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THE EFFECT OF LSD UPON SPONTANEOUS PGO WAVE ACTIVITY AND REM SLEEP IN THE CAT

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Summary—The effect of D-lysergic acid diethylamide (LSD) upon ponto-geniculo-occipital (PGO) wave activity was studied in the cat. The results include the following observations: (1) During the acute phase of LSD's action (90–120 min), the PGO waves which appeared in the visual system were identical to those which normally accompany eye movement in the alert animal (PGO_W). (2) A pattern of 4–8/sec activity, not ordinarily present in the cortical EEG during arousal, began to dominate the recording in the intervals between PGO_W as the dose of LSD was increased to a maximum of 800 μg/kg. (3) A prolonged period of slow wave sleep followed the acute phase of drug action. There was a delay in the return of REM sleep and a delay in the appearance of the PGO waves associated with this state (PGO_{REM}).

The results oppose the hypothesis that the hallucinogenic effect of LSD is a result of the release of PGO_{REM} into the state of wakefulness.

D-Lysergic acid diethylamide (LSD) induces profound alterations in visual perception in man (JARVIK, 1967) and for this reason the effect which the drug exerts upon the visual system has been studied extensively. Numerous attempts have been made to define the influence of LSD upon evoked potentials in the lateral geniculate nucleus (EVARTS, LANDAU, FREYGANG and MARSHALL, 1955; EVARTS, 1958; BISHOP, FIELD, HENNESSY and SMITH, 1958; BISHOP, BURKE and HAYHOW, 1959) and the visual cortex (MARRAZZI and HART, 1955; EVARTS *et al.*, 1955; PURPURA, 1956; ROVETTA, 1956; KOELLA and WELLS, 1959). At the single unit level, the technique of microiontophoresis has been used to study the effect of LSD upon the discharge rate of neurones in the lateral geniculate nucleus (CURTIS and DAVIS, 1962; TEBĒCIS and DI MARIA, 1972) and the effect of the drug upon the receptive fields of cells in this nucleus has been investigated (HORN and MCKAY, 1973). Taken as a whole, these studies suggest that LSD has a depressant effect upon neuronal activity within the visual system, but the findings are of little help in explaining the drug's ability to induce visual hallucinations in man.

A rather different approach to the problem of LSD's action upon the visual system has evolved from studies of the sleeping animal. During the rapid eye movement (REM) phase of sleep, bursts of unit activity and associated slow potentials appear in the visual system of the cat (BROOKS and BIZZI, 1963; BIZZI, 1966) and it has been suggested that these events may be related to the visual imagery that occurs during dreaming in man (MORUZZI, 1963; MORRISON and POMPEIANO, 1966; JOUVET, 1967; DEMENT, 1969). The slow potentials, termed ponto-geniculo-occipital waves (PGO_{REM}), are usually synchronous with the eye movements of REM sleep. The PGO_{REM} have been studied extensively (BROOKS, 1967, 1968a,b) and can easily be distinguished from the similar activity (PGO_W) which accompanies eye movement in the alert animal (BROOKS and GERSHON, 1971). The PGO_{REM} appear to be confined to REM sleep by a serotonergic gating mechanism formed by neurones within the raphe nuclei. According to the model proposed by BROOKS and GERSHON (1968, 1971), neurones within the raphe exert a tonic inhibitory influence upon the pacemaker for PGO_{REM}, positioned within the reticular formation of the pons, and this influence is lifted only when these neurones decrease their discharge rate during REM sleep. Raphe neurones displaying discharge characteristics consistent with this model have been described (MCGINTY, HARPER and FAIRBANKS, 1973). Disruption of this gating mechanism, achieved either by drug treatment (DELORME, JEANNEROD and JOUVET, 1965; DELORME, FROMENT and JOUVET, 1966; BROOKS

and GERSHON, 1968, 1971; DEMENT, 1969) or by lesions in the region of the raphe nuclei (SIMON, GERSHON and BROOKS, 1973) allows PGO_{REM} to occur during wakefulness and in some instances this is accompanied by behaviour which suggests that the animal is perceiving visual hallucinations (DEMENT, 1969).

These findings are particularly intriguing because they suggest a mechanism by which LSD might induce the reported alterations in visual function. D-Lysergic acid diethylamide is known to inhibit neuronal activity within the raphe nuclei (AGHAJANIAN, FOOTE and SHEARD, 1968, 1970; AGHAJANIAN, HAIGLER and BLOOM, 1972). If the raphe neurones which are thought to regulate PGO_{REM} are influenced in this manner by the drug, then the indirect effect of LSD upon the pacemaker would be one of disinhibition. Thus, it would be reasonable to propose that PGO_{REM} appear during wakefulness following treatment with LSD and that this is the basis for the disturbance in visual perception. Rather similar schemes have been advanced recently to explain the effect of LSD upon sensory transmission (GUILBAUD, BESSON, OLIVERAS and LIEBESKIND, 1973) and upon the startle response (DAVIS and SHEARD, 1974).

The hypothesis that LSD causes PGO_{REM} to appear during wakefulness has been tested in two laboratories and conflicting results have been reported (FROMENT and ESKAZAN, 1971; STERN, MORGANE and BRONZINO, 1972). Therefore, the objective of the present study is to resolve this matter by defining in detail the effect of LSD upon both PGO wave activity and REM sleep.

METHODS

Experiments were performed on a series of eight adult cats. Stainless steel bipolar electrodes were implanted in the lateral geniculate nucleus and the marginal gyrus during an initial surgical procedure performed under pentobarbital anaesthesia. All electrodes had an inter-electrode distance of 2–3 mm, and the centre wire tips of the cortical electrodes were inserted into the underlying white matter in order to obtain transcortical recordings. Electrodes for use in recording eye movement were passed through the frontal sinus and positioned in the median aspect of each orbit. In some experiments needle electrodes, for EMG recording, were sewn into the posterior cervical muscles.

Recording sessions started 2–3 days after surgery and usually continued for 3–4 months. During each session, the animal was placed in a light-tight chamber and allowed complete freedom of movement. Cables passed from the implanted electrodes through a 24 contact slip-ring to an Offner Type R dynograph. In some cases a Mentor N750 Window Discriminator was used to detect lateral geniculate PGO_{REM} and these were counted on a Gerbrands cumulative recorder.

After initial control recordings, the LSD observations were begun. The drug was obtained from the Centre for studies of Narcotic and Drug Abuse of the National Institute of Mental Health and was administered intraperitoneally in dosages of 2·5, 10, 25, 50, 100, 200, 400 and 800 μg/kg. Each dose was tried in at least 5 different animals and 4 of the 8 cats received all 8 dosages. The spacing between injections was adjusted to minimize cumulative effects, with the result that a complete dose–response study in any one animal usually required several weeks of recording. Following injection of LSD, the animal's behaviour was observed closely during the acute phase of drug action (1–3 hr) and continuous EEG recordings were obtained for 10–48 hr.

At the termination of each experiment, an excessive dose of pentobarbital was administered and the brain was perfused with formalin. Serial sections of brain tissue, stained by Weil and cresyl violet techniques, were prepared and examined to determine the position of each electrode.

RESULTS

The cortical EEG, recorded from the marginal gyrus of the normal animal

Recordings from the marginal gyrus of the alert cat show intervals of "low voltage fast activity" separated from each other by single or grouped waves of high amplitude (Fig. 1A). These waves, termed PGO_W (BROOKS and GERSHON, 1971), are composed

of an initial surface positive deflection followed by a surface negative one of longer duration. Each cortical PGO_W bears a rather precise temporal relationship to an accompanying eye movement (BROOKS, 1968a,b). As long as the animal showed an active interest in its environment, eye movements occurred at least every few seconds and the cortical EEG tended to remain of low amplitude in the intervals between the corresponding PGO_W. In comparing Figure 1 and subsequent records with those of previous studies it is essential to bear in mind that cortical PGO_W are restricted to the marginal and suprasylvian gyri (BROOKS, 1968b) and cannot be detected unless transcortical electrodes are used (BROOKS, 1967). Thus, comparable records from earlier studies (Fig. 1A of BRADLEY and ELKES, 1957; Fig. 1A of STERMAN, KNAUSS, LEHMANN and CLEMENTE, 1965) do not show PGO_W, but otherwise closely resemble Figure 1A of this study.

When the animals lost interest in the environment and sat or lay quietly with the head still held up and the eyes opened or closed, in some animals brief periods of 4–8/sec activity appeared between infrequent eye movements and associated PGO_W (Fig. 1B). This mixture of PGO_W and rhythmic cortical activity is relatively rare in most cats, and the animal quickly returns to the alert state or passes on to a drowsy one. This transitional state of repose corresponds closely to the "quiet resting, relaxed state" of BRADLEY and ELKES (1957, Fig. 1B) and the "awake-drowsy" state of URSIN (1968).

When the animals lay down, rested their head, closed their eyes and assumed a normal sleeping posture, then eye movement and PGO_W no longer occurred and the cortical EEG resembled that of Figure 1C. During this drowsy state, uninterrupted 4–8/sec activity often dominated the EEG recorded from the marginal gyrus, but both lower and higher frequencies were often present. Wakefulness ended and "light slow wave sleep" (URSIN, 1968) began during this period, but it is impossible to specify a precise point of transition. This state is equivalent to the "drowsy" one that has been described in previous studies (BRADLEY and ELKES, 1957; STERMANN *et al.*, 1965).

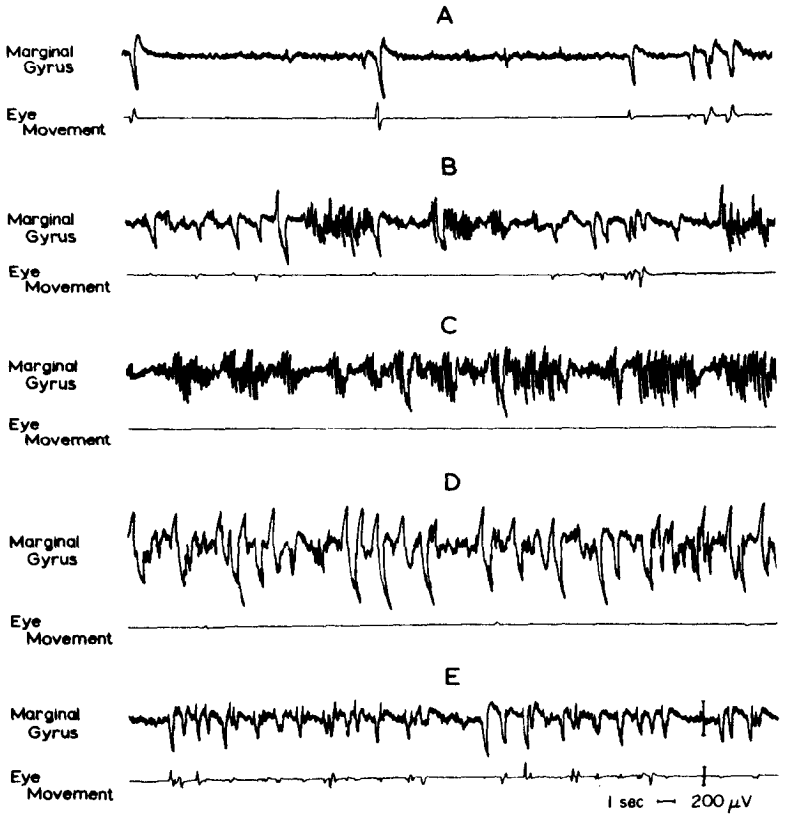

Fig. 1. Normal cortical EEG. A: alert; B: quiet repose; C: drowsy; D: deep slow wave sleep; E: REM sleep. In this and subsequent cortical recordings, a downward deflection indicates that the surface has become positive with respect to the underlying white matter.

As the animal fell more deeply asleep, the cortical EEG gradually changed to a pattern of high amplitude, low frequency waves (Fig. 1D). URSIN (1968) has termed this "deep slow wave sleep". With the appearance of REM sleep, the EEG diminished in amplitude and PGO_{REM} appeared (Fig. 1E).

The acute effect of small doses (2·5–50 μg/kg) of LSD

The lowest 2 doses of LSD used in this study (2·5 and 10 μg/kg) produced no consistent changes in either animal behaviour or the cortical EEG. When the dose was increased to 20–50 μg/kg, subtle changes in behaviour which started a few minutes after each injection, become apparent. The animals became alert and attentive. They appeared more curious than usual about their visual environment and eye movement consistently increased as they explored their surroundings. Their behaviour was in no way bizarre or inappropriate. The animals responded normally to petting and it was, if anything, easier to attract their attention with visual stimuli. Concomitant with these minimal alterations in behaviour there was an equally subtle change in the EEG recorded from the marginal gyrus. Each eye movement was accompanied by a PGO wave, but during the intervening periods of ocular fixation, 4–8/sec waves of relatively large amplitude tended to appear (Fig. 2A, B). The frequency of this activity, following equal doses of LSD, varied slightly from animal to animal (cf. Fig. 2A with Fig. 2E) but for each animal the appearance of the recording was rather similar to that obtained during the

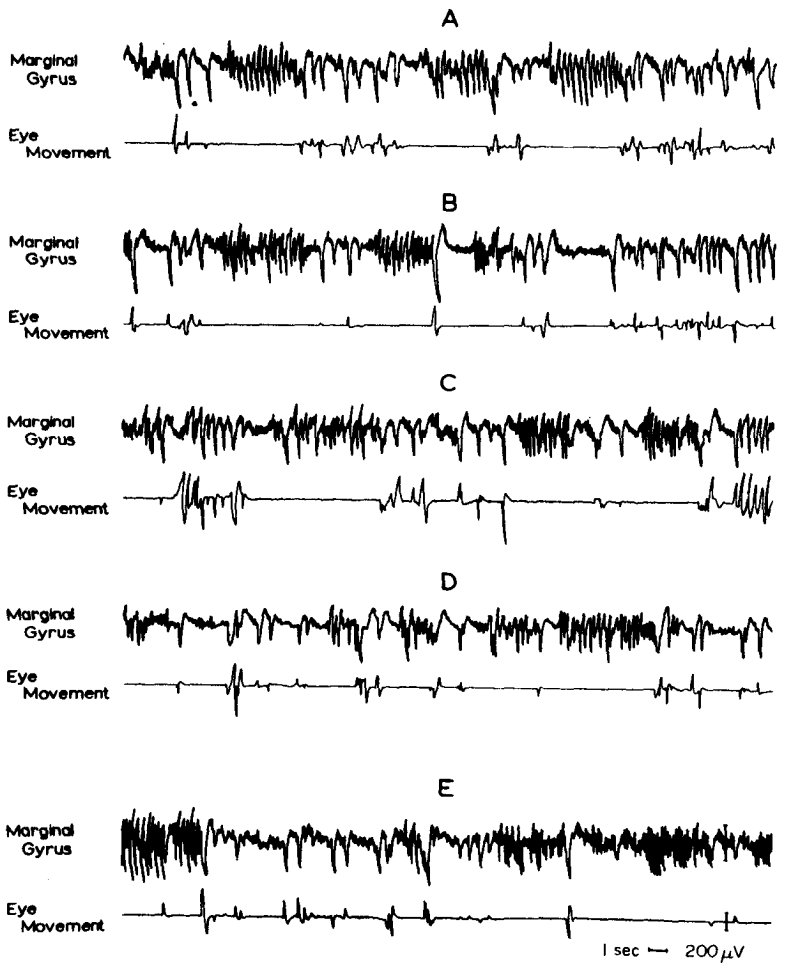

Fig. 2. Effect of small and moderate doses of LSD upon the cortical EEG. A: 25 μg/kg; B: 50 μg/kg; C: 100 μg/kg; D: 200 μg/kg; E: 25 μg/kg. Records A–D from the same animal as Figure 1; record E from a second animal. All recordings obtained 15 min after injection of LSD.

transition from wakefulness to the drowsy state (cf. Fig. 2A with Fig. 1B). The significant point is that following LSD, this 4–8/sec activity appeared in animals which were extremely alert, a situation never observed without drug treatment. The change in the cortical EEG, like the mild alteration in behaviour, was most obvious 5–10 min after the injection of LSD, and then slowly diminished, with both behaviour and recordings appearing normal 90–120 min later.

The acute effect of moderate doses (100–200 μg/kg) of LSD

These doses of LSD caused an accentuation of the behavioural changes which have already been described. The 4–8/sec activity continued to intrude into the intervals between PGO waves in the cortical EEG (Fig. 2 C,D). When the animal's chamber was well illuminated, the frequency of eye movements and PGO waves was quite high, but in complete darkness, eye movements were commonly lacking and the 4–8/sec cortical rhythm appeared uninterrupted and uniform from one minute to the next.

In order to determine whether the PGO waves which appeared after LSD are the equivalent of PGO_W or PGO_{REM}, the characteristics of the waves were carefully investigated. Three tests serve to distinguish between these similar forms of PGO wave activity (BROOKS and GERSHON, 1971): (1) cortical PGO_W are attenuated in amplitude in the dark whereas cortical PGO_{REM} are not; (2) lateral geniculate PGO_W are either of low amplitude or impossible to detect when compared with PGO_{REM} recorded from the same electrode; and (3) cortical PGO_{REM} often contain an initial surface negative component never present in cortical PGO_W. Applying each of these tests it is apparent that the PGO waves which accompany each eye movement during the first 120 min following the injection of LSD were PGO_W rather than PGO_{REM}. Thus, the cortical waves were reduced in amplitude when the animal was placed in the dark (Fig. 3 A,B), the lateral geniculate waves were small and difficult to detect (Fig. 3 C,D) and the cortical waves never contained an initial surface negative component (compare the

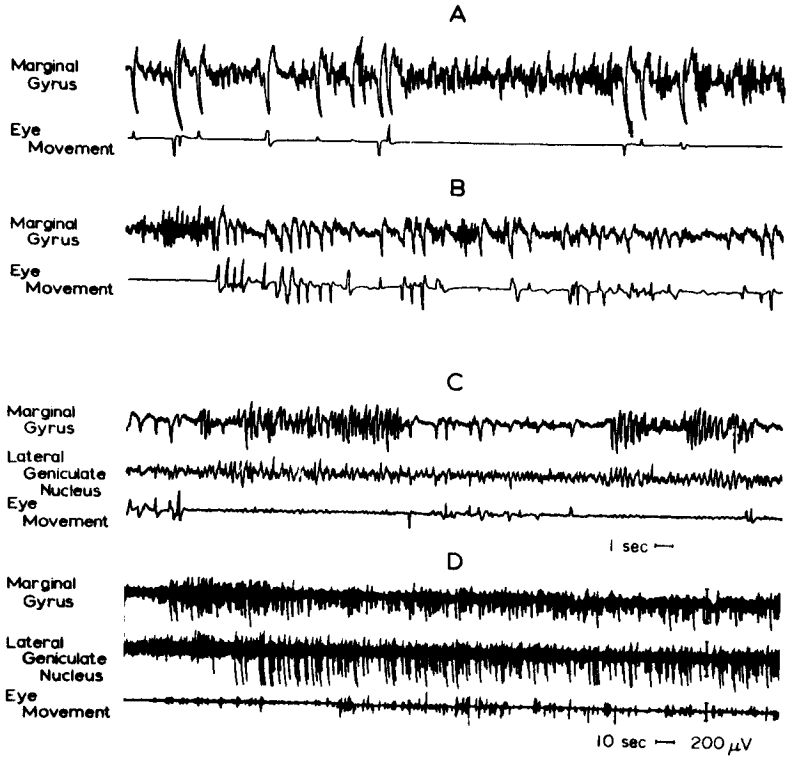

Fig. 3. Characteristics of PGO wave activity after LSD, 100 μg/kg. A: recording in light and B: recording in complete darkness from the same animal. C: recording 15 min after injection of LSD and D: recording during REM sleep from the same animal.

cortical readings of Figs. 2 and 3 with that of Fig. 1 E). Comparable findings were obtained throughout the 2·5–800 μg/kg dose range of LSD used in these experiments.

The acute effect of large doses (400 *and* 800 μg/kg) *of* LSD

When the dose of LSD was increased to these levels, gross abnormalities in behaviour became apparent. The attentiveness, observed after lower doses of the drug, was so excessive that the animals became acutely apprehensive and alarmed. The hind limbs often seemed to collapse, or be actively withdrawn, with the result that the forelimbs were braced to hold the trunk upright. In some cases, the animals were relatively immobile and an extremity placed in an odd, awkward position remained there for many minutes. More commonly, the animals were hyperactive and excitedly explored the cage. Some hissed at an approaching hand, but rarely attacked it, and they often responded with a startle to petting. The pupils were maximally dilated, salivation in some cases was excessive and the animals occasionally showed chewing movements or vomited.

Despite this rather frantic behaviour, the animals did not give the impression of actively pursuing or attacking "imaginary" visual stimuli. The increased exploratory activity was accompanied by an increase in eye movement, and each such movement was associated with a normal PGO_W in the cortical EEG (Fig. 4A). If the interval between eye movements exceeded 1–2 sec, a burst of 4–8/sec activity filled this gap in the cortical EEG (Fig. 4B). In contrast to the situation with lower doses of LSD, presentation of novel visual stimuli failed to suppress this activity for more than a few seconds, even though most animals appeared aware of such stimuli and would follow moving ones. Periods of hyperactivity often alternated with long intervals during which the animal stared blankly into space. During these stares the eyes remained open; the animal was immobile and very prominent 4–8/sec activity was present in the cortical EEG. The frequency of 4–8/sec activity decreased as the dose of LSD was increased (Fig. 4 C,D). Many of the abnormalities that were prominent following large

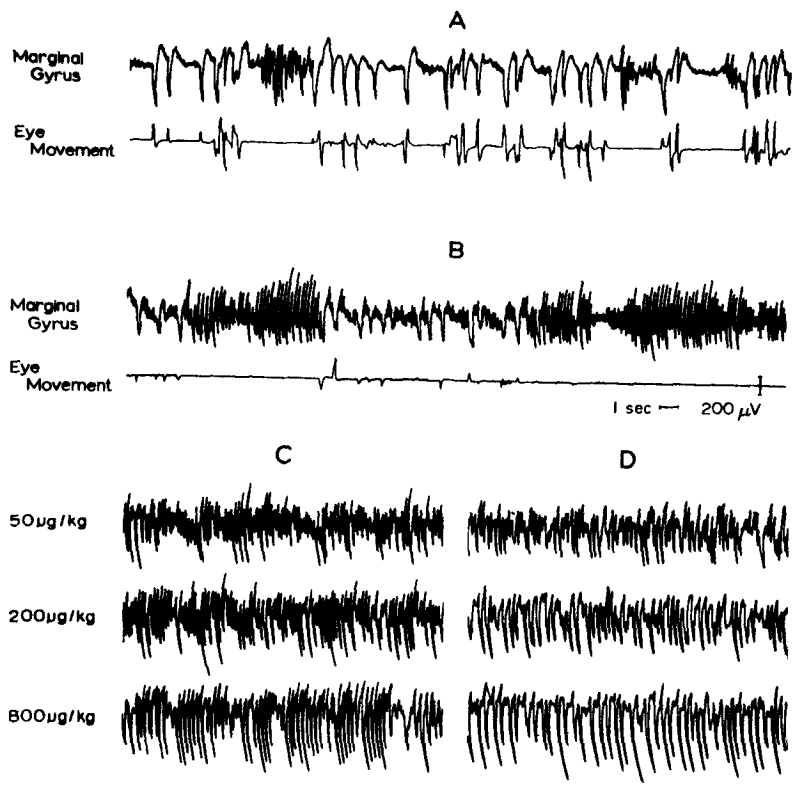

Fig. 4. Effect of large dose of LSD upon the cortical EEG. A and B: recordings after 400 μg/kg LSD: C and D: effect of the dose of LSD upon the frequency of 4–8/sec activity. B and C from same animal. A and D from two other animals.

doses of the drug (staring behaviour, motor impairment, pupillary dilitation) were present, but less obvious, in some animals following moderate doses.

Recovery from the acute effects of LSD

The abnormalities in both electrical activity and behaviour which have been described, gradually gave way to a more normal picture after 90–120 min. The rhythmic cortical EEG was replaced by one of lower frequency and greater irregularity. The animals assemed a normal resting posture and showed relatively little interest in their surroundings. From a behavioural point of view, they appeared to sleep when left undisturbed, but could always be aroused with moderate sensory stimuli. Despite a return of what appeared to be normal slow wave sleep, there was a definite delay in the onset of the first episode of REM sleep. A typical example of recovery is shown in Figure 5.

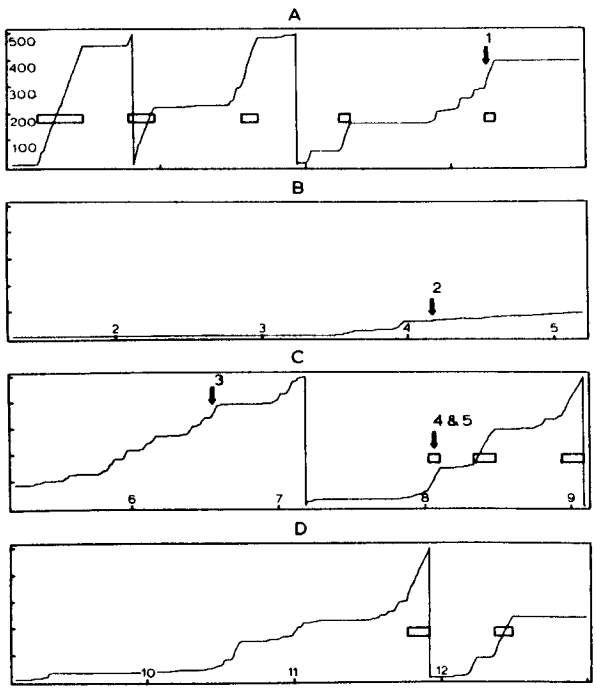

Fig. 5. Effect of LSD upon PGO_{REM} and REM sleep. Cumulative record is of PGO_{REM}, recorded from the lateral geniculate nucleus, and bars denote episodes of REM sleep. A: control recording; B, C, D,: recording following LSD 200 μg/kg. Time in hr is indicated on x axis and wave count on y axis. Record B begins 1 hr 15 min after the injection of LSD and numbers show elapsed time following drug treatment. Arrows show when records of Figure 6 were obtained.

In this instance, the first period of REM sleep, as judged by changes in the cortical EEG, the appearance of eye movement and loss of cervical muscle tone, occurred 8 hr after the injection of LSD (200 μg/kg). There was an associated suppression of PGO_{REM}, with the first waves of this type appearing 3·5 hr after administration of LSD. This example is also typical in showing a gradual return of PGO_{REM}, either singly or in groups, during the long period of slow wave sleep which precedes the first episode of REM sleep (Fig. 5; Fig. 6, records 2 and 3). When REM sleep finally returned, PGO_{REM} appeared an unusually long time before the changes in the cortical EEG which mark the start of the episode (Fig. 6, compare records 4 and 5 with record 1). The suppression of PGO_{REM} and REM sleep increased in duration with larger doses of LSD and the nature of this relationship is shown in Figure 7.

DISCUSSION

The results of the present study directly oppose the hypothesis that this disturbance in visual function induced by LSD is due to the occurrence of PGO_{REM} in the alert

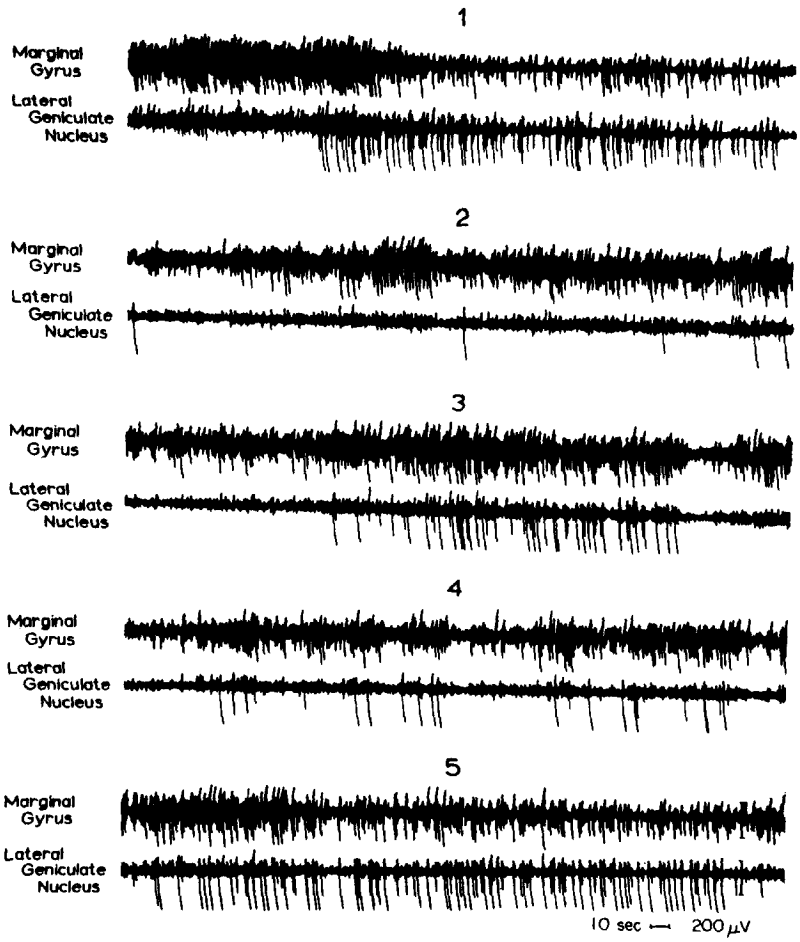

Fig. 6. Recovery from LSD 200 μg/kg. Recordings obtained at the times indicated in Figure 5. 1 is a control episode of REM sleep. 5 follows directly after 4 and shows the first episode of REM sleep to occur during recovery from LSD.

animal. During the acute phase of the drug's action, there was an increase in eye movement, which correlated with the animals' attentive and inquisitive behaviour, and each eye movement was accompanied by a PGO_W in the cortical EEG. Thus, "the possibility that the hallucinogenic properties of certain psychotropic drugs are related to the entrance of PGO spike activity into waking" (Stern *et al.*, 1972) must be rejected, at least with respect to LSD. The PGO waves do occur following treatment with this drug, but they are the type of waves which normally appear in the alert animal, i.e. PGO_W.

If any feature of the cortical EEG bears a relationship to the hallucinogenic activity of LSD, it is more likely to be the 4–8/sec activity. A very similar pattern has been described by Bradley and Elkes (1957) and the tendency for hallucinogenic drugs to induce a low frequency, high voltage cortical EEG, often termed hypersynchrony, has been noted in many other studies (Speck, 1957; Adey, Bell and Dennis, 1962; Fairchild, Alles, Jenden and Mickey, 1967; Lindsley, Carpenter, Killam and Killam, 1968; Scotti de Carolis, Lipparini and Longo, 1969; Fujimori and Himwich, 1969; Winters and Wallach, 1970; Florio, Fuentes, Ziegler and Longo, 1972). Although this EEG pattern has often been referred to as seizure activity, this term seems inappropriate since 4–8/sec activity is always suppressed by eye movement, and, at least briefly, by novel visual stimuli. The implication in most of these studies is that hallucinatory drugs induce an abnormal type of cortical electrical activity. It appears more accurate to state that with low or moderate doses of LSD, the effect is a shift in the relationship

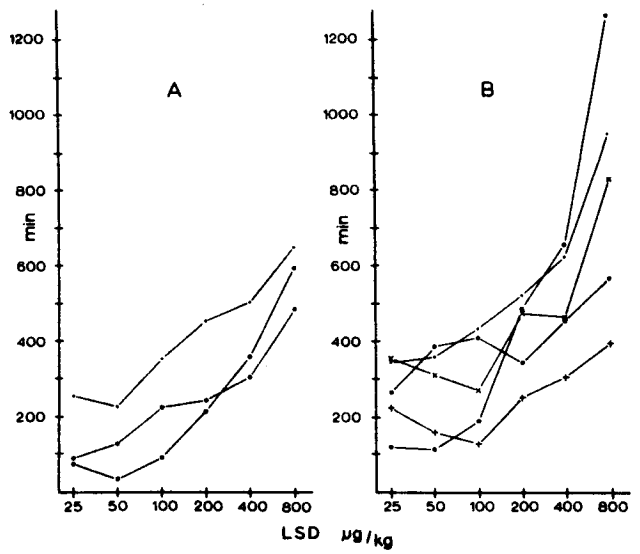

Fig. 7. Delay in return of PGO_{REM} (A) and REM sleep (B) as a function of the dose of LSD.

between the cortical EEG and behaviour. The result is that the 4–8/sec activity, which normally occurs when the animal is resting quietly and not attending to visual stimuli, intrudes into the alert state. Since this activity comes to dominate the cortical EEG at the very moments when the analysis of visual stimuli must be in progress—periods of ocular fixation between exploratory eye movements in the attentive animal—it is reasonable to guess that it may be associated with impaired visual function. The prolonged stares, that become more obvious as the dose of LSD is increased, may represent the behavioural counterpart of this impairment or distortion of visual perception. SCOTTI DE CAROLIS *et al.* (1969) and FLORIO *et al.* (1972) have advanced the belief that a drug's ability to induce hypersynchrony in the cortical EEG may be an indication that it possesses hallucinatory action and WINTERS and WALLACH (1970) have based a "theory of hallucinosis" on similar findings. The result of the present study give some support to this concept.

In evaluating the significance of 4–8/sec activity in the cat, it may be important to recognize that in many respects it closely resembles alpha activity in man. Both are prominent in the visual cortex, both are enhanced when attention to visual stimuli is minimal and both are suppressed by eye movement. Of equal interest is the close resemblance between 4–8/sec activity and the pattern of post-reinforcement synchronization recorded from the visual cortex of the cat (MARCZYNSKI, HACKETT, SHERRY and ALLEN, 1971). Post-reinforcement synchronization normally occurs when a hungry cat presses a lever to receive a milk reward. The wave activity occurs as the animal consumes the milk and is present only if the testing cage is illuminated. MARCZYNSKI (1972) has shown that post-reinforcement synchronization appears when animals are tested in complete darkness following treatment with LSD (25 µg/kg), and he suggests that the drug may act by direct stimulation of visual afferent pathways. However, both his data and the present experiments indicate that the behavioural testing procedure is, to a great extent, irrelevant in animals treated with LSD, since 4–8/sec activity appears spontaneously under these conditions. If 4–8/sec activity and post-reinforcement synchronization are equivalent, if is more reasonable to suggest that LSD directly induces an affective state similar to that which the animal normally experiences during consumption of a reward.

The results of the present study show that LSD delays the onset of REM sleep, and that the delay becomes longer as the dose of LSD is increased. It is unlikely that this finding can be attributed to the excitatory effect of LSD, since REM sleep does not return until long after the acute effects of the drug are over. This REM-delaying

action is compatible with the report that LSD decreases the percentage of REM sleep and that the effect is most prominent during the first hours of sleep following drug treatment (HOBSON, 1964). After the period of excitement, LSD seems to induce a long interval of slow wave sleep with cortical synchrony. In this respect, the action of the drug closely resembles that of the serotonin precursor, 5-hydroxytryptophan. 5-Hydroxytryptophan(5-HTP) has also been shown to delay the onset of REM sleep (JOUVET, 1967). Thus, in acting to promote a period of slow wave sleep and to delay the return of REM sleep, LSD appears to be mimicking prominent effects of serotonin.

Finally, LSD has been shown to delay the appearance of PGO_{REM}. Viewed in terms of the serotonergic gating model for the regulation of these waves (BROOKS and GERSHON, 1971), this result is the reverse of what one would predict if the dominant action of the drug were to inhibit raphe neurones. JOUVET (1967) has shown that 5-HTP also suppresses PGO_{REM} for several hours. The most probable explanation of these findings is that both LSD and 5-HTP exert a postsynaptic inhibitory influence upon the neurones which act as a pacemaker for PGO_{REM}. Such an action would enhance the tonic inhibitory effect exerted on the pacemaker by the serotonergic neurones of the raphe. This mode of action is consistent with the observations that LSD: (1) may stimulate serotonin receptors (ANDÉN, CORRODI, FUXE and HÖKFELT, 1968); (2) rarely antagonizes the inhibitory effects of serotonin (ROBERTS and STRAUGHAN, 1967; BOAKES, BRADLEY, BRIGGS and DRAY, 1970); and (3) often inhibits neurones which serotonin also inhibits (TEBĒCIS and DI MARIA, 1972). The hypothesis that LSD suppresses PGO_{REM} by acting directly upon the pacemaker for these waves is currently being tested.

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