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REVIEW

Hallucinogens as discriminative stimuli in animals: LSD, phenethylamines, and tryptamines

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Abstract
Background Although man's first encounters with hallucinogens predate written history, it was not until the rise of the sister disciplines of organic chemistry and pharmacology in the nineteenth century that scientific studies became possible. Mescaline was the first to be isolated and its chemical structure determined. Since then, additional drugs have been recovered from their natural sources and synthetic chemists have contributed many more. Given their profound effects upon human behavior and the need for verbal communication to access many of these effects, some see humans as ideal subjects for study of hallucinogens. However, if we are to determine the mechanisms of action of these agents, establish hypotheses testable in human subjects, and explore the mechanistic links between hallucinogens and such apparently disparate topics as idiopathic psychosis, transcendental states, drug abuse, stress disorders, and cognitive dysfunction, studies in animals are essential. Stimulus control by hallucinogens has provided an intuitively attractive approach to the study of these agents in nonverbal species.
Objective The intent of this review is to provide a brief account of events from the time of the first demonstration of hallucinogen-induced stimulus control to the present. In general, the review is limited to lysergic acid diethylamide (LSD) and the hallucinogenic derivatives of phenethylamine and tryptamine.
Results The pharmacological basis for stimulus control by LSD and hallucinogenic phenethylamines and tryptamines is serotonergic in nature. The 5-HT_{2A} receptor appears to be the primary site of action with significant modulation by other serotonergic sites including 5-HT_{2C} and 5-HT_{1A} receptors. Interactions with other neurotransmitters, especially glutamate and dopamine, are under active investigation. Most studies to date have been conducted in the rat but transgenic mice offer interesting possibilities.
Conclusions Hallucinogen-induced stimulus control provides a unique behavioral tool for the prediction of subjective effects in man and for the elucidation of the pharmacological mechanisms of the action of these agents.

Keywords Hallucinogens · Drug-induced stimulus control · Lysergic acid diethylamide (LSD) · Mescaline · (−)-2,5-dimethoxy-4-methylamphetamine (DOM) · Psilocybin · Bufotenine · *N*,*N*-dimethyltryptamine (DMT) · Phencyclidine (PCP)

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Historical perspective

Hallucinogens, most often in the form of crude botanical extracts, have been known to man for thousands of years (Schultes and Hofmann 1980). However, scientific investigation of these drugs awaited the rise, in the nineteenth century, of organic chemistry and experimental pharmacology. Indeed, it was not until Heffter's (1896) isolation of mescaline in 1896 from the cactus, *Lophophora williamsii*, and the determination of its chemical structure (3,4,5-trimethoxyphenylethylamine) by Spath (1919) that a well-defined substance could be said to produce hallucinations. In view of the remarkable alterations in thought and perception produced by hallucinogens and because of the

essentially subjective nature of a major portion of the effects of these drugs, it is not surprising that self-experimentation played a prominent role in the initial investigation of drugs such as mescaline (Heffter 1897), 3,4-methylenedioxy-*alpha*-methylphenylethylamine (Alles 1959), lysergic acid diethylamide (LSD; Hofmann 1959), *N*,*N*-dimethyltryptamine (DMT; Szara 1956, 1957), and psilocybin (Hofmann 1968). No account of the self-administration of psychoactive drugs would be complete without reference to Ann Shulgin and Alexander Shulgin (1991, 1997), whose personal experiences with an extensive series of tryptamines and phenethylamines are compiled in two volumes. However, even in those instances when adequate experimental designs have been employed in clinical studies (e.g., Gouzoulis-Mayfrank et al. 2005, 2006; Griffiths et al. 2006; Hollister et al. 1968, 1969a, b; Isbell et al. 1961, 1967; Snyder et al. 1968; Vollenweider et al. 1996, 1998a; Wolbach et al. 1962a, b), ethical considerations have placed significant constraints on the type of experiments undertaken. Thus, in seeking what the late Leo Hollister called the Holy Grail of pharmacology, the mechanism of action of drugs, investigators have often turned to infrahuman species. In so doing, certain ethical and legal problems are avoided and a wider range of experimental manipulation becomes permissible but, then, there arise questions of interpretation and extrapolation.

It is generally assumed that the biological events that precede and accompany chemically induced hallucinations in man have some counterpart in lower species. Early infrahuman studies of hallucinogens employed what Peter Dews, the founder of behavioral pharmacology, referred to as "isolated bits of dying tissue." These usually took the form of a section of smooth muscle situated in a tissue bath so that contraction and relaxation might be quantified (e.g., Wooley and Shaw 1954; Winter and Gessner 1968). While studies such as these provided valuable insights into the possible mechanisms of the action of hallucinogens, including a role for serotonin (Gaddum 1953), it was natural to seek behavioral correlates of human hallucinogenesis in animals. In a typical series of experiments, a profile of hallucinogenic activity was drawn using, it sometimes seemed, whatever behavior was at hand. The dependent variables ranged from neuropharmacological indices (Corne and Pickering 1967; Martin and Eades 1970; Silva and Calil 1975) to nonconditioned behavior (Dixon 1968; Schneider and Chenoweth 1970; Silva and Calil 1975) to operant behavior (Smythies and Sykes 1964; Uyeno 1969; Uyeno and Mitoma 1969; Silva and Calil 1975). Consensus as to the predictive ability of these approaches was achieved seldom if ever. It was propitious therefore that Ira Hirschhorn, as a part of his Ph.D. thesis research, successfully trained both LSD and mescaline as discriminative stimuli in the rat (Hirschhorn and Winter 1971). The technique of hallucinogen-induced stimulus control was then transferred, first by Hirschhorn's colleague, Martin Schechter, and then by Hirschhorn himself, to the laboratory of John Rosecrans where it flourished (Glennon et al. 1979; Hirschhorn and Rosecrans 1974; Rosecrans and Glennon 1979; Schechter and Rosecrans 1972) On a purely intuitive basis, the study of the stimulus properties of hallucinogens is more attractive than, for example, analysis of LSD-impaired rope-climbing ability (Winter and Flataker 1956).

Scope of this review

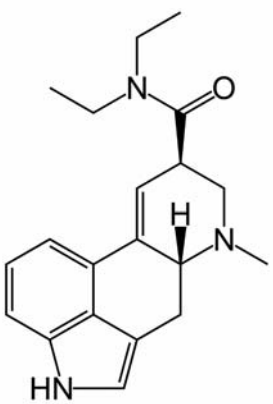
A dictionary definition of hallucination seems simple enough: a perception of objects with no reality (Webster 1993). That apparent simplicity belies the range of potentially hallucinogenic chemicals and the complexity of human responses to those agents. In deference to that range and to that complexity, this review is restricted to the stimulus effects of LSD, tryptamines, and phenethylamines. Only passing mention will be made of anticholinergics, cannabinoids, exotic agents such as salvinorin, and all those other drugs which properly lay claim to the title *hallucinogen*. It is true that some attention will be paid to the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists as represented by phencyclidine (PCP) but only with respect to their possible commonalities with the objects of this review. I have made no attempt to be encyclopedic in my coverage but would direct the interested reader to the comprehensive list of stimulus control studies provided by the Drug Discrimination Bibliographic Database (Stolerman and Kamien 2004), to earlier reviews of hallucinogen-induced stimulus control (Winter 1974; Appel et al. 1982; Glennon 1999; Winter et al. 1999), and to the more general recent reviews of hallucinogens by Nichols (2004) and by Fantegrossi et al. (2008a). I have relied upon the primary literature and have attempted to avoid references to book chapters as these are often difficult to acquire. In general, I have uncritically accepted the conclusions expressed in the papers cited but too often, in my opinion, those conclusions would have been strengthened by statistical analysis. Tests of significance may merely confirm the obvious but in many instances they will rid us of illusions born of random variation. Throughout this review, I will follow the convention, adopted from animal psychophysics, that the stimulus effects of a trained drug generalize to a specified degree to a tested drug, not *vice versa*. Finally, I will attempt no further definition of *hallucinogen* beyond saying that if a chemical mimics in human subjects the subjective effects of LSD or a tryptamine such as psilocybin or a phenethylamine such as mescaline, then it is a hallucinogen.

Chemical classes

LSD and the tryptamines are often lumped together as "indoleamine hallucinogens". It is true that one can trace within the elegant structure of LSD (Fig. 1) the indole nucleus common to the tryptamines. However, it is equally true that one can find phenethylamine. More important, based on evidence both biochemical and behavioral, LSD and the tryptamines are sufficiently different to justify separate categories. To this end, I here classify LSD as an ergoline (Nichols 2004) to distinguish it from the tryptamines. Figure 2 illustrates tryptamine, an endogenous neurochemical, as well as its hallucinogenic relatives, DMT, 5-methoxy-DMT (5-MeO-DMT), and psilocybin together with its presumed active derivative, psilocin (4-hydroxy-DMT). The hallucinogenic efficacy of bufotenine (5-hydroxy-DMT) has been a matter of contention for some time (Shulgin and Shulgin 1997, pages 473–478; Torres and Repke 2006). The phenethylamine hallucinogens (Fig. 3) are simple ring-substituted derivatives either of the endogenous neurochemicals, phenethylamine or amphetamine (*alpha*-methylphenethylamine). Mescaline is representative of the former neurochemical, 2,5-dimethoxy-4-methylamphetamine (DOM) of the latter neurochemical. However, whatever classification scheme is adopted, it is impossible to discuss these groups in isolation because of the overlap between them both experimentally and mechanistically. This is not to say that intriguing differences between the groups do not continue to emerge.

Neurochemical bases of stimulus control by hallucinogens

Serotonin Soon after the discovery of LSD by Hofmann in 1943 and the identification of serotonin as 5-hydroxytryptamine (Rapport 1949), it was recognized (a) that LSD might act via a serotonergic mechanism



lysergic acid diethylamide [LSD]

Fig. 1 Structure of the ergoline hallucinogen lysergic acid diethylamide

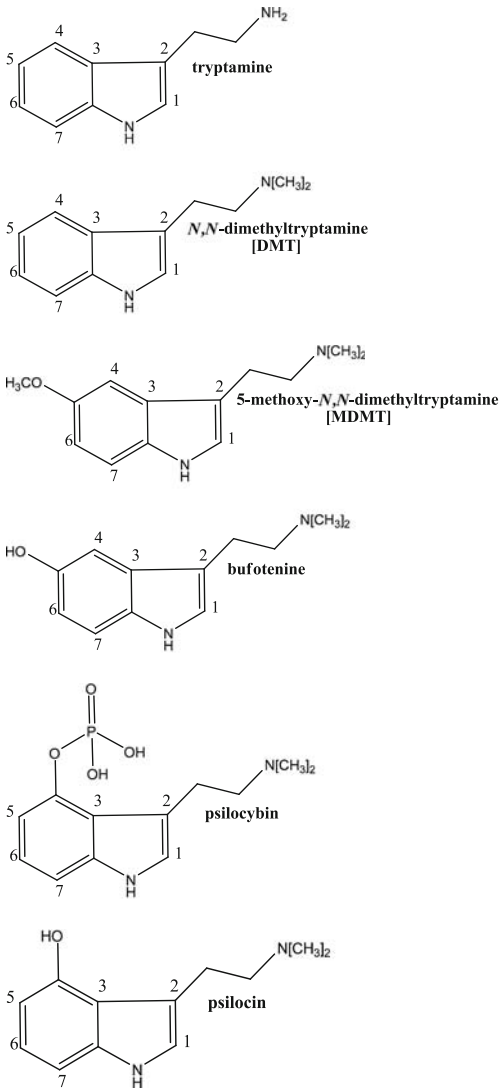


Fig. 2 Structures of tryptamine, bufotenine, and hallucinogenic tryptamines

(Gaddum 1953, 1957; Wooley and Shaw 1954) and (b) that the clinical syndromes produced by mescaline and DOM are quite similar to those following LSD and DMT (Hoch et al. 1952; Hollister et al. 1969a, b). That LSD, tryptamines, and phenethylamine hallucinogens might have a common mechanism was suggested by a number of observations. In human subjects (Balistrieri and Fontanari 1959; Wolbach et al. 1962b) as well as in animals (Appel and Friedman 1968; Winter 1971), cross-tolerance develops between LSD and mescaline. Furthermore, it was known that serotonergic antagonists block some of the nonbehavioral effects of phenethylamine hallucinogens in animals (Cheng et al. 1973; Horita et al. 1972). With respect to the stimulus effects of phenethylamine hallucinogens, antagonism of mescaline-induced stimulus control by the nonselective serotonergic antagonists was reported

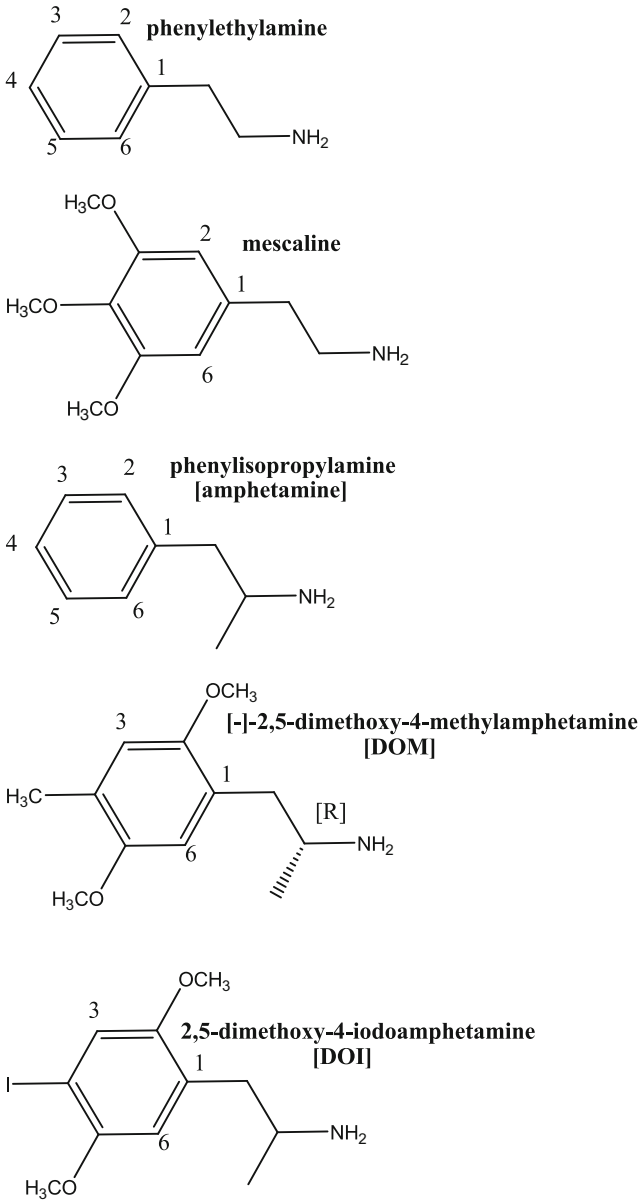


Fig. 3 Structures of phenethylamine and amphetamine together with ring-substituted hallucinogenic derivatives

independently by Browne and Ho (1975) and by Winter (1975). This observation was then extended to include other antagonists of serotonin and other hallucinogens including LSD (Kuhn et al. 1978), DOM (Winter 1978), and DMT (Young et al. 1982). It thus appeared appropriate to apply the term "serotonergic hallucinogen" to these structurally disparate drugs.

Two factors complicated this simple picture; the second of these was yet to appear but the first was evident at the time. The antagonists then available, drugs such as cinanserin, methysergide, cyproheptadine, mianserin, and pizotyline (BC-105), were nonselective with respect to other neurotransmitter systems and, indeed, some had behaviorally evident partial agonist effects in LSD-trained rats (Colpaert et al. 1982). Even the wonderfully efficacious LSD antagonist, pirenperone (Colpaert et al. 1982), was soon shown to have activity as a dopamine D_2 receptor antagonist (Meltzer et al. 1983).

The factor yet to be discovered was the complexity of the serotonergic family of drug receptors. The original classification by Gaddum and Picarelli (1957) of serotonin receptors as either M or D, those blocked by morphine and by dibenzyline, respectively, was based on studies in smooth muscle and is now largely forgotten. In contrast, the two subtypes designated 5-HT_1 and 5-HT_2 by Peroutka and Snyder (1979) remain with us today but in a refined and expanded state that now includes 14 serotonin receptors categorized into seven families (5-$HT_{1\text{-}7}$; Nichols and Nichols 2008). Glennon et al. (1983, 1984) implicated the 5-HT_2 receptor in hallucinogenesis based upon a high degree of correlation between affinities for the 5-HT_2 receptor and both potency in substituting for DOM-induced stimulus control as well as hallucinogenic potency in man. However, the subsequent discovery of the 5-HT_{2C} receptor (Pazos et al. 1984) with a high level of structural and functional similarities to the 5-HT_{2A} receptor as well as the demonstration that indoleamine and phenethylamine hallucinogens are partial agonists at the 5-HT_{2C} receptor (Sanders-Bush et al. 1988; Burris et al. 1991) demanded consideration of this serotonin receptor subtype. Fiorella et al. (1995a) employed antagonist correlation analysis to address the question of the relative roles of the 5-HT_{2A} and the 5-HT_{2C} receptors in stimulus control mediated by LSD and DOM. A series of ten serotonergic antagonists nonselective for the 5-HT_{2A} and the 5-HT_{2C} receptors but with differing selectivity ratios for those receptors was used to block LSD-induced stimulus control and the generalization of LSD to DOM. The conclusion from this study was that stimulus control by LSD and the generalization of LSD to DOM are mediated by 5-HT_{2A} receptors. More direct evidence was provided by the antagonism of DOM-induced stimulus control by a newly discovered antagonist, AMI-193, having 2,000-fold selectivity for the 5-HT_{2A} receptor as compared with the 5-HT_{2C} receptor (Ismaiel et al. 1993). However, like pirenperone before it, AMI-193 was found to have functionally significant activity as a dopamine D_2 antagonist (Czoty and Howell 2000). The current consensus is that differentiation of stimulus effects mediated by 5-HT_{2A} and 5-HT_{2C} receptors, respectively, is best accomplished with M100907 (MDL 100,907), a drug initially reported by Kehne et al. (1996) to have a potency ratio of 102 for binding affinity at 5-HT_{2A}/5-HT_{2C} receptors, a selectivity ratio of 1,283 for antagonism of 5-HT-stimulated inositol phosphate accumulation in NIH 3T3 fibroblast cells expressing 5-HT_{2A} or 5-HT_{2C} receptors, and a potency ratio

of 2,647 for binding affinity at 5-HT_{2A}/DA D_2 receptors. Subsequent studies employing a variety of receptor sources and competing ligands have yielded selectivity ratios ranging from 16 (Knight et al. 2004) to 186 (Schreiber et al. 1995; PDSP 2008). Despite the relatively low selectivity value found by Knight et al. (2004) using cloned human 5-HT_{2A} and 5-HT_{2C} receptors and radiolabeled 2,5-dimethoxy-4-iodoamphetamine (DOI), M100907 was the most selective of 22 antagonists tested. The efficacy of M100907 as an antagonist of hallucinogen-induced stimulus control in the rat was first demonstrated by Schreiber et al. (1994) for DOI and has now been extended to include, among others, LSD, 5-MeO-DMT, and DOM. An interesting complication was added by Dekeyne et al. (2002, 2003) who observed that M100907 can establish stimulus control in the rat and suggested that the effect is mediated by antagonism of 5-HT_{2A} receptors with possible involvement of *alpha*$_1$ adrenoceptors and other yet to be identified mechanisms.

Despite the considerable evidence pointing to the 5-HT_{2A} receptor as the primary site mediating the stimulus effects of LSD and the phenethylamine hallucinogens, other serotonergic receptor subtypes almost certainly play at least a modulatory role (Darmani et al. 1990). Prominent among these are the 5-HT_{1A} receptor as well as the aforementioned 5-HT_{2C} receptor. With respect to the latter receptor, Fiorella et al. (1995b) observed that potentiation of the stimulus effects of LSD caused by serotonin depletion (White et al. 1980) was accompanied by the upregulation of the 5-HT_{2C} receptor. In addition, potentiation of the stimulus effects in rats of DOM and LSD by NMDA antagonists appears to involve a significant 5-HT_{2C}-receptor-mediated component (Eckler et al. 2004; Winter et al. 2005b). Although not directly related to hallucinogenesis, it is of interest that Cunningham and her colleagues (Filip and Cunningham 2003; Filip et al. 2006; Bubar and Cunningham 2006) have presented data in support of a modulatory role for the 5-HT_{2C} receptor in the discriminative stimulus effects of cocaine.

Evidence implicating activity at the 5-HT_{1A} receptor as a mediator of stimulus control by the tryptaminergic hallucinogen, 5-MeO-DMT, will be discussed in somewhat greater detail below. With respect to the 5-HT_{1A} receptor as a modulating factor in stimulus control by hallucinogens, the data are both extensive and contradictory. In a study of membrane excitability of pyramidal neurons in rat cortex, it was found that the 5-HT_{1A} agonist, 8-OH-DPAT, and the 5-$HT_{2A/C}$ agonist, (−)-2,5-dimethoxy-4-bromo-amphetamine (DOB), have opposite effects thus suggesting the hypothesis that activation of 5-HT_{1A} and 5-HT_2 receptors have opposing effects (Araneda and Andrade 1991). Behavioral data in support of these results include antagonism by 5-HT_{1A} agonists of DOI-induced head twitch (Arnt and Hyttel 1989; Schreiber et al. 1995; Darmani et al. 1990) and wet dog shakes (Willins and Meltzer 1997) in the rat, effects widely accepted as indicative of agonist activity at 5-HT_{2A} receptors. In a study of stimulus control in the rat by the 5-HT_{1A} agonist, flesinoxan, it likewise was concluded that 5-HT_{1A} receptor activation has an inhibitory effect on activation of 5-HT_{2A} receptors (Herremans et al. 1999). Against this background, it is difficult to reconcile the observation that DOM-induced stimulus control is potentiated by 8-OH-DPAT (Glennon 1991). Furthermore, LSD-induced stimulus control was found by Reissig et al. (2005) to be potentiated by 8-OH-DPAT as well as by the 5-HT_{1A} receptor agonists, buspirone, gepirone, and ipsapirone. The potentiating effects of these agents were completely antagonized by the 5-$HT_{1A/7}$ receptor-selective antagonist, WAY-100,635. It is clear that further studies will be needed to resolve apparent inconsistencies.

Dopamine Despite the abundant evidence of a primary role for serotonergic mechanisms in the actions of indoleamine and phenethylamine hallucinogens and the emerging evidence for glutamatergic factors, note must also be taken of dopamine and possible serotonergic–dopaminergic–glutamatergic interactions. On the basis of drug discrimination data in the rat, Marona-Lewicka and Nichols (2007) have proposed that stimulus control by LSD occurs in two phases, the first mediated by serotonin and a second later phase mediated by dopamine, and that this dopaminergic component is not shared by phenethylamine or tryptamine hallucinogens (Marona-Lewicka et al. 2005). The same group (Marona-Lewicka et al. 2008) subsequently suggested a primary role for the dopamine D_4 receptor. It should be noted however that, in a study in human subjects, the dopamine D_2 antagonist, haloperidol, significantly altered some of the subjective effects of psilocybin (Vollenweider et al. 1998a). Furthermore, psilocybin reduced [^{11}C]raclopride binding potential as measured by positron emission tomography (Vollenweider et al. 1999). In the latter study, the authors concluded that this effect must be indirect in nature, citing a 1975 report that psilocin has only negligible affinity for dopamine receptors (Creese et al. 1975). However, in light of the provocative data presented by the Nichols group, our present knowledge of multiple dopamine receptor subtypes, the continued discovery of more selective dopaminergic ligands, and renewed interest in hallucinogens as tools for the understanding of psychosis, this issue clearly is worthy of further investigation.

Glutamate In considering hallucinogens as psychotomimetics, clear distinctions have been drawn between noncompetitive antagonists at the NMDA subtype of

glutamate receptor and serotonergic hallucinogens. The respective subjective effects of glutamatergics and serotonergics in human subjects are quite different (Luby et al. 1959; Hofmann 1959; Carroll 1990) and their presumed mechanisms are distinct (Koek 1999; Winter et al. 2000a). Recently, however, there has been an increasing recognition that these systems do not operate in isolation but, instead, that there are complex and ever changing interactions between them. Illustrative of such interactions is the observation of potentiation of the stimulus effects in rats of DOM and LSD by ketamine, dizocilpine, and PCP (Winter et al. 2000a, 2004). An explanation for such interactions is provided by the hypothesis that glutamate release represents a final common pathway for the actions both of serotonergic and of glutamatergic hallucinogens (Aghajanian and Marek 1999, 2000). Though the mechanisms of these interactions are largely unknown, there is evidence that the NMDA antagonists do not act directly upon 5-HT_{2A} receptors (Rabin et al. 2000) and that the 5-HT_{2C} receptor may play a significant role (Eckler et al. 2004; Winter et al. 2005b). Direct testing of the hypothesis that glutamate release is correlated with behavioral effects of both serotonergics and glutamatergics has been greatly aided by the discovery of a family of ligands for group II (mGlu2/3) metabotropic glutamate receptors. These agents, exemplified by the antagonist LY341495 and the agonist LY379268, are able to increase and to decrease, respectively, glutamate release in vivo. It was observed in rats trained with LSD as a discriminative stimulus that LY379268 produced significant, albeit intermediate, antagonism of LSD-induced stimulus control and that LY341495 resulted in potentiation of the stimulus effects of LSD (Winter et al. 2004). These results provide significant behavioral support for the hypothesis of Aghajanian and Marek (1999) that hallucinogenesis is glutamatergically mediated. It remains to be seen whether the interactions observed between LSD and the metabotropic glutamatergic ligands generalize to the tryptamine and phenethylamine hallucinogens. Were these matters not already sufficiently complex, Benneyworth et al. (2008) have reported that chronic treatment in a drug discrimination study with the phenethylamine hallucinogen, DOB, attenuates the behavioral effects of the mGlu2/3 receptor agonist, LY379268. This finding has implications for all investigations of the stimulus effects of drugs and, perhaps, may explain differences noted when results from discrimination studies are compared with dependent variables requiring only acute treatment. With respect to possible links between glutamate, hallucinogens, and psychosis, it is most interesting that an agonist at mGlu2/3 receptors has been found to be efficacious in the treatment of schizophrenia (Patil et al. 2007).

Tryptamine hallucinogens

5-methoxy-N,N-dimethyltrypamine Against the background provided above implicating the 5-HT_{2A} receptor as the primary site of action of LSD and the phenethylamine hallucinogens and the 5-HT_{2C} receptor as a significant modulatory site, the tryptamine hallucinogens are puzzling. In terms of stimulus generalization, there is no absence in the literature of reports that the tryptamine hallucinogens mimic LSD and the phenethylamines and vice versa. Nonetheless, there have been repeated intimations that the pattern of antagonism of the tryptamines may differ from that of LSD (Young et al. 1982, 1983, 1986). Later suggestions focus on the 5-HT_{1A} receptor (Marona-Lewicka and Nichols 1995). In a particularly interesting study, Blair et al. (2000) reported that ring fluorination of hallucinogenic tryptamines reduced the degree of mimicry of the stimulus effects of LSD by these drugs while at the same time diminishing their affinity for the 5-HT_{1A} receptor. The tryptamines, ranging from classic agents such as DMT (Sai-Halasz et al. 1958) to a series of ring- and amine-substituted agents such as DPT (Fantegrossi et al. 2008b; Li et al. 2008), 2,5-dimethoxy-4-*n*-propylthiophenethylamine (Fantegrossi et al. 2005), and 5-methoxy-*N*,*N*-diisopropyltryptamine (Fantegrossi et al. 2006), are unquestionably hallucinogenic (Shulgin and Shulgin 1997) yet binding data regularly indicate that their highest affinity is for 5-HT_{1A} receptors. Indeed, a study by Spencer et al. (1987) concluded that stimulus control by 5-MeO-DMT in the rat is mediated by 5-HT_{1A} receptors. This conclusion was fully supported by a subsequent investigation (Winter et al. 2000b) that employed WAY-100,635, an agent not yet discovered at the time of the work by Spencer et al. The latter study suggested as well that 5-MeO-DMT differs from LSD and DOM with respect to the serotonergic element which mediates stimulus control in the rat but that it shares with those drugs a functionally significant interaction with 5-HT_2 receptors. In support of this hypothesis, 5-MeO-DMT as well as the closely related analog, DMT, displays partial agonist activity at the 5-HT_{2A} receptor expressed in PC12-5-HT_{2A} cells (Rabin et al. 2002). Left unanswered at this time is the question of whether activity at the 5-HT_{1A} receptor plays a functionally significant role in hallucinogenesis by the tryptamines.

Psilocybin In reports of drug-induced stimulus control, psilocybin has been found to substitute fully for racemic DOM (Silverman and Ho 1980) and mescaline (Appel and Callahan 1989) thus suggesting a 5-HT_2-mediated effect because phenethylamines such as DOM (Pauwels et al. 1993) and, presumably, mescaline have negligible affinity for 5-HT_{1A} receptors. Furthermore, Vollenweider et al.

(1996) observed that the subjective effects in normal subjects of psilocybin are blocked by ketanserin (Vollenweider et al. 1996, 1998a), an antagonist with low nanomolar affinity for 5-HT_{2A} receptors (Richelson and Souder 2000) and only micromolar affinity for 5-HT_{1A} receptors (Boess and Martin 1994). Receptor binding data provided no clue in that Blair et al. (2000) observed K_I values for psilocin of 49, 25, and 10 nM for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, respectively. Nonetheless, given the close structural similarity of 5-MeO-DMT and both psilocybin and psilocin (Fig. 2), it was expected that psilocybin-induced stimulus control in the rat would have a salient element mediated by agonist activity at the 5-HT_{1A} receptor. That expectation was not realized (Winter et al. 2007). Instead, it was found that, while the full generalization of psilocybin to LSD and DOM is completely blocked by M100907, psilocybin itself is only partially antagonized. Most remarkable, psilocybin-induced stimulus control was diminished not at all by WAY-100,635. It appears that there remains much to be learned regarding the tryptamine family of hallucinogens and, in particular, the functional effects of ligands at 5-HT_{1A} receptors. Our fascination with these drugs is further heightened by the continued interest in the human pharmacology of DMT (Strassman 1991) and a possible role for bufotenine as an endogenous psychotogen (RJ Strassman, personal communication). That the 5-HT_{1A} receptor might provide a link between the serotonergic and glutamatergic systems is suggested by the emergence of aripiprazole, an atypical antipsychotic with agonist activity at 5-HT_{1A} receptors (Bortolozzi et al. 2007); PCP-induced deficits in social interaction and recognition memory in rats are ameliorated by aripiprazole and these effects of aripiprazole are antagonized by WAY-100,635 (Bruins Slot et al. 2005; Snigdha and Neill 2008; Nagai et al. 2008).

Species differences The majority of studies of stimulus control by hallucinogens have been done in the rat, most often employing a two-lever choice procedure. This uniformity has the virtue of making much of the literature directly comparable. On the other hand, possible species differences are obscured. Unfortunately, there is little to be said about possible differences between the rat and primates, whether monkey or man, for the simple reason that few studies have been conducted in the latter species. Indeed, I am aware of only two investigations which employed infrahuman primates. Nielson (1985) trained four monkeys (*Cercopithecus aethiops*) with LSD and Li et al. (2008) established DOM as a discriminative stimulus in four rhesus monkeys. Given this paucity, one cannot draw broad conclusions but it is of interest that while the data of Li et al. for DOM are consistent with findings in the rat, e.g., complete antagonism by M100907, Nielsen observed a maximum of 55% antagonism of LSD by pirenperone and no blockade by pizotyline, results clearly at odds with the rat literature. In the only study in which rats and monkeys were compared directly, Jones et al. (1998) observed approximately 50% generalization of PCP to LSD in rats but no consistent evidence of generalization in the four monkeys tested. Turning to human subjects, the stimulus effects of a number of psychoactive drugs have been well characterized (for reviews, see Chait et al. 1984; Kamien et al. 1993; Brauer et al. 1997; Dykstra et al. 1997) but, to my knowledge, there have been no reports of the training or cross testing of LSD or any of the tryptamine–phenethylamine hallucinogens. It should be noted that methylenedioxymethamphetamine (MDMA, Ecstasy), a drug sometimes said to be hallucinogenic, has been examined in human subjects trained to simultaneously discriminate *d*-amphetamine, *meta*-chlorophenylpiperazine, and placebo (Johanson et al. 2006). MDMA shared some effects with both reference drugs and all three increased scores on the hallucinogen rating scale (Strassman et al. 1994) but none of the participants reported hallucinations nor were hallucinations observed by Vollenweider et al. (1998b) despite some references to this paper to the contrary. While the consensus is that MDMA is not hallucinogenic, drug discrimination studies in animals indicate a number of interesting generalizations, almost always partial in nature, to hallucinogens and *vice versa*. The complexities of the animal data are well represented by the elegant work of Baker and her colleagues (Baker and Taylor 1997; Baker et al. 1995; Goodwin and Baker 2000; Goodwin et al. 2003) using both two- and three-choice tasks.

Beginning with the training of mice with amphetamine by Snoddy and Tessel (1983), this species has been used infrequently relative to the rat. Nevertheless, a number or other drugs have been examined including hallucinogens of the noncompetitive NMDA antagonist type, PCP (Middaugh et al. 1988; English et al. 1999) and dizocilpine (MK-801; Geter-Douglas and Witkin 1999). In the first report of stimulus control by a hallucinogen of the indole–phenethylamine type, Smith et al. (2003) employed racemic DOI (Shulgin and Shulgin 1991). This was followed soon after by reports of the training of LSD (Benneyworth et al. 2005; Winter et al. 2005a). Broadly speaking, the results were compatible with earlier studies in the rat. DOI generalized fully to LSD and to DOB and DOI-induced stimulus control was fully antagonized by M100907 (Smith et al. 2003). In LSD-trained mice, full generalization was observed to DOB (Benneyworth et al. 2005) and to DOM (Winter et al. 2005a). An unexpected finding in both studies of LSD was the absence of complete blockade of the stimulus effects of LSD by the selective 5-HT_{2A} selective antagonist, M100907, results clearly at odds with those in the rat. On the basis of partial antagonism by selective 5-HT_{2C} receptor antagonists,

Benneyworth et al. (2005) suggested a significant role for this receptor while Winter et al. (2005a) invoked the 5-HT_{1A} receptor in attempting to explain rate suppression following M100907 and the combination of the antagonist with LSD, effects not observed in the rat.

With the advent of techniques to genetically modify mice, this species provides the advantage that a particular gene can be deleted to produce knockout (KO) mice (Gingrich and Hen 2001; Bucan and Abel 2002; Seong et al. 2002). Although KO mice have been employed in investigations of the stimulus effects of nicotine (Stolerman et al. 2004), cocaine (Chausmer et al. 2002; Katz et al. 2003; Elliot et al. 2003), and ethanol (Shannon et al. 2004); until recently, there have been no studies of hallucinogens reported. In 2007, Krall et al. described an investigation in which the stimulus effects of LSD were examined in mice lacking the serotonin transporter (SERT; Bengel et al. 1998). Previous work had shown that the changes in SERT KO mice due to gene deletion are restricted almost exclusively to the serotonergic system including reduction in 5-HT_{1A} and 5-HT_{2A} receptors. Krall et al. (2007) observed that C57BL/6 mice homozygous for the null mutation ($SERT^{-/-}$) were impaired in their ability to establish stimulus control with LSD as compared with littermate controls ($SERT^{+/+}$). Obvious experiments yet to be reported include the assessment of the stimulus effects of hallucinogens in mice in which 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptors, respectively, have been knocked out.

Compound stimuli Selective agonists and antagonists are among the most powerful tools for analyzing the stimulus effects of hallucinogens. Progress in establishing mechanisms of action of psychoactive drugs has been and continues to be dependent upon the discovery of ever more selective ligands. We are fortunate at this time to have available the 5-HT_{2A} receptor antagonist, M100907 (Kehne et al. 1996), and the 5-$HT_{1A/7}$ receptor antagonist, WAY-100,635 (Gozlan et al. 1995). Many of the apparent contradictions found in the drug discrimination literature may be reconciled if we assume that a drug may function as a compound stimulus with each element mediated by a distinct pharmacological receptor. For example, according to the Berry-Ator hypothesis of specificity in drug discrimination, asymmetrical generalizations are explained in terms of differential salience of individual elements of the compound stimulus depending upon experimental factors including the training drug, the dose of that drug, etc. (Ator and Griffiths 1989). Given the fact that LSD binds with high affinity to a variety of receptors (Leysen 1985), it is a prime candidate to function as a compound stimulus. Figure 4 illustrates the use of M100907 and WAY-100,635 to rationalize the effects of 8-OH-DPAT in rats trained with LSD as a discriminative stimulus. It is seen

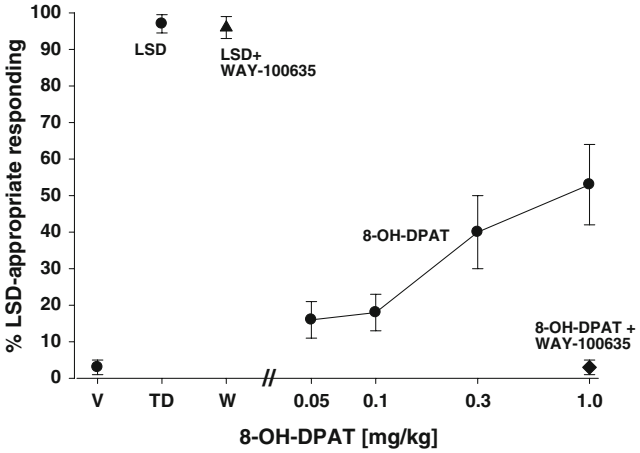


Fig. 4 Effects of a range of doses of 8-OH-DPAT alone and in combination with WAY-100,635 (0.3 mg/kg, SC) in rats trained with LSD (0.1 mg/kg) as a discriminative stimulus. Each point represents the mean of 9–12 animals. The *points* at *V* and *TD* on the abscissa are for the saline and LSD training conditions, respectively. The *point* at *W* on the abscissa is for the combination of the training dose of LSD and WAY-100,635 (redrawn from Reissig et al. 2005)

that the generalization of LSD to 8-OH-DPAT is intermediate in nature and that this intermediate generalization is completely antagonized by WAY-100,635. In contrast, stimulus control by LSD is influenced not at all by WAY-100,635. The conclusion to be drawn is that LSD does indeed induce a compound stimulus which includes elements mediated by both 5-HT_{2A} and 5-HT_{1A} receptors. The former element is witnessed by the complete antagonism of LSD-induced stimulus control by M100907 (Winter et al. 2004). The latter element is evident only when generalization of LSD to a 5-HT_{1A} receptor agonist is tested. A final note: we must remain aware of the sometimes-ephemeral nature of the title *selective* when applied to a drug. For example, with respect to WAY-100,635, agonist activity at the dopamine D_4 receptor has been reported (Chemel et al. 2006; Marona-Lewicka et al. 2008). Nonetheless, Martel et al. (2007) express confidence in the selectivity of WAY-100,635 for the 5-HT_{1A} receptor as compared with the dopamine D_4 receptor. As noted above, various estimates have been provided for the selectivity ratio of M100907 for the 5-HT_{2A} and 5-HT_{2C} receptors, respectively. We can only hope that synthetic chemists will eventually provide uniquely selective agonists and antagonists at every receptor of interest to those who study stimulus control by hallucinogens.

Epilog During the 30-year life of the Society for Stimulus Properties of Drugs, study of stimulus control by hallucinogens in animals has come a long way from the time when an anonymous reviewer described results (Winter 1978)

submitted to the *Journal of Pharmacology and Experimental Therapeutics* as having "a scent of the occult." Today, preclinical analysis of the stimulus effects of potentially psychoactive drugs has gained near universal acceptance. More important, in my opinion, are stimulus control studies that seek the still elusive mechanisms of action of hallucinogens. There remain of course those who question the relevance to the human condition of studies of hallucinogens in animals. Might hallucination be a uniquely human experience and, even if not, how are we to demonstrate, in the absence of verbal communication, the validity of an animal model of complex human behavior? My answer to those critics is that if we can agree that all translations of data from nonhuman species to predictions for man involve, to use Weinberg's term (1972), a transscientific residue, then our task in studying the stimulus effects in animals of hallucinogens and other drugs whose actions in man include a prominent subjective component is to make predictions for man which are amenable to clinical verification. In the wise words of Lawrence Berra, "it's tough to make predictions, especially about the future." Nonetheless, if the rebirth of human studies of hallucinogens is at hand (Doblin 2002; Morris 2008), we may envisage a time when close relationships exist between those who study hallucinogens in man and in animals, a time when hypotheses based on animal data are quickly confirmed, or rejected, in the clinical laboratory.

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