Psychedelics: preclinical insights provide directions for future research

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Recently, psychedelics have emerged as promising therapeutics for numerous neuropsychiatric disorders. While their potential in the clinic has yet to be fully elucidated, understanding their molecular and biological mechanisms is imperative as these compounds are becoming widely used both in therapeutic and recreational contexts. This review examines the current understanding of basic biology, pharmacology, and structural biology in an attempt to reveal both the knowns and unknowns within the field.

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INTRODUCTION

Psychedelic drugs have been used for millennia by indigenous peoples and over the past century by others for recreational, spiritual and therapeutic purposes [1, 2]. In this review, we will refer to psychedelic drugs as those which induce a lysergic acid diethylamide (LSD)-like effect in humans via activation of 5-HT_{2A} serotonin (5-hydroxytryptamine; 5-HT) receptors [2]. As mentioned by others in this series, psychedelic drugs have had increasing interest over the past decade because small-scale clinical trials have shown that drugs like psilocybin and LSD have robust, rapid and enduring therapeutic actions for depression and anxiety [3–8]. Psychedelic drugs have also been suggested to have potential utility for many other conditions including chronic pain, cluster and migraine headaches, and obsessive-compulsive disorder among many others [2]. As definitive Phase III trials have not yet been concluded, there are currently no FDA-approved uses of psychedelic drugs for any condition. At the federal level, psychedelics remain Schedule I drugs; however, many have been decriminalized in several municipalities and the state of Oregon in the US despite the lack of evidence for their utility. Here we will focus on the postulated mechanisms of action of psychedelic drugs and provide a perspective on their potential as transformative neurotherapeutics.

PSYCHEDELIC DRUG PHARMACOLOGY AND MOLECULAR MECHANISMS OF ACTION

It is well established that the mind-altering actions of psychedelic drugs are due principally to the activation of 5-HT_{2A} receptors. Initial evidence came from studies in the 1950s which noted the structural similarities between LSD and 5-HT [9] (Fig. 1). LSD was initially described as a serotonergic antagonist [10, 11] although later studies by Aghajanian et al. showed it is a serotonergic agonist with potent actions at raphe neurons [12]. Later studies showed that LSD has actions at dopamine [13] and other biogenic amine receptors [14]. Biochemical evidence for the actions of LSD at 5-HT receptors came from radioligand binding studies, which demonstrated that LSD interacts with a 5-HT2-like serotonin receptor [15]. These studies led, ultimately, to the discovery of the relatively selective radioligand [^{125}I]-DOI, which preferentially interacts with the high-affinity agonist state of 5-HT2 receptors [16, 17]. More recent studies have shown that LSD is a high-affinity agonist for more than 20 biogenic amine receptors [18] including virtually all 5-HT, dopamine and noradrenergic receptors.

Studies in mice and rats showed that psychedelics induce a variety of behaviors including, most notably, the head-twitch response (HTR) [19]. The HTR was later demonstrated to be induced by other 5-HT2 agonists like quipazine [20], which had been developed as a potential antidepressant [21]. More definitive evidence for the involvement of 5-HT2 receptors in the actions of psychedelic drugs came from studies performed by Glennon et al. who showed a direct correlation between the ability of drugs to interact with cortical 5-HT_{2A} receptors labeled with [^{3}H]-Ketanserin and the induction of HTR [22]. Although several non-psychedelic drugs induce the HTR in mice and rats, to date there are no bona fide psychedelic drugs that are negative in this assay [2]. Furthermore, Halberstadt et al. have recently shown a correlation between HTR and potency of many psychedelic compounds [23]. Psychedelic drugs were later observed to potently activate other 5-HT2-family receptors including the 5-HT_{2C} [24] and 5-HT_{2B} [25] (Fig. 1).

Data from human studies using the relatively selective 5-HT_{2A} antagonist ketanserin [26] are more definitive. Initial studies with psilocybin showed that pretreatment with ketanserin blocked most [27–30] but not all of psilocybin's psychoactive actions in human volunteers [31, 32]. Notably, the psychedelic actions of psilocybin were abolished by pretreatment with ketanserin, although some effects on cognition were apparently 5-HT_{1A} mediated [31, 32]. For other psychedelic drugs, the data published to date show that ketanserin pretreatment blocks its psychedelic effects in humans [33, 34]. Given the fact that ketanserin has several off-target actions at other biogenic amine receptors (e.g.,

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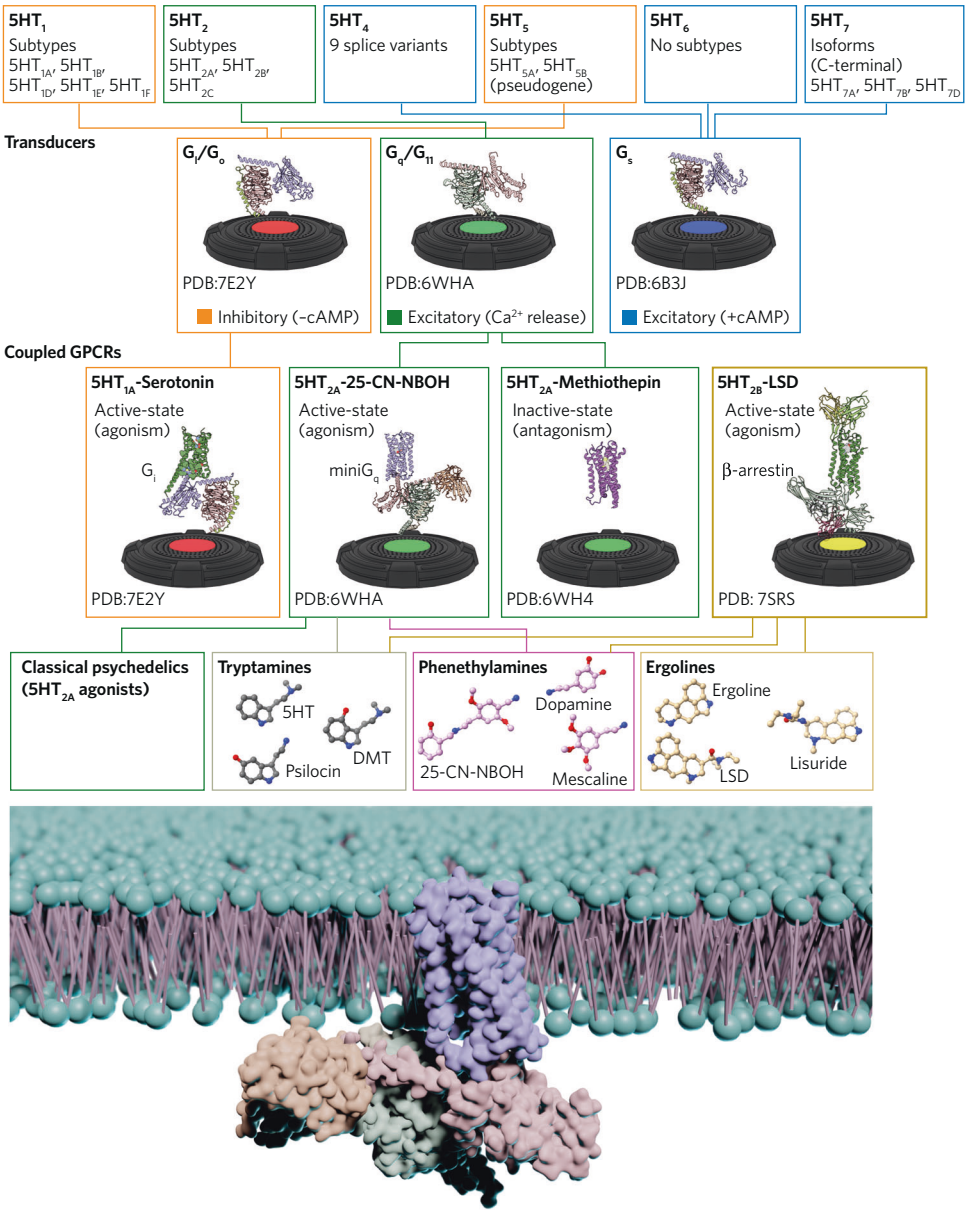

Fig. 1 Overview of the 5-HT (5-HT$_{1-7}$) family of receptors and their canonical coupling pathways. The inhibitory Gi/o is shown in red, the excitatory Gq is shown in green, the excitatory Gs is shown in blue, and the arrestin transducer pathway is shown in yellow. Lines pointing to which receptor families canonically interact with each transducer are shown. PDB accession codes are present for each structure in the figure. The different classes of 5-HT$_{2A}$ agonists are also shown (both hallucinogenic and non-hallucinogenic). The tryptamines are shown in gray (representative compound is the endogenous serotonin (5-HT) and non-psychedelic), the phenethylamines are shown in pink (representative compound is dopamine and non-psychedelic), and the ergolines are shown in tan (representative compound is the ergoline backbone). The very bottom is an artistic rendering of PDB accession 6WHA (25-CN-NBOH bound 5-HT$_{2A}$ heterotrimeric complex) present in a lipid bilayer.

5-HT$_{2C}$ antagonism, α1-adrenergic antagonism) use of more selective 5-HT$_{2A}$ antagonists such as pimavanserin [35], which has an appreciable affinity for 5-HT$_{2C}$ receptors might be suitable for human studies while M100907 (which is quite selective) is available for studies with rodents [36] (Fig. 2).

Moreover, the molecular details regarding psychedelic drug actions at the 5-HT$_{2A}$ receptor have been characterized. For instance, both x-ray [37] and cryogenic electron microscopic (cryo-EM) studies of psychedelic [38] and non-psychedelic [39] drugs interacting with 5-HT$_{2A}$ receptors have been obtained (Fig. 3). R-69, which was found to be non-hallucinogenic in rodent models, interacts with the 5-HT$_{2A}$ receptor through the canonical salt-bridge (present in all aminergic receptors) D155$^{3.32}$ and is positionally facing TM5 to interact with S242$^{5.46}$ (Fig. 3) in which the indole nitrogen of 5-HT is observed to interact based on other 5-HT receptor structures [39]. Subsequently, many interactions are recapitulated with the potent hallucinogen 25-CN-NBOH, but the N-benzyl portion of the compound sterically "pushes" down on the toggle switch tryptophan (W336$^{6.48}$) potentially playing a role in signaling bias and/or activation efficacy of the receptor (Fig. 3) [38]. In a direct comparison with hallucinogenic vs non-hallucinogenic molecules, LSD and lisuride crystal structures are available [38, 40]. Notably, the lisuride structure has an intrusive lipid in the orthosteric pocket pushing the position of the compound slightly compared to the LSD structure. While there is some evidence of lipids interacting with the orthosteric site in the 5-HT$_{2A}$ receptor, it remains unclear whether the lipid present in this structure is functionally relevant or an artifact of crystallization [40].

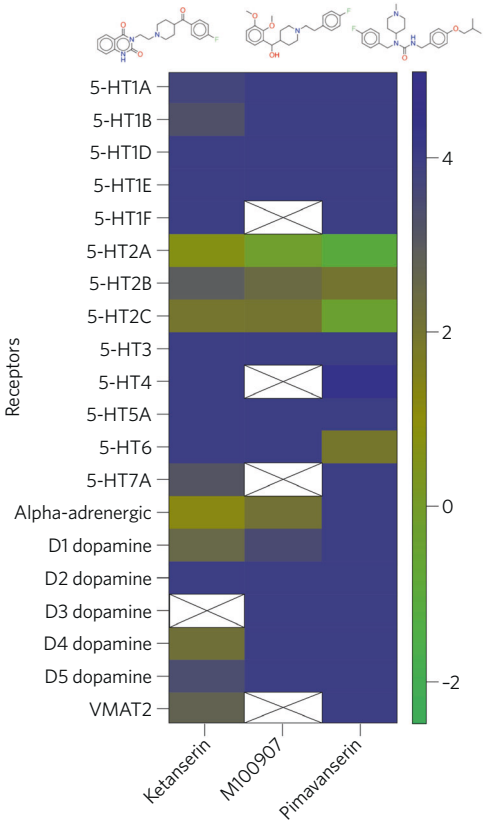

Fig. 2 Interactions with the widely used antagonists ketanserin, M100907, and pimavanserin against the 5-HT, dopamine, and alpha-adrenergic receptor families. The heatmap is representative of radioligand binding affinities, with green being more potent and blue being less potent. Data obtained from KiDatabase (https://pdsp.unc.edu/databases/kidb.php).

In addition, we also have details regarding the molecular requirements for specifying both G protein and arrestin-ergic signaling downstream of the closely related 5-HT_{2B} receptor [41] (Fig. 3). Utilizing LSD, Cao et al. were able to structurally resolve the 5-HT_{2B} receptor in the arrestin bound state, the Gq bound state, and the receptor without any transducer (transducer-free) by cryo-EM (Fig. 3) [41]. Remarkably, few changes within the orthosteric pocket and ligand binding mode occur between these states. However, it was noticed that TM6 was pushed farther out in the arrestin complex compared to the Gq-coupled state, while the transducer-free exhibited the smallest conformational change compared to the inactive state (Fig. 3). These movements are correlated with the position of the toggle switch tryptophan ($W^{6.48}$) and could indicate a potential molecular mechanism for signaling bias.

Finally, the active state structures for the 5-HT_{2C} receptors have also been solved with the classical psychedelic psilocin as well as the 5-HT_{2C} selective agonist lorcaserin [42]. One key difference in the orthosteric site between 5-HT_{2A} and 5-HT_{2C} is at 5.46 (S242 and A222, respectively). Examining the psilocin structure, one could postulate that due to the potential loss of an H-bond on the indole N in 5-HT_{2C}, the active conformation of psilocin in the orthosteric pocket will be slightly altered in the 5-HT_{2A} receptor (Fig. 3) [42].

With regard to receptor signaling, it is well established from studies done nearly 40 years ago that 5-HT_{2A} receptors couple to Gαq and modulate phosphoinositide hydrolysis (Fig. 4) [43–45]. This leads to both the mobilization of intracellular calcium via IP3-mediated release, activation of protein kinase C [46] and activation of Ca++ channels (Fig. 4) [47]. 5-HT_{2A} receptors apparently are desensitized via direct phosphorylation [48] and subsequent arrestin binding via the third intracellular loop of the 5-HT_{2A} receptor [49] and likely other sites including the C-terminal region [41, 50]. 5-HT_{2A} receptors are also phosphorylated by RSK2 ribosomal S6 kinase [51], which exerts a tonic brake, or a reduction in the population of receptors available of ligand potentiated secondary messenger transduction, on 5-HT_{2A} signaling (Fig. 4) [52]. Notably, RSK2-mediated phosphorylation alters the signaling properties of 5-HT_{2A} receptors [53, 54]. Signaling via both Gq [55] and arrestin [56] appears essential for the actions of some psychedelic drugs in vivo.

In terms of interactions with other transducer proteins, most studies have indicated that 5-HT_{2A} receptors selectively activate Gq-family proteins [38, 57]—at least in transfected cells in vitro. In vivo studies with Gq hetereozygote mice revealed that the behavioral actions of psychedelics are attenuated [55]. In addition, electrophysiological studies have shown that the 5-HT_{2A}-mediated excitation of cortical neurons is insensitive to pertussis toxin [58]. As well, quite recent studies have shown that this excitation in 5-HT_{2A}-identified neurons is abolished by pre-incubation with a selective Gq inhibitor in studies in mice [59]. In support of this hypothesis, quite recent studies have shown that the ability of psychedelic drugs to induce rapid firing of 5-HT_{2A} receptors on identified neurons requires Gq activation [59]. By contrast, one report suggested that in rat renal mesangial cells 5-HT_{2A} receptors may couple to a Gi-like protein [60]. Similarly, others have reported potential coupling to Gi-like proteins in the brain in vivo [61]. Taken together, these findings indicate that 5-HT_{2A} receptors primarily couple to Gq-like G proteins and definitive studies are needed to clarify the role and potential relevance of interactions with other G protein transducers.

5-HT_{2A} receptors are also found in multi-protein complexes in neurons in vivo and these interactions are essential for many of the actions of psychedelic drugs in vitro and in vivo. Thus, collaborative studies first demonstrated that the MAP1A microtubule-associated protein interacts with 5-HT_{2A} receptors in vitro and in vivo [62] in intracellular vesicles. 5-HT_{2A} receptors are also complexed with a number of PDZ-domain-containing proteins including PSD-95 [63, 64] and kalirin-7 (Fig. 4) [65]. The interactions with PSD-95 (Fig. 5) are essential for the biochemical and behavioral effects of psychedelics [64], while interactions with kalirin-7 are involved in psychedelic drug-induced spine formation [65]. Finally, 5-HT_{2A} receptors also form complexes with caveolin-1 [66]. This interaction with caveolin-1 (CAV1) is essential for optimal 5-HT_{2A}-mediated signaling in vitro [66] and in vivo [67]. Genetic deletion of CAV1 attenuates the signaling and behavioral actions of psychedelic drugs in vivo [67]. These results are consistent with models suggesting that 5-HT_{2A} receptors exist in large multi-protein complexes in neurons in vivo and that these interactions are essential for many of the effects of psychedelic drugs (Fig. 5).

Following 5-HT_{2A} receptor activation, induction of spines and dendritic processes rapidly occurs [68]. The Rac guanine nucleotide exchange factor (RacGEF) kalirin-7 is essential for the immediate phase of this process [68], while TrkB activation may also play a role in more long-term actions [69]. The effects of psychedelics on spine formation occur within 30 min [68] and may be maintained for several weeks after a single administration in mice [70]. There has been increasing speculation that the potential therapeutic actions of psychedelic drugs may be mediated via the enhancement of spinogenesis and neuronal plasticity in cortical neurons [2], although definitive studies are lacking.

One of the complications encountered upon investigating the role of psychedelics in vivo is the fact that rodent and human 5-HT_{2A} receptors differ significantly in pharmacology—particularly for tryptamines and ergolines [71, 72]. In this regard, it has been shown by our lab and others that a single amino acid $Ser242^{5.46}$

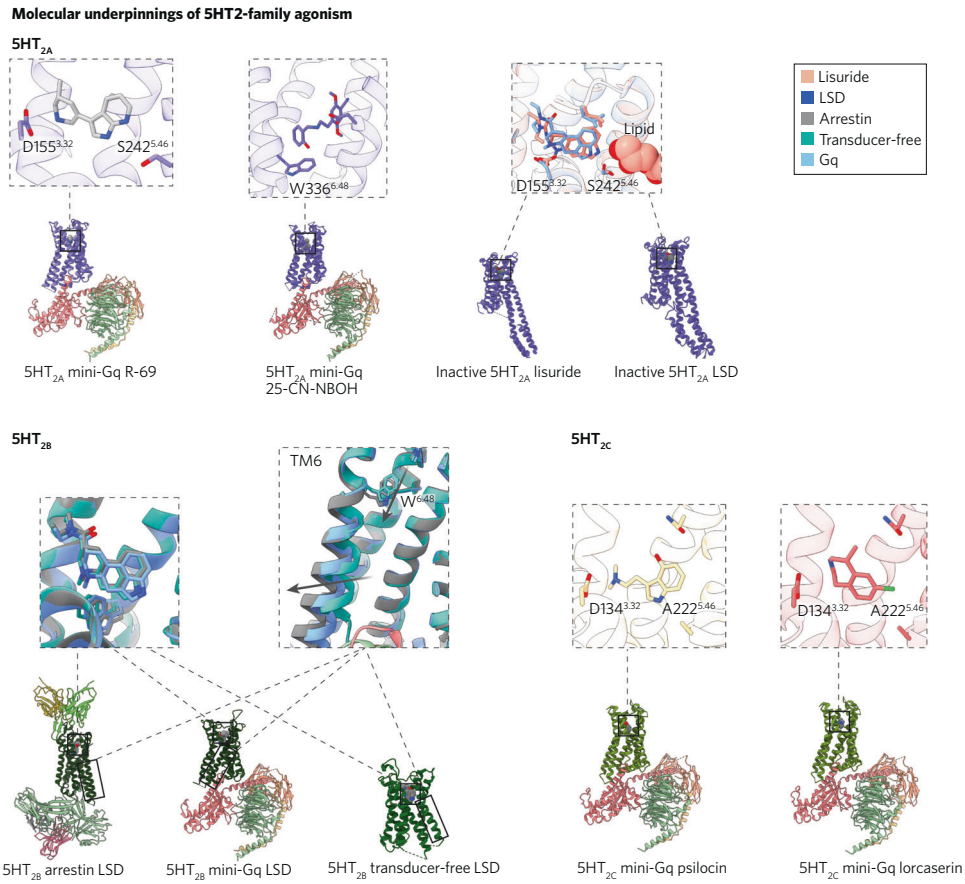

Fig. 3 Structures showing the molecular interactions over the entirety of the 5-HT2 family. Subsets reveal specific interactions mentioned in the text. The top blue panel is representative of structures of 5-HT$_{2A}$ shown in cartoon representation. PDB Accession codes: receptor bound with R-69 and the mini-Gq heterotrimer – 7RAN, receptor bound with 25-CN-NBOH and the mini-Gq heterotrimer – 6WHA, receptor-bound LSD crystallization construct – 6WGT, receptor-bound Lisuride crystallization construct – 7WC7. The 5HT$_{2A}$ receptor is shown in cornflower blue for all the structures while in the heterotrimeric-bound structures, the mini-Gαq is shown in salmon, the β subunit is shown in green, the γ subunit is shown in yellow, and the stabilizing single-chain-Fab-16 (scFv16) is shown in orange. The stick representations showcase the respective ligands in the orthosteric pocket with specific interactions between the receptor and ligand highlighted, while the intrusive lipid is shown in the sphere representation for the lisuride structure. The bottom left panel is a representative structure of 5-HT$_{2B}$ bound to LSD. PDB Accession codes: Arrestin coupled – 7SRS, Gq coupled – 7SRR, and Transducer-free – 7SRQ. In this panel, the receptor is shown in dark green. For the arrestin coupled structure (top) β-arr1 is shown as a light sea green, with the respective stabilizing Fabs shown as the other colors. The mini-Gq couple heterotrimer coupled structure (middle) has a similar color as the 5-HT$_{2A}$ structures with the mini-Gαq shown in salmon, the β subunit shown in green, the γ subunit shown in yellow, and the stabilizing scFv16 shown in orange. The transducer-free complex (solved by cryo-EM), or receptor alone (bottom) is shown in dark green. The left box showcases LSD occupying the orthoseric pocket and highlights specific interactions with the receptor. The right box showcases the differences in the activation of TM6 between the various transducer-coupled states. Upon ligand activation, TM5/6 undergo a conformational change from the inactive state, in which the intracellular side of the helices are packed closer to the core of the receptor, to the active state characterized by the swinging outward and the ligand-activated state presented in the figure. The bottom right panel is a representative structure of the 5-HT$_{2C}$ receptor. PDB Accession codes: receptor bound with psilocin – 8DPG and the mini-Gq heterotrimer and the receptor bound with lorcaserin and the mini-Gq heterotrimer – 8DPF. The black boxes represent the respective ligands in the orthosteric site showcased as sticks with specific interaction(s) in the receptor also shown. The 5-HT$_{2C}$ receptor is shown in olive, the mini-Gαq is shown in salmon, the β subunit is shown in green, the γ subunit is shown in yellow, and the stabilizing single-chain-Fab-16 (scFv16) is shown in orange.

where it is Ala242$^{5.46}$ in rodents [38, 71, 72]. This Ser242Ala mutation greatly accelerates the dissociation rate of LSD at the 5-HT$_{2A}$ receptor [38] and decreases the affinity and potency of a variety of psychedelic and non-psychedelic ergolines and tryptamines [71, 72].

In addition, several non-synonymous single-nucleotide polymorphisms (SNPs) for the 5-HT$_{2A}$ receptor have been identified (see https://gnomad.broadinstitute.org/gene/ENSG00000102468?dataset=gnomad_r2_1; see ref. [73]). Of these, several have been reported to affect the agonist binding affinities, potencies and efficacies of several psychedelic and non-psychedelic 5-HT$_{2A}$ agonists and antagonists [48, 74, 75]. Importantly, the effects of various SNPs on 5-HT$_{2A}$ function were drug-specific and there were no SNPs that uniformly affected agonist or antagonist potency, affinity or efficacy [48, 74, 75]. Taken together, these results indicate that naturally occurring 5-HT$_{2A}$ receptor variants can have significant and unpredictable effects on drug actions.

In addition to the on-target actions of psychedelic drugs at 5-HT$_{2A}$ receptors, all known psychedelic drugs active in humans have substantial activity at other GPCRs [2]. LSD, for example, is a potent agonist at essentially every serotonin, dopamine and noradrenergic receptor in the brain [76]. Radioligand binding assays have also suggested a robust polypharmacological profile for all tested psychedelic drugs [77] although these studies do not clarify whether psychedelic drugs are agonists or antagonists at these receptors. While there are indications that the therapeutic

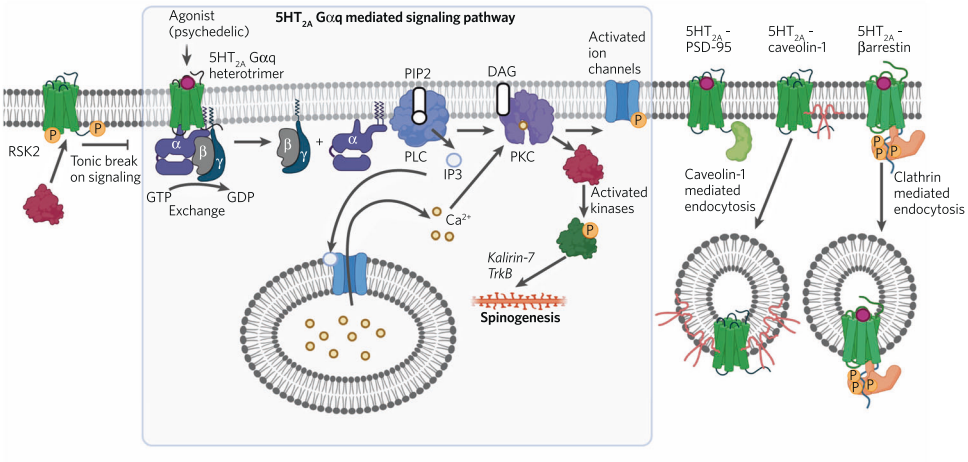

Fig. 4 Representative signaling cascades and complexes of the 5-HT$_{2A}$ receptor. Shown in the box is the canonical Gαq signaling pathway leading to spinogenesis and the potentially therapeutic mechanism of psychedelics. Other signaling mechanisms represented in the figure: the phosphorylation of the receptor by RSK2 leading to a tonic break on receptor signaling; interaction of the 5-HT$_{2A}$ receptor with PSD-95, which has been found to be essential for signaling; β-arrestin recruitment to the receptor and the canonical clathrin-mediated endocytosis of the receptor; and interaction between the receptor and caveolin-1.

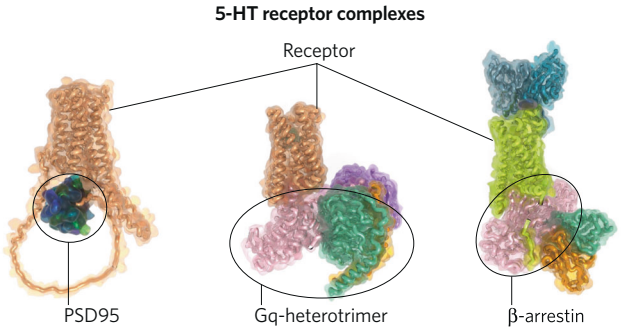

Fig. 5 Representative structures of the various possible interacting proteins with 5-HT$_2$ receptors. The left is the Alphafold-multimer-v2 created structure [130] of 5-HT$_{2A}$ and truncated PSD-95 complex. The middle is the 5-HT$_{2A}$ Gq complex (PDB Accession 6WHA) and the left is the 5-HT$_{2B}$ βarr1 complex (PDB Accession 7SRS).

actions require 5-HT$_{2A}$ receptor activation [69, 78, 79], currently, there is no definitive evidence in support of this mechanism, and indeed, at least one study has suggested that these effects are independent of 5-HT$_{2A}$ activation [80].

Perhaps the most consequential off-target actions of psychedelic drugs are at the 5-HT$_{2B}$ serotonin receptor. All tested psychedelic drugs are potent 5-HT$_{2B}$ agonists [76, 81, 82] or bind with appreciable affinity to 5-HT$_{2B}$ receptors [77]. We [83] and others [84] demonstrated that drugs that induce valvular heart disease in humans after chronic administration are potent 5-HT$_{2B}$ agonists [85]. This includes many anti-migraine drugs (e.g., ergotamine; [85]), drugs used in treating Parkinson's Disease [85] as well as illicit drugs such as MDMA and MDA [86]. Indeed chronic administration of all of these drugs in humans is associated with clinically significant valvulopathy in as many as 30% of patients [87–91]. Taken together, these findings suggest that chronic treatment with psychedelic drugs, as could occur with so-called "microdosing", may have unanticipated and serious side effects.

Interactions with other receptors could be important for both the therapeutic actions as well as other potential side effects of psychedelic drugs. As previously mentioned, one study has suggested the therapeutic actions of psilocybin are 5-HT$_{2A}$-independent in mice [80].

UNANSWERED QUESTIONS

How do psychedelic and non-psychedelic drugs differentially interact with 5-HT$_{2A}$ receptors?

It is now well known that a number of non-psychedelic medications and their active metabolites including fenfluramine and norfenfluramine [83], several ergot derivatives used in treating Parkinson's disease and migraine headaches including ergotamine, lisuride, pergolide and bromocriptine [92], the trazodone metabolite m-CPP [93] and other drugs are potent 5-HT$_{2A}$ agonists. Importantly, these medications are devoid of psychedelic drug-like actions in humans at typical therapeutic doses although hallucinations have occasionally been reported when large doses of fenfluramine [94] or m-CPP [95] have been administered. In addition, bromocriptine and other ergots when used at therapeutic doses in Parkinson's disease occasionally induce hallucinations [96]. Finally, Br-LSD, which is a weak partial agonist of human 5-HT$_{2A}$ receptors, is devoid of psychedelic actions in humans [97]. Importantly, several newly synthesized 5-HT$_{2A}$ agonists with antidepressant drug-like actions are devoid of psychedelic drug-like actions in mice including TBG [98], the lumateperone derivative IHCH-7113 [40] and the tetrahydropyridine R-69 [99]. Taken together, these reports indicate that activation of 5-HT$_{2A}$ receptors per se is insufficient to induce a psychedelic experience. It is currently unknown why some 5-HT$_{2A}$ agonists are psychedelic and further structural biology studies could elucidate these distinctions. As well, given the complicated polypharmacology of known psychedelic drugs [100], it is conceivable that actions at other molecular targets are essential for their effects. Thus, for instance, even though ketanserin blocks psychedelic actions of LSD and psilocybin in humans [27, 34], ketanserin has potent actions at other 5-HT2-family receptors, adrenergic receptors and the vesicular monoamine transporter [26, 101–103], to name but a few. Accordingly, the ability of ketanserin to block the actions of psychedelics in humans does not by itself provide unequivocal evidence for the causal role of 5-HT$_{2A}$ receptors in their actions. Studies with more selective and potent 5-HT$_{2A}$ antagonists could clarify this issue.

Do psychedelic and non-psychedelic 5-HT$_{2A}$ agonists have differential signaling downstream of 5-HT$_{2A}$ receptors?

It has been known since the 1980s that various 5-HT$_{2A}$ agonists differ in their signaling processes. Thus, Felder et al. [104] reported that some 5-HT$_{2A}$ agonists might activate arachidonic acid (AA) release independent of Gq-mediated activation of phospholipase

C. These findings have been validated and extended by others [105–107], although whether a drug is apparently psychedelic or not is irrelevant to whether or not it also activated AA release. Subsequently, Gonzales-Maeso et al. reported that psychedelic 5-HT_{2A} agonists differ from non-psychedelic drugs by selective activation of a pertussis toxin-sensitive pathway involving Src activation [61]. This group has also reported that a heterodimeric complex between mGluR2 metabotropic glutamate and 5-HT_{2A} receptors may be responsible for these actions [108–110]. Others have provided data suggesting the complex as such is not essential for the actions of psychedelics at 5-HT_{2A} receptors [111]. This group [111] also reported that 5-HT_{2A} receptors coupled efficiently to Gq pathways but not to Gi signaling. One potential approach to test the hypothesis that Gq and not Gi signaling is essential for the actions of psychedelics in vivo would be to use a chemogenetic approach. Thus, for instance, expressing Gq- and Gi-DREADDs [112] in 5-HT_{2A} neurons and stimulating them with deschloroclozapine [113] or alternative ligands [114] and observing potential behavioral actions could address these issues.

Are the putative therapeutic actions of psychedelic drugs mediated by 5-HT_{2A} receptor activation?

Currently, there are no selective 5-HT_{2A} agonists which are approved for use in humans and the available psychedelic drugs have a complex polypharmacologic profile. Moreover, a rich area to explore is how this polypharmacological profile can be modulated to treat various disorders. Although no studies have been performed in humans, the available preclinical data support, with some exceptions, actions at 5-HT_{2A} receptors are essential for their therapeutic drug-like actions in rodents [40, 79, 98, 115] . As previously mentioned, there is some evidence that 5-HT_{2A} activation by psilocybin is insufficient to induce an antidepressant-like response [80] and there have also been reports that some of LSD's actions are mediated by 5-HT_{5A}-serotonin [116] and D_2-dopamine [117] receptors. The availability of selective 5-HT_{5A}- [118] and D_2 antagonists should prove invaluable for determining the role of these off-target actions for psychedelic actions. Finally, to definitively address this question, human studies utilizing 5-HT_{2A} antagonists prior to psychedelic drug administration or the use of selective 5-HT_{2A} agonists in human trials will be essential.

How are the putative therapeutic actions of psychedelics mediated?

Current hypotheses suggest that psychedelics may exert their therapeutic drug-like actions via enhancing synaptic plasticity [2]. These findings are based largely on prior studies demonstrating that psychedelic drugs induce both rapid [68, 69] and sustained [70] augmentation of dendritic spine formation and plasticity in cortical neurons in vitro and in vivo, consistent with their expression at dendritic spines [119, 120]. It has long been known that conventional antidepressant drugs [121, 122] as well as novel antidepressants like ketamine require spine formation for their therapeutic drug-like actions [123, 124]. This pathway requires various post-synaptic density proteins [68] as well as the activation of TrkB receptors by BDNF [125]. With regard to this, psychedelic drugs have long been known to enhance BDNF levels [126] and TrkB inhibition can attenuate the actions of psychedelic drugs on spine formation [69].

DISCUSSION AND DIRECTIONS FOR FUTURE BASIC RESEARCH ON PSYCHEDELICS

As is clear from the foregoing, there are many potentially significant areas for continued research on psychedelics. These include determining: (1) how psychedelic and non-psychedelic 5-HT_{2A} agonists differentially interact with the receptor; (2) how signal transduction downstream of 5-HT_{2A} receptors differs among various psychedelic and non-psychedelic agonists; (3) whether on- or off-target actions of psychedelics are essential for their putative therapeutic actions; and (4) how are the potential therapeutic actions of psychedelic drugs mediated. Central to these unanswered questions is the overarching question of whether non-psychedelic 5-HT_{2A} agonists may retain at least some of the therapeutic actions of psychedelic drugs.

As mentioned previously, a number of drugs that do not induce a psychedelic drug-like action in rodents have been recently discovered including TBG [98], IHCH-7113 [40] and R-69 [39]. To this list, we may also add the legacy compound Ariadne [127], Br-LSD [128] and, in some cases, lisuride [129] which have all shown efficacy in preliminary clinical trials and reports. Such medications have the potential to transform our treatment of many neuropsychiatric conditions.

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ADDITIONAL INFORMATION

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