50
-75 μg.	0	+25	0	+25	0	+25	0	+25	+25	+25	+25
-75 μg.	0	+25	+25	+25	+25	+50	0	+50	0	+25	+50
JB318-15 mg.	+12.5	+60	0	+12.5	−67.5	+25	−25	+50	0	+75	0
-12.5 mg.	0	+75	0	+37.5	0	+37.5	+12.5	+100	0	+25	+50
-10 mg.	0	+50	+50	+37.5	0	+12.5	0	+37.5	+25	0	+12.5
-10 mg.	+25	+40	0	+50		+25	+12.5	+37.5	+37.5	+25	+25
-10 mg.	0	+25	0	+12.5	0	+12.5	−25	+12.5	−25	+25	0
-10 mg.	+25	+50	+50	+50	+75	+85	+25	+50	0	+25	+75
-10 mg.	+25	+25	+25	0		0	+50	+25	+25	+25	+25
- 7.5 mg.	+12.5	+67.5	+25	+37.5	+50	+37.5	+12.5	+50	+25	+25	+37.5
	N=7	N=15	N=7	N=14	N=7	N=14	N=10	N=15	N=9	N=14	N=13
	T=0	T=0	T=0	T=0	T=6	T=0	T=12	T=0	T=6	T=0	T=0
	P <.05	P <.01	P <.05	P <.01	P <NS	P <.01	P <NS	P <.01	P <.05	P <.01	P <.01

* All differences in microvolts.

2, and 16 and not significant at intensities 4 and 8. When the effects of both drugs were evaluated separately the a-wave changes were not significant at any intensity. Since the a-wave is usually more resistant to circulatory or drug effects it is not surprising that the amplitude changes were smaller and less frequent than those of the b-wave.

Comment

The results of the dark adaptation and ERG studies demonstrate significant changes in retinal function in association with hallucinations.

The changes in visual threshold or dark adaptation were evident in the entire rod portion of the curve and indicated a mild impairment of rod function. These changes consisted of an elevation of the entire rod adaptation curve and a delay in the rod-cone break. The absence of change in the cone portion of the adaptation curve indicates a lack of measurable drug effect on cone function.

The finding of an increase in the amplitude of the b-wave of the ERG can be interpreted in several ways. An improvement in retinal function or an increase in retinal blood flow could produce such a change. To interpret this change as an improvement of retinal function is unreasonable in this study, since a corresponding improvement of dark adaptation, rather than the impairment which occurred, would be expected. It is also unlikely that a change in retinal blood flow occurred, since it has been shown that there is no change in cerebral blood flow under the influence of LSD.[26]

An increase in the scotopic b-wave has been noted in mild circulatory disturbances in man. This response, designated as "supernormal" by Karpe,[27] has been described in patients with papilledema,[28] early, incomplete, or branch venous obstructions,[29] branch arteriolar obstructions,[30] hypertension,[31] and in the congestive phase of acute glaucoma.[28] Finally, a retinal toxin in low doses or as an initial effect of any dose may produce an increase in the scotopic b-wave. Noell has noted this effect in rabbits with sodium azide, pentobarbital (Nembutal), and trichloroethylene in low doses.[32] Granit demonstrated that the scotopic b-wave is markedly decreased in amplitude during prolonged use of ethyl-ether.[33] He indicated that, at times, an initial effect may be a temporary increase in the b-wave amplitude. Nakajima demonstrated an increase in the

scotopic b-wave amplitude as a temporary initial change caused by many of the aminophenoxyalkane compounds in rabbits; these agents eventually produced a depression of this wave and ultimate retinal damage.[34] In another study the same author reported the effect of 6 compounds causing an inhibition of retinal respiration and 4 compounds causing an inhibition of retinal glycolysis.[35] All of the inhibitors of retinal respiration and certain dinitriles (glycolysis inhibitors) caused an initial increase in the scotopic b-wave. The b-wave eventually decreased in amplitude corresponding to a degeneration of the retina.

In the present study, in view of the visual threshold findings, we interpret that the increase in amplitude of the scotopic b-wave is caused by an impairment of retinal function such as might occur after a mildly toxic agent or during a hypoxic period.

We have not attempted to measure effects other than those on the retina. Whether or not the hallucinogenic agents had other effects on the visual apparatus, it is clear that they induced retinal changes at the same time they induced hallucinations. These findings suggest that these hallucinations may be mediated, at least in part, through changes in retinal function. A previous report citing the failure of LSD (1μg. per kilogram) to induce hallucinations in two blind subjects with optic nerve pathology lends support to this thesis.[36] One subject had a history of methyl alcohol poisoning and the other a severed optic nerve caused by a gunshot wound.

Summary

The retinal effects of 2 hallucinogens, N-ethyl-3-piperidyl benzilate hydrochloride (JB 318) and *d*-lysergic acid diethylamide (LSD-25), were studied in 19 trained human subjects. The drugs were used in both hallucinogenic and nonhallucinogenic doses. The retinal effects of 2 analogues of the hallucinogens were also studied. These drugs, N-ethyl 3-piperidyl diphenyl acetate (JB 808) and 1-methyl d lysergic acid butanolamide tartrate (UML-491), had autonomic and central effects similar to the hallucinogenic drugs but did not produce hallucinations. The retinal functions studied were dark adaptation and electroretinographic responses.

Fifteen subjects hallucinated after larger doses of either JB 318 or LSD 25 and significant changes in the ERG or in dark adaptation values occurred. In the ERG the primary change was a consistent increase of the scotopic b-wave amplitude. The a-wave amplitude also increased in many records after larger doses of the hallucinogenic agent. In dark-adaptation studies the changes were an elevation of the entire rod threshold and a delay in the rod-cone break.

No significant changes in retinal function were found in 6 subjects receiving smaller nonhallucinogenic doses of LSD and JB 318, in 4 subjects receiving nonhallucinogenic analogues of these agents, and in 14 subjects participating in control trials without drugs.

The changes noted were interpreted as hypoxic or toxic retinal effects of the hallucinogen. The findings indicate that the hallucinogenic effect of these psychotomimetic agents is related to concomitant changes in retinal function.

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