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Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens

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Abstract

Serotonergic hallucinogens produce profound changes in perception, mood, and cognition. These drugs include phenylalkylamines such as mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM), and indoleamines such as (+)-lysergic acid diethylamide (LSD) and psilocybin. Despite their differences in chemical structure, the two classes of hallucinogens produce remarkably similar subjective effects in humans, and induce cross-tolerance. The phenylalkylamine hallucinogens are selective 5-HT_2 receptor agonists, whereas the indoleamines are relatively non-selective for serotonin (5-HT) receptors. There is extensive evidence, from both animal and human studies, that the characteristic effects of hallucinogens are mediated by interactions with the 5-HT_{2A} receptor. Nevertheless, there is also evidence that interactions with other receptor sites contribute to the psychopharmacological and behavioral effects of the indoleamine hallucinogens. This article reviews the evidence demonstrating that the effects of indoleamine hallucinogens in a variety of animal behavioral paradigms are mediated by both 5-HT_2 and non-5-HT_2 receptors.

Keywords

hallucinogen; LSD; psilocybin; serotonin; drug discrimination; locomotor activity; head twitch; 5-HT_{1A} receptor

1. Introduction

Hallucinogens are a class of pharmacological agents that increase the intensity and lability of affective responses and produce profound distortions of perceptual processes encompassing the visual, auditory and tactile modalities. These compounds, in the form of botanical preparations, have been used by humans for thousands of years to induce states of mysticism and inebriation (Schultes and Hofmann, 1980). Notable examples include the peyote cactus (*Lophophora williamsii*), which contains mescaline; *teonanácatl* mushrooms containing psilocin and psilocybin; and *ayahuasca*, a decoction prepared from the bark of β-carboline-containing *Banisteriopsis* species in combination with plants containing *N*,*N*-dimethyltryptamine (DMT). Hallucinogen use has remained relatively stable over the past decades, but these drugs are becoming more widely available with increased access to psychoactive natural products and the extant knowledge base on the use and preparation of these compounds introduced through the internet. For example, the sacramental use of

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ayahuasca originated in South America, but in recent years the use of this hallucinogen has spread to Europe and North America. Research into the profound effects of hallucinogens on perception has shaped our neurobiological understanding of consciousness and informed our understanding of neuropsychiatric disorders. For example, the notion that psychotic states seen in schizophrenia may involve serotonin (5-HT) dysfunction arose in part from the observed psychedelic effects of (+)-lysergic acid diethylamide (LSD) and other classical serotonergic hallucinogens (Geyer and Vollenweider, 2008; Quednow et al., 2010).

2. Chemical Structure of Hallucinogens

As shown in Figure 1, classical hallucinogens belong to two classes of chemicals: (1) indoleamines, including the ergoline LSD and indolealkylamines such as DMT, 5-methoxy-DMT (5-MeO-DMT), psilocin, and 4-phosphoryloxy-DMT (psilocybin); (2) phenylalkylamines, such as the phenethylamines mescaline and 2,5-dimethoxy-4-bromophenethylamine (2C-B), and the phenylisopropylamines 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-methylamphetamine (DOM), and 2,5-dimethoxy-4-bromoamphetamine (DOB). Recently, highly potent rigid analogs of hallucinogenic phenylalkylamines have been synthesized in which the alkoxy ring substituents are incorporated into furanyl and/or pyranyl rings (e.g., 1-(8-bromobenzo[1,2-b; 4,5-b]difuran-4-yl)-2-aminopropane (“Bromo-Dragonfly”; Parker et al., 1998), or the ethylamine side chain is conformationally constrained by incorporation into a cycloalkane ring (e.g., TCB-2; McLean et al., 2006). Radioligand binding studies have shown that phenylalkylamine hallucinogens are highly selective for 5-HT_2 sites (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors), and some of these compounds display over 1000-fold selectivity for agonist-labeled 5-HT_2 receptors versus 5-HT_1 sites (Titeler et al., 1988;Herrick-Davis and Titeler, 1988;Pierce and Peroutka, 1989). By contrast, indolealkylamines are relatively non-selective for 5-HT receptors, displaying moderate to high affinity for 5-HT_1 and 5-HT_2 subtypes (Pierce and Peroutka, 1989;McKenna et al., 1990;Deliganis et al., 1991;Blair et al., 2000). Tables I and II show the binding profiles of psilocin and DMT, respectively, for 5-HT receptors. It has been reported that DMT is a σ_1 receptor agonist with moderate affinity (K_D = 14.75 μM; Fontanilla et al., 2009); however, it is not clear whether this interaction contributes to the effects of DMT because the affinity of the drug for 5-HT_{1A} and 5-HT_{2A} receptors is ~2-orders of magnitude greater than for σ_1 binding sites (see Table II). Further, other σ_1 receptor agonists (e.g., cocaine) are not hallucinogenic, making it unlikely that σ_1 activation by DMT plays a primary role in mediating its hallucinogenic effects. Certain indolealkylamines, including DMT, *N*,*N*-dipropyltryptamine (DPT), 5-MeO-DMT, and 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) block 5-HT uptake at micromolar concentrations (Nagai et al., 2007;Sogawa et al., 2007;Cozzi et al., 2009) and serve as substrates for the 5-HT transporter (Cozzi et al., 2009). As shown in Table III, LSD binds to a number of 5-HT receptors with high (nanomolar) affinity (Peroutka, 1994), and also interacts with dopaminergic and adrenergic receptors.

3. Unitary Effects of Serotonergic Hallucinogens in Humans

Despite differences in their chemical structure, the classical hallucinogens LSD, psilocybin, mescaline, and DOM produce extremely similar experiences in humans (Isbell, 1959; Wolbach et al., 1962a,b; Rosenberg et al., 1964; Snyder et al., 1967; Hollister et al., 1969; Shulgin and Shulgin 1991, 1997). By contrast, the subjective effects of hallucinogens are readily distinguished from the effects of drugs in other pharmacological classes, including anticholinergics, stimulants, entactogens, and NMDA antagonists (Gershon and Olariu, 1960; Rosenberg et al., 1963; Gouzoulis-Mayfrank et al., 1999, 2005). Tolerance rapidly develops to the effects of hallucinogens, and indoleamine and phenylalkylamine hallucinogens produce cross-tolerance (Balestrieri and Fontanari, 1959; Abramson et al.,

1960; Isbell et al., 1961; Wolbach et al., 1962a). The similarity of their psychopharmacological effects and their ability to produce cross-tolerance indicate that indoleamine and phenylalkylamine hallucinogens act through a common receptor mechanism. It is generally accepted, based on evidence reviewed below, that the unitary mechanism responsible for the effects of serotonergic hallucinogens is activation of the 5-HT_{2A} receptor (Halberstadt and Nichols, 2010; Nichols, 2004). Given the high affinity and selectivity of DOB and other phenylisopropylamine hallucinogens for 5-HT_2 subtypes (Mos et al., 1992; Pierce and Peroutka, 1989; Herrick-Davis and Titeler, 1988; Leysen, 1989; Titeler et al., 1988), it follows that a member of the 5-HT_2 receptor family is likely to be responsible for mediating the effects of these compounds. Nevertheless, although the unitary pharmacological effects of hallucinogens are mediated by the 5-HT_{2A} receptor, this does not preclude the possibility that the interaction of indoleamines with non-5-HT_2 receptors does have psychopharmacological and behavioral consequences. This article will review the evidence showing that both 5-HT_2 and non-5-HT_2 receptors contribute to the behavioral effects of indoleamine hallucinogens.

4. Recent Clinical Studies of Hallucinogens

Although neglected for several decades, clinical testing of hallucinogens has resumed in recent years (Vollenweider and Kometer, 2010). The majority of this clinical work has focused on psilocybin (Vollenweider et al., 1997; Gouzoulis-Mayfrank et al., 1999; Moreno et al., 2006; Griffiths et al., 2006; Grob et al., 2010), although mescaline (Hermle et al., 1992, 1998) and DMT (Strassman and Qualls, 1994; Strassman et al., 1994; Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007) have also been studied.

Most of the studies listed above were designed to characterize the subjective and physiological effects of hallucinogens. Studies have also examined whether psilocybin is effective at reducing symptoms in patients with obsessive-compulsive disorder (OCD) (Moreno et al., 2006), and anxiety in terminal cancer patients (Grob et al., 2010). Other groups have revisited the hypothesis that hallucinogens can be used to model the symptoms of psychosis in normal subjects. Gouzoulis-Mayfrank and colleagues (Gouzoulis-Mayfrank et al., 2005) conducted a double-blind crossover study comparing the subjective effects of DMT with those of the noncompetitive NMDA antagonist *S*-ketamine. This study is notable because it demonstrated that DMT produced effects that primarily resembled the positive symptoms of schizophrenia, whereas the effect of *S*-ketamine resembled the negative and cognitive symptoms of schizophrenia. In addition to confirming that serotonergic and glutamatergic hallucinogens evoke distinguisible psychological effects, these findings clearly demonstrate that both drug classes can be used to model different aspects of schizophrenia.

Vollenweider and colleagues have conducted a series of studies examining the contribution of 5-HT and dopamine (DA) receptors to the subjective and behavioral effects of psilocybin in human volunteers. These studies have demonstrated that most of the subjective effects of psilocybin are blocked by the 5-HT_2 antagonist ketanserin (20–50 mg, p.o.; Vollenweider et al., 1998; Carter et al., 2005, 2007). Similar findings were reported for the mixed D_2/5-HT_{2A} antagonist risperidone (0.5–1.0 mg, p.o.), whereas the DA D_2 antagonist haloperidol (0.021 mg, i.v.) produced very little blockade of psilocybin effects (Vollenweider et al., 1998). Taken together, these findings confirm that the hallucinogenic effects of psilocybin are mediated primarily by the 5-HT_{2A} receptor. This conclusion is supported by the results of a recent PET study with the 5-HT_{2A} ligand [^{18}F]altanserin, which demonstrated that the intensity of psilocybin-induced subjective effects is directly correlated with 5-HT_{2A} occupation in the anterior cingulate and medial prefrontal cortices (Quednow et al., 2010). Importantly, however, ketanserin does not block some of the effects of psilocybin, including

slowing of binocular rivalry, impairment of multiple object tracking, and reduction of measures of arousal and vigilance (Carter et al. 2005, 2007). Although the 5-HT_{2A} receptor is responsible for most of the effects of psilocybin, it is clear that interactions with non-5-HT_{2A} receptors also contribute to the effects of the drug.

The mechanism for the subjective effects of DMT has also been investigated clinically. Blockade studies with low doses of the nonselective 5-HT_2 antagonist cyproheptadine produced inconclusive results (Tueting et al., 1992), and the sedative effects of cyproheptadine precluded testing higher doses (Strassman, 2001). By contrast, Strassman has reported that the mixed 5-$HT_{1A/1B}$/β-adrenergic antagonist pindolol markedly potentiates the subjective effects of DMT (Strassman, 1996). Since DMT has only low affinity for β-adrenergic receptors, this finding indicates that interactions with 5-HT_{1A} receptors serve to attenuate the action of DMT at the 5-HT_{2A} receptor. It is likely that the effects of other indoleamines at the 5-HT_{2A} receptor are also modulated by their 5-HT_{1A} agonist activity.

5. Presynaptic Versus Postsynaptic Effects of Hallucinogens

It was recognized as early as 1954 that the profound intoxicating effects of LSD are likely to result from interactions with serotonin (5-hydroxytryptamine, 5-HT) in the brain (Wolley and Shaw, 1954). Although it was soon widely accepted that the hallucinogenic effects of LSD result from effects on central serotonergic systems, it took several more years for researchers to find evidence that directly supported this contention. In 1968, Aghajanian and colleagues found that intravenous LSD (10–20 μg/kg) completely inhibits the firing of serotonergic neurons in the dorsal (DRN) and median (MRN) raphe nuclei in rats (Aghajanian et al., 1970, 1968). It was subsequently demonstrated that psilocin, DMT, and 5-MeO-DMT induced similar raphe-depressant effects in rats and cats (Aghajanian et al., 1970; Aghajanian and Haigler; 1975; Mosko and Jacobs, 1977; Trulson et al., 1981). The microiontophoretic application of these agents directly to raphe cells allowed workers to determine that the depressant effects of indoleamines upon raphe firing are mediated by somatodendritic 5-HT autoreceptors (Aghajanian and Haigler, 1975; de Montigny and Aghajanian, 1977).

There is extensive evidence that LSD and other indoleamine hallucinogens inhibit the firing of serotonergic DRN neurons by activating 5-HT_{1A} receptors. Like the indoleamine hallucinogens, 5-HT_{1A} receptor-selective agonists (e.g., 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), ipsapirone, gepirone, and buspirone) inhibit DRN firing (Fornal et al., 1994; Blier and de Montigny, 1990; VanderMaelen et al., 1986; Sprouse and Aghajanian, 1985; de Montigny et al., 1984). It has also been shown that 5-HT_{1A} antagonists block the inhibition of DRN neuronal activity induced by LSD (Romero et al., 1996; Queree et al., 2009). As noted earlier, hallucinogenic indoleamines, including LSD, psilocin, DMT, 5-MeO-DMT, *N*,*N*-diethyltryptamine (DET), and *N*,*N*-dipropyltryptamine (DPT), bind to the 5-HT_{1A} receptor with moderate to high affinity (Pierce and Peroutka, 1989; McKenna et al., 1990), and are potent agonists at 5-HT_{1A} receptors negatively coupled to adenylate cyclase (DeVivo and Maayani, 1986; Dumuis et al., 1988; Deliganis et al., 1991; Blair et al., 2000; Thiagraj et al., 2005). LSD is estimated to suppress DRN firing in rats with an EC_{50} of 4.6 nM (Bennett and Aghajanian, 1976), consistent with the reported affinity of LSD for the rat 5-HT_{1A} receptor, with K_i values ranging from 3.9 to 5.1 nM (Monte et al., 1995; Huang et al., 1994; Peroutka, 1986). Anatomical studies have confirmed that 5-HT_{1A} receptors are primarily expressed in the DRN and MRN as somatodendritic autoreceptors (Mengod et al., 1996; Pompeiano et al., 1992; Pazos and Palacios, 1985). Indeed, following the destruction of 5-HT-containing nerve cells by intracerebral injection of the selective serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT), the density of

[^{3}H]8-OH-DPAT- labeled 5-HT_{1A} binding sites in the DRN is greatly reduced (Pranzatelli et al., 1994; Hensler et al., 1991; Verge et al., 1985).

In addition to their depressant effects upon raphe activity, LSD, psilocin, DMT, and 5-MeO-DMT inhibit cells downstream from the raphe nuclei by stimulating postsynaptic 5-HT_{1A} receptors. These agents are approximately 4 to 5 times more potent at presynaptic than postsynaptic sites (de Montigny and Aghajanian, 1977; Aghajanian and Haigler, 1975; Haigler and Aghajanian, 1974), and thus they tend to preferentially inhibit DRN cells while leaving downstream neurons relatively unaffected. The preferential action of indoleamine hallucinogens on somatodendritic 5-HT_{1A} autoreceptors contrasts with the effect of 5-HT, which inhibits cells in the DRN and in DRN target regions with similar potencies (de Montigny and Aghajanian, 1977; Haigler and Aghajanian, 1974). The ability of indoleamine hallucinogens to selectively inhibit DRN cells probably results from the marked (>50%) 5-HT_{1A} receptor reserve present on the cell bodies of serotonergic raphe cells (Cox et al., 1993) but not on postsynaptic membranes (Yocca et al., 1992). It has been shown that 5-HT_{1A} receptors in the DRN and hippocampus couple preferentially to Gi_3 and Go, respectively (Mannoury La Cour et al., 2006), and this difference in G-protein coupling may also contribute to the different efficacies of indoleamine hallucinogens at presynaptic versus postsynaptic sites. The evidence outlined above led to the hypothesis that by selectively depressing the activity of neurons in the DRN and thereby decreasing 5-HT release, hallucinogens remove the tonic inhibition of downstream neurons mediated by 5-HT. It was theorized that LSD and related agents induce hallucinogenic effects indirectly by disinhibiting brain regions targeted by DRN efferents. The observation by Haigler and Aghajanian (1974) that LSD, at an intravenous dose of 20 μg/kg, accelerates the firing of cells targeted by inhibitory DRN projections provided additional support for the “presynaptic hypothesis” of hallucinogen action.

Further research identified several problems with this hypothesis:

1. Trulson and coworkers observed dissociations between the behavioral and raphe inhibitory effects of hallucinogens. The depression of DRN neuronal firing induced by LSD in cats is transient and does not correspond to the time course of LSD-induced behavioral effects (Trulson et al., 1981; Trulson and Jacobs, 1979b). Further, low doses of LSD and psilocin produce significant behavioral alterations but have negligible effects on DRN unit activity (Trulson et al., 1981).
2. Although humans and laboratory animals develop tolerance to the effects of LSD and other hallucinogens after chronic administration, DRN neurons fail to develop a tolerance to the inhibitory effects of those drugs (Trulson et al., 1981; Lee and Geyer, 1980; Trulson et al., 1977a). By contrast, 5-HT_{2A} receptors are downregulated by treatment with LSD, psilocybin, DOI, DOB, and DOM (Owens et al., 1991; Buckholtz et al., 1990; Leysen et al., 1989; McKenna et al., 1989; Buckholtz et al., 1985; Trulson and Jacobs, 1979a).
3. Antagonists at postsynaptic 5-HT receptors, including mainserin, ketanserin, and metergoline, attenuate many of the behavioral effects of LSD but fail to block the effect of that drug upon DRN activity (Trulson, 1986; Jacobs, 1985; Heym et al., 1984).
4. Phenylalkylamine hallucinogens such as mescaline, DOI, and DOM have inconsistent effects upon raphe firing (Penington, 1996; Penington and Reiffenstein, 1986; Trulson et al., 1981; Haigler and Aghajanian, 1973; Aghajanian et al., 1969), and bind to 5-HT_{1A} sites with negligible affinity (Leysen, 1989; Pierce and Peroutka, 1989b; Titeler et al., 1988). Furthermore, DOM is completely inactive as a 5-HT_{1A} receptor agonist (Pauwels et al., 1993).

5. Despite that fact that the LSD congener lisuride has high-affinity for the 5-HT_{1A} receptor (Millan et al., 2002; Marona-Lewicka et al., 2002) and inhibits the firing of DRN neurons when administered to rats at intravenous doses of 1 to 5 μg/kg (Pieri et al., 1983; Rogawski and Aghajanian, 1979; Laurent and Pieri, 1978), it is not a hallucinogenic drug in humans (Herrmann et al., 1977).

6. Even though they completely suppress the firing of serotonergic neurons in the raphe nuclei, selective 5-HT_{1A} receptor agonists are not hallucinogenic when administered to humans. Indeed, buspirone and ipsapirone are used clinically as anxiolytic agents. As was found with the indoleamine hallucinogens, 8-OH-DPAT and gepirone act preferentially on presynaptic 5-HT_{1A} sites (Blier et al., 1993). Hence, the ability of hallucinogenic indoleamines to selectively activate presynaptic 5-HT_{1A} receptors *per se* is not responsible for their psychoactive effects.

7. If the effects of hallucinogens are mediated by inhibition of raphe neurons, then destruction of the raphe nuclei should evoke behavioral alterations identical to those produced by hallucinogens. Likewise, hallucinogens should have only minimal effects on behavior when administered to animals with raphe lesions because the anatomical locus where these agents act is not intact. However, lesioning the midbrain raphe nuclei of laboratory animals does not produce hallucinogen-like behavioral effects (Appel et al., 1970) nor does it diminish the effectiveness of mescaline or other hallucinogens (Geyer et al., 1979; Browne, 1978).

All of the aforementioned evidence contradicts the hypothesis that inhibition of the raphe nuclei plays a primarily mechanistic role in the effects of hallucinogenic agents. The ability to evoke a cessation of serotonergic cell firing is clearly an epiphenomenon unrelated to the production of hallucinogenic activity. Importantly, some of the evidence against the presynaptic hypothesis indicated that postsynaptic 5-HT receptor mechanisms are likely involved in mediating the effects of this class of agents. Hence, the presynaptic hypothesis of hallucinogen action is untenable and has correctly been abandoned in favor of a postsynaptic mechanism.

6. Behavioral Effects of Hallucinogens

6.1 Drug Discrimination

The phenomenon of drug-induced stimulus control has been applied successfully to the study of hallucinogens, and these methodologies have proven especially useful when applied to the mechanistic analysis of these compounds. Hirschhorn and Winter first demonstrated in 1971 that rats can be trained to discriminate mescaline and LSD from saline using standard two-lever operant procedures (Hirschhorn and Winter, 1971), and it was subsequently shown that many classical hallucinogenic drugs (e.g., LSD, mescaline, DOM, DOB, DOI, psilocybin, 5-MeO-DMT, and DPT) are capable of serving as discriminative stimuli in the drug discrimination paradigm (Glennon et al., 1979, 1982, 1983a; Young et al., 1981; Glennon, 1988; Winter et al., 2007; Fantegrossi et al., 2008). The interoceptive stimulus cues evoked by a variety of hallucinogenic agents in laboratory animals appear to be uniform in nature, as cross-generalization occurs between all of these drugs. Most drug discrimination studies with hallucinogens have employed rats, although pigeons (Jarbe, 1980), mice (Smith et al., 2003; Benneyworth et al., 2005; Winter et al., 2005), and rhesus monkeys (Li et al., 2008, 2009) have also been used. The drug discrimination assay displays pronounced pharmacological specificity, and members of other drug classes, including opiates, sedatives, stimulants, NMDA antagonists (e.g., phencyclidine and ketamine), salvinorin A, cannabinoids, and anticholinergics, consistently fail to evoke hallucinogen-like

stimulus effects (Glennon et al., 1982; Appel and Cunningham, 1986; Killinger et al., 2010). There is also evidence demonstrating that hallucinogens and 5-HT_{1A} receptor-selective agonists produce distinct interoceptive cues (Koek and Colpaert, 1989).

6.1.1 Involvement of 5-HT_{2A} receptors in the stimulus effects of hallucinogens—The hallucinogen discriminative stimulus is blocked to varying degrees by a variety of non-selective 5-HT antagonists, including methysergide, metergoline, mianserin, methiothepin, and cyproheptadine (Fiorella et al., 1995b; Schreiber et al., 1994; Glennon et al., 1986; Colpaert et al., 1982; Kuhn et al., 1978). The high-affinity, selective 5-HT_2 receptor antagonists pirenperone and ketanserin are also potent and highly efficacious antagonists of the discriminative stimulus properties of DOM and LSD (Colpaert and Janssen, 1983; Colpaert et al., 1982), and of DOM-stimulus generalization to LSD, mescaline, and 5-MeO-DMT (Glennon et al., 1983b). Based on these findings, Glennon and colleagues (Glennon et al., 1983b) proposed that the stimulus effects of hallucinogenic drugs are mediated by the 5-HT_{2A} receptor. It was soon demonstrated that a significant correlation (r = 0.938) exists between the 5-HT_{2A} affinities of various phenylalkylamine hallucinogens and their ED_{50} values obtained from stimulus generalization studies using 1.0 mg/kg DOM as the training drug (see Fig. 2); also observed was a significant correlation (r = 0.90–0.97) between the 5-HT_{2A} receptor affinities and the potencies of these drugs in humans (Sadzot et al., 1989; Titeler et al., 1988; Glennon et al., 1984). Taken together, these findings strongly indicate that the stimulus effects of hallucinogens are mediated by the 5-HT_{2A} receptor.

The existence of the 5-HT_{2C} receptor was first proposed by Pazos and associates in 1984, and these and other workers were able to label 5-HT_{2C} sites in porcine and rat choroid plexus membranes with radioligands such as [^{3}H]5-HT, [^{3}H]mesulergine, and [^{125}I]2-iodo-LSD (Hoyer et al., 1986*b*; Yagaloff and Hartig, 1985; Cortés et al., 1984; Pazos et al., 1984). Soon after the discovery of 5-HT_{2C} sites, it was recognized that LSD binds to 5-HT_{2C} sites with nanomolar affinity (Egan et al., 1998; Peroutka, 1994; Titeler et al., 1988; Yagaloff and Hartig, 1985). Subsequent work demonstrated that phenylalkylamine and indolealkylamine hallucinogens bind to 5-HT_{2C} receptors with moderately high-affinity (Glennon et al., 1994, 1992a; Titeler et al., 1988). Binding studies using agonist radioligands have shown that hallucinogens are relatively nonselective for 5-HT_{2A} and 5-HT_{2C} receptors (Porter et al., 1999; Nelson et al., 1999).

The observation that hallucinogens interact with 5-HT_{2C} receptors confounded the hypothesis that activation of 5-HT_{2A} receptors is the primary mechanism for the effects of serotonergic hallucinogens. This hypothesis was proposed prior to the discovery of 5-HT_{2C} sites, and was partially based on evidence demonstrating that ketanserin and pirenperone block the behavioral effects of hallucinogens in several animal paradigms. However, ketanserin and pirenperone exhibit less than a 100-fold difference in affinity for 5-HT_{2A} receptors versus 5-HT_{2C} receptors, and therefore display only moderate selectivity for the 5-HT_{2A} receptor (Newton et al., 1996; Hoyer, 1988a,b). It was also reported that there is a significant correlation (r = 0.78) between the affinities of various phenylalkylamine hallucinogens for 5-HT_{2C} receptors and their psychoactive potency in humans (Titeler et al., 1988). However, 5-HT_{2A} and 5-HT_{2C} receptors display parallel structure-affinity relationships for ligand binding (Nelson et al., 1999; Glennon et al., 1994; Glennon et al., 1992b), so it is not clear whether this correlation is due to the involvement of 5-HT_{2C} receptors in the effects of hallucinogens or whether it merely reflects the relationship between 5-HT_{2A} and 5-HT_{2C} binding affinities. Because the potency of hallucinogens strongly correlates with their 5-HT_{2A} receptor affinity, and given that the 5-HT_{2A} and 5-HT_{2C} affinities of hallucinogens are correlated, it might be expected that a correlation

between hallucinogen potency and 5-HT_{2C} affinity would exist even if the 5-HT_{2C} receptor played absolutely no role in the effects of these compounds.

The potent action of hallucinogens at 5-HT_{2C} receptors has led to speculation that 5-HT_{2C} receptor occupation may play an important mechanistic role in the action of hallucinogenic drugs (Sanders-Bush, 1994; Burris et al., 1991; Glennon, 1990; Sanders-Bush et al., 1988; Titeler et al., 1988). In order to determine whether the 5-HT_{2C} receptor is involved in mediating the discriminative stimulus effects of hallucinogens, attempts have been made to block the effects of hallucinogens with 5-HT_2 subtype-selective antagonists. Before 1993, the most selective agent known was the butyrophenone neuroleptic spiperone, an antagonist at dopaminergic D_2/D_4 and serotonergic 5-HT_{1A} receptors that displays 500- to 1000-fold higher affinity for 5-HT_{2A} than for 5-HT_{2C} binding sites (Metwally et al., 1998; Hoyer, 1988b; Sanders-Bush and Conn, 1986). Unfortunately, most (but not all) of the antagonist blockade studies with spiperone produced inconclusive results because the compound can severely disrupt responding when administered in combination with LSD or DOM (Fiorella et al., 1995b; Glennon, 1991; Appel and Cunningham, 1986; Colpaert et al., 1982). It has been reported, however, that the ether analog of spiperone (AMI-193), a 5-HT_{2A} receptor antagonist with 2,150-fold selectivity versus 5-HT_{2C} sites, blocks DOM-induced stimulus control in rats at very low doses (ED_{50} = 0.003 mg/kg) without altering the response rate (Ismaiel et al., 1993). More recently, it has been demonstrated that stimulus control in animals trained with DOI (Schreiber et al, 1994; Smith et al, 1999, 2003), DOM (Li et al., 2007, 2008), LSD (Winter et al., 2004; Gresch et al., 2007), and 2C-T-7 (Fantegrossi et al., 2005) is blocked by the highly selective 5-HT_{2A} antagonist M100907 (formerly MDL 100,907). The LSD cue is also blocked by MDL 11,939, a 5-HT_{2A} antagonist with high selectivity versus the 5-HT_{2C} receptor (Marona-Lewicka and Nichols, 2007). The apparent lack of 5-HT_{2C} involvement in the stimulus effects of hallucinogens is supported by the fact that even high doses of the mixed 5-$HT_{2C/2B}$ antagonists SB 200,646A and SB 206,553 fail to alter DOI- and LSD-induced responding in rats (Smith et al., 1998, 1999; Schreiber et al., 1994; Gresch et al., 2007). It has also reported that the selective 5-HT_{2C} antagonist SB 242,084 does not block the psilocybin discriminative stimulus (Winter et al., 2007). Furthermore, an antagonist correlation analysis study (Fiorella et al., 1995b) found that the rank order of potencies for blockade of LSD-like stimulus effects by 5-HT_2 antagonists parallels their binding affinities for the 5-HT_{2A} receptor (r = 0.95) but not for the 5-HT_{2C} receptor (r = −0.29). In sum, it appears that the hallucinogen discriminative stimulus is mediated by the 5-HT_{2A} receptor and not by the 5-HT_{2C} receptor.

6.1.2 Complex Stimulus Effects of LSD—Numerous studies, cited above, demonstrate that the interoceptive state governing hallucinogen discrimination in animals is mediated primarily by 5-HT_{2A} receptor interactions. Although the phenylalkylamines and the indoleamines act *via* a common 5-HT_{2A} mechanism, the former agents have high affinity only for 5-HT_2 receptors and therefore produce a discriminative stimulus which is less complex and more selective than that of the indoleamines (Fiorella et al., 1995b; Glennon, 1988). For example, Fiorella and colleagues (Fiorella et al., 1995b) examined the correlation between the 5-HT_{2A} affinity of ten 5-HT antagonists and their median effective dose (ID_{50} values) for blocking the LSD stimulus and found that 5-HT_{2A} receptor affinity alone could only account for 56% of the variance in the LSD-antagonist potencies of the compounds; however, interactions with the 5-HT_{2C} receptor did not account for the remaining variability in antagonist potency. In contrast to the above findings, variance in the potency for inhibiting *R*-(–)-DOM substitution in LSD-trained animals was almost completely accounted for by 5-HT_{2A} affinity (Fiorella et al., 1995b). These data support the notion that LSD evokes a compound stimulus, whereas the phenylalkylamine cue displays greater selectivity with respect to the 5-HT_{2A} receptor. Moreover, there is considerable evidence that higher doses of antagonists are consistently required to block the LSD discriminative stimulus than

are required to block phenylalkylamine-induced stimulus control (Meert, 1996; Fiorella et al., 1995a; Koek et al., 1992). Indeed, while cinanserin potently antagonizes DOM and mescaline, it is much less effective against LSD- and 5-MeO-DMT-appropriate responding (Young et al., 1986; Glennon et al., 1983a; Kuhn et al., 1978). Such findings are indicative of the complex nature of the LSD cue.

LSD evokes a compound stimulus; although the most salient component of the LSD stimulus is transduced through the 5-HT_{2A} receptor, it appears that ancillary interactions with other monoamine receptors are responsible for secondary non-essential components of the LSD stimulus complex (Marona-Lewicka and Nichols, 1995; Meert et al., 1989; Winter and Rabin, 1988). The secondary elements of the LSD cue have been attributed to occupation of 5-HT_{1A} receptors (Marona-Lewicka and Nichols, 1995; Winter and Rabin, 1988) and DA D_2 receptors (Meert, 1996; Meert et al., 1989; Minnema and Rosecrans, 1984; Appel et al., 1982). As with any drug possessing complex stimulus properties, the nature of the LSD discriminative stimulus will vary depending upon the training and testing conditions.

There is considerable evidence that the 5-HT_{1A} subtype contributes to the discriminative effects of LSD. It has been reported that LSD, at a dose of 0.48 μmol/kg, elicits intermediate levels of drug-lever selection in rats trained with 1.2 μmol/kg 8-OH-DPAT (Arnt, 1989). Unfortunately, trials with larger doses of LSD were precluded because the partial generalization was accompanied by severe disruption of behavior. When ipsapirone was tested in LSD-discriminating rats it occasioned a maximum of 71% drug-lever responding (i.e., partial substitution; Arnt, 1989). 8-OH-DPAT has also been shown to produce partial substitution in rats and mice trained to discriminate LSD (Winter and Rabin, 1988; Benneyworth et al., 2005; Reissig et al., 2005). Interestingly, data from drug discrimination studies with yohimbine reveal that this drug can fully substitute for LSD in rats (Colpaert, 1984; Marona-Lewicka and Nichols, 1995; Appel et al., 1999), though this finding has been disputed by Winter (Winter, 1978; Fiorella et al., 1995c). Although normally classified as a α_2-adrenoceptor antagonist, yohimbine actually displays comparable affinities for α_2-adrenoceptors and 5-HT_{1A} sites (Winter and Rabin, 1992). Cross-substitution has been observed to occur between yohimbine, 8-OH-DPAT, and ipsapirone (Winter and Rabin, 1992; Sanger and Schoemaker, 1992; Winter, 1988), indicating that the yohimbine discriminative stimulus is mediated primarily by the 5-HT_{1A} receptor (Winter and Rabin, 1992). Given these facts, the observation by Marona-Lewicka and Nichols (1995) that yohimbine but not the selective α_2-adrenoceptor antagonist RS 2026-197 substitutes for LSD indicates that there is a 5-HT_{1A}-mediated stimulus component common to both yohimbine and LSD.

LSD binds to DA D_1, D_2, D_3, D_4, and D_5 receptors with high affinity (Marona-Lewicka et al., 2009; Nichols et al., 2002; Watts et al., 1995; Table III), and acts as a partial agonist at DA D_1 and D_2 receptors (Seeman et al., 2009; Watts et al., 1995) and as a full agonist at DA D_4 receptors (Marona-Lewicka et al., 2009). There is some evidence that interactions with DA receptors contribute to the LSD cue. For example, rats trained with 0.25 mg/kg of the DA D_1/D_2 agonist apomorphine respond to LSD with partial generalization (Appel et al., 1982). However, although the apomorphine cue is antagonized by the D_2 antagonist haloperidol but not the 5-HT antagonist pizotifen, substitution of LSD for apomorphine could be blocked by pizotifen but not haloperidol, implicating serotonergic mechanisms rather than dopaminergic mechanisms in the substitution. The mixed 5-HT_{2A}/D_2 antagonist risperidone blocks the LSD cue with much greater potency than the 5-HT_2 antagonist ritanserin. Specifically, risperidone blocks LSD discrimination with 414 times the potency of ritanserin (Meert, 1996; Meert and Awouters, 1991; Meert et al., 1990), a finding that is surprising because risperidone has only slightly higher affinity for the 5-HT_{2A} receptor than

ritanserin (Leysen, 1990). Although 0.63 mg/kg ritanserin produces full occupation of 5-HT_{2A} sites, it fails to attenuate the LSD stimulus; ritanserin must be administered at 40 mg/kg to completely antagonize the LSD cue, and at that dose ritanserin produces significant occupation of catecholamine receptors (Koek et al., 1992; Meert et al., 1990). By contrast, risperidone and ritanserin display nearly identical potencies as antagonists of the DOM cue (Meert, 1996). These findings indicate that both 5-HT_{2A} and DA D_2 receptor interactions contribute to the interoceptive state governing LSD discrimination, whereas only the 5-HT_{2A} receptor is involved in DOM discrimination. Supporting this conclusion is the fact that the potency of ritanserin as an antagonist of LSD stimulus control is markedly potentiated when administered in combination with low doses of haloperidol (Meert and Awouters, 1991). Stimulus antagonism studies have shown that DA antagonists alone have no effect on the discriminability of LSD (Kuhn et al., 1978; White and Appel, 1982). Therefore, it appears that the LSD cue is most effectively and potently antagonized by concurrent blockade of 5-HT_{2A} and DA sites. In this regard, risperidone is similar in potency to the combination of ritanserin and haloperidol.

Recent reports indicate that that the dopaminergic component of the LSD discriminative stimulus is time-dependent (Marona-Lewicka et al., 2005). Drug discrimination studies using LSD as the training drug have typically used 15–30 min pretreatment times, and have shown consistently that 5-HT_{2A} antagonists block LSD-induced stimulus control. However, when rats are trained to discriminate LSD with a longer 90 min pretreatment time, the resulting stimulus cue evoked by LSD is mediated by D_2-like receptors and not by 5-HT_{2A} receptors (Marona-Lewicka and Nichols, 2007; Marona-Lewicka et al., 2009). These findings demonstrate that the stimulus effects of LSD occur in two temporal phases, the first phase involving 5-HT_{2A} receptors and the second involving DA receptors. It is not clear whether the delayed dopaminergic cue is a direct effect of LSD or is produced by a LSD metabolite with selective DA agonist activity.

6.1.3 Complex stimulus effects of indolealkylamine hallucinogens—Similar to LSD, certain hallucinogenic indolealkylamines produce stimulus effects that are both DOM- and 8-OH-DPAT-like. For instance, the hallucinogen 5-methoxy-*N*,*N*-dipropyltryptamine (5-MeO-DPT), which displays nearly identical affinities for 5-HT_{1A} receptors (K_i= 4.0 nM) and agonist-labeled 5-HT_{2A} receptors (K_i= 7.1 nM), produces complete generalization in animals trained with DOM and in animals trained with 8-OH-DPAT (Glennon et al., 1988b). The 5-MeO-DMT discriminative stimulus also involves 5-HT_{1A}-and 5-HT_{2A}-mediated components. Generalization occurs between DOM, LSD, and 5-MeO-DMT regardless of which is used as the training drug. Winter and Rabin (1988) proposed that the ability of 5-MeO-DMT to substitute for DOM involves 5-HT_{2A} receptors whereas the ability of 5-MeO-DMT to substitute for LSD involves both 5-HT_{1A} and 5-HT_{2A} receptors. Not only do the discriminative stimulus properties of 5-MeO-DMT vary depending upon conditions of training and testing, however, but may also depend upon the dose of 5-MeO-DMT. Nevertheless, there is evidence that 5-MeO-DMT-induced stimulus control primarily involves 5-HT_{1A} receptors, with 5-HT_{2A} receptors playing only a secondary role (Winter et al., 2000; Schreiber and DeVry, 1993; Spencer et al., 1987). This conclusion is consistent with the fact that the behavioral response to the drug in rats and mice is predominantly 5-HT_{1A}-mediated (Lucki et al., 1984; Tricklebank et al., 1985; Smith and Peroutka, 1986; Berendsen et al., 1989; Eison and Wright, 1992; Sanchez et al., 1996; Krebs-Thomson et al., 2006; Halberstadt et al., 2010). The 5-MeO-DMT discriminative stimulus completely generalizes to 8-OH-DPAT and ipsapirone (Winter et al., 2000; Schreiber and DeVry, 1993; Spencer et al., 1987), and the ability of these and other agents to substitute for 5-MeO-DMT is correlated with their 5-HT_{1A}, but not 5-HT_{2A}, affinities (Spencer et al., 1987). Both WAY 100635 and pindolol antagonize the 5-MeO-DMT cue and its generalization to 8-OH-DPAT and ipsapirone (Winter et al., 2000; Spencer et al., 1987). By contrast, the 5-HT_2 antagonists

pirenperone, ketanserin, and ritanserin are much less effective antagonists. Several studies have shown that 5-MeO-DMT evokes intermediate levels of 8-OH-DPAT-like responding followed by considerable behavioral disruption at higher doses (Schreiber and DeVry, 1993; Arnt, 1989; Glennon, 1986). After pretreatment with ketanserin, however, 5-MeO-DMT engenders complete substitution in 8-OH-DPAT-trained animals (Fozard et al., 1986). As such, it would appear that the 5-HT_{2A} agonist activity of 5-MeO-DMT is responsible for the behavioral disruption. There is other evidence that 5-HT_{2A} receptor activation can disrupt 5-HT_{1A}-mediated stimulus control: response rates are severely depressed when animals trained to discriminate 8-OH-DPAT are given DOM in combination with the training drug (Arnt, 1989). Interestingly, administration of 5-MeO-DMT to animals trained with ipsapirone results in full drug-appropriate responding (Spencer and Traber, 1987). This observation raises the question of why 5-MeO-DMT disrupts responding in 8-OH-DPAT-trained animals but not in ipsapirone-trained animals. Given that ipsapirone is a less efficacious 5-HT_{1A} agonist than is 8-OH-DPAT (Dumuis et al., 1988), the most plausible explanation is that whereas low, non-disruptive doses of 5-MeO-DMT can fully mimic ipsapirone, 5-MeO-DMT fails to fully mimic 8-OH-DPAT because the doses required to evoke full substitution also induce significant 5-HT_{2A} receptor activation, leading to behavioral disruption.

There is also evidence that the hallucinogen DPT produces a discriminative stimulus that is mediated by interactions with both 5-HT_{2A} and 5-HT_{1A} receptors. DPT produces complete generalization in rats trained with DOM (Li et al., 2007; Li et al., 2009) and partial generalization in animals trained with LSD (Fantegrossi et al., 2008), effects that are fully blocked by M100907. However, in animals trained to discriminate 1.5 mg/kg DPT, pretreatment with a combination of WAY-100,635 and M100,907 was much more effective at antagonizing stimulus control than was either antagonist given alone, indicating that DPT elicits a compound stimulus involving both 5-HT_{1A} receptor- and 5-HT_{2A} receptor-mediated components (Fantegrossi et al., 2008). Likewise, although psilocybin-induced stimulus control is mediated primarily by the 5-HT_{2A} receptor, with the 5-HT_{1A} receptor playing no apparent role (Winter et al., 2007), the ability of DPT to evoke partial generalization in animals trained with psilocybin appears to involve interactions with both 5-HT_{1A} and 5-HT_{2A} receptors (Fantegrossi et al., 2008).

6.2 5-HT Behavioral Syndrome

Administration of 8-OH-DPAT to rats produces a 5-HT behavioral syndrome that includes flat body posture, reciprocal forepaw treading, hindlimb abduction, and lateral head weaving (Hjorth et al., 1982; Smith and Peroutka, 1986). The behavioral effects of 8-OH-DPAT are very similar to those produced by treatment with a 5-HT precursor in combination with a monoamine oxidase (MAO) inhibitor (Grahame-Smith, 1971). Indoleamine hallucinogens, including 5-MeO-DMT, LSD, and DPT, can also induce components of this behavioral syndrome (Li et al., 2007; Tricklebank et al., 1985; Trulson et al., 1976). By contrast, phenylalkylamine hallucinogens do not reliably produce the 5-HT behavioral syndrome. The ability of 8-OH-DPAT and 5-MeO-DMT to induce the 5-HT behavioral syndrome is blocked by WAY-100635 and pindolol, and therefore the syndrome is likely mediated by 5-HT_{1A} receptors (Tricklebank et al., 1984, 1985; Sanchez et al., 1996). It appears that these 5-HT_{1A} receptors are located postsynaptically because destruction of central serotonergic projections with 5,7-DHT does not prevent 5-MeO-DMT and LSD from inducing the behavioral syndrome (Sloviter et al., 1978; Trulson et al., 1976). Compared to the doses of LSD and 5-MeO-DMT that inhibit DRN firing, relatively high doses of those indoleamines are required to induce the 5-HT behavioral syndrome. For example, although 75 μg/kg (IP) LSD completely inhibits the firing of serotonergic DRN neurons in rats (Gallagher and Aghajanian, 1975), much higher doses of LSD (400–1000 μg/kg) are required to induce

hindlimb abduction, head weaving, and forepaw treading (Trulson et al., 1976). This discrepancy probably reflects the fact that for 5-HT_{1A} receptors there is a large receptor reserve present in the DRN but not in postsynaptic regions (Yocca et al., 1992). Indeed, although the 5-HT_{1A} partial agonists buspirone, ipsapirone, and gepirone inhibit the firing of DRN neurons (and thus behave as full agonists presynaptically), they block the ability of 8-OH-DPAT and 5-MeO-DMT to induce the behavioral syndrome (Smith and Peroutka, 1986; Scott et al., 1994).

The 5-HT_{1A} agonists 8-OH-DPAT, buspirone, ipsapirone, flesinoxan, and lisuride induce lower lip retraction (LLR) in rats (Marona-Lewicka et al., 2002; Berendsen et al., 1989; Joordens et., 1998; Berendsen and Broekkamp, 1987). WAY-100,635 blocks LLR induced by 8-OH-DPAT, demonstrating that this behavioral response involves activation of 5-HT_{1A} receptors (Joordens et al., 1998). Microinjection of 8-OH-DPAT directly into the MRN induces LLR, indicating that 5-HT_{1A} receptors expressed by MRN neurons are responsible for mediating this behavior (Berendsen et al., 1994). Interestingly, 5-MeO-DMT and DPT induce LLR only in animals that have been pretreated with a 5-HT_{2A} antagonist (Berendsen et al.,, 1989; Li et al., 2007). It has also been shown that DOI and the 5-HT_{2C} agonist *m*-chlorophenylpiperazine (mCPP) can attenuate lower lip retraction induced by 8-OH-DPAT (Kleven et al., 1997), indicating that 5-HT_{2A} and/or 5-HT_{2C} receptors act to attenuate the behavioral effects of 5-HT_{1A} receptor activation. These findings indicate that the activity of 5-MeO-DMT and DPT at 5-HT_2 receptors acts to functionally antagonize LLR induced by 5-HT_{1A} receptor activation.

6.3 Exploratory and Investigatory Behavior

Tests of drug effects on locomotor activity have been used frequently to assess psychoactive agents for stimulant or depressant activity. However, studies examining the effects of hallucinogens on behavior in an open field produce inconsistent results and fail to distinguish the effects of hallucinogens from those of other drug classes (Brimblecombe, 1963; Cohen and Wakeley, 1968; Kabes et al., 1972; Silva and Calil, 1975). Given the complex nature of hallucinogen effects, it is not surprising that the locomotor paradigm produces inconclusive results because it does not provide a qualitative assessment of behavior and fails to assess whether changes in sensitivity to environmental stimuli contribute to the behavioral effect. The Behavioral Pattern Monitor (BPM) is a combination of activity and holeboard chambers that provides quantitative and qualitative measures of unconditioned locomotor and investigatory activity in rats, and can be used to assess for changes in the response of animals to environmental stimuli (Geyer et al., 1986). Statistical assessment of the geometrical and dynamical structure of motor behavior in the BPM has proven very useful in characterizing drug effects in rats (Geyer 1982, 1990; Geyer et al 1986; Gold et al 1988; Geyer and Paulus 1992). Using the BPM it is possible to differentiate statistically the effects of various stimulants at doses that produce comparable increases in locomotion but marked differences in qualitative aspects of behavior involving spatiotemporal patterns of locomotion and investigatory responses directed at specific environmental stimuli (Geyer et al 1986, 1987; Gold et al 1989; Geyer and Paulus 1992, 1996; Geyer and Callaway 1994).

6.3.1 Effects of hallucinogens on exploratory and investigatory behavior in rats—

When phenylalkylamine (mescaline, DOM, DOI, and DOET) and indolealkylamine (psilocin, DMT, 5-MeO-DMT, and 5-methoxy-α-methyltryptamine) hallucinogens are tested in rats in a novel BPM environment they produce a characteristic behavioral profile: (1) there is reduced locomotor activity; (2) the frequency of investigatory behaviors (rearings and holepokes) is diminished; and (3) avoidance of the center of the BPM chamber is increased (Geyer et al., 1979; Adams and Geyer, 1985a; Wing et al., 1990; Hameleers et al.,

2007). Figure 3 illustrates the behavioral profile of psilocin in the BPM. The effects of hallucinogens are not observed when animals are tested in a familiar environment, and thus likely reflect potentiation of the neophobia displayed by rats in a novel environment. It has been theorized that the diminution of the behavioral effects of hallucinogens in a familiar test environment occurs because hallucinogen-treated animals are more willing to explore the BPM chambers once the stimuli associated with the test environment become less threatening due to habituation. LSD has similar effects on investigatory behavior and center entries (Adams and Geyer, 1985b), but it has biphasic effects on locomotor behavior with activity initially suppressed and then increasing over time (Mittman and Geyer, 1991). Mescaline and DOM can also produce biphasic effects on locomotor activity, but this occurs only after relatively high doses are administered (100 mg/kg and ≥5 mg/kg, respectively; Yamamoto and Ueki, 1975; Palenicek et al., 2008). The effects of hallucinogens on investigatory and exploratory behavior in the BPM are distinct from those produced by other drug classes, including lisuride (Adam and Geyer, 1985c), 5-HT releasers such as 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) (Gold et al., 1988; Callaway et al., 1990; Paulus and Geyer, 1992), 5-HT_1 agonists (Mittman and Geyer, 1989; Rempel et al., 1993), psychostimulants (Geyer et al., 1986, 1987), and NMDA antagonists (Lehmann-Masten and Geyer, 1991; Bakshi et al., 1999)

Pretreatment with the 5-HT_2 antagonists ritanserin and ketanserin blocks the effects of DOI, DOM, and mescaline in the BPM (Wing et al., 1990; Mittman and Geyer, 1991). The effects of DOI are blocked by M100907 but not by the selective 5-$HT_{2C/2B}$ antagonist SER-082, and are therefore likely mediated by the 5-HT_{2A} receptor and not by the 5-HT_{2C} receptor (Krebs-Thomson et al., 1998). The action of the indoleamines in the BPM is more complex mechanistically. The initial suppression of locomotor activity induced by LSD is blocked by 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), whereas ritanserin (Mittman and Geyer, 1991) and M100907 (Ouagazzal et al., 2001) block LSD-induced hyperactivity . Thus, both 5-HT_{1A} and 5-HT_{2A} receptors appear to contribute to the behavioral effects of LSD in the BPM, and this finding is supported by the fact that chronic treatment with either 8-OH-DPAT or DOI produces cross-tolerance with LSD in this behavioral paradigm (Krebs and Geyer, 1994). The effects of low doses of 5-MeO-DMT are antagonized by WAY-100635 but not by M100907 (Krebs-Thomson et al., 2006), and thus are likely mediated by 5-HT_{1A} receptors. However, when 5-MeO-DMT is administered in combination with a behaviorally inactive dose of a MAO_A inhibitor such as harmaline, clorgyline, or pargyline, it produces LSD-like delayed hyperactivity that is blocked by the 5-HT_{2A}-selective antagonist MDL 11,939 and is sensitive to the novelty of the testing environment (Halberstadt et al., 2008). Thus, both 5-HT_{1A} and 5-HT_{2A} receptors mediate the effects of LSD and 5-MeO-DMT in the BPM.

6.3.2 Effects of hallucinogens on exploratory and investigatory behavior in mice—The original BPM was designed for rats, but we have also tested hallucinogens in a mouse version of the BPM (Risbrough et al., 2006; Halberstadt et al., 2009). In mice, DOI, mescaline, DOM, DOET, and DOPR reduce investigatory behavior and produce effects on locomotor activity that follow an inverted U-shaped dose-response function, with low and moderate doses increasing activity and higher doses decreasing activity (Halberstadt et al., 2009; Halberstadt et al., in preparation). The increase in locomotor activity induced by 1.0 mg/kg DOI or 25 mg/kg mescaline is absent in 5-HT_{2A} receptor knockout mice, suggesting the involvement of 5-HT_{2A} receptors. Conversely, the reduction in locomotor activity produced by 10 mg/kg DOI is potentiated in 5-HT_{2A} knockout mice and attenuated by SER-082, indicating that the decrease in activity is mediated by the 5-HT_{2C} receptor. This conclusion is supported by the fact that selective 5-HT_{2C} agonists decrease locomotor activity in mice (Halberstadt et al., 2009; Fletcher et al., 2009). By contrast to the

phenylalkylamine hallucinogens, psilocin, DMT, 5-MeO-DMT, and LSD produce decreases in locomotor activity, investigatory behavior, and time spent in the center of the mouse BPM chambers (Halberstadt et al., 2010; Halberstadt et al., unpublished observations). The effects of psilocin and 5-MeO-DMT are blocked by WAY-100635 but are not altered by the selective 5-HT_{2C} antagonist SB 242,084 or by 5-HT_{2A} receptor gene deletion. Thus, the effects of indoleamines in the mouse BPM are mediated by 5-HT_{1A} receptors, whereas the effects of the phenylalkylamines are mediated by 5-HT_{2A} and 5-HT_{2C} receptors. Figure 4 compares the effects of DOM and 5-MeO-DMT on locomotor activity in the mouse BPM. These studies demonstrate that phenylalkylamine and indoleamine hallucinogens produce disparate effects on exploratory and investigatory behavior in mice, behavioral differences that are not readily apparent when these agents are studied in rats.

6.4 Prepulse Inhibition of Startle

Prepulse inhibition (PPI) describes the phenomenon where the startle response is attenuated when preceded by a weak prestimulus. PPI has been used as an operational measure of sensorimotor gating and has been found to be deficient in patients with a variety of psychiatric illnesses, including schizophrenia. LSD, DOI, DOB, mescaline, and 5-MeO-DMT disrupt PPI in rats (Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1994; Johansson et al., 1995; Varty and Higgins, 1995; Ouagazzal et al., 2001; Krebs-Thomson et al., 2006; Palenicek et al., 2008; Halberstadt and Geyer, 2010). The decrease in PPI induced by DOI and LSD is blocked by the highly selective 5-HT_{2A} antagonists M100907 and MDL 11,939 but not by the 5-HT_{2C} antagonist SB 242,084, the 5-$HT_{2C/2B}$ antagonist SER-082, or the 5-HT_{1A} antagonist (+)WAY-100135 (Sipes and Geyer, 1995a; Ouagazzal et al., 2001; Halberstadt and Geyer, 2010), demonstrating the involvement of 5-HT_{2A} receptors. In comparison with DOI and LSD, the mechanism for the effect of 5-MeO-DMT on PPI in rats is more complex: the effect of 5-MeO-DMT is attenuated by pretreatment with either SER-082 or WAY-100,635, but not by M100907 (Krebs-Thomson et al., 2006). The non-hallucinogenic LSD congener lisuride also disrupts PPI in rats, and thus can be considered to be a LSD false-positive (Halberstadt and Geyer, 2010). However, LSD and lisuride disrupt PPI in rats via distinct mechanisms, and the effect of lisuride is blocked by the selective DA D_2/D_3 antagonist raclopride but is unaffected by pretreatment with MDL 11,939 (Halberstadt and Geyer, 2010). This finding indicates that the 5-HT_{2A} agonist activity of lisuride does not contribute to the effects of the drug on PPI.

The effects of DOI on PPI in rats appear to be mediated specifically by actions in the ventral pallidum, since bilateral infusion of DOI directly into the ventral pallidum but not into the nucleus accumbens produces disruption of PPI (Sipes and Geyer, 1997). It is likely that the effects of DOI on PPI are mediated by activation of 5-HT_{2A} receptors in the ventral pallidum because local infusion of M100907 attenuated the effects of systemic DOI on PPI. However, the possibility remains that dopamine receptors in the ventral pallidum or in other brain regions may play a downstream role in the PPI-disruptive effects of DOI because haloperidol and raclopride can also block the effect of systemic DOI on PPI (Sipes and Geyer, 1994; Halberstadt and Geyer, unpublished observations). It is not currently clear whether the ventral pallidum plays a role in mediating the ability of LSD and 5-MeO-DMT to disrupt PPI in rats.

Activation of 5-HT_{1A} receptors has opposing effects on sensorimotor gating in rats and mice. In rats, selective 5-HT_{1A} agonists such as 8-OH-DPAT, buspirone, gepirone, and ipsapirone decrease PPI (Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1995b). Conversely, in 129/SV and Balb/c mice, treatment with 8-OH-DPAT increases PPI (Dulawa et al., 1998; Dulawa et al., 2000; Gogos et al., 2008). The ability of 8-OH-DPAT to increase PPI is blocked by the 5-HT_{1A} antagonist WAY-100,635 and is absent in 5-HT_{1A} knockout mice. Interestingly, we have found that 5-MeO-DMT and psilocin produce dose-dependent

increases in PPI in 129/SvEv mice (Powell et al., 2003; Fig. 5A,B). The ability of 5-MeO-DMT to increase PPI was partially attenuated by pretreatment with 1.0 mg/kg WAY-100,635, indicating that 5-HT_{1A} receptors are involved in mediating this effect (Fig. 5C).

Clinical studies have demonstrated that psilocybin can alter PPI in human volunteers. Gouzoulis-Mayfrank et al (1988) reported that psilocybin increases PPI in humans when an interstimulus interval (ISI) of 100 ms was used for the prepulse trials. However, Vollenweider et al. (2007) found that psilocybin increases PPI at long ISIs (120–2000 ms) but reduces PPI when shorter ISIs of 30 ms are used. Thus, the effects of psilocybin on PPI are dependent on the testing parameters. The receptor mechanism(s) responsible for the effects of psilocybin on PPI in humans have not yet been investigated. In contrast to the effect of psilocybin, administration of DMT by continuous i.v. infusion (Heekeren et al., 2007) or orally as a component of *ayahuasca* (Riba et al., 2002) has no effect on PPI in human subjects.

6.5 Head Twitch Response

Corne and Pickering reported in 1967 that a variety of hallucinogens, including LSD, psilocybin, psilocin, DMT, and mescaline, produce a head twitch response (HTR) in mice consisting of a paroxysmal rotational movement of the head (Corne and Pickering, 1967). This behavior had been observed previously to occur after systemic administration of the 5-HT precursor 5-hydroxytryptophan (Corne et al., 1963). It was subsequently demonstrated that LSD, 5-MeO-DMT, DOM, and mescaline also induce the HTR when administered to rats (Yamamoto and Ueki, 1975; Bedard and Pycock, 1977). In rats, the HTR often involves not only the head but also the neck and trunk of the animal, and thus the behavior has also been referred to as the wet-dog shake in that species (Bedard and Pycock, 1977).

Evidence linking the HTR to the 5-HT_{2A} receptor emerged almost immediately after 5-HT_{2A} binding sites were first detected by radioligand binding studies (Peroutka and Snyder, 1979; Peroutka et al., 1981). Specifically, Leysen reported in 1982 that there is a significant correlation ($r = 0.88$) between the 5-HT_{2A} affinity of a series of 19 5-HT antagonists and their potency for blocking mescaline-induced HTR in rats (Leysen et al., 1982). It was later shown that the ability of 5-HT antagonists to block the HTR induced by DOI is also significantly correlated ($r = 0.83$) with 5-HT_{2A} affinity (Schreiber et al., 1995). Studies have also demonstrated that the HTR evoked by DOI in rats is blocked by the selective 5-HT_{2A} antagonist M100907 but not by the selective 5-HT_{2C} antagonist SB 242,084 or the mixed 5-$HT_{2C/2B}$ antagonist SB 200,646A (Schreiber et al., 1995; Vickers et al., 2001). Likewise, HTR induced by DPT, 5-MeO-DIPT, and TCB-2 in mice is blocked by M100907 and MDL 11,939 (Fantegrossi et al., 2006, 2008; Fox et al., 2009). It has also been reported that 5-HT_{2A} knockout mice do not display the HTR in response to administration of LSD, DOI, DOM, DOB, mescaline, psilocin, 1-methylpsilocin, DMT, or 5-MeO-DMT (Gonzalez-Maeso et al., 2007; Keiser et al., 2009; Halberstadt et al., 2010), conclusively linking the HTR to 5-HT_{2A} activation. Further, genetic restoration of the 5-HT_{2A} receptor to the cortex of 5-HT_{2A} knockout mice restores the ability of LSD to induce the HTR (Gonzalez-Maeso et al., 2007)

Expression of 5-HT_{2A} receptor-induced HTR can be modified by activity at a variety of receptors, including 5-HT_{1A}. Selective 5-HT_{1A} agonists, including 8-OH-DPAT, attenuate the HTR induced by DOI in mice and rats (Arnt and Hyttel, 1989; Heaton and Handley, 1989; Darmani et al., 1990a; Schreiber et al., 1995; Willins and Meltzer, 1997). Furthermore, although 5-MeO-DMT induces the HTR, pretreatment with 5-MeO-DMT dose-dependently reduces DOI-induced HTR in mice (Darmani et al., 1990a). This finding raises the possibility that activation of the 5-HT_{1A} receptor by 5-MeO-DMT and other

indoleamines may attenuate their ability to induce the HTR. Experiments with LSD, however, demonstrate that the response to the drug is not altered by deletion of the 5-HT_{1A} receptor gene (Gonzalez-Maeso et al., 2007). Given the especially potent 5-HT_{1A} agonist activity of 5-MeO-DMT, additional studies are needed to determine whether the 5-MeO-DMT dose-response for HTR is altered in 5-HT_{1A} knockout mice. Finally, it is important to note that some discrepancies exist regarding the interaction between 5-HT_{1A} receptors and 5-HT_{2A}-induced HTR; indeed, whereas WAY-100,635 can potentiate DOI-induced HTR in rats (Willins and Meltzer, 1997), it has also been reported that WAY-100,635 can antagonize DPT-induced HTR in mice (Fantegrossi et al., 2008). It is not clear whether this discrepancy reflects species differences or is indicative of pharmacological differences between phenylalkylamines and indoleamines. This issue is further complicated by the fact that 5-HT_{1A} antagonists such as WAY-100635 and *S*-(-)-UH-301 can themselves provoke HTR in mice through a mechanism that purportedly involves elevation of 5-HT release and subsequent 5-HT_{2A} receptor activation (Darmani and Reeves, 1996; Darmani, 1998).

There is also evidence that the 5-HT_{2C} receptor can regulate the HTR induced by 5-HT_{2A} receptor activation. The 5-HT_2 agonist Ro 60-0175, which is ~30-fold selective for 5-HT_{2C} receptors *vs* 5-HT_{2A} receptors (Martin et al. 1998), does not induce the HTR in rats unless administered in combination with SB 242,084 (Vickers et al. 2001). This finding indicates that the ability of Ro 60-0175 to induce the HTR via 5-HT_{2A} receptor activation is suppressed by its interaction with the 5-HT_{2C} receptor. Ro 60-0175 has also been shown to inhibit the HTR induced by DOI in mice (Fantegrossi et al., 2010). Fantegrossi and colleagues have reported that the HTR induced by DOI, 2C-T-7, DPT, and 5-MeO-DIPT in NIH Swiss and Swiss-Webster mice typically follows an inverted U-shaped dose-response function (Fantegrossi et al., 2005, 2006, 2008, 2010). The descending limb of the DOI response is shifted to the right by SB 242,084, indicating that the 5-HT_{2C} receptor is responsible for the inhibition of HTR that occurs at higher doses (Fantegrossi et al., 2010). By contrast, it has been reported that 5-HT_{2C} knockout mice display a significant reduction in DOI-induced HTR (Canal et al., 2010). Although compensatory developmental adaptations in 5-HT_{2C} knockout mice may have contributed to these contradictory findings, the same investigators found that pretreatment with SB 242,084 reduced the magnitude of the HTR to DOI in C57BL/6J and DBA/2J mice (Canal et al., 2010). It is not clear why those two groups obtained such discrepant results with DOI in animals pretreated with SB 242,084, but the fact that the studies used different strains of mice may have been a contributing factor. It has been reported that there are strain differences in 5-HT_{2C} receptor mRNA editing (Calcagno and Invernizzi, 2010; Hackler et al., 2006). Editing of 5-HT_{2C} receptor mRNA can dramatically alter G-protein coupling (Burns et al., 1997), and thus differences in 5-HT_{2C} editing could potentially alter how 5-HT_{2A} and 5-HT_{2C} receptors interact in different strains of mice.

6.6 Ear Scratch Response

Deegan and Cook first reported in 1958 that administration of mescaline produces stereotypic hindlimb scratching of the head and ears in mice but not in other species (Deegan and Cook, 1958). Later work showed that DOM, DOI, DOET, and the 4-ethoxy analog of mescaline (escaline) also induce the ear-scratch response (ESR) (Kulkami et al., 1973; Yim et al., 1979; Darmani et al., 1990b; Gonzalez-Maeso et al., 2007). It appears that the ESR is mediated by 5-HT_{2A} receptors, because the effect of DOI is blocked by ketanserin and spiperone (Darmani et al., 1990b). It should be noted that the ESR is not induced by indoleamine hallucinogens (Yim et al., 1979). In fact, LSD and 5-MeO-DMT actually block the ESR induced by mescaline, DOM, and DOI (Chen and Bohner, 1960; Borsey et al., 1964; Darmani et al., 1990b). Based on the finding that the DOI-induced ESR is also inhibited by the 5-$HT_{1A/1B}$ agonist RU 24969 but not by the 5-HT_{1A} agonist 8-OH-

DPAT (Darmani et al., 1990b), it appears that blockade of the ESR by the indoleamine hallucinogens involves interactions between 5-HT_{2A} and 5-HT_{1B} receptors. This hypothesis needs to be evaluated by testing indoleamine hallucinogens in 5-HT_{1B} knockout mice or in mice pretreated with a selective 5-HT_{1B} antagonist.

7. Conclusions

Despite the structural differences between indoleamine and phenylalkylamine hallucinogens, these agents evoke a nearly identical spectrum of behavioral effects in rats and provoke similar mental and subjective states in humans. As summarized in this review, it is clear that activation of the 5-HT_{2A} receptor plays a primary mechanistic role in mediating the behavioral effects of the indoleamine and phenylalkylamine classes of serotonergic hallucinogens. Indeed, there is a wide consensus that administration of 5-HT_{2A} antagonists blocks the effects of hallucinogens on HTR, drug discrimination, exploratory and investigatory behavior, and sensorimotor gating in rats. Most importantly, clinical investigations have shown that 5-HT_{2A} antagonists block most, although certainly not all, of the subjective and behavioral effects of psilocybin (Vollenweider et al., 1998; Carter et al., 2005, 2007). Recent experiments have also demonstrated 5-HT_{2A} involvement in the discriminative stimulus effects of hallucinogens in non-human primates (Li et al., 2008). Lastly, there tends to be a strong correlation between the behavioral potencies of hallucinogens in animals and humans and 5-HT_{2A} binding affinity (Glennon et al., 1984; Titeler et al., 1988; Sadzot et al., 1989). Thus, over the last two decades, most research focusing on the mechanism of action for the unitary pharmacological effects of serotonergic hallucinogens has concentrated primarily on effects mediated by 5-HT_{2A} receptors.

It is currently accepted that extremely potent phenylisopropylamine (“amphetamine”) hallucinogens such as DOB and DOI are highly selective for 5-HT_2 sites, and it thus follows quite logically that the behavioral effects of those compounds are likely to be exclusively 5-HT_2-mediated. By contrast, the indoleamine hallucinogens are not 5-HT_2 selective and bind to a much larger set of monoamine receptors. Although the two classes of hallucinogens produce similar effects, it is likely that the ancillary receptor interactions of indoleamine hallucinogens modulate their overall effects on perception, cognition, and behavior. Consistent with the complexity of the binding profiles of indoleamine hallucinogens, there is evidence that the behavioral profiles of these compounds are more complex than those of their phenylalkylamine counterparts.

A large amount of evidence demonstrates that both 5-HT_{1A} and 5-HT_{2A} receptors are responsible for the behavioral effects of indoleamine hallucinogens. This conclusion is derived extensively from drug discrimination studies and from studies on the exploratory and investigatory behavior of rats in the BPM. Additionally, indoleamine hallucinogens elicit behavioral components of the 5-HT syndrome (lateral head weaving, hindlimb abduction, backward locomotion, and lower lip retraction) and direct inhibitory effects on the firing of serotonergic DRN neurons that are rarely, if ever, induced by phenylalkylamine hallucinogens. There is also evidence that 5-HT_1 receptor activation by indoleamines acts to suppress expression of HTR, ESR, and other 5-HT_{2A}-mediated behavioral effects, a conclusion that is supported by some clinical data (Strassman, 1996).

For LSD, DA receptors appear to play an additional role in mediating certain aspects of the behavioral effects of the drug, especially in the drug discrimination paradigm. Freedman has noted that in humans there seems to be a secondary temporal phase of LSD action that involves ideas of reference or paranoid ideation, effects not seen with indolealkylamines or phenylalkylamines (Freedman, 1984). Based on that observation, Nichols and colleagues (Marona-Lewicka et al., 2005) have theorized that the paranoid stage of the LSD

intoxication may be related to the (delayed) dopaminergic discriminative stimulus effects of LSD and the delayed hyperactivity produced by LSD in the rat BPM. Nichols has also suggested that secondary non-5-HT_{2A} receptor-effects of LSD may be at least partially responsible for the exquisitely high behavioral potency of that drug relative to other serotonergic hallucinogens (Nichols, 1997).

In addition to LSD, other hallucinogens have been found to produce biphasic behavioral effects. In rats, the combination of 5-MeO-DMT and a MAO inhibitor produces an initial decrease in locomotor activity followed by a gradual increase in activity that is mediated by 5-HT_{2A} receptors (Halberstadt et al., 2008). Similar findings have been reported for high doses of DOM and mescaline (Yamamoto and Ueki, 1975; Palenicek et al., 2008), although the receptor mechanisms responsible for the biphasic effects of those agents have not been elucidated. We have also found that administration of high doses of phenylalkylamine hallucinogens to mice can produce biphasic locomotor effects that are mediated by 5-HT_{2A} and 5-HT_{2C} receptors. Thus, both indoleamine and phenylalkylamine hallucinogens can produce effects in the drug discrimination and locomotor activity paradigms that occur in discrete temporal phases. Further studies are needed to determine whether pharmacokinetic or pharmacodynamic factors are responsible for the biphasic behavioral profiles displayed by certain hallucinogens.

The finding that hallucinogens are agonists at the 5-HT_{2C} receptor has confounded the hypothesis that these agents act via a 5-HT_{2A}-dependent mechanism. There is a growing consensus, however, that the effects of hallucinogens are not mediated by the 5-HT_{2C} receptor, and it appears that activity at the 5-HT_{2C} receptor actually serves to attenuate many of the behavioral effects of hallucinogens. The ability of DOI to reduce prepulse inhibition in rats is significantly attenuated by treatment with the 5-HT_{2C}-selective agonist WAY-163909 (Marquis et al. 2007). We have shown that 5-HT_{2A} and 5-HT_{2C} receptors exert opposing effects on locomotor activity in mice (Halberstadt et al., 2009). Similar findings have been reported for HTR (Vickers et al., 2001; Fantegrossi et al., 2010). Importantly, recent clinical trials with the selective 5-HT_{2C} agonist lorcaserin for weight loss have shown that this compound does not produce any hallucinogen-like effects (Smith et al., 2009, 2010). Given the lack of significant neuropsychiatric effects of lorcaserin, it appears highly unlikely that hallucinogen binding to 5-HT_{2C} receptors contributes to hallucinogenesis.

Recently, evidence has emerged that there are sometimes substantial differences between the effects of serotonergic and dopaminergic drugs on behaviors in rats and mice that cannot be ascribed to cross-species differences in the behavioral paradigms per se. As an example, PPI studies with DA agonists have shown that pharmacological antagonists and KO mice reveal diametrically opposite effects in mice vs rats (Ralph-Williams et al., 2002; Doherty et al., 2008). Similar species differences have been noted for PPI studies with hallucinogens, with indolealkylamine hallucinogens disrupting PPI in rats but increasing PPI in mouse strains. Indeed, for PPI the mouse results may actually be more predictive of effects of hallucinogens on PPI in humans (Gouzoulis-Mayfrank et al., 1988), although the effects observed in human volunteers are heavily dependent on the testing parameters used (Vollenweider et al., 2007).

We have recently reported evidence that indoleamine and phenylalkylamine hallucinogens evoke distinct effects on exploratory and investigatory behavior in mice. This finding contrasts with data from rats, which showed that the two classes of hallucinogens evoke similar behavioral profiles. In mice, moderate doses of DOI (Halberstadt et al., 2009) and mescaline produce increases in locomotor activity that are mediated by the 5-HT_{2A} receptor. By contrast, indoleamine hallucinogens such as psilocin and 5-MeO-DMT produce

decreases in locomotor activity that are mediated by the 5-HT_{1A} receptor (Halberstadt et al., 2010). These findings demonstrate that it is possible to differentiate these two classes of hallucinogens behaviorally. Further, in light of the PPI data, it appears that mice may be highly sensitive to the 5-HT_{1A}-mediated behavioral effects of indoleamine hallucinogens. Thus, in contrast to rats, mice may serve as a useful rodent species to probe the contribution of 5-HT_{1A} receptors to indoleamine-induced behavioral effects. It is important to note that evidence has been reported previously that phenylalkylamine and indoleamine hallucinogens can be distinguished by their behavioral effects – the former but not the latter class of agents induce the ESR in mice. However, the recent evidence from the mouse BPM is among the first to demonstrate that the two structural classes of hallucinogens can induce distinct behavioral profiles. Additional studies, both in rodents and humans, are necessary to determine the significance of these behavioral differences and to explore whether there are subtle behavioral differences in the human psychopharmacology of these compounds. More generally, there is a need for clinical trials that directly compare the behavioral and subjective effects of a variety of phenylalkylamine and indoleamine hallucinogens in human volunteers. Given the recent resurgence in human testing of hallucinogens, it may be possible to conduct these trials in the near future.

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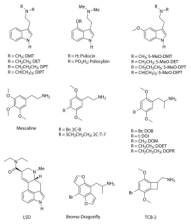

Figure 1.
Chemical structures of indoleamine and phenylalkylamine hallucinogens.

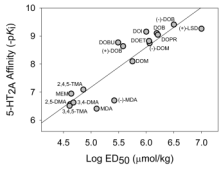

Figure 2.

Relationship between binding affinity at [$_3$H]DOB-labeled 5-HT$_{2A}$ receptors in rat frontal cortex and ED$_{50}$ values for stimulus generalization in rats trained with 1.0 mg/kg DOM (r = 0.90). Data taken from: Titeler et al., 1988. DMA, dimethoxyamphetamine; DOB, 2,5-dimethoxy-4-bromoamphetamine; DOBU, 2,5-dimethoxy-4-butylamphetamine; DOET, 2,5-dimethoxy-4-ethylamphetamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine; DOPR, 2,5-dimethoxy-4-propylamphetamine; LSD, lysergic acid diethylamide; MDA, 3,4-methylenedioxyamphetamine; MEM, 2,5-dimethoxy-4-ethoxyamphetamine; TMA, trimethoxyamphetamine.

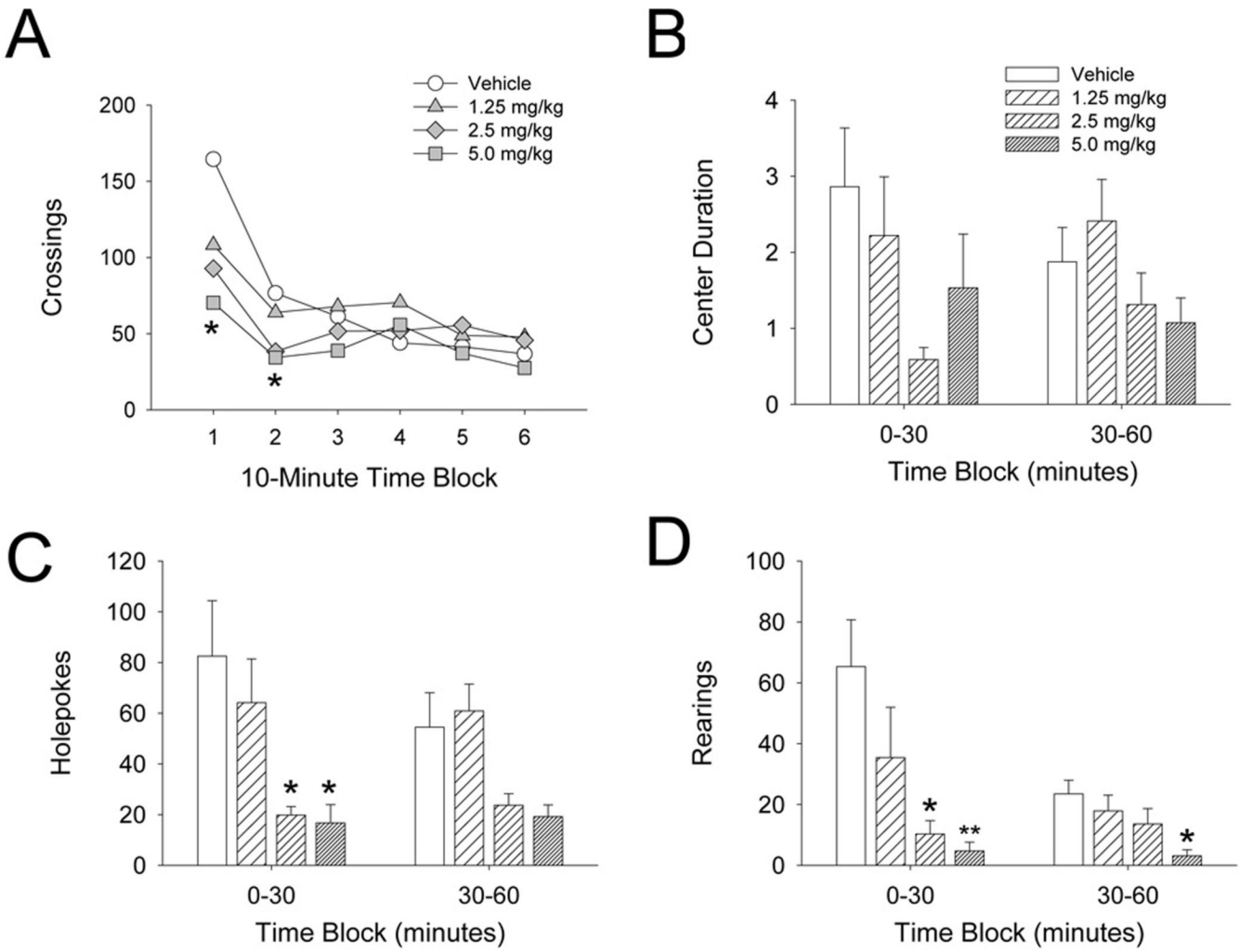

Figure 3.

Effect of psilocin on the exploratory and investigatory behavior of rats in the Behavioral Pattern Monitor (BPM). (A) Effect on crossings, a measure of locomotor activity. (B) Effect on time spent in the center region of the BPM chamber (in minutes). (C) Effect on the number of holepokes. (D) Effect on the number of rearings. Data is shown as mean (A) or mean ± SEM (B–D). *$p<0.05$, **$p<0.01$ versus vehicle control (Tukey's test).

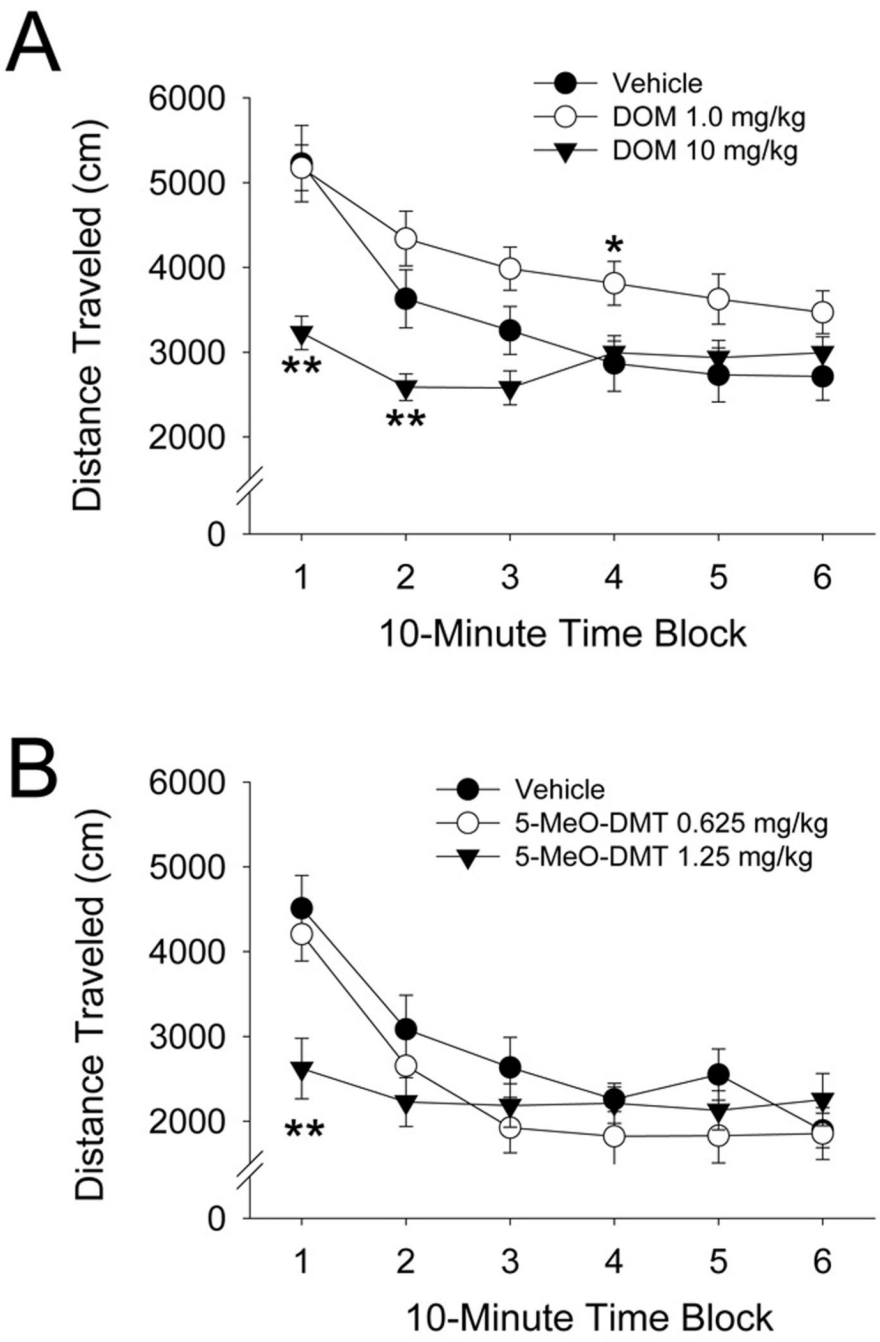

Figure 4.
Effects of DOM hydrochloride (A) and 5-MeO-DMT (B) on locomotor activity (distance traveled) in mice. Data is shown as mean ± SEM. *p<0.05, **p<0.01 versus vehicle control (Tukey's test).

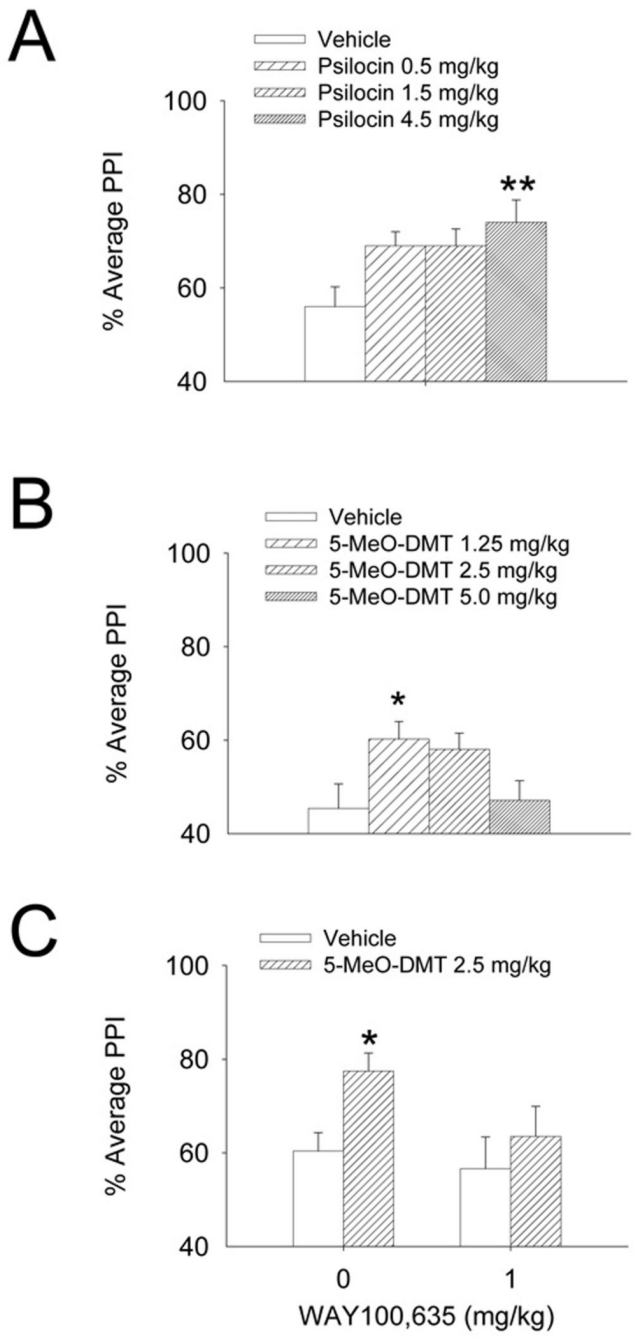

Figure 5.

Effects of 5-MeO-DMT and psilocin on prepulse inhibition of startle (PPI) in 129/SvEv mice. (A) 5-MeO-DMT dose-dependently increased PPI. (B) Psilocin dose-dependently increased PPI. (C) The ability of 5-MeO-DMT to increase PPI was partially reversed by pretreatment with the selective 5-HT_{1A} antagonist WAY-100,635. Data is shown as mean ± SEM. *$p<0.05$, **$p<0.01$ versus vehicle control (Tukey's test).

Table I

Binding of psilocin to 5-HT and other monoamine receptors

Binding site	K_i (nM)[1]
SERT	3801
5-HT_{1A}	567.4
5-HT_{1B}	219.6
5-HT_{1D}	36.4
5-HT_{2A}	107.2
5-HT_{2B}	4.6
5-HT_{2C}	97.3
5-HT_3	> 10,000
5-HT_5	83.7
5-HT_6	57.0
5-HT_7	3.5
α_{1A}	> 10,000
α_{1B}	> 10,000
α_{2A}	1379
α_{2B}	1894
α_{2C}	> 10,000
β_1	> 10,000
D_1	> 10,000
D_2	> 10,000
D_3	2645
D_4	> 10,000
D_5	> 10,000
H_1	304.6

[1] Data from the NIMH Psychoactive Drug Screening Program (http://pdsp.med.unc.edu).

Table II

Binding of DMT to 5-HT receptors

Binding site	K_i (nM)[1]
5-HT_{1A}	183
5-HT_{1B}	129
5-HT_{1D}	39
5-HT_{1e}	517
5-HT_{2A}	127
5-HT_{2B}	184
5-HT_{2C}	360
5-HT_{5a}	2135
5-HT_{6}	464
5-HT_{7a}	206

[1] Data from: Keiser et al., 2009

Table III

Binding of (+)-LSD to 5-HT and other monoamine receptors

Binding site	K_i (nM)[1]
5-HT_{1A}	1.1
5-HT_{1B}	3.9
5-HT_{1e}	93.0
5-HT_{2A}	3.5
5-HT_{2B}	30.0
5-HT_{2C}	5.5
5-HT_{5a}	9.0
5-HT_6	6.9
5-HT_7	6.6
α_2	37[2]
β_1	140
β_2	740
D_1	180
D_2	120
D_3	27
D_4	56
D_5	340
H_1	1540

[1] Data from: Nichols et al., 2002

[2] Data from: Marona-Lewicka and Nichols, 1995