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LSD and Tryptamine Effects on Sleep/Wakefulness and Electrocorticogram Patterns in Intact Cats*

David C. Kay and William R. Martin

National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, Kentucky 40583, U.S.A.

Abstract. Effects of intravenous infusions of LSD (3.75, 7.5, 15 μg/kg over 5 min; crossover $N = 4$) and tryptamine (0.04, 0.08, 0.12 mg/kg/min for 150 min; crossover $N = 6$) were compared to saline in intact cats through observation of five sleep/waking patterns. Electrocorticogram (ECoG) was analyzed for frequency band indices and mean amplitude and frequency. LSD increases wakefulness and drowsiness and decreases spindle sleep and rapid eye movement (REM) sleep during the first 75 min (period 1). The increase in active wakefulness and decrease in REM sleep persist during period 2, with an increase in spindle sleep thereafter. LSD increases delta index and ECoG amplitude, with a decrease in ECoG frequency; these effects peaked in period 2. Tryptamine increases wakefulness and drowsiness during period 1, with decreases in spindle sleep and REM sleep. The increase in quiet wakefulness and decrease in REM sleep persist during period 2, but no significant tryptamine effect is seen in sleep/waking patterns after infusion ceases. ECoG frequency increases during tryptamine infusion (periods 1 and 2), while ECoG amplitude increases during periods 2 and 3. Thus LSD and tryptamine both increase wakefulness, decrease spindle sleep, and decrease REM sleep.

Key words: LSD – Tryptamine – Arousal – REM sleep – Period analysis

Data that have accumulated support the hypothesis that LSD acts on CNS tryptamine receptors (Martin and Eades, 1970; Kay et al., 1973; Martin et al., 1976) and that tryptamine is a neurotransmitter or neuromodulator (Martin et al., 1976). LSD effects on perception and mood are well established (cf. Hollister, 1968); however, its effects on the electroencephalogram (EEG) remain controversial (Martin and Sloan, 1977). Tryptamine's effects on sleep states have not been previously studied. This investigation was designed to describe quantitatively and to compare the effects of graded but small doses of LSD and tryptamine on sleep/waking and EEG patterns in the freely moving intact cat.

Materials and Methods

The six male cats used in this study, weighing 3.9–4.5 kg, were operated under i.v. pentobarbital anesthesia. A multiple depth electrode with six recording sites at 1.0-mm intervals was implanted with its maximum depth at the genu of the hippocampus (A 2.0, L 10.0, +3.0) (Snider and Niemer, 1961). Stainless steel machine screws were fastened into the skull over the visual cortex (P 2.0, R 2.0), auditory cortex (A 5.0, R 15.0), associational cortex (A 15.0, R 10.0), and somasthetic cortex (A 25.0, R 5.0) for recording the ECoG. Longer stainless steel screws were implanted in the front sinus over the orbits to record the electrooculogram (EOG). A nichrome wire loop was inserted through the nuchal muscle below the supraoccipital crest in order to record an electromyogram (EMG). Reference electrodes consisted of a screw in the frontal sinus rostral to bregma, as well as a nichrome wire loop in the interparietal crest. All electrode wires were connected to a miniature plug, which was then fastened to the skull with dental acrylic. In the same or in a later operation, a silicone elastomer catheter was implanted through an external jugular vein into the superior vena cava, and its external portion was covered by a protective harness thereafter. Cats were allowed 7–14 days to recover from surgery and to adapt to the experimental chamber.

For each experiment, a cat was placed in one of two sound-attenuated chambers inside a sound-attenuated room. A masking noise within each chamber was kept at an intensity just great enough to eliminate orienting responses to noise by the other cat, and the chamber light was maintained at a low intensity. A cat's ability to sleep was not obviously disturbed by these conditions. Behavior of each cat was monitored by TV. Room temperature was maintained at 23° C. Food, water, sawdust for toilet, and a towel, fixed to the floor for bedding, were provided in each chamber. Electrical activity was

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recorded through a mercury-pool swivel in the chamber ceiling by a Grass electroencephalograph. Selected channels were recorded on a Honeywell 5600 tape recorder ($1^7/_8$ in/s).

Intravenous solutions were infused by pump at 0.5 cc/min through a cannula in the swivel and then through the jugular catheter. The minimum interval between studies was 2 days after tryptamine or saline or 7 days after LSD. All tryptamine doses were studied prior to LSD, so potential persistent tolerance and cross tolerance induced by LSD (Lindsley et al., 1968) were minimized. The acute effects of LSD on the EEG are known to dissipate within 7 days (Adey et al., 1965; Jacobs et al., 1976), even at much larger dosages, so the weekly interval was judged to be adequate. All drugs were dissolved in normal saline and then infused through a sterile 0.22-mm filter at the same time of morning in each session. Before each experiment, the polyvinyl tubing was sterilized with isopropyl alcohol, and then extensively rinsed with sterile saline. All drug doses, and a saline infusion, were administered in a crossover design for both LSD ($N = 4$) and tryptamine ($N = 6$).

The LSD doses (3.75, 7.5 or 15.0 µg/kg) were infused over 5 min, with the records being analyzed for three consecutive 75-min periods after the infusion onset. The saline control and the tryptamine doses (0.04, 0.08, or 0.12 mg/kg/min) were infused over 150 min, with the records being analyzed for the 150 min of infusion and then for the first 75 min after infusion. Excessive diarrhea and vomiting seen with doses above 0.12 mg/kg/min in a pilot study limited the tryptamine dosage.

Sleep/waking behavior patterns were derived from five measures, which were recorded for at least 400 min/experiment: two ECoG (visual, other), a bilateral EOG, a nuchal EMG, and a hippocampal EEG. The visual ECoG, EOG, and EMG data were also recorded on magnetic tape.

Each portion of the record was assigned to one of five patterns: (1) *active wakefulness*, with body movements, episodes of increased EMG, increased eye movements (EOG), and mixed hippocampal EEG frequencies (theta and faster); (2) *quiet wakefulness*, with low amplitude ECoG and EMG, eye movements without an increase in nuchal EMG, absence of hippocampal theta, and absence of ECoG delta activity or spindle bursts; (3) *drowsiness*, with low amplitude EMG, no eye movements (EOG), no ECoG spindle bursts, but ECoG delta activity (1 – 3 c/s, at least 50 µv PTP); (4) *spindle sleep*, with large episodic ECoG spindle bursts (6 – 16 c/s), often with ECoG delta activity, and usually decreased EMG, no eye movements, and no hippocampal theta activity; and (5) *REM sleep*, with desynchronized low amplitude ECoG (except for episodic PGO spikes), bursts of rapid eye movements, slow and regular hippocampal theta (4 – 8 c/s) activity, and low amplitude nuchal EMG (except for episodic twitches). Each pattern had to persist for at least 10 s to be so defined.

The visual ECoG was further analyzed. Data were passed through an Ithaco No. 4251 filter (40 c/s low pass; 24 db/octave roll-off rate) prior to A/D conversion (256/s) in a PDP-12 digital computer. Period (baseline crossing) analysis was then performed by means of a program written by Computer Security Systems (155 West 68th St., New York, N.Y. 10023).

Beginning with the onset of each infusion, 225 min of ECoG were analyzed in 4-s epochs, with summaries over the total time, as well as of three consecutive 75-min segments. The delta (0.5 – 3.07 c/s) index, theta (3.11 – 7.6 c/s) index, alpha (7.8 – 11.8 c/s) index, sigma (12.6 – 14.4 c/s) index, and beta (15.8 – 33 c/s) index were calculated for each 4-s epoch, as well as the mean ECoG frequency (c/s) and mean RMS voltage for that epoch.

Analysis of Data. For tryptamine, the crossover design allowed the construction of a 6 cat × 4 condition table for both 75-min halves (early: 0 – 75 min; late: 75 – 150 min) of the infusion, as well as for the total infusion (0 – 150 min) and postinfusion (150 – 225 min) periods. For LSD, the crossover design permitted the construction of a 4 cat × 4 condition table for each of the three consecutive 75-min postinfusion periods (0 – 75; 75 – 150; 150 – 225 min), as well as for the total postinfusion (225 min) period. For each table, a two-way analysis of variance (Snedecor and Cochran, 1967) was performed, with the variance between drug conditions then partitioned into three components: placebo/drug, linear regression, and quadratic regression. Significant component effects were defined at $P < 0.10$, $P < 0.05$, and $P < 0.01$ levels.

Such analyses of variance were calculated for the six sleep/wakefulness patterns (active wakefulness, quiet wakefulness, total wakefulness, drowsiness, spindle sleep, and REM sleep). Such tables and analyses were also calculated for five visual ECoG frequency band measures (delta, theta, alpha, sigma, and beta indices), one amplitude measure (RMS voltage), and the mean visual ECoG frequency measure.

Results

LSD. Wakefulness was clearly increased (Fig. 1) and spindle sleep (Fig. 1) and REM sleep decreased by LSD in a dose-related fashion for 75 min after infusion onset (Table 1). Thereafter, the EEG and sleep/waking patterns became more complex. Although REM sleep remained depressed throughout the analysis period, spindle sleep increased late in the experiment for the high dose. During the latter period, spindle sleep was interrupted by brief episodes of eye movements with EEG desynchronization; this pattern was unusual during spindle sleep for the saline condition. Although LSD initially produced marked change in sleep/waking state (0 – 75 min), there were no comparable significant changes in EEG frequency as assessed by baseline crossing. From 75 – 150 min after infusion, LSD produced a statistically significant and dose-related increase in EEG delta activity and dose-related decreases in alpha, sigma and beta activity (Table 2). The biological significance of these ECoG effects is uncertain.

Tryptamine. Wakefulness (Fig. 2) showed no significant placebo/drug difference, but did show a significant dose-related increase (Table 1) in the first 75 min of tryptamine infusion; drowsiness was greater than during placebo, with significant decreases in spindle sleep and REM sleep. The increase in quiet wakefulness and decrease in REM sleep (Fig. 2) persisted throughout the entire perfusion period (150 min). Although spindle sleep and REM sleep tended to increase and wakefulness to decrease after the cessation of infusion, these changes in sleep/waking pattern were not consistent.

Tryptamine (Table 2) produced few significant changes in the ECoG: amplitude increased, delta index tended to decrease, and faster ECoG frequencies (alpha, sigma, beta) tended to be more prevalent. These tendencies were most evident 75 – 150 min after infusion onset, which differed from the peak sleep/waking effects (0 – 75 min after infusion onset).

When 10 µg (10 µl) of tryptamine were injected into the third ventricle of one cat during sleep, it sup-

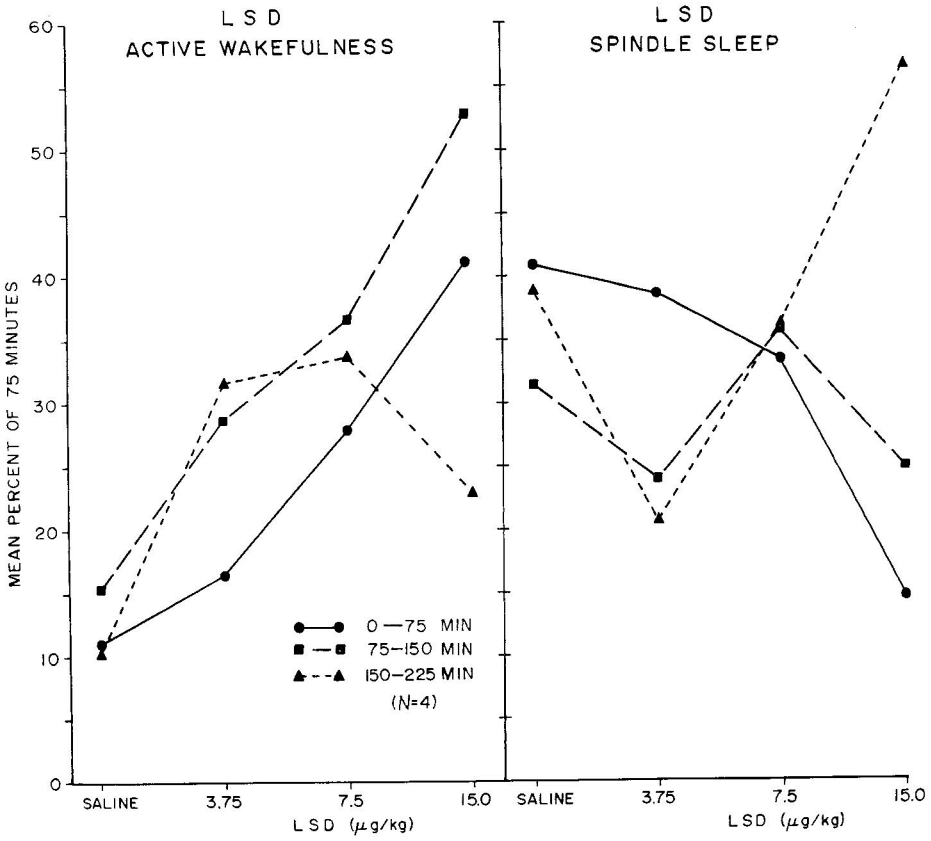

Fig. 1. Time of active wakefulness and spindle sleep after saline and 3.75, 7.5, and 15 μg/kg doses of LSD. *Each point:* mean percentage time of 4 cats for a given 75-min time period (0–75, 75–150, and 150–225 min after infusion onset) under a given drug condition

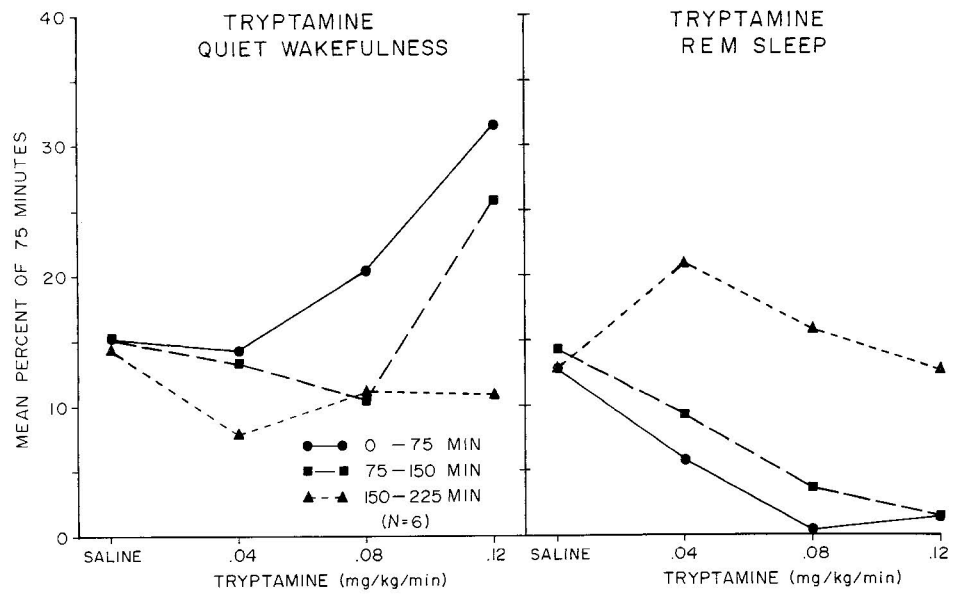

Fig. 2. Time of quiet wakefulness and REM sleep after saline and 0.04, 0.08, and 0.12 mg/kg/min infusions of tryptamine for 150 min. *Each point:* mean percentage time of 6 cats for a given 75-min time period (0–75, 75–150, and 150–225 min after infusion onset) under a given drug condition

Table 1. Effects on sleep/waking patterns

A. LSD ($N = 4$)

Sleep/waking state	Period 1 (0–75 min)				ANOVA	Period 2 (75–150 min)				ANOVA	Period 3 (150–225 min)				ANOVA
	SAL	LSD				SAL	LSD				SAL	LSD			
		3.75	7.5	15			3.75	7.5	15			3.75	7.5	15	
Active waking	11.0***	16.4	27.9	41.1	L***	15.2***	28.7	36.6	52.8	L**	10.2	31.6	33.2	22.9	
Quiet waking	19.2	8.7	16.2	13.8		20.0**	12.6	11.2	5.7		19.0	12.3	12.8	6.0	
Total waking	30.2*	25.1	44.1	54.8	L***	35.2	41.2	47.8	58.5		29.2	43.9	46.0	28.9	
Drowsy	19.9	26.0	22.4	27.2	L**	22.0	32.2	16.6	16.6	L*	21.9	26.9	14.0	12.4	
Spindle	40.9	38.6	33.2	14.3	L**	31.4	23.9	35.7	24.9		38.8	20.6	36.0	56.6	L**
REMS	9.0*	10.4	0.3	3.6	L**Q**	11.4***	2.6	0	0		10.1*	8.5	4.0	2.0	L*

B. Tryptamine ($N = 6$)

Sleep/waking state	Period 1 (0–75 min)				ANOVA	Period 2 (75–150 min)				ANOVA	Period 3 (150–225 min)				ANOVA
	SAL	Tryptamine				SAL	Tryptamine				SAL	Tryptamine			
		0.04	0.08	0.12			0.04	0.08	0.12			0.04	0.08	0.12	
Active waking	12.9	4.2	11.3	15.5	L**	13.5*	6.8	5.4	7.2		12.7	9.0	7.3	7.0	
Quiet waking	15.1	14.2	20.3	31.5	L**	15.0	13.2	10.4	25.7	L*	14.4	7.9	11.1	10.8	
Total waking	28.0	18.4	31.6	47.0	L***	28.4	20.0	15.8	33.0		27.2	16.9	18.4	17.8	
Drowsy	16.7**	26.3	37.8	29.4		18.9	24.0	31.6	27.2		17.8	10.6	19.3	18.4	
Spindle	42.7	49.6	30.4	22.3	L***	38.5	46.8	48.9	38.5		42.4	51.7	46.4	51.0	
REMS	12.6***	5.7	0.3	1.4		14.2***	9.2	3.6	1.3	L*	12.6	20.8	15.8	12.7	

Mean effects (in % of 75-min segment) on six sleep/waking patterns by LSD (3.75, 7.5, 15 µg/kg), tryptamine (0.04, 0.08, 0.12 mg/kg/min) and saline (SAL) infusions. For each 75 min segment, results of an analysis of variance (ANOVA) are indicated for linear regression (L) and/or quadratic regression (Q). Also, significant placebo/drug difference is indicated for each SAL pattern. * $P < 0.10$, ** $P < 0.05$, *** $P < 0.01$

Table 2. LSD and tryptamine effects on EEG patterns

A. LSD ($N = 4$)

EEG measures	Period 1 (0–75 min)				ANOVA	Period 2 (75–150 min)				ANOVA
	SAL	LSD				SAL	LSD			
		3.75	7.5	15			3.75	7.5	15	
VRMS (μV)	9.6**	14.0	13.2	13.4		8.8**	13.2	13.1	13.6	
Delta (%)	34.6	35.3	34.9	36.2		31.5**	33.9	35.8	41.4	L**
Theta (%)	38.5	38.9	38.9	38.1		39.0	38.8	39.7	36.5	
Alpha (%)	12.1	12.0	12.0	11.9		13.4**	12.6	11.2	10.1	L**
Sigma (%)	4.6*	4.4	4.3	4.2		4.9**	4.7	4.0	3.5	L***
Beta (%)	10.2	9.5	9.9	9.6		11.2**	10.0	9.3	8.5	L*
Freq. (c/s)	6.6	6.4	6.6	6.5		7.0***	6.6	6.4	6.0	L**

B. Tryptamine ($N = 6$)

EEG measures	Period 1 (0–75 min)				ANOVA	Period 2 (75–150 min)				ANOVA
	SAL	Tryptamine				SAL	Tryptamine			
		0.04	0.08	0.12			0.04	0.08	0.12	
VRMS (μV)	8.9	11.6	11.6	11.2		8.8*	11.2	13.3	12.0	
Delta (%)	32.7	26.8	27.6	26.3		32.7	26.5	31.0	28.9	
Theta (%)	41.0	41.3	41.9	40.3		40.1	41.0	42.1	39.6	
Alpha (%)	12.4	15.4	14.5	18.6		12.9	14.9	13.3	14.9	
Sigma (%)	4.4*	5.4	5.2	5.7		4.5	5.6	4.5	5.4	Q*
Beta (%)	9.5	11.2	10.8	12.0		9.8	11.9	9.0	11.2	Q**
Freq. (c/s)	6.6*	7.3	7.1	7.4		6.6	7.4	6.6	7.2	Q*

Mean effects per 75-min segment on seven visual ECoG measures by LSD (3.75, 7.5, 15 μg/kg), tryptamine (0.04, 0.08, 0.12 mg/kg/min), and saline (SAL) infusions. Mean RMS voltage of the visual ECoG (VRMS) is reported in μV; five ECoG frequency band indices (delta, theta, alpha, sigma, and beta) are reported in % time; mean ECoG frequency (Freq.) is reported in c/s. For each 75 min segment, results of an analysis of variance (ANOVA) are indicated for linear regression (L) and/or quadratic regression (Q). Also, significant placebo/drug difference is indicated for each measure. * $P < 0.10$, ** $P < 0.05$, *** $P < 0.01$

pressed REM sleep within 2 min with the appearance of active wakefulness (restlessness) within 9 min. Brief ECoG spindling returned at 34 min and 53 min. With a second injection, ECoG spindling disappeared within 1 min and active wakefulness again appeared (within 3 min); ECoG spindling did not recur until after 63 min. At that point, a third injection of 10 μg of tryptamine led to the temporary disappearance of ECoG spindling within 2 min, but this effect was quickly overshadowed by increased spindling 60–70 min after the second injection. The cat became restless after the first two injections but not after the third injection.

Discussion

LSD has decreased REM sleep (Hobson, 1964; Stern et al., 1972; Zolovick et al., 1973; Brooks, 1975) and increased wakefulness (Bradley and Elkes, 1957; Hobson, 1964; Stern et al., 1972; Zolovick et al., 1973) in intact cats. Most of these investigators have found disruption of REM sleep with relatively low doses (2–10 μg/kg) of LSD, while wakefulness was clearly produced by higher doses (20–40 μg/kg). The present study indicates the wakefulness produced by LSD (3.75–15 μg/kg) is dose-related and is at least as sensitive a measure of LSD effect as is the disruption of REM sleep. Even larger doses (25–800 μg/kg) of LSD have produced mydriasis, greater arousal, EEG desynchronization, restlessness, and bizarre behavior (Lindsley et al., 1968; Winters et al., 1969; Brooks, 1975). LSD has also increased arousal and EEG activation in encephale isolé cats (Bradley and Key, 1958; Takagi et al., 1958; Kay et al., 1973).

Tryptamine effects on EEG and sleep/waking patterns have not been studied extensively. Bradley and Marley (1965) found that 0.25–1.0 mg/kg of i.v. tryptamine produced a short behavioral and EEG

arousal with hypertension in the encephale isolé cat. These changes were briefer, but similar to those produced by α-methyltryptamine. Mydriasis and multiple muscle spasms were seen with α-methyltryptamine but not with tryptamine. In this regard, Martin and Eades (1970) found that tryptamine produced mydriasis in the chronic spinal dog. Kay et al. (1973) found that replicated 0.5 mg/kg/min i.v. infusions of tryptamine for 2 min in six encephale isolé cats produced EEG desynchronization (decreased EEG delta and alpha spectral power), hypertension, and tachycardia. The present study demonstrates subtle but significant dose-related arousal by small doses (0.04–0.12 mg/kg/min) of tryptamine in intact cats. This investigation indicates that both LSD and tryptamine produce a change in arousal level characterized by decreased amount of REM and spindle sleep and increased wakefulness.

The mode of the CNS arousal effect of LSD or tryptamine is not yet clear. Several kinds of evidence indicate that the CNS may have functional tryptaminergic systems. Tryptamine is known to be present in the CNS of man, steer, cat, dog, guinea pig, and rat (Martin et al., 1972, 1976; Saavedra and Axelrod, 1972; Snodgrass and Horn, 1973; Sloan et al., 1975), and is released from multiple areas of the dog brain (Martin et al., 1974, 1976). Its greatest concentration is in the spinal cord and basal ganglia (Martin et al., 1972; Snodgrass and Horn, 1973). Possibly, one such tryptaminergic system subserves an arousal function.

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