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DISSOCIATIONS BETWEEN THE EFFECTS OF HALLUCINOGENIC DRUGS ON BEHAVIOR AND RAPHE UNIT ACTIVITY IN FREELY MOVING CATS*

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SUMMARY

The hypothesis that the action of hallucinogenic drugs is mediated by a depression of the activity of brain serotonergic (raphe) neurons was tested by examining the behavioral effects of several hallucinogenic drugs while concurrently monitoring the activity of raphe neurons in freely moving cats. LSD produced a dose-dependent decrease in raphe unit activity and a dose-dependent increase in certain behaviors (e.g. limb flick and abortive groom), and the peak of the behavioral and unit changes were temporally correlated. However, there were three important dissociations between the behavioral and electrophysiological effects of LSD. Firstly, low doses of LSD produced only small decreases in raphe unit activity but significant behavioral changes. Secondly, the duration of LSD-induced behavioral changes significantly outlasted the depression of raphe unit activity. And thirdly, raphe neurons were at least as responsive to LSD during tolerance as they were in the nontolerant condition. Psilocin produced a dose-dependent decrease in raphe unit activity, while the behavioral changes were not dose-related. However, the peak behavioral changes corresponded to the maximal depression of raphe unit activity. The phenylethylamine hallucinogens, DOM and mescaline, both produced large behavioral changes but no overall effect on raphe neurons. Following administration of DOM or mescaline, some raphe units showed a significant increase, while some showed a significant decrease, and others showed no change in activity. Therefore, the phenylethylamine hallucinogens may exert a depressant effect upon a subset of serotonin-containing neurons, and an amphetamine-like excitatory effect upon an-

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other subset of these neurons. Consistent with previous studies, all hallucinogens produced a high concentration of slow waves in the cortical EEG. Following administration of LSD or psilocin, the appearance of slow waves in the EEG was often associated with a transitory decrease in unit activity, while this was not observed for the phenylethylamine hallucinogens. The present data, in conjunction with recent data from other laboratories, suggest that the serotonin hypothesis of hallucinogenic drug action should be re-evaluated.

INTRODUCTION

A considerable body of neurochemical and electrophysiological evidence suggests that LSD and related hallucinogens may exert their dramatic psychological effects by means of an action upon central serotonergic neurotransmission[2,9,12,37]. The most compelling of these data come from electrophysiological studies demonstrating that administration of small quantities of LSD and other hallucinogens selectively depress the discharge rate of brain serotonin-containing raphe neurons in rats[3,15]. When these drugs are applied microiontophoretically to raphe target neurons in the forebrain, they have little effect. Based on these and other data, Aghajanian and Haigler proposed the following model to account for drug-induced hallucinogenesis: LSD and related drugs act preferentially upon serotonin-containing raphe neurons in the midbrain to suppress their activity[7,15], and because of serotonin's inhibitory synaptic action in the forebrain, this depression of raphe unit activity produces a disinhibition of target neurons in the visual and limbic systems, giving rise to two of the most salient features of the action of hallucinogenic drugs: alterations of visual perception, and rapid and dramatic changes in mood[4].

It should be pointed out, however, that this hypothesis is based solely on electrophysiological data obtained from immobilized and/or anesthetized animals. Therefore, several years ago we began to study the behavioral effects of hallucinogens in conjunction with various electrophysiological and neurochemical measures. The availability of an electrophysiological technique that permits stable and long-term recordings from central nervous system neurons in the freely moving cat[16,33], together with an animal behavior model for the action of hallucinogens which parallels the major characteristics of the actions of these drugs in humans[20,21,31], made these studies feasible. (No claim is made that this model is isomorphic with human hallucinations, but simply that there are close parallels between the major parameters.)

In our first experiment, we administered various doses of 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) a molecularly simple hallucinogen[32]. We found that the onset, peak and offset of the behavioral changes were very closely related, temporally, to the onset, peak and offset of depression of dorsal raphe unit activity. Furthermore, both the behavioral and unit changes showed clear dose–response relationships. We felt that these data with 5-MeODMT provided perhaps the strongest evidence in favor of the serotonin hypothesis of hallucinogenic drug action.

The present study more fully explores the relationship between the behavioral and electrophysiological effects of hallucinogenic drugs in freely moving cats. We

investigated the effects upon raphe unit activity of an additional indole nucleus hallucinogen, psilocin, and the effects of two phenylethylamine hallucinogens, 2,5-dimethoxymethamphetamine and mescaline. As a control for the catecholamine-releasing action of these latter drugs, we also studied the effects of amphetamine on raphe unit activity. Finally, we have examined the behavioral and electrophysiological effects of what many consider the prototypic hallucinogen, lysergic acid diethylamide (LSD), which contains both indole and phenylethylamine moieties.

METHODS

Under pentobarbital anesthesia, 29 adult female cats were implanted with a microdrive, consisting of two inner cannulae (separated by 1 mm), which could be lowered through two outer guide cannulae. It was positioned at an angle of 45° behind the vertical so that the tip of the anterior cannula was 5.5 mm above and 5.0 mm caudal to the center of the dorsal raphe nucleus. Two bundles of microelectrodes, each consisting of three 32 μm and three 62 μm diameter insulated nichrome wires, were then lowered through the inner cannulae and glued at points where the tips were approximately 1 mm above and 1 mm caudal to the dorsal raphe nucleus (anterior bundle coordinates: AP (—) 1.5, H (+) 1.0, L 0.0). When the inner cannulae were manually advanced, the microelectrodes were moved anteroventrally through the brain. Gross electrodes for recording the electroencephalogram (EEG), electro-oculogram (EOG) and neck electro-myogram (TMG) were implanted according to standard techniques.

Electrical potentials were led from the cat by a counterweighted cable system and slip ring assembly. Potentials from the microelectrodes were amplified, filtered (band pass 0.5–10 kHz), monitored continuously on an oscilloscope and stored on magnetic tape. Unit activity was separated from background noise by means of a variable threshold gate-Schmitt trigger. The Schmitt trigger output was used to obtain an on-line output of the cell discharge through a speaker and on a polygraph. EEG, EOG and EMG potentials were simultaneously displayed on polygraph paper.

During a 4–6 week postoperative period, the cats were habituated to a sound-attenuating chamber (65 × 65 × 95 cm high) with a 66 dB masking noise. All recordings were conducted during the light portion of the light–dark cycle (on 07.00 h, off 19.00 h). Behavior was continuously monitored on a T.V. screen and scored 'on-line' on polygraph paper.

Experimental sessions began with a baseline recording period which contained periods of both active and quiet waking. Then an intraperitoneal injection of either saline (0.5 ml/kg) or one of the following drugs was given: LSD tartrate (10 or 50 μg/kg), brom-LSD (BOL, 50 μg/kg), psilocin (25, 100 or 750 μg/kg), mescaline HCl (5 mg/kg), 2,5-dimethoxy-4-methamphetamine HCl (DOM, 50, 250 or 1000 μg/kg), or D-amphetamine sulfate (2.5 or 5.0 mg/kg) (doses expressed as the salt). Raphe unit activity and behavior were directly monitored and scored for the next 1–8 h by an experimenter 'blind' to the treatment condition. The definitions of the behavioral categories employed have been described in detail in our previous studies of

hallucinogenic drugs, e.g. refs. 21 and 32. Only one drug injection was given for each unit, and at least one week elapsed between successive injections in the same cat, with the exception of the LSD tolerance study. In this latter case, a second injection of 50 μg/kg of LSD was given 24 h after the initial injection of 50 μg/kg. The effects of LSD (50 μg/kg) on non-serotonergic neurons outside the raphe nucleus was also investigated. The various drugs and doses were counterbalanced within cats.

At the completion of the study, the cats were deeply anesthetized with sodium pentobarbital, the microdrives were moved to the positions where the final unit recording for each cat was obtained, and a 20 μA direct current was passed for 10 sec through the electrodes from which units had been recorded. The cats were then perfused intracardially with physiological saline followed by 10% formalin, and then 5% potassium ferrocyanide in formalin (Prussian blue reaction). The brains were then removed and 50 μm thick frozen sections were cut through the pons and mesencephalon. Sections were mounted on slides, stained with Neutral red, and recording sites (blue spots) located and electrode tracks reconstructed with the aid of a microscope. This permitted the localization of all recording sites by extrapolation from the final recording locus.

The following statistical analyses were performed on the unit activity data. For each drug, a one-way analysis of variance (ANOVA) of the dose effect (including saline as a dose of 0.0 mg/kg) was performed. This was followed by statistical analysis of the difference between means of saline vs each dose of the drug at each time point postinjection using 2-tailed t-tests. Finally, drug-induced changes in the activity of individual units were assessed by comparing the mean discharge rate of the unit during the time of its maximal change postinjection with its baseline (preinjection) discharge rate. A change from the baseline of the mean $\pm$ 2 S.D. is significant at the $P < 0.05$ level.

For statistical analysis of the behavioral data, group means of saline baseline for each behavior were compared with the group means of the corresponding behavior for each dose of each drug at each time point post-injection using 2-tailed t-tests. In addition, the overall change in each behavior from saline baseline during the first hour post-injection was assessed (Table I).

RESULTS

During baseline recordings, 95 of the neurons examined displayed the slow regular activity characteristic of serotonergic neurons[33]. Baseline unit activity was stable over time for a given behavioral state, showing less than 5% variation. Upon histological examination, these 95 cells were found to be localized on, or near, the midline within the dorsal raphe nucleus (Fig. 1). Seven neurons which displayed irregular, high-frequency discharge rates were also studied and were found to be localized outside (lateral and/or ventral to) the dorsal raphe nucleus.

Following the administration of LSD, cats displayed the characteristic behavioral syndrome consisting of limb flicking, abortive grooming, head shaking and investigatory responses, as previously described[20,21]. Of these behaviors, the limb flick has proven to be the most sensitive and reliable index of hallucinogenic drug

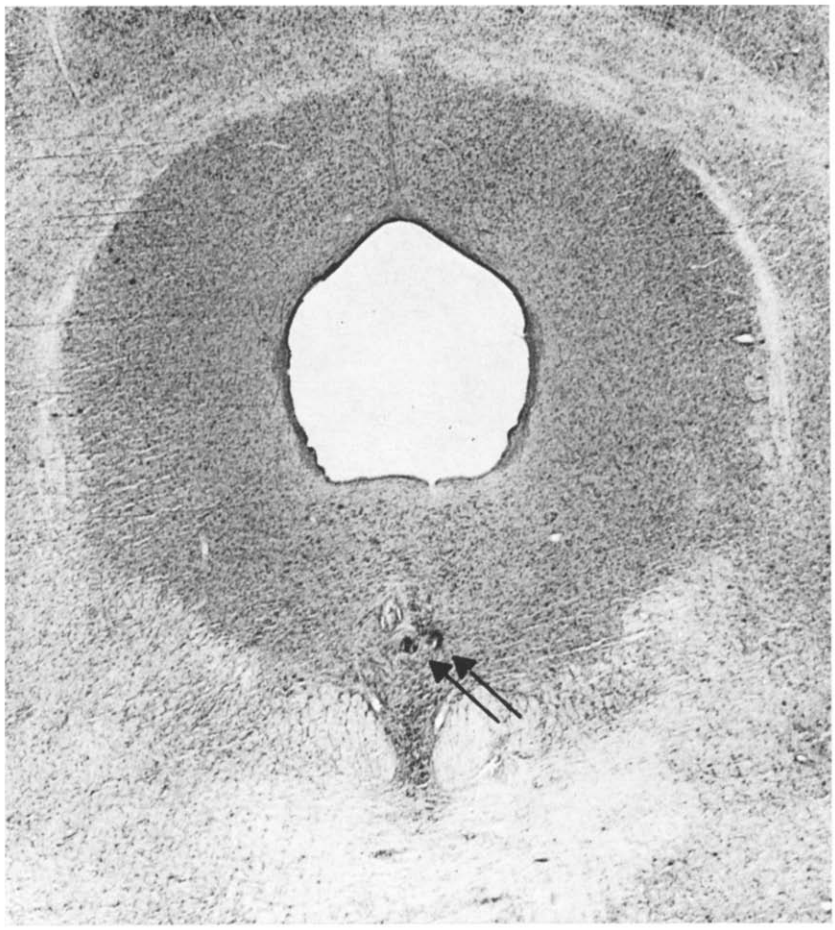

Fig. 1. Histological localization of recording sites. This photograph shows two Prussian blue reactions in the dorsal raphe nucleus. The spots were produced by passing a 20 μA direct current through two nichrome microelectrodes and then perfusing the tissue with a 5% potassium ferrocyanide solution. The section is stained with a contrasting Neutral red to facilitate microscopic localization of the blue spots.

action[21,31], and was therefore used for the correlational analysis between raphe unit activity and behavior in this study. LSD produced a dose-dependent decrease in raphe unit activity ($P < 0.05$, ANOVA) and a dose-dependent increase in the rate of limb flicking ($P < 0.05$, ANOVA) (Fig. 2). A significant decrease in unit activity usually occurred within 5–10 min postinjection, and limb flicks usually began to appear during this time interval. The peak limb flick rate occurred between 30 and 60 min postinjection, a time course which corresponded to the maximal depression of raphe unit activity (Fig. 2).

A dose of 10 μg/kg of LSD produced a significant depression of raphe unit activity from saline control levels (—11.8 to —17.5%, $P < 0.05$) at each time point between 5 and 60 min postinjection, with the exception of the 45 min time point (Fig. 2). Seven of the 10 units tested at this dose showed a significant decrease in activity.

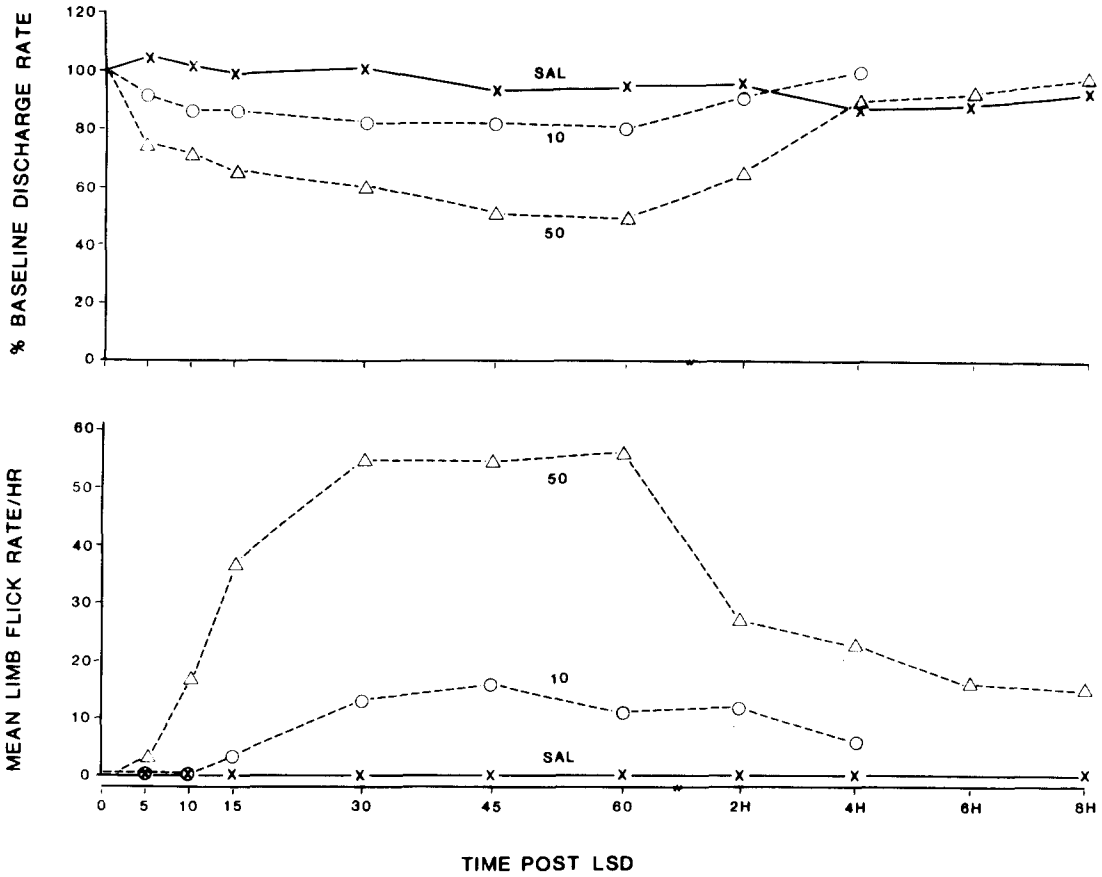

Fig. 2. Time course of the effects of LSD (10 and 50 μg/kg) and saline on the activity of dorsal raphe neurons (upper panel) and the occurrence of limb flicks (lower panel). Note that the behavioral change outlasts the change in unit activity for both doses of LSD. Measures of variance about the mean are omitted from all figures for the sake of clarity. The numbers 0–60 represent minutes.

Unit activity had returned to baseline levels within 2 h postinjection, whereas the limb flick rate was significantly above baseline for at least 4 h ($P < 0.02$). The low dose of LSD also produced significant increases in head shaking and yawning (Table I).

A dose of 50 μg/kg of LSD produced a significant decrease in raphe unit activity from saline control levels (—29.2 to —43.5%, $P < 0.01$) at each time point between 5 min and 2 h postinjection. The discharge rate of 28 of the 30 raphe units was significantly decreased by the 50 μg/kg dose of LSD (Fig. 3). Unit activity returned to baseline levels within 4 h postinjection, while the limb flick rate was significantly above baseline for at least 8 hours ($P < 0.01$). A dose of 50 μg/kg of LSD also produced significant increases in abortive grooming, head shaking, staring, investigatory or play behavior and yawning (Table I).

Twenty-four hours after the initial dose of LSD (50 μg/kg), a second dose of 50 μg/kg was virtually without behavioral effect (e.g. only 0.3 limb flicks/h, no abortive

TABLE I

Behavioral effects of LSD, psilocin, DOM and mescaline

Drug	*n*	*Dose (μg/kg)*	*Behavior (mean frequency/h ± S.E.M.)*							
			Flick	*Abortive groom*	*Shake*	*Groom*	*Stare*	*Investigatory or play behavior*	*Hallucinatory -like behavior*	*Yawn*
Saline	8	—	0.0	0.0	2.8±1.1	3.2±1.2	0.9±0.5	0.2±0.2	0.0	0.0
LSD	10	10	10.4±3.2*	2.3±1.9	9.8±1.8**	6.0±3.1	4.1±24	4.3±2.9	0.8±0.6	2.4±0.9*
	30	50	46.4±3.1***	6.9±1.1**	32.6±3.9**	12.6±2.7	10.1±1.7*	8.4±1.9*	1.8±0.8	7.2±1.6*
Psilocin	5	25	1.8±0.9*	0.8±0.6	5.8±3.3	10.0±4.9	3.6±3.8	2.8±1.3	0.4±0.4	1.4±0.8
	5	100	4.2±1.9*	0.2±0.2	8.4±2.4*	4.0±1.9	3.6±1.2*	2.0±0.4**	0.0	0.6±0.7
	6	750	1.0±0.9	0.0	2.4±2.2	0.8±0.7	5.7±2.3*	0.8±0.7	0.2±0.2	0.2±0.2
DOM	5	50	13.4±7.4*	1.4±0.8*	18.2±10.0	7.6±2.7	5.8±3.8	2.4±0.8**	1.6±1.3	2.6±1.2*
	5	250	29.8±11.1**	8.3±3.2**	43.3±3.6**	10.0±5.1	1.0±1.2	4.0±1.8*	0.8±0.9	15.5±4.8**
	5	1000	13.8±6.0*	1.0±1.1	6.4±1.7	7.8±6.8	0.6±0.4	2.4±1.6	4.4±2.6	1.2±0.8
Mescaline	8	5000	6.6±2.6**	0.8±0.5	4.5±1.8	1.5±1.1	3.0±2.0	0.3±0.2	0.0	1.6±1.6

Differs significantly from saline control, 2-tailed *t*-test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

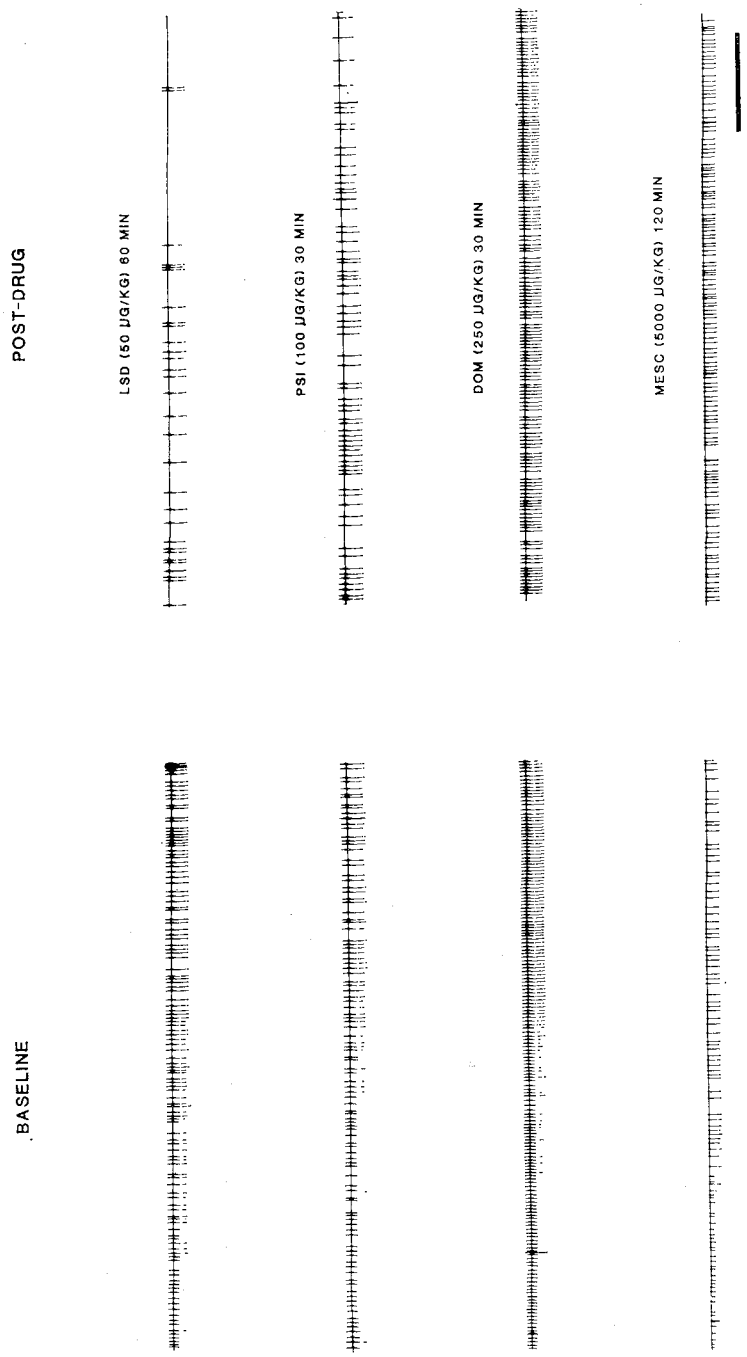

Fig. 3. Typical raphe unit responses to various hallucinogenic drugs at the time of their peak behavioral effect. The spikes are triggered standard pulse outputs of a spike height discriminator which are written out on polygraph paper. Time marker represents 10 sec.

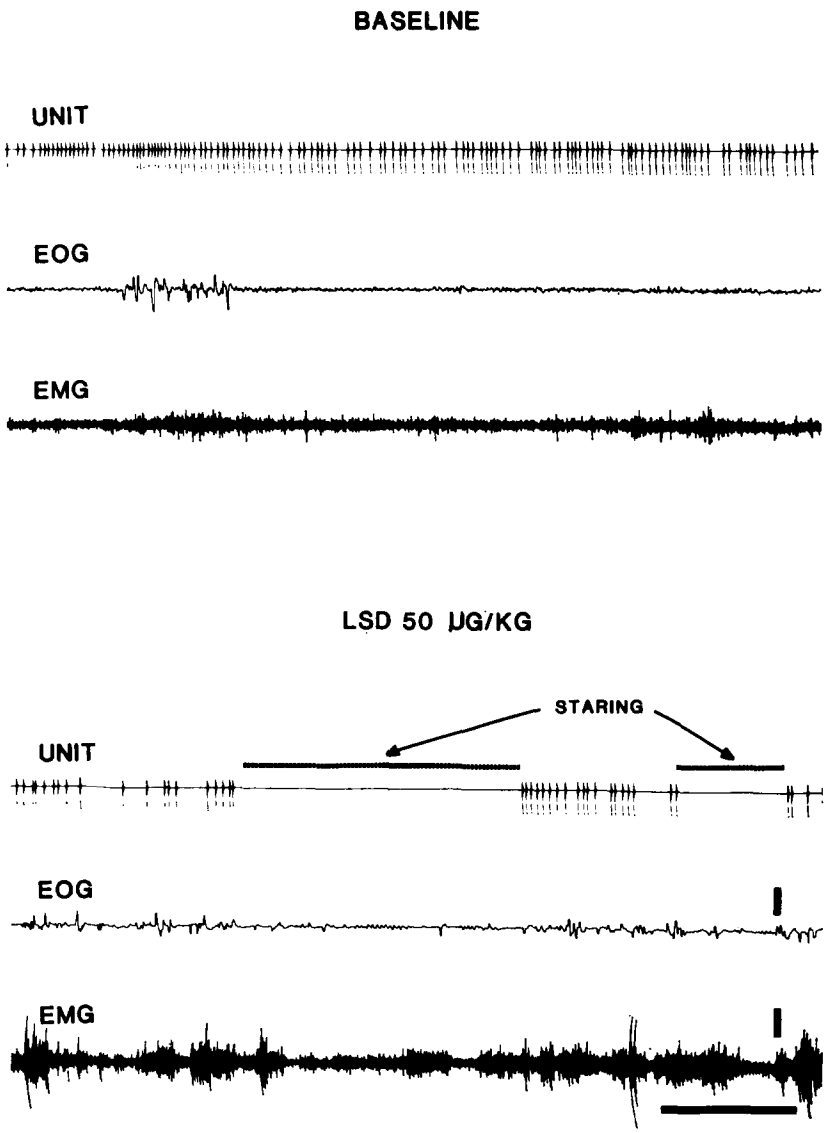

Fig. 4. Activity of a raphe neuron which showed a significant depression of activity in response to LSD (50 μg/kg) as compared to baseline, and then a complete suppression during staring. Note the paucity of both eye movements (EOG) and phasic electromyographic (EMG) activity during staring. Calibrations: EOG, 50 μV; EMG, 100 μV; time, 10 sec.

grooming or investigatory behavior, 3.1 shakes and 1.6 stares/h) but it produced an even greater maximal decrease (—62.4%, $P < 0.01$) in raphe unit activity.

A number of common features characterized the relationship between the effects of LSD and the other hallucinogenic drugs upon unit activity and behavioral or electrophysiological measures. The activity of a number of raphe units was completely suppressed for periods of from 5 to 30 sec during staring (Fig. 4). This occurred in

approximately 50% of the cells tested with LSD, and was much more common at the higher dose, and was also observed following psilocin and DOM administration, but on a smaller percentage of the cells. This phenomenon was not observed following mescaline administration. Although LSD produced an overall decrease in raphe unit activity of approximately 40% after a dose of 50 μg/kg, presentation of an arousing stimulus, such as a click or light flash, would consistently result in a large, but transitory, increase in unit activity, often returning to predrug levels (Fig. 5). This was also seen following psilocin administration. LSD and the other hallucinogens also produced a dominance of slow waves in the EEG. With LSD (especially at 50 μg/kg), these slow waves appeared within 5–10 min postinjection and persisted for 4–8 h.

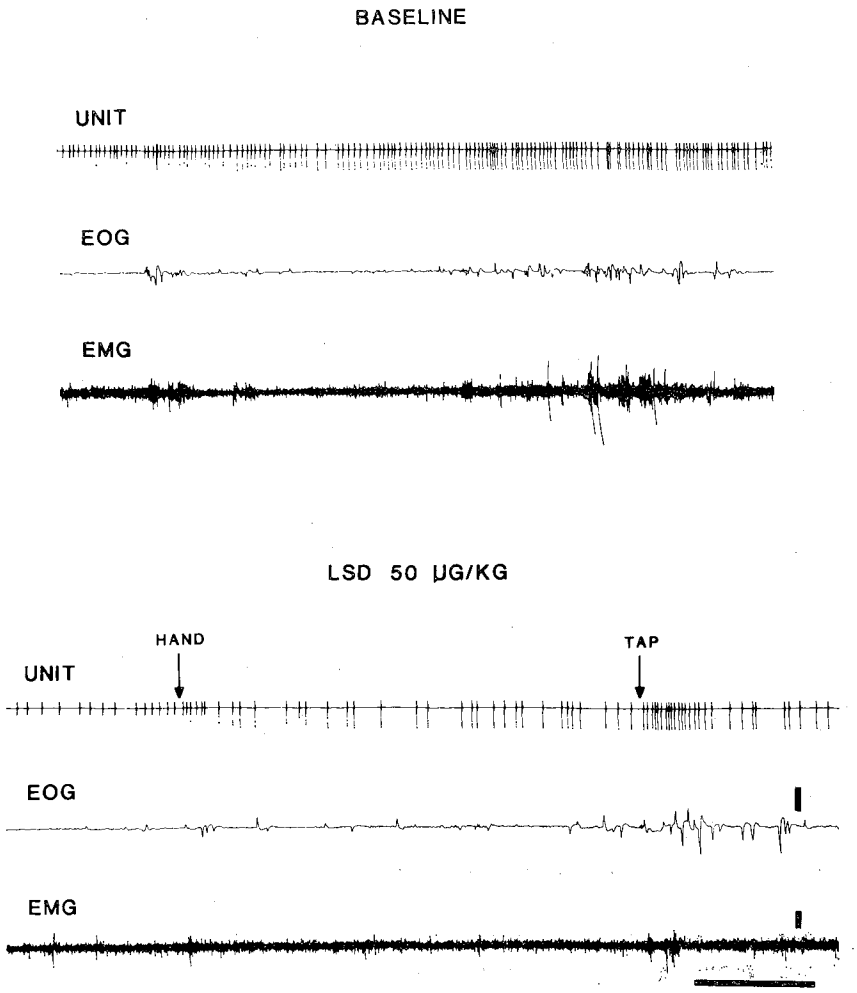

Fig. 5. Activity of a raphe neuron which was significantly depressed by LSD (50 μg/kg) as compared to baseline, but which manifested a phasic increase in rate in response to two mildly arousing stimuli. In the first case, the experimenter moved his hand into the cat's field of vision, and in the second case, the experimenter tapped on the experimental chamber. Note that the activity in response to these stimuli returns approximately to baseline. See legend to Fig. 4 for abbreviations and calibrations.

Raphe unit activity frequently showed a sharp decrease in association with the occurrence of slow waves in the EEG following administration of LSD or psilocin.

Neither saline nor BOL had any significant effect on either raphe unit activity or behavior. LSD (50 μg/kg) produced no significant effect on non-serotonergic cells outside the dorsal raphe nucleus.

Psilocin produced a dose-dependent decrease in raphe unit activity ($P < 0.05$, ANOVA), while the rate of limb flicking significantly increased at 25 and 100 μg/kg doses, but then decreased at the highest dose, 750 μg/kg. A significant decrease in unit activity usually occurred within 5–10 min postinjection. The peak limb flick rate occurred between 10 and 30 min postinjection, a time course which corresponded to the maximal depression of raphe unit activity (Fig. 6).

None of the raphe cells tested at a dose of 25 μg/kg of psilocin showed a significant change in their activity. This low dose of the drug, however, produced

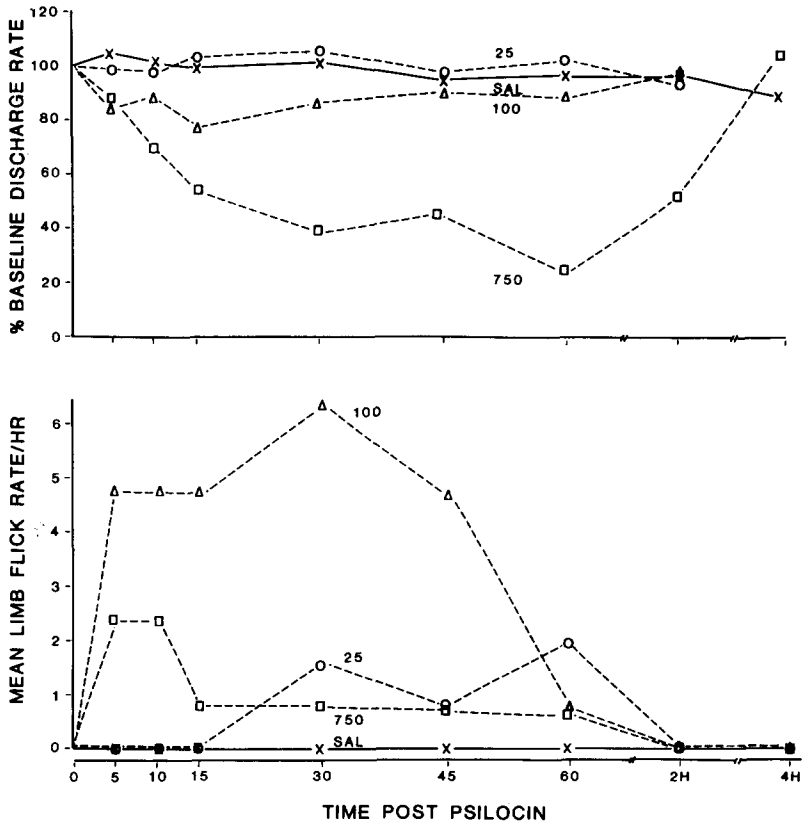

Fig. 6. Time course of the effects of psilocin (25, 100 and 750 μg/kg) and saline on the activity of dorsal raphe neurons (upper panel) and the occurrence of limb flicks (lower panel). Note that the maximal behavioral effect is produced by the intermediate dose of psilocin. See legend to Fig. 2 for further details.

small, but significant, increases in the rate of limb flicking and investigatory or play behavior (Table I). Following the 100 μg/kg dose, raphe unit activity was significantly decreased from saline baseline only at 5 (—22.4%) and 15 min (—23.1%) postinjection ($P < 0.05$, t-test), while the limb flick rate was significantly increased at 5, 10, 15, 30 and 45 min postinjection ($P < 0.05$, t-test). Four of the 5 cells tested at 100 μg/kg showed a significant decrease in activity (Fig. 3). This dose of psilocin also produced significant increases in head shaking, staring, and investigatory or play behavior (Table I). The highest dose of psilocin (750 μg/kg) produced significant decreases in raphe unit activity (—31.4 to —71.6%) as compared to saline baseline ($P < 0.01$, t-test) at each time point between 10 and 60 min postinjection (Fig. 6). All 6 of the units tested at this dose showed a significant decrease in activity. Unit activity was still significantly decreased (—43.7%, $P < 0.02$) at 2 h postinjection, but had returned to baseline levels by 4 h after psilocin administration. Interestingly, the highest dose of psilocin produced no significant increase in the rate of limb flicking (Table I).

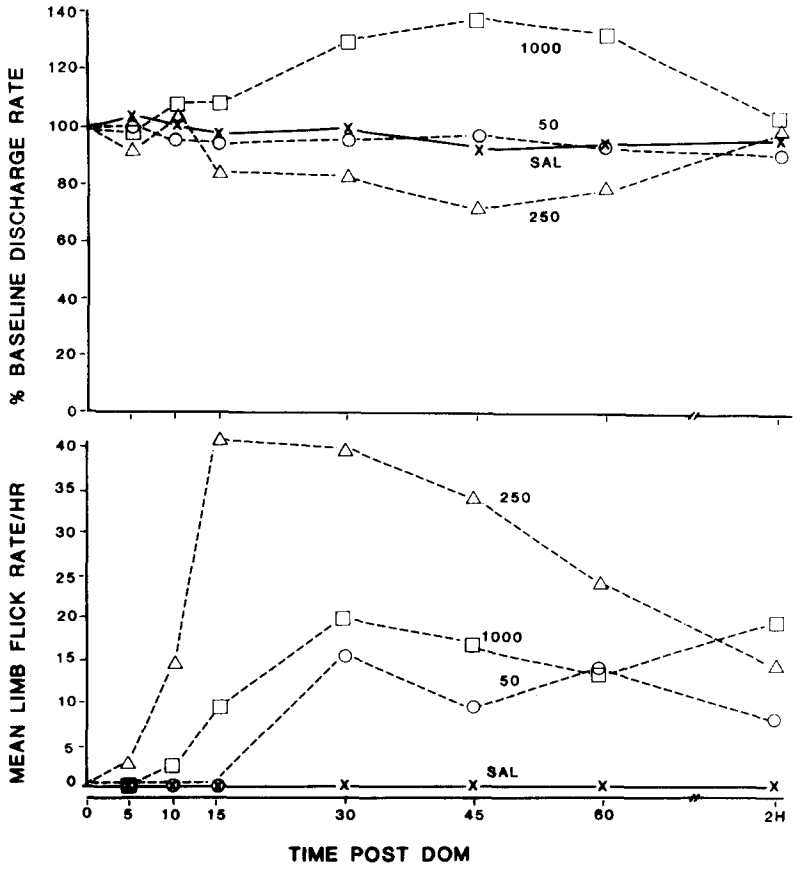

Fig. 7. Time course of the effects of DOM (50, 250 and 1000 μg/kg) and saline on the activity of dorsal raphe neurons (upper panel) and the occurrence of limb flicks (lower panel). See legend to Fig. 2 for further details.

There was no dose-dependent change in raphe unit activity following administration of DOM ($P > 0.2$, ANOVA). The lowest dose of the drug (50 μg/kg) produced no significant change in raphe unit activity, as compared to saline baseline, at any time point (Fig. 7). None of the cells tested at the low dose of DOM showed any significant change in their activity. This dose of the drug, however, produced significant increases in the rate of limb flicking, abortive grooming, investigatory or play behavior and yawning (Table I). The intermediate dose of DOM, 250 μg/kg, produced a significant decrease in raphe unit activity only at 45 min postinjection (—23.6%, $P < 0.05$, t-test). (Fig. 7); and only 2 of the individual units showed a significant decrease in activity. This dose of the drug produced significant increases in the rate of limb flicking, abortive grooming, head shaking, investigatory or play behavior, and yawning (Table I). The highest dose of DOM, 1000 μg/kg, produced a significant increase in raphe unit activity at 30 (+29.2%), 45 (+43.4%) and 60 min (+37.7%) postinjection ($P < 0.05$, t-test). Three of the 5 individual units tested at the high dose of DOM showed a significant increase in their activity, and the other 2 showed no significant change. Unit activity returned to baseline levels within 2 h postinjection.

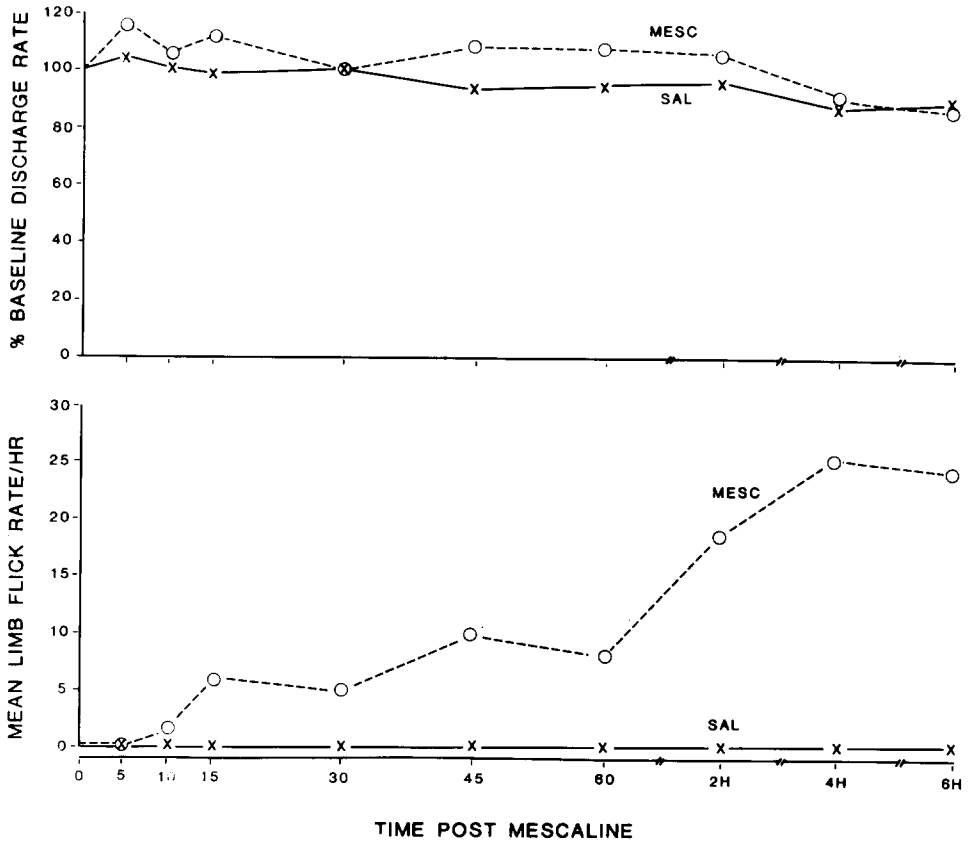

Fig. 8. Time course of the effects of mescaline (5000 μg/kg) and saline on the activity of dorsal raphe neurons (upper panel) and the occurrence of limb flicks (lower panel). See legend to Fig. 2 for further details.

The 1000 μg/kg dose of DOM produced a significant increase in the rate of limb flicking by 15 min postinjection (Fig. 3), and persisted for at least 2 h.

Administration of mescaline (5000 μg/kg) produced no significant overall change in raphe unit activity (Fig. 8). Three of the units showed a significant increase in activity (Fig. 3), 3 showed a significant decrease, and 2 showed no significant change. The only significant behavioral change observed following mescaline administration was in the rate of limb flicking (Table I). The onset of limb flicking following mescaline treatment showed a long latency, and peaked only 4–6 hours after mescaline administration (Fig. 8). Most cats vomited within a few minutes after mescaline administration, but otherwise appeared healthy. This single dose of mescaline (5000 μg/kg) was chosen for the present study because our previous studies had shown that higher doses were too toxic, and lower doses were without significant behavioral effects[19]. Mescaline consistently produced a high concentration of slow waves in the EEG, which began approximately 20 min postinjection and persisted for at least 3–4 h. In contrast to the LSD and psilocin findings, but in agreement with the results with DOM, the appearance of slow waves in the EEG following mescaline administration was rarely accompanied by a transitory change in raphe unit activity.

Amphetamine administration produced no overall significant change in raphe unit activity ($P > 0.2$, ANOVA). The lower dose of the drug, 2.5 mg/kg, resulted in a mean, non-significant, increase in unit activity (+22.0 to +54.2%) at each time point between 5 min and 3 h postinjection. Two of the individual units showed a significant increase in activity, while one showed a significant decrease and two showed no significant change. The activity of those units that showed a significant change returned to baseline levels within 4 h postinjection. The higher dose of amphetamine, 5.0 mg/kg, also resulted in an overall non-significant increase in unit activity of between +19.0 and +39.7%, and this increase in unit activity persisted for at least 3 h postinjection. Two of the units showed a significant increase in activity, and one showed no change. Amphetamine administration did not elicit any of the behaviors, e.g. limb flick, abortive groom, etc., characteristic of hallucinogenic drugs. The only behavioral changes induced by amphetamine administration were stereotyped behaviors whose form varied considerably among cats. In the most common type of stereotypy, the cat assumed a fixed gross body position, usually sitting, and displayed high frequency movements of the eyes and head. These behaviors usually began within 10 min postinjection, and persisted for up to 4–8 h. Administration of amphetamine also produced strong sympathomimetic signs in some cases (e.g. mydriasis, salivation, panting and vomiting), particularly at the higher dose.

DISCUSSION

In contrast with our previous data with 5MeODMT, showing strong temporal correlations between behavioral and raphe unit changes[32], the present study reveals a number of important dissociations between the behavioral and raphe unit effects of hallucinogenic drugs. Perhaps most surprising is the apparent lack of any consistent effect common to the various drugs.

Our results with psilocin, also a simple indole-nucleus hallucinogen, most closely parallels the results obtained with 5MeODMT. Psilocin produced a dose-dependent decrease in raphe unit activity, and the onset of the electrophysiological and behavioral changes were temporally correlated. Furthermore, the maximal depression of unit activity roughly corrresponded to the peak behavioral effect. However, there were two dissociations between the behavioral and electrophysiological effects of psilocin. Firstly, the lowest dose of the drug (25 μg/kg) produced a small, but significant, increase in the rate of limb flicking, but no significant change in raphe unit activity. Secondly, the highest dose of psilocin, 750 μg/kg, produced a very large depression of raphe unit activity, but no significant increase in the rate of limb flicking. This may be attributable to a direct agonist action of psilocin on postsynaptic serotonin receptors at this high dose. Since the limb flick response is apparently due to an inactivation of central serotonergic neurotransmission[18], a direct agonist action of a drug upon postsynaptic serotonin receptors would be expected to block the response. Interestingly, cats that received the high dose of psilocin often showed a splaying of the limbs, a behavior reminiscent of the 'serotonin syndrome' elicited by increased synaptic serotonin in other species[17].

In the case of the phenylethylamine hallucinogens, there were no overall correlations between the electrophysiological and behavioral effects of the drugs. DOM, at the two lower doses (50 and 250 μg/kg) produced no overall significant changes in raphe unit activity, but resulted in large behavioral changes. At the highest dose tested (1000 μg/kg), DOM produced highly significant behavioral changes in the presence of large *increases* in raphe unit activity. Neurochemical studies have shown that DOM decreases serotonin turnover[6,22], which would appear inconsistent with the electrophysiological results in the present study. These neurochemical studies, however, were performed in rats, and DOM has been shown to depress the activity of a subgroup of raphe neurons in rats[3]. Only 2 of 15 cells tested in the present study showed a significant decrease in activity following DOM administration. Thus, in the absence of neurochemical studies of serotonin turnover in cats, it is not known whether a dissociation exists between the neurochemical and electrophysiological measures of the activity of the serotonin system.

The same general set of circumstances exists with respect to mescaline. In the present study, mescaline produced large behavioral changes with no accompanying overall change in raphe unit activity. Neurochemical studies of the effects of mescaline on the serotonin system have yielded conflicting results. Freedman et al.[10] reported that low doses of the drug decreased 5-HIAA levels, while high doses increased brain 5-HIAA. Consistent with this high dose effect, Tilson and Sparber[29] reported that mescaline increased release and/or re-uptake of serotonin. Tonge and Leonard[30], however, reported the opposite result, i.e. mescaline was found to increase serotonin levels and decrease brain 5-HIAA. These neurochemical studies, again, were conducted in rats, and Aghajanian et al.[3] found that a subgroup of raphe cells were inhibited by mescaline in rats. Three of the 8 cells testeds with mescaline in the present study showed a significant decrease in activity. Aghajanian et al.[3] also reported that amphetamine had a general excitatory effect on raphe neurons, which agrees with the

present results that the majority of raphe neurons in freely moving cats showed an increase in activity following amphetamine administration. Therefore, the inconsistent results with DOM and mescaline may be partly due to their exerting an inhibitory effect on one subset of serotonin-containing neurons, and an amphetamine-like excitatory effect on another subset of these neurons.

Our LSD data provide evidence both for and against the serotonin hypothesis of hallucinogenic drug action. LSD produced dose-dependent decreases in raphe unit activity and dose-dependent increases in the rate of limb flicking. Furthermore, as with 5MeODMT and psilocin, the peak behavioral and unit changes were temporally correlated. In addition, these effects were somewhat specific in that the changes in behavior and unit activity were not seen in response to BOL (a non-hallucinogenic congener of LSD), and LSD produced no significant changes in the activity of non-serotonergic cells.

There were, however, three important dissociations between raphe unit activity and the behavioral changes. First, as with 5MeODMT and psilocin, low doses of LSD produced only small decreases in raphe unit activity but produced significant behavioral changes. This result may simply be evidence that subtle changes in the activity of these neurons may precipitate dramatic behavioral changes. It probably also reflects the additional actions of LSD, such as dopaminergic effects[19,24,35] in eliciting the behaviors under study. In this regard, it is interesting that both 5MeODMT and psilocin, which are virtually devoid of dopaminergic actions, produced much smaller maximal behavioral changes, while DOM and mescaline, which possess potent dopaminergic effects, elicited much larger behavioral changes.

The second dissociation between the electrophysiological and behavioral effects of LSD is that the behavioral changes following LSD significantly outlasted the raphe unit changes. This finding may be explained by the continuing depression of serotonin release after raphe unit activity has returned to baseline[13]. It may also be due to a rapid change in sensitivity of neurons receiving a serotonergic projection from the raphe. The third dissociation is that raphe unit activity was at least as responsive to LSD during tolerance as during the nontolerant condition. The decrease in raphe unit activity during tolerance may be offset by a compensatory neuronal change, perhaps in raphe target neurons. We have recently gathered some preliminary evidence in support of this hypothesis from receptor binding studies[34].

Many raphe neurons displayed a virtually complete suppression of activity in association with staring following administration of hallucinogenic drugs. These neurons never showed this dramatic slowing of their activity during spontaneous staring in the non-drugged condition. The large decrease in activity during post-drug staring may be the result of a synergistic effect between the lowered level of arousal during this state (as indicated by decreased EOG activity and decreased tonic EMG activity during staring) and the direct inhibitory influence of the hallucinogen on raphe cells. These data are also consistent with our more general hypothesis that raphe unit activity may be inversely related to various forms of behavioral inhibition[33]. Finally, it is important to note that, at present, it is not clear which is the cause and which the effect in this relationship between staring and depressed raphe unit activity.

In agreement with previous studies[1,8,14,27,36], all hallucinogens produced a high concentration of slow waves in the EEG. Most of these previous studies used higher drugs doses or different routes of administration, making it difficult for any direct quantitative comparison. The consistent finding of hallucinogen-induced EEG synchronization, together with the generally depressed raphe unit activity following administration of these drugs, may provide insight into understanding hallucinations and, more generally, other altered states of consciousness. Following administration of an hallucinogen, we see an animal that is fully awake, but with an EEG pattern and raphe unit activity which normally occur during the drowsy state or slow wave sleep. Thus, in a given behavioral situation, an altered state of consciousness may be due, in part, to a key brain mechanism, such as the serotonin system, functioning in a manner appropriate to a different behavioral situation.

In conclusion, these and our previous data showing correlations between both the onset and peak of the behavioral and raphe unit changes for 5Me ODMT, psilocin and LSD, provide some support for the serotonin hypothesis of hallucinogenic drug action, especially in the broader context of the entire literature on the mechanisms of action of hallucinogenic drugs[5,11,32]. On the other hand, the several important dissociations between raphe unit activity and behavior make a simplistic serotonin theory of hallucinogenic drug action untenable. Further evidence for dissociation between drug-induced raphe unit activity and behavioral effects comes from a recent study by Rogawski and Aghajanian[25], who showed that lisuride (an ergot derivative structurally related to LSD) is 5–10 times as potent as LSD in depressing raphe neuronal activity, but has never been reported to produce hallucinations after acute administration to humans[26,28]. McGall and Aghajanian[23] recently reported that LSD, psilocin and related hallucinogens sensitize serotonin and norepinephrine receptors on motoneurons in the facial nucleus. While it is not readily apparent how an action on the facial nucleus (or other brain stem nuclei) could account for drug-induced hallucinations, if this phenomenon occurs throughout the central nervous system, the mechanism of receptor sensitization might contribute to the psychedelic effects of these drugs. It is interesting to note that all three neurotransmitters (serotonin, dopamine and norepinephrine) investigated in any detail for their involvement in drug-induced hallucinogenesis seem to play an important role in this process. Given the complexity of the psychological and perceptual changes in induced by these drugs, a great deal surely remains to be discovered.

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