The Stimulus Effects of Serotonergic Hallucinogens in Animals

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INTRODUCTION

Mankind has known of naturally occurring hallucinogens for thousands of years (Schultes and Hofmann 1980), but less than one-tenth of one millennium has passed since it could be said with confidence that a pure chemical of known structure is hallucinogenic (Heffter 1897; Spath 1919). That chemical was mescaline, a representative of the phenethylamine subclass of the serotonergic hallucinogens. The other subclass, the indoleamines, is perhaps best represented by lysergic acid diethylamide (LSD), a drug whose hallucinogenic properties were discovered by Albert Hofmann on April 16, 1943 (Hofmann 1959). That both the indoleamines and the phenethylamines are properly classified together as serotonergic hallucinogens has become apparent only in the last 2 decades.

The remarkable alterations in thought and perception produced by hallucinogens have been described by many. In some instances, carefully selected human volunteers have received these drugs in rigidly controlled studies (Isbell et al. 1959; Martin and Sloan 1977; Strassman, this volume). In others, investigators have told of the effects of hallucinogens following self-administration. These reporters have ranged from persons without scientific training (DeCurtis 1987) to distinguished scientists such as Hofmann (1959), Szára (1957), and Shulgin (this volume; Shulgin et al. 1986). But to seek out the most intimate mechanisms by which hallucinogens work their magic, and in the process to make discoveries of ultimate benefit to humanity, researchers are obliged to use other species.

In turning to animals to aid in understanding of hallucinogens, major ethical problems are avoided, but, concomitantly, there arise questions of relevance. Is there a suitable animal model of hallucination, a phenomenon thought by many to be a uniquely human experience? Most of those who work with animals find comfort in the knowledge that the

fundamental biochemical and physiological aspects of neuronal function are remarkably similar across species. On the other hand, hallucinations are primarily expressed in behavioral terms, and, in the absence of verbal communication, one is hard pressed to demonstrate the validity of animal models of complex human behavior. This chapter describes how the study of serotonergic hallucinogens as discriminative stimuli has already enlarged the knowledge of these drugs and how these studies in animals have led to hypotheses testable in humans.

STIMULUS CONTROL

A discriminative stimulus is any feature of an animal's environment that is correlated with a schedule of reinforcement (Kelleher and Morse 1968). Operant behavior that is reinforced only in the presence of a specified stimulus soon occurs with greater frequency in the presence of the stimulus than in its absence. The behavior is then said to be under the control of the stimulus. Discriminative stimuli may act on one or more of a variety of receptors, both external and internal.

In classic studies of visual discrimination, pigeons were trained to emit a particular response in the presence of light of a specified frequency. When an organism has been conditioned to respond to a particular stimulus, other similar stimuli also increase the probability of elicited response. This ability of stimuli other than the training stimulus to evoke a conditioned response is known as stimulus generalization. However, as the character of the tested stimuli becomes less and less like the training stimulus, the degree of generalization declines in a regular fashion; a generalization gradient is observed. Thus, for example, a pigeon that has been reinforced after pecking a key only when it is illuminated with yellow light will emit progressively fewer responses as the illuminating color is gradually shifted toward the red and violet ends of the spectrum, It is obvious that stimulus control offers an investigator the opportunity to ask questions about the perception of light by a nonverbal species in both normal and pathological states (Stebbins 1970).

If the correlation of a schedule of reinforcement with the falling of photons upon eye receptors can induce stimulus control, then might a similar correlation of reinforcement between drug interaction and its receptors likeu ise come to control behavior? The answer is yes. Beginning with the studies reported by Conger (1951), many hundreds of investigations have shown that a variety of drugs can induce stimulus

control. (For a recent review, see Colpaert and Balster 1988). By analogy with visual discriminations, drug-induced stimulus control offers the opportunity to ask questions, and occasionally to receive answers, regarding the effects of psychoactive drugs in nonverbal species. Because these stimuli are engendered, not in some totally mysterious fashion but by drug-receptor interactions, researchers may hope to learn not only about the nature of the stimuli but also about the biochemical and molecular processes from which they arise.

HALLUCINOGEN-INDUCED STIMULUS CONTROL

Hirschhorn and Winter (1971) reported that the prototypic serotonergic hallucinogens mescaline and LSD are able to induce stimulus control in rats (figures 1 and 2). Furthermore, it was found that the stimulus effects of mescaline and LSD differ not only from those of drugs from distinct pharmacological classes such as stimulants (Winter 1975*a*) and depressants (Hirschhorn and Winter 1975) but also from nonindoleamine, nonphenethylamine hallucinogens (Shannon 1981; Silverman and Ho 1978; Swedberg and Jarbe 1986).

In the United States and elsewhere, hallucinogens have traditionally been classified as drugs of abuse together with stimulants, depressants, and opiates. However, unlike the latter categories of drugs, hallucinogens do not function as reinforcers in animals (Deneau et al. 1969). For this reason hallucinogens are not amenable to study in animals using the very powerful operant techniques for self-administration. Against this background, the 'potential value of drug-induced stimulus control for the identification, characterization, and scheduling of potential hallucinogens prior to their use in human subjects is readily apparent (Winter 1974).

SEROTONERGIC HALLUCINOGENS

Soon after the discovery of LSD by Hofmann, it was recognized that the clinical syndromes produced by the phenethylamine hallucinogens, mescaline and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), are quite similar to those following indoleamine hallucinogens such as LSD and N,N-dimethyltryptamine (DMT) (Hoch et al. 1952; Hollister et al. 1969). That the phenethylamines and the indoleamines might be acting via a common mechanism and that the mechanism might be serotonergic in nature was suggested by a number of observations. In

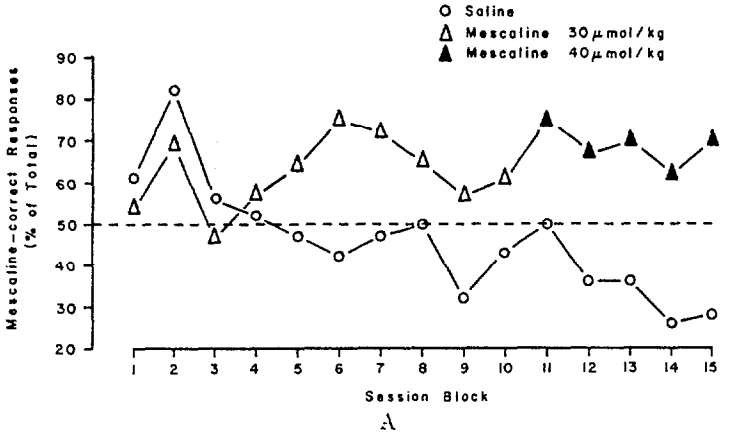

FIGURE 1. *Discriminated responding following the injection of mescaline or saline. Each point is the mean of 2 determinations in each of 4 animals. Circles represent experiments in which saline was injected 5 minutes before the session. Triangles represent identical experiments in which either 7.4 mg/kg (open triangles) or 9.9 mg/kg (closed triangles) of mescaline was given. Ordinate: number of responses on the mescaline-correct lever in the first 5 minutes of the session, expressed as a percentage of total responses. Abscissa: successive blocks of 4 sessions. From Hirschhorn and Winter 1971, by permission*

human subjects (Balistrieri and Fontanari 1959; Wolbach et al. 1962) as well as in animals (Appel and Freedman 1968; Winter 1971), cross-tolerance develops between LSD and mescaline. In addition, both groups of hallucinogens produce similar effects on the firing rate of serotonergic neurons (Aghajanian et al. 1970) and on the level and rate of turnover of serotonin in the brain (Tonge and Leonard 1969). Finally, it was known that serotonergic antagonists block some of the nonbehavioral effects of phenethylamine hallucinogens in animals (Cheng et al. 1973; Horita and Hamilton 1972; Huang and Ho 1972).

Antagonism of mescaline-induced stimulus control in rats by cinanserin, a serotonergic antagonist, was reported independently by Browne and Ho (1975) and by Winter (19753). This observation was then extended to

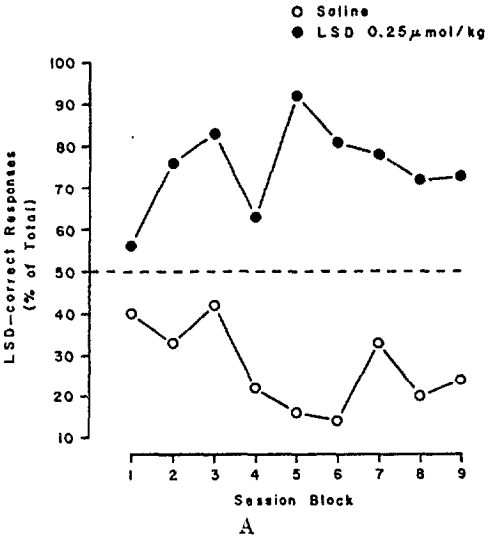

FIGURE 2. *Discriminated responding following the injection of LSD or saline. Closed circles: LSD [0.12 mg/kg]. Open circles: saline. All other details are as in figure 1.*

include other antagonists of serotonin and other hallucinogens including LSD, DOM, and DMT (Glennon et al. 1982; Kuhn et al. 1977; Winter 1978*a*). The phenomenon is illustrated in figure 3 for LSD and in figure 4 for DOM. Based upon data such as those shown, it appears appropriate to apply the term "serotonergic hallucinogens" to both the indoleamines and the phenethylamines.

PARTIAL AGONISTS

Because of the crucial role played by antagonists in the characterization of a variety of drugs including hallucinogens, it is important to examine certain assumptions regarding the antagonists to be used. This is especially important when drugs shown to be antagonists in one or another in vitro, isolated tissue, or biochemical assay systems are used in intact animals in behavioral experiments.

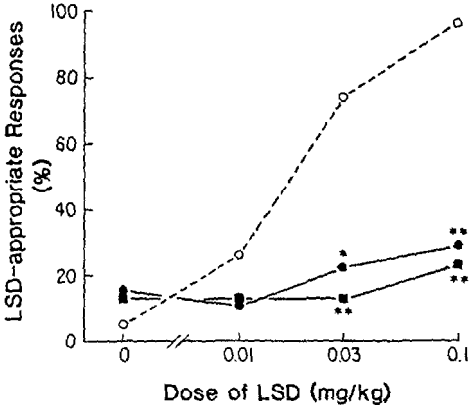

FIGURE 3. *The effects of LSD alone (open circles) and in the presence of either pizotyline (closed circles; 10 mg/kg) or pirenperone (closed squares: 0.16 mg/kg) in rats trained with LSD (0.1 mg/kg) as a discriminative stimulus. LSD and the antagonists were injected 15 min and 60 min, respectively, before testing. The values given at the zero dose level are the effects of saline, pizotyline, and pirenperone when given alone. Each is the mean of 2 determinations in each of 10 subjects. All other points represent the mean of I determination in each of 10 animals. Ordinate: Mean percentage of responses on the LSD-appropriate lever. Abscissa: dose plotted on a log scale. Statistical comparisons are with the value for LSD alone; *:p less than 0.05; **: p less than 0.01. From Winter and Rabin 1988 by permission*

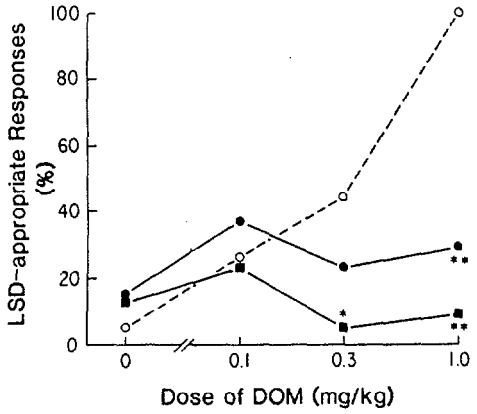

FIGURE 4. *The effects of DOM alone (open circles) and in the presence of either pizotyline (closed circles) orpirenperone (closed squares) in rats trained with LSD as a discriminative stimulus. DOM was injected 15 min before testing. All other details are as in figure 3.*

As has been noted above, blockade of the stimulus effects of indoleamine and phenethylamine hallucinogens by serotonergic antagonists has provided powerful evidence of an underlying mechanism mediated by 5-hydroxytryptamine (5-HT). However, stimulus control also permits the identification not only of full agonists and pure antagonists but also those drugs with mixed properties, the partial agonists. Data published by Colpaert and colleagues (1982) provide excellent examples.

Figures 5 through 7 show the agonistic effects (upper panels) and the antagonistic effects (lower panels) of a series of serotonergic antagonists in rats trained with LSD as a discriminative stimulus. It is obvious that a full spectrum of activity is represented. Methysergide, cyproheptadine, and mianserin are significantly LSD-like (figure 5, upper panel) and are, as would be expected from their agonistic effects, only marginally effective as antagonists (lower panel). Pizotifen (also known as BC-105

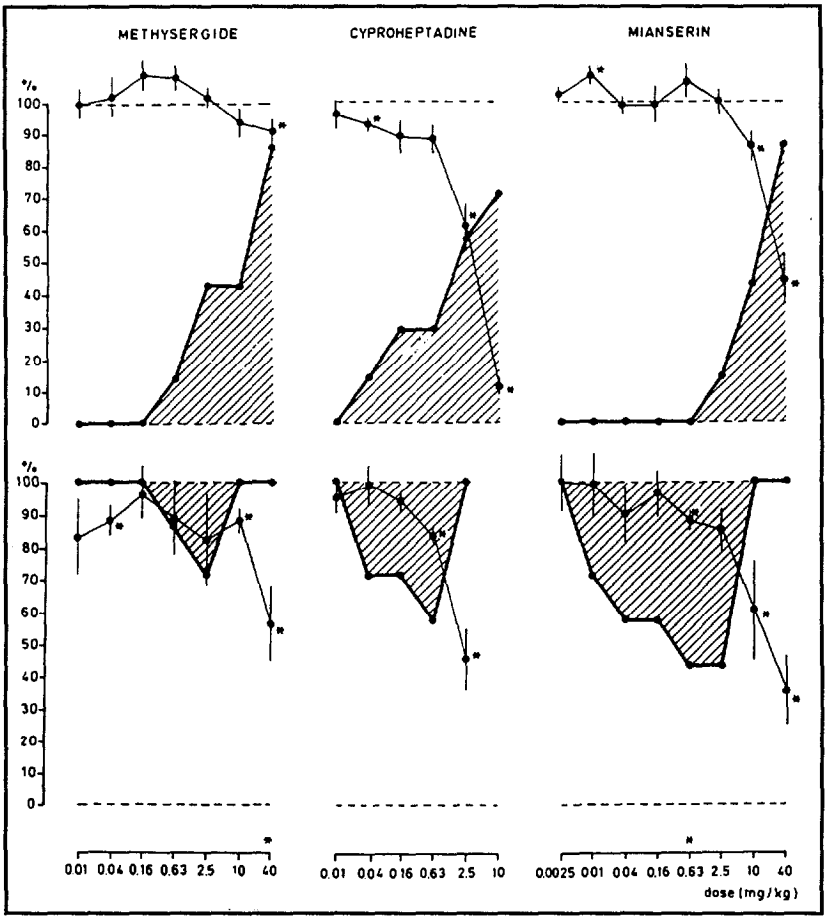

FIGURE 5. *Agonist and antagonist effects of methysergide, cyproheptadine, and minaserin in rats trained with LSD [0.16 mg/kg] and saline. Upper panel: agonistic effects [thick line] and suppression of response rate [thin line] by the test drug when given alone. Lower panel: antagonistic effects [thick line] and suppression of response rate [thin line] by the test drug when given prior to the training dose of LSD. Ordinate: percentage of rats choosing the LSD-appropriate lever [thick line] and response rate [thin line] expressed as a percentage of saline-control rate. Abscissa: dose of test drugs. From Colpaert et al., 1982, by permission*

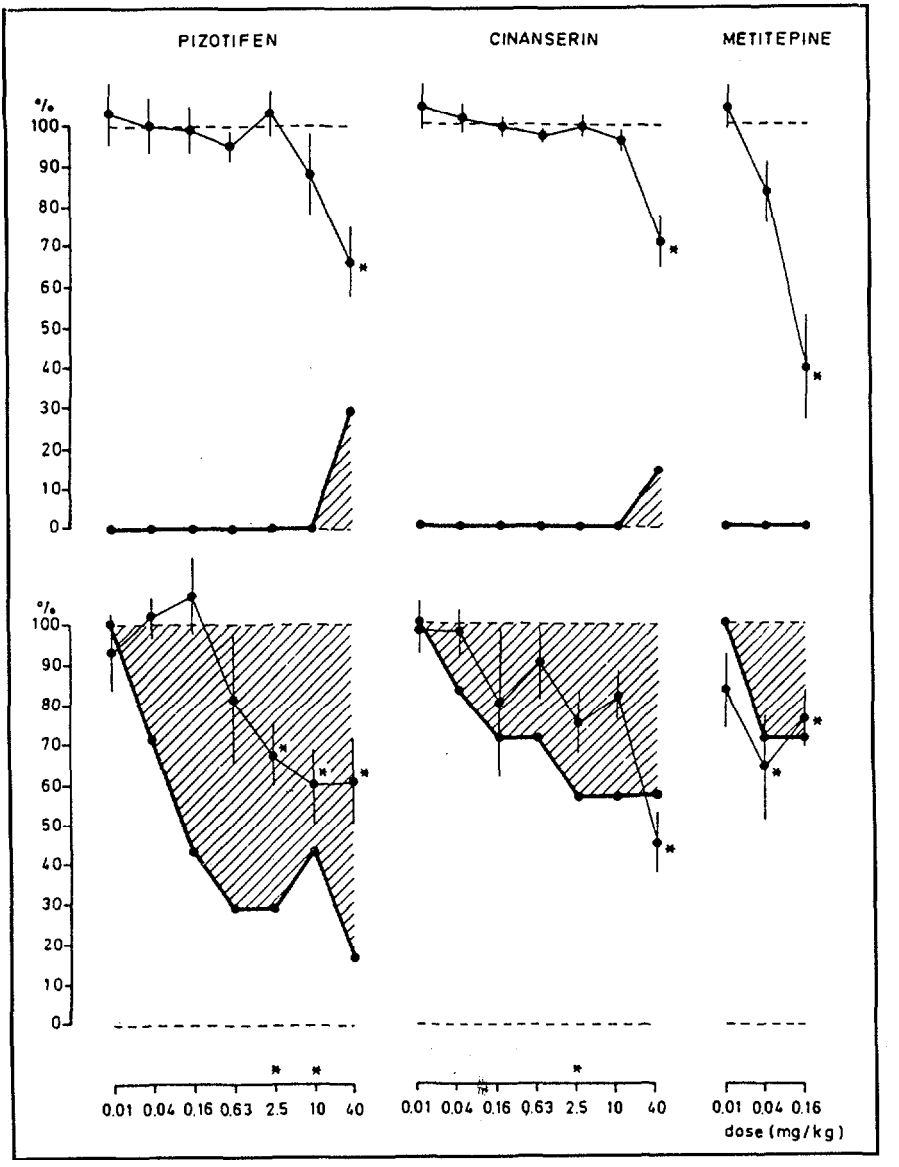

FIGURE 6. *Agonist and antagonist effects of pizotifen, cinanserin, and metitepine in rats trained with LSD [0.16 mg/kg] and saline. All other details are as in figure 5.*

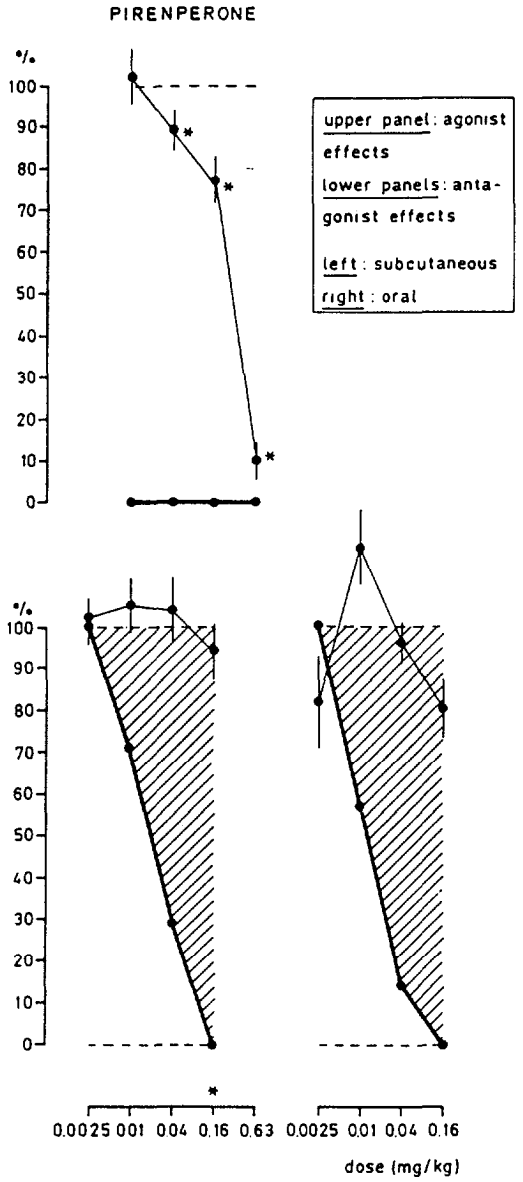

FIGURE 7. *Agonist and antagonist effects of pirenperone in rats trained with LSD [0.16 mg/kg] and saline. All other details are as in figure 5.*

and as pizotyline), cinanserin, and metitepine (figure 6) are clearly less agonistic, but only pizotifen approaches being a complete antagonist. Finally, figure 7 provides convincing evidence that pirenperone is devoid of LSD-like stimulus effects and is a complete antagonist of LSD at doses that have only modest effects upon rate of responding.

Of the three purported antagonists showing the highest degree of LSD-like stimulus effects in the rat, two-methysergide and cyproheptadine-are claimed to be sometimes associated with hallucinations in humans. It is clear that drug-induced stimulus control provides the means to assess full agonists, pure antagonists, and those drugs that exhibit intermediate degrees of activity. It is likely that extrapolation from animals to humans is most problematic for the last-named group of drugs.

INTERMEDIATE RESULTS AND THE BERRY-ATOR HYPOTHESIS

One of the most remarkable features of drug-induced stimulus control is that animals trained with a drug of one pharmacological class do not always exhibit drug-appropriate responses when tested with a drug of another class even at doses known to have stimulus properties. For example, rats trained with morphine sulfate (6 milligrams per kilogram [mg/kg]) versus saline emit primarily saline-appropriate responses when tested with ethanol at a dose of 630 mg/kg, despite the fact that stimulus control is readily established in rats trained with a 630 mg/kg dose of ethanol versus saline (Winter 1975*c*). However, observations such as these should not diminish the appreciation of what have been called "intermediate results" (Winter 1978*b*).

In the larger context of stimulus control, it was noted above that a generalization *gradient* is observed. As the tested stimulus becomes less and less like the conditioned stimulus, the probability of response emission becomes less and less. With respect to drug-induced stimulus control, a clear example of a stimulus gradient is seen when subjects trained with saline versus a specified dose of a drug are tested with a range of lesser doses of that drug. As expected, intermediate degrees of drug-appropriate responding occur.

Despite the ready acceptance of intermediate results in the context of dose-response relationships, there has been some reluctance to accept similar intermediate degrees of generalization when subjects trained with one drug are tested with other drugs. That such intermediate results may be informative is illustrated by an examination of the comparative stimulus properties of p-methoxyamphetamine (PMA) and LSD.

In studies that employed an animal model of hallucination based on patterns of conditioned avoidance responses, PMA was characterized as having a typical hallucinogenic profile similar to that of LSD (Smythies et al. 1967; 1970). However, rats trained with PMA as a discriminative stimulus and tested with LSD gave a maximum of only about 50 percent PMA-appropriate responses (Winter 1984). When rats were trained with LSD and tested with PMA, the results were as shown in table 1. At a dose of PMA of 1 mg/kg, 48 percent of the responses were LSD-appropriate. At 3 mg/kg the percentage rose to 75 percent, but only half of the tested animals responded.

As shown in figure 3, LSD-induced stimulus control is completely antagonized by the serotonergic antagonist pizotyline. As seen in table 2, the intermediate degree of generalization of LSD to a dose of 1 mg/kg PMA is likewise blocked by pizotyline. Is the conclusion to be that PMA-induced stimulus control is partially mediated by a serotonergic mechanism? As attractive as that conclusion may be, the data in table 2 argue against ‘it. The table shows that PMA-induced stimulus control is not significantly antagonized by a dose of pizotyline that completely blocks the partial substitution of PMA for LSD.

TABLE 1. *Effects of PMA in rats trained with LSD (0.1 mg/kg)*

Dose of PMA (mg/kg)	N	Percent LSD choice
0.3	10	11
1	10	48
3	5	75

NOTE: Ten animals were tested at each dose. N = the number which completed the test session. Redrawn from Winter (1984).

TABLE 2. *Effects of PMA alone and in combination with pizotyline in rats trained with either PMA or LSD*

Training drug (mg/kg)	Dose of PMA (mg/kg)	Dose of pizotyline (mg/kg)	N	Cross test
PMA	3	0	6	98
(3)	3	3	6	96
	3	10	6	90
LSD	1	0	6	52
(0.1)	1	3	6	16

NOTE: Six animals were tested at each dose. N = the number which completed the test session. Redrawn from Winter (1984).

An explanation for this apparent paradox is provided by what has come to be known as the Berry-Ator hypothesis. Specifically, asymmetrical generalizations are explained in terms of differential salience of certain elements of a compound discriminative stimulus depending on the training drug (Ator and Griffiths 1989). Although originally proposed to account for the observation that baboons trained with pentobarbital generalize to lorazepam, but lorazepam-trained subjects do not reliably generalize to pentobarbital, the Berry-Ator hypothesis is also applicable to the data for LSD and PMA shown in tables 1 and 2. Specifically, the intermediate results obtained with PMA in rats trained with LSD indicate a stimulus component common to both drugs. Blockade by pizotyline of both LSD and the intermediate effects of PMA in rats trained with LSD suggest that the shared component is serotonergic in nature. Nonetheless, the failure of pizotyline to antagonize PMA-induced stimulus control in rats trained with the drug indicates that the serotonergic component of the action of PMA is not essential for the induction of stimulus control. Furthermore, the serotonergic effect of PMA is manifest only when PMA is tested in subjects trained with a drug such as LSD whose major stimulus effects are mediated by 5-HT.

CORRELATIONS BETWEEN HUMANS AND ANIMALS

How much can a rat or other nonverbal species tell us about the human experience with hallucinogens? In the present context, what can drug-induced stimulus control by serotonergic hallucinogens tell us about their mechanisms of action in humans? Can drug-induced stimulus control provide the means to reliably predict whether a drug fresh from the synthetic chemist will produce hallucinations in human subjects? One approach to answering these questions is to examine the ability of animals to classify drugs correctly as being either hallucinogenic or nonhallucinogenic on the basis of their stimulus properties. A convenient way to pursue this approach is in terms of false negatives and false positives.

FALSE NEGATIVES

A false negative is a drug known to be hallucinogenic in man, yet fails to mimic other known hallucinogens *of the same class* trained as discriminative stimuli in animals. "Of the same class" is emphasized because of the well-established fact, noted above, that drugs such as LSD, phencyclidine, tetrahydrocannabinol, and atropine are all properly called hallucinogens, yet each is pharmacologically distinct. Thus, the false negatives to be considered at this time are those within the class designated as serotonergic hallucinogens.

In theory, false negatives have a finite probability of occurrence. For example, imagine two drugs, A and B, that share a common hallucinogen-inducing effect in humans. Further imagine that the shared effect of drugs A and B is reflected in a distinctive discriminative stimulus in animals. However, drug A does not generalize to drug B, because drug B suppresses behavior in a chosen animal species at doses lower than those required to elicit the hallucinogen-specific stimulus. The principle is clear: an animal in which all behavior has been obliterated cannot answer questions about discriminative stimuli.

In practice, the clearest example of a false negative among the serotonergic hallucinogens was provided by Koerner and Appel(1982). Rats trained to discriminate between 4-phosphoryloxy-DMT (psilocybin) and saline generalized to 4-hydroxy-DMT (psilocin) and LSD but failed to generalize to mescaline.

Koerner and Appel (1982) regarded their data as evidence of "the inability of existing drug discrimination procedures to detect 'hallucinogenicity' in drugs (p. 134)." This assessment may be too harsh in view of the numerous demonstrations of the similarities between the stimulus effects of various indoleamine and phenethylamine hallucinogens and, more specifically, the blockade of the stimulus effects of both psilocybin and mescaline by the serotonergic antagonist, cinanserin (Silverman and Ho 1978). A gentler interpretation is that, despite their similarities, each member of the class of serotonergic hallucinogens is a distinct pharmacological entity, and as such each would be expected to have distinctive features in its stimulus complex. Ironically, the more thorough the research, the more likely it is that such distinctive features will be detected. As a practical matter, one might wish to characterize an unknown drug against several serotonergic hallucinogens. It should be noted as well that in a subsequent study by Appel and Callahan (1989), mescaline-trained rats generalized fully to psilocybin.

FALSE POSITIVES

False positives are of greater concern than false negatives with respect to the discriminative power of drug-induced stimulus control, but at the same time they are of perhaps greater heuristic value. A false positive is a drug known to be devoid of hallucinogenic activity in humans but which nonetheless fully mimics known serotonergic hallucinogens in animals.

Before discussing false positives, it must be noted that interpretation of animal data is sometimes hampered by the inadequacy of available clinical data. For example, 2, 3, 4-trimethoxyphenethylamine (2,3,4-TMPEA) is a structural isomer of mescaline that was reported to have no psychotropic effects (Shulgin 1964; Shulgin and Shulgin 1991). On that basis it was used to test the hypothesis that the different pharmacologic properties of hallucinogens and nonhallucinogens in man are reflected in distinctive stimuli in rats. Only after it was found that rats appeared unable to distinguish between the effects of mescaline and 2,3,4-TMPEA (Winter 1973) was the author's attention drawn to a citation of 2,3,4-TMPEA hallucinogenic activity in schizophrenic patients (Slotta and Muller 1936). The proper interpretation of this set of observations or their implications for schizophrenia remains uncertain.

One may argue on theoretical grounds, as argued above for false negatives, that true false positives should occasionally arise. If one imagines two drugs, C and D, to possess a shared hallucination-inducing property and drug D to also be a very potent emetic agent, one may remain unaware of D's hallucinogenic activity for the simple reason that hallucinogenic doses are never reached in vomiting human subjects. On the other hand, if the emetic effect is species-specific, C and D would be expected to generalize to one another in an emesis-resistant species and thus yield a false positive.

Despite the foregoing caveats, false positives have been identified. Understanding them is essential to a valid judgment of the efficacy of drug-induced stimulus control as a practical tool for the study of serotonergic hallucinogens. Although a number of candidates present themselves, only lisuride and 2-(1-piperazinyl) quinoline maleate (quipazine) are discussed in detail in this chapter.

Lisuride is an ergot that is usually classified as a dopaminergic agonist. As such, it has a therapeutic role in the treatment of Parkinson's disease. Lisuride is generally regarded as being nonhallucinogenic and quite different from LSD in its actions. Despite their distinctive effects in humans, complete symmetrical generalization of LSD and lisuride has been reported (Holohean et al. 1982; White and Appel 1982*a*,*b*).

The observation that the stimulus effects of LSD and lisuride are differentially antagonized by serotonergic and dopaminergic antagonists (Cunningham and Appel 1987; White and Appel 1982*c*) is of obvious pharmacologic interest. However, it does not resolve the question of lisuride as a false positive. What is required is a demonstration that animals can behaviorally differentiate the two drugs. A series of experiments by Callahan and Appel (1990) provided just such a demonstration.

Rats were presented with three levers simultaneously. Each lever was associated with one of three conditions: saline, LSD, or lisuride. The doses of LSD and lisuride were chosen to be comparable in their stimulus effects when tested in animals trained with lisuride and LSD, respectively, versus saline. As shown in figure 8, the rats learned to discriminate between the three training conditions. Furthermore, when dose-response tests were done with a range of doses of LSD and lisuride, there was a graded distribution of responses between the saline-appropriate lever and the LSD- and lisuride-appropriate levers, respectively. Thus, in the

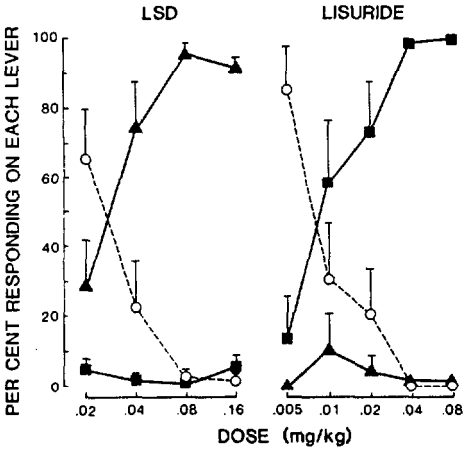

FIGURE 8. *Dose-response relationships for LSD [left panel] and lisuride [right panel] in rats trained to discriminate LSD [0.08 mg/kg] from lisuride [0.04 mg/kg] from saline. Responding on the LSD-appropriate lever is indicated by triangles, on the lisuride-appropriate lever by squares, and on the saline-appropriate lever by circles. Ordinate: percent responding on the indicated lever. Abscissa: dose of test drugs. From Callahan and Appel 1990, by permission*

three-lever choice trial, no evidence of cross-generalization between LSD and lisuride was seen; the issue of lisuride as a false positive is resolved.

The second false positive to be discussed is quipazine, a drug thought to act as an agonist at both central and peripheral serotonergic receptors. Stimulus control induced by quipazine was first reported by White and

colleagues (1977). They also observed complete generalization of quipazine to LSD. Furthermore, the generalization is symmetrical in that quipazine completely mimics LSD in rats trained with the latter drug (Winter 1979). A recent example of LSD generalization to quipazine is shown in figure 9. There it is obvious that quipazine's mimickry of LSD is not due to lisuride-like effects. Indeed, in keeping with a serotonergically mediated event, quipazine-induced stimulus control and substitution of quipazine for LSD are blocked by a variety of serotonergic antagonists (White et al. 1977; Winter 1979). It should be noted that in mescaline-trained subjects, only an intermediate level of generalization to quipazine was observed (Winter 1979).

When normal human volunteers were given 25 mg of quipazine by mouth in a double-blind cross-over study and tested using the Addiction Research Center Inventory (ARCI) (Hill et al. 1963), no LSD-like subjective effects were observed (Villarreal, personal communication, Dec. 12, 1977). However, at this dose there was a high incidence of nausea, flatulence, gastrointestinal discomfort, and diarrhea. Similarly, an anecdotal report of effects of quipazine in a single subject suggests "low dose mescaline-like effects followed by the onset of dysphoric effects including nausea!' (Daumier, personal communication, July 27, 1976). Interestingly, three of four monkeys given quipazine by intramuscular (IM) injection developed projectile vomiting while exhibiting behavioral signs similar to those induced by LSD (Schlemmer, Jr., personal communication, Jan. 14, 1977).

When the admittedly fragmentary data for quipazine in man, monkey, and rat are taken as a whole, there is some similarity to the hypothetical false positive described earlier in this section; that is, a drug which would induce hallucinations in man were it not for a limiting side effect that is present to a lesser degree in nonhuman primates and absent in the rat. Given the high affinity of quipazine for 5-HT_3 receptors and the known antiemetic effects of certain 5-HT_3 antagonists, the present hypothesis might be tested by determining the hallucinogenic activity of quipazine in humans pretreated with a drug such as ondansetron. (For a review of 5-HT_3 receptors and ligands, see Kilpatrick et al. 1990.)

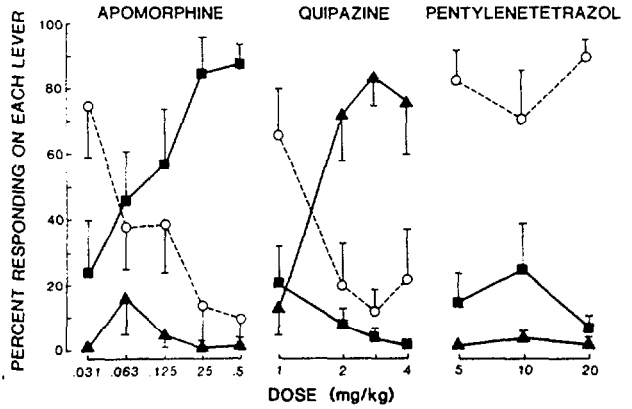

FIGURE 9. *Dose-response relationships for apomorphine, quipazine, and pentylenetetrazole in rats trained to discriminate LSD [0.08 mg/kg] from lisuride [0.04 mg/kg] from saline. All other details are as in figure 8.*

SEROTONERGIC RECEPTOR SUBTYPES

Behavioral pharmacology has elsewhere been referred to as a marriage of convenience between psychology and pharmacology (Winter 1978*b*). Nowhere are the difficulties of that marriage more evident than in the application of stimulus control to serotonergic hallucinogens. While behavioral techniques have been slowly maturing, there has been an exponential growth in the knowledge of the pharmacology, molecular biology, and functional significance of serotonergic receptors. The light cast by the discovery of each new receptor subtype permits—nay, requires—constant reexamination and reinterpretation of behavioral data. The serotonergic receptors designated 5-HT_2 and 5-HT_{1C} illustrate this point.

The role of the 5-HT_2 receptor in the actions of serotonergic hallucinogens appears well established (Glennon et al. 1985; Glennon, this volume). However, the discovery of the 5-HT_{1C} receptor subtype (Pazos et al. 1984) and the realization that there is often a close correlation between affinities for the 5-HT_2 and 5-HT_{1C} sites (Glennon 1990; Sanders-Bush and Breeding 1988; Titeler et al. 1988) have led to speculation that the 5-HT_{1C} receptor may play an independent or complementary role in-hallucinogenic activity (Sanders-Bush and

Breeding 1991; Titeler et al. 1988). This hypothesis is supported by the observation that LSD, but not its nonhallucinogenic congeners, is an agonist at 5-HT_{1C} receptors as indicated by stimulation of phosphoinositide hydrolysis (Burris et al. 199 1; Sanders-Bush, this volume.) It is obvious that each of these biochemical advances calls for the investigation of possible behavioral correlates. The investigation of the discriminative stimulus properties of drugs reputed to have selectivity for the 5-HT_{1C} receptor should prove informative. One such agent presently under study is *m*-chlorophenylpiperazine (MCPP) (Winter and Rabin 1992).

CONCLUSION

Although much has been learned regarding the stimulus effects of serotonergic hallucinogens, this area of investigation remains exciting in its promise. The observation that atypical antipsychotic drugs such as clozapine have high affinity for serotonergic receptors has given new life to the old idea that there may be a connection between exogenous hallucinogens and endogenous hallucinogenic processes. Increasing awareness of interactions between chemically distinct neurotransmitters encourages a broader mechanistic view. On an experimental level, researchers have perhaps become too set in their ways. For example, recent work in the author's laboratory (Fiorella et al., in press; Palumbo et al., in press) indicates that so simple a design feature as pretreatment time may have a significant influence upon the stability of DOM-induced stimulus control and, by inference, upon the nature of the cue which is trained. A continued effort is needed to identify those pharmacological features of hallucinogen-induced stimulus control in animals and their correlates in humans.

Twenty years ago, Winter (1972) stated, "It remains to be established whether study of the stimulus properties of drugs will permit the early identification of hallucinogens or will contribute in any significant way to our understanding of hallucinogens." (Winter 1974, p. 831). Evidence gathered during the intervening two decades, some of which is reviewed here and elsewhere in this volume, has answered both questions in the affirmative. Others appear to be encouraged as well: "Drug discrimination has proven to be a reliable, sensitive, and specific procedure that provides a powerful tool in the analysis of neuropharm-acological mechanisms underlying the behavioral effects of diverse classes of drugs." (Koek et al. 1992, pp. 97-98). With the long-awaited

resumption of tests in human subjects (Strassman, this volume) and the guidance provided by ever more sophisticated chemical, biochemical, and molecular techniques, the continued investigation of the stimulus properties of serotonergic hallucinogens promises to enhance the understanding not only of these agents as drugs of abuse, but also to elucidate the normal, pathological, and perhaps even supranormal functioning of the brain.

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