Serotonin Receptor Involvement in an Animal Model of the Acute Effects of Hallucinogens

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INTRODUCTION

To facilitate the study of hallucinogenic drugs in the whole animal, investigators have explored a variety of animal behavioral measures that potentially could parallel hallucinogenic activity in humans (see Glennon, this volume), In the development of such models, d-lysergic acid diethylamide (LSD), the most well-known and potent of the hallucinogens, has been used most frequently as the prototype drug. Structurally an ergot alkaloid compound, LSD acts on the serotonin (5-hydroxytryptamine [5-HT]) system as a partial agonist at both 5-HT_{1A} and 5-$HT_{1C/2}$ receptors (Peroutka and Snyder 1979; Sanders-Bush et al. 1988). In attempting to model the behavioral effects of hallucinogens in humans, considerable research has focused on examining the responsiveness of animals to discrete phasic stimuli. Such studies have revealed that LSD reduces the rate of habituation of reflex responding (Geyer et al. 1978; Izquierdo 1975; Miliaressis and St. Laurent 1974) and produces alterations in both conditioned and unconditioned responding consistent with enhanced reactivity to irrelevant stimuli without direct alterations of sensory thresholds (Key 1964*a*,*b*; Key and Bradley 1960). Unfortunately, none of these effects has been demonstrated to be both common to a variety of hallucinogens and uncharacteristic of nonhallucinogens (Geyer et al. 1978; Stoff et al. 1978), criteria that are vital to an animal model of hallucinogenic activity.

More recently, researchers have attempted to use the elicitation by hallucinogens of animal behaviors that are not typically observed in normal animals as indicators of hallucinogenic action. While problems of nonselectivity still apply to most such behaviors, including increased initial startle responses, flat body posture, forepaw treading, and lower lip retraction (Arnt and Hyttel 1989; Berendsen and Broekkamp 1991; Braff and Geyer 1980; Johansson et al. 1990), other behaviors may be more specifically associated with hallucinogens. For example, behaviors such as head twitches and shakes have been elicited by hallucinogenic

compounds but not by nonhallucinogenic 5-HT agonists of the 5-HT_{1A} receptor such as 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) (Berendsen and Broekkamp 1991; Darmani et al. 1990*a,b*). However, most of these responses are elicited only by relatively high doses of hallucinogenic drugs and are difficult to quantitate by automated procedures. Further, such measures provide no information about the psychological processes influenced by the hallucinogens and are difficult to relate directly to the subjective effects of hallucinogens in humans.

Among the most widely used and successful approaches to assessing the hallucinogenic activity of drugs is the drug discrimination (DD) procedure discussed in more detail elsewhere in this volume (Glennon; Winter). While this procedure has demonstrated considerable predictive validity, the psychological nature of the effect(s) being detected is difficult to define. Furthermore, the procedure requires that the animals be treated repeatedly with the hallucinogen being studied. Such repeated administrations prevent the application of the procedure to the study of the acute effects of hallucinogens, which is important because of the rapidity with which tolerance occurs to the effects of hallucinogens in humans.

HALLUCINOGEN EFFECTS ON EXPLORATORY BEHAVIOR

Recent studies of the effects of acute administrations of hallucinogens on spontaneous behaviors of experimental animals have revealed consistent and specific effects on the normal behavioral repertoire of the animals that can be studied efficiently with automated procedures. The initial evaluations of the effects of LSD on locomotor activity yielded seemingly inconsistent results. Depending on the specific parameters used in each particular study, hallucinogens were found to increase, decrease, or produce no change in the amount of locomotor or investigatory behavior.

This apparent inconsistency is now understood as being a reflection of the fact that the effects of hallucinogens on spontaneous activity are demonstrably dependent on the size of the experimental chamber (Hughes 1973), the nature and degree of stimulation from the test environment (Cunha and Masur 1978), the animal's degree of familiarity with the test environment (Adams and Geyer 1985*a;* Tilson et al. 1975), and the manner in which the animals are handled prior to testing (Geyer and Light 1979). Thus, the changes in locomotor or investigatory

behavior produced by hallucinogenic drugs are critically dependent on the precise nature of the environmental context in which the animals are tested. Furthermore, this variability in the effects of hallucinogens on measures of locomotion suggests that locomotion *per se* is not directly affected by these drugs. Rather, the changes in locomotion appear to be secondary to the effects of hallucinogens on the animal's sensitivity to environmental stimuli. As in humans, hallucinogens do not lead to consistent effects on the level of arousal as reflected in measures of motor activity; rather, hallucinogens alter the manner in which the organism's behavior is influenced by the environment.

To examine this hypothesis more directly, several researchers have studied the effects of hallucinogens on the exploratory behavior of animals. One of the most common tests of exploration uses a holeboard, which is simply a chamber with holes placed in the floor and/or walls. These holes serve as specific stimuli that burrowing animals such as rats readily investigate. Hence, measures of the frequency or duration of "holepokes" are viewed as indices of the animal's investigatory tendencies (File and Wardill 1975). In an extensive series of studies, LSD and several other hallucinogens were found to produce dose-dependent alterations in the temporal distribution of holepokes, consisting of an initial reduction and subsequent increase during a 24-minute test (Geyer et al. 1979). This temporal distribution of responding was found to be unaltered by variations in preinjection time, suggesting that it was related to drug-induced alterations in responsiveness to the environment rather than to the time-course of drug action. Additional studies using the holeboard confirmed that the initial decrease in exploration was attributable to an interaction between the effects of the drug, the animal's exposure to the stimuli associated with handling, and the introduction of the rat to the novel chamber (Geyer and Light 1979). These effects were therefore interpreted as an LSD-induced enhancement of the animal's responsiveness to the test environment.

A BEHAVIORAL PROFILE OF HALLUCINOGEN EFFECTS

Subsequent studies have more thoroughly characterized the effects of hallucinogenic drugs on the responsiveness of rats to environmental stimuli by simultaneously monitoring both locomotor and investigatory responses in the behavioral pattern monitor (BPM) system. The BPM is a combination of an open-field activity monitor and a holeboard. By tracking the movements of the animals within a Cartesian coordinate

system of infrared photobeams, the BPM enables analyses of quantitative and qualitative changes in patterns of locomotor and investigatory activity (Geyer 1990). The BPM is a 30.5 x 61.0 centimeter (cm) black Plexiglas™ chamber illustrated schematically in figure 1. Ten 2.5 cm holes are placed in the chamber (three in each long wall, one in one short wall, and three in the floor). Photocells in each hole detect investigatory holepokes. A touchplate 15.2 cm above the floor allows detection of rearings when contact is made by the animal between the metal floor and the metal touchplate. A 4 x 8 grid of infrared photobeams detects the animal's position in an X-Y plane. Every 200 milliseconds (ms) the computer sampled the status of all the beams in each chamber, enabling reconstruction of the path taken by the animal and calculation of a variety of descriptive statistics that reflect changes in the amount or pattern of the activity.

When rats were tested by placing them directly into a novel BPM chamber (forced exploration), a consistent effect of LSD was a dose-dependent reduction of exploration in the first half of an hour-long test session (Adams and Geyer 1982). In order to ensure that the behaviors being studied were as natural as possible in a laboratory setting, all studies were conducted in the dark phase of the animal's day-night cycle when nocturnal animals such as rats are typically most active. To maximize the exploratory behavior of the control animals and minimize the influences of extraneous factors, the animals were tested in dark chambers that were kept scrupulously clean. In addition, it has proven essential that the animals be handled as gently and consistently as possible as exemplified by the demonstrated influence of handling on the behavioral effects of LSD (Geyer and Light 1979). During the week before testing, animals were also acclimated to the handling associated with transport to the laboratory and injections.

Under these controlled conditions the number of photobeam interruptions (movements) was decreased very consistently by reasonably low doses of LSD as illustrated in figure 2a (Adams and Geyer 1982, 1985*a*). At the same time both holepokes and rearings, two measures of investigatory behavior, were also decreased by LSD (figure 3). These results confirmed the findings of Geyer and Light (1979) and extended those findings to include activity and rearings as well as holepokes. These decreases were limited to the initial 30 minutes of the test session, although a variety of other drugs decreased activity throughout the hour-long test session (Mittman and Geyer 1989). Further, these decreases in locomotor and investigatory behavior were specifically

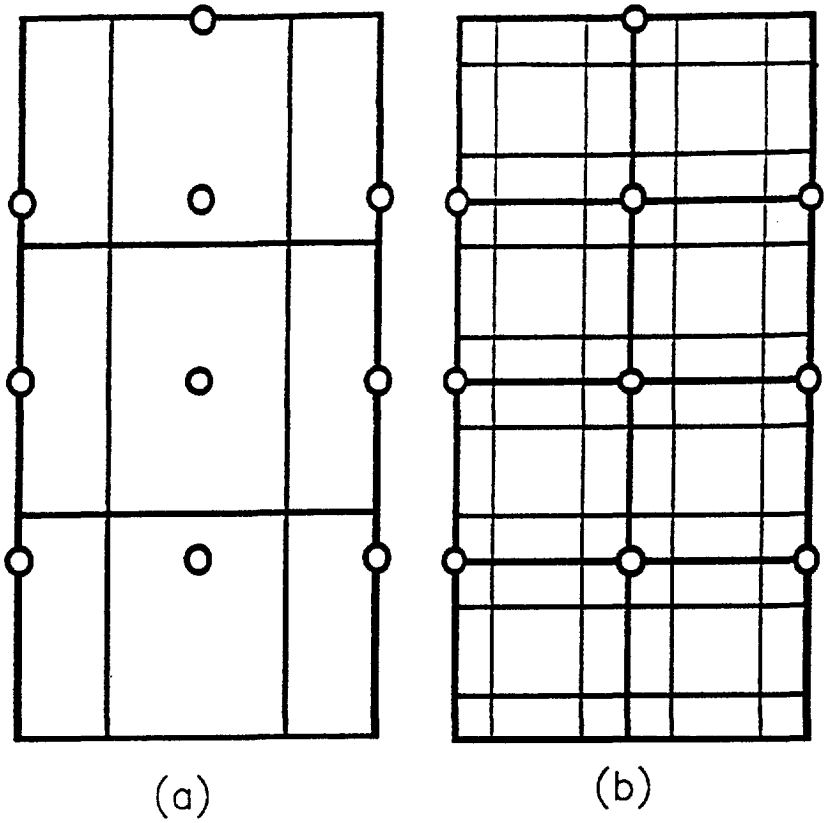

FIGURE 1. *Diagrammatic representation of the BPM chamber (30.5 x 61 cm). (a) shows black lines indicating regions, unequal areas used to define transitions from one region to another for assessment of locomotor patterns. (b) Infrared photobeams are represented here by thin black lines and are used to define movements, a measure of locomotor activity. Sectors, equal 15 cm squares, are indicated by thick black lincs and are used to define crossings, a measure of horizontal locomotion.Wall and floor holes are portrayed by open circles and are used to define investigatory holepokes.*

related to the animal's initial exploration of the novel chamber rather than the time-course of the drug's action. Hence, the effect of LSD is not limited to the investigation of discrete stimuli and cannot be described as generalized sedation, but appears to reflect a more pervasive influence of the drug on responsiveness to a wide range of environmental stimuli.

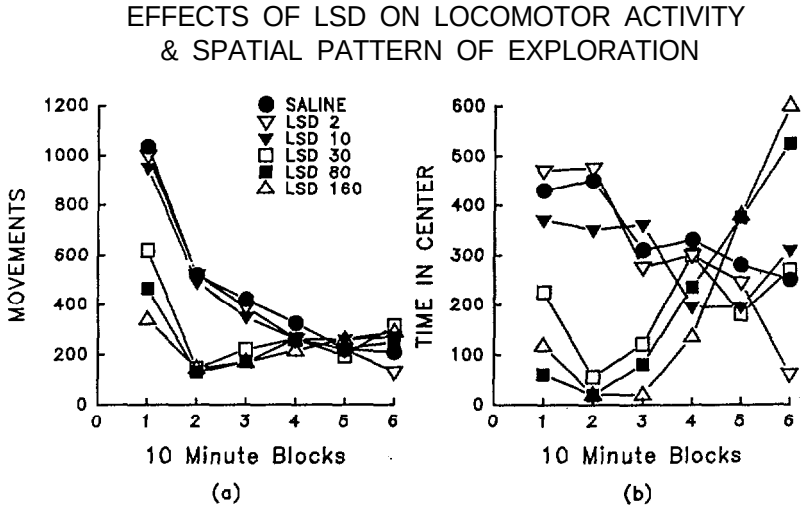

FIGURE 2. *Disruption of spatial pattern and amount of locomotor activity by LSD. Six groups of 10 male rats each were tested in the BPM chambers 10 min following injections (SC) of 0, 2, 10, 30, 80, or 160 ug/kg LSD. LSD dose-dependently decreased both (a) movements (total photobeam breaks in the BPM) and (b) the time the animals spent in the center of the chamber (refer to figure 1 for center region representation) in tenths of a second. (Values are group means per 10-min block of time, $p<0.05$). Redrawn from data presented in Adams and Geyer 1985a.*

One of the most robust and sensitive measures of the effect of LSD is the decrease in the amount of time that the animal spends in the center of the chamber, as illustrated in figure 2b. Because the tendency of rats to explore a novel environment is generally believed to compete for expression with the opposite tendency to avoid novel and open spaces (Berlyne 1966; Montgomery 1955), the pattern of effects produced by LSD suggests that the drug enhances the latter tendency. Analyses of the spatial patterns of locomotion reveal that LSD's initial suppression of activity and holepokes were best correlated with a reduction in entries into, and time spent in, the central region of the chamber (Adams and Geyer 1982, 1985*a).* As illustrated by computer-generated displays of locomotor patterns (figure 4), the effects of LSD on exploration of novel and central areas are profound (Adams and Geyer 1985*a*). It has long been recognized that normal rats tend to avoid large, open spaces (Barnett

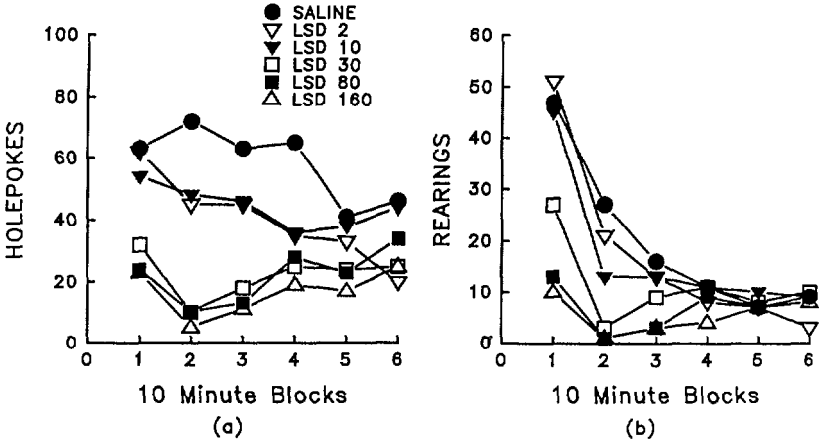

FIGURE 3. *Disruption of exploratory behavior by LSD. Six groups of male rats (n = 10) were tested in the BPM 10 min after receiving injections (sc) of 0, 2, 10, 30, 80, or 160 µ/kg LSD. LSD produced significant dose-dependent decreases in both (a) the number of holepokes made during testing and (b) the number of rearings against the wails. (Values are group means per 10-min block, $p<0.05$). Redrawn from data presented in Adams and Geyer 1985a.*

1963). As with the exaggerated response of hallucinogen-treated rats to the aversive aspects of the exposed central region of the chamber, there is also an increased tendency of hallucinogen-treated rats to avoid novel chambers altogether.

To further clarify the nature of this effect, animals were tested in a free exploration paradigm (Welker 1957) in which a familiar home cage is connected to the open field. When rats were allowed to enter and leave the novel chamber at will, LSD produced dose-dependent reductions in the amount of time spent in the novel chamber without an alteration in the overall rate of locomotor or investigatory responses while they were in the chamber (Adams and Geyer 1982) (figure 5). Hence, the effect is not attributable to sedation; rather it reflects an alteration in the responsiveness of the animal to the nature of the test chamber itself. In

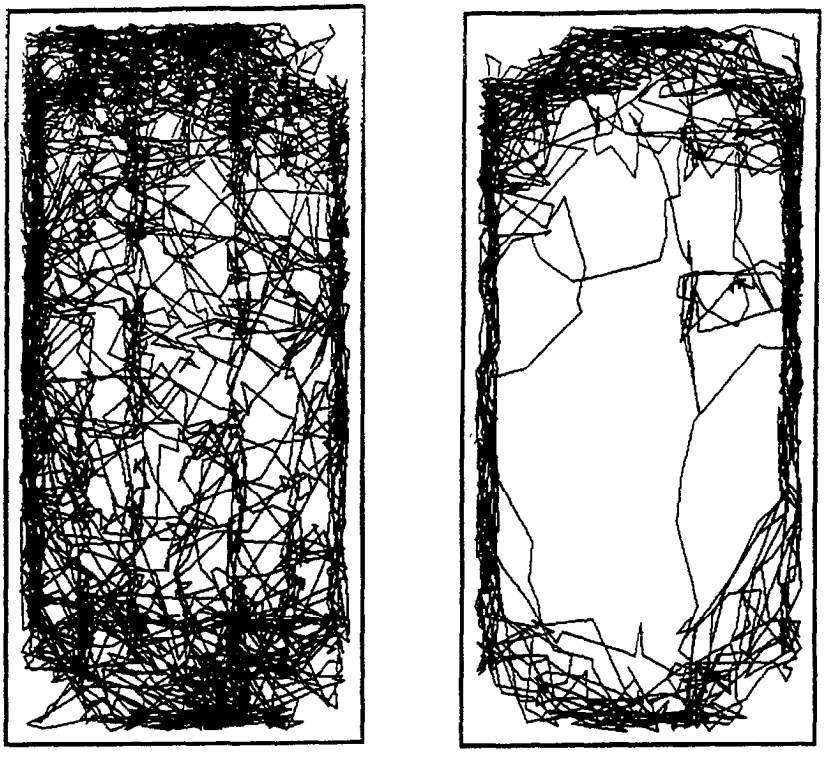

FIGURE 4. *Computer-generated display of the locomotor path produced during the initial 30 min of testing in the BPM by two different representative rats treated with (a) saline or (b) 60 μ/kg LSD. In contrast to the varied path the saline-treated rat takes, the LSD-treated animal makes few center entries, prefers one corner of the chamber, and circles the periphery of the BPM chamber.*

further studies, it was found that the initial suppression of activity induced by LSD was absent when animals were tested in a familiar environment (figure 6*a*). The fact that familiarizing an animal with the test environment attenuates the suppression of locomotor activity induced by hallucinogens suggests that LSD potentiates the normal neophobia exhibited by rats when confronted with a novel environment (Adams and Geyer 1985*a*).

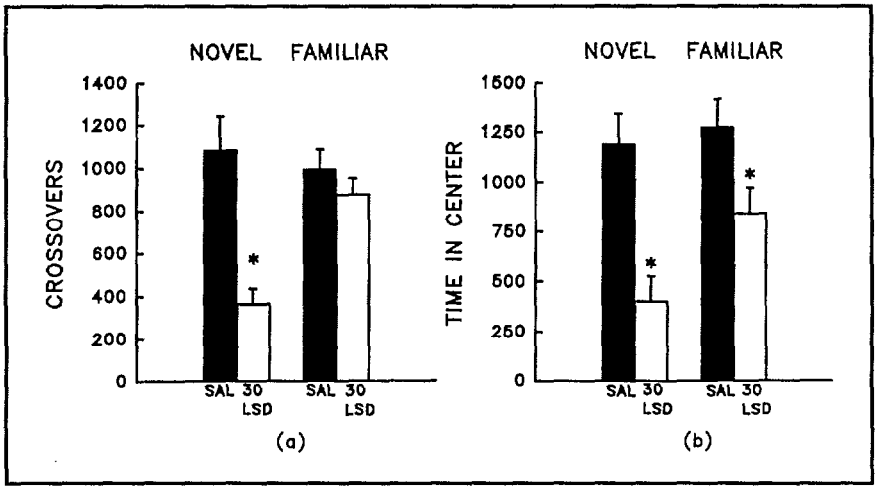

FIGURE 5. *Disruption of locomotor activity by LSD. Five groups of male rats (n = 8-10) were tested in a modified BPM chamber that allowed animals to move freely between the BPM and a home cage environment (free exploration). Ten min prior to testing, injections (SC) of 0, 2, 10, 30, or 80 µ/kg LSD were given. LSD significantly decreased the number of crossovers (movements between 15 cm square sectors) but had no effect on the rate of locomotor activity (crossovers/min). (Values are means from total counts or transforms performed on 60 min totals, p<0.001). Redrawn from data presented in Adams and Geyer 1982.*

By contrast, the decrease in time spent in the center of the chamber was still evident in the familiar environment (figure 6*b*), indicating that LSD potentiates the normal animal's response to aversive or threatening environmental stimuli, in this case the center of the chamber, even in a familiar environment. This effect has been characterized as an increase in agoraphobia. Thus, in the typical novel environment paradigm, LSD potentiates both neophobia and agoraphobia (Adams and Geyer 1985*a*).

One of the most stringent tests of the specificity of any behavioral model of the effects of LSD involves comparison of the effects of LSD in the model to the effects of lisuride in the model. Lisuride is a behaviorally potent derivative of isolysergic acid that closely resembles LSD in both chemical structure and neurochemical effects. Nevertheless, in normal humans, lisuride appears to produce none of the perceptual changes or

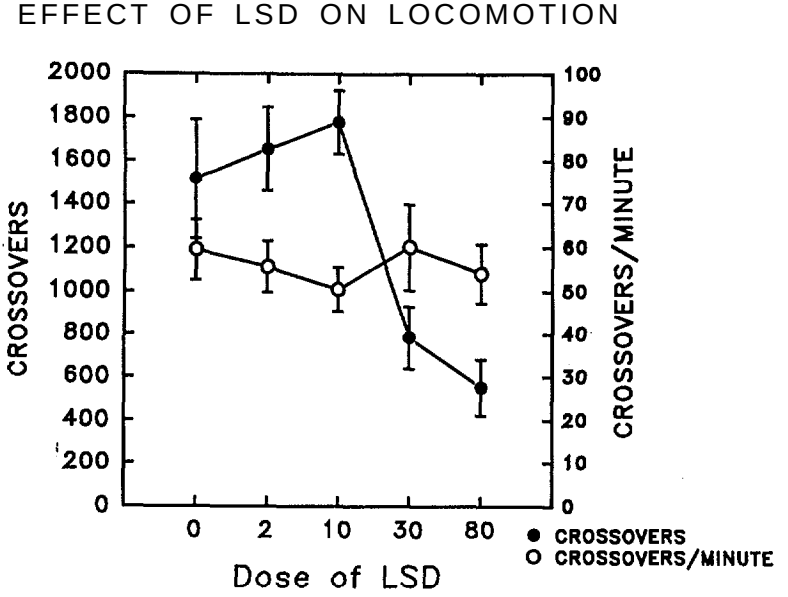

FIGURE 6. *Impact of familiarization with test chamber on LSD's effects on the spatial pattern and amount of locomotor activity. Four groups of male rats (n = 10-16) were tested in the BPM 10 min after receiving injections of either saline or 30 µ/kg LSD (SC). The novel groups were tested only once, while the familiar groups were tested after two previous exposures (without injections) to the BPM. In a novel environment, 30 µ/kg LSD significantly decreased (a) crossovers (movements between 15 cm square sectors) and (b) the time spent in the center of the chamber.However, in a familiar environment, the effects of LSD were attenuated on (a) crossovers, but not on (b) the time spent in the center of the chamber. (Values are group means for the first 30 min of testing, $p<0.05$). Redrawn from data presented in Adams and Geyer 1985a.*

intensifications of responsiveness that are characteristic of hallucinogens (Herrmann et al. 1977). In rats, low doses of lisuride produced sedation with no evidence of an enhanced avoidance of open or novel spaces, while higher doses produced stereotyped patterns of locomotor hyperactivity that were quite different from the effects of high doses of LSD (Adams and Geyer 1985*c*).

A further distinction between the behavioral effects of lisuride and LSD was revealed by the drugs' interactions with the neuroleptic haloperidol. Haloperidol blocked the hyperactivity produced by high doses of lisuride but failed to alter the effects of LSD on enhanced responsiveness to the environment (Adams 1983). Thus, this animal model of hallucinogenic activity was sensitive enough to discriminate easily between lisuride and LSD, two compounds that differ primarily with respect to their hallucinogenic effects.

One of the hallmarks of the effects of hallucinogens in humans is the rapidity with which tolerance occurs to their acute effects (Freedman 1981; Freedman et al. 1964; Isbell et al. 1956; Mandell and Geyer 1976). Hence, any behavioral effect in an animal model purporting to reflect the physiology underlying the defining effects of hallucinogens in humans is expected to exhibit rapid tolerance. As shown in figure 7, LSD's effects on locomotor activity in rats showed partial tolerance 24 hours after a single dose and complete tolerance following five daily injections. Tolerance was also observed to the effects of LSD on investigatory holepokes and rearing after five consecutive injections of LSD (Adams and Geyer 1985*a*). Thus, this profile of behavioral effects is especially sensitive only to the acute effects of LSD, which are presumed to be those most relevant to the subjective effects reported by humans.

While all the hallucinogens tested in this paradigm produced a behavioral profile similar to that of LSD, other psychoactive drugs do not. Table 1 lists the psychoactive drugs that have been examined in full dose-response studies using this paradigm. In addition to the ergot derivative LSD, similar effects have been observed with both phenylalkylamine hallucinogens such as mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM) and indoleamine hallucinogens such as psilocin and N,N-dimethyltryptamine (DMT) (Adams and Geyer 1985*b;* Geyer et al. 1979).

By contrast, nonhallucinogenic congeners of both LSD and DOM fail to produce this behavioral profile. Furthermore, drugs from a variety of other categories produce no effects or different effects in this model. Among the common false positives that frequently occur in establishing the specificity of animal models of hallucinogens, lisuride and apomorphine are notable in that they are readily discriminated from the hallucinogens in this model (Adams and Geyer 1985*c;* Geyer et al. 1986). Quipazine is one drug that shares 5-HT_2/5-HT_{1C} agonist properties with

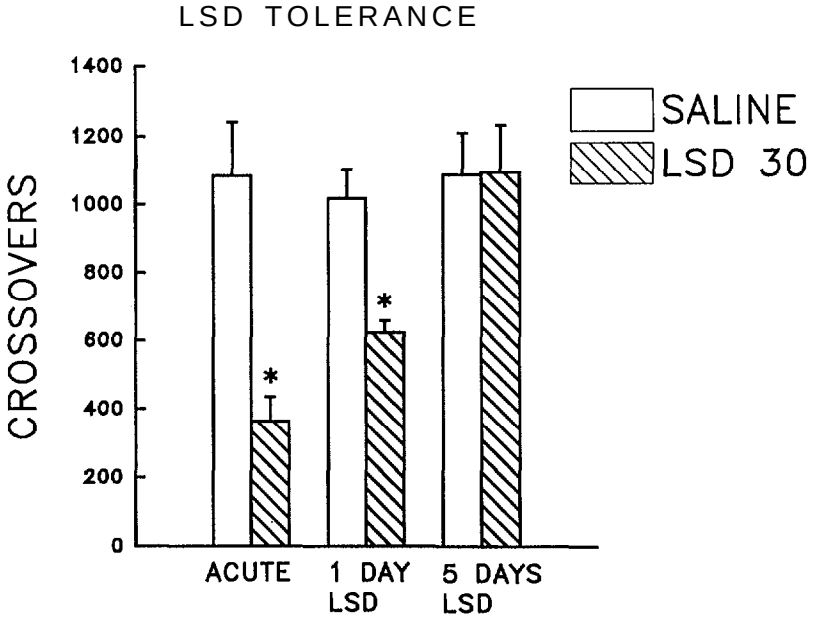

FIGURE 7. *Tolerance to the effects of LSD on locomotor activity. Six groups of male rats (n = 6) were pretreated chronically with either saline or LSD (30 µ/kg SC) daily. Two groups received five daily injections of saline and were tested 24 hrs later in the BPM 10 min after injections of either saline or 30 µ/kg LSD [ACUTE]. Two groups received four daily injections of saline and an injection of 30 µ/kg LSD on the fifth day, and then were tested on the sixth day after injections of either saline or LSD (30 µ/kg SC) [1 DAY LSD]. Two groups received five daily injections of LSD (30 µ/kg SC) and were tested the next day 10 min after injections of saline or 30 µ/kg LSD (n = 14) [5 DAYS LSD]. The acute effects of LSD, e.g. decreasing crossovers (movements between 15 cm square sectors), were partially blocked by a single injection of LSD and completely blocked by five days of chronic LSD treatment. (Values are group means for the first 30 min of testing, $p<0.05$). Redrawn from data presented in Adams and Geyer 1985a.*

TABLE 1. *This table summarizes data presented in: Adams and Geyer 1985a, b, c; Callaway et al. 1991; Geyer and Frampton 1988; Geyer et al. 1979, 1986; Gold et al. 1988; Lehmann-Masten and Geyer 1991; Mittman and Geyer 1989; Rempel et al., in press; and Wing et al. 1990.*

HALLUCINOGENS EXHIBITING PROFILE	DRUGS EXHIBITING DIFFERENT PROFILES	
LSD	8-OH-DPAT	AMPHETAMINE
DOM	BUSPIRONE	APOMORPHINE
DOET	GEPIRONE	COCAINE
DOPR	IPSAPIRONE	SCOPOLAMINE
MESCALINE	TFMPP, mCPP	NICOTINE
PSILOCIN	RU-24969	CAFFEINE
DMT	DMA, DOAM	CLENBUTEROL
5-MeO-DMT	MDMA, MDA	CLONIDINE
(QUIPAZINE)	MBDB, PCA	NADOLOL
	LISURIDE	MORPHINE
	METHYSERGIDE	PCPA
	CYPROHEPTADINE	FLUOXETINE
	HALOPERIDOL	CHLORIMIPRAMINE
	PROPRANOLOL	PHENCYCLIDINE
	RITANSERIN	DIZOCILPINE
	PINDOLOL	

the classical hallucinogens but that is not clearly established as being hallucinogenic in humans. As it produces a comparable behavioral profile, quipazine appears to be similar to the hallucinogens (Wing et al. 1990). Whether this drug represents a false positive cannot be easily determined without more adequate studies of its effects in humans.

In table 1, indirect serotonin agonists such as MDMA and MDA are listed as being different from the classical hallucinogens, despite the fact that they have been classified in legal terms together with hallucinogens and have been described as having related effects. As reviewed in detail elsewhere (Geyer and Callaway 1994), these compounds differ markedly from both typical psychostimulants and classical hallucinogens in terms of their behavioral effects and mechanisms of action and should be considered as a distinct class of drugs. In summary, the increased

avoidance of novel and open spaces induced by LSD in rats appears to satisfy several requirements for an animal model of hallucinogenic activity. First, the effect is common to all the hallucinogens tested at doses that generally correspond to the potencies of these drugs in humans. Second, this profile of effects has not been reproduced by any of the nonhallucinogenic drugs tested, including inactive congeners of hallucinogens. Third, tolerance to this increased avoidance effect of LSD develops at a rate is comparable to that observed in humans.

SEROTONERGIC MECHANISMS OF HALLUCINOGEN EFFECTS

In order to investigate the mechanisms of action of hallucinogens, a number of studies have examined the 5-HT receptor subtypes that contribute to the hallucinogen-induced behavioral profile of an increased avoidance of novel and open spaces. In the authors' laboratory, three approaches to this investigation have been used. First, selective 5-HT agonists have been tested. Second, 5-HT receptor antagonists, such as they are, have been tested for their ability to block the effects of the respective agonists. Third, due to the limited set of 5-HT antagonists, cross-tolerance paradigms have been used to examine the involvement of particular receptor subtypes in the behavioral effects of the agonists.

Serotonin Agonists

Of the phenalkylamine hallucinogens which are more selective for the 5-HT_{1C}/5-HT_2 receptor sites, mescaline and 2,5-dimethoxy-4-iodo-amphetamine (DOI) as well as other 5-HT_{1C}/5-HT_2 agonists produced dose-related decreases in the initial levels of exploratory activity in the same BPM paradigm used to characterize the effects of LSD (Wing et al. 1990). In each case, these decreases were accompanied by preferential decreases in entries into and time spent in the center of the chamber. As with LSD, this suppression of exploratory behavior was attenuated significantly when rats were familiarized with the testing chamber prior to the administration of DOI (Wing et al. 1990). Similarly, as shown in figure 8, acute administration of the 5-HT_{1C}/5-HT_2 agonist DOM suppressed locomotion and both entries into and time spent in the center of the BPM chamber (Adams and Geyer 1985*b).* Familiarization with the chamber diminished the effect of DOM on exploratory locomotion but not on the rats' tendency to enter the center of the chamber (figure 8).

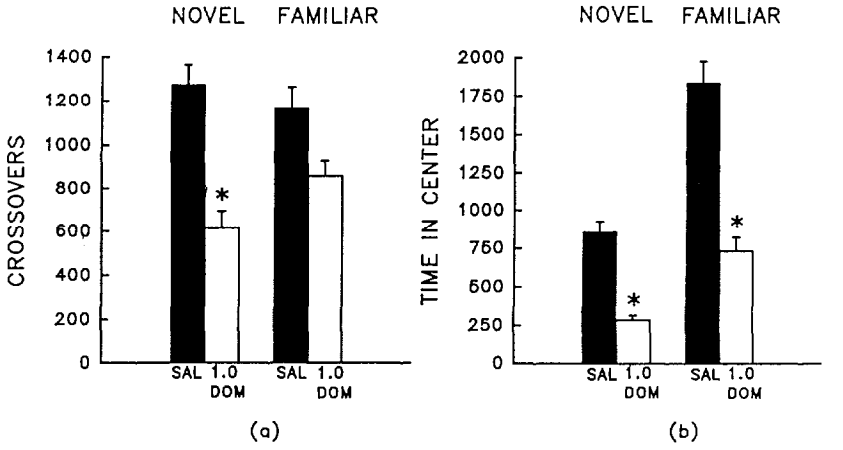

FIGURE 8. *Impact of familiarization with test chamber on DOM's effects on the spatial pattern and amount of locomotor activity. Four groups of 10 male rats each were tested in the BPM 10 min after receiving injections of either saline or 1.0 mg/kg DOM (SC). The novel groups were tested only once, while the familiar groups were tested after two previous exposures (without injections) to the BPM. In a novel environment, 1.0 mg/kg DOM significantly decreased both (a) crossovers (movements between 15 cm square sectors) and (b) the time spent in the center of the chamber. However, in a familiar environment, the effects of DOM were attenuated on (a) crossovers, but not on (b) the time spent in the center of the chamber. (Values are group means for the first 30 min of testing, $p<0.05$). Redrawn from data presented in Adams and Geyer 1985b.*

Thus, as with LSD, phenalkylamine hallucinogens such as mescaline, DOI, and DOM suppress exploratory locomotion and time spent in the center. As with LSD, the effects of DOI and DOM on locomotion are diminished when a familiar test chamber is used, although familiarization does not suppress the potentiation of agoraphobia as operationally measured by the time spent in the center of the chamber. Similarly, the indoleamine hallucinogen N,N-dimethyltryptamine (DMT) also preferentially suppressed both entries into the center and investigatory holepokes when rats were tested in a novel BPM chamber (Adams and Geyer 1985*b*). Thus, LSD and more selective 5-HT_{1C}/5-HT_2 agonists exaggerate the animal's normal responses to aversive sensory stimuli. In

the novel environment, this potentiation of sensory responsiveness is expressed as initial decreases in exploratory behavior. In a familiar environment, the effect is expressed in a more specific decrease in visits to the open area in the center of the chamber.

The 5-HT_{1A} agonists, which are not generally considered hallucinogenic, have also been tested in this behavioral paradigm. Buspirone, 8-OH-DPAT, gepirone, and ipsapirone all produced decreases in locomotor activity in a novel environment. The decreases were superficially similar to those produced by the 5-HT_{1C}/5-HT_2 agonists (Mittman and Geyer 1989). Unlike the mixed 5-HT_{1A} and 5-HT_{1C}/5-HT_2 agonist LSD, the more selective 5-HT_{1A} compounds produced decreases in center entries that were strictly proportional to the decreases in other measures of activity and were typically maintained throughout the test session. Furthermore, in contrast to the effects of LSD or phenalkylamine hallucinogens, the effects of the 5-HT_{1A} agonists were not attenuated when the animals were tested in a familiar environment (figure 9). These decreases were more indicative of a general suppression of motor behavior rather than of a specific potentiation of the animals' neophobic and agoraphobic responses to threatening stimuli (Mittman and Geyer 1989). Thus, hallucinogenic 5-HT agonists such as the 5-HT_{1C}/5-HT_2 agonists DMT, DOI, and mescaline were found to produce behavior similar to that produced by LSD, while 5-HT_{1A} agonists that were not hallucinogenic produced behavior more akin to a generalized sedation rather than the behavioral profile elicited by LSD administration.

Serotonin Antagonists

The effects of the 5-HT_{1C}/5-HT_2 and 5-HT_{1A} agonists in this paradigm can be distinguished pharmacologically as well as behaviorally. Mittman and Geyer (1991) showed that the effects of the 5-HT_{1C}/5-HT_2 agonist DOI on exploratory locomotion and time spent in the center were blocked effectively by the 5-HT_{1C}/5-HT_2 antagonist ritanserin as shown in figure 10. Similar effects were obtained with the 5-HT_{1C}/5-HT_2 antagonist ketanserin using a variety of 5-HT_{1C}/5-HT_2 hallucinogens (Wing et al. 1990). By contrast, the effects of the 5-HT_{1A} agonist 8-OH-DPAT were completely insensitive to ketanserin (Wing et al. 1990).

However, administration of the 5-HT_1 antagonist (and beta-adrenergic antagonist) propranolol did not yield receptor-specific effects (figure 11). When propranolol was used as an antagonist to the 5-HT_{1A} agonist

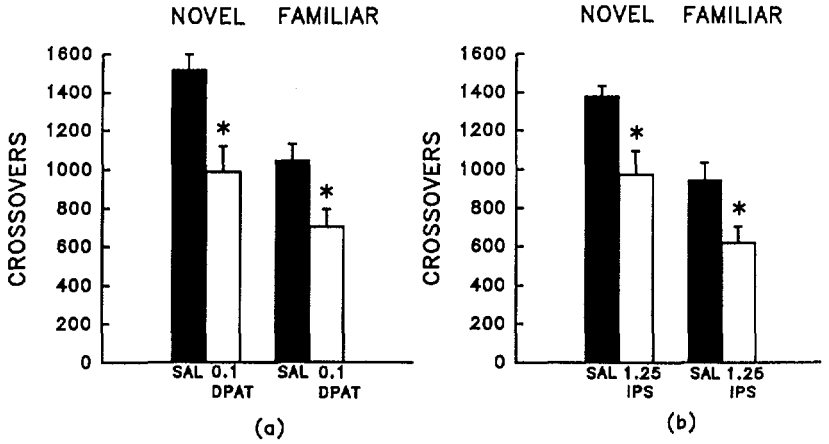

FIGURE 9. *Effect of familiarization with test chamber on 5-HT$_{1A}$ agonists' effects on locomotor activity. Rats were tested in the BPM 10 min after receiving injections of either saline or drµ. The novel groups were tested only once, while the familiar groups were tested after two previous exposures (without injections) to the BPM. (a) Four groups of 10 male rats each were tested 10 min after injections of either saline or 8-OH-DPAT (0.1 mg/kg SC). In a novel environment, 8-OH-DPAT significantly decreased crossovers (movements between 15 cm square sectors). In a familiar environment 8-OH-DPAT also significantly decreased crossovers. (b) Four groups of male rats (n = 11) were tested in the BPM 10 min after receiving SC injections of either saline or 1.25 mg/kg ipsapirone (IPS). In a novel environment, ipsapirone significantly decreased crossovers. In a familiar environment, ipsapirone also significantly decreased crossovers. Redrawn from data presented in Mittman and Geyer 1989.*

8-OH-DPAT and the 5-HT$_{1C}$/5-HT$_2$ agonist DOI, the hypoactivity induced by both 8-OH-DPAT and DOI was attenuated by administration in the first 10 minutes of testing in the BPM (figure 11). Thus, the effects of the 5-HT$_{1A}$ agonists are blocked by 5-HT$_1$ antagonists but not by 5-HT$_{1C}$/5-HT$_2$ antagonists, arguing for receptor-specific antagonism. However, the 5-HT$_{1C}$/5-HT$_2$ agonist DOI is blocked either by the 5-HT$_{1C}$/5-HT$_2$ antagonist or the 5-HT$_1$ antagonist, which indicates either a

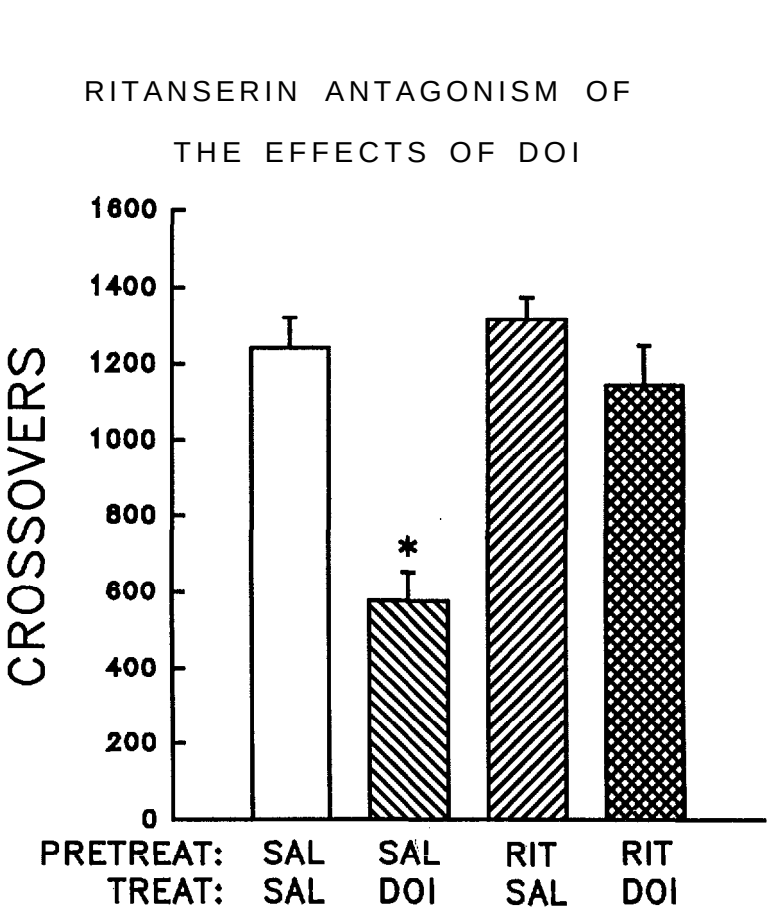

FIGURE 10. *Antagonism of 5HT-1C/2 agonist effects by a 5HT-1C/2 antagonist. Four groups of male rats (n = 9) were tested in the BPM 30 min after receiving pretreatment SC injections of either saline or 2.0 mg/kg ritanserin (RIT) and 10 min after receiving treatment injections of either saline or 0.27 mg/kg DOI (SC). DOI alone significantly decreased crossovers (movements between 15 cm square sectors); but the effects of DOI were antagonized when rats were pretreated with ritanserin. (Values are group means for the first 30 min, $p<0.005$). Redrawn from data presented in Mittman and Geyer 1991.*

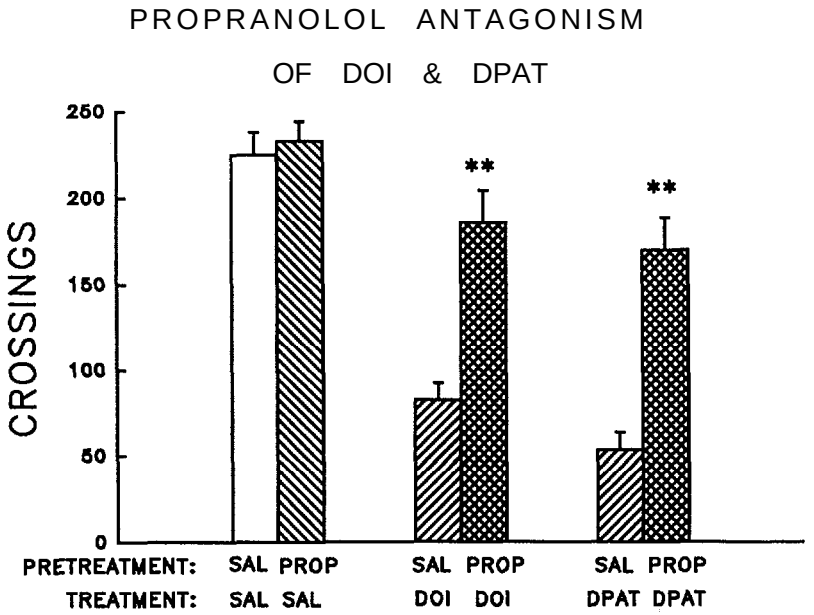

FIGURE 11. *Antagonism of 5-HT$_{1A}$ agonist and 5-HT$_{1C}$/5-HT$_2$ agonist effects by a 5-HT$_1$ antagonist. Six groups (n = 10-11) of male rats were tested in the BPM 30 min after receiving pretreatment injections of either saline or 10.0 mg/kg propranolol (SC) and 10 min after receiving treatment injections of either saline, DOI (1.0 mg/kg SC), or 8-OH-DPAT (DPAT) (0.5 mg/kg SC). Both DOI and 8-OH-DPAT significantly decreased crossings (movements between 15 cm square sectors) for the initial 10 min of testing; these effects were antagonized by pretreatment with propranolol. (Values are group means for the first 10 min of testing; $F(2,57) = 8.07$, $p<0.01$).*

nonspecific antagonism or an interaction between the 5-HT$_{1A}$ and 5-HT$_{1C}$/5-HT$_2$ receptors.

Similar studies using ritanserin and propranolol as pretreatments prior to the administration of LSD yielded interesting results. Recent speculation about the differential functions of the 5-HT$_{1A}$ and the 5-HT$_{1C}$/5-HT$_2$ receptors in LSD action has led to the hypothesis that the hallucinogenic action of LSD is due to its binding to the 5-HT$_{1C}$/5-HT$_2$ receptor complex. The prevailing view currently holds that hallucinogenic action

is due to actions mediated via the 5-HT_{1C}/5-HT_2 receptor complex. As evidence for this hypothesis, some studies have correlated the 5-HT_2 binding affinity of a drug with its hallucinogenic potency (Glennon et al. 1984; Titeler et al. 1988).

However, because of the paucity of dose-finding studies in humans, these studies have been unable to thoroughly examine the indoleamine and ergot alkaloid hallucinogens, although LSD and some indoleamines have been examined. These studies have focused instead primarily on the phenalkylamine hallucinogens such as mescaline, DOI, and DOM. LSD appears to be more closely related to the indoleamines, which include DMT and psilocybin (Mandell and Geyer 1976). Correlations between 5-HT_{1C}/5-HT_2 function and hallucinogenic potency have yet to be studied for the indoleamines or the ergots as groups. Therefore, the relative contributions of 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors in hallucinogenic action have not been established definitively, especially for the indoleamine and ergot alkaloid hallucinogens.

Because the prevailing view is that classical hallucinogens act primarily via agonist actions at 5-HT_{1C}/5-HT_2 receptors, it was predicted that the 5-HT_{1C}/5-HT_2 antagonist ritanserin would block the effects of LSD, whereas the 5-HT_1 antagonist propranolol would not. Instead, ritanserin only partially blocked the effects of LSD, as did propranolol. Only the combination of ritanserin and propranolol completely blocked the effects of LSD (Mittman and Geyer 1991). These results suggest a role for the 5-HT_{1A} receptor as a contributor to the behavioral effects of LSD. Perhaps, as suggested by the antagonist studies, there is an interaction between the 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors. To explore further the contributions of the receptors to the effects of LSD, an approach based on the apparent tolerance associated with 5-HT agonists was used.

TOLERANCE AND CROSS-TOLERANCE TESTS

The previous attempts to use antagonists to block specific receptor sites when testing LSD, a mixed 5-HT_{1A} and 5-HT_{1C}/5-HT_2 agonist, were problematic primarily because of the lack of selective 5-HT_{1A} antagonists. Unfortunately the common 5-HT_1 antagonist propranolol is an antagonist at both 5-HT_{1A} and 5-HT_{1B} sites and is a ß-adrenergic blocker as well. Without selective antagonists, it was difficult to assess the respective contributions of the receptor subtypes to the effects of LSD on locomotor and investigatory behavior.

Alternatively, another approach is that of tolerance. Chronic administration of a selective 5-HT_{1A} agonist such as 8-OH-DPAT produces tolerance to the acute effects of 8-OH-DPAT (Berendsen and Broekkamp 1991; Johansson et al. 1990; Larsson et al. 1990; Pranzatelli and Pluchino 1991). Similarly, tolerance has also been reported to the acute effects of DOI, a 5-HT_{1C}/5-HT_2 agonist, after repeated administration (Berendsen and Broekkamp 1991; Darmani et al. 1990*a;* Pranzatelli and Pluchino 1991). In the serotonin system, it appears that receptor regulation is not an adequate explanation for tolerance, as behavioral tolerance is seen in the absence of receptor change (Trulson 1985). Nevertheless, binding studies have demonstrated that chronic administration of both 8-OH-DPAT and DOI result in decreased numbers of 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptor sites, respectively (Buckholtz et al. 1988; Larsson et al. 1990; McKenna et al. 1989; Pranzatelli 1991).

It is well established that tolerance to LSD in humans is striking for the rapidity with which it occurs (Freedman et al. 1964; Isbell et al. 1956; Mandell and Geyer 1976). In animals, tolerance or partial tolerance to the acute effects of LSD administration has also been demonstrated for most behaviors (Adams and Geyer 1985*a;* Appel and Freedman 1968; Bridger 1975; Carter and Appel 1978; Geyer and Light 1979; Murray et al. 1977; Rech et al. 1975; Trulson 1985; Winter 1971), although some behavioral paradigms may be resistant to tolerance induction (Braff and Geyer 1980; Bridger 1975; Murray et al. 1977).

Cross-tolerance regimens were used to elucidate the contribution of 5-HT_{1A} receptor action to the effects of LSD on locomotor activity. These experiments were designed to test the hypothesis that the effects of LSD in the BPM model are influenced by 5-HT_{1A} function and by 5-HT_{1C}/5-HT_2 function, thus supporting a combination of 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptor action.

Tolerance to 8-OH-DPAT and DOI

First, it was determined whether tolerance to the selective agonists would exhibit cross-tolerance to a different selective agonist. The hypothesis, based on earlier research (Berendsen and Broekkamp 1991; Darmani et al. 1990*a;* Johansson et al. 1990; Nash et al. 1989; Pranzatelli and Pluchino 1991), was that the 5-HT_{1A} and 5-HT_{1C}/5-HT_2 agonists 8-OH-DPAT and DOI, respectively, would both show tolerance but that cross-tolerance between the two drugs would not occur.

The most robust acute effect of 8-OH-DPAT administration, that of decreasing the number of movements made by the rat in the BPM in the first 10 minutes of an hour-long test session, was attenuated when 8-OH-DPAT was administered repeatedly every 12 hours for 5 days (figure 12). That is, tolerance was observed to the effects of 8-OH-DPAT when it was given chronically.

A similar pattern of tolerance was observed with DOI (figure 12). A diminished effect of the challenge dose of DOI occurred in animals pretreated chronically with DOI. As predicted, the repeated administration of DOI produced no significant cross-tolerance to the effects of an acute dose of 8-OH-DPAT (figure 12). However, the chronic administration of 8-OH-DPAT produced some cross-tolerance to the effects of a challenge dose of DOI (figure 12). Thus, the expected tolerance to the effects of 8-OH-DPAT and DOI occurred. Although DOI produced no cross-tolerance to 8-OH-DPAT, some cross-tolerance was found when DOI was tested in rats pretreated with 8-OH-DPAT (Krebs and Geyer 1994). Thus, the tolerance regimens were sufficient to produce significant tolerance, but this tolerance was not completely specific pharmacologically to each receptor subtype.

These effects are similar to what was observed when the 5-HT_1 antagonist propranolol was able to block some of the effects of the 5-HT_{1C}/5-HT_2 agonist DOI (figure 11). The partial cross-tolerance to DOI after chronic 8-OH-DPAT administration may reflect an interaction between 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors. Such an interaction has been suggested previously (Amt and Hyttel 1989; Darmani et al. 1990*b;* Krebs and Geyer 1994) and will require further studies to elucidate.

Tolerance to LSD and 8-OH-DPAT

A parallel study examined cross-tolerance between the effects of 8-OH-DPAT and LSD. Based on previous studies (Adams and Geyer 1985*a*), tolerance for the effects of LSD was expected. Based on its affinity to 5-HT_{1A} receptors, chronic LSD pretreatment was expected to produce cross-tolerance to the effects of 8-OH-DPAT treatment. The most important hypothesis was that 8-OH-DPAT pretreatment would produce cross-tolerance to the effects of LSD, suggesting either that 5-HT_{1A} receptors contribute to the effects of LSD or that 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors interact functionally. In either case, reciprocal cross-tolerance between 8-OH-DPAT and LSD was hypothesized. As before, tolerance to the effects of 8-OH-DPAT was evident (figure 13).

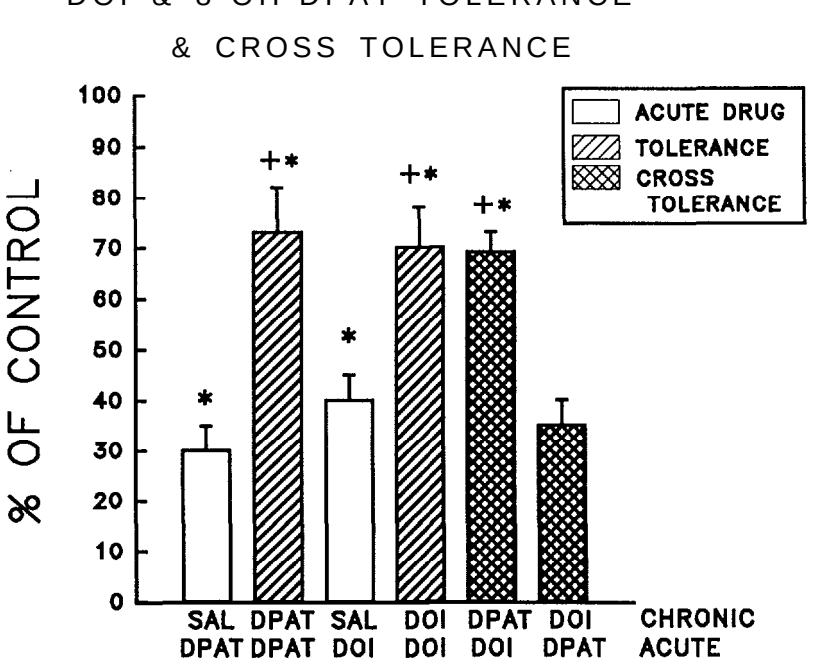

FIGURE 12. *Asymmetrical cross-tolerance between 5-HT_{1A} and 5-HT_{1C}/5-HT_2 agonists. Nine groups of male rats (n = 7-8) were pretreated chronically every 12 hrs for 5 days with either saline, DOI (1.0 mg/kg SC), or 8-OH-DPAT (0.5 mg/kg SC).Thirty-six hrs after the last pretreatment, rats were tested in the BPM 10 min after receiving treatment injections of either saline, 1.0 mg/kg DOI, or 0.5 mg/kg 8-OH-DPAT (DPAT). Both DOI and 8-OH-DPAT significantly decreased movements, a measure of global motor activity; these effects were significantly attenuated when the corresponding pretreatmeqts of DOI and 8-OH-DPAT were given, respectively. Also, cross-tolerance occurred to the effects of DOI when 8-OH-DPAT was the pretreatment, but no attenuation of 8-OH-DPAT's effects occurred when DOI was the pretreatment. (Values are percentages of group means of movements for corresponding control groups, for the first 10 min of testing, $p<0.05$). An * represents a significant difference from control, while a + represents a significant difference from the acute drμ group. Each symbol indicates significant tolerance or cross-tolerance, while both symbols together indicate partial tolerance or cross-tolerance. Redrawn from data presented in Krebs and Geyer 1994.*

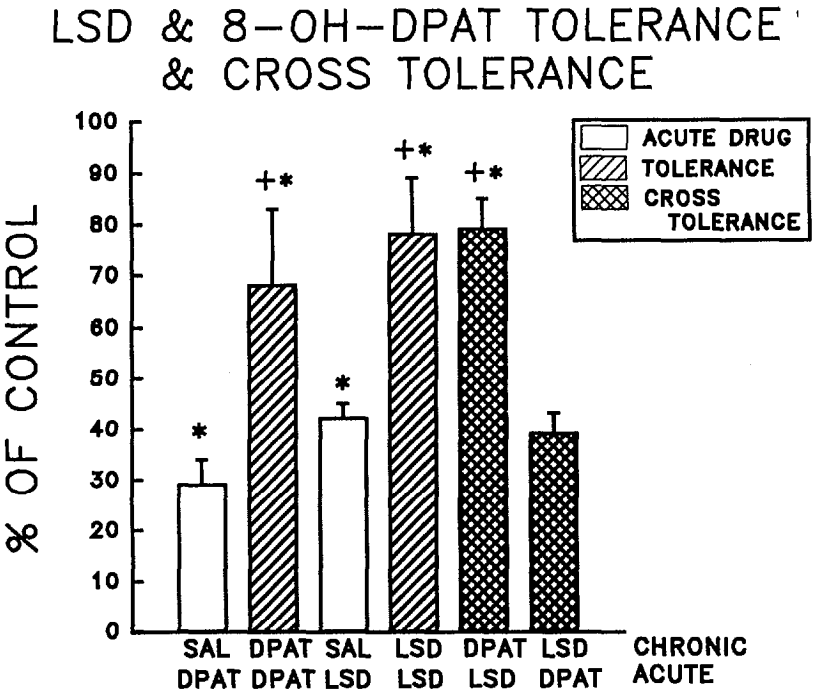

FIGURE 13. *Asymmetrical cross-tolerance between LSD and 5-HT$_{1A}$ agonist. Nine groups of male rats (n = 8) were pretreated chronically every 12 hrs for five days with either saline, 8-OH-DPAT (DPAT) (0.5 mg/kg SC), or LSD (60 µ/kg SC). Thirty-six hrs after the last pretreatment, rats were tested in the BPM 10 min after receiving treatment injections of either saline, 0.5 mg/kg 8-OH-DPAT, or 60 µ/kg LSD. Both LSD and 8-OH-DPAT significantly decreased movements, a measure of global motor activity; these effects were significantly attenuated when the corresponding pretreatments of LSD and 8-OH-DPAT were given, respectively, Also, cross-tolerance occurred to the effects of LSD when 8-OH-DPAT was the pretreatment, but no attenuation of 8-OH-DPAT's effects occurred when LSD was the pretreatment. (See figure 12 for explanation of values and symbols). Redrawn from data presented in Krebs and Geyer 1994.*

Also, the effects of LSD on movements showed tolerance after the chronic regimen was performed (figure 13). In animals chronically pretreated with 8-OH-DPAT every 12 hours for 5 days, the effects of LSD were significantly diminished. Thus, cross-tolerance to LSD was observed after the chronic administration of 8-OH-DPAT.

This result was consistent with the previous observation that propranolol partially blocks this effect of LSD, and further suggests that 5-HT_{1A}-related systems participate in these behavioral effects of LSD. However, even after chronic 8-OH-DPAT pretreatment a significant effect of LSD was still evident, indicating that the cross-tolerance was only partial. The reciprocal comparison did not evidence cross-tolerance. As seen in figure 13, animals pretreated chronically with LSD did not exhibit cross-tolerance to the effects of 8-OH-DPAT (Krebs and Geyer 1994). This nonreciprocal cross-tolerance is hypothesized to have occurred because the dose of LSD used did not occupy 5-HT_{1A} receptor sites as effectively as did the dose of 8-OH-DPAT, although the doses were equated in terms of the acute behavioral effects of the two drugs. The major finding of asymmetrical partial cross-tolerance between 8-OH-DPAT and LSD indicates that the effects of LSD on locomotor behavior, as defined by movements, are influenced by 5-HT_{1A} receptor function.

Tolerance to LSD and DOI

A parallel cross-tolerance study was performed with DOI and LSD. Because the previous study indicated that DOI tolerance was marginal when animals were treated every 12 hours for 5 days (figure 12), the chronic regimen was increased to injections every 12 hours for 8 days. As shown in figure 14, tolerance to the effects of both DOI and LSD was replicated. The effects of LSD were diminished somewhat in animals chronically pretreated with DOI, indicating that partial cross-tolerance to the effects of LSD occurred (figure 14). However, there was no reciprocal cross-tolerance when animals were chronically pretreated with LSD and challenged with DOI (Krebs and Geyer 1994). Therefore, the major finding of partial cross-tolerance to LSD after chronic DOI administration indicates that the effects of LSD on locomotion are influenced by the action of the 5-HT_{1C}/5-HT_2 system.

Taken together, evidence of partial cross-tolerance between 8-OH-DPAT and LSD and between DOI and LSD indicates that the behavioral effects of LSD are influenced by a combination of 5-HT_{1A} and 5-HT_{1C}/5-HT_2

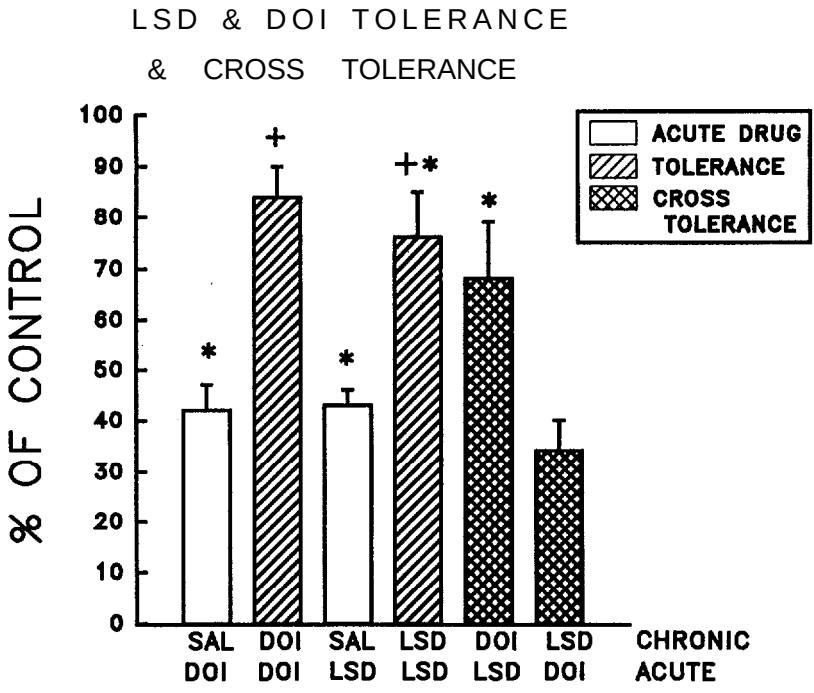

FIGURE 14. *Asymmetrical cross-tolerance between LSD and 5-HT$_{1C}$/5-HT$_2$ agonist. Nine groups of male rats (n = 7-8) were pretreated chronically every 12 hrs for eight days with either saline, DOI (1.0 mg/kg SC), or LSD (60 µ/kg SC).Thirty-six hrs after the last pretreatment, rats were tested in the BPM 10 min after receiving treatment injections of either saline, 1.0 mg/kg DOI, or 60 µ/kg LSD.Both LSD and DOI significantly decreased movements, a measure of global motor activity; these effects were significantly attenuated when the corresponding pretreatments of LSD and DOI were given, respectively. Also, cross-tolerance occurred to the effects of LSD when DOI was the pretreatment, but no attenuation of DOI's effects occurred when LSD was the pretreatment. (See figure 12 for explanation of values and symbols). Redrawn from data presented in Krebs and Geyer 1994.*

receptor action or that 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors interact in the modulation of this behavior. Accordingly, the prevailing view that the action of the 5-HT_{1C}/5-HT_2 receptor is primarily responsible for hallucinogenic activity may be true for the phenalkylamine hallucinogens, but this interpretation cannot completely explain the action of the less selective 5-HT_{1A}/5-HT_{1C}/5-HT_2 ergot alkaloid LSD.

There is some evidence of an interaction between the 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors. In one study it was found that the effect of the 5-HT_{1A} agonist 8-OH-DPAT was significantly increased when rats were treated simultaneously with DOI, a 5-HT_{1C}/5-HT_2 agonist. Interestingly, the effect of DOI on head twitches was inhibited by simultaneous treatment with 8-OH-DPAT (Arnt and Hyttel 1989). Moreover, the increased forepaw treading induced by cotreatment with 8-OH-DPAT and DOI was partially inhibited by high doses of either the 5-HT_2 antagonists, ritanserin and ketanserin, or the 5-HT_1 and ß-adrenoceptor antagonist (-)-alprenolol. Furthermore, the effects of the 5-HT_2 antagonists were synergistic with those of (-)-alprenolol in their ability to block the forepaw treading induced by the agonist combination (Arnt and Hyttel 1989). This synergistic relationship was interpreted as an asymmetrical interaction between the 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors.

Another study has replicated some of these findings by demonstrating that the head twitch response induced by the 5-HT_{1C}/5-HT_2 agonist DOI was significantly inhibited by simultaneous administration of the 5-HT_{1A} agonist 8-OH-DPAT, but not by the 5-HT_{1B}/5-HT_C agonist 1-(3-trifluromethylphenyl)piperazine (TFMPP) (Darmani et al. 1990*b*). These researchers argue for a pharmacological interaction between the 5-HT_{1A} and 5-HT_2 receptors that manifests itself in a 5-HT_{1A} inhibitory action on 5-HT_2 receptor-modulated behavior (Darmani et al. 1990*b*).

These results, taken together with the asymmetrical cross-tolerance results (Krebs and Geyer 1994) and the propranolol antagonism of DOI discussed earlier, suggest that there may indeed be interactions between the 5-HT_{1A} and 5-HT_{1C}/5-HT_2 receptors. With further investigation, the BPM system may be able to shed light on the nature of this interaction by more thoroughly characterizing the effects of 5-HT_{1A} agonists and hallucinogens. With more detailed analyses of phenalkylamine, indoleamine, and ergot alkaloid hallucinogens, clarification of the mechanisms of action of these drugs should be possible.

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