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Molecular targets of psychedelic-induced plasticity

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Abstract

Psychedelic research across different disciplines and biological levels is growing at a remarkably fast pace. In the prospect of a psychedelic drug becoming again an approved treatment, much of these efforts have been oriented toward exploring the relationship between the actual psychedelic effects and those manifestations of therapeutic interest. Considering the central role of the serotonin 5-HT_{2A} receptor in the distinct effects of psychedelics in human psyche, neuropharmacology sits at the center of this debate and exploratory continuum. Here we discuss some of the most recent findings in human studies and contextualize them considering previous preclinical models studying phenomena related to synaptic plasticity. A special emphasis is placed on knowledge gaps, challenges, and limitations to evaluate the underpinnings of psychedelics' potential antidepressant action.

Keywords

5-HT2A receptor; GPCR; hallucinogens; LSD; psychedelics; serotonin

Psychedelics have been part of our cultures since ancient times (Fantegrossi et al., 2008; Glennon, 1994; Hanks & González-Maeso, 2016a, 2016b; Nichols, 2016; Rucker et al., 2018). This family of psychoactive drugs includes naturally occurring alkaloids such as psilocybin which is the main active component found in more than 100 species of "magic" mushrooms including *Psilocybe cyanescens* in Europe and the west coast of the U.S., and *Psilocybe cubensis* in South America and parts of Mexico, mescaline which is the principal active compound in the peyote cactus (*Lophophora williamsii*) native to Mexico and southwestern Texas, bufotenin which is found in the gland secretion of certain toads'

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AUTHORS' CONTRIBUTIONS

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CONFLICT OF INTEREST

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skin (*Bufonidae*), and dimethyltryptamine (DMT)—found in different vegetable sources such as *Mimosa* sp. root bark and *Psychotria viridis* leaves, one the main ingredients of ayahuasca, a brew traditionally used for ceremonial purposes in the Amazon region made in combination with roots of *Banisteriopsis caapi* that render this psychedelic orally active by virtue of the monoamine oxidase A inhibitors contained in this vine (Abraham et al., 1996; Halpern, 2004). The paradigmatic psychedelic of the 20th century, lysergic acid diethylamide (LSD), however, is hemisynthetic in nature. It was first synthesized in 1938 by Dr Albert Hofmann, who also serendipitously discovered its psychopharmacological effects in 1943 while working on ergot derivatives from *Claviceps purpurea* in search for respiratory stimulants at Sandoz Pharmaceuticals in Basel, Switzerland (Hofmann, 1979). All these drugs have in common a battery of acute (within minutes to hours) effects in humans that include profound changes in processes related to perception, cognition, sensory processing, and mood. As substances listed in DEA Schedule I, elucidating the mechanisms by which psychedelics induce their unique neuropsychological effects has been an important objective of drug abuse research for decades (Halpern & Pope, 1999; Heal et al., 2018; Krebs & Johansen, 2013). Currently, however, psychedelics are not considered addictive—although some can produce tolerance in rodents (Smith et al., 2014), they lack reinforcement effects (Johnson et al., 2018). Notably, more recent clinical work as well as preclinical findings in rodents suggest that psychedelics, and particularly psilocybin, behave as fast-acting and long-lasting therapeutic agents against a number of psychiatric conditions that include depression (Carhart-Harris et al., 2016, 2021; Davis et al., 2020; Griffiths et al., 2016), and substance use disorders (Bogenschutz et al., 2015; Krebs & Johansen, 2012). Although the molecular pharmacology of this family of drugs is notoriously complex (Inserra et al., 2021), one receptor emerges from the plethora of neurotransmitter receptors that psychedelics interact with as the main mediator of psychedelics' most distinct effects. Thus, previous gene deletion models in mice (Gonzalez-Maeso et al., 2003, 2007) and pharmacological antagonism in both rodents (de la Fuente Revenga et al., 2019, 2020; Halberstadt & Geyer, 2013) and healthy volunteers (Schmid et al., 2015; Vollenweider et al., 1998) have clearly established the prominent role of the serotonin (or 5-hydroxytryptamine) 5-HT$_{2A}$ receptor (5-HT$_{2A}$R) in the mechanism of action of psychedelics. For a general review about classification and pharmacology of serotonin 5-HT receptors, see here (Barnes et al., 2021).

Serotonergic psychedelics are classified into two main groups that include phenethylamines such as mescaline and its synthetic analog 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), and tryptamines. The latter group can be subdivided into two subgroups: simple tryptamines such as psilocybin and its active metabolite psilocin, and DMT, which contains an indole ring and shows substantial structural flexibility, and ergoline derivatives such as LSD (Hanks & González-Maeso, 2016a, 2016b; Nichols, 2004). Most of the medicinal chemistry, molecular pharmacology, and behavioral work in rodent models has been conducted with psychedelics that belong to these three families and hence most of the chemical structure–psychedelic activity relationships reported to date belong into a relatively narrow chemical space. This, however, does not exclude the possibility that compounds that possess different structural cores may also behave as psychedelics so long they exhibit pharmacological mimicry. Recent examples that support this concept include

the HIV antiretroviral medication efavirenz (Dalwadi et al., 2016, 2018; Gatch et al., 2013) and quipazine (de la Fuente Revenga et al., 2021a), an *N*-substituted piperazine in which development as a potential antidepressant was halted. It has been demonstrated that both efavirenz and quipazine activate the serotonin 5-HT_{2A}R and induce behavioral signatures characteristic of psychedelic action in rodent models. While largely anecdotal, their departure from the structural orthodoxy of phenethylamines and tryptamines sets a new frontier in the exploration of chemical spaces populated by novel 5-HT_{2A}R agonists as well as the role of additional monoaminergic G protein-coupled receptors (GPCRs).

Preclinical research with psychedelics largely relies on rodent models that bear high predictive values but are not exempt from substantial limitations (Hanks & Gonzalez-Maeso, 2013). One of such limitations is their translational validity. It is tempting to speculate that the alterations induced upon acute administration of psychedelics in processes related to perception and sensory processing are uniquely human and therefore difficult, if not impossible, to model in rats and mice. In 1990, it was reported that the phenethylamine psychedelic DOI induced a dose-dependent increase in ear-scratch response in mice (Darmani et al., 1990). While this behavior is not preserved in humans exposed to a psychedelic drug, the effect in rodents was prevented by pre-administration of serotonin 5-$HT_{2A/2C}$R antagonists such as ketanserin (Darmani et al., 1990)—a drug that was also shown to block the hallucinogenic effects of psilocybin and LSD in humans (Schmid et al., 2015; Vollenweider et al., 1998). Head-twitch behavior (a rapid side-to-side movement of the head) represents a similar case—while naturally present in rodents, the frequency of manifestation increases abruptly with all the psychedelic serotonin 5-HT_{2A}R agonists studied so far (Canal, 2012; Hanks & Gonzalez-Maeso, 2013). This behavior, which was originally reported in 1955 (Woolley, 1955), is not induced by closely related 5-HT_{2A}R agonists that lack psychedelic potential in humans, such as lisuride and ergotamine (Gonzalez-Maeso et al., 2003, 2007). It has also been demonstrated that there is a high correlation between the potency of psychedelic-induced head-twitch behavior in rodents and their behavioral subjective effects in humans (Halberstadt et al., 2020). Based on these and other preclinical findings, this behavior is widely used as a mouse behavioral proxy of human hallucinogenic potential. However, it is important to remark that there are still a few examples of false positives that are able to induce head-twitch behavior in rodents—these include cannabinoid CB_1 receptor agonists (Darmani and Pandya, 2000; Darmani et al., 2003) and α_2-adrenergic receptor antagonists (Matsumoto et al., 1997). Another potential false positive is the serotonin precursor 5-hydroxytryptophan (5-HTP). At relatively high doses, this intermediate metabolite of the essential amino acid L-tryptophan has been shown to induce a robust increase in mouse head-twitch behavior that is prevented by 5-HT_{2A}R antagonists (Schmid & Bohn, 2010; Schmid et al., 2008). 5-HTP has been used for the treatment of a variety of conditions related to potential alterations in serotonin levels that include depression, insomnia, and migraines. While psychedelic-like events do not appear to concern in such studies, the allometric scales of the doses of 5-HTP employed in the rodent head-twitch studies can exceed by orders of magnitude the doses of 5-HTP used safely in humans.

Related to the molecular target responsible for the distinct interoceptive cue elicited by psychedelics, Richard Glennon and his team reported a significant correlation between the

affinity of multiple psychedelic agents and their potencies (EC_{50} values) using both drug discrimination with 2,5-dimethoxy-4-methylamphetamine (DOM) as the training drug in rats and human hallucinogenic potencies of these agents (Glennon et al., 1984). About 15 years later, studies in healthy volunteers suggested the psychedelic psilocybin-induced schizophrenia-like related effects, including ego-disorders, affective changes, loosened associations, and perceptional alterations–these behavioral disruptions were blocked dose-dependently by the 5-$HT_{2A/2C}$R antagonist ketanserin (Vollenweider et al., 1998). A similar conclusion related to the role of the 5-HT_{2A}R in the acute effects of psychedelics was recently reached by testing the effects of LSD in healthy subjects (Schmid et al., 2015). Mouse and rat head-twitch behavior induced by psychedelics is also blocked by 5-$HT_{2A/2C}$R and 5-HT_{2A}R antagonists, including ketanserin and M100907, respectively, as well as by genetic deletion of the *5-HT_{2A}R* (*Htr2a*) gene in mice (Hanks & Gonzalez-Maeso, 2013). It is therefore accepted that the 5-HT_{2A}R is the principal target responsible for the hallucinogenic-like effects in humans and head-twitch behavior in mice upon acute psychedelic administration. However, the potential role of this serotonin receptor in the post-acute antidepressant-like behavioral and synaptic plasticity effects induced by psychedelics still remains to be fully elucidated.

Depression and other mood disorders represent a psychiatric condition that affects approximately 5% of the adult population (Kessler et al., 2003; Krishnan & Nestler, 2008). Traditional monoaminergic antidepressants, such as fluoxetine, have the ability to reduce depression in some depressive patients, but their clinical effects require a long-lasting (weeks to months) administration and there is a high percentage of patients with depression that does not respond to the currently available antidepressant medications (Duman & Aghajanian, 2012; Insel & Wang, 2009). Based on the relatively recent clinical effects of the dissociative drug ketamine, a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, showing robust, rapid (a few hours following administration) and sustained (several days on average) antidepressant effects following a single administration (typically intravenous) at a sub-anesthetic dose (Abdallah et al., 2015; Berman et al., 2000), more recent studies have provided convincing evidence that classical psychedelics, particularly naturally occurring compounds such as psilocybin and DMT in the ayahuasca brew, also behave as rapid-acting antidepressant medications (Carhart-Harris et al., 2016, 2021; Davis et al., 2020; Griffiths et al., 2016; Kyzar et al., 2017; Vollenweider & Kometer, 2010). Dendritic spines are small protrusions studding neuronal dendrites located at the postsynaptic sites of most excitatory synapses in brain regions including frontal cortex and the hippocampus (Koleske, 2013; Spruston, 2008). Santiago Ramón y Cajal was the first to observe these small protrusions using his famous Golgi staining. A number of studies in animal models as well as postmortem human brain samples from subjects with depression and controls has provided evidence that mood disorders occur in conjunction with a reduction in the density of dendritic spines, particularly in the frontal cortex (Duman & Aghajanian, 2012; Liu & Aghajanian, 2008; Nestler et al., 2002; Russo & Nestler, 2013). In 2009, studies in rat cortical neuronal primary cultures suggested that the psychedelic DOI induced a rapid (observed 30 min upon drug administration) and transient (returned to control levels by 60 min) effect on dendritic spine remodeling (Jones et al., 2009). This was corroborated with additional *in vitro* studies in cortical neuronal primary cultures

with the psychedelics DOI, DMT, and LSD (Ly et al., 2018). Additionally, these studies showed that the effects of psychedelics on *in vitro* structural plasticity were blocked by the 5-$HT_{2A/2C}$R antagonist ketanserin (Ly et al., 2018). Using an in vivo 3D automated method for quantitative structural analysis, it has also been suggested that a single administration of the psychedelic DOI produced fast-acting effects on mouse frontal cortex dendritic spine structure with a selective augmentation of the density of transitional stubby and dynamic thin spines in cortical pyramidal neurons, but not mature mushroom spine density (de la Fuente Revenga et al., 2021b). This structural synaptic remodeling event induced by DOI was not observed in 5-HT_{2A}R knockout mice (de la Fuente Revenga et al., 2021b). Together, these *in vitro* (Ly et al., 2018) and *in vivo* (de la Fuente Revenga et al., 2021b) findings suggest that expression of the 5-HT_{2A}R is necessary for the effects of a single administration of the psychedelics DOI, DMT, and LSD on changes in frontal cortex dendritic spine structural plasticity (Figure 1).

Intriguingly, this does not seem to be the case for the tryptamine psychedelic psilocybin. Thus, it has been reported that ketanserin pretreatment did not prevent phenotypes related to psilocybin-induced synaptic strengthening of hippocampal synapses, although under these experimental conditions ketanserin was only able to partially, and not fully, reduce psilocybin-induced head-twitch behavior (Hesselgrave et al., 2021). Additional investigation is necessary to fully understand the pharmacological reason behind this lack of effect of the 5-$HT_{2A/2C}$R antagonist ketanserin on synaptic plasticity events induced by psilocybin, but a potential explanation is the time (1 h) between antagonist and agonist administration when ketanserin might be metabolized. More recently, it has also been reported that ketanserin given 10 min prior to psilocybin was able to fully block head-twitch behavior, and under these experimental conditions, the effect of coadministration of this 5-$HT_{2A/2C}$R antagonist with psilocybin on frontal cortex dendritic spine density was not statistically different from that of the ketanserin alone group, suggesting that pharmacological blockade of 5-$HT_{2A/2C}$Rs prevents the post-acute effects of psilocybin on frontal cortex structural plasticity. However, under these experimental conditions, the ketanserin +psilocybin group showed an increase in frontal cortex dendritic spine head width as compared to the ketanserin alone group (Shao et al., 2021). Ketanserin targets the human 5-HT_{2A}R with higher affinity as compared to human 5-HT_{2C}R, whereas this ligand is considered a non-selective mouse 5-HT_2R antagonist (Barnes et al., 2021). Since these inter-species differences in its pharmacological profile also imply that ketanserin may not fully bock the 5-HT_{2A}R population in psychedelic-target brain regions, such as the frontal cortex in mouse models, it is clear that additional work will be necessary to fully understand the main molecular target/s on the cell surface responsible for the long-lasting effects of the different classes of psychedelics on synaptic plasticity and associated behaviors via engagement of downstream mechanisms known to involve processes such as tropomyosin receptor kinase B (TrkB), mammalian target of rapamycin (mTOR), brain-derived neurotrophic factor (BDNF), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors, and/or metabotropic glutamate receptor 2 (mGluR2) (Benvenga et al., 2018; De Gregorio et al., 2021; Ly et al., 2018; Moreno et al., 2011). This exploration of cell membrane transducers becomes particularly relevant considering the pronounced pharmacological promiscuity of psilocybin and other psychedelics. It is worth noting that

both 5-HT_{1A}R and 5-HT_{2A}R constitute targets within range for drugs currently approved for the treatment of mood disorders, anxiety, and depression, such as buspirone and trazodone (Kessler et al., 2003; Krishnan & Nestler, 2008). Potential alternative molecular targets include a number of class A GPCRs, such as 5-HT_{2C}R (Canal et al., 2010), and 5-HT_{5A}R (Grailhe et al., 1999) as well as dopaminergic (De Gregorio et al., 2016; Inserra et al., 2021; Marona-Lewicka & Nichols, 2007; Marona-Lewicka et al., 2005; Rickli et al., 2016) and adrenergic (Inserra et al., 2021; Rickli et al., 2016) receptors, which have already been involved in some of the acute behavioral effects of psychedelics in rodents. Particularly, it has been suggested that the later (90–120 min after psychedelic exposure) temporal phase of LSD administration on discriminative stimulus is mediated via D_2 receptors (Marona-Lewicka & Nichols, 2007; Marona-Lewicka et al., 2005) (Figure 1). Additionally, some fundamental questions still remain open as the pro-synaptic effects of psychedelics cannot simply be generalized as therapeutically positive. Synaptic plasticity events in regions related to reward can reinforce drug-seeking behaviors in addiction. For example, psychoactive drugs of abuse such as cocaine increased the density of dendritic spines in medium spiny neurons of the nucleus accumbens (Maze et al., 2010). Similarly, plasticity events underlie the development of chronic pain (Cunha et al., 2020). Causal research is also necessary to determine if psychedelic-induced changes in frontal cortex dendritic spine density are responsible for the post-acute effects of psychedelics. Related to this concept, an increase in the density of immature thin dendritic spines has also been shown in the frontal cortex of a genetic rat model related to schizophrenia (Sanchez-Gonzalez et al., 2021).

Dosing is also deserving of consideration. The occurrence of psychedelics' subjective effects on human psyche occurs once a certain threshold is exceeded. However, it has been posed that below such threshold, therapeutic and/or adaptive benefits can readily manifest. Earlier anecdotal reports suggested that psychedelic microdosing, which involves regularly consuming a small, sub-perceptual amount of psychedelics substances such as psilocybin or LSD, may have the potential to enhance creativity and efficiency, increase performance on problem-solving tasks, and treat neuropsychiatric conditions including depression and Alzheimer's disease (Cameron et al., 2020; Kuypers et al., 2019). These overarching claims were recently challenged by studies suggesting that subjective effects of microdosing in volunteers were not different than placebo and hence largely explained by positive expectation (Kaertner et al., 2021; Szigeti et al., 2021). The study of microdosing in human subjects bears significant challenges considering that the drugs of study are subject to heavy legal burdens and the so-called positive effects appear to be of interest in the community rather than in a clinical-controlled setting. In this regard, preclinical research offers a more accessible platform to characterize the molecular and behavioral fingerprints of psychedelics across the dose range. Although the additional investigation is necessary to further define better preclinical models of microdosing in animal models, it is worth mentioning the recent studies in male and female Sprague Dawley rats showing either reduced effects of microdosing with DMT on models of depression such as reduced immobility time in the forced swim test or absence of effect in more elaborated behaviors such as fear conditioning and extinction (Cameron et al., 2019). Additionally, and opposite to the effects observed upon post-acute DMT administration, these findings also suggested

that chronic, intermittent low doses of DMT led to a decrease in the dendritic spine density in the frontal cortex of female, but not, male rats (Cameron et al., 2019).

One of the still open questions is whether the fast-acting and long-lasting beneficial effects of psychedelics, particularly psilocybin, on a number of neuropsychiatric conditions that range from depression and alcoholism to post-traumatic stress disorder and cluster headache are observed as a repercussion of the action of these agents in complex neuropsychological processes such as ego-dissolution, depersonalization, oceanic boundlessness or visionary re-structuralization (Schmid et al., 2015; Vollenweider et al., 1998). It has also been reported that classical psychedelics occasion reliable and measurable mystical-type experiences in healthy volunteers (Griffiths et al., 2008). In this case, preclinical research and animal models offer little value as surrogates to study the phenomenology of such events. From a translational perspective, it would be challenging, perhaps unfeasible, to ascertain whether these intricate behavioral disruptions are necessary for their therapeutic-related phenotypes in rodents. Despite such limitations, it has been shown that rodent models replicate some of the clinically relevant post-acute effects of psychedelics in human subjects. Thus, a number of recent publications supports the notion that a single administration of different families of psychedelics such as the phenethylamine DOI and the tryptamines psilocybin and LSD produce long-lasting (5 weeks after administration) antidepressant-related behavior in mice and rats when evaluating behavioral despair or passivity such as the forced swim test (Cameron et al., 2018; de la Fuente Revenga et al., 2021b; Hibicke et al., 2020). Additionally, it has also been reported that a single dose with the DMT facilitates the extinction of cued fear memory in rats (Cameron et al., 2018), whereas a single administration of the psychedelic DOI accelerated contextual fear extinction via the 5-HT_{2A}R in mice (de la Fuente Revenga et al., 2021b). Using sucrose and female urine preference as a model of anhedonic behavior, it was validated the chronic stress led to anhedonic-related behavior in male mice. A single injection with psilocybin reduced stress-induced anhedonic behavior (Hesselgrave et al., 2021). However, this behavioral phenotype was not prevented by pretreatment with the serotonin 5-$HT_{2A/2C}$R antagonist ketanserin (Hesselgrave et al., 2021). Although as mentioned above under these experimental conditions ketanserin only partially blocked psilocybin-induced head-twitch behavior (Hesselgrave et al., 2021), these findings suggest that opposite to what had been observed with DOI, DMT, and LSD (de la Fuente Revenga et al., 2021b; Ly et al., 2018), the effects of psilocybin on post-acute antidepressant-related behavior do not require activation of the 5-HT_{2A}R. Considering that both newly synthesized putative non-psychedelic yet highly selective 5-HT_{2A}R agonists such as tabernanthalog (Cameron et al., 2021), as well as already classical non-psychedelic 5-HT_{2A}R agonists such as lisuride (Nakamura et al., 1989), reduce alcohol-and heroin-seeking behavior, and produce antidepressant-like effects antidepressant-like effects in rodents, it is tempting to speculate that the psychosis-related behavior induced by psychedelic 5-HT_{2A}R agonists is not necessary for the post-acute beneficial effects induced by other psychedelics such as psilocybin or LSD. Alternatively, although their antidepressant and anxiolytic clinical effects are mild, it is rather surprising that the involvement of the 5-HT_{1A}R on the abovementioned traits has not been established considering that this target has been validated in the treatment of anxiety by azapirones such as buspirone and the high affinity for the 5-HT_{1A}R of LSD and psilocybin's active form:

psilocin. Additional investigation will be necessary to unravel this still open question about the molecular target and signaling mechanisms responsible for the therapeutic potential of these ligands.

Most cell signaling pathways regulate gene expression in response to extracellular cues, and receptor activation can cause concentration-dependent changes in the level of induction of specific genes *in vitro* in cell cultures (Wurmbach et al., 2002; Yuen et al., 2002). Using traditional gene expression assays including oligonucleotide and cDNA microarrays, it was reported that intraperitoneal administration of psychedelics such as DOI and LSD leads to changes in expression of a number of genes including transcription factors such as *c-Fos*, *Egr-1*, and *Egr-2* that showed maximal change at approximately 60 min following drug exposure (Gonzalez-Maeso et al., 2003, 2007; Nichols et al., 2003; Nichols & Sanders-Bush, 2002). However, these changes in gene expression were not observed two hours after psychedelic administration. More recent findings have suggested that gene expression depends on the ability of the transcriptional machinery to access DNA, which is tightly packed into chromatin. The status of chromatin organization depends on epigenetic factors, such as DNA methylation and histone modifications that primarily occur on their amino-terminal tails. Hence these epigenetic mechanisms lead to stable changes in gene expression that are mediated via altered chromatin structure without modification of DNA sequence and remain largely plastic throughout all periods of brain development and aging (Bastle & Maze, 2019; Graff & Tsai, 2013). Unlike psilocybin, DOI exhibits a pronounced preference for 5-HT_2Rs thus offering some built-in discriminative power to segregate the effects of psychedelics via 5-HT_{2A}R from other interactions that can operate as potential confounding factors. Using MOWChIP-seq with H3K27ac (Cao et al., 2015; Zhu et al., 2019) and Smart-seq2 (Picelli et al., 2013, 2014) assays in neuronal nuclei from the frontal cortex of mice, recent findings suggest that a single dose of DOI leads to changes in chromatin organization particularly at enhancer regions of genes involved in the synaptic assembly that stretched for at least one week after the psychedelic exposure (de la Fuente Revenga et al., 2021b). Further, DOI-induced alterations in the neuronal epigenomic landscape overlapped with genetic loci associated with psychiatric conditions that included schizophrenia, depression, and attention deficit hyperactivity disorder (de la Fuente Revenga et al., 2021b). These data suggest that epigenetic mechanisms may underlie at least some of the long-lasting antidepressant action induced upon psychedelic administration, but also raise concerns about the limitations in patients with underlying genetic risk for psychosis.

Psychedelics produce a myriad of acute and post-acute behavioral alterations in both humans and animal models, including the promotion of spinogenesis in brain regions such as the frontal cortex. The robust and sustained antidepressant and plastic effects reported are suggestive of therapeutic potential for treatment-resistant depression and other neuropsychiatric disorders. Although recent findings provided evidence about the pathways affected by psychedelics and potentially involved in their post-acute beneficial effects, questions about the initiator molecular target(s) and causality of downstream signaling pathways still remain open. Utilizing behavioral, molecular, and epigenetic tools, ongoing and future studies are working to determine how psychedelics are exerting their beneficial effects and what factors may be important to consider when using these compounds to treat depression and other neuropsychiatric conditions.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Abbreviations

5-HTP	5-hydroxytryptophan
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors
BDNF	brain-derived neurotrophic factor
DMT	dimethyltryptamine
DOI	1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane
DOM	2,5-dimethoxy-4-methylamphetamine
GPCR	G protein-coupled receptor
LSD	lysergic acid diethylamide
mGluR2	metabotropic glutamate receptor 2
MOWChIP-seq	microfluidic oscillatory washing-based chromatin immunoprecipitation followed by sequencing
mTOR	mammalian target of rapamycin
TrkB	tropomyosin receptor kinase B
NMDA	*N*-methyl-D-aspartate
5-HT	serotonin or 5-hydroxytryptamine

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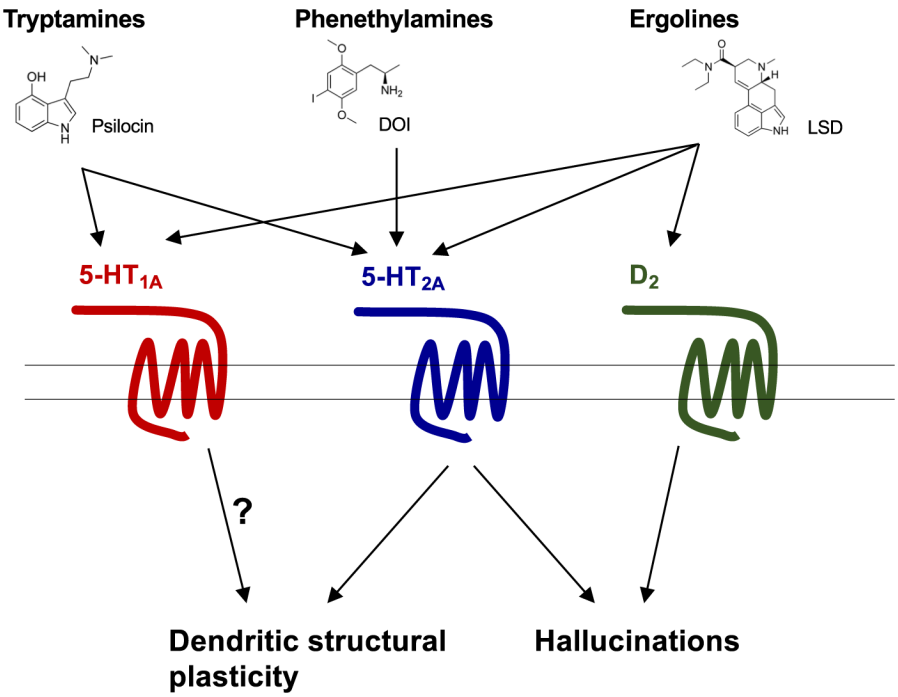

FIGURE 1.

Schematic summarizing receptor targets and their potential involvement in therapeutic effects of different structural classes of psychedelics. Tryptamine psilocin activates both serotonin 5-HT_{1A} and 5-HT_{2A} receptors, contributing to hallucinogenic-like behavior, but the role of the 5-HT_{1A} in structural plasticity remains unknown. Phenethylamine DOI is more selective for 5-HT_2 receptors, with a higher affinity to 5-HT_{2A}R, which is thought to contribute to both structural plasticity and hallucinogenic-like behavior. Ergoline LSD activates dopamine D_2 receptors as well as 5-HT_{1A} and 5-HT_{2A} receptors, which leads to hallucinogenic-like behavior, but it is unknown how LSD's polypharmacology influences synaptic structural plasticity