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Effects of LSD on the Spontaneous and Evoked Activity of Retinal and Geniculate Ganglion Cells

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Summary. The effect of LSD 25 (i. v. injection) on the spontaneous and evoked activity of the visual system was investigated in cats. 50 γ/kg did not change significantly the ERG and the visual cortical evoked potential. The spontaneous discharge rate of 14 out of 21 retinal ganglion cells showed an increase which reached its maximum within 20–30 min and which could still be present 1 hour following the injection. One third of the retinal units showed a slight depression of their spontaneous discharge rate with about the same time course. Single units of the LGN showed about the same behaviour. The response to light stimulation was slightly increased in some units and light induced inhibition was slightly shortened. The possible mechanism of the LSD-effect on retinal ganglion cell activity is discussed.

Key-Words: LSD — Retina — LGN — Single Unit Activity — Cat.

Introduction

The effect of LSD on the spontaneous and evoked activity of the brain has been investigated within the last 20 years by several authors (see reviews of Evarts, 1957; Purpura, 1968). A desynchronization of the EEG has been described (Bradley and Elkes, 1957; Himwich, 1956) and the effect of rhythmical medial thalamic stimulation (recruiting response) was also depressed. The specific sensory evoked potentials were either increased (Purpura, 1956) or only little influenced (Koella and Wells, 1959). At high doses (1 mg/kg) a transmission block in the LGN was described (Evarts *et al.*, 1955; Bishop *et al.*, 1959). Large spontaneous potentials of the electroretinogram (ERG) and an increase of the light evoked ERG-potentials were reported (Apter and Pfeiffer, 1957). The mass activity of the optic nerve was found to be increased (Schwartz and Chenney, 1965). Besides these effects of LSD on the specific afferent systems, its action on the limbic, the non-specific thalamo-cortical and the reticular systems have been pointed out by several authors (Adey *et al.*, 1962; Bradley and Wolstencroft, 1964; Stumpf, 1964), but after reviewing the literature on LSD-action, Purpura (1968) came to the conclusion

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that "a coherent and generally acceptable picture of the manner in which LSD exerts its effects on higher nervous functions remains obscure".

The experiments reported in this paper were done in order to provide material on the effect of LSD on the single unit level in the retina and LGN. A preliminary report of these experiments was presented at a meeting of the German Physiological Society (Mouriz-Garcia and Creutzfeldt, 1967).

Methods

Preparation and Recording. The experiments were done on adult cats. The initial operation was performed under ether-anaesthesia. The fixation points of the stereotactic instrument were infiltrated with novocaine. A hole of approximately 6 mm in diameter was drilled in the region of the recording coordinates and the dura was opened. After the operation, the ether-anaesthesia was stopped and the animal was immobilized by Flaxedil i.v. The body temperature was maintained by a heating pad. The recordings never began before 2, in most experiments 3 hours after the end of the ether anaesthesia. The EEG was monitored throughout the experiment and was mostly of the synchronized type as seen in relaxation and drowsiness.

The activity of retinal ganglion cells was recorded with steel microelectrodes (tip diameter 3—5 μ, resistance $< 10\ M\Omega$) from the optic tract, that of geniculate neurones either in the LGN itself or from the optic radiation. During the experiment the neuronal activity was recorded on tape.

Visual Stimulation. The pupils were dilated with atropine and synephrine and the eyes covered with contact lenses. The animal faced a plane white screen at a distance of 1.5 m, which was diffusely illuminated with about 3 lux. For testing the responses a light stimulus of 150 to 300 lux and 1—2 sec duration was projected. The diameter of the test stimulus was between 1—3° according to the size of the receptive field which was determined before the recording.

Investigation of Single Neurones. In each experiment only one single neurone was investigated. The spontaneous activity was first recorded during 5—10 min and evaluated at 1—3 min intervals in order to get a measure of the reference activity. The responses to 20 light stimuli shone into the center and surround of the receptive field were recorded. After another resting period of 3 min a dose of 50—60 γ/kg LSD 25 was slowly injected into the forelimb vein. The spontaneous and light evoked activity was then recorded at regular time intervals. In some experiments 50—60 γ/kg were reinjected several times at 12 min intervals without changing the recording scheme.

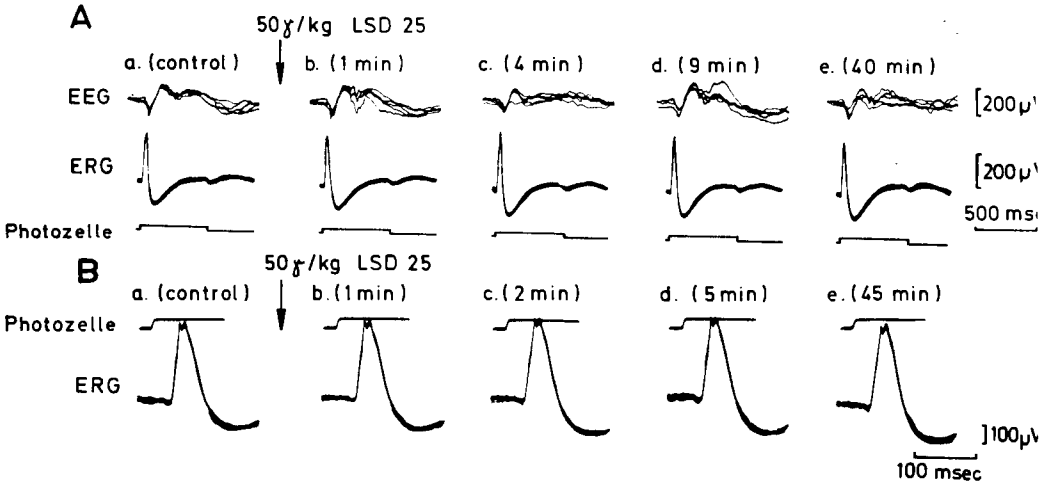

Fig. 1. Cortical evoked potential and ERG before and after LSD 25. Intravenous injection of 50 γ/kg LSD between a and b. Time after injection indicated above each record. Diffuse light stimulus marked below the records (upwards deflection: light on). Monopolar EEG-recording: upward deflection indicates negativity of active electrode. ERG: positivity of corneal electrode upward. Superimposition of about 5 responses

After the experiment the tape-recorded action potentials were transformed into standard impulses by a Schmitt-trigger and given into a CAT-400 C or IBM 1130 computer. The discharge rate of 2 sec intervals and interval histograms were calculated. Post stimulus histograms were made by averaging the response to 20 identical light stimuli.

The ERG was recorded with a silverball electrode from the corneal surface against an indifferent electrode fixed in the bone above the frontal sinus. A monopolar recording of the cortical evoked potential was obtained from the surface of the visual cortex.

Results

Spontaneous Activity. 50—100 γ/kg LSD given intravenously had only little effect on the ERG and the cortical evoked response. Representative records of the ERG of two experiments are shown in Fig. 1. All that can be noted is a slight increase of the B-wave the significance of which is questionable. No spontaneous slow oscillatory potentials were observed as in the experiments of Apter and Pfeiffer (1957) and the shape and single components of the ERG-potential were unaltered. The cortical evoked potential was also unaltered (Fig. 1 A).

14 out of 21 retinal ganglion cells showed a more or less pronounced increase of their spontaneous discharge rate (Fig. 2). This increase started

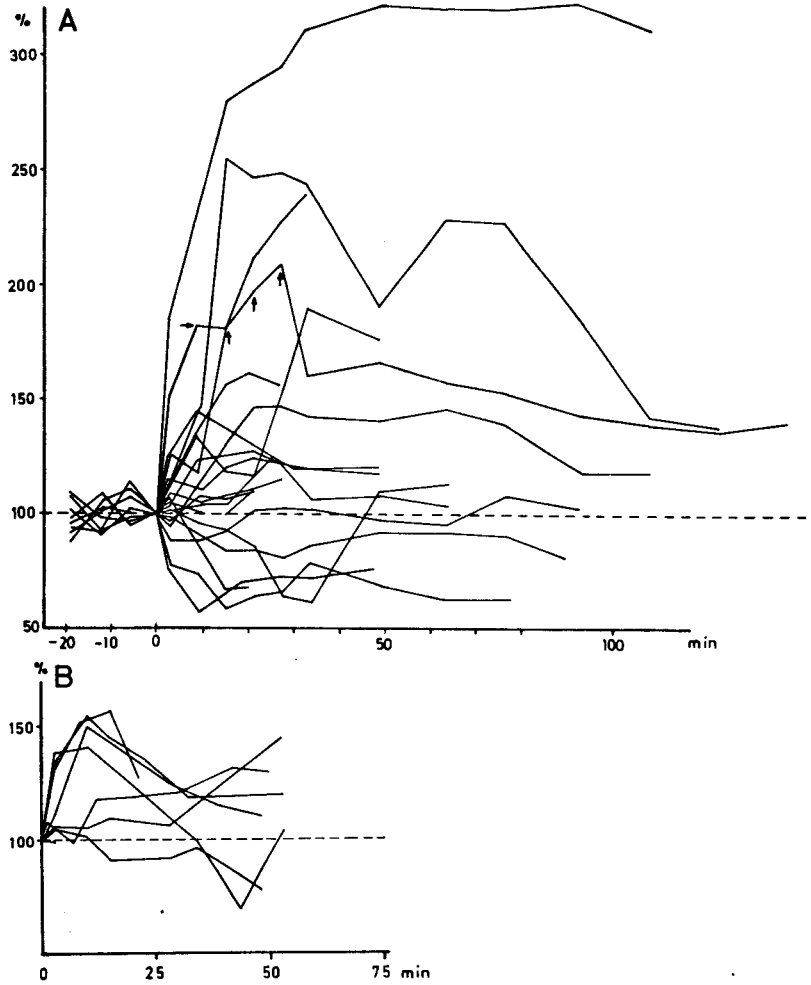

Fig. 2. Discharge rate of optic tract fibres (*A*) and geniculate neurones (*B*) after i. v. injection of 40—50 γ/kg LSD 25. Ordinate: discharge rate in per cent of the first control measurement. The discharge rate of each measurement is the mean value over 3 min preceding the points of the plots (s. methods). Abscissa: Time before and after injection of 40—50 γ/kg LSD 25 (injection at zero). The curve with the arrows is from an optic tract fibre where several injections of 50 γ/kg were given at the times indicated by the arrows

1—3 min after the injection and reached its maximum between 10 and 20 min later. It then stayed at an increased level for 30 min or longer. In some units which could be kept for more than 2 hours, the spon-

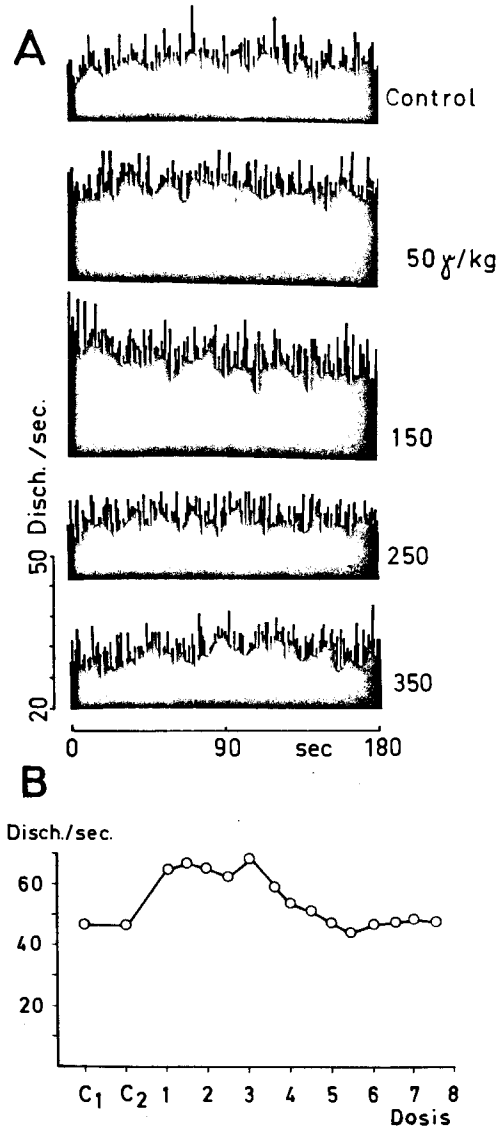

Fig. 3. Histograms of the spontaneous discharge rate of an optic tract neurone after repetitive injection of LSD 25. 50 γ/kg LSD 25 were injected every 12 min. The total dosis is indicated at the right of each histogram. The histograms (A) are from the first 3 min following each additional injection. Bin width 1 sec. The diagram (B) shows the mean discharge rate during the first 3 min after each additional injection of 50 γ/kg LSD

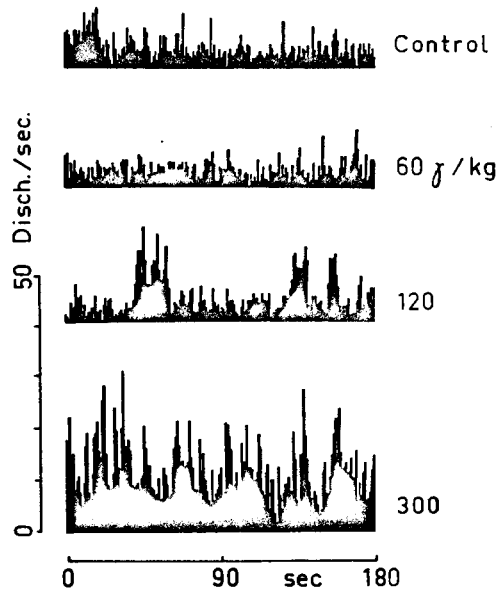

Fig. 4. Histogram of the spontaneous discharge rate of an LGN-neurone after repetitive injections of LSD 25. Same experimental arrangement as in Fig. 3 A. Note the less regular geniculate activity in comparison to that of the optic tract neurone

taneous activity stayed at a higher level, in others it returned to the control level within about an hour.

Repetitive injections of 50 γ/kg may lead to a further increase of the spontaneous activity, but the later doses were never as effective as the first ones, in some units the usually observed decrease from the initial activation was somewhat delayed but appeared in spite of further LSD-injections. This is demonstrated in the example of Fig. 3.

7 out of 21 retinal ganglion cells showed a decrease of their spontaneous discharge rate following 50 γ/kg LSD (see Fig. 2A). This decrease had the same time course as the increase of the activated neurones, but the discharge rate was never depressed below 50% of the control level. There was no relation between the type of neurone (on- or off-center) and its response to LSD.

The type of discharge did not show any significant change after LSD. The interval histograms were of the same type as those during the control period (exponential distribution with initial dead time) and only showed a slight elevation of the initial peak. Multimodal distributions as found during barbiturate anaesthesia (Schmidt and Creutzfeldt, 1968) or after cooling (Heiss *et al.*, 1968) were not seen.

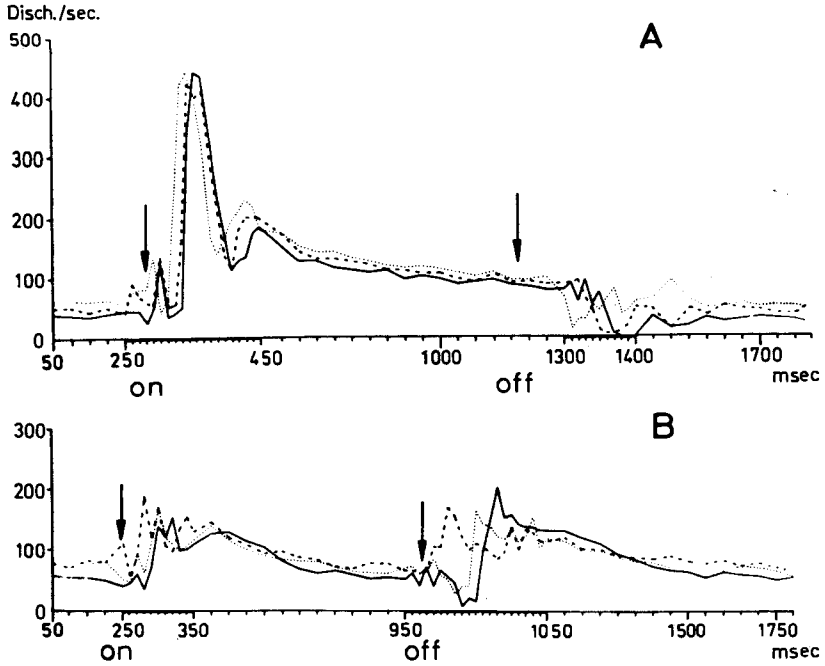

Fig. 5. A and B. Effect of LSD on the response of an on-centre neurone of the optic tract. A: Small spot of light shone into the on-centre, B: into the off-surround. Continuous line: PSTH before, dashed line: 10 min after, dotted line: 20 min after i. v. injection of 50 γ/kg LSD. Averaged PSTH of 20 stimuli each. Bin width 50 msec except between 250—450 msec and 1300—1400 msec, where it was 10 msec

Only 7 LGN-neurones could be recorded long enough to assess their response to LSD. 4 were activated and 3 did not show a clear response (Fig. 2 B). The activation period was shorter than in optic tract fibres. A characteristic feature of the LGN response was a tendency to periodic changes of the spontaneous discharge rate at higher doses, and a further increase of the activity even at high doses (Fig. 4).

Response Activity. The receptive field organization of retinal and geniculate ganglion cells did not show any significant changes after LSD. Quantitavely, the responses were slightly stronger or weaker dependant on the drug effect on the spontaneous activity. In the activated neurones the response latencies were slightly shortened (primary responses: 5—10 msec, secondary activation after initial on- or off-inhibition up to 25 msec, Fig. 5).

Discussion

The present observations on the effect of LSD on the spontaneous activity of individual neurones of the retina are largly agreement

with results of gross recordings from the optic tract (Schwartz and Cheney, 1965). About two thirds of the sample of the retinal ganglion cells investigated in this study showed a marked activation of their maintained activity, and the depression of the remaining third was less pronounced, so that an increase of the gross activity of the optic tract would result.

The similar effect of LSD on the activity of LGN-neurones does not imply a specific action on LGN-neurones, since it can be explained by an increased (or decreased) drive from the retina. The late activation of LGN neurones after repetitive doses of LSD may be due to activation through non-specific systems since it did not have a counterpart in the optic tract. The small effect on the visually evoked activity in the optic tract and the LGN units is in line with the lack of any significant alteration of the ERG and the cortical visual evoked potential shown in our experiments.

The findings reported here do not add much to the mechanism of LSD-action. In the context of the hypothesis that it is related to the serotonin (5-HT) metabolism (Giarman, 1968) it may be remembered that in the retina only dopamine containing neurones have yet been found (Häggendal and Malmfors, 1963). Intra-arterial application of 5-HT produced an inhibition, norepinephrine either excitation or inhibition of retinal ganglion cells (Straschill, 1968). The direct action of high doses of LSD on geniculate neurones, applied either electrophoretically (Curtis and Davis, 1962) or by intracarotidal injection (Bishop *et al.*, 1968; Evarts *et al.*, 1955) is inhibitory rather than excitatory. Ergometrine, which is chemically related to LSD, also depresses retinal ganglion cell activity after intracarotidal injection. In the isolated optic tectum, no clear effect on the electrically evoked potential was seen, but the 5-HT induced reduction of this potential could be eliminated by LSD (Kawai and Yamamoto, 1968).

The slow time course of LSD action in our experiments is against a direct action on nerve membranes or synapses, and rather supports the assumption of an indirect metabolic effect. In this context the similar course of LSD-action on retino-geniculate activity and on the brain levels of 5-HT (Freeman *et al.*, see Giarman, 1968) may be noted. It seems therefore possible that LSD at low dosage does not act directly on retinal and geniculate cells but only by disturbance of the monoamine metabolism.

It may be discussed briefly whether the observed effects on retinal activity can be related to the behavioral and psychophysical effects of LSD. Schwartz and Cheney (1965b) denied such a relation because of the different time course of the neurophysiological and the behavioural changes. But the time course of the activity changes found in our experiments is not much different from that described in behavioural

observations in animals. Only the duration of such behavioural alterations was generally longer (Hamilton, 1960). A slight increase in visual threshold was found in pigeons at a dosis of LSD comparable to that used in our experiments (Blough, 1957). It may therefore be justified to correlate at least some initial behavioural and psychopathological effects with the neurophysiological findings. It is conceivable that minor changes of spontaneous discharge rate and evoked activity may result in misinterpretations of the visual environment by the brain and interpreted as illusions and/or hallucinations. In connection with similar but also only slight functional disturbances of other receptors and brain structures, i.e. from a slight disorganization of the total brain activity, feelings of unreality and strangeness may result.

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