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Review

Recent advances in the neuropsychopharmacology of serotonergic hallucinogens

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HIGHLIGHTS

- Serotonergic hallucinogens are classified as phenylalkylamines and indoleamines.
- The two classes of hallucinogens produce similar subjective effects in humans and show cross-tolerance.
- Hallucinogen effects are primarily mediated by the serotonin 5-HT2A receptor.
- Many effects of hallucinogens are mediated in the prefrontal cortex.

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ABSTRACT

Serotonergic hallucinogens, such as (+)-lysergic acid diethylamide, psilocybin, and mescaline, are somewhat enigmatic substances. Although these drugs are derived from multiple chemical families, they all produce remarkably similar effects in animals and humans, and they show cross-tolerance. This article reviews the evidence demonstrating the serotonin 5-HT_{2A} receptor is the primary site of hallucinogen action. The 5-HT_{2A} receptor is responsible for mediating the effects of hallucinogens in human subjects, as well as in animal behavioral paradigms such as drug discrimination, head twitch response, prepulse inhibition of startle, exploratory behavior, and interval timing. Many recent clinical trials have yielded important new findings regarding the psychopharmacology of these substances. Furthermore, the use of modern imaging and electrophysiological techniques is beginning to help unravel how hallucinogens work in the brain. Evidence is also emerging that hallucinogens may possess therapeutic efficacy.

Contents

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1. Introduction

Hallucinogenic drugs have been used by humans for thousands of years, but western scientists only became interested in these substances beginning in the late 1800s. These agents produce profound changes in consciousness. Because other drug classes can sometimes produce effects that overlap with those of the hallucinogens, it has been important to develop a formal definition for these compounds. This has turned out to be a difficult and contentious task. Hallucinogens have been defined as agents that alter thought, perception, and mood without producing memory impairment, delirium, or addiction [1,2]. However, this definition is overly broad because it fails to exclude a wide-range of agents that are generally not classified as hallucinogens, such as cannabinoids and NMDA antagonists. It is now recognized that hallucinogens produce similar discriminative stimulus effects [3] and act as agonists of the serotonin-2A (5-HT_{2A}) receptor [4]. Therefore, it has been proposed [5] that in addition to having the characteristics listed above, hallucinogens should also bind to the 5-HT_{2A} receptor and produce full substitution in animals trained to discriminate the prototypical hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM). For this reason, hallucinogens are often categorized as classical hallucinogens or serotonergic hallucinogens. This article will review the pharmacology of hallucinogens, including their mechanism-of-action, their effects in animals and humans, and recent findings regarding how they interact with specific brain regions.

2. Pharmacology of hallucinogens

2.1. Receptor interactions

Classical hallucinogens can be divided into two main structural classes: *indoleamines* and *phenylalkylamines* [6]. Indoleamines include the tetracyclic ergoline (+)-lysergic acid diethylamide (LSD) and the chemically simpler indolealkylamines, which includes *N*,*N*-dimethyltryptamine (DMT), *N*,*N*-dipropyltryptamine (DPT), 5-methoxy-DMT (5-MeO-DMT), and psilocybin (4-phosphoryloxy-DMT) and its active *O*-dephosphorylated metabolite psilocin (4-hydroxy-DMT). DMT is found in several hallucinogenic snuffs used in the Caribbean and in South America. It is also a component of *ayahuasca*, an infusion or decoction prepared from DMT-containing plants in combination with species of *Banisteriopsis* containing β-carboline alkaloids that act as monoamine oxidase inhibitors [7]. Psilocybin and its metabolite psilocin are the active components of hallucinogenic *teonanácatl* mushrooms belonging to the genus *Psilocybe*.

The phenylalkylamines can be subdivided into phenethylamines, such as mescaline from the peyote cactus (*Lophophora williamsii*), 2,5-dimethoxy-4-bromophenethylamine (2C-B), and 2,5-dimethoxy-4-iodophenethylamine (2C-I), and phenylisopropylamines ("amphetamines"), including DOM, 2,5-dimethoxy-4-iodoamphetamine (DOI), and 2,5-dimethoxy-4-bromoamphetamine (DOB). Although *N*-alkyl substituted phenylalkylamines are usually inactive as hallucinogens, the addition of a *N*-benzyl group to phenethylamines can dramatically increase their activity, and *N*-benzylphenethylamines are a new class of potent hallucinogenic compounds [8]. Examples of *N*-benzylphenethylamine hallucinogens include *N*-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (25I-NBOMe) and *N*-(2-methoxybenzyl)-2,5-dimethoxy-4-bromophenethylamine (25B-NBOMe). The chemical structures of many of these hallucinogens are illustrated in Fig. 1. Nichols and colleagues have also developed conformationally restricted derivatives of phenylalkylamine hallucinogens: bromo-DragonFLY (1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane; [9]); TCB-2 ((4-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine; [10]); and 2*S*,6*S*-DMBMPP ((2*S*,6*S*)-2-(2,5-dimethoxy-4-bromobenzyl)-6-(2-methoxyphenyl)piperidine; [11]). Likewise, lysergic acid 2,4-dimethylazetidide was developed as a rigid analog of LSD that shows similar in vivo potency [12]. Fig. 2 shows examples of rigid hallucinogen analogs.

Phenylalkylamine hallucinogens are selective for 5-HT_2 receptors, including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} sites [13–15]. The indolealkylamines, by contrast, bind non-selectively to 5-HT receptors. Certain indolealkylamines, most notably DMT and some of its derivatives, bind to σ_1 receptors [16] and the trace amine receptor [17], and are substrates for the 5-HT transporter (SERT) [18,19]. However, compared with σ_1 and SERT, tryptamines are more potent at 5-HT_{1A} and 5-HT_{2A} receptors by several orders of magnitude, so the former sites probably do not contribute to the hallucinogenic response. LSD and other ergoline hallucinogens display high affinity for 5-HT receptors, as well as dopaminergic and adrenergic receptors (reviewed by: [6,20]).

2.2. Pharmacology of the 5-HT_{2A} receptor

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT, see Fig. 3) has potent contractile effects upon smooth muscle, especially rat uterus and guinea pig ileum. The first indication that there are multiple 5-HT receptor subtypes came from studies conducted by Gaddum and Picarelli [21]. They reported that treatment with either dibenzyline or morphine alone could only partially block the effect of 5-HT on guinea pig ileum. However, in tissue exposed to dibenzyline for 30 min, morphine markedly antagonized 5-HT-induced contraction, and dibenzyline acted as a full 5-HT antagonist in tissue previously exposed to morphine. These findings demonstrated that 5-HT was acting through two different receptor classes (type D and type M) to induce contraction of guinea pig ileum.

Soon after the development of radioreceptor techniques to demonstrate receptor binding, this methodology was applied to the investigation of 5-HT receptors. The first radioligands utilized were [^{3}H]LSD and [^{3}H]5-HT [22,23]. Both of those radioligands bind to rat brain membranes with high-affinity in a reversible,

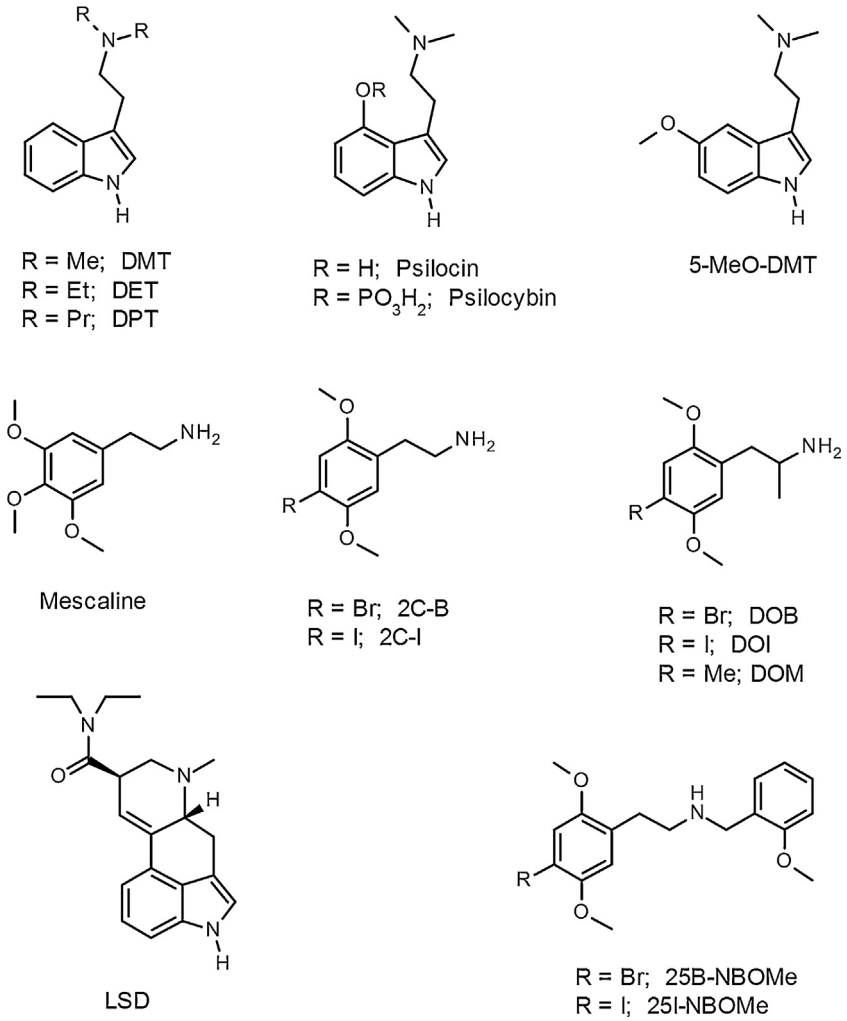

Fig. 1. Chemical structures of indolealkylamine, phenylalkylamine, and ergoline hallucinogens.

saturable, and stereoselective manner, suggesting they are interacting with specific recognition sites. After introduction of the dopamine antagonist radioligand [^{3}H]spiperone, it was recognized that [^{3}H]spiperone binds to 5-HT receptors distinct from the sites labeled by [^{3}H]5-HT [24]. The sites labeled by [^{3}H]5-HT and [^{3}H]spiperone were designated as 5-HT$_1$ and 5-HT$_2$ receptors, respectively, and it was recognized that [^{3}H]LSD labels both sites. The D receptor was eventually shown to be equivalent to the 5-HT$_2$ receptor, whereas the M receptor is pharmacologically distinct from 5-HT$_1$ sites and was later classified by Bradley and coworkers [25] as the 5-HT$_3$ receptor. The 5-HT$_2$ receptor class was later reorganized to include three subtypes: 5-HT$_{2A}$ (equivalent to the site known historically as the 5-HT$_2$ receptor or the D receptor), 5-HT$_{2B}$ (formerly known as the 5-HT$_{2F}$ receptor), and 5-HT$_{2C}$ (formerly known as the 5-HT$_{1C}$ receptor) [26].

The 5-HT$_{2A}$ receptor couples to Gq and activates phospholipase Cβ (PLCβ) signaling, resulting in the hydrolysis of membrane phospholipids to inositol triphosphate (IP$_3$) and diacylglycerol,

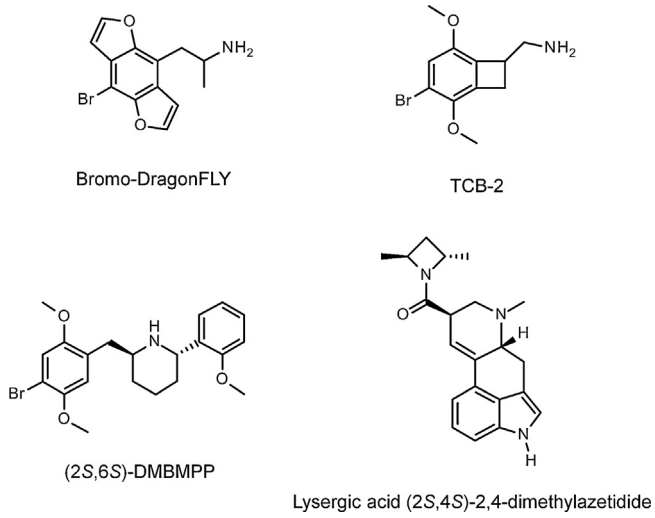

Fig. 2. Chemical structures of conformationally restricted hallucinogens.

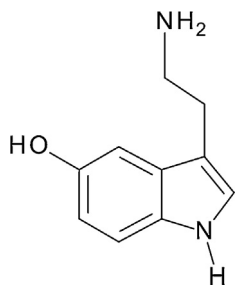

Fig. 3. Structure of serotonin.

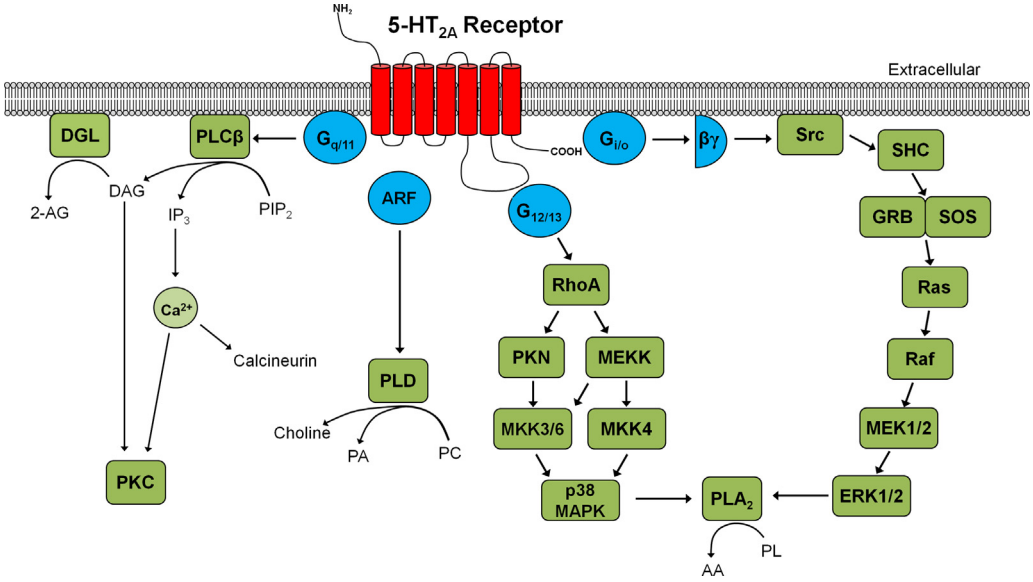

Fig. 4. Signaling pathways coupled to the 5-HT_{2A} receptor. *Abbreviations*: AA, arachidonic acid; 2-AG, 2-arachidonoylglycerol; ARF, ADP-ribosylation factor-1; DAG, diacylglycerol; DGL, diacylglycerol lipase; ERK1/2, extracellular-regulated kinases 1 and 2; GRB, growth factor receptor-bound protein 2; IP_3, inositol triphosphate; p38 MAPK, p38 mitogen-activated protein kinase; MEK1/2, mitogen/extracellular signal-regulated kinases 1 and 2; MKK3/6, MAPK kinases 3 and 6; MKK4, MAPK kinase 4; MEKK, MAPK kinase kinase; PA, phosphatidic acid; PC, phosphatidyl choline; PIP_2, phosphatidylinositol 4,5-biphosphate; PKC, protein kinase C; PKN, protein kinase N; PL, phospholipids; PLCβ, phospholipase Cβ; PLD, phospholipase D; SHC, Src homology 2 domain containing transforming factor; SOS, son of sevenless homolog.

and mobilization of intracellular Ca^{2+} (see Fig. 4). There is evidence that 5-HT_{2A} is coupled to several non-canonical signaling pathways, including β-arrestin-2, *Src* (potentially involving $G_{i/o}$-associated Gβγ subunits), extracellular-regulated kinase (ERK), p38 mitogen-activated protein (MAP) kinase, phospholipase A_2 (downstream from ERK 1,2 and p38 MAP kinase), Akt, and phospholipase D (dependent on the small G protein ADP-ribosylation factor-1 (ARF1)) [27–30]. However, the signaling pathways responsible for mediating the characteristic effects of hallucinogens have not been conclusively identified. Activation of the canonical Gq-PLCβ signaling pathway is apparently not sufficient to produce hallucinogen-like behavioral effects in animal models [28,31,32]. Multiple signaling pathways may be involved because the behavioral response to DOI is partially blunted in Gq knockout mice [33]. Schmid and colleagues have reported that β-arrestin-2 is not required for the behavioral effects of DOI and 5-MeO-DMT [29,34]. There also does not appear to be a direct relationship between phospholipase A_2 activation and generation of hallucinogen effects [32].

3. Evidence that serotonergic hallucinogens belong to a unitary class

3.1. Subjective effects

Despite having different chemical structures, phenylalkylamine, tryptamine, and ergoline hallucinogens produce remarkably similar subjective effects [35–42]. It is very difficult for hallucinogen-experienced subjects to distinguish between psilocybin and LSD if those substances are administered in a blinded fashion, with the only apparent difference being the duration of action [41]. Similar findings have been reported when mescaline, LSD, and psilocybin are compared in the same subjects [37–39]. By contrast, the effects of hallucinogens can be distinguished from those of other drug classes. The effects of classical hallucinogens and anticholinergic agents are qualitatively distinct [43,44]. Studies using the Addiction Research Center Inventory (ARCI) instrument [45] have confirmed that the effects of LSD are dissimilar from those of (+)-amphetamine [46] and Δ^9-tetrahydrocannabinol [47]. The ARCI can also distinguish between the subjective responses to 20 mg (+)-amphetamine and an *ayahuasca* preparation containing the equivalent of a 1 mg/kg dose of DMT [48]. Although it does not appear that any studies have directly compared the experiences produced by classical hallucinogens and the κ-opioid receptor agonist salvinorin A from *Salvia divinorum*, there is evidence that the phenomenology of salvinorin A is unique [49], and the ARCI is relatively insensitive to the effects of salvinorin A [50].

Several recent studies have compared the effects of hallucinogens and other drug classes using psychometrically validated instruments. One instrument that has been widely used to assess the subjective response to hallucinogens is the Altered States of Consciousness Questionnaire (APZ), as well as well as APZ variants such as the APZ-OAV and the 5D-ASC. These rating scales are designed to assess altered states of consciousness independent of their etiology [51,52]. The APZ and APZ-OAV include three core dimensions: *Oceanic Boundlessness* (OB), *Anxious Ego Dissolution* (AED) and *Visionary Restructuralization* (VR). The OB dimension reflects a pleasant state of depersonalization and derealization, the AED dimension measures dysphoric effects such as ego disintegration, delusions, loss of self-control, thought disorder, and anxiety, and the VR dimension involves elementary and complex visual hallucinations and perceptual illusions (see Table 1). Mescaline, psilocybin, and DMT produce profound increases in OB, AED and VR scores [52–56]. Another instrument is the Hallucinogen Rating Scale (HRS), which was specifically designed to measure the effects of parenteral DMT [57]. Double-blind studies have confirmed the APZ and the HRS can distinguish the effects of psilocybin and mescaline from those of (+)-methamphetamine, methylphenidate, and 3,4-methylenedioxyethylamphetamine [53,55,58]. *Ayahuasca* also elicited significantly greater effects than (+)-amphetamine on 4 of 6 subscales of the HRS [48].

A double-blind crossover study comparing DMT and the NMDA antagonist (*S*)-ketamine found DMT produces effects that more closely resemble the positive symptoms of schizophrenia, whereas the effects of (*S*)-ketamine are more similar to the negative and catatonic symptoms of schizophrenia [59]. Subjects experienced vivid visual hallucinations after treatment with DMT but not with (*S*)-ketamine; this difference was reflected by scores in the VR

Table 1
Core dimensions of the APZ [52].

Dimension	Symptoms assessed
Oceanic Boundlessness (OB)	*Positive derealization* *Positive depersonalization* *Altered sense of time* *Positive mood* *Mania-like experience*
Anxious Ego Dissolution (AED)	*Anxious derealization* *Thought disorder* *Delusion* *Fear of loss of control*
Visionary Restructuralization (VR)	*Elementary hallucinations* *Visual pseudohallucinations* *Synesthesia* *Changed meaning of percepts* *Facilitated recollection* *Facilitated imagination*

dimension of the APZ-OAV, which was more strongly affected by DMT than by (*S*)-ketamine. Another notable difference between ketamine and serotonergic hallucinogens is that ketamine does not produce mystical experiences [60], whereas hallucinogens induce these states with some reliability [58,61–64].

Vollenweider and colleagues have conducted a psychometric assessment of APZ-OAV data pooled from 43 studies with psilocybin, (*S*)-ketamine, and the entactogen 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") [65]. Examination of the factorial structure of the APZ-OAV revealed the OB, AED and VR scales are multidimensional, and Vollenweider et al. were able to extract 11 new homogenous APZ-OAV scales that are very effective at differentiating the subjective effects of psilocybin, (*S*)-ketamine, and MDMA. There are clear differences in the relative magnitude of drug effects on several of the new scales; for example MDMA has strong effects on *blissful state*, (*S*)-ketamine produces the largest increase in *disembodiment*, and *complex imagery* and *elementary imagery* are most strongly influenced by psilocybin. Fig. 5 compares the effects of psilocybin

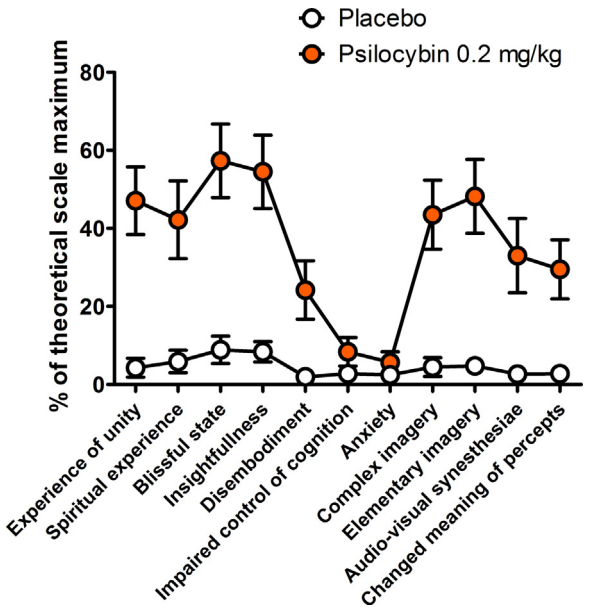

Fig. 5. Subjective effects of psilocybin as measured by the 5-Dimension Altered States of Consciousness instrument (5D-ASC). The values reported by Grob et al. [56] were re-analyzed using the 11 new homogenous APZ subscales developed by Studerus et al. [65]. Values are the mean (SEM) percentages of the total possible score. The placebo was niacin.

and placebo on the new homogeneous APZ-OAV subscales. In summary, even though there are some similarities between the subjective effects of serotonergic hallucinogens, NMDA antagonists, psychostimulants, and entactogens, the effects produced by the latter three drug classes are clearly distinct from those elicited by classical hallucinogenic drugs.

3.2. Tolerance and cross-tolerance

Tachyphylaxis (tolerance) develops rapidly to the effects of classical hallucinogens. If LSD and DOM are administered repeatedly at daily intervals tolerance is observed after 1–3 days and there is eventually nearly a complete loss of response [66–69]. Tolerance occurs with a variety of phenylalkylamine, indolealkylamine, and ergoline hallucinogens, and compounds from these classes exhibit symmetrical cross-tolerance [37,41,42,68,70–72]. Importantly, cross-tolerance does not occur between LSD and (1) (+)-amphetamine [46], (2) the anticholinergic *N*-methyl-3-piperidyl benzilate [73], or (3) Δ^9-tetrahydrocannabinol [47]. Similar findings have been reported by parallel studies in laboratory animals [74–79]. The fact that serotonergic hallucinogens produce similar experiences and induce cross-tolerance indicates that these compounds share a common mechanism of action.

4. Involvement of the 5-HT$_{2A}$ receptor in hallucinogen effects

4.1. Evidence from human studies

Multiple, converging lines of evidence point to 5-HT$_{2A}$ receptor activation as the unitary mechanism responsible for mediating hallucinogenesis. Indoleamine and phenylalkylamine hallucinogens bind to 5-HT$_2$ sites with moderate to high affinity [80–83]. Although indoleamine hallucinogens show relatively promiscuous binding profiles, phenylisopropylamine hallucinogens such as DOM and DOB are highly selective for 5-HT$_2$ receptors [13,15] and therefore it is likely that their effects are mediated by a member of the 5-HT$_2$ family. Additionally, there is a very strong correlation (r = 0.90–0.97) between 5-HT$_{2A}$ receptor affinity and human hallucinogenic potency [13,82,84]. Another compelling finding is that 5-HT$_{2A}$ receptor blockade ameliorates most of the effects of psilocybin in human subjects. A series of studies conducted by Franz Vollenweider and colleagues at the University Hospital of Psychiatry in Zürich have shown that the effects of psilocybin (215–260 μg/kg, p.o.) on the OB, AED, and VR dimensions of the APZ-OAV and 5D-ASC are completely blocked by pretreatment with either the 5-HT$_{2A/2C}$ antagonist ketanserin or the mixed 5-HT$_{2A}$/D$_2$ antagonist risperidone [85–90]. By contrast, pretreatment with the dopamine D$_2$ antagonist haloperidol had no effect on psilocybin-induced VR scores and actually intensified the effect of psilocybin on scores in the AED dimension [85]. Ketanserin also blocks the effects of psilocybin on a variety of neurophysiological measures in humans, including tests of spatial working memory [85], prepulse inhibition of acoustic startle [90], N170 visual-evoked potentials [89], semantic interference in the Stroop test [90], and recognition of emotional facial cues in a go/nogo task [88]. Furthermore, a positron emission tomography (PET) study with the 5-HT$_{2A}$ radiotracer [^{18}F]altanserin has shown that the intensity of the response to psilocybin is directly correlated with the level of 5-HT$_{2A}$ occupation [91].

4.2. Evidence from animal behavioral models

Because of regulatory constraints on human studies, animal behavioral models are the primary methodology used to study hallucinogens in vivo. Although it has been difficult to develop

appropriate models of hallucinogenic activity because of the variability and complexity of their effects, several animal models have made important contributions to our understanding of hallucinogen pharmacology. Importantly, although there are some exceptions, almost all the behavioral effects of hallucinogens studies in laboratory animals are mediated by the 5-HT_{2A} receptor.

4.2.1. Drug discrimination

Laboratory animals can be trained to discriminate hallucinogens from saline using operant conditioning techniques. Rats are the species most commonly employed, although mice and monkeys have also been used. Many classical hallucinogens have been used as training drugs, including LSD, mescaline, DOM, DOB, DOI, psilocybin, 5-MeO-DMT, DMT, and DPT [3,92–102]. All of these hallucinogens produce cross-generalization, suggesting that they evoke similar interoceptive stimulus cues. By contrast, drugs from other pharmacological classes do not produce hallucinogen-like stimulus effects [3,101,103]. There is a great deal of evidence that the discriminative stimulus effects of hallucinogens are mediated by the 5-HT_{2A} receptor. For example, Glennon and colleagues conducted substitution tests with 22 hallucinogens in rats trained to discriminate 1 mg/kg DOM from saline and found that the ED_{50} values for stimulus generalization are highly correlated ($r = 0.938$) with 5-HT_{2A} binding affinity [84]. Another study with 18 hallucinogens found a strong correlation ($r = 0.90$) between ED_{50} values for stimulus generalization to 1 mg/kg DOM and affinity at 5-HT_{2A} receptors labeled with [^{3}H]DOB [13]. The stimulus effects of hallucinogens can be blocked by the selective 5-HT_2 antagonists ketanserin and pirenperone [4,96,104–106]. Blockade by ketanserin and pirenperone, however, does not eliminate the possibility of 5-HT_{2C} receptor involvement because those antagonists are relatively nonselective for 5-HT_{2A} versus 5-HT_{2C} sites. Importantly, M100907, a 5-HT_{2A} antagonist with high selectivity versus the 5-HT_{2C} receptor, blocks stimulus control in animals trained with DOI [97,107–109], DOM [101,110], *R*-(−)-DOM [111], LSD [98,112–114], and psilocybin [99]. Conversely, neither the selective 5-HT_{2C} antagonist SB 242,084 nor the mixed 5-$HT_{2C/2B}$ antagonists SB 200,646A and SB 206,553 block stimulus control induced by DOI, LSD, or psilocybin [99,107–109,114]. Furthermore, Fiorella et al. [115] tested eleven 5-HT_2 antagonists and found the rank order of potencies for blocking *R*-(−)-DOM substitution in LSD-trained rats parallels their affinities for 5-HT_{2A} ($r = 0.95$) but not for 5-HT_{2C} ($r = -0.29$).

Although most phenalkylamines are relatively nonselective for 5-HT_{2A} versus 5-HT_{2C}, 2*S*,6*S*-DMBMPP displays 124-fold selectivity for 5-HT_{2A} receptors [11]. Although racemic *trans*-DMBMPP is less selective, it still shows 98-fold higher affinity for 5-HT_{2A} over 5-HT_{2C} receptors. Importantly, *trans*-DMBMPP fully substitutes in rats trained to discriminate 0.08 mg/kg LSD. By contrast, several studies have demonstrated that 5-HT_{2C} agonists fail to mimic the hallucinogen discriminative stimulus. Neither 1-(3-trifluoromethylphenyl)piperazine (TFMPP) nor *m*-chlorophenylpiperazine (*m*CPP) substitute for DOM, DOI, or LSD [103,116,117]. These findings demonstrate that 5-HT_{2A} activation is sufficient to produce hallucinogen-like stimulus effects. Furthermore, 5-HT_{2C} activation does not play a role in mediating the hallucinogen discriminative stimulus cue. The available data provide strong support for the conclusion that hallucinogens evoke a uniform discriminative stimulus cue that is mediated by the 5-HT_{2A} receptor.

Although it is clear that the 5-HT_{2A} receptor is primarily responsible for generating hallucinogen-induced stimulus control, interactions with other receptors may contribute to or modify the stimulus effects of hallucinogens. This appears to be especially true for indoleamines, which are much less selective than phenylalkylamines for 5-HT_{2A} sites. For example, there

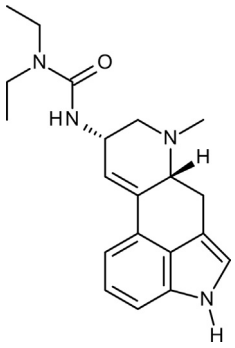

Fig. 6. Chemical structure of lisuride.

appears to be a time-dependent dopaminergic component to the LSD discriminative stimulus in rats [118,119]. There is evidence that the 5-HT_{1A} receptor also contributes to the discriminative stimulus effects of LSD. 5-HT_{1A} agonists such as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and ipaspirone produce partial substitution in rats and mice trained with LSD [98,120–122]. The 5-HT_{1A} antagonist WAY-100635 does not alter LSD discrimination in rats [114,122,123], but the 5-HT_{1A} receptor may make an more prominent contribution to the LSD cue in mice because discrimination can be partially blocked by administration of either WAY-100635 or M100907 [98]. However, the ability of *R*-(−)-DOB to substitute for LSD in mice is completely blocked by M100907 but not by WAY-100635, demonstrating the stimulus element generated by 5-HT_{1A} is a non-essential component of the LSD cue and not a shared aspect of hallucinogen pharmacology. Although certain indolealkylamines produce compound stimulus cues involving both 5-HT_{1A}- and 5-HT_{2A}-mediated components [100,124,125], 5-HT_{1A} receptors do not play a role in the interoceptive effects of psilocybin [99] or 5-methoxy-*N*,*N*-diisopropyltryptamine [126].

A potential confound associated with drug discrimination studies is the possibility of "false positive" results. False-positives occur where an animal trained to discriminate a hallucinogen generalizes to a drug that is known to be non-hallucinogenic in humans. Lisuride is one example of drug that can produce false-positive results. Lisuride is an isolysergic acid derivative that is structurally similar to LSD (see Fig. 6), and acts as an agonist at a variety of serotonergic, dopaminergic, and adrenergic receptors [12,14,127–130]. Despite the fact that lisuride has high affinity for the 5-HT_{2A} receptor and acts as an agonist [32,128,131], it is not hallucinogenic in humans [132–135] and has been used clinically to treat migraine and Parkinson's disease. Some studies have found that lisuride produces full substitution in rats trained with either LSD, DOI, or DOM [136–139], but in other studies it produced only partial substitution [129,140]. Although clearly some degree of similarity exists between the stimulus cues evoked by lisuride and classical hallucinogens, there are also subtle differences because rats can be trained to discriminate between lisuride and LSD using three-choice (drug–drug–vehicle) discrimination procedures [141]. Discrimination studies where animals are trained to discriminate between LSD and another drug such as pentobarbital or cocaine also appear to be less sensitive to lisuride-induced false-positive responses [139].

González-Maeso et al. [28] have proposed that the behavioral differences between LSD and lisuride are due to 5-HT_{2A} functional selectivity. They found LSD and lisuride both activate $G_{q/11}$ signaling via the 5-HT_{2A} receptor, but only LSD increases the cortical expression of the immediate early genes *egr-1* and *egr-2* by activating $G_{i/o}$ and *Src* [28]. Therefore, they hypothesized that LSD is hallucinogenic because it is capable of activating specific signaling mechanisms that are not recruited by lisuride. Alternatively, the

Table 2
The selective 5-HT_{2A} antagonist M100907 blocks the head twitch response induced by hallucinogens in rats and mice.

Hallucinogen			M100907			Species	Reference
Drug	Dose	Route[a]	Potency[b]	Effective dose[c]	Route[a]		
5-MeO-DMT	30 mg/kg	IP	ID_{50} = 0.03		IP	Mouse	[448]
5-MeO-DMT	10 mg/kg	IP		0.05 mg/kg	IP	Mouse	[29]
DPT	3 mg/kg	IP		0.01 mg/kg	IP	Mouse	[100]
DOI	2.5 mg/kg	IP	ID_{50} = 0.005	0.04 mg/kg	SC	Rat	[160]
DOI	3 mg/kg	IP		1 mg/kg	IP	Rat	[169]
R-(−)-DOI	3 mg/kg	IP	ID_{50} = 0.01	0.1 mg/kg	SC	Mouse	[449]
DOI	2.5 mg/kg	IP		0.25 mg/kg	IP	Mouse	[33]
DOI	2 mg/kg	IP		0.3 mg/kg	IP	Mouse	[450]
DOI	1 mg/kg	IP		0.05 mg/kg	IP	Mouse	[34]
DOI	1 mg/kg	IP		0.25 mg/kg	SC	Mouse	[167]
DOI	1 mg/kg	IP		0.025 mg/kg	SC	Mouse	[173]
2C-I	3 mg/kg	SC	ID_{50} = 0.0045	0.1 mg/kg	SC	Mouse	[156]
25I-NBOMe	0.3 mg/kg	SC	ID_{50} = 0.0062	0.1 mg/kg	SC	Mouse	[156]
25I-NBMD	3 mg/kg	SC	ID_{50} = 0.0015	0.1 mg/kg	SC	Mouse	[156]

[a] IP, intraperitoneal; SC, subcutaneous
[b] ID_{50} = inhibitory $dose_{50}$ in mg/kg.
[c] Dose of M100907 that produced 90–100% blockade of the head twitch response.

reason why lisuride fails to recruit $G_{i/o}$ may have nothing to do with functional selectivity, and could be a consequence of its low intrinsic efficacy at 5-HT_{2A} [31,32,131]. Although animals trained with DOM will generalize to lisuride [137,138], the response to DOM is attenuated when it is co-administered with lisuride [142]. The fact that lisuride induces a response when administered alone but act as an antagonist in the presence of a full agonist (DOM) is consistent with the behavior of a partial agonist.

4.2.2. Head twitch response

Many mammalian species display a paroxysmal rotational shaking of the head in response to mechanical or chemical irritation of the pinna. Mice show a similar behavior, known as the head twitch response (HTR), after administration of hallucinogens [143–145]. Hallucinogens also induce head twitches in rats, but in that species the behavior often involves both the head and the trunk [146,147]. The responses made by rats are sometimes called wet-dog shakes because they resemble the behavior of a dog drying itself after emerging from the water. It is important to recognize that the HTR can occur in response to administration of 5-HT precursors (e.g., L-tryptophan and L-5-hydroxytryptophan) and drugs that increase 5-HT release (e.g., fenfluramine and *p*-chloroamphetamine), and therefore the behavior is not specific to hallucinogens [148–151]. Nonetheless, the HTR has gained prominence as a behavioral proxy in rodents for human hallucinogen effects because the HTR is one of only a few behaviors that can reliably distinguish hallucinogenic and non-hallucinogenic 5-HT_{2A} agonists [28]. Indeed, even high doses of lisuride fail to induce the HTR in mice [28,152].

It is well-established that phenylisopropylamine and indoleamine hallucinogens induce the HTR (reviewed by: [20]), but the literature is less clear with regard to phenethylamine hallucinogens. Many studies have demonstrated that mescaline produces head twitch behavior in rats and mice [144,146,153]. It has also been reported that the hallucinogen 2,5-dimethoxy-4-*n*-propylthiophenethylamine (2C-T-7) induces the HTR in mice [154]. Studies in rats, however, have shown 2C-I, 2C-B, and 2,5-dimethoxy-4-methylphenethylamine (2C-D) do not induce the HTR [155]. In contrast to those findings, we recently reported 2C-I and the *N*-benzyl derivatives 25I-NBOMe and *N*-(2,3-methylenedioxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (25I-NBMD) produce dose-dependent increases in HTR behavior in C57BL/6J mice [156]. 25B-NBOMe also induces the HTR in mice [157]. The discrepant findings with regard to 2C-I and other phenethylamines may reflect the fact that mice are more sensitive than rats to the HTR induced by 5-HT_{2A} partial agonists. 2C-I has relatively low intrinsic activity at the 5-HT_{2A} receptor [155,158], and it may not have sufficient efficacy to provoke head twitches in rats. Nevertheless, we are not aware of any serotonergic hallucinogens that do not produce the HTR in mice.

The kinematics of the HTR induced by DOI have been characterized in C57BL/6J mice and Sprague-Dawley rats [152]. When mice make a head twitch, the head rapidly twists from side-to-side. Each HTR consists of 5–11 head movements, with the head movements occurring at 78–98 Hz (i.e., each head movement lasts approximately 11 msec). The behavior is similar in rats but in that species the frequency of head movement is lower. One drawback to traditional HTR studies is that they require direct behavioral observation that can be extremely time-consuming. However, as we have recently demonstrated, it is possible to detect the behavior with a head-mounted magnet and a magnetometer coil, providing a highly sensitive, semi-automated assessment of the behavior [152,156].

The HTR induced by hallucinogens and other 5-HT agonists is closely linked to 5-HT_{2A} activation. It was proposed in 1982 that the mescaline-induced HTR is mediated by the 5-HT_{2A} receptor, based on the fact that the relative potency of 5-HT antagonists to block the behavior is correlated (r = 0.875) with their 5-HT_{2A} affinity [159]. Similar findings were later reported for the HTR induced by DOI [160,161]. Numerous studies have shown M100907 blocks the HTR induced by hallucinogens (Table 2). For example, we found M100907 blocks the HTR induced by the hallucinogen 25I-NBOMe with an ID_{50} = 6.2 μg/kg (Fig. 7; [156]). Based on ex vivo binding data it is unlikely M100907 produces any appreciable occupation of 5-HT_{2C} receptors at that dose level [162]. Studies have also demonstrated that the highly selective 5-HT_{2A} antagonist MDL 11,939 blocks the HTR induced by DOI and TCB-2 in mice [163,164]. Mice lacking the 5-HT_{2A} receptor gene do not produce head twitches in response to mescaline, DOI, DOM, LSD, DMT, 5-MeO-DMT, psilocin, or 1-methylpsilocin [28,165,166], although the response can be rescued by selectively restoring the 5-HT_{2A} receptor gene to cortical regions [28]. By contrast, 1 mg/kg DOI produces a significant (albeit somewhat blunted) HTR in 5-HT_{2C} knockout mice [167]. The fact that DOI can provoke head twitches in 5-HT_{2C} knockout mice but not in 5-HT_{2A} knockout mice strongly indicates the 5-HT_{2A} receptor is the member of the 5-HT_2 family responsible for mediating the HTR. Similarly, there is a consensus in the literature that the ability of DOI to induce the HTR is not blocked by selective 5-HT_{2C} antagonists or mixed 5-$HT_{2C/2B}$ antagonists [160,168–171].

Although it has been conclusively established that the 5-HT_{2C} receptor is not required for generation of the HTR, there

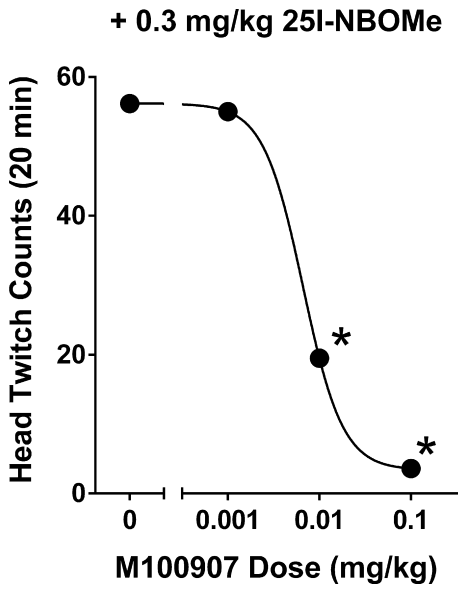

Fig. 7. Effect of pretreatment with the selective 5-HT_{2A} antagonist M100907 on the head twitch response induced by 0.3 mg/kg 25I-NBOMe in C57BL/6J mice. Data are presented as group means for 20-min test sessions. $^{*}p < 0.01$, significant difference from 25I-NBOMe alone. Data from Ref. [156].

is some evidence that 5-HT_{2C} sites may play a modulatory role. 5-HT_2 agonists that are selective for 5-HT_{2C} sites, such as (*S*)-6-chloro-5-fluoro-α-methyl-1*H*-indole-1-ethanamine (Ro 60-0175), 6-chloro-2-(1-piperazinyl)pyrazine (MK-212), and *m*CPP, do not induce the HTR in rats unless administered in combination with the 5-HT_{2C} antagonist SB 242,084 [170]. There is also evidence that the ability of DOI to induce the HTR is significantly attenuated by pretreatment with selective 5-HT_{2C} agonists, including Ro 60-0175, CP-809,101, and *m*CPP [160,171–173]. These findings indicate 5-HT_{2C} activation suppresses expression of the HTR. Likewise, DOI produces a biphasic dose–response curve in NIH Swiss and Swiss-Webster mice, and SB 242084 reportedly shifts the descending arm of the DOI response to the right [171]. Here again there is evidence that the 5-HT_{2C} receptor can inhibit the HTR. On the other hand, as was noted above, Canal and colleagues have reported that 5-HT_{2C} knockout mice show a blunted HTR to 1 mg/kg DOI [167]. Furthermore, in contrast to many other reports, the same investigators found pretreatment with SB 242,084 or SB 206,553 diminished the magnitude of the HTR induced by 1 mg/kg DOI in C57BL/6J and DBA/2J mice [167,173]. It is not clear why the 5-HT_{2C} receptor attenuates the HTR in certain studies and augments the response in others, but Fantegrossi et al. [171] have argued these differences may be strain dependent. For example, there are strain differences in the editing of 5-HT_{2C} mRNA [174,175]. Since 5-HT_{2C} editing can influence the downstream coupling of the receptor [176], the nature of the interactions between 5-HT_{2A} and 5-HT_{2C} could potentially vary by mouse strain.

4.2.3. Prepulse inhibition of startle

Prepulse inhibition (PPI) refers to the phenomenon where a weak prestimulus presented prior to a startling stimulus will attenuate the startle response; PPI is often used as an operational measure of sensorimotor gating, and reflects central mechanisms that filter out irrelevant or distracting sensory stimuli [177]. Rats treated with DOI [178,179], DOB [180], LSD [181,182], mescaline [183], and 2C-B [184] show reductions in PPI. These effects can be blocked by M100907 and MDL 11,939 [179,181,182,185]. By contrast, neither SB 242,084 nor the 5-$HT_{2C/2B}$ antagonist SER-082 are effective. Although one study found haloperidol can block the PPI disruption produced by hallucinogens [178], this was not replicated by subsequent investigations [181,186]. Lisuride also disrupts PPI in rats, but this effect is blocked by the $D_{2/3}$ antagonist raclopride and not by MDL 11,939 [182].

4.2.4. Interval timing

Temporal perception can be markedly altered by hallucinogens. Subjects under the influence of mescaline and LSD often report that their sense of time appears to speed up or slow down, or they may experience a sensation of timelessness [187–191]. Psilocybin also alters performance on laboratory measures of timing [192].

Temporal perception can be assessed in rodents using interval timing paradigms. For example, in the free-operant psychophysical task, animals are trained to respond on two levers, and they must respond on one lever during the first half of the trial and on the other lever during the second half [193]. In the discrete-trials task, animals are trained to press one lever in response to short duration stimuli and another lever in response to long duration stimuli, and are then challenged with a variety of stimulus durations [194]. DOI disrupts the performance of rats in both of these tasks [195–197]. Although DOI affects performance in the discrete trials task, it does not affect performance in a similar task where rats have to discriminate different light intensities, indicating that DOI is specifically influencing temporal perception and not disrupting stimulus control or attentional processes [198]. The effect of DOI in the discrete-trials task and that free-operant task are blocked by ketanserin and M100907 [196,197], demonstrating the involvement of 5-HT_{2A}.

4.2.5. Exploratory and investigatory behavior

Measures of locomotor activity are often used to characterize the effects of psychoactive drugs on exploratory behavior. Locomotion alone, however, is not necessarily a reliable measure of exploration because it includes does not distinguish specific exploratory responses to environmental stimuli from other types of motor activity [199]. Given the complexity of hallucinogen effects, it is not surprising that hallucinogens cannot be distinguished from other drug classes using traditional open field locomotor measures [144]. However, multivariate assessment methods have been more successful. One example is the Behavioral Pattern Monitor (BPM), which combines features from activity chambers and holeboards and provides quantitative as well as qualitative measures of the spatial and temporal structure of activity [200,201]. BPM studies have shown hallucinogens produce a very characteristic profile of behavioral effects. When rats are tested in unfamiliar BPM chambers after administration of hallucinogens (including mescaline, DOM, DOI, LSD, DMT, 5-MeO-DMT, and psilocin), the animals display reduced amounts of locomotor activity, rearings, and holepokes at the beginning of the test session, and avoidance of the center of the BPM chamber is increased [202–205]. Most of these effects are markedly diminished in animals habituated to the BPM chambers, indicating that hallucinogens act by enhancing neophobia. The ability of hallucinogens to increase the avoidance of novel (and potentially threatening) test chambers by rats may be analogous to the enhanced sensitivity and reactivity to environmental stimuli that occurs in humans [206].

Extensive testing has confirmed this pattern of effects in the BPM is highly specific to hallucinogens [200,207–210]. For example, although 8-OH-DPAT and other selective 5-HT_{1A} agonists reduce locomotor activity, rearings, and holepokes in rats, these effects are not influenced by environmental familiarity and hence are likely to reflect sedation [208]. When Adams and Geyer [211] compared lisuride and LSD in the BPM, they found the two compounds produce markedly different patterns of effects. Lisuride produces effects that are similar to those of apomorphine and other

dopamine agonists, with sedative effects occurring at low doses and perseverative patterns of hyperactivity occurring at higher doses.

The 5-HT_{2A} receptor is responsible for mediating most of the effects of hallucinogens in the rat BPM. It was first shown that ritanserin and ketanserin block the effects of mescaline, DOM, and DOI in the BPM, indicating 5-HT_2 involvement [204]. Later studies demonstrated that the effects of DOI are blocked by M100907 but not by SER-082 [212], confirming mediation by 5-HT_{2A}. The action of indoleamine hallucinogens in the BPM is more complex mechanistically, with 5-HT_{1A} and 5-HT_{2A} receptors contributing to the effects of LSD and 5-MeO-DMT [205,213–215].

Hallucinogens have also been tested in a version of the BPM designed for mice [216]. In contrast to rats, phenylalkylamine and indolealkylamine hallucinogens produce disparate effects on exploratory and investigatory behavior in C57BL/6J mice. Phenylalkylamines, including DOI, mescaline, and TCB-2, inhibit investigatory behavior and alter locomotor activity in a dose-dependent manner, increasing activity at low to moderate doses and reducing activity at high doses [217,218]. Other groups have reported similar findings with DOM and DOI in mice [146,219–221]. The increase in locomotor activity induced by 1 mg/kg DOI, 25 mg/kg mescaline, or 3 mg/kg TCB-2 is blocked by low doses of M100907 and is absent in 5-HT_{2A} knockout mice. By contrast, the reduction of locomotor activity induced by 10 mg/kg DOI is attenuated by SER-082. Taken together, it appears that 5-HT_{2A} and 5-HT_{2C} receptors have countervailing effects on locomotor activity, with 5-HT_{2A} activation increasing activity and 5-HT_{2C} activation reducing activity. Administration of psilocin and 5-MeO-DMT to C57BL/6J mice reduces locomotor activity and investigatory behavior [166]. These effects are blocked by WAY-100635 but are unaffected by SB 242,084 or by 5-HT_{2A} gene deletion. Similarly, 5-MeO-DMT has no effect on activity in 5-HT_{1A} knockout mice [222]. Hence, whereas the phenylalkylamines act through 5-HT_2 sites to alter behavior in the mouse BPM, indoleamine hallucinogens appear to act via the 5-HT_{1A} receptor.

4.3. Tolerance studies

As noted in Section 3.2, serotonergic hallucinogens produce a profound degree of tolerance and cross-tolerance in animals and humans. Although very little is known about the mechanisms leading to the development of tolerance to hallucinogens in humans, there is evidence in animals that tolerance is linked to 5-HT_{2A} downregulation. Rats treated repeatedly with DOM, LSD, or psilocin show a significantly lowered density of 5-HT_{2A} receptors in several brain regions [223–225]. Binding to 5-HT_{1A}, 5-HT_{1B}, α_2, β_1, or D_2 receptors is unaffected. Another study demonstrated that treatment with 1 mg/kg DOI for 8 days produced a significant reduction in the density of 5-HT_{2A} receptors in the cortex, but there was no change in 5-HT_{2C} receptor expression [109]. An identical treatment regimen caused tolerance to develop in rats trained to discriminate DOI. Likewise, there is a significant reduction of 5-HT_{2A}-stimulated [^{35}S]GTPγS binding in the medial prefrontal cortex (mPFC) and anterior cingulate cortex in rats treated with LSD (0.13 mg/kg/day) for 5 days [226]; this indicates tolerance to LSD is associated with a reduction of 5-HT_{2A} signaling.

Although most hallucinogens produce tolerance in humans, DMT seems to be the exception. It has been reported that DMT does not evoke tolerance in man, even after an intramuscular (IM) dosage regimen of 0.7 mg/kg twice daily for five days [227]. More recently, Strassman et al. [228] found there was no tolerance to the subjective effects of DMT in volunteers who received four intravenous (i.v.) injections of 0.3 mg/kg at 30 min intervals. In vitro experiments have shown that exposure to LSD or DOI desensitizes 5-HT_{2A} and 5-HT_{2C} receptors in transfected cell lines [108,229]. However, after exposure to DMT, 5-HT_{2C} receptors showed desensitization but there was no change in the response to 5-HT_{2A} activation [108]. These observations suggest that DMT fails to induce tolerance because it does not desensitize the 5-HT_{2A} receptor.

5. Hallucinogen effects on neuronal activity

5.1. Locus coeruleus

The locus coeruleus (LC), located in the dorsal pons, is the source of almost all noradrenergic projections in the CNS. LC neurons are responsive to sensory stimuli, especially of a novel or arousing nature, and the firing of LC neurons is markedly increased by noxious stimulation (reviewed by: [230]). Intravenous administration of mescaline (2 mg/kg), LSD (5–10 μg/kg), DOM (20–80 μg/kg), DOB (50–100 μg/kg), or DOI (16–50 μg/kg) profoundly enhances the responses of LC neurons to sensory stimuli while simultaneously depressing their spontaneous firing [231–234]. After administration of hallucinogens, the enhancement of responsiveness is so pronounced that even innocuous sensory stimuli normally ineffective at driving LC cell firing will evoke a response [231]. The ability to produce opposite effects upon spontaneous and sensory-evoked LC firing is a specific property of LSD-like drugs, as other pharmacological agents that alter the basal activity of LC cells (e.g., (+)-amphetamine, clonidine, desipramine, or idazoxan) do not alter evoked LC firing [231,232,234]. The observation that hallucinogens decrease the spontaneous activity of LC cells is supported by the work of Done and Sharp [235] who found that DOI and DOB lower the concentration of NE in hippocampal dialysates, which indicates those compounds decrease tonic NE release from LC projections.

The effects of hallucinogens upon LC unit activity appear to be mediated by 5 HT_{2A} receptors. The 5-HT_2 antagonists ketanserin and ritanserin have been shown to block the actions of hallucinogens in the LC [232,233]. Furthermore, Szabo and Blier [236] found that the ability of DOI to alter the activity of LC neurons is abolished by M100907. Nonetheless, 5-HT_{2A} receptors are sparsely distributed within the LC (e.g., [237]), and application of the 5-HT_{2A}/5-HT_3 agonist quipazine or hallucinogens such as DOI directly into the LC does not mimic the effects of their systemic administration [232–234,238]. Intravenous administration of mescaline and LSD also had no effect on the ability of locally applied acetylcholine, glutamate (Glu), or substance P to excite LC neuronal activity [231]. Presumably then, hallucinogens act upon LC afferents, altering the firing of LC cells indirectly by modulating the activity of one or more input pathways.

Chiang and Aston-Jones [234] reported that the decrease in LC spontaneous firing induced by DOI could be blocked by the $GABA_A$ receptor antagonists bicuculline and picrotoxin, whereas the ability of DOI to enhance sensory-evoked LC responses was blocked by the NMDA receptor antagonist 2-amino-5-phosphonopentanoic acid but not by the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). Thus, hallucinogens appear to tonically activate GABAergic input to LC and concomitantly facilitate glutamatergic sensory input. It is likely that the nucleus prepositus hypoglossi (PrH), an area known to provide direct GABAergic inhibitory input into the LC [239,240], mediates the hallucinogen-induced inhibition of spontaneous LC activity. Although one group reported that microinjection of quipazine directly into the PrH did not alter LC unit activity in the rat [238], subsequent work confirmed that DOI depolarizes PrH neurons [241]. Moreover, electrolytic lesions of PrH significantly attenuate the ability of systemic quipazine injections to reduce the frequency of LC unit discharge [238]. This strongly implicates the PrH or one of its afferents as the site through which 5-HT_{2A} agonists modulate spontaneous LC firing. The identity of the specific LC afferent(s)

responsible for the hallucinogen-induced facilitation of LC glutamatergic sensory input is currently unknown. Although the nucleus paragigantocellularis in the ventrolateral rostral medulla is a major source of excitatory input into the LC [234,242], the ability of somatosensory stimuli to excite the LC is unaffected by lesions of nucleus paragigantocellularis [243]. The LC also receives excitatory input from the prefrontal cortex (PFC), both directly and indirectly [244–246], and the excitatory effects of hallucinogens on the LC may be mediated by those pathways. As will be discussed below in Section 5.2, hallucinogens increase the firing of PFC projection neurons.

The LC projects heavily to cortex, where there is overlap between the distribution of α_1-adrenoceptors and 5-HT$_{2A}$ receptors [247]. Interestingly, in the PFC, α_1-adrenoceptors and 5-HT$_{2A}$ receptors have similar effects on the activity of layer V pyramidal neurons [248]. Hallucinogens increase the intensity of sensory experiences and affective responses, and it is tempting to speculate that the LC may contribute to these effects. Indeed, the ability of LSD to potentiate neophobia in rats in the Behavioral Pattern Monitor is diminished by depletion of norepinephrine from LC projections [249].

5.2. Prefrontal cortex (PFC)

5.2.1. Effects on PFC network activity in vitro

It is now recognized that the PFC is an important site of action for hallucinogens. The 5-HT$_{2A}$ receptor is expressed heavily in the PFC and adjacent cortical regions, particularly in lamina V [237,250–252]. In situ hybridization histochemistry has confirmed that most of the cells in monkey and human PFC express 5-HT$_{2A}$ mRNA [253]. Likewise, in rats, a large percentage of the cells in the superficial, middle, and deep layers of the secondary motor, anterior cingulate (ACA), prelimbic (PrL), and infralimbic (IL) areas express 5-HT$_{2A}$ mRNA [254,255]. Almost all prefrontal pyramidal neurons express the 5-HT$_{2A}$ receptor, with the receptor localized primarily to the proximal apical dendrites [237,252,256,257]. In addition to pyramidal neurons, 5-HT$_{2A}$ receptors are also expressed by subsets of parvalbumin- and calbindin-positive interneurons [253,255,256,258–260]. Approximately 20–25% of the glutamic acid decarboxylase-positive cells in PFC express 5-HT$_{2A}$ mRNA [253]. From their morphology these interneurons appear to be basket cells and chandelier cells [258]. GABAergic interneurons expressing parvalbumin and calbindin are sources of perisomatic inhibition that synchronize the oscillatory firing of large ensembles of pyramidal neurons [261–263]. Therefore, 5-HT$_{2A}$ receptors are likely to have direct and indirect effects on the activity of pyramidal cells (see Fig. 8).

Electrophysiological studies have shown that 5-HT$_{2A}$ activation (with DOB or DOI) produces several effects on the membrane properties of layer V pyramidal neurons: there is a moderate depolarization, spike-frequency accommodation is reduced, and the afterhyperpolarization (AHP) that normally follows a burst of spikes is replaced by a slow depolarizing afterpotential (sADP) [264–266]. The effect on AHP is mediated by activation of PLCβ signaling, which inhibits one of the currents (I_{sAHP}) underlying the AHP [267,268]; the induction of sADP is probably a consequence of activating a Ca^{2+}-dependent nonselective cation channel (I_{CAN}). Both of these effects increase the excitability of pyramidal neurons [269]. DOI also produces a 5-HT$_{2A}$-dependent inhibition of voltage-dependent Na^+-currents and L-type Ca^{2+}-currents in PFC pyramidal cells via the PLCβ–IP_3–protein kinase C and PLCβ–IP_3–calcineurin signaling cascades, respectively, effects that would likely influence dendritic integration [270,271].

Hallucinogens have profound effects on excitatory and inhibitory transmission in medial PFC (mPFC) in vitro. Recordings from brain slices have shown that DOI and other 5-HT$_{2A}$ agonists

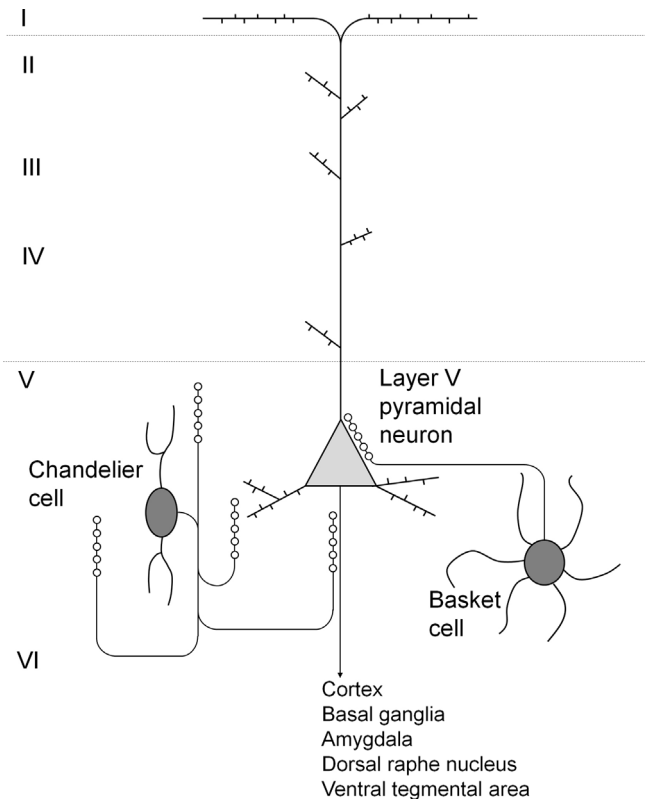

Fig. 8. Distribution of 5-HT$_{2A}$ receptors in neurons in layer V of the prefrontal cortex. 5-HT$_{2A}$ receptors are expressed by glutamatergic pyramidal neurons and GABAergic basket cells and chandelier cells. Hallucinogens increase the frequency of spontaneous EPSCs and IPSCs in layer V pyramidal neurons by enhancing recurrent glutamatergic and GABAergic network activity.

produce a marked enhancement of the frequency and amplitude of spontaneous excitatory postsynaptic potentials/currents (EPSPs/EPSCs) in most layer V pyramidal neurons in mPFC [272,273,456]. These effects are mediated by an increase in Glu release and subsequent activation of postsynaptic AMPA receptors [272,274]. Because these studies failed to locate any glutamatergic mPFC neurons that were driven to fire action potentials by 5-HT$_{2A}$ activation, it was initially thought that the increase in Glu release was caused by local activation of the terminals of glutamatergic thalamocortical afferents [275,276]. However, although the ability of 5-HT to induce EPSCs is lost after deletion of the 5-HT$_{2A}$ gene (*htr2A*$^{-/-}$ mice), the effect can be rescued by selective restoration of 5-HT$_{2A}$ receptors to pyramidal neurons in the forebrain [277]. The *htr2A*$^{-/-}$ mice used by Weisstaub et al. were generated by inserting a floxed Neo-stop cassette between the promoter and the coding region, so the gene could be rescued by crossing the mice with *Emx1-Cre*$^{+/-}$ mice (which selectively expresses Cre recombinase in the forebrain). The fact that the EPSCs were rescued in *htr2A*$^{-/-}$ × *Emx1-Cre*$^{+/-}$ mice shows that projections from thalamus and other subcortical structures are not being directly excited by 5-HT$_{2A}$ receptors. More recent work has identified a subpopulation of pyramidal neurons in mPFC deep layer V that are depolarized and excited by DOI [278], indicating hallucinogens induce spontaneous EPSCs by increasing recurrent glutamatergic network activity. 5-HT$_{2A}$ receptor activation also increases the frequency of spontaneous IPSCs in pyramidal neurons [456], an effect that is mediated by activation of neighboring GABAergic interneurons [260,279]. Therefore, it appears hallucinogens recruit glutamatergic and GABAergic neurons, which produces a marked enhancement of excitatory and inhibitory recurrent network activity in mPFC [280,281]. This conclusion is supported by microdialysis

Table 3
Receptor agonists and antagonists that modulate the electrophysiological effects of 5-HT_{2A} activation in the mPFC also alter the head twitch response in rats and mice.

Receptor	Ligand pharmacology	5-HT_{2A}-induced sEPSCs in layer V pyramidal neurons[a]	DOI-induced head twitch response[a]
5-HT_{2A}	Antagonist	↓ M100907 [272,278,290]	↓ M100907 [160]
5-HT_{2C}	Antagonist	Ø SB242084 [248,278]	Ø SB242084 [170,171]
AMPA	Antagonist	↓ LY293558 [272,274]	↓ LY293558 [274]
		↓ LY300164 [274]	↓ GYKI 52466 [274]
		↓ CNQX [273,278,290]	↓ DNQX [451]
			↓ NBQX [452]
μ-opioid	Agonist	↓ DAMGO [286]	↓ Morphine [453]
		↓ Endomorphin-1 [286]	↓ Buprenorphine [454]
			↓ Fentanyl [454]
$mGlu_{2/3}$	Agonist	↓ LY354740 [287]	↓ LY354740 [273,455]
		↓ LY379268 [273,287]	↓ LY379268 [273]
	Antagonist	↑ LY341495 [287]	↑ LY341495 [455]
Adenosine A_1	Agonist	↓ N^6-Cyclopentyladenosine [288]	↓ N^6-Cyclohexyladenosine [445]

CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; DAMGO, [D-Ala^2, N-$MePhe^4$, $Gly\text{-}ol^5$]-enkephalin; DNQX, 6,7-dinitroquinoxaline-2,3-dione; NBQX, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide; sEPSCs, spontaneous excitatory postsynaptic currents.
[a] The specified ligand reduces the response (↓), has no effect (Ø), or enhances the response (↑).

data showing that hallucinogens increase extracellular levels of Glu [282–284] and GABA [285] in mPFC.

There is evidence that enhancement of glutamatergic activity in mPFC plays an important role in mediating the effects of hallucinogens. Manipulations that suppress the facilitation of recurrent glutamatergic network activity, including the use of $mGlu_{2/3}$ agonists, μ-opioid agonists, adenosine A_1 agonists, and AMPA antagonists [273,286–290], block many of the neurochemical and behavioral effects of hallucinogens. These interactions have been demonstrated most extensively for the HTR (see Table 3), a 5-HT_{2A}-mediated behavior that can be provoked by infusion of DOI directly into the mPFC [291,292]. Likewise, the discriminative stimulus effects of LSD are attenuated by the $mGlu_{2/3}$ agonist LY379268 and augmented by the $mGlu_{2/3}$ antagonist LY341495 [112], and there is evidence that the LSD stimulus cue is mediated by activation of 5-HT_{2A} receptors in the ACA [114]. Another example is the ability of DOI to increase impulsive responding in rats, which is attenuated by administration of LY379268 systemically or directly into mPFC [293,294]. In addition to 5-HT_{2A} antagonists, $mGlu_{2/3}$ agonists and AMPA antagonists also block the ability of DOI to increase cortical expression of BDNF and the immediate-early genes *c-fos*, *erg-2*, and *Arc* [289,294–298]. Evidence has emerged that $mGlu_2$ and 5-HT_{2A} receptors can form heteromeric complexes in cortex [298,299], and these complexes may mediate the crosstalk that occurs between these receptors. It is important to note, however, that it has not been conclusively demonstrated that the heterodimers are responsible for the interactions between 5-HT_{2A} and $mGlu_2$ [300,301], and it is possible the crosstalk is purely functional and occurs at the circuit level. $mGlu_2$ receptors function predominantly as presynaptic autoreceptors [302], so $mGlu_2$ activation could potentially suppress 5-HT_{2A}-induced spontaneous EPSCs by reducing Glu release from axon terminals.

5.2.2. *Effects on PFC network activity in vivo*

Recent studies have examined the effects of hallucinogens on PFC activity in vivo. Extracellular recordings from anesthetized rats have shown that DOI (0.05–0.8 mg/kg, i.v.) and 5-MeO-DMT (0.1 mg/kg, i.v., in combination with the monoamine oxidase inhibitor clorgyline) produce a net excitatory effect on pyramidal neurons in the PrL, IL, and ACA regions of mPFC [303–305]. Individual pyramidal neurons are either excited (38–53%), inhibited (27–35%), or show no response. It appears that these effects are mediated by recruitment of glutamatergic and GABAergic neurons because the excitatory response to DOI is blocked by LY379268 and the inhibitory response is blocked by the $GABA_A$ antagonist picrotoxinin [303,304]. These effects are also blocked by 5-HT_{2A} antagonists. In contrast to those findings, another group has reported that higher doses of DOI (3–5 mg/kg, i.p.) tend to inhibit the firing of pyramidal cells in ACA and the ventral, dorsolateral, and lateral orbitofrontal cortices of behaving rats [306].

Despite the discrepant findings outlined above, hallucinogens produce strikingly similar effects on cortical network activity in anesthetized and freely moving rats. Under anesthesia or during slow-wave sleep, cortical networks display slow (0.5–1 Hz) and delta (1–4 Hz) oscillations [307–309] that reflect alternations between periods of silence (DOWN states) and periods of depolarization with repetitive spiking (UP states). This contrasts with the active waking state, which is characterized by fast rhythms in the gamma range (30–80 Hz) that play a putative role in a multitude of perceptual and cognitive functions [310–314]. Recordings of local field potentials (LFPs) from the PFC have shown DOI reduces low-frequency oscillations in anesthetized rats [315], and dampens gamma oscillations in freely moving rats [306]. DOI also desynchronizes the firing of pyramidal neurons so that their activity is no longer coupled to LFPs [306,315]. 5-MeO-DMT has similar effects on low-frequency PFC network activity in anesthetized rats [305]. Taken together, these findings demonstrate that hallucinogens disrupt the oscillatory activity of cortical networks and reduce the likelihood that individual pyramidal neurons will fire in synchrony.

Similar to the LFP data in rats, magnetoencephalographic (MEG) recordings in humans have shown that psilocybin (2 mg, i.v.) produces broadband reductions in cortical oscillatory power [316]. Dynamic causal modeling of the MEG data indicates that psilocybin reduces cortical synchrony by increasing the excitability of deep-layer pyramidal neurons. Likewise, electroencephalographic studies have reported that *ayahuasca* (containing the equivalent of 0.85 mg/kg DMT) reduces cortical oscillatory power across multiple frequency bands [317,318]. Since cortical oscillations play a fundamental role in a diverse set of mental processes and are required for the coordination of neural processing [319–324], it is tempting to speculate that the reduction of neuronal synchrony by hallucinogens could be responsible for mediating many of their effects on perception and cognition. Along these lines, there is evidence that schizophrenia patients show deficits of gamma oscillations and synchrony [325–328] and reductions in slow-wave sleep [329], and it has been hypothesized that these abnormalities play an important role in the pathophysiology of psychosis.

Neuroimaging studies have demonstrated that hallucinogens alter activity in the frontal cortex. Studies using PET and single-photon emission computed tomography (SPECT) have consistently found that hallucinogens produce frontal hyperactivity. Administration of mescaline sulfate (500 mg, p.o.) produces a hyperfrontal

metabolic pattern, especially in the right hemisphere [53]. PET studies with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) have shown that psilocybin (0.20–0.36 mg/kg, p.o.) also produces a hyperfrontal pattern, with robust metabolic increases in frontolateral and frontomedial cortical regions and ACA [54,330]. Similar patterns of brain activation were found in subjects administered a *yahuasca* as part of a SPECT study [331]. By contrast, it has been argued, based on functional MRI (fMRI) data, that psilocybin *reduces* resting-state brain activity [332]. In that study, volunteers received 2 mg i.v. psilocybin and regional blood flow and venous oxygenation were assessed using arterial spin labeling and blood-oxygen level-dependent (BOLD) fMRI scans. Psilocybin reduced blood flow and BOLD signal in ACA and mPFC, and there was evidence of reduced coupling between mPFC and the posterior cingulate cortex. Based on those results, Carhart-Harris, Nutt, and colleagues concluded that psilocybin reduces activity and connectivity in core nodes of the default-mode network, brain regions that are active during the resting state and potentially involved in introspective processes (for more information, see: [333–335]). It remains to be determined why psilocybin produces such discrepant effects in PET and fMRI studies. One potential explanation is that the hemodynamic responses measured by fMRI are actually better correlated with cortical oscillatory activity than with neuronal firing [336–340]. Indeed, recent work by Artigas and co-workers confirms the decoupling of BOLD measures and spiking in rats [305]. According to their report, 5-MeO-DMT (0.1 mg/kg, i.v.) increased the firing rate of mPFC pyramidal cells by 215%, but significantly reduced the BOLD signal (measured by fMRI) and the power of low-frequency oscillations (measured by LFP recordings). Therefore, PET and fMRI studies may be assessing different types of neurophysiological responses to psilocybin, with PET measuring effects on neuronal firing (reflected by changes in metabolic activity and [^{18}F]FDG uptake) and fMRI measuring effects on cortical oscillatory activity. Alternatively, it is possible that the hemodynamic changes induced by psilocybin are unrelated to its hallucinogenic effects. Psilocybin and its *O*-dephosphorylated metabolite psilocin activate the 5-HT$_{1A}$ receptor in vivo [20,166], and 5-HT$_{1A}$ agonists are known to alter hemodynamic measures in cingulate cortex and other brain regions [341].

5.2.3. Interactions of the PFC with other structures: cortical and subcortical sites

Since most of the projections from PFC to cortical and subcortical regions originate from pyramidal neurons in deep layers V–VI, hallucinogens could potentially profoundly alter how the PFC regulates activity in downstream regions. Indeed, there is some evidence that hallucinogens excite efferent projections from the PFC. For example, DOI activates serotonergic neurons in the dorsal raphe nucleus indirectly by exciting the projection from mPFC [303,342]. Similar findings have been reported for the projection to the ventral tegmental area [303]. Additionally, a recent study by Mocci et al. [284], Mocci et al. [284] assessed whether 5-HT$_{2A}$ receptors modulate the activity of the projection from mPFC to nucleus accumbens (NAc). Retrodialysis of DOI into the mPFC increased the extracellular level of Glu in the NAc by 174%, indicating that DOI activates NAc-projecting mPFC neurons. According to another report, 5-HT$_{2A}$ receptors excite cortico-cortical projections originating from mPFC [343]. In that study, microiontophretic application of 5-HT excited pyramidal neurons with commissural/callosal projections. Because 5-HT had no effect in the presence of the selective 5-HT$_{2A}$ antagonist MDL 11,939, the most reasonable interpretation is that the excitation is mediated by 5-HT$_{2A}$ receptors, but this needs to be confirmed using a selective agonist.

The PFC exerts top-down executive control over processing in temporal and parietal cortices [344–347]. As shown by FDG-PET imaging, psilocybin increases absolute cerebral metabolic rates in the parietal and temporal cortices [54,348]. It is conceivable that hallucinogens could enhance the activity of neuronal ensembles in those regions by driving the firing of glutamatergic projections from the PFC. Moreover, 5-HT$_{2A}$ receptors are expressed at high to moderate densities in temporal and parietal cortical areas [349–353], so the influence exerted by the PFC would act in concert with any local response induced by hallucinogens. Hallucinogenic drugs produce body image changes, derealization, and depersonalization [354,355], effects that are specifically linked to altered activity in fronto-parietal cortex and occipital cortex [356]. This is not surprising because the posterior parietal cortex is part of the dorsal visual stream and generates multiple egocentric representations of space [357–359]. Likewise, hallucinogens enhance memory recall [360], sometimes producing extremely vivid recollections. Since the medial temporal lobe plays a crucial role in the storage and recall of autobiographical memories [361], it has been proposed that hallucinogen effects on memory recall may be linked to activation of this region.

The amygdala, which is involved in generating fear responses and processing the emotional context of sensory input [362], is another subcortical structure potentially affected by changes in the activity of mPFC projections. An fMRI BOLD study in healthy volunteers revealed that psilocybin (0.16 mg/kg p.o.) reduces activation of the amygdala by negative and neutral pictures, and the BOLD signal change was inversely correlated with reports of increased positive mood [363]. Likewise, an electrical neuroimaging study conducted by the same group found psilocybin impairs processing of facial expression valence in the amygdala and other limbic regions [364]. In healthy subjects, there is an inverse correlation between the density of mPFC 5-HT$_{2A}$ binding and the responsiveness of the amygdala to threatening stimuli [365], suggesting processing in the amygdala is regulated by 5-HT$_{2A}$ receptors in mPFC. Hence, the ability of psilocybin to reduce emotional processing in the amygdala could potentially be a consequence of increased inhibitory top-down control from the PFC [364].

The IL subregion of mPFC impairs fear conditioning by inhibiting central amygdaloid nucleus output neurons, which project to brainstem and hypothalamic sites responsible for expressing fear responses [366]. Although it was not initially clear how mPFC inhibits the amygdala because the projection is glutamatergic [367,368], the mechanism is now believed to involve excitation of GABAergic neurons in the intercalated nuclei of the amygdala [369–371]. Psilocybin and TCB-2 have been shown to facilitate the extinction of fear conditioning in C57BL/6J mice [372,373], which could be a consequence of activating the projection from IL to the intercalated nuclei. However, it has not been ruled out that psilocybin and TCB-2 are acting directly in the amygdala; excitatory and inhibitory neurons in the amygdala express 5-HT$_{2A}$ receptors [374,375], and DOI and other 5-HT$_{2A}$ agonists act locally to produce direct excitatory and indirect inhibitory effects in the amygdala [376–378].

5.2.4. Interactions of the PFC with other structures: effects on cortico-striato-thalamo-cortical (CSTC) loops

It has been theorized that hallucinogen-induced altered states may arise in part through effects on cortico-striato-thalamo-cortical (CSTC) feedback loops [348,356,379]. CSTC loops are parallel, anatomically segregated circuits relaying information between the basal ganglia, thalamus, and cortex [380,381]. In each circuit, projections from multiple cortical regions converge in specific subregions of the striatum. The striatum, in turn, projects to the pallidum, which sends feedback to the cortex via the thalamus. In this regime, the thalamus serves as a filter that restricts or gates the flow of sensory and cognitive information to the cortex. There has been some debate about the exact number of CSTC loops

[382,383], but at least five have been putatively identified, each serving a different function. The limbic loop, for example, receives input from the temporal lobe, ACA, and medial orbitofrontal cortex, and links the ventral striatum (including NAc, lateral caudate, and ventromedial putamen), ventral pallidum (VP), and mediodorsal thalamus. Vollenweider and Geyer [356] have proposed that psilocybin reduces thalamic filtering by activating 5-HT_{2A} receptors in the limbic CSTC loop, resulting in excessive stimulation of frontal regions, hyperfrontality, and symptoms such as sensory overload and hallucinations.

Although involvement of CSTC loops in the effects of hallucinogens is admittedly speculative, it does receive some support from the fact that hallucinogens disrupt PPI in humans and in animal models [90,178,179,182,183,384]. Importantly, PPI is regulated by components of the limbic CSTC loop, including mPFC, NAc, and VP [385]. The VP appears to be responsible for the disruption of PPI by hallucinogens [386]. DOI disrupts PPI when infused directly into the VP, but not when infused into the NAc. Likewise, infusion of M100907 into the VP prevents systemically administered DOI from disrupting PPI. It is important to note, however, that the PPI-disruptive effects of DOI are partially blocked when M100907 is infused into the dorsal striatum, so it is not entirely certain that the VP is the only site of action for DOI.

5.3. Visual cortex

Hallucinogens produce profound effects on visual perception. This includes visual distortions such as micropsia or macropsia, kinetopsia, pareidolias, hyperchromatopsia, dysmorphopsia, and polyopia-like trailing phenomena; elementary imagery composed of multicolored geometric patterns; and complex imagery with scenes, objects, and people (see Fig. 5). The visual imagery induced by hallucinogens is extremely vivid and can be observed with the eyes open or closed. When scientists began to experiment with mescaline at the end of the nineteenth century almost all of their work focused on the visual phenomenology [387–392]. Despite its highly subjective nature, the drug-induced imagery has been characterized in great detail [393,394]. Heinrich Klüver [393] was the first to recognize that all of the elementary geometric hallucinations induced by mescaline are elaborated variations of four basic forms, which he called *form constants*: (a) tunnels and funnels, (b) spirals, (c) lattices and checkerboards, and (d) cobwebs. The form constants are not unique to hallucinogens and can occur during a variety of hallucinatory states, including migraine aura [395], epilepsy [457], sensory isolation [396], viewing flickering light [397,398], and electrical cortical stimulation [399,400].

Several theoretical explanations for geometric visual hallucinations have been proposed based on retinocortical mapping and the architecture of V1 [401–405]. According to these mathematical models, excitation of V1 neurons produces self-organizing patterns of activity that correspond to Klüver's form constants. The excitation of V1 is presumably driven by 5-HT_{2A} receptors because ketanserin blocks the visual hallucinations induced by psilocybin [85,89]. There are moderate to high densities of 5-HT_{2A} receptors in V1 [349,350,353,406], with the highest level occurring in geniculorecipient sublayer IVcβ [350]. Similar to other cortical regions, almost all glutamatergic pyramidal neurons and relatively few GABAergic interneurons in V1 express 5-HT_{2A} mRNA [407,408]. A recent electrophysiology study conducted in anesthetized macaque monkeys revealed that DOI produces a combination of excitatory and inhibitory effects in V1, exciting neurons with low firing rates and inhibiting neurons with high firing rates [407]. Since neuronal firing in V1 is driven by visual stimuli, one possible interpretation is that DOI reduces the response to visual input while enhancing spontaneous internally driven activity. It is fairly well-established that hallucinogens reduce retinocortical transmission [409–411]. Indeed, psilocybin inhibits N170 visually evoked potentials in human subjects via 5-HT_{2A} [89,412]. Visual input stabilizes network activity in V1 by driving inhibitory interneurons [413]. Therefore, a reduction of visual input, coupled with an increase in the excitability of pyramidal neurons, could destabilize network activity in area V1, generating patterns of neuronal firing that are perceived as geometric form constants.

In contrast to the elementary visual hallucinations, which are linked to area V1, complex visual hallucinations probably arise from 5-HT_{2A} activation in higher level visual areas. There is evidence that excitation of Brodmann area (BA) 19 and BA 37 can produce complex visual hallucinations [414–416]. Among patients with Parkinson's disease, approximately 22% experience complex visual hallucinations [417]. Their visual hallucinations are linked to elevated levels of 5-HT_{2A} receptor binding in ventral visual pathway [418,419], and can be ameliorated by blocking 5-HT_{2A} receptors. For example, a PET imaging study with [^{18}F]setoperone found that visual hallucinations in Parkinson's patients are associated with unusually high levels of 5-HT_{2A} binding in the inferooccipital gyrus (BA 19), fusiform gyrus (BA 20 and BA 37), and inferotemporal gyrus (BA 20) [418]. According to another study conducted *post-mortem*, Parkinson's patients with visual hallucinations show elevated levels of 5-HT_{2A} binding in the inferolateral temporal cortex (BA 21) [419]. Two clinical trials have shown that the selective 5-HT_{2A} inverse agonist pimavanserin reduces the severity of hallucinations in Parkinson's disease [420,421]. The atypical antipsychotics clozapine and risperidone, which block the 5-HT_{2A} receptor, are also effective against the visual hallucinations [422–424].

6. Summary

Despite the complexity of hallucinogen effects, we are beginning to understand how these substances work in the brain. The 5-HT_{2A} receptor was first identified about thirty years ago as a possible site of action of hallucinogens. It is now clear that most of the effects of hallucinogens are mediated by 5-HT_{2A} activation. Although the vast majority of this evidence was derived from studies in animals, the resumption of human studies with hallucinogens has provided additional support.

Recent clinical trials have provided a highly detailed characterization of hallucinogen effects. However, most of this work has focused on one hallucinogen (psilocybin). By comparison, very little is known about the effects of other agents. This is especially true for ergoline and phenylalkylamine hallucinogens. One of the most characteristic properties of hallucinogens is how unpredictable their effects can be. The exact nature of the experience is highly variable and depends on the mood and expectations of the subject (the "set") as well as the environment in which the drug is ingested (the "setting") [189,425–427]. Depending on the circumstances, the effects of hallucinogens may be perceived as being highly pleasurable or highly aversive (e.g., Aldous Huxley's description of mescaline as "heaven and hell"). Although hallucinogens act in a relatively unspecific manner [428], and hence a broad range of experiences are possible, previous clinical studies have confirmed that there is also a great deal of similarity between the effects of different hallucinogens. In other words, although it is impossible to predict exactly what type of experience will be produced by, for example, LSD or psilocybin, it appears that for the most part any experience produced by LSD can also occur with psilocybin. Thus, volunteers could not identify any clear differences between the subjective effects of those two compounds when administered by blind dosing [37–39,41]. However, those studies need to be repeated using modern psychometric assessment methods. Additionally, it is not clear to what extent those findings extend to other hallucinogens, or even to higher doses of LSD and psilocybin. One

potentially unique aspect of the LSD experience is that it reportedly occurs in two distinct temporal phases [206,427,429,430], but this needs to be confirmed by future investigations.

It appears that 5-HT_{2A} activation is a common characteristic of serotonergic hallucinogens and is responsible for mediating their shared effects, but this does not eliminate the possibility that other receptors may play an ancillary role. There are pharmacological differences between the phenalkylamine, tryptamine, and ergoline classes, as well as between specific compounds within each class, and these differences could potentially influence the subjective effects [20]. The receptors activated by hallucinogens may be analogous to individual musical notes that can be played in combination to generate chords associated with unique subjective impressions [431], with 5-HT_{2A} receptor activation being akin to the root note. Extramural investigations have attempted to categorize the existence of subtle subjective differences between the effects of different hallucinogens (e.g., [432,433]). However, it is not clear to what extent the apparent differences between individual compounds are influenced by expectation and by other factors. There are also dose- and route-dependent variations in the effects of hallucinogens, which can alter both the intensity and the qualitative nature of the response. Furthermore, even individual subjects may experience markedly different responses to the same drug on different occasions [434]. The possibility exists that for hallucinogen effects, there may be just as much intra-drug variability as there is inter-drug variability. Only detailed, well-controlled clinical trials comparing multiple compounds over a wide range of doses will answer these questions. Nevertheless, it seems to be fairly well established that there are marked qualitative differences between the effects produced by serotonergic hallucinogens and by members of other drug classes. Although it was recently reported that subjects administered high doses of the NMDA antagonist dextromethorphan under double-blind conditions identified it as a classical hallucinogen when they were asked to classify it pharmacologically [435], there are major confounds associated with this study. First, Reissig et al. [435] acknowledged that most if not all of the study participants were expecting to receive psilocybin, and this may have influenced their response to dextromethorphan. Second, the subjects did not receive a hallucinogen as an active control, so the study did not actually quantify the similarity between the effects of dextromethorphan and hallucinogens. It is also surprising that none of the subjects classified dextromethorphan as a dissociative anesthetic, since dextromethorphan is abused for its dissociative-like effects [436] and produces phencyclidine- and ketamine-like discriminative stimulus effects in rats [437,438].

Over the last decade, there has been renewed interest into the potential therapeutic uses for hallucinogens. Psilocybin can induce highly meaningful spiritual experiences [58], and some subjects have reported experiencing positive changes in mood and behavior that persist for many months [62]. It may be possible to exploit these effects therapeutically. Recent clinical trials have investigated whether psilocybin has efficacy against anxiety in terminal cancer patients [56], and LSD has been tested as a potential adjunct for psychotherapy [439]. Several follow-up studies are currently in progress. It is anticipated that these and other studies will yield important insights into the psychopharmacology of hallucinogens, as well as showing whether there are potential medical uses for these drugs.

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