CHAPTER 4.7

Serotonin and Serotonin Receptors in Hallucinogen Action

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Abstract: Hallucinogens are a class of substances that induce profound changes in perception and cognition. A closely related drug, 3,4-methylenedioxymethamphetamine (MDMA), produces euphoria and a feeling of empathy, with minimal sensory distortion. Both of these classes of substances produce their effects by interacting with the serotonergic system. This chapter will review the receptor interactions that contribute to the behavioral effects of serotonergic hallucinogens and MDMA. In rodents, the behavioral effects of hallucinogens such as lysergic acid diethylamide (LSD), psilocybin and mescaline are primarily mediated by activation of 5-HT_{2A} receptors. There is evidence, however, that 5-HT_{1A} receptors, 5-HT_{2C} receptors and dopamine receptors may play a secondary role. The molecular requirements for interaction of hallucinogens with the 5-HT_{2A} receptor are well-defined on the basis of structure–activity relationships. By contrast with the hallucinogens, MDMA is a potent releaser of monoamines that has complex effects on serotonergic, dopaminergic and noradrenergic systems. In recent years, psilocybin and MDMA have been administered to human volunteers in controlled clinical trials. Human studies confirm that the 5-HT_{2A} receptor plays a primary role in mediating the subjective effects of psilocybin, whereas the effects of MDMA are largely attributable to carrier-mediated release of serotonin. These findings emphasize the importance of clinical investigation of hallucinogenic drugs. Additionally, there is a growing consensus that these drugs are likely to show therapeutic efficacy in the treatment of certain psychiatric disorders.

Keywords: 5-HT_{2A} receptor, behavior, drug discrimination, entactogen, hallucinogen, head twitch, locomotor activity, MDMA, psychedelic, prepulse inhibition.

Abbreviations: 5-HT, serotonin; 5-MeO-DMT, 5-methoxy-*N,N*-dimethyltryptamine; AED, Anxious Ego Dissolution; AMPH, amphetamine; APZ, Altered States of Consciousness rating scale; BPM, Behavioral Pattern Monitor; DMT, *N,N*-dimethyltryptamine; DPT, *N,N*-dipropyltryptamine; DOB, 2,5-dimethoxy-4-bromoamphetamine; DOET, 2,5-dimethoxy-4-ethylamphetamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine; DRN, dorsal raphe nucleus; EL2, extracellular loop 2; HTR, head-twitch response; LSD, lysergic acid diethylamide; MBDB, 1-(1,3-benzodioxol-5-yl)-N-methylbutan-2-amine; MDE, N-ethyl-3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; OB, Oceanic Boundlessness; PPI, prepulse inhibition; RV, Reduction of Vigilance; SERT, 5-HT transporter; VR, Visionary Restructuralization.

Introduction

Hallucinogenic drugs have been used by humans for thousands of years to diagnose and cure disease, induce mystical and spiritual states, and produce euphoria and inebriation (Schultes and Hofmann, 1980). Typically, these drugs have been derived from botanical sources. Some examples include the mescaline-containing peyote cactus (*Lophophora williamsii*), which is legally used in the United States by members of the Native American Church; *teonanácatl* mushrooms (a species of *Psilocybe* containing psilocybin and psilocin), which have a history of ceremonial use in Mexico; and *ayahuasca,* an infusion or decoction prepared from the bark of β-carboline-containing species of *Banisteriopsis* to which admixture plants containing *N,N*-dimethyltryptamine (DMT) are typically added. Modern scientific investigation of the hallucinogens began with the identification of mescaline as the active principal of peyote by Arthur Heffter in 1897.

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Christian Müller & Barry Jacobs (Eds.)
Handbook of Behavioral Neurobiology of Serotonin
ISBN 978-0-12-374634-4

DOI: 10.1016/B978-0-12-374634-4.00035-6

The discovery of the potent hallucinogenic effects of lysergic acid diethylamide (LSD) by Albert Hoffmann in 1943 markedly increased scientific interest in these substances.

The publication of the first description of the hallucinogenic effects of LSD (Stoll, 1947) coincided with the initial isolation and characterization of serotonin (5-HT) (Rapport *et al.*, 1948). In 1953, Gaddum reported that LSD antagonized the contractile effect of 5-HT on the isolated uterine smooth muscle (Gaddum, 1953). It was soon recognized, however, that LSD acts as a 5-HT agonist in some assay systems (Shaw and Woolley, 1956). It is now widely accepted that LSD and other hallucinogens are agonists or partial agonists at 5-HT receptors (Glennon, 1990).

The psychological effects produced by hallucinogens are highly subjective, usually including changes in thought and mood, depersonalization, and perceptual alterations that may include visual hallucinations, synesthesias and tactile sensations. The effects of serotonergic hallucinogens are distinguishable from those of other drug classes such as dissociative anesthetics (e.g., phencyclidine, ketamine), κ-agonists (e.g., salvinorin A), and cannabinoids, which produce some hallucinogen-like effects.

Soon after the discovery of LSD it was recognized that there are similarities between the effects of hallucinogens and the symptomatology of schizophrenia, and LSD and mescaline were used experimentally to produce a model psychosis. There is now renewed interest in the possibility that hallucinogens may be useful therapeutic drugs, and the efficacy of psilocybin in the treatment of obsessive-compulsive disorder and as an anxiolytic in terminal cancer patients has been investigated in clinical trials (Biello, 2006; Moreno *et al.*, 2006). It also has been claimed that 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') has value as an adjunct to psychotherapy. MDMA produces mood elevation and an increased sense of empathy with little sensory disruption. The effects of MDMA are distinct from those typically produced by hallucinogens, however, and it has been proposed that MDMA is an entactogen, a distinct class of drugs (Nichols, 1986).

The mechanism of action of hallucinogens and entactogens such as MDMA has been the subject of intense investigation. This chapter will review the receptor interactions that contribute to the behavioral effects of hallucinogens and MDMA.

Receptors mediating the behavioral effects of hallucinogens in animals

5-HT$_{2A}$ receptor

The 5-HT$_{2A}$ receptor is a $G_{q/11}$-coupled receptor that is linked to the phosphoinositide hydrolysis signaling cascade (Nichols and Nichols, 2008). Members of both the indoleamine and phenylalkylamine classes of hallucinogens bind to 5-HT$_{2A}$ receptors with high affinity. Phenylalkylamine hallucinogens such as 2,5-dimethoxy-4-methylamphetamine (DOM), 2,5-dimethoxy-4-iodoamphetamine (DOI), and 2,5-dimethoxy-4-bromoamphetamine (DOB) are highly selective for 5-HT$_2$ receptor subtypes (Titeler *et al.*, 1988; Pierce and Peroutka, 1989), and there is a general consensus in the literature that the behavioral effects of hallucinogens are primarily mediated by the 5-HT$_{2A}$ receptor (Nichols, 2004).

Drug discrimination

Much of what is known about the mechanism of action of hallucinogenic drugs has been derived from drug discrimination studies. Rats can be trained to discriminate hallucinogens (including LSD, mescaline, DOM, DOI, DOB, DPT, psilocybin and 5-methoxy-DMT (5-MeO-DMT) from saline using two-lever operant procedures (Hirschhorn and Winter, 1971; Glennon *et al.*, 1982). Cross-generalization occurs between these training drugs, indicating that they produce similar interoceptive stimulus effects. By contrast, members of other drug classes reliably fail to evoke hallucinogen-like stimulus effects (Glennon *et al.*, 1982; Appel and Cunningham, 1986).

Glennon and colleagues first proposed in 1983 that the behavioral effects of hallucinogens are mediated by activation of 5-HT$_2$ receptors (Glennon *et al.*, 1983). This proposal was based on the finding that the high-affinity, selective 5-HT$_2$ antagonists pirenperone and ketanserin are highly effective antagonists of the discriminative stimulus properties of DOM and LSD (Colpaert *et al.*, 1982; Colpaert and Janssen, 1983), and of DOM-stimulus generalization to LSD, mescaline, and 5-MeO-DMT (Glennon *et al.*, 1983). It was subsequently demonstrated that a robust linear correlation ($r = 0.938$) exists between the 5-HT$_2$ affinities of a series of phenylalkylamine hallucinogens and their ED_{50} values for substitution in animals trained with DOM (Glennon *et al.*, 1984). An antagonist correlation analysis confirmed that there is a strong correlation between the 5-HT$_{2A}$ affinity of a series of 5-HT antagonists and their potencies for blocking LSD stimulus generalization to *R*-(−)-DOM (Fiorella *et al.*, 1995). Additionally, stimulus control in animals trained with LSD (Winter *et al.*, 2004), DOI (Smith *et al.*, 1999; Schreiber *et al.*, 1994) and DOM (Li *et al.*, 2007) is blocked by M100907, a highly selective 5-HT$_{2A}$ antagonist. Taken together, these findings demonstrate that interactions with the 5-HT$_{2A}$ receptor are required for hallucinogens to induce discriminative stimulus effects.

Head-twitch response

Hallucinogens evoke a variety of stereotypical motor responses in laboratory animals, including ear scratch in mice, head twitch in mice and rats, reciprocal hindleg body scratch in gerbils, limb flicks and abortive grooming in cats, and limb jerks in primates. The head-twitch response (HTR), which in mice consists of a paroxysmal rotational movement of the head (Corne and Pickering, 1967), is one of the best characterized of the hallucinogen-induced stereotypies. Administration of hallucinogens to rats induces an analogous behavior ('wet-dog shakes') that typically involves not only the head but also the neck and trunk. There is extensive evidence that the 5-HT_{2A} receptor mediates the hallucinogen-induced HTR. The first evidence for a linkage between 5-HT_2 receptors and the HTR induced by hallucinogens was the finding that the potencies of 19 5-HT antagonists to block the mescaline HTR is significantly correlated ($r = 0.88$) with their 5-HT_2 affinity (Leysen *et al.*, 1982). Similar findings were later reported for the HTR induced by DOI (Schreiber *et al.*, 1995). It was also demonstrated that ketanserin blocks the HTR to DOI (Darmani *et al.*, 1990). Although ketanserin is an antagonist at 5-HT_{2A} and 5-HT_{2C} receptors, the fact that the HTR to DOI is completely blocked by M100907, but not by the highly selective 5-HT_{2C} antagonist SB 242,084 confirmed that the behavior is mediated by the 5-HT_{2A} receptor and not by the 5-HT_{2C} receptor (Vickers *et al.*, 2001). Further evidence for a link between 5-HT_{2A} receptors and head twitch was provided by the recent finding that the ability of LSD, DOI, DOM, DOB, mescaline and psilocin to induce the HTR is abolished in 5-$HT_{2A}^{-/-}$ knockout mice (González-Maeso *et al.*, 2007).

Exploratory and investigatory behavior

Measures of unconditioned locomotor activity are frequently used to assess compounds for stimulant or depressant effects. Tests of hallucinogens using conventional open-field measures, however, produce inconsistent results and fail to distinguish the effects of hallucinogens from those of non-hallucinogenic agents (Brimblecombe, 1963; Cohen and Wakeley, 1968; Kabes *et al.*, 1972; Silva and Calil, 1975). Given the complexity of the effects of hallucinogens, it is not surprising that the locomotor paradigm produces inconclusive findings because it does not provide a qualitative assessment of behavior and does not measure whether there are changes in sensitivity to environmental stimuli. The Behavioral Pattern Monitor (BPM), a combination of activity and holeboard chambers, was designed to overcome the shortcomings of open-field measurements (Geyer, 1990). The BPM provides both quantitative and qualitative measures of unconditioned locomotor and investigatory activity in rats, and can be used to assess animals for changes in responsivity to environmental stimuli.

Hallucinogens produce a characteristic profile of behavioral effects in the BPM. When phenylalkylamine (mescaline, DOM, DOI and DOET) and indolealkylamine (psilocin, DMT and 5-MeO-DMT) hallucinogens are tested in a novel environment, they decrease locomotor activity and investigatory behaviors (rearings and hole-pokes) and increase avoidance of the center of the chamber (Geyer *et al.*, 1979; Adams and Geyer, 1985a; Wing *et al.*, 1990). These effects are not observed when animals are tested in a familiar environment, and have been attributed to exacerbation of the neophobia and agoraphobia normally exhibited by rats. LSD has similar effects on investigatory behavior and center entries (Adams and Geyer, 1985b), but it produces a biphasic locomotor pattern with activity initially suppressed and then increasing as time progresses (Mittman and Geyer, 1991).

Most of the effects of DOI in the BPM paradigm are blocked by M100907 but not by the 5-$HT_{2C/2B}$ antagonist SER-082, and are therefore likely mediated by activation of 5-HT_{2A} receptors (Krebs-Thomson *et al.*, 1998). Mechanistically, the effect of the indoleamines in the BPM is more complex. For example, both the mixed 5-HT_1/β-adrenergic antagonist propranolol (Mittman and Geyer, 1991) and the selective 5-HT_{1A} antagonist WAY-100635 (Krebs-Thomson and Geyer, 1996) block the initial suppression of locomotor activity induced by LSD, whereas LSD-induced hyperactivity is blocked by M100907 (Ouagazzal *et al.*, 2001) and the 5-HT_2 antagonist ritanserin (Mittman and Geyer, 1991). The effects of 5-MeO-DMT are antagonized by WAY-100635 but not by M100907 (Krebs-Thomson *et al.*, 2006), indicating that they are mediated by 5-HT_{1A} receptors. However, when 5-MeO-DMT is administered in combination with a MAO-A inhibitor such as harmaline or clorgyline, it produces LSD-like late hyperactivity that is completely blocked by the 5-HT_{2A}-selective antagonist MDL 11,939 (Halberstadt *et al.*, 2008). In summary, the effects of LSD and 5-MeO-DMT in the BPM are mediated by both 5-HT_{1A} and 5-HT_{2A} receptors.

Prepulse inhibition of startle

Acoustic startle responses are attenuated when preceded by a weak prestimulus, a phenomenon known as prepulse inhibition (PPI). PPI serves as an operational measure of sensorimotor gating and has been found to be deficient in patients with a variety of psychiatric illnesses, including schizophrenia. Hallucinogens, including LSD, DOI, DOB and 5-MeO-DMT, disrupt PPI in rats (Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1994; Johansson

et al., 1995; Ouagazzal *et al.*, 2001). The decrease in PPI induced by DOI and LSD is blocked by M100907 but not by SB 242,084 or SER-082 (Sipes and Geyer, 1995; Ouagazzal *et al.*, 2001), demonstrating the involvement of 5-HT_{2A} receptors. Compared with DOI and LSD, the mechanism for the effect of 5-MeO-DMT on PPI is more complex and involves interactions with both 5-HT_{1A} and 5-HT_{2C} receptors (Krebs-Thomson *et al.*, 2006).

5-HT_{2C} receptor

Phenylalkylamine and indoleamine hallucinogens bind to 5-HT_{2C} receptors with high affinity, and are relatively non-selective for 5-HT_{2A} versus 5-HT_{2C} receptors (Nelson *et al.*, 1999; Porter *et al.*, 1999). The discovery that hallucinogens interact with 5-HT_{2C} receptors confounded the hypothesis that activation of 5-HT_{2A} receptors is the primary mechanism by which LSD-like drugs act (Glennon *et al.*, 1984). This hypothesis was proposed prior to the discovery of 5-HT_{2C} sites, and was partially based on evidence demonstrating that ketanserin and other classical 5-HT_{2A} antagonists block the behavioral effects of hallucinogens in various animal paradigms. Unfortunately, those serotonin antagonists are now known to act at both 5-HT_{2A} and 5-HT_{2C} sites. The potent action of hallucinogens at 5-HT_{2A} and 5-HT_{2C} receptors has led authors to speculate that hallucinogenesis may be mediated by interactions with both of these receptor populations (Titeler *et al.*, 1988; Glennon, 1990). In fact, Sanders-Bush and others have gone so far as to suggest that 5-HT_{2C} receptor occupation plays a primary mechanistic role in the action of hallucinogenic drugs (Burris *et al.*, 1991).

There is a significant correlation between the affinities of phenylalkylamine hallucinogens for 5-HT_{2C} receptors and their potencies to evoke psychoactive effects in humans and to substitute in DOM-trained animals (Titeler *et al.*, 1988). Nevertheless, 5-HT_{2A} and 5-HT_{2C} receptors display parallel structure–affinity relationships for ligand binding (Nelson *et al.*, 1999), so it is possible that the observed correlation between 5-HT_{2C} receptor affinity and hallucinogen potency merely reflects the relationship between 5-HT_{2A} and 5-HT_{2C} affinities. Importantly, for a series of structurally diverse 5-HT_2 antagonists, the rank order of potencies for blocking LSD-like stimulus effects (Fiorella *et al.*, 1995) and DOI-induced HTR (Schreiber *et al.*, 1995) does not parallel their 5-HT_{2C} affinity. These findings strongly indicate that interactions with 5-HT_{2C} receptors are not primarily responsible for mediating the behavioral effects of hallucinogens. Further, 5-$HT_{2C/2B}$ antagonists (SB 200,646A, SB 206,553, and SER-082) and the selective 5-HT_{2C} antagonist SB 242,084 consistently fail to block the effects of hallucinogens in a variety of behavioral paradigms (Schreiber *et al.*, 1994; Sipes and Geyer, 1995; Krebs-Thomson *et al.*, 1998; Wettstein *et al.*, 1999; Smith *et al.*, 1999; Ouagazzal *et al.*, 2001; Winter *et al.*, 2007). Although findings suggesting that 5-HT_{2C} receptor interactions may contribute to or modify the effects of some hallucinogens have occasionally been reported (Smith *et al.*, 2003; Krebs-Thomson *et al.*, 1998, 2006), the vast majority of evidence demonstrates that the behavioral effects of these drugs are not dependent on the 5-HT_{2C} receptor.

5-HT_{1A} receptor

LSD and other indoleamine hallucinogens are agonists at 5-HT_{1A} autoreceptors, and the indoleamines potently inhibit the firing of serotonergic neurons in the dorsal raphe nucleus (DRN) (Aghajanian *et al.*, 1968, 1970). Indoleamine hallucinogens also directly inhibit firing in many DRN target regions, but at low doses they preferentially inhibit DRN cells while leaving downstream neurons virtually unaffected (Haigler and Aghajanian, 1974; DeMontigny and Aghajanian, 1977). The finding that hallucinogens are more potent at presynaptic than postsynaptic sites led to the proposal that by depressing the activity of neurons in the DRN and thereby decreasing 5-HT outflow, hallucinogenic drugs remove the tonic inhibition of downstream neurons mediated by serotonin. Further research, however, identified several problems with this 'presynaptic hypothesis' of hallucinogen action. One of the most serious discrepancies was the finding that phenylalkylamine hallucinogens such as mescaline and DOM display negligible 5-HT_{1A} binding affinity and do not consistently depress DRN firing (Haigler and Aghajanian, 1973; Penington and Reiffenstein, 1986). Furthermore, selective 5-HT_{1A} agonists such as buspirone, ipsapirone and flesinoxan inhibit DRN cell firing but are not hallucinogenic.

The ability to inhibit DRN cell firing is clearly an epiphenomenon unrelated to hallucinogenesis. Nonetheless, the 5-HT_{1A} agonist activity of indoleamines does appear to contribute to their behavioral effects. As was noted earlier, the effects of LSD and 5-MeO-DMT in the BPM are partially mediated by the 5-HT_{1A} receptor. There is also considerable evidence that the 5-HT_{1A} receptor plays a role in the discriminative stimulus effects of LSD and 5-MeO-DMT. LSD elicits intermediate levels of drug-lever selection in rats trained with the 5-HT_{1A} agonist 8-OH-DPAT, and the 5-HT_{1A} agonist ipsapirone elicits partial substitution in LSD-trained animals (Arnt, 1989). Likewise, the LSD stimulus completely generalizes to the mixed 5-HT_{1A} agonist/α_2-adrenoceptor antagonist yohimbine (Colpaert, 1984; Marona-Lewicka and Nichols, 1995). 8-OH-DPAT and ipsapirone produce full substitution

in animals trained with 5-MeO-DMT (Spencer *et al.*, 1987; Schreiber and DeVry, 1993; Winter *et al.*, 2000). In fact, it has been reported that WAY-100635 and the mixed 5-HT_1/β-adrenergic antagonist pindolol are more effective than pirenperone and ketanserin at blocking stimulus control by 5-MeO-DMT, indicating that the 5-MeO-DMT discriminative stimulus involves a substantial 5-HT_{1A} receptor-mediated component (Spencer *et al.*, 1987; Winter *et al.*, 2000). These observations are consistent with evidence that the behavioral response to 5-MeO-DMT in rats is predominantly mediated by the 5-HT_{1A} receptor (Tricklebank *et al.*, 1985; Krebs-Thomson *et al.*, 2006).

There is also evidence that activation of the 5-HT_{1A} receptor can inhibit 5-HT_{2A} receptor-induced behavioral effects. 8-OH-DPAT pretreatment dose-dependently attenuates the head-twitch response to DOI in rats and mice (Arnt and Hyttel, 1989; Berendsen and Broekkamp, 1990; Darmani *et al.*, 1990), and the reciprocal hindleg body scratch induced by DOI in the gerbil (Eison and Wright, 1992). Furthermore, although both 8-OH-DPAT and DOI reduce locomotor activity in rats, there is an infra-additive interaction when the two drugs are co-administered, suggesting that they act as functional antagonists (Krebs-Thomson and Geyer, 1998).

5-$HT_{5,6,7}$ receptors

Indoleamine hallucinogens such as LSD, 5-MeO-DMT and psilocin bind with relatively high affinity to 5-HT_5, 5-HT_6, and 5-HT_7 receptors. Until recently, however, there were few pharmacological tools available to probe 5-HT_5, 5-HT_6, and 5-HT_7 sites, and therefore there has been no systematic investigation to determine whether these receptors contribute to the behavioral effects of the indoleamines. Experiments conducted in 5-$HT_{5A}^{-/-}$ knockout mice indicate that the ability of LSD to increase exploratory behavior is partially dependent on the 5-HT_{5A} receptor (Grailhe *et al.*, 1999). It has been reported that the 5-HT_6 receptor is not involved in the LSD-induced decrease of PPI in rats (Ouagazzal *et al.*, 2001). Although interactions with 5-HT_5, 5-HT_6, and 5-HT_7 receptors may modulate the effects of the indoleamines, given the low affinity of the phenylalkylamines for these receptors it is unlikely that any of these sites are responsible for mediating the characteristic behavioral effects of hallucinogens.

Dopamine receptors

Based on evident similarities between the symptoms of schizophrenia and those of the so-called 'model psychosis' induced by hallucinogenic drugs, and because dopamine antagonists such as chlorpromazine and haloperidol have been used to counteract hallucinogen-induced psychotic episodes and panic reactions, it has been proposed that interactions with dopaminergic systems are involved in the mechanism of action of hallucinogens. It is now well established that indolealkylamine and phenylalkylamine hallucinogens lack appreciable affinity for dopamine receptors; consequently, it is unlikely that direct interactions with dopamine receptors are responsible for the behavioral effects of those agents. Conversely, like many other ergot alkaloids, LSD binds to D_1, D_2, D_3, D_4 and D_5 receptors (Nichols *et al.*, 2002), and acts as a partial agonist at D_1 receptors (Watts *et al.*, 1995).

There is evidence that dopaminergic mechanisms play a role in the discriminative stimulus properties of LSD. Although the 5-HT_{2A}/D_2 antagonist risperidone and the 5-HT_2 antagonist ritanserin bind to the 5-HT_{2A} receptor with comparable affinities (Leysen, 1990), risperidone blocks LSD discrimination with 414 times the potency of ritanserin (Koek *et al.*, 1992). A 0.63-mg/kg dose of ritanserin produces full occupation of 5-HT_{2A} sites in rats, yet fails to attenuate the LSD stimulus; it is not until a much higher dose of 40 mg/kg is administered, where ritanserin is capable of interacting with catecholamine receptors, that it can completely antagonize the LSD cue (Meert *et al.*, 1990; Koek *et al.*, 1992). Conversely, risperidone and ritanserin antagonize the DOM cue with similar potencies (ED_{50} values of 0.024 mg/kg and 0.15 mg/kg, respectively; Meert, 1996). Taken together, these findings argue that both 5-HT_{2A} and D_2 receptor interactions contribute to the interoceptive state governing LSD discrimination, whereas DOM discrimination involves only the 5-HT_{2A} receptor. In support of this conclusion, it was observed that the ED_{50} of ritanserin for blocking LSD stimulus control is reduced 53-fold when administered in combination with 0.04 mg/kg haloperidol (Meert and Awouters, 1991). It has also recently been reported that the dopaminergic component of the LSD discriminative stimulus is time-dependent (Marona-Lewicka *et al.*, 2005). Studies that have trained rats to discriminate LSD have typically used pretreatment times of 15–30 minutes, and have consistently shown that the LSD cue is blocked by 5-HT_{2A} antagonists. When a longer pretreatment time of 90 minutes is used, however, the resulting LSD cue is apparently mediated by D_4 receptors rather than by 5-HT_{2A} receptors (Marona-Lewicka *et al.*, 2008).

Chemistry and structure–activity relationships

As discussed above, the serotonin 5-HT_{2A} receptor is now generally considered to be the key target for hallucinogens (Nichols, 2004). As such, one might therefore expect the

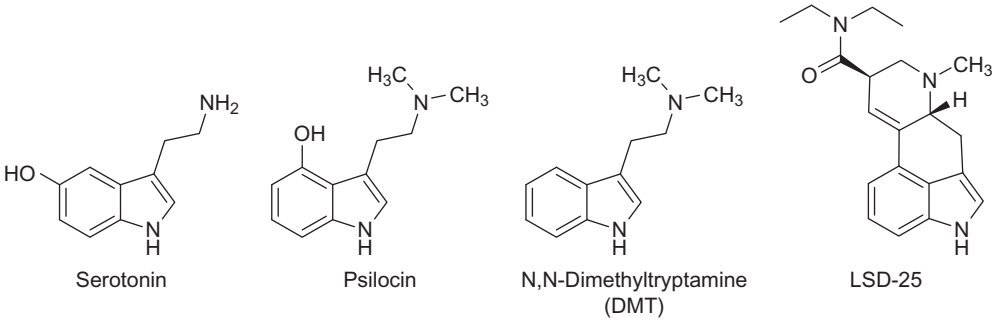

Figure 1 The structures of the natural transmitter serotonin and the tryptamine-type hallucinogens psilocin, DMT and LSD.

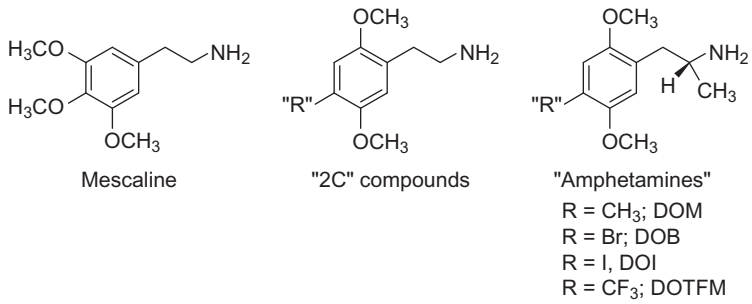

Figure 2 The structures of mescaline, the prototypical phenethylamine hallucinogen, and general formulas for synthetic substituted hallucinogenic phenethylamines and 'amphetamines'. For the alpha-substituted amphetamines, the stereoisomer with the *R*-(−)- absolute configuration (shown) is more potent.

hallucinogens to bear some structural resemblance to serotonin. This relationship is quite evident with the simple tryptamines and with the tetracyclic ergoline LSD. Indeed, it was the recognition that the tryptamine fragment within the structure of LSD also was the core feature of serotonin itself that first led to the realization that serotonin might play a role in behavior. A comparison of the structures of serotonin and the hallucinogens DMT, 5-methoxytryptamine, psilocin and LSD is presented in Figure 1. It is not difficult to understand why all of these structures interact with serotonin receptors, because of their close structural resemblance. Although LSD is a more complex molecule, the tryptamine core fragment is still readily apparent.

What is less clear, though, is how the phenethylamine type hallucinogens (Figure 2) interact with serotonin receptors. The only apparent similarity is a basic nitrogen atom two carbon atoms removed from an aromatic system. Recent mutagenesis studies of the 5-HT_{2A} receptor have, however, begun to reveal the basis for the requirement of certain structural features of the phenethylamines to interact with the receptor (Figure 3).

Studies of the mutant S239A 5-HT_{2A} receptor have demonstrated that it is this serine residue, in transmembrane helix 5, that likely hydrogen bonds to the 5-hydroxy group of serotonin, as well as to the 5-methoxy group of the 2,5-dimethoxy-substituted phenethylamines (Braden and Nichols, 2007). Figure 4 suggests possible binding modes for the 2,5-dimethoxy-substituted phenethylamines and the tryptamines, based on those studies.

This view could explain why a primary amine is most potent for the phenethylamines, with *N*-alkyl or *N,N*-dialkyl derivatives being essentially inert, whereas tertiary amines are potent in the tryptamine series. That is, one might envision that the binding site must 'shrink' or compress to accommodate a phenethylamine. That is most readily achieved by rotation of the side-chain of Asp155 in transmembrane helix 3. If this aspartate engages the amino group in an 'end on' conformation for the phenethylamines, it might be speculated that *N*-alkyl groups would hinder that interaction. By contrast, aspartate residue could engage the amino group of the tryptamines through an approach more perpendicular to the plane of the molecule. In this event, *N*-alkyl groups would be expected to have less of an effect on the ligand interaction. The argument can likely be extended to understand the binding of LSD, because its structure is so rigid that interaction of Asp155 with the protonated electron pair of the amino group can only occur through an 'axial' approach to the amine moiety.

Substitution of an alpha-methyl group on the phenethylamine side-chain gives more potent compounds.

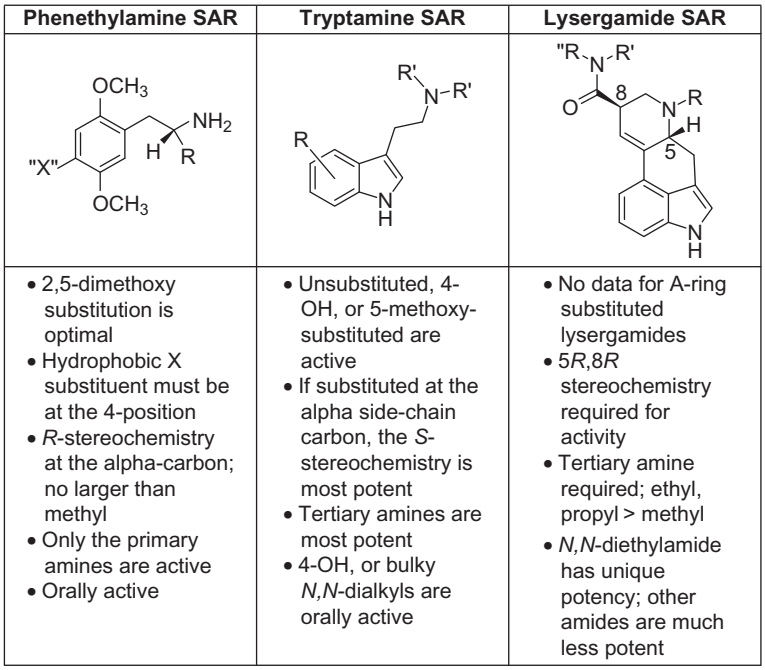

Figure 3 Summary of structure–activity relationships (SAR) for classes of hallucinogens.

There are at least three possible explanations, all of which probably make some contribution. First of all, the alpha methyl will retard metabolic deamination, giving better oral availability and increased *in vivo* stability. Second, the alpha methyl adds significant hydrophobicity, leading to better brain penetration. Finally, *R*-alpha-methyl-substituted phenethylamines generally are more efficacious in activating second messenger systems than their non-alkylated congeners (Parrish *et al.*, 2005). At least for the phenethylamines ('amphetamines') the alpha methyl group enhances the intrinsic activity, possibly through an interaction with a critical phenylalanine residue in transmembrane helix 6. The steric limitation in this region is very strict, however, as any larger alkyl group, even an ethyl, destroys activity.

Interestingly, the stereochemistry is reversed for alpha-substituted tryptamines. One may speculate that the two classes of ligands bind in such a way as to project the alpha-methyl groups into the same general region of the receptor, but there are no data to support that supposition. The different lengths of the ligands also may be a key here. For example, Figure 4 illustrates *S*-(+)-alpha-methyl serotonin and the more potent *R*-(−)- isomer of a rigid phenethylamine. In these orientations, representing potential receptor-bound conformations, the distance from the side-chain amino nitrogen to the 5-oxygen atom is 6.1 and 6.6 Ångstroms for the phenethylamine and the tryptamine, respectively.

Incorporating the 2- and 5-methoxy groups into furan or dihydrofuran rings gives compounds that are more potent, but, more importantly, establishes the binding orientations for the two methoxys. Simulating docking experiments suggest that the 2-methoxy group of the phenethylamines engages Ser159 through a hydrogen bond (Braden, 2007). Attempts to test that hypothesis with the S159A mutant receptor gave a protein that had such drastically reduced function that it was not possible to examine the effect of the presence or absence of the 2-methoxy of the ligand.

Although substitution at the 6-indole position of the tryptamines renders them inactive (Blair *et al.*, 2000), substituting the phenethylamines at the 4-position is essential to provide good activity. Again, the different sizes of the phenethylamines and tryptamines are likely at the heart of this observation. Simulating docking experiments suggest that the 4-substituent of the phenethylamines projects into a hydrophobic area of the receptor between transmembrane helices 3, 4 and 5 created by residues Phe234, Ile206 and Val156. It may be that the larger indole ring of the tryptamines projects into this space, and additional bulk attached to the ligand in this region creates too large a steric footprint for the receptor to accommodate.

3,4,5-substituted phenethylamines (e.g., mescaline) do not bind in the same way as the 2,4,5-substituted compounds, because site specific mutations of the receptor lead to different effects on 2,4,5- vs the 3,4,5- substituted

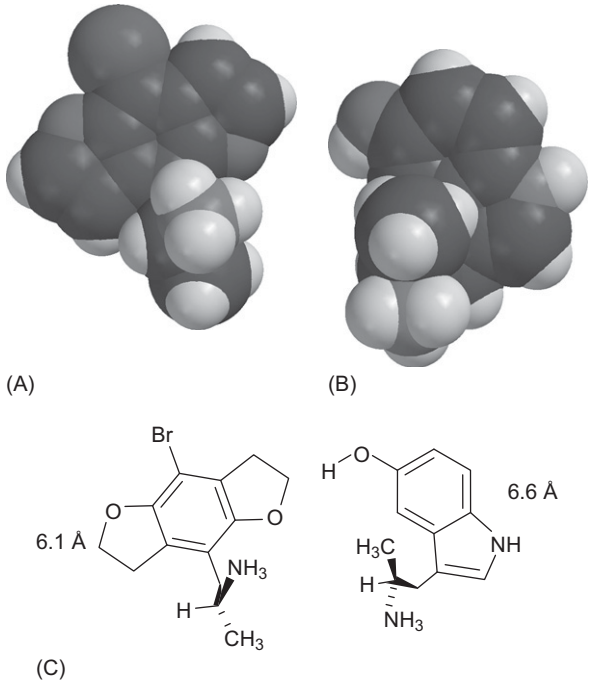

Figure 4 Comparison of the *R*-(−)- isomer of a potent difuranobenzene phenethylamine type hallucinogen (A) with *S*-(+)-α-methylserotonin (B). Although the stereochemistry at the carbon bearing the alpha-methyl is reversed for the phenethylamines and the tryptamines, the lengths of the ligands, differing by about 0.5 Ångstroms (C), could be the underlying reason for this reversal. The bicyclic aromatic indole system of the tryptamines is longer than the phenyl ring of the phenethylamines, and thus when the side-chain is extended, the tryptamines will occupy a larger space in the receptor. Because the receptor evolved to accept serotonin, a tryptamine, the perspective must be one that the phenethylamines somehow adapt themselves to a binding site that prefers tryptamines. To see the full color version of this figure please refer to the color plate at the back of the book. Copies produced via our print on demand service do not contain color plates. If your copy does not have the color plate, please go to this website to view the figure in color www.elsevierdirect.com/companions/9780123746344

compounds (Braden, 2007). Nevertheless, a hydrophobic 4-alkoxy substituent in the 3,4,5-substituted compounds also gives highest activity in this series (Nichols and Dyer, 1977; Shulgin and Shulgin, 1991), and simulated docking into homology models of the receptor suggests that this substituent projects into the same receptor space as the 4-substituent in the 2,4,5-substituted series.

The rigid nature of LSD limits its conformational flexibility upon binding. Mutagenesis studies suggest that the indole NH hydrogen bonds to Ser242 in transmembrane helix 5 (Braden and Nichols, 2007), and the electron pair on the amine nitrogen is probably directed in an axial orientation toward the conserved aspartate in helix 3.

Very little structural modification can be tolerated by ergolines related to LSD. The stereochemistry at both the 5- and 8-positions must be of the *R* configuration, shown in Figures 1 and 4. Inversion at C(8) affords iso-LSD, which is inactive. Halogenation at the 2-indole of LSD position affords antagonists such as BOL that lack hallucinogenic activity. Although N(1)-acetylation leads to an active compound, this molecule is actually a prodrug and the *N*-acetyl is readily cleaved *in vivo* to afford LSD itself.

The bulky diethylamide moiety is relatively limited in its conformational flexibility (Pfaff *et al.*, 1994), and virtually any modification of the diethylamide gives about an order of magnitude decrease in potency. Constraining the diethylamide into a 2,4-dimethylazetidide, however, did lead to a compound with potency comparable to LSD in the rat drug discrimination paradigm (Nichols *et al.*, 2002) The stereoisomer with the 2*S*,4*S*-absolute configuration in the azetidine ring gave the most potent lysergamide, demonstrating that the receptor binding site for the amide moiety of LSD is stereospecific, and uniquely complementary to the diethylamide function. Simulating docking experiments show that the diethylamide moiety is forced to project toward extracellular loop 2 (EL2), suggesting that EL2 may play an important role in LSD binding in the 5-HT_{2A} receptor, as is now known for many other GPCRs.

The only structural modification known to enhance activity is homologation of the N(6)-alkyl group. That is, replacing the N(6)-methyl with an ethyl, n-propyl, or n-allyl gives compounds slightly more active than LSD in rat behavioral models (Hoffman and Nichols, 1985).

Receptors mediating the behavioral effects of MDMA in animals

MDMA (Figure 5) is a potent monoamine-releasing drug (Johnson *et al.*, 1986; Nichols *et al.*, 1986; Baumann *et al.*, 2008). Neurochemical studies have demonstrated that MDMA binds to monoamine transporters, is a substrate for the transporters, and increases the non-exocytotic release of serotonin, dopamine and norepinephrine. MDMA also displays moderate affinity for 5-HT_{2A} receptors (Lyon *et al.*, 1986).

As contrasted with the hallucinogenic amphetamines, where the stereochemistry at the alpha side-chain carbon bearing the methyl group is *R*, the stereochemistry in the side-chain of the more potent enantiomer of MDMA is *S*, which corresponds to that of the psychostimulant amphetamines. The alpha-methyl can be homologated to an ethyl

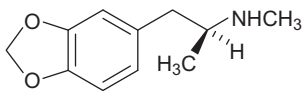

Figure 5 The structure of 3,4-methylenedioxymethamphetamine (MDMA).

group with retention of activity, and the *N*-methyl that is present in MDMA is not tolerated in the hallucinogenic amphetamines. These structural features are strong evidence that MDMA is not simply a hallucinogenic amphetamine, but belongs to a distinct class of psychoactive agents called entactogens (Nichols *et al.*, 1986; Nichols and Oberlender, 1990).

Drug discrimination

Rats can be trained to discriminate MDMA from vehicle (Schechter, 1987; Oberlender and Nichols, 1988). The MDMA stimulus completely generalizes to drugs that produce MDMA-like subjective effects in humans, including N-ethyl-3,4-methylenedioxyamphetamine (MDE) and 1-(1,3-benzodioxol-5-yl)-N-methylbutan-2-amine (MBDB) (Oberlender and Nichols, 1988; Glennon and Misenheimer, 1989). By contrast, the MDMA stimulus does not generalize to LSD or DOM (Oberlender and Nichols, 1988), and MDMA does not substitute in rats trained with LSD (Nichols *et al.*, 1986). These findings demonstrate that the stimulus cue evoked by MDMA is clearly distinct from that produced by hallucinogens.

The neurochemical basis for the discriminative stimulus effects of MDMA is complex, and is incompletely characterized. The fact that MDMA generalizes to the indirect 5-HT agonists norfenfluramine (Schechter, 1988) and *p*-methoxyamphetamine (Nichols and Oberlender, 1989) indicates that 5-HT release plays a role in the stimulus effects of MDMA. The finding that the 5-HT antagonist pizotyline completely blocks MDMA discrimination (Young *et al.*, 2005) is consistent with 5-HT receptor mediation of MDMA stimulus control, but the identity of the specific 5-HT receptor subtype(s) involved remains to be elucidated. There is some disagreement in the literature regarding the extent to which the MDMA stimulus generalizes to the selective 5-HT_{1A} receptor agonist 8-OH-DPAT (Schechter, 1988; Glennon and Young, 2000). Nonetheless, the finding that the 5-HT_{1A} antagonist NAN-190 fails to block MDMA discrimination completely (Glennon *et al.*, 1992) suggests that 5-HT_{1A} receptors do not play a primary role in MDMA discrimination. Although the 5-HT_2 antagonists ketanserin and pirenperone partially attenuate MDMA stimulus control (Glennon *et al.*, 1992), it is unlikely that 5-HT_2 receptor subtypes contribute appreciably to the MDMA discriminative stimulus because DOM does not substitute in animals trained with MDMA. In light of the structural similarities between MDMA and amphetamine, and given the fact that both drugs increase dopamine release, it does not seem unreasonable to assume that there may be a psychostimulant-like component to the MDMA interoceptive stimulus. Indeed, the MDMA stimulus completely generalizes to *S*-(+)-amphetamine (AMPH) and cocaine (Oberlender and Nichols, 1988; Khorana *et al.*, 2004). At the same time, however, MDMA does not substitute in animals trained with either AMPH or cocaine (Oberlender and Nichols, 1988; Khorana *et al.*, 2004). The asymmetric generalization between MDMA and AMPH indicates that MDMA produces a compound stimulus, with one element of the MDMA cue being AMPH-like. It has been reported that AMPH does not substitute in animals trained with (+)-MBDB (Oberlender and Nichols, 1990), a compound that produces symmetrical cross-generalization with MDMA. (+)-MBDB increases 5-HT release but has little effect on dopamine release (Johnson *et al.*, 1986). Taken together, these findings indicate that the most salient component of the MDMA stimulus (i.e., the (+)-MBDB-like effect) is transduced via 5-HT release, with dopamine release mediating a secondary nonessential AMPH-like component. The fact that dopamine antagonists have little or no effect on MDMA discrimination (Schechter, 1988; Glennon *et al.*, 1992) provides further support for the conclusion that dopamine release is not essential for the induction of MDMA stimulus control.

Locomotor activity

Administration of MDMA to rats and mice produces an increase in locomotor activity that is accompanied by thigmotaxis (Gold *et al.*, 1988). MDMA does not induce hyperactivity in 5-HT transporter $(SERT)^{-/-}$ knockout mice (Bengel *et al.*, 1998) or in rats pretreated with 5-HT uptake inhibitors (Callaway *et al.*, 1990), indicating that the effect of MDMA is dependent on carrier-mediated release of 5-HT. There is considerable evidence that 5-HT_{1B} and 5-HT_{2A} receptors mediate the locomotor response to MDMA (McCreary *et al.*, 1999; Scearce-Levie *et al.*, 1999; Fletcher *et al.*, 2002; Ball and Rebec, 2005). However, there is also a dopaminergic component to the MDMA locomotor response (Gold *et al.*, 1989; Baumann *et al.*, 2008). MDMA is a potent releaser of dopamine, and there is a significant correlation between MDMA-induced hyperlocomotion and extracellular dopamine levels in the nucleus accumbens (Baumann *et al.*, 2008). Antagonist and gene deletion studies have confirmed that MDMA acts partially via D_1 and D_2 receptors to increase locomotor activity (Ball *et al.*, 2003; Bubar *et al.*, 2004; Risbrough *et al.*, 2006). Recently, it was reported that the selective α_1-adrenoceptor antagonist prazosin can block the locomotor response to MDMA (Selken and Nichols, 2007), demonstrating that MDMA-induced norepinephrine release also contributes to the locomotor effects of the drug.

Prepulse inhibition of startle
PPI is attenuated by MDMA and MDE in rats and mice (Mansbach *et al.*, 1989; Dulawa and Geyer, 1996; Kehne *et al.*, 1996). Padich *et al.* (1996) have shown that the ability of MDMA to disrupt PPI is completely blocked by M100907, indicating 5-HT_{2A} receptor involvement. Pretreatment with haloperidol did not block the effect of MDMA on PPI. Several other indirect 5-HT agonists, including *p*-chloroamphetamine and fenfluramine, have also been shown to disrupt PPI (Kehne *et al.*, 1996; Padich *et al.*, 1996). As was found with MDMA, the effect of fenfluramine on PPI is dependent on 5-HT_{2A} receptors (Padich *et al.*, 1996).

Clinical studies of hallucinogens in humans

Assessment of hallucinogen-induced altered states of consciousness

The 'Altered States of Consciousness' (APZ) rating scale is a self-administered questionnaire that was developed by Dittrich to assess alterations of consciousness (Dittrich, 1998). Numerous clinical trials have confirmed that the APZ rating scale is sensitive to the effects of hallucinogens, including DMT, psilocybin, *ayahuasca* and mescaline (Hermle *et al.*, 1992; Vollenweider *et al.*, 1997; Dittrich, 1998; Vollenweider *et al.*, 1998a; Gouzoulis-Mayfrank *et al.*, 1999, 2005; Riba *et al.*, 2002; Hasler *et al.*, 2004; Griffiths *et al.*, 2006). Dittrich has proposed that the subjective effects of hallucinogens can be divided into three major dimensions: (1) 'Oceanic Boundlessness' (OB), (2) 'Anxious Ego Dissolution' (AED), and (3) 'Visionary Restructuralization' (VR). The OB dimension is similar to classical mystical experiences, and involves a pleasant state of depersonalization and derealization. The AED dimension includes dysphoric effects such as anxiety, thought disorder, delusions, fear of losing control, and ego disintegration. The VR dimension includes perceptual phenomena such as visual hallucinations and illusions, synesthesia, and changes in the meaning of percepts. Studies using an updated version of the APZ, the 5D-ASC, have shown that psilocybin also increases scores in a dimension known as 'Reduction of Vigilance' (RV), which includes measures of drowsiness, cognitive impairment and decreased alertness (Hasler *et al.*, 2004; Carter *et al.*, 2007; Vollenweider *et al.*, 2007). Psilocybin can produce auditory effects, but only when high doses are administered (Hasler *et al.*, 2004). An [^{18}F]FDG PET study has demonstrated that psilocybin increases cerebral glucose metabolic activity in the prefrontal cortex, anterior cingulate, temporomedial cortex and putamen, and the increased metabolic rate within those regions was found to be significantly correlated with subjective effects in the OB, VUS and AED dimensions (Vollenweider *et al.*, 1997).

Mechanism of hallucinogen effects in humans

One focus of investigation has been to determine how interactions with specific neurotransmitter systems contribute to the effects of hallucinogens in humans. A few early studies addressed this issue by attempting to block the effects of LSD with serotonin, dopamine and norepinephrine receptor antagonists (Isbell and Logan, 1957; Isbell *et al.*, 1959). Unfortunately, due to the fact that high-affinity receptor-selective antagonists were not available at the time, those studies failed to link the action of hallucinogens to any particular transmitter system. The recent resumption of human hallucinogen studies has coincided with the development of selective antagonist ligands, and these compounds have been used to assess how interactions with serotonergic and dopaminergic receptors contribute to the effects of hallucinogens.

DMT
Meltzer and colleagues (Tueting *et al.*, 1992) examined whether the moderately selective 5-$HT_{2A/2C}$ antagonist cyproheptadine and the D_2 antagonist haloperidol could block the psychological effects induced by DMT in normal human volunteers. Neither drug effectively blocked the effects of DMT, and in some subjects the effects of DMT were actually intensified by pretreatment with cyproheptadine. The finding that cyproheptadine intensified the effects of DMT is intriguing in light of reports that high doses of cyproheptadine produce LSD-like behavioral effects in rats (Colpaert *et al.*, 1982). Nonetheless, it is not clear that the dose of cyproheptadine used in the study (4 mg, p.o.) produces significant occupation of 5-HT_2 sites. The mixed 5-$HT_{1A/1B}$/β-adrenergic antagonist pindolol has been used to assess the involvement of 5-HT_{1A} receptors in the response to DMT (Strassman, 1996). Pretreatment with pindolol markedly intensified the subjective effects of DMT, suggesting that activation of 5-HT_{1A} receptors by DMT acts to attenuate the hallucinogenic effects of the drug.

Psilocybin

As part of a series of studies of the effects of psilocybin in human volunteers, Vollenweider and colleagues have assessed the effect of pretreatment with the 5-HT_{2A} antagonist ketanserin, the mixed D_2/5-HT_{2A} antagonist

risperidone, and haloperidol. The effects of psilocybin on the OB, AED and VR dimensions of the APZ were reduced by pretreatment with 20 mg ketanserin (p.o.) and almost completely blocked by pretreatment with either 40 or 50 mg ketanserin (Vollenweider *et al.*, 1998a; Carter *et al.*, 2007). Likewise, pretreatment with 0.5 and 1.0 mg risperidone (p.o.) produced partial and complete blockade, respectively, of the subjective effects of psilocybin (Vollenweider *et al.*, 1998a). Conversely, haloperidol was much less effective, producing only partial blockade of psilocybin effects in the OB dimension, while actually increasing scores in the AED dimension. Taken together, these findings confirm that the hallucinogenic effects of psilocybin in humans are primarily mediated by actions at the 5-HT_{2A} receptor, with D_2 receptor interactions playing only a minor role.

Effect of MDMA in humans

The effects of MDMA and the related homolog MDE in humans have been examined in clinical trials. Treatment with either MDMA or MDE produced effects such as heightened mood, a sense of relaxation, empathy, feelings of closeness to others, stimulation, and minor perceptual and cognitive disturbances (Hermle *et al.*, 1993; Vollenweider *et al.*, 1998b). Although MDMA and MDE did produce some psychostimulant- and hallucinogen-like effects, a double-blind placebo controlled study confirmed that the subjective effects of the entactogens are distinct from those of *S*-(+)-methamphetamine and psilocybin (Gouzoulis-Mayfrank *et al.*, 1999). The latter study also found that the effects of MDE on core APZ dimensions were intermediate between those of psilocybin and *S*-(+)-methamphetamine, providing additional confirmation that differences exist between the subjective effects of these three drugs. Interestingly, in trials comparing the two enantiomers of MDE, the *S*-enantiomer produced entactogenic effects whereas the *R*-enantiomer elicited mainly dysphoric effects (Spitzer *et al.*, 2001). This finding distinguishes MDE from phenylisopropylamine hallucinogens such as DOM, DOB and DOET, for which the *R*-enantiomer is the more active stereoisomer (Shulgin, 1973; Shulgin *et al.*, 1971; Snyder *et al.*, 1974).

Mechanism of MDMA effect in humans

Pretreatment with the selective 5-HT reuptake inhibitor citalopram significantly attenuated most of the subjective effects of MDMA, consistent with the proposed involvement of carrier-mediated 5-HT release in the effects of MDMA (Liechti *et al.*, 2000a; see also this volume). Citalopram also blocked the cardiovascular response to MDMA (Liechti and Vollenweider, 2000a) and inhibited the effect of MDMA on PPI (Liechti *et al.*, 2001). Pretreatment with ketanserin produced some attenuation of the subjective effects of MDMA (Liechti *et al.*, 2000b). However, the most significant reduction of MDMA effects by ketanserin occurred in the VR dimension of the APZ, indicating that 5-HT_{2A} receptors are responsible for the effects of MDMA on perception. Haloperidol pretreatment reduced the euphoric effects of MDMA but increased MDMA-induced dysphoria (i.e., scores in the AED dimension) (Liechti and Vollenweider, 2000b). Neither ketanserin nor haloperidol blocked the cardiovascular effects of MDMA (Liechti and Vollenweider, 2000b; Liechti *et al.*, 2000b) or the ability of the drug to increase PPI (Liechti *et al.*, 2001). Pretreatment with pindolol did not substantially alter either the subjective effects of MDMA or its effect on measures of cognitive performance (Hasler *et al.*, 2008). The fact that interactions with the 5-HT_{1A} receptor do not appear to contribute to the effects of MDMA in humans stands in contrast to the preclinical evidence in rodents indicating that the 5-HT_{1A} receptor plays a role in the behavioral effects of MDMA (Millan and Colpaert, 1991; Glennon and Young, 2000; Morley *et al.*, 2005). In summary, these findings demonstrate that the subjective effects of MDMA are largely attributable to increases in 5-HT release, with D_2 and 5-HT_{2A} receptor stimulation contributing to the mood-elevating and hallucinogen-like perceptual effects, respectively, of MDMA.

Summary

Over the past three decades, substantial progress has been made toward understanding how hallucinogens exert their complex behavioral effects. It is now well established that serotonergic hallucinogens bind to the 5-HT_{2A} receptor, and a large body of preclinical evidence demonstrates that the behavioral effects of the hallucinogens are primarily mediated by interactions with the 5-HT_{2A} receptor. Importantly, due to the recent resumption of human clinical studies with hallucinogens, it has been possible to confirm that the 5-HT_{2A} receptor also plays a primary role in the effects of hallucinogens in humans.

The drug MDMA has been a topic of intense study in recent years. Although there is some overlap between the effects of entactogens and hallucinogens, there are considerable pharmacological differences between these two classes of compounds. The effects of MDMA are largely attributable to increases in the release of serotonin, a fact that has been confirmed in clinical studies with human subjects. Studies of MDMA and the hallucinogens have

proven to be extremely informative regarding the pharmacology of these agents. These investigations have also provided insight into how the central serotonergic system acts to modulate behavior.

Most recently, in a study where psilocybin was administered to normal human volunteers, effects were characterized by a majority of the subjects as among the most meaningful experiences of their lives. Positive effects on mood and behavior were manifest, and at 14-month follow-up were still significantly above values prior to the study (Griffiths *et al.*, 2006, 2008). Several clinical studies are now under way to determine whether these effects may provide value in reduction of stress and anxiety in the treatment of cancer patients. It is anticipated that future investigations with hallucinogens, especially research conducted in humans, will yield additional insight into the psychopharmacology of hallucinogens and the behavioral influence of serotonin.

Acknowledgements

This work was supported by National Institute on Drug Abuse (NIDA) Awards DA025412 and DA002925 (A. L. Halberstadt) and DA002189 (D.E. Nichols).

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