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Serotonergic Psychedelics: Experimental Approaches for Assessing Mechanisms of Action

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Abstract

Recent, well-controlled – albeit small-scale – clinical trials show that serotonergic psychedelics, including psilocybin and lysergic acid diethylamide, possess great promise for treating psychiatric disorders, including treatment-resistant depression. Additionally, fresh results from a deluge of clinical neuroimaging studies are unveiling the dynamic effects of serotonergic psychedelics on functional activity within, and connectivity across, discrete neural systems. These observations have led to testable hypotheses regarding neural processing mechanisms that contribute to psychedelic effects and therapeutic benefits. Despite these advances and a plethora of preclinical and clinical observations supporting a central role for brain serotonin 5-HT_{2A} receptors in producing serotonergic psychedelic effects, lingering and new questions about mechanisms abound. These chiefly pertain to molecular neuropharmacology. This chapter is devoted to illuminating and discussing such questions in the context of preclinical experimental approaches for studying mechanisms of action of serotonergic psychedelics, classic and new.

Keywords

α Adrenergic; 5-HT_{2A}; 5-HT_{2C}; Cingulate cortex; Head-twitch; Ketanserin; Psychedelic mechanisms; Receptor binding; Receptor conformations; Receptor dimers; Receptor function; Serotonin; Signal transduction

1 Introduction

Humans have been reporting their experiences with psychoactive substances in exquisite detail for centuries, at least. In the mid 1800s, J. J. Moreau de Tours wrote about hashish intoxication (Moreau 1973). Sigmund Freud later scripted his personal relationship with cocaine (Freud and Byck 1975). Ann and Alexander Shulgin then gave the world *PiHKAL* (Shulgin and Shulgin 1991) and *TiHKAL* (Shulgin and Shulgin 1997), books describing mostly novel psychedelic drugs and their effects. Fast-forward to today, we see the practice of self-reporting experiences with psychoactive substances is rampant, organized, archived, and accessible (e.g., Erowid.org). The surge of information about new psychoactive substances reported on the internet paralleling the surge in online vendors selling such

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"research chemicals" has catalyzed their spread and use. Systematic research aimed to discover and document their unique mechanisms has, understandably, lagged behind.

Fortunately for researchers, most novel psychedelics still fit within familiar chemotype classes and have overlapping pharmacology with their classic predecessors – mainly 5-$HT_{2(A, B, and C)}$ receptor agonist activity in the case of serotonergic psychedelics that include lysergamides (e.g., LSD), tryptamines (e.g., psilocybin and DMT), and phenethylamines (e.g., mescaline and including phenylisopropylamines, e.g., DOB). Chemists have synthesized dozens of relatively obscure serotonergic psychedelics, which have appeared recently on the clandestine market. Examples include lysergamides like AL-LAD (Brandt et al. 2017b) and PARGY-LAD, tryptamines like 5-MeO-DALT (Cozzi and Daley 2016), and phenylethylamines like bk-2C-B, the β-ketone analog of 2C-B and 25C-NBOMe, another analog of 2C-B (Halberstadt 2017). Recent literature covers what is currently known regarding the physiological, psychological, and visual perceptual effects of serotonergic psychedelics, their neuropharmacology and effects on human brain functional connectivity, their use as potential medicines, their inherent risks, and the phenomenology of the psychedelic experience (Halberstadt 2017; Kometer and Vollenweider 2016; Liechti 2017; Nichols 2016; Nichols et al. 2017; Preller and Vollenweider 2016). This chapter covers preclinical research strategies used to elucidate common and divergent mechanisms of serotonergic psychedelics, classic and new.

2 5-HT_{2A} Receptors: The End of the Beginning

For research probing mechanisms, it is clear we have reached the end of the beginning – a cadre of researchers agree that 5-HT_{2A} receptor activation is necessary for most of the psychoactive effects of serotonergic psychedelics (Kometer et al. 2013; Kraehenmann et al. 2017; Nichols 2016; Preller et al. 2017; Vollenweider et al. 1998). To understand mechanisms, though, requires delineating atomic-level drug and receptor interactions and attendant consequences on signal transduction (Wacker et al. 2017) and cellular intrinsic excitability, subsequent short-term and long-term effects on electrochemical communication within and between micro- and macroneural circuits (Petri et al. 2014), as well as the interplay of neural circuits with the user's personality, psychological and cognitive state, personal history and genetic background ("set"), and the external environment ("setting") (Studerus et al. 2012).

Questions from these wide-ranging levels of analyses remain. At the highest level, self-reported subjective experiences, there appear to be differences in effects (beyond pharmacokinetics) across and even within classes of serotonergic psychedelics (Glennon 1992; Shulgin and Shulgin 1991, 1997). Although representatives from each chemotype class can induce similar, visual "form constants" of the lattice and tunnel types (elementary psychedelic patterns) (Kometer and Vollenweider 2016), users typically report differences in their "body load," stimulant and entactogenic effects, the degree to which they produce "organic" or "synthetic" visual or aural hallucinations, and how deeply and clearly they affect emotional and cognitive states. For example, the psychedelic 5-HT_{2A} agonist, DIPT, appears to produce distinct aural, hallucinatory effects (Blough et al. 2014; Rickli et al. 2016; Shulgin and Shulgin 1997), whereas DMT (and analogs including 5-MeO-DMT) is

distinguished by its marked proclivity to induce complex hallucinations (Strassman 2001), such as visual hallucinations of things, entities, or events separated from consensus reality. If the effects of different serotonergic psychedelics can be distinguished reliably, then what, mechanistically, differentiates them? Are differences caused by unique, dynamic, active conformations of 5-HT_{2A} receptors, or do some serotonergic psychedelics preferentially target distinct populations of 5-HT_{2A} receptors, e.g., pre- or postsynaptic (Bécamel et al. 2017)? Alternatively, other receptor targets or 5-HT_{2A} receptors functionally linked to other systems, for example, the endocannabinoid system (Best and Regehr 2008; Parrish and Nichols 2006), may contribute to psychedelic effects. Furthermore, unique 5-HT_2 receptor homo- or heterodimers or oligomers could be the mechanistic target of serotonergic psychedelics.

3 Binding Events and Cellular Signal Transduction

3.1 Radioligand Receptor Binding

Radioligand receptor binding assays were integral in determining that 5-HT_2 receptors were the primary targets of classic psychedelics, such as LSD and DOB (Glennon et al. 1984), and radiolabeled psychedelics applied in autoradiography of brain of slices determined the location of psychedelic receptor targets across neural systems in rodents (McKenna et al. 1987; McKenna and Saavedra 1987). Presently, researchers are developing selective 5-HT_{2A} agonist radioligands to analyze 5-HT_{2A} receptors in humans, using PET imaging techniques (Johansen et al. 2017), and a recent clinical study employing [^{11}C]Cimbi-36, a selective 5-HT_2 agonist, reports dense expression of 5-HT_2 receptors across all cortical regions, but limited expression in subcortical regions (Beliveau et al. 2017).

Radioligand competition binding and saturation binding assays are used to quantify the affinity, or strength of interaction, of new compounds at receptors. In a competition binding assay, a compound with unknown affinity at the receptor of interest is added to a multi-well microplate at increasing concentrations across wells, typically at half-log units, together with a radiolabeled ligand, with known affinity at the receptor of interest, at one fixed concentration (e.g., its K_d at the receptor, the equilibrium dissociation constant of the ligand). Cell membranes expressing the receptor are then added to the wells, and the mixture is incubated for a period of time until equilibrium is achieved, i.e., the amount of free ligand and ligand bound to the receptor remains constant. The contents of the wells are then rapidly passed through a fiberglass filter mat that collects radioligand bound to receptor but permits free radioligand to pass through. Samples are then added to scintillation cocktail, and a scintillation counter detects the amount of radioactivity emitted from each sample over a fixed time (e.g., counts per minute). The affinity, K_i (equilibrium dissociation constant of a ligand determined in inhibition studies), of the unknown is then determined by fitting a nonlinear dose-response inhibition curve, calculating the concentration of the compound required to displace 50% of the radioligand from the receptor, followed by correction incorporating the radioligand's affinity and concentration (Cheng and Prusoff 1973).

Saturation binding assays include a similar workflow, but the radionuclide is attached chemically to the compound with unknown affinity at the receptor of interest. The radioligand is then incubated, with tissue expressing the receptor, at increasing

concentrations across wells. The affinity, K_d, of the radioligand, or the concentration required to occupy 50% of the receptors at equilibrium, is then calculated, as well as the saturating concentration, which can be used to calculate the density of receptor binding sites labeled by the radioligand, or B_{max}. For details, refer to McKinney and Raddatz (2006). A saturation binding assay provides a more accurate affinity value than a single competition binding assay, due to the fact that a radioligand in a competition assay may selectively bind a subset of receptors existing in specific conformations – or may interact with unique receptor amino acids with which the unknown compound may not interact. In other words, K_i values at a specific receptor population may be different depending on the radioligand used, but K_d values remain constant.

Agonist affinities at G-protein-coupled receptors (GPCRs) are strongly affected by the state of G-proteins linked to them. Agonists stabilize active receptor conformations – receptors bound to guanine nucleotide-free Gα proteins – and then dissociate slowly from these active conformations, imparting high affinity at them (DeVree et al. 2016). Thus, competition binding assays in the presence or absence of non-hydrolyzable guanine nucleotides (e.g., GTPγS which blocks agonist high-affinity binding) can be used to determine the affinity of ligands at inactive or active receptor conformations. Moreover, since agonist ligands typically have a higher affinity at receptors labeled with agonists (high-affinity, K_H) compared to antagonists (low-affinity, K_L), comparisons of these affinities can be used as first-pass screens to test novel ligands for agonist activity. Also, functional efficacies of 5-HT_2 ligands correlate strongly with their K_L to K_H ratios (Egan et al. 2000).

Radioligand binding assays can also be used to measure ligand—receptor association and dissociation rates (Sykes et al. 2010). Ligand—receptor kinetics data can inform efficacy, selectivity, and duration of action in vivo (de Witte et al. 2016). A ligand's residence time at a receptor—the duration of time a ligand is bound to a receptor—may also be a critical factor for recruiting intracellular signaling molecules. Receptor-mediated activation of cellular cascades may be time-dependent; if an agonist ligand's dissociation rate is too quick, a substantial proportion of a cellular cascade may remain inactive. Recently, scientists showed that LSD has a relatively long residence time at the 5-HT_{2A} receptor (Wacker et al. 2017). Such studies may inform mechanistic differences between serotonergic psychedelics. The actions of DMT, for example, are very short-lived compared to LSD. It may be discovered that residence time dictates transduction signals that initiate unique cellular psychedelic cascades. LSD potently recruits β-arrestin2 to 5-HT_{2A} receptors, but mutating lysine residue 229 to alanine to decrease LSD's residence time strongly reduces β-arrestin2 recruitment to 5-HT_{2A} (Wacker et al. 2017).

Classic psychedelics of the tryptamine and lysergamide chemotypes are not selective for 5-HT_2 receptors. Psilocin, for example, has appreciable affinity (between 4 and 220 nM K_i) at human 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_5, 5-HT_6, and 5-HT_7 receptors, c.f. PDSP database (Roth et al. 2000). Novel serotonergic psychedelics, such as *N*-benzylphenethylamines, and putatively psychedelic *N*-benzylated-5-methoxytryptamines, possess high affinity at 5-HT_2 receptors but also bind to other receptors. For example, 25I-NBOMe has significant affinity (<300 nM K_i) at μ-opioid, κ-opioid, and histamine H1 receptors (Nichols et al. 2008). Others have also observed activity of certain *N*-benzylphenethylamines at H1 (K_i as low as

80 nM), α1A- and α2A-adrenergic (K_i as low as ~300 nM) receptors (Rickli et al. 2015b), rendering them somewhat similar to LSD, which is promiscuous (PDSP database). Relative to their 2C-x classic hallucinogen predecessors, these drugs have substantially greater selectivity for 5-HT_2 over 5-HT_{1A} receptors (Rickli et al. 2015b). Many *N*-benzylated-5-methoxytryptamines and *N*-benzylphenethylamines also possess significant affinity at 5-HT_6, and *N*-3-iodobenzyl-5-methoxytryptamine also has significant activity at 5-HT_7 receptors (Nichols et al. 2015). A recent report of 25CN-NBOH, however, shows that this compound is very selective at 5-HT_2 receptors compared to a host of other receptors; the only relevant affinities (K_i ~300 nM or less) noted are at human 5-HT_6 and rat sigma-1 and sigma-2 (Jensen et al. 2017).

3.2 Receptor Functional Assays

Serotonergic psychedelics stimulate 5-HT_2 receptor – $G\alpha_q$ signaling, as measured by activation of phospholipase C-β, causing increases in phosphoinositide hydrolysis, thereby stimulating inositol phosphate production and activation of protein kinase C (Jope et al. 1994; Sanders-Bush et al. 1988); this is the canonical 5-HT_2 receptor pathway. Most experimenters focus on activation of Gα subunits, because of technical challenges measuring βγ activation from $G\alpha_q$-coupled receptors (Kadamur and Ross 2013). Laborious techniques to assess ligand functional effects involving chromatography-based detection or anion exchange columns (Felder et al. 1990; Hide et al. 1989) have frequently been replaced by relatively simple, high-throughput, kit assays that employ highly selective, fluorophore-labeled monoclonal antibodies that bind signaling molecules (Canal et al. 2013b). With the advent of protocols and toolkits to measure ligand-stimulated 5-HT_2-β-arrestin2 recruitment, researchers increasingly examine this event, especially with the objective to determine ligand bias (Kenakin 2016; Wacker et al. 2017; Wang et al. 2013).

Other signaling pathways activated by 5-HT_2 receptors, such as $G\alpha_{13}$-dependent or $G\alpha_{13}$-independent phospholipase D pathways (Barclay et al. 2011; McGrew et al. 2002), remain difficult to measure. The workflow can include extraction steps and chromatography and is low-throughput (Walker et al. 2004). Accordingly, much less is known about how psychedelics affect these cellular signaling cascades. For similar reasons, the activity of psychedelics is not fully characterized at other members of the $G\alpha_q$ subclass or other signaling pathways that may be linked endogenously to 5-HT_2 receptors, including $G\alpha_q$-p63RhoGEF-RhoA, $G\alpha_{11}$, $G\alpha_{12}$, $G\alpha_{14}$, $G\alpha_{15}$, and $G\alpha_{16}$ (Milligan and Kostenis 2006). 5-HT_2 receptor activation stimulates calcium mobilization, but this response can be triggered by $G\alpha_q$-dependent increases in inositol phosphates, i.e. IP_3, that activate IP_3 receptors (Ca^{2+} release channels) on endoplasmic reticulum, or by activation of Ca^{2+} permeable channels on cell membranes. There is much to be discovered about the ability of 5-HT_2 receptors to modulate activity of distinct ion channels important for neurotransmission. It is incumbent to determine the effects of serotonergic psychedelics at noncanonical signal transduction pathways, because the 5-HT_{2A} intracellular signals that generate psychedelic effects remain mysterious (Nichols 2016).

Although there are correlations between the psychedelic potencies of phenethylamines, their phenylisopropylamine counterparts, and 5-HT_{2A} agonist efficacy to stimulate inositol

phosphate production (Moya et al. 2007; Parrish et al. 2005), LSD, one of the most potent psychedelics, is a notoriously weak 5-HT_{2A} agonist at this pathway (Berg et al. 1998; Egan et al. 1998a). Moreover, high-affinity agonist binding of several 5-HT_{2A} ligands does not correlate with efficacy to stimulate 5-HT_{2A}-mediated inositol phosphate production (Roth et al. 1997). Also, ligand efficacy at this pathway does not correlate with efficacy to substitute for LSD or DOM in drug discrimination tests (Rabin et al. 2002). Serotonergic psychedelics are most often observed to be partial agonists at the 5-HT_{2A} inositol phosphate production pathway, relative to 5-HT. This extends across all classes of serotonergic psychedelics, classic and new, including *N*-benzylphenethylamines, DOB, 2C-B, novel tryptamines, psilocin, and LSD (Acuna-Castillo et al. 2002; Moya et al. 2007; Parrish et al. 2005; Rickli et al. 2015b, 2016).

Lorcaserin (Belviq®, a 5-HT_{2C}-preferring agonist for obesity), however, efficaciously stimulates 5-HT_{2A}-mediated inositol phosphate production in vitro (75% efficacy compared to 5-HT at human 5-HT_{2A} receptors) (Thomsen et al. 2008), and at clinical doses, likely stimulates this 5-HT_{2A} receptor pathway. From the FDA briefing document (NDA22529):

> Assuming that distribution of lorcaserin in monkeys and humans is most comparable, brain levels of lorcaserin may reach 430 ng/ml or 1.7 µM from the clinical dose of 10mg bid. This concentration of lorcaserin would be expected to activate central 5HT2A and potentially [5HT]2B receptors, assuming that lorcaserin has access to receptor sites in the CNS.

Yet, at this dose, lorcaserin is not psychedelic. As a benzazapine, it is also structurally quite different from any of the serotonergic psychedelics – rehashing thoughts that chemotype, and by extension chemotype-dependent stabilization of special 5-HT_{2A} psychedelic conformations, drives psychedelic effects. Other structurally unique ligands that activate 5-HT_{2A}-$G\alpha_q$ signaling, including the piperazine mCPP, also do not elicit psychoactive effects like the serotonergic psychedelics. It has been argued that increased activity at 5-HT_{2C} relative to 5-HT_{2A} receptors, which mCPP and lorcaserin possess, attenuates psychedelic effects (Fantegrossi et al. 2010), but several observations disprove this postulation (Canal and Morgan 2012). For example, all serotonergic psychedelics are 5-HT_{2C} agonists, and psychedelic effects do not abate by increasing dose, i.e., by increasing stimulation of 5-HT_{2C} receptors.

The classic first-generation antipsychotic, chlorpromazine (Thorazine®), a potent antagonist at the 5-HT_{2A}-$G\alpha_q$-inositol phosphate pathway (Canton et al. 1994), does “not significantly influence the somatic and psychological disturbances” caused by LSD (Clark and Bliss 1957). Others reported that chlorpromazine attenuates, but does not fully block, the psychedelic effects of LSD (Isbell and Logan 1957) or DOM (Snyder et al. 1967) – chlorpromazine doses ranged from 50 to 200 mg (P.O.). Also peculiar is that the non-hallucinogenic 5-HT_{2A} lysergamides, ergotamine and BOL-148, do not significantly alter the psychoactive effects of psilocybin or LSD, respectively, in humans (Clark and Bliss 1957; Pokorny et al. 2016). Though, ergotamine may not readily cross the blood-brain barrier (Verhoeff et al. 1993), and BOL-148 appears to elicit psychoactive effects in some people (Richards et al. 1958). Collectively, these data cast major doubt on the 5-HT_2-$G\alpha_q$-inositol phosphate pathway as a central mediator of psychedelic effects. Direct in vivo

support for this conclusion emanates from a preclinical study that showed knockout of $G\alpha_q$ does not eliminate (but does attenuate) the 5-HT_{2A}-dependent head-twitch response induced by the psychedelic phenylisopropylamine DOI (Garcia et al. 2007).

Knockout of β-arrestin2 in mice has *no* effect on the DOI-elicited head-twitch response (Schmid et al. 2008) and actually increases the head-twitch response elicited by 5-MeO-DMT (Schmid and Bohn 2010). Moreover, measurements of other signal transduction molecules in vitro, including 5-HT_{2A}-$G\alpha_{i/o}$-elicited arachidonic acid release (phospholipase A activation) do not reveal unique signaling properties of psychedelics, and like the phospholipase C-β-inositol phosphate pathway, many psychedelics are partial agonists relative to 5-HT (Kurrasch-Orbaugh et al. 2003a, b; Moya et al. 2007). Gonzalez-Maeso's group has focused on alternative 5-HT_2-$G\alpha_{i/o}$ signaling in vivo. They show that serotonergic psychedelics, but not lisuride (considered a non-hallucinogenic 5-HT_{2A} agonist), alter gene expression through pertussis toxin-sensitive $G\alpha_{i/o}$ signaling (Gonzalez-Maeso et al. 2007). It should be noted, however, that gene expression changes peak after the induction of behavioral responses, thus, likely do not cause them (Gonzalez-Maeso et al. 2007). Nevertheless, in vitro studies show that pertussis toxin decreases DOI- and LSD-elicited inositol phosphate production and abolishes their potentiation of Erk1,2 phosphorylation but does not impact lisuride and ergotamine responses (Karaki et al. 2014).

These observations show that our understanding of serotonergic psychedelic mechanisms is unripe, and creative studies need to be conducted. For example, clozapine (Clozaril®), an inverse agonist at the 5-HT_{2A}-$G\alpha_q$-inositol phosphate pathway (Egan et al. 1998b) and arguably the most effective antipsychotic (Wenthur and Lindsley 2013) activates 5-HT_{2A}-mediated AKT phosphorylation, an effect blocked by the selective 5-HT_{2A} antagonist M100907 (Schmid et al. 2014). Also, like other 5-HT_{2A} agonists, clozapine causes 5-HT_{2A} receptor internalization, whereas ketanserin does not (Raote et al. 2013). Recent studies also revealed that psilocin is a 5-HT reuptake inhibitor, i.e., blocks the serotonin transporter, SERT (Blough et al. 2014; Rickli et al. 2016). Also, classic psychedelics can activate TAAR1 and sigma-1 receptors (Bunzow et al. 2001; Fontanilla et al. 2009; Simmler et al. 2016). Intriguingly, 2C-B, traditionally viewed as a selective 5-HT_2 agonist, has an inhibitory potency at SERT similar to MDMA (Montgomery et al. 2007); similar effects were observed with DIPT (Rickli et al. 2016). Moreover, DMT causes serotonin efflux from SERT with efficacies similar to MDMA (Rickli et al. 2016).

Despite micromolar 5-HT_{1A} affinities (Rickli et al. 2015b), *N*-benzylphenethylamines retain potent psychedelic effects. Also, benzofurans, such as 5-APB and 6-APB, are potent and efficacious 5-HT_{2B} agonists but have very low potency at 5-HT_{2A} receptors. They also stimulate efflux of DA and 5-HT and have activity at TAAR1 receptors (Iversen et al. 2013; Rickli et al. 2015a), but anecdotal reports note that psychedelic effects are relatively minor compared to classic psychedelics. These observations provide further credence that the 5-HT_{2A} receptor, but not 5-HT_{1A}, 5-HT_{2B}, TAAR1, or monoamine transporters, initiates psychedelic effects. These and other proteins may modulate psychedelic effects. The 5-HT_{1A} partial agonist (and β-adrenergic antagonist (Hoffmann et al. 2004)), pindolol, for example, strongly potentiates psychedelic effects of DMT (Strassman 2001). In conclusion,

despite the central role of 5-HT_{2A} receptors in producing psychedelic effects, we are still lurking in a fuzzy arena regarding mechanisms after the receptor binding event.

3.3 X-Ray Crystallography

Molecular modeling, molecular dynamics simulations, medicinal chemistry, and molecular pharmacology studies, employing point mutations of 5-HT_{2A} receptor amino acids that alter ligand-receptor molecular interactions, help illustrate how serotonergic psychedelics interact with the 5-HT_{2A} receptor (Braden and Nichols 2007; Braden et al. 2006; Chambers and Nichols 2002; Choudhary et al. 1995; Isberg et al. 2011; Perez-Aguilar et al. 2014). The new gold standard, however, for deciphering the precise fit of a ligand at a receptor and the conformation(s) of the receptor it stabilizes is to isolate crystals of the receptor with the ligand bound, and to develop atomic-level resolution (low ångström, i.e., <3.0 Å) crystallographic images of them. Numerous, resolved GPCR crystal structures with agonists, antagonists, or inverse agonists bound have been reported recently (Hua et al. 2016, 2017; Thal et al. 2016; Wang et al. 2017) and are poised to quickly evolve the structure-based drug discovery process (Ranganathan et al. 2017).

The 5-HT_{2B} crystal structure with LSD bound revealed how a classic psychedelic precisely interacts with a 5-HT_2 receptor and delivered a putative snapshot of a psychedelic receptor conformation (Wacker et al. 2017). LSD binds in the orthosteric pocket of 5-HT_{2B}, which is characterized by many hydrophobic side chains from residues in transmembranes III, V, VI, and VII; recent mutagenesis studies and a resolved 5-HT_{2C} crystal structure confirm that this pocket is also quite similar in the 5-HT_{2C} receptor (Canal et al. 2011; Cordova-Sintjago et al. 2014; Liu et al. 2017; Peng et al. 2018). The basic nitrogen of the ergoline system forms a salt bridge with aspartic acid residue D135 in transmembrane III – this critical interaction is conversed across aminergic GPCRs (Katritch et al. 2013). LSD's ergoline system has aromatic interactions with F340 and F341 in transmembrane VI, and its indole nitrogen hydrogen bonds with G221 in transmembrane V. LSD binds differently than ergoline, as ergoline's indole nitrogen forms a distinct hydrogen bond with T140 in 5-HT_{2B}'s transmembrane VII (Wang et al. 2013), a bond not seen with LSD-5-HT_{2B}. Mutating the homologous residue in 5-HT_{2C} to alanine significantly reduces 5-HT's affinity and agonist potency to stimulate 5-HT_{2C}-phosphoinositide hydrolysis (Liu et al. 2017).

LSD also interacts with the previously described extended binding pocket of 5-HT_{2B} (Wang et al. 2013); specifically, its ethyl groups interact with residues W131 and L132 in transmembrane III, and L362 in transmembrane VII. These interactions may be key to LSD's psychedelic effects, as molecular modeling and ligand docking at 5-HT_{2A} appear to show that they persist for LSD but are lost with LSA, which lacks the diethylamide moiety of LSD (Wacker et al. 2017). (Though, L132 in 5-HT_{2B} is I132 in 5-HT_{2A}.) *TiHKAL* (Shulgin and Shulgin 1997) describes an LSA self-report from Albert Hoffman (who discovered LSD):

> An i.m. administration of a 500 microgram dose led to a tired, dreamy state with an inability to maintain clear thoughts. After a short period of sleep, the effects were gone and normal baseline was recovered within five hours. Other observers have confirmed this clouding of consciousness leading to sleep.

This report illustrates that LSA is substantially less psychoactive than LSD. Since it is distinct from LSD only in its lack of the diethylamide moiety, the hydrophobic interactions between the diethyl structures and 5-HT_{2A} may be central to LSD's psychedelic effects via 5-HT_{2A}. LSA is as efficacious as LSD at activating 5-HT_{2A}- $G\alpha_q$-mediated calcium flux and 5-HT_{2A}-mediated β-arrestin2 recruitment, but 1–2 orders of magnitude less potent (Wacker et al. 2017).

The LSD-5-HT_{2B} structure has similar conformational features as active GPCRs, but with a bias towards a β-arrestin2 state; this was subsequently confirmed in functional assays that show LSD has a potency bias towards β-arrestin2 versus $G\alpha_q$ signaling (Wacker et al. 2013, 2017). These data may suggest that 5-HT_{2A}- β-arrestin2 signaling contributes significantly to psychedelic effects. However, knockout of β-arrestin2 does not reduce the 5-HT_{2A}-mediated head-twitch response caused by two psychedelics, DOI and 5-MeO-DMT (Schmid and Bohn 2010; Schmid et al. 2008). Resolution of 5-HT_{2A} crystal structures with serotonergic psychedelics from the phenethylamine and tryptamine classes may reveal commonalities regarding ligand-receptor interactions and receptor conformations that may ignite the psychedelic experience (Nichols 2017). However, crystal structures (~3 Å) of the β2-adrenergic receptor with an antagonists or inverse agonists bound did not reveal robust conformational differences, suggesting ligands with different functional properties may alter receptor dynamics more so than receptor structure (Wacker et al. 2010). Because ligand-receptor signaling is a dynamic, spatial-temporal process (Grundmann and Kostenis 2017), advanced molecular dynamics (Saleh et al. 2017) describing ligand–receptor–G-protein-binding sequences may be needed to reveal the subtleties of psychedelics acting at 5-HT_{2A} receptors.

4 Preclinical Animal Models

4.1 Head-Twitch Response

The psychedelic-induced head-twitch response in rodents was first reported in 1956 (Keller and Umbreit 1956; Winter and Flataker 1956), and validation of the assay was provided in 1967 (Corne and Pickering 1967). Since then, numerous groups have shown that serotonergic psychedelics elicit the behavior via a 5-HT_{2A} mechanism. Tested psychedelics include LSD, psilocybin, psilocin, DMT, mescaline, 5-MeO-DMT, 5-MeO-DIPT, DPT, 2C-T-7, DOM, DOB, DOI, 2C–I, and several new phenethylamines, tryptamines, and lysergamides (Brandt et al. 2016, 2017a, b; Canal and Morgan 2012; Corne and Pickering 1967; Fantegrossi et al. 2005, 2006, 2008; Halberstadt and Geyer 2013, 2014, 2017; Halberstadt et al. 2011; Moya et al. 2007; Nichols et al. 2015).

Mice display a head-twitch response – observed as rapid, lateral rotations of the head (Halberstadt and Geyer 2013) – commencing within a few minutes after peripheral administration of a psychedelic, and with phenylisopropylamines, the response peaks in about 10 min and persists for at least 2 h (Canal and Morgan 2012). 5-HT_{2A} antagonists block the head-twitch in mice, rats, and the least shrew (Canal and Morgan 2012; Darmani et al. 1994; Halberstadt and Geyer 2017; Schreiber et al. 1995), whether administered before or after induction of the head-twitch response, as observed in C57BL/6J mice (Canal et al. 2013a). Serotonergic psychedelics do not elicit a head-twitch response in 5-HT_{2A} knockout

mice, but restoration of 5-HT_{2A} receptors to cortical neurons restores the ability of psychedelics to elicit the response (Gonzalez-Maeso et al. 2007).

What has made the head-twitch response particularly attractive for studying serotonergic psychedelic mechanisms is that lisuride does not produce it in mice (Gonzalez-Maeso et al. 2007; Halberstadt and Geyer 2013). Lisuride does, however, elicit a head-twitch response in the least shrew (Darmani et al. 1994), which appears a particularly sensitive species; (±)-DOI, 0.63 mg/kg, elicits an average of 263 head-twitches in 30 min, whereas lisuride, 1.25 mg/kg, elicits an average of 49 head-twitches in the same time period (Darmani et al. 1994). As a comparison, adult, male C57BL/6J mice exhibit about 30–40 head-twitches in a 10-min period after (±)-DOI, 1 mg/kg (Canal and Morgan 2012; Halberstadt and Geyer 2013). Furthermore, lisuride is a low-efficacy 5-HT_{2A} agonist (Berg et al. 1998) and appears to be distinguished from other 5-HT_{2A} agonists, especially, by its weak potency and efficacy at stimulating intracellular calcium mobilization; for example, its efficacy relative to 5-HT is ~49%, whereas LSD's efficacy is ~85% (Cussac et al. 2008). A recent study reports a significant correlation between the potencies of phenethylamines and tryptamines to activate 5-HT_{2A}-mediated calcium mobilization and their potencies to elicit the head-twitch response (Nichols et al. 2015). Calcium mobilization can be independent of the phospholipase C-β-IP_3 receptor pathway, and this signaling pathway does not appear to control all psychoactive effects, as noted above. Thus, these results provide an intriguing possibility that IP_3 receptor-independent calcium mobilization may uniquely contribute to psychedelic effects.

Nevertheless, there are clear false positives in the head-twitch assay. The 5-HT releaser *d*-fenfluramine is non-hallucinogenic but elicits the head-twitch in mice (Darmani 1998) – fenfluramine does, however, displace the 5-HT_{2A} agonist radioligand [^{11}C]Cimbi-36 from binding sites in primate brains (Yang et al. 2017), suggesting that the head-twitch may be sensitive to drugs that indirectly stimulate 5-HT_{2A} receptors. False negatives also show that it has questionable translational validity. To illustrate, anecdotal reports note that cannabis – psychoactive due to THC partial agonist activity at cannabinoid 1 (CB1) receptors – potentiates serotonergic psychedelic effects in humans. However, numerous compounds that stimulate CB1 receptors, including THC, eliminate the head-twitch elicited by DOI, whereas the CB1 inverse agonist, SR 141716A (Rimonibant®), can elicit the head-twitch (Ceci et al. 2015; Darmani 2001; Darmani et al. 2003; Darmani and Pandya 2000; Egashira et al. 2004, 2011).

The psychedelic-elicited head-twitch response can be modulated, albeit mostly suppressed, by a number of compounds that target receptors other than 5-HT_{2A}, including 5-HT_{2C}, 5-HT_{1A}, glutamate NMDA, AMPA and mGluR2, α-adrenergic, and dopamine D2 receptors, and others; regardless of the modulatory effect, selective 5-HT_{2A} blockade abolishes the head-twitch (Canal and Morgan 2012). Thus, the 5-HT_{2A} receptor appears to functionally interact with numerous neurotransmitter systems. Some mice including C57BL/6J mice naturally exhibit the head-twitch at low levels. For example, we have observed scores of adult, male, drug-naïve C57BL/6J mice, and each exhibits ~2–5 robust head-twitches in 10 min (Canal et al. 2013a); others report similar observations (Halberstadt and Geyer 2013). Interestingly, it too is blocked by selective 5-HT_{2A} antagonism (Canal et al. 2013a),

corroborating the conclusion that the 5-HT_{2A} receptor, regardless of whether it is activated by a psychedelic or by endogenous mechanisms, mediates the head-twitch response.

Many novel lysergamides including 1P–LSD, LSZ, and AL-LAD elicit a dose-dependent head-twitch in C57BL/6J mice (Brandt et al. 2016, 2017b). LSM-775 does not produce a head-twitch in C57BL/6J mice unless they are pretreated with a 5-HT_{1A} antagonist (Brandt et al. 2017a). LSM-775 also appears to lack psychedelic effects in humans, which is peculiar, as other psychedelics are potent and efficacious 5-HT_{1A} agonists, including LSD (Pauwels et al. 1993), and as noted above, the 5-HT_{1A} partial agonist, pindolol, potentiates the psychedelic effects of DMT (Strassman 2001). Moreover, the potent 5-HT_{1A} agonist (±)-8-OH-DPAT enhances the stimulus effects of DOM (Glennon 1991). However, 5-HT_{1A} agonists including both enantiomers of 8-OH-DPAT potently block the head-twitch response elicited by some, but not all, serotonergic psychedelics (Canal et al. 2015; Dursun and Handley 1993; Goodwin and Green 1985), and the 5-HT_{1A} antagonist/dopamine D2/D3 agonist S(-)-UH-301 alone can elicit a head-twitch response in mice (Darmani and Reeves 1996).

4.2 Drug Discrimination

The two-lever, appetitive, drug discrimination task is an authoritative, preclinical tool for determining psychedelic drug mechanisms in vivo. A food-motivated animal is trained in an operant task, under one of several reinforcement schedules, to press one lever for a food reward when it is under the influence of a training drug, and the other lever when it is not. Once the animal clearly shows it can discriminate or recognize the effects of the drug by successfully pressing the correct lever on repeated trials, e.g., with accuracy ≥80% (typically requiring several weeks of training), it can then be treated with test drugs to observe whether they substitute (partially to fully) for the training drug, or when co-administered with the training drug, suppress (partially to fully) its discriminative stimulus effects. For example, if a test drug causes animals to make ≥80% of their responses on the lever associated with the training drug, investigators infer that the two compounds produce similar subjective or stimulus effects. Conversely, if a test drug causes animals to make ≤20% of their responses on the lever associated with the training drug, investigators infer that the test drug does not produce subjective effects that are like the training drug. Even if the test drug has discriminative effects, if they are unlike the training drug, animals typically default to responding by pressing the vehicle-associated lever. If a test drug causes animals to split their responses between the levers, then investigators infer that it has effects somewhat similar to the training drug (Glennon and Young 2011). Like the head-twitch procedure, drug discrimination can provide information regarding drug pharmacokinetics and pharmacodynamics (e.g., drug onset, duration, potency, and mechanism of action), and drug discrimination has high predictive validity, i.e., it translates well to human subjects. Importantly, the drug discrimination procedure distinguishes psychoactive drugs from various classes, and germane here, primates trained using two-choice drug discrimination unmistakably distinguish different types of hallucinogens, e.g., κ-opioid agonist hallucinogens from NMDA antagonist hallucinogens and from serotonergic psychedelics (Butelman et al. 2010). For a detailed study of the drug discrimination procedure, including

its utility and arguments regarding its superiority relative to other behavioral assays, see Glennon and Young (2011).

Early drug discrimination studies with rodents that showed 5-HT_{2A} antagonists reduce the stimulus effects of diverse serotonergic psychedelics (Glennon 1992; Glennon et al. 1983) provided commanding evidence that 5-HT_{2A} receptor activation is their unifying and common mechanism. This evidence was corroborated by studies employing DOx psychedelics, which are 5-HT_2 selective agonists, as test drugs that substitute for LSD (Fiorella et al. 1995). Other studies confirmed that selective blockade of 5-HT_{2A} receptors, i.e., by M100907 (Kehne et al. 1996; Palfreyman et al. 1993), occludes the discriminative stimulus effects of some serotonergic psychedelics in rats and primates (Li et al. 2007, 2009a; May et al. 2009; Schreiber et al. 1994).

Recent studies employing drug discrimination in rats show that novel psychedelics including 25I-, 25B-, and 25C-NBOMe, and 5-MeO-DALT fully substitute for DOM; interestingly, the NBOMe drugs also substitute for MDMA, but 5-MeO-DALT does not (Gatch et al. 2017). This study and others illustrate the utility of drug discrimination assays to differentiate unique effects of different serotonergic psychedelics. The selective 5-HT_{2C} antagonist SB242084 (1 mg/kg) blocks ~70% of DIPT lever responding but does not affect the DMT discriminative stimulus (Carbonaro et al. 2015). Intriguingly, also from this study, M100907 does not completely block the discriminative stimulus effects of DIPT but does completely block DMT's effects. Also, 2C-T-7 only partially substitutes for psilocybin and LSD (~40% and ~75%, respectively) in rats at a dose (1 mg/kg) that appears to be maximal for eliciting the head-twitch response in mice (Fantegrossi et al. 2005; Winter et al. 2007). Also from these studies, psilocybin at 1 mg/kg partially (~50%) substitutes for LSD, and M100907 completely blocks the substitution. M100907 (0.5 mg/kg) also completely blocks 2C-T-7's stimulus effects. M100907 (0.2 mg/kg) partially (~40%) blocks psilocybin's stimulus effects, whereas (±)-8-OH-DPAT mostly (~80%) blocks them; the effect of (±)-8-OH-DPAT is not blocked by the selective 5-HT_{1A} antagonist, WAY-100635 (0.2 mg/kg), nor does this compound on its own (up to 0.6 mg/kg) alter the stimulus effects of psilocybin. In humans, however, the non-hallucinogenic 5-HT_{1A} receptor partial agonist buspirone reduces psilocybin-induced simple and complex hallucinations (Pokorny et al. 2016). Clearly, different mechanisms contribute to the stimulus effects of different serotonergic psychedelics, though, again, like the head-twitch response, 5-HT_{2A} receptors appear to control a significant portion of the effects, with some exceptions. This translates well to humans, as the psychedelic effects of both psilocybin and LSD are blocked by a fairly selective 5-HT_{2A} antagonist, ketanserin – though see Sect. 3.6.

Similar to the head-twitch model, compounds targeting receptors other than 5-HT_{2A} modulate the discriminative stimulus effects of serotonergic psychedelics, and false positives, false negatives, and misunderstood results have emerged (Benneyworth et al. 2005; Reissig et al. 2005; Winter 2009). For example, lisuride substitutes for a number of serotonergic psychedelics in the two-lever drug discrimination paradigm; however, this can be overcome by training animals to discriminate two training drugs and vehicle. Thus, when animals are trained to discriminate lisuride, LSD, and vehicle, lisuride does not substitute for LSD (Appel et al. 2004). Regarding false negative responses, LSD, DOM, and DOI

substitute for fenfluramine (Glennon 1991; McCreary et al. 2003). DOI, at 1 mg/kg, engenders rats to respond to the (±)-fenfluramine (2 mg/kg)-associated lever ~73% of the time, and this effect is completely blocked by the 5-HT_{2B}/5-HT_{2C} inverse agonist, SB206553 (1 mg/kg); interestingly, M100907 also dose-dependently attenuates (but does not fully block) the effect (McCreary et al. 2003). In C57BL/6J mice, SB206553 suppresses the DOI-elicited head-twitch response (Canal et al. 2010, 2013a), suggesting that 5-HT_{2B} or 5-HT_{2C} receptors may contribute to DOI's effects. Often overlooked, M100907 has relevant affinity at mouse and human 5-HT_{2C} receptors (K_i ~40–100 nM (Canal et al. 2013a); PDSP certified), where it acts as a 5-HT_{2C} inverse agonist with potency and efficacy similar to the well-appreciated 5-HT_{2C} inverse agonist, clozapine (Herrick-Davis et al. 2000; Kehne et al. 1996; Navailles et al. 2006; Rauser et al. 2001).

MDMA nearly (~80%) substitutes for DMT and similarly nearly (~80%) substitutes for methamphetamine in two-lever drug discrimination assays (Gatch et al. 2009). mGluR2 activation, which suppresses DOB- and DOI-elicited head-twitches, fails to alter discriminative stimulus effects of DIPT, DMT, and DOB in mice (Benneyworth et al. 2008; Carbonaro et al. 2015; Griebel et al. 2016). However, the prolonged training regimen and multidosing of serotonergic psychedelics that drug discrimination requires may cause functional changes in mGluR2 receptors that mask effects of mGluR2 activation (Benneyworth et al. 2008). Interestingly, the 5-HT_3 antagonist/5-HT_4 agonist zacopride potently and efficaciously reduces the discriminative stimulus properties of DOM (and MDMA) (Glennon et al. 1992). Finally, unique serotonergic psychedelics may produce different stimulus properties depending on their training dose or depending on when the training drug is administered prior to engaging in the associative learning task. For example, LSD's stimulus effects are 5-HT_{2A} mediated 30 min after its administration but appear to be dopamine D2 receptor mediated 90 min after administration (Marona-Lewicka et al. 2005). Interpretation of results from drug discrimination studies should consider different targets engaged by training drugs administered at different doses and at different times.

5 Measuring Localized and System Effects in the Brain

Recent, clinical neuroimaging studies have revealed serotonergic psychedelic effects that may explain not only neural perturbations that underlie visual hallucinations, e.g., decreases in alpha oscillations in visual cortex (Carhart-Harris et al. 2016; Kometer et al. 2013; Kometer and Vollenweider 2016), but also psychotherapeutic benefits of serotonergic psychedelics. One hypothesis, supported by recent observations, is that psychedelics have entropic effects on cortical activity, razing entrenched functional connectivity while sprouting new patterns of connectivity (Carhart-Harris et al. 2014; Petri et al. 2014; Tagliazucchi et al. 2014, 2016); for detailed discussions of this evolving topic, refer to Atasoy et al. (2017), Carhart-Harris et al. (2017), and Viol et al. (2017). Studies show that brains from subjects with treatment-resistant depression exhibit hyperactivity (entrenchment) within certain circuits, including the subcallosal cingulate white matter, which has been subsequently targeted by deep-brain stimulation (Mayberg et al. 1997; Riva-Posse et al. 2017). Psilocybin helps relieve treatment-resistant depression (Carhart-Harris et al. 2017), and intriguingly, psilocybin and LSD alter activity within the cingulate cortex and functional connectivity between the cingulate cortex and other brain systems (Carhart-Harris

et al. 2012, 2016). These neural perturbations correlate with dissolution of ego boundaries (loss of the self), suggesting the possibility that this psychedelic phenomenon may, in certain individuals, help relieve psychiatric distress (c.f. Griffiths et al. 2016; Ross et al. 2016; Vollenweider 2001).

Preclinical strategies can provide additional spatial and temporal precision and a reductionist understanding of mechanisms which span genetic, molecular, cellular, and neural systems. Approaches to measure localized effects include direct brain injections, via drug infusions through stereotaxically implanted cannulae as well as systemic injections followed by measurements of changes in neurochemicals in discrete neural systems, e.g., via in vivo microdialysis combined with high-performance liquid chromatography and/or liquid chromatography-mass spectrometry or voltammetry detection (Bucher and Wightman 2015; Kennedy 2013). Measurements of electrophysiological effects on distinct brain cell types in distinct brain regions, e.g., via multichannel recordings from precisely implanted electrodes or from brain slice preparations (Du et al. 2017), can provide information about 5-HT_2 effects on cell and network excitability, neurotransmission, and neuroplasticity. Invasive approaches also allow researchers to measure, for example, psychedelic-induced changes in DNA methylation (epigenetics), RNA transcription (gene expression), protein synthesis, and phosphorylation (posttranslational modifications). Serotonergic psychedelics alter the expression of genes that contribute to synaptic plasticity, providing physiological evidence that these compounds cause persistent changes in the brain that may underlie their therapeutic effects (Martin and Nichols 2017). For example, 24-h treatment of 45-day-old, brain organoids with 5-MeO-DMT alters the expression of proteins involved in memory consolidation, cytoskeletal organization, and inflammation, e.g., CaMKII, ephrin-B2, and NF-κB, respectively (Dakic et al. 2017).

Invasive techniques also permit analyses of interactions between receptor targets and other proteins. 5-HT_{2A} and 5-HT_{2C} receptors directly bind to synaptic scaffolding proteins, such as PSD-95 (Becamel et al. 2004; Xia et al. 2003). Also, 5-HT_{2A} and glutamate mGluR2 receptors interact closely, and their interaction may be a key mechanism underlying psychedelic effects (Benneyworth et al. 2007; Delille et al. 2012; Gonzalez-Maeso et al. 2008; Lee et al. 2014; Moreno et al. 2011). Similarly, analyzing gene expression patterns allows researchers to observe which genes the brain expresses in regions where receptor targets of serotonergic psychedelics are expressed. Using the Allen Brain Atlas online resource, one can see that the gene coding for 5-HT_{2A} receptors, *HTR2A*, is expressed in cortical brain regions that overlap very closely with expression of the gene coding for one of the subunits of glutamate NMDA receptors, *NR2A*, which the psychedelic dissociative ketamine targets. This connection fits well with results from PET (^{18}fluorodeoxyglucose) imaging studies that show psilocybin and ketamine produce similar prefrontal cortex-limbic activation patterns in humans (Vollenweider 2001).

5.1 Serotonergic Psychedelics Impact on Neurotransmission

The effects of serotonergic psychedelics on neurotransmission have only been resolved partially. After systemic injections in rodents, serotonergic psychedelics increase glutamate in the cortex and also the ventral tegmentum area (Muschamp et al. 2004; Pehek et al. 2006;

Scruggs et al. 2003). They also increase dopamine release in the cortex, but not the nucleus accumbens or the striatum (Di Matteo et al. 2000; Gudelsky et al. 1994; Pehek and Hernan 2015; Pehek et al. 2001, 2006). DOI increases acetylcholine release in the prefrontal cortex and the hippocampus (Nair and Gudelsky 2004; Zhelyazkova-Savova et al. 1997, 1999); also Nair and Gudelsky (2004) show that mescaline increases acetylcholine release in the prefrontal cortex, but not the hippocampus. DOI decreases norepinephrine release in the hippocampus (Done and Sharp 1992), though this study was performed in anesthetized rats. Finally, DOI increases GABA release in the prefrontal cortex (Abi-Saab et al. 1999). Most of the neurochemical effects of compounds in the aforementioned studies were blocked by 5-HT_2 antagonists.

Early studies showed that serotonergic psychedelics increase brain 5-HT levels (Freedman and Giarman 1962; Giarman and Freedman 1965), but few studies since have systematically dissected this effect. One study shows that peripherally administered DOI has no effect on 5-HT release in the prefrontal cortex (Gobert and Millan 1999), yet others show that DOI significantly decreases 5-HT release there, in anesthetized rats (Martin-Ruiz et al. 2001; Wright et al. 1990). Other studies show that direct prefrontal cortex application of DOI increases 5-HT release there (Amargos-Bosch et al. 2004; Bortolozzi et al. 2003; Martin-Ruiz et al. 2001) or has no effect (Wright et al. 1990). Still another shows that DOI decreases 5-HT release from cortical slices while concordantly increasing GABA release; the increase in GABA release caused by DOI is also observed using cortical synaptosome preparations (Luparini et al. 2004). Finally, direct striatal DOI application increases 5-HT release there (Abellan et al. 2000).

A few recent studies have employed electrophysiological approaches to examine effects on neurotransmission. The 5-HT_{2A} agonist and putative psychedelic, TCB-2, inhibits pyramidal neurons in layer 6 of the prefrontal cortex (Tian et al. 2016); an earlier study showed that 5-HT_2 receptor activation stimulates (presumably) GABA interneurons in layer 2/3 of piriform cortex (Gellman and Aghajanian 1994). 5-HT_2 receptors also increase activity of layer 5 GABAergic interneurons and glutamatergic pyramidal neurons (Aghajanian and Marek 1997; Spindle and Thomas 2014; Weber and Andrade 2010; Zhang and Arsenault 2005). These results align with the robust expression of 5-HT_2 receptors on both GABAergic and glutamatergic neurons in the cortex (Puig et al. 2010; Willins et al. 1997). Finally, a recent study shows that low-dose LSD inhibits dorsal raphe nuclei 5-HT firing, and high-dose LSD additionally decreases firing of ventral tegmentum area dopamine neurons; the former effects are blocked by haloperidol and M100907, and latter effects are blocked by haloperidol, WAY-100635, and the TAAR1 antagonist, EPPTB (De Gregorio et al. 2016).

5.2 Neural Systems Underlying Serotonergic Psychedelic Effects

Elaine Sanders-Bush's group combined brain microinfusions with drug discrimination to directly test the contribution of the anterior cingulate cortex to the discriminative stimulus properties of LSD; they found that local infusions of LSD substitute for systemically administered LSD, and that local infusions of M100907 block LSD's discriminative stimulus properties (Gresch et al. 2007). Similarly, DOI directly infused into the anterior cingulate cortex elicits a head-twitch response, which is blocked by systemic injections of

M100907 (Willins and Meltzer 1997). Despite these major findings, few other studies have directly assessed the involvement of other neural systems in serotonergic psychedelic effects (Halberstadt and Geyer 2017). Most information is based on correlation analyses from clinical trials, but these reports support preclinical observations. PET imaging with [^{18}F]altanserin, a 5-HT$_{2A}$ antagonist radioligand, showed that psilocybin's receptor occupancy in the anterior cingulate and medial prefrontal cortices correlates with psychedelic intensity (Quednow et al. 2010). Functional changes in the brain caused by serotonergic psychedelics include activity increases and decreases as well as modulation of interactions within and across cortical regions, between the thalamus and cortex, hippocampus, amygdala, and cortex, and across regions typically not functionally associated, typifying entropic effects of serotonergic psychedelics – some of these changes significantly correlate with distinct psychedelic effects (c.f. Carhart-Harris et al. 2016; Mueller et al. 2017; Palhano-Fontes et al. 2015; Petri et al. 2014; Tagliazucchi et al. 2016).

6 On Ketanserin, Conformations, and Dimerization

Reports from clinical trials conclude that the psychedelic effects of psilocybin and LSD are mediated by 5-HT$_{2A}$ receptors, because they are blocked by ketanserin (40 mg, P.O.), typically viewed as a selective 5-HT$_{2A}$ antagonist (Kometer et al. 2012; Kraehenmann et al. 2017; Preller et al. 2017; Quednow et al. 2012). Haloperidol, typically viewed as a selective dopamine D2 antagonist, is much less effective than ketanserin at blocking psilocybin's effects, but risperidone, an antipsychotic with combined D2/5-HT$_2$ activity, is as effective as ketanserin (Vollenweider et al. 1998).

Ketanserin, however, at <2 nM concentration labels a site(s) distinct from 5-HT$_{2A}$ receptors in several species, including humans, and in several neural systems, notably the striatum, substantia nigra, and raphe nuclei; in rats, this site appears to control the release of the dopamine metabolite DOPAC from dopamine nerve terminals (Leysen et al. 1987; Lopez-Gimenez et al. 1998; Pazos et al. 1987). Recently, Glennon commented on ketanserin's off-target effects (Glennon 2017):

> The lack of ketanserin's selectivity for 5-HT$_2$ receptors over some other receptors, notably histamine receptors and certain adrenoceptors, was a drawback when brain homogenates were being employed as the receptor source.

Importantly, M100907, viewed as one of the most selective, commercially available 5-HT$_{2A}$ antagonists, only effects ~50% of ketanserin-appropriate lever responding in rats trained to discriminate ketanserin from saline; prazosin, an α1-adrenergic receptor antagonist, combined with M100907 causes full substitution (Li et al. 2009b). These observations suggest that ketanserin blocks α1-adrenergic receptors in vivo, which produces a subjectively recognizable effect. Importantly, α1-adrenergic receptors co-localize with 5-HT$_{2A}$ receptors in the prefrontal cortex (Santana et al. 2013), suggesting they may functionally interact in vivo. In addition to α1-adrenergic receptors, ketanserin also has relevant (off-target) affinity at human H1, 5-HT$_{1D}$, 5-HT$_{1F}$, and 5-HT$_{2C}$ receptors (Boess and Martin 1994; Bonhaus et al. 1995; Domenech et al. 1997; Ghoneim et al. 2006), and 5-HT$_{2C}$ receptors also co-localize with 5-HT$_{2A}$ receptors in certain parts of the cortex (Santana and Artigas 2017).

When considering haloperidol's inefficacy at blocking psychedelic effects of psilocybin in humans and DOI's discriminative stimulus properties in rats (Schreiber et al. 1994; Vollenweider et al. 1998), it should be noted that haloperidol has no activity at 5-HT_{2C} receptors but possesses relevant affinity at 5-HT_{2A} receptors (Herrick-Davis et al. 2000; Kroeze et al. 2003; Leysen et al. 1993; Rauser et al. 2001; Richelson and Souder 2000). Conversely, ketanserin and risperidone are efficacious 5-HT_{2C} inverse agonists that also have high affinity at 5-HT_{2A} (Hartman and Northup 1996; Herrick-Davis et al. 2000; Richelson and Souder 2000). Moreover, in competition binding assays, risperidone and ketanserin recognize two 5-HT_{2A} receptor sites (defined by two slopes in the displacement curves) labeled with [^{3}H](±)-DOB, whereas haloperidol recognizes only one site. In functional assays, each drug antagonizes 5-HT_{2A}-stimulated inositol phosphate production and arachidonic acid release, but risperidone and ketanserin antagonize the latter in a biphasic manner similar to their binding characteristics (Brea et al. 2009). The authors suggest that the pharmacological differences are due to differential recognition of 5-HT_{2A} receptor homodimers – that risperidone and ketanserin bind 5-HT_{2A} homodimers, but haloperidol does not. It is, therefore, intriguing to consider that haloperidol may be ineffective at blocking psilocybin's psychedelic effects, because it may not block putative 5-HT_{2A} homodimers activated by psilocybin, whereas ketanserin and risperidone may. Risperidone potently blocks 5-HT_{2} mediated activation of (presumably) GABAergic interneurons in piriform cortex, whereas haloperidol, up to 10 μM, only weakly blocks these effects (Gellman and Aghajanian 1994). Alternatively, since haloperidol has negligible affinity at 5-HT_{2C} receptors, by extension, it may not be able to bind 5-HT_{2A}-5-HT_{2C} heterodimers, which were recently observed in vitro and in brains (Moutkine et al. 2017). Co-activation of 5-HT_{2A} and 5-HT_{2C} receptors has been postulated as a mechanism underlying serotonergic psychedelic effects (Burris et al. 1991; Canal et al. 2010).

Finally, a couple of recent clinical trials suggest that 5-HT_{2A} receptor activation may not be necessary or sufficient to produce all of the psychoactive effects of serotonergic psychedelics. Ketanserin (40 mg, P.O.) does not entirely block the effects of an ayahuasca brew (containing DMT, harmine, harmaline, and THH); notably, it does not block "modifications in time perception," feeling "high," or "visions" (Valle et al. 2016). This report suggests that there is a mechanism other than 5-HT_{2A} at large, and the authors propose to further investigate sigma-1 receptor activation (Valle et al. 2016). Alternatively, ketanserin may not block unique 5-HT_{2} receptor ensembles and/or conformations stabilized by ayahuasca. [^{125}I]DOI autoradiography studies show that 5-HT_{2A} and 5-HT_{2C} receptors exist in multiple conformations across neural systems in the rat brain, and ketanserin and M100907 have different affinities at them (Lopez-Gimenez et al. 2013). Collectively, then, data suggest that different 5-HT_{2} antagonists may selectively block unique 5-HT_{2} receptor homodimer or heterodimer ensembles and/or receptor conformations – it remains unclear which are the mechanistic targets of psychedelics. Clearly, more serotonergic psychedelics research aimed at elucidating their mechanisms needs to be conducted.

7 Conclusions

Recent experiments have begun to unveil neuropsychological mechanisms of serotonergic psychedelics, and clinical studies with ketanserin support a central role for serotonin 5-HT_{2A}

receptors in producing psychedelic effects. There remains fertile ground, however, for much more discovery. Unknown are the cellular signal transduction conduits of 5-HT_2 receptor activation, the 5-HT_2 receptor – protein interactions, and the neural circuits and neurochemical processes within those circuits, that produce distinct psychedelic effects, e.g., “oceanic boundlessness” or “visionary restructuralization” (Dittrich 1998). Also mysterious are the mechanisms underlying unique psychoactive effects engendered by unique psychedelics. Indeed, it is unclear whether all serotonergic psychedelics can induce psychedelic effects matching those of LSD – experiencing oneness with the universe or an all-encompassing unity, transcending time and space, tapping into the unconscious or experiencing archetypes, and an ethereal, positive, overwhelming luminescent, mental state filled with awe and profound philosophical, spiritual, or religious meaning that is ineffable with words (Pahnke et al. 1970; Pahnke and Richards 1966). Future discoveries will weave together reductionist and emergentist points of view to construct lucid neurobiological pictures illuminating how serotonergic psychedelics work.

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Abbreviations

1P-LSD	1-Propionyl-lysergic acid diethylamide
25C-NBOMe	*N*-(2-Methoxybenzyl)-2,5-dimethoxy-4-bromophenethylamine
25CN-NBOH	*N*-(2-Hydroxybenzyl)-2,5-dimethoxy-4-cyanophenylethylamine
25I-NBOMe	*N*-(2-Methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine
2C-B	4-Bromo-2,5-dimethoxyphenethylamine
2C-I	4-Iodo-2,5-dimethoxyphenethylamine
2C-T-7	2,5-Dimethoxy-4-propylthiophenethylamine
5-APB	5-(2-Aminopropyl)benzofuran
5-HT	5-Hydroxytryptamine (serotonin)
5-MeO-DALT	5-Methoxy-*N,N*-diallyltryptamine
5-MeO-DIPT	5-Methoxy-*N,N*-diisopropyltryptamine
5-MeO-DMT	5-Methoxy-*N,N*-dimethyltryptamine
6-APB	6-(2-Aminopropyl)benzofuran

AL-LAD	N^6-allyl-6-norlysergic acid diethylamide
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
bk-2C-B	β-Keto-2,5-dimethoxy-4-bromophenethylamine
BOL-148	2-Bromo-lysergic acid diethylamide
CB1	Cannabinoid 1 receptor
DA	Dopamine
DIPT	*N,N*-Diisopropyltryptamine
DMT	*N,N*-Dimethyltryptamine
DOB	2,5-Dimethoxy-4-bromoamphetamine
DOI	2,5-Dimethoxy-4-iodoamphetamine
DOM	2,5-Dimethoxy-4-methylamphetamine
DOPAC	3,4-Dihydroxyphenylacetic acid
DPT	*N,N*-Dipropyltryptamine
IP_3	Inositol 1,4,5-trisphosphate
LSA	Lysergamide
LSD	Lysergic acid diethylamide
LSM-775	Lysergic acid morpholide
LSZ	Lysergic acid 2,4-dimethylazetidide
mCPP	*meta*-Chlorophenylpiperazine
MDMA	3,4-Methylenedioxymethamphetamine
mGluR2	Metabotropic glutamate receptor 2
NMDA	*N*-Methyl-D-aspartate
PARGY-LAD	N^6-Propynyl-6-norlysergic acid diethylamide
PET	Positron emission tomography
SERT	Serotonin transporter
TAAR1	Trace amine-associated receptor 1
TCB-2	1-(3-Bromo-2,5-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl) methanamine
THC	Δ^9-Tetrahydrocannabinol

THH Tetrahydroharmine

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