LSD: Effects on sleep patterns and spiking activity in the lateral geniculate nucleus

The mode of action of D-lysergic acid diethylamide (LSD) on the central nervous system has been intensively investigated and reviewed[15,25]. Some principal biochemical findings are that LSD elevates brain serotonin, decreases its main metabolite, 5-hydroxyindole acetic acid[14,26], and decreases serotonin turnover[3]. LSD also lowers the firing rates in neurons in the raphé nuclear complex[1,2], an area high in serotonin[9], and decreases the release of serotonin following electrical stimulation of the raphé area[8,23]. These studies, conducted mainly in the rat, have supported the view that the psychoactive action of LSD is due to either direct or indirect antagonism of brain serotonin[2,4,29]. We now present evidence, employing an electrophysiological indicator, that LSD markedly alters the endogenous electrical activity of the visual system of the cat and propose that this may be related to the antagonism of central serotonergic neurons by LSD.

In various mammals, including the cat, marked spiking activity (PGO spikes) is found in the EEG obtained from the pons, lateral geniculate nucleus (LGN), and occipital cortex during and shortly preceding rapid eye movement (REM) sleep[6,21]. Much less frequent spikes of smaller amplitude are also recorded during waking[5,21]. Comparatively little is known concerning the mechanisms which generate these spikes, although it has been shown in several studies that the administration of serotonin antagonists such as *p*-chlorophenylalanine (PCPA), *p*-chloromethamphetamine, and reserpine to cats produces a marked increase in spike activity during waking and slow-wave sleep[10–12]. To date, these are the only drugs known to elevate the amount of spiking outside of the REM sleep period and the hypothesis has been formulated that serotonin might normally act to restrict PGO spikes to REM sleep[12]. The present study was undertaken in order to examine the effects of LSD and brom-LSD (a non-hallucinogen[19] with potent anti-serotonin effects on peripheral systems) upon the distribution of PGO spikes in various states of arousal.

Following a minimum of three baseline recording sessions, female cats bearing chronically implanted electrodes in the neocortex, hippocampus, LGN, neck muscle and right frontal sinus (the latter for recording eye movements) were injected, i.p., with either 10, 20 or 40 μg/kg of LSD or with 40 μg/kg of brom-LSD. Polygraphic recording sessions were obtained for 10 h on the day of injection and for 6 h on the following day. LSD at 40 μg/kg in 7 cats on day 1 significantly increased waking from 31% $\pm$ 2 (mean $\pm$ S.E.M.) of baseline recording time to 60% $\pm$ 4 while slow-wave sleep decreased from 56% $\pm$ 2 to 37% $\pm$ 2 and REM decreased from 13% $\pm$ 1 to 2% $\pm$ 1. On the day following LSD injection (day 2), however, sleep–waking patterns returned to baseline levels. LSD at 10–20 μg/kg in 4 animals produced insignificant effects on the amount of waking and slow-wave sleep although REM was reduced to approximately 50% of baseline. These findings are in general agreement with those previously reported by Hobson[17] in the cat. Brom-LSD (40 μg/kg) in 4 animals did not appreciably alter the sleep profile at this same dose of LSD that greatly lowered slow-wave sleep and REM sleep.

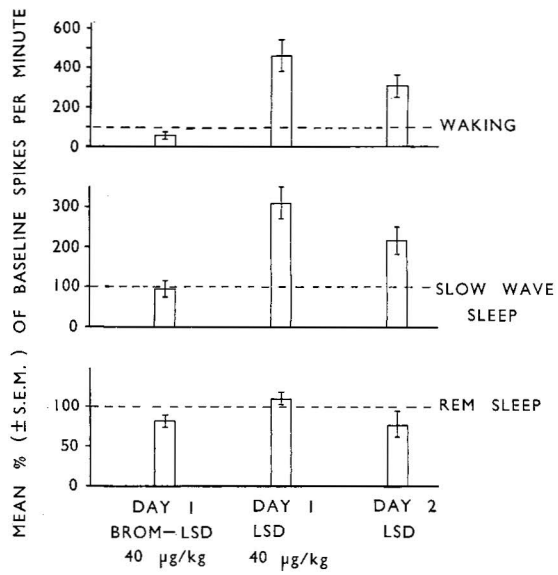

Fig. 1. The effects of brom-LSD and of LSD upon PGO spike rate in the LGN during waking, slow-wave sleep and REM sleep (n = 4). The mean (± S.E.M.) PGO spike rates during baseline were: waking, 4.5 ± 0.2 spikes/min; slow-wave sleep, 4.9 ± 0.3; REM sleep, 41.9 ± 2.1. Human observers identified and counted spikes based upon their waveform and a minimum amplitude difference of 50 μV between spike peak and background EEG. Only cats who showed PGO spikes which were clearly distinguishable from normal EEG oscillations in waking, slow-wave sleep, and REM sleep were employed. The sample time during which PGO spikes were counted averaged 45 min for waking, 155 min for slow-wave sleep and 45 min for REM.

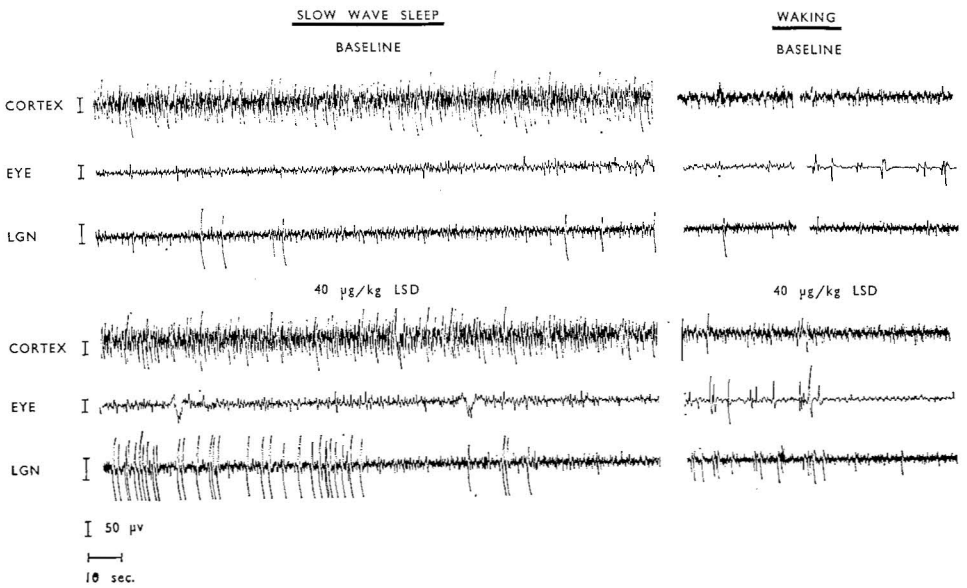

Fig. 2. Baseline and post-LSD (40 μg/kg) EEG recordings of PGO spikes in the LGN during slow-wave sleep and waking. PGO spike rates during REM sleep did not change. The 'break' in the baseline waking record indicates two samples, one with eye movements and one without.

Visual inspection of the LGN recordings following 20 μg/kg of LSD indicated increased PGO activity in waking and slow-wave sleep, but since the 40 μg/kg dose appeared to produce the largest effects these results were selected for analysis. LSD did not appear to alter PGO spike amplitude in either waking or sleep. The LGN spike densities, *i.e.*, the number of spikes per minute in waking and sleep is shown in Fig. 1. LSD (40 μg/kg) significantly ($P < 0.05$, two-tailed paired t-test) increased the spike density in waking and slow-wave sleep on days 1 and 2 even though on day 2 sleep–waking profiles were normal. REM spike density showed insignificant changes even though total REM time was drastically reduced. Changes in PGO spike frequencies are shown in Fig. 2.

The waking spike density counts following LSD do not include large portions of waking-time due to the presence of movement artifacts in the EEG record during vigorous arousal and visual attentiveness which usually lasted up to 4 h following LSD administration. Since this time period may be considered to contain the maximum effects of LSD then the spike density in Fig. 1 no doubt actually under-represents the increase in spike frequency during waking induced by LSD. Increased eye movement activity following LSD cannot account for the PGO spike effect since spike rates were elevated in segments of waking time which were without eye movements, in slow-wave sleep (no eye movements), and during waking in cats paralyzed with Flaxedil (gallamine triethiodide, n = 4).

The change in the rate of occurrence of slow-wave sleep and waking spikes after 40 μg/kg of LSD is not simply due to a general increase of spike frequencies in all states since REM spike rates did not change. This is more clearly shown in Fig. 3 which compares the distribution of PGO spikes in REM sleep and slow-wave sleep. We find that in normal cats 70% of the total number of PGO spikes occurring during

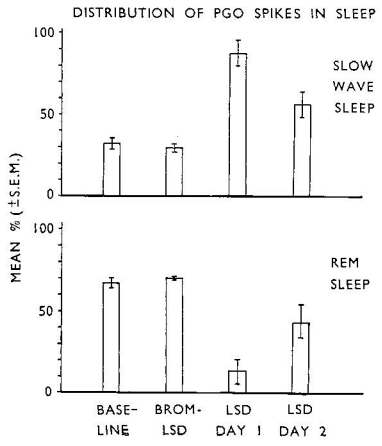

Fig. 3. The proportion of PGO spikes in REM and slow-wave sleep (n = 4) after administration of brom-LSD (40 μg/kg) or LSD (40 μg/kg). LSD increased the percentage of PGO spikes occurring in slow-wave sleep up to almost 80% of the PGO spikes which occurred during sleep. This was due to an increase in PGO spike rate in slow-wave sleep and to a large decrease in the amount of REM sleep time.

sleep are found in REM sleep. Following LSD (40 μg/kg) the percentage of 'sleep' PGO spikes occurring in REM on day 1 is reduced from 70% to approximately 20% with slow-wave sleep containing 80% of the PGO spikes after LSD. Similar effects occurred on day 2 even though normal amounts of REM time occurred. Brom-LSD did not alter sleep–waking profiles or the distribution of PGO spikes.

The effects of LSD on PGO spiking appear to be similar to the effects of the more well-established serotonin antagonists PCPA and reserpine. In cats PCPA, reserpine, and LSD substantially increase the number of PGO spikes which occur outside of REM sleep[10–12] as well as reduce the amount of time spent in slow-wave and REM sleep. On the other hand, brom-LSD, a potent antagonist of serotonin (in peripheral systems)[19], did not alter sleep–waking profiles or PGO spike patterns. This is probably due to the weak central action of brom-LSD since several other studies have shown that the central nervous system effects of brom-LSD are small compared to those of LSD[2,3,14,26] even when brom-LSD is applied directly to the brain[4].

PGO spikes mainly occur during REM sleep, the sleep state associated with reports of dreaming in man[16,28]. The question arises as to whether the psychotropic effects of LSD are related to the increased occurrence of PGO spikes in waking and drowsy states (also see Evarts[13]). There are, however, several considerations. In the present study the identity of PGO spikes recorded in the LGN during REM sleep to those seen in waking (before or after LSD) is not certain[7] and no detailed attempt to correlate specific behavioral activities with the occurrence of PGO spikes was made. Also, the effects of reserpine (a non-hallucinogen which increases waking PGO spikes) on sleep differ in man (REM sleep is increased) and in cat (REM sleep is decreased)[18] and, therefore, the PGO response to reserpine may also differ in these two species (however, these sleep differences may be dose-related). Psychotropic effects of PCPA on normal humans have not yet been reported. The observation of enhanced phasic activity (eye movements) during non-REM sleep in man after LSD administration[24] is similar to the present result in cats of increased PGO activity during slow-wave sleep. The possibility that the hallucinogenic properties of certain psychotropic drugs are related to the entrance of PGO spike activity into waking merits further investigation. The recent report by Safer[27] that sleep deprivation in man enhanced the psychotropic effects of LSD also supports this interpretation since sleep loss presumably increases the number of PGO spikes which can then be discharged.

One possible mechanism by which LSD could increase PGO spiking in waking and slow-wave sleep may be due to its powerful antagonism of 'serotonergic neurons' in the raphé complex. There is good evidence from pharmacological and anatomical studies that the integrity of the anterior raphé system is necessary for the occurrence of normal sleep–waking patterns and for the restriction of most PGO spikes to REM sleep[20,22]. Thus, the LSD induced reduction of neural firing in the raphé nuclei[2,4] may be related to the increase in PGO spike activity in waking and slow-wave sleep. We are now determining whether changes in the PGO spikes seen following peripheral injection of LSD are due to LSD's action on raphé neurons by applying small amounts of LSD directly to the raphé nuclei and to other brain stem sites.

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Neurophysiology Laboratory,
Worcester Foundation for Experimental Biology,
Shrewsbury, Mass. 01545 (U.S.A.)

WARREN C. STERN
PETER J. MORGANE
JOSEPH D. BRONZINO

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