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Dissociations Between the Effects of Hallucinogens on Behavior and Raphe Unit Activity in Behaving Cats

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TRULSON, M E *Dissociations between the effects of hallucinogens on behavior and raphe unit activity in behaving cats* PHARMACOL BIOCHEM BEHAV **24**(2) 351–357, 1986 —The hypothesis that hallucinogenic drugs exert their behavioral effects by an action at pre- or postsynaptic serotonin receptors was evaluated by co-administering various drugs that possess either serotonin agonist or antagonist properties, while concurrently monitoring behavior and the electrophysiological activity of serotonin-containing dorsal and median raphe neurons in freely moving cats Co-administration of the serotonin receptor blockers, metergoline or mianserin, with lysergic acid diethylamide (LSD) produced no change in the inhibitory effects of LSD on raphe neurons, but produced a dose-dependent blockade of the behavioral effects of LSD in the cat The latter data suggest that perhaps LSD exerts its behavioral effects by an action at postsynaptic serotonin receptors Co-administration of drugs that increase synaptic serotonin, L-5-hydroxytryptophan, tranylcypromine, fluoxetine or p-chloramphetamine with LSD greatly potentiated the inhibitory effect of LSD on raphe unit activity, but also produced dose-dependent decreases in these behavioral effects of LSD in the cat Thus, both enhancing the activity at postsynaptic serotonin receptors and receptor antagonism blocked the behavioral effects of LSD Co-administration of dopamine receptor blockers, haloperidol or chlorpromazine, produced no significant change in the response of raphe neurons to LSD, but these drugs also produced a dose-dependent blockade of the behavioral effects of LSD in the cat Co-administration of the dopamine agonists, apomorphine or d-amphetamine, however, potentiated the behavioral effects of LSD, while producing a partial reversal of the inhibitory effects of LSD on raphe unit activity The results are discussed in the context of using animal models to study the possible actions of hallucinogens in humans

Hallucinogens Raphe unit activity Serotonin Dopamine Animal models

A large amount of data has accumulated to suggest that hallucinogens produce their psychological and perceptual effects via an action upon central serotonergic neurotransmission [1, 2, 11, 12, 13] Based upon a variety of these studies, Aghajanian and Haigler [3,15] proposed the following model to account for drug-induced hallucinogenesis Lysergic acid diethylamide (LSD) and related drugs selectively suppress the activity of serotonin (5HT)-containing raphe neurons in the midbrain, and because of the inhibitory synaptic action of 5HT in forebrain structures, this depression of raphe cell firing results in a disinhibition of target neurons in the visual and limbic systems This, in turn, gives rise to two of the most characteristic aspects of hallucinogenic drug action, i e , alterations of visual perception and rapid and dramatic changes in mood

This hypothesis, however, was derived solely from data obtained in electrophysiological experiments utilizing immobilized and/or anesthetized animals In order to examine the activity of raphe neurons in unrestrained animals, we refined an electrophysiological technique [47] originally developed by McGinty and Harper [25] which permits stable and long-term recordings of raphe neurons in freely moving cats This technique, together with a cat behavior model for the action of hallucinogens [18, 19, 38, 41, 42] which parallels the major characteristics of the actions of these drugs in humans, made it possible to study the behavioral effects of hallucinogens in conjunction with the electrophysiological measures While this behavioral model is not totally specific for hallucinogens, it is useful in studying various aspects of the actions of hallucinogenic drugs [22, 23, 36, 37, 38, 54]

In our first study [46] we examined the behavioral and electrophysiological effects of the molecularly simple indole-nucleus hallucinogen, 5-methoxy-N-N- dimethyltryptamine (5-MeODMT) We found that the onset, peak and offset of the behavioral changes were very closely related, temporally, to the onset, peak, and offset of the suppression of dorsal raphe (RD) unit activity In addition, both the behavioral and unit changes showed clear dose-response relationships at 10, 50 and 250 μg/kg Therefore, these data with 5-MeODMT provided strong evidence in support of the 5HT hypothesis of hallucinogenic drug action, as originally proposed by Aghajanian and his colleagues

We then examined the effects of other hallucinogens, including psilocin, mescaline, 2,5-dimethoxy-4- methylamphetamine (DOM) and LSD and found a number of important dissociations between these behavioral effects of LSD in the cat and RD unit activity Perhaps most surprising was the lack of any consistent effect across the various drugs [40] LSD produced a dose-dependent decrease in raphe unit activity at 10, 50 and 100 μg/kg and a dose-dependent increase in certain behaviors (e g , limb flick and abortive grooming), and the peak of the behavioral and unit changes were tem-

TABLE 1

BEHAVIORAL EFFECTS OF LSD (50 μg/kg) IN CATS*

Treatment	Limb Flick	Abortive Groom	Head Shakes	Groom	Stare	Investigatory Behavior	Hallucinatory-like Behavior	Yawn
Saline	0 1 ± 0 1	0 0 ± 0 0	3 1 ± 0 4	4 6 ± 0 9	1 2 ± 0 2	0 9 ± 0 5	1 2 ± 0 4	0 5 ± 0 1
LSD	42 4 ± 0 1†	7 4 ± 0 6†	37 2 ± 2 1†	19 4 ± 1 1†	12 7 ± 0 5†	11 2 ± 0 6†	9 1 ± 1 0†	8 6 ± 0 7†

*Data are presented as mean frequency per hour ± S E M s

†Differs significantly from saline control, 2-tailed t-test $p<0$ 01 N=79 per group

porally correlated However, there were three important dissociations between the behavioral and electrophysiological effects of LSD First, 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 non-tolerant condition Psilocin produced a dose-dependent decrease in raphe unit activity at 25, 100 and 750 μg/kg The behavioral changes following psilocin, however, were not dose-related However, peak behavioral changes following psilocin corresponded to the maximal depression of RD unit activity The phenylethylamine hallucinogens, mescaline and DOM, both produced large behavioral changes but no overall significant effect on RD unit activity Following administration of mescaline or DOM, some RD units showed a significant increase in activity, 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 5HT-containing RD neurons, and an amphetamine-like excitatory effect upon another subset of these cells

Our next studies extended this analysis to 5HT-containing neurons in the nucleus centralis superior (NCS) and nucleus raphe pallidus (RPA) [39,48] LSD produced a dose-dependent decrease in NCS unit activity at 10, 50 and 100 μg/kg and a dose-dependent increase in limb flicking, abortive grooming, and related behaviors, and the peak behavioral and unit changes were temporally correlated By contrast, LSD had little effect upon 5HT-containing RPA neurons 5-MeODMT also produced a dose-dependent decrease in NCS unit activity at 10, 50 and 250 μg/kg and dose-dependent behavioral changes Similar to our LSD data, 5-MeODMT was found to have no overall significant effect on RPA unit activity, except at the highest dose level Psilocin produced dose-dependent decreases in NCS unit activity at 25, 100 and 750 μg/kg whereas the behavioral changes were not dose-related, in agreement with our previous studies Psilocin also had relatively little effect on the activity of RPA neurons, even at the highest dose level (750 μg/kg) The phenylethylamine hallucinogens produced large changes in these cat behaviors, but no significant effect on raphe unit activity in either the NCS or RPA Overall, these data question the hypothesis that the effects of hallucinogens are attributable to an inactivation of central serotonergic neurotransmission

Numerous studies using drug-discrimination paradigms strongly support a role for 5HT in mediating the behavioral effects of LSD and other hallucinogens [17, 20, 32, 52, 53] These studies suggested that hallucinogens exert their effects by acting on postsynaptic 5HT receptors In addition, earlier studies from our laboratory have shown that LSD, particularly at high doses, produces a "serotonin syndrome" which appears to be a function of the activation of post-synaptic serotonin receptors [49]

McCall and Aghajanian [24] recently reported that LSD, psilocin and related hallucinogens sensitized 5HT and norepinephrine (NE) receptors on motor neurons in the facial nucleus If this phenomenon occurs throughout the central nervous system, the mechanism of receptor sensitization might contribute to the psychedelic effects of these drugs Indeed, recent studies have emphasized the importance of postsynaptic 5HT receptors in mediating the behavioral effects of LSD in cats [16,55]

In the present study we examined the effects of 5HT agonists and antagonists upon LSD-induced behavioral and electrophysiological changes of neurons in the RD and NCS in order to more fully elucidate the relative importance of pre- and postsynaptic 5HT receptors in mediating the behavioral effects of hallucinogenic drugs in cats In addition, we examined the behavioral and electrophysiological effects of dopamine (DA) agonists and antagonists, since recent studies have suggested that LSD might exert its effects by an action at DA receptors [10, 27, 37, 50, 51]

METHOD

Under sodium pentobarbital anesthesia (35 mg/kg, IP), adult female (N=39) and male (N=25) cats (2 3–3 6 kg) were implanted with a microdrive, consisting of two inner cannulae (separated by 1 mm), which could be lowered through two outer guide cannulae The microdrive 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 RD Two bundles of microelectrodes, each consisting of three 32 micron and three 64 micron diameter insulated nichrome wires, were then lowered through the inner cannula and glued at points where the tips were approximately 1 mm above and 1 mm caudal to the RD (anterior bundle coordinates AP −1 5, H +1 0, L 0 0 An additional 36 cats (19 female, 17 male) were implanted with the same type of microdrive, except that these cats were implanted with electrodes placed above the NCS The coordinates for the anterior bundle were AP −2 8, H −1 0, L 0 0 When the inner cannulae were manually advanced, the microelectrodes moved anteroventrally through the brain Gross electrodes for recording the electroencephalogram (EEG), electro-oculogram (EOG) and neck electromyogram (EMG) 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 an audio monitor 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 60 dB masking noise All recordings were made during the light portion of the light/dark cycle (lights on 0800 hours, lights off 2000 hours) Behavior was continuously monitored on a television screen and scored on-line on the polygraph record

Experimental sessions began with a baseline recording period (20–30 minutes) which contained periods of both active and quiet waking Then an IP injection of either saline (0 5 ml/kg) plus LSD tartrate (50 μg/kg) or LSD (50 μg/kg) in combination with one of the following drugs was given metergoline (0 25–1 50 mg/kg), mianserin (0 25–1 25 mg/kg), L-5-hydroxytryptophan (5HTP, 5, 10, 25, or 50 mg/kg), fluoxetine (1, 2 5, 5, or 10 mg/kg), tranylcypromine (1, 2, 4, or 8 mg/kg), p-chloramphetamine (1, 2 5, or 5 mg/kg), haloperidol (0 25, 0 5, or 1 0 mg/kg), chlorpromazine (1 0, 5 0, or 10 mg/kg), apomorphine (2, 4, 6, or 8 mg/kg) or d-amphetamine (1 0, 2 5, or 5 0 mg/kg) Drug pretreatments were administered 20 minutes prior to LSD, with the exception of apomorphine, which was administered 5 minutes prior to LSD

Raphe unit activity and behavior were monitored for the next 1 to 8 hours by an experimenter unaware of the treatment condition The definitions of the behavioral categories employed have been described in detail on our previous studies of hallucinogenic drugs [19,45] Only one drug combination was given for each unit and at least one week elapsed between successive injections in the same cat None of the cats was given more than three drug combinations

At the completion of the study, the cats were deeply anesthetized with sodium pentobarbital (40 mg/kg, IP), 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 seconds 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 micron thick frozen sections were cut through the brainstem 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 (six 10 second samples of unit activity were obtained for each time point at 5 minute intervals) For each drug co-administered with LSD, a one-way ANOVA of the dose effect (including saline as a dose of 0 μg/kg) was performed This was followed by statistical analysis of the difference between means of saline versus each dose of the drug at each time point post-injection using 2-tailed *t*-tests

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 co-administered with LSD 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

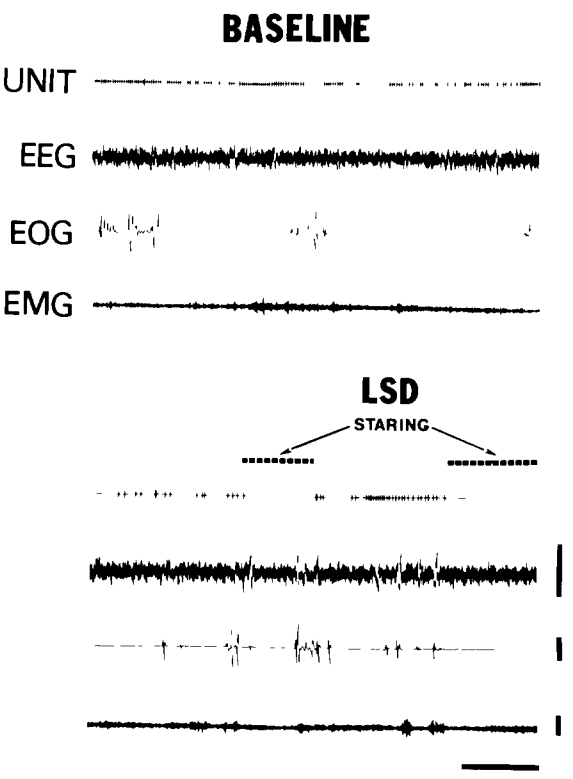

FIG 1 Activity of an NCS unit which showed a significant depression of activity in response to LSD (50 μg/kg) as compared to baseline, and then a complete suppression during staring Note the paucity of both eye movements (EOG) and phasic electromyographic (EMG) activity during staring Limb flicking was not observed during periods of staring, but occurred at the end of a staring episode, when NCS unit activity increased Calibrations EOG, 50 μV, EMG, 100 μV, time, 10 sec

RESULTS AND DISCUSSION

Following the administration of LSD, cats displayed the characteristic behavioral syndrome consisting of excessive limb flicking, abortive grooming, head shaking, grooming, staring, investigatory behavior, hallucinatory-like behavior, and yawning (Table 1) as previously described [19,41] Of these behaviors, the limb flick has proven to be the most sensitive and reliable index of hallucinogenic drug action [19,42], and was therefore used for the correlational analysis between raphe unit activity and behavior in the present study

During baseline recordings, 186 of the neurons examined displayed the slow, regular activity characteristic of serotonergic neurons [34] Baseline unit activity was stable over time for a given behavioral state, showing less than 5% variation Upon histological examination, 114 of these recording sites were found to be localized on, or near, the midline within the RD, while the remaining sites were found to be localized within the NCS Following administration of LSD, a significant decrease in unit activity usually occurred within 5–10 minutes post-injection for neurons in both the RD

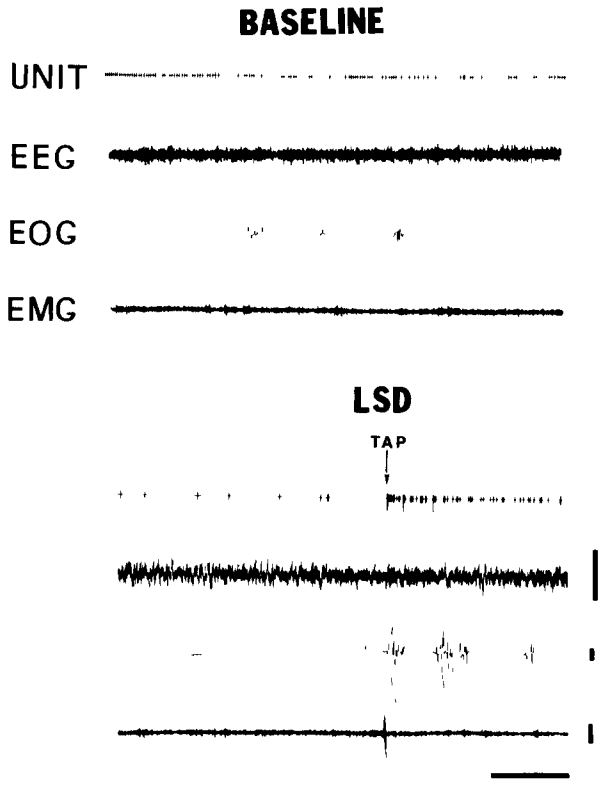

FIG 2 Activity of an NCS neuron which was significantly depressed by LSD (50 μg/kg) as compared to baseline, but which manifested a phasic increase in rate in response to mildly arousing stimuli The experimenter tapped on the recording chamber to arouse the animal Both unit activity and the rate of limb flicking increased in response to this stimulus Note that unit activity in response to this stimulus returned approximately to baseline See legend of Fig 1 for abbreviations and calibrations

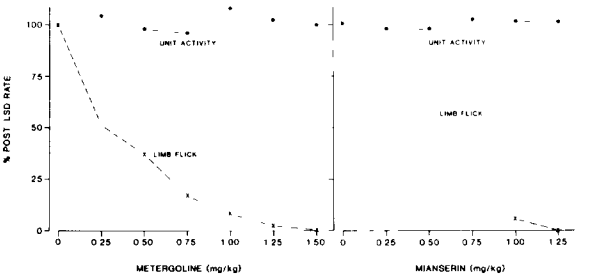

FIG 3 Effects of two serotonin receptor blockers, metergoline (left) and mianserin (right) on LSD-induced limb flicking and raphe unit activity The data are expressed as percent post-LSD rate following a 50 μg/kg dose of LSD This dose of LSD produces a 50% decrease in raphe unit activity and approximately 40 limb flicks per hour RD and NCS unit activity are combined, since each showed a similar response to LSD administration The serotonin receptor blockers produced a dose-dependent blockade of the behavioral effects of LSD, but did not change LSD-induced inhibition of raphe unit activity

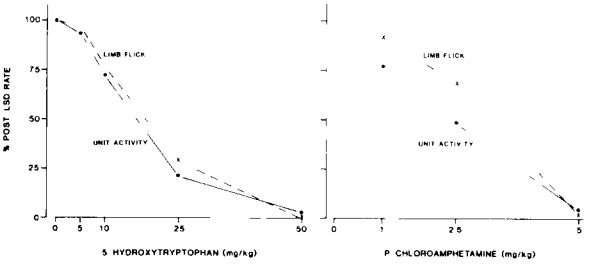

FIG 4 Effects of 5-hydroxytryptophan and p-chloroamphetamine on LSD-induced changes in raphe unit activity and limb flicking See legend of Fig 3 for further details

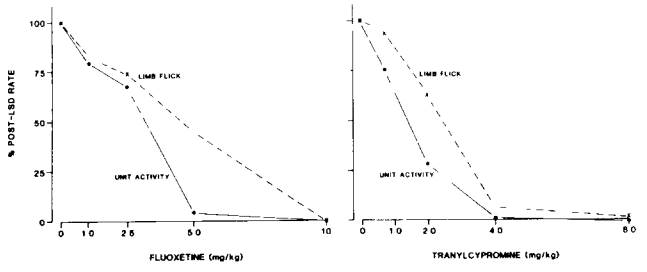

FIG 5 Effects of fluoxetine and tranylcypromine on LSD-induced changes in raphe unit activity and limb flicking See legend of Fig 3 for further details

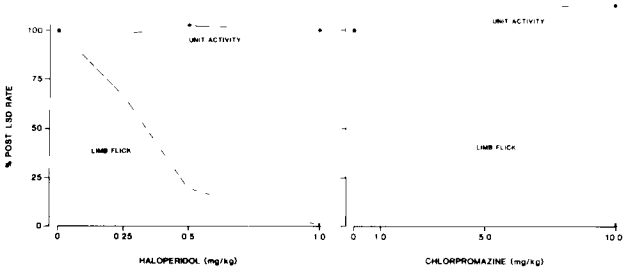

FIG 6 Effects of haloperidol and chlorpromazine on LSD-induced changes in raphe unit activity and limb flicking See legend of Fig 3 for further details

and NCS, and limb flicks usually began to appear during this time interval The peak limb flick rate occurred between 30 and 60 minutes post-injection The time course corresponded to the maximal depression of raphe unit activity The maximal depression of raphe unit activity in both the RD and the NCS following LSD (50 μg/kg) was approximately 50% of baseline values While the discharge pattern following saline administration was very regular, unit activity was much more irregular, in addition to being much slower, following LSD administration The activity of many raphe units was completely suppressed for periods of from 5–30 seconds during staring (Fig 1) Although the overall activity of raphe units was decreased by approximately 50% following LSD administration, unit activity was not significantly changed from baseline levels during periods of active movement, while at other times unit activity was totally inhibited The rate of occurrence of limb flicking was most prominent during periods of active movement, when unit activity was frequently restored to near baseline levels, as previously described [29] In contrast, few of these behaviors occurred

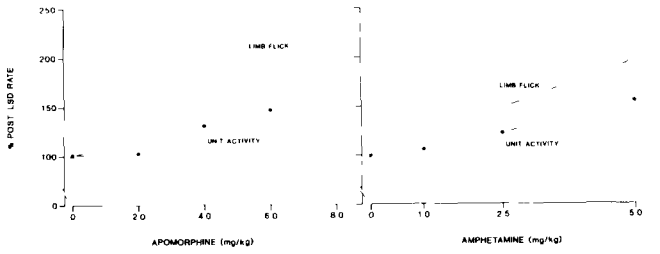

FIG 7 Effects of apomorphine and d-amphetamine on LSD-induced changes in raphe unit activity and limb flicking See legend of Fig 3 for further details

during periods when the animals were inactive, such as during staring

Following administration of LSD, unit activity could be restored to normal for short periods of time by an arousal response, such as tapping on the recording chamber This action both restored unit activity to near baseline levels and also increased the rate of limb flicking (Fig 2) Together these findings provide evidence against a presynaptic action of LSD on raphe neurons as being the critical factor for mediating behavioral effects of the drug

Co-administration of 5HT receptor blocking agents, metergoline or mianserin, produced a dose-dependent blockade of the behavioral effects of LSD, while producing no change in the LSD-induced depression of raphe unit activity (Fig 3) These data suggest that this behavioral effect of LSD in the cat may be attributable, at least in part, to an action at postsynaptic 5HT receptors Mianserin and metergoline are 5HT receptor blockers that have been demonstrated to possess a selective effect for binding to $5HT_2$ versus $5HT_1$ receptor types [21] LSD, on the other hand, has been shown to be an agonist at both $5HT_1$ and $5HT_2$ receptors, possessing nearly equal affinity for each receptor type [26] The hypothesis that LSD exerts its behavioral effects by acting at postsynaptic 5HT receptors is supported by studies that have shown that the hallucinogenic effects of LSD are decreased in humans following blockade of postsynaptic 5HT receptors [14,28]

If LSD exerts its behavioral effects by a 5HT agonist action, then one might predict that co-administration of another 5HT agonist with LSD would potentiate the behavioral effects of the drug However, co-administration of 5HT agonists, such as 5-hydroxytryptophan (5HTP), a monoamine oxidase inhibitor (tranylcypromine), a 5HT reuptake blocker (fluoxetine), or a 5HT-releasing agent (p-chloroamphetamine), all produced a dose-dependent blockade of these behavioral effects of LSD in cats, while each of these drugs produced a dose-dependent potentiation of the inhibitory effect of LSD on raphe neurons in the RD and NCS (Figs 4 and 5) None of these indirect-acting agonists produce any characteristic LSD-like behaviors when administered alone However, they did suppress raphe unit activity when administered alone

Since previous studies have shown that the behavioral syndrome in the cat can also be elicited by apomorphine [37,54], a potent DA agonist, we examined the effects of co-administering apomorphine with LSD on raphe unit activity and behavior These studies reveal that apomorphine produced a dose-dependent potentiation of these behavioral effects of LSD in the cat, while partially reversing the inhibitory effect of LSD on raphe neurons in the RD and NCS

TABLE 2

EFFECTS OF LSD IN HUMANS

1	Perceptual
	altered shapes and colors
	visual hallucinations
	synesthesia
	distorted time sense
2	Affective and Cognitive
	large and rapid mood changes
	difficulty in thinking
	depersonalization
	dreamlike feelings
3	Somatic
	dizziness
	weakness
	tremors
	nausea
	creeping or tingling sensations of the skin

(Fig 6) The administration of d-amphetamine, a potent DA-releasing agent, also potentiated the behavioral effects of LSD, and partially antagonized the inhibitory effects of LSD on raphe neurons (Fig 6) In contrast to apomorphine, amphetamine does not elicit the characteristic behaviors produced by hallucinogens in cats upon acute administration Chronic administration of amphetamine, however, does elicit these behavioral effects [44] Both apomorphine and amphetamine produce mixed effects on raphe unit activity when administered alone That is, some units showed an increase in activity, some showed a decrease, while the majority showed no significant change

We next examined the effects of DA receptor antagonists on the behavioral and raphe unit effects of LSD Administration of haloperidol, a selective DA receptor blocker, produced a dose-dependent blockade of these behavioral effects of LSD in cats, but produced no significant change in the LSD-induced inhibition of raphe unit activity (Fig 7) Similarly, chlorpromazine, also a DA receptor blocker, produced a dose-dependent decrease in the LSD-induced behavioral effects, while producing no significant change in the discharge rate of raphe neurons ($p > 0.2$, two-tailed t-test) following LSD administration (Fig 7) These latter data suggest that the LSD-induced limb flick in cats may be mediated partially by an action at postsynaptic DA receptors

The interaction of LSD with DA receptors has been observed in other models For example, LSD has been shown to stimulate DA-sensitive adenylate cyclase [51] and to bind to postsynaptic DA receptors [10] LSD also elicits contralateral turning in rats with unilateral 6-hydroxydopamine lesions [50] Furthermore, DA receptor blockers have been found to be effective in partially blocking the psychological effects of LSD in humans following an acute overdose of the drug [8]

The present data, together with our previous data showing correlations between both the onset and peak of the behavioral and raphe unit changes for 5-MeODMT, psilocin, and LSD provide some support for the 5HT hypothesis of hallucinogenic drug action, especially when considered in the broader context of the entire literature on the mechanism of action of hallucinogenic drugs [4, 7, 13, 30, 40, 43] On the other hand, the several important dissociations between

raphe unit activity and these behavioral effects of LSD in cats make a simplistic 5HT hypothesis of hallucinogenic drug action untenable Further evidence for a dissociation between drug-induced changes in raphe unit activity and behavioral effects comes from a recent study by Rogawski and Aghajanian [29] who showed that lisuride (an ergot derivative structurally related to LSD) was 5–10 times as potent as LSD in depressing RD neuronal activity, but does not typically induce hallucinations after acute administration to humans [31,33] McCall and Aghajanian [24] recently reported that LSD, psilocin and related hallucinogens sensitize 5HT and NE receptors on motor neurons in the facial nucleus If this phenomenon occurs throughout the brain, the mechanism of receptor sensitization might contribute to the psychedelic effects of these drugs It is interesting to note that all three monoamine neurotransmitters (5HT, DA, and NE) investigated in any detail for their involvement in drug-induced hallucinogensis seem to play a role in this process [34] Given the complexity of these psychological and perceptual changes induced by these drugs, a simplistic hypothesis concerning their mechanism of action seems unrealistic That is, it seems unlikely that a single neurotransmitter system could account for all of the behavioral and psychological effects of hallucinogenic drugs in humans

LSD induces a variety of different behavioral, psychological and physiological effects in humans, which vary among individuals A partial list of these effects is presented in Table 2 While behavioral and physiological effects can be observed directly in animals, it is difficult to use an animal model for studying the psychological and perceptual effects of these drugs, since it is impossible to know what a non-verbal organism is experiencing The various animal models that have been used to study the actions of hallucinogenic drugs, such as the limb flick model in cats, limb jerk model in monkeys, and discriminative stimulus studies in rats, may well measure different aspects of the action of hallucinogenic drugs Therefore, many of the apparent discrepancies in the neuropharmacological actions of the hallucinogenic drugs may be due to the fact that the various animal models measure different aspects of hallucinogenic drug action

In addition to the animal behavioral models that have been used to study the actions of hallucinogenic drugs, neurochemical and electrophysiological measures have been employed as well A combination of these neurophysiological, biochemical, and behavioral animal models will most likely ultimately lead to the discovery of the critical mechanisms of action for producing the characteristic psychological and perceptual effects of hallucinogens in humans

CONCLUSIONS

The effects of LSD in humans are so complex that they are not likely due to a single neural mechanism Therefore, we should abandon any attempt to find the one and only animal model for studying the actions of hallucinogens A fruitful approach for future hallucinogen research would be to identify what aspect of LSD's action the various animal models measure, and then elucidate the mechanisms for that specific action Integrating the information derived from the use of the various model systems should lead to a better understanding of the neural bases of the overall hallucinogenic experience

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