Symposium

Beyond the 5-HT_{2A} Receptor: Classic and Nonclassic Targets in Psychedelic Drug Action

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Serotonergic psychedelics, such as psilocybin and LSD, have garnered significant attention in recent years for their potential therapeutic effects and unique mechanisms of action. These compounds exert their primary effects through activating serotonin 5-HT_{2A} receptors, found predominantly in cortical regions. By interacting with these receptors, serotonergic psychedelics induce alterations in perception, cognition, and emotions, leading to the characteristic psychedelic experience. One of the most crucial aspects of serotonergic psychedelics is their ability to promote neuroplasticity, the formation of new neural connections, and rewire neuronal networks. This neuroplasticity is believed to underlie their therapeutic potential for various mental health conditions, including depression, anxiety, and substance use disorders. In this mini-review, we will discuss how the 5-HT_{2A} receptor activation is just one facet of the complex mechanisms of action of serotonergic psychedelics. They also interact with other serotonin receptor subtypes, such as 5-HT_{1A} and 5-HT_{2C} receptors, and with neurotrophin receptors (e.g., tropomyosin receptor kinase B). These interactions contribute to the complexity of their effects on perception, mood, and cognition. Moreover, as psychedelic research advances, there is an increasing interest in developing nonhallucinogenic derivatives of these drugs to create safer and more targeted medications for psychiatric disorders by removing the hallucinogenic properties while retaining the potential therapeutic benefits. These nonhallucinogenic derivatives would offer patients therapeutic advantages without the intense psychedelic experience, potentially reducing the risks of adverse reactions. Finally, we discuss the potential of psychedelics as substrates for post-translational modification of proteins as part of their mechanism of action.

Introduction

Serotonergic psychedelics are gaining rapid support because of their fast-acting therapeutic effects for a plethora of neuropsychiatric conditions, including depression, anxiety, post-traumatic stress disorder, substance use disorders (SUDs), anorexia, and chronic pain. Serotonergic psychedelics (e.g., LSD, psilocybin [and its active metabolite, psilocin], N,N-dimethyltryptamine [DMT], 2,5-dimethoxy-4-iodoamphetamine [DOI]) are generally defined by their agonism of the serotonin (5-HT) receptor 2A (5-HT_{2A}). However, to say that psychedelics exert all their potential therapeutic effects through 5-HT_{2A} activation is unlikely. As a group of compounds, they target many 5-HT receptors and interact with multiple other neurotransmitter systems.

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While the *in vivo* occupancy of the 5-HT_{2A} receptor correlated with induced psychedelic experiences (Madsen et al., 2019), and 5-HT_{2A} is necessary for the perceptual effects of the serotonergic psychedelics (Halberstadt and Geyer, 2011), the breadth of receptor agonism suggests it may not be sufficient for therapeutic effects (Fig. 1). For example, all tested serotonergic psychedelics showed potent binding to the 5-HT_{2B} and 5-HT_{2C} receptors (Nelson et al., 1999), and recent findings suggest that the neuroplastic effects of psychedelics may be dependent on tropomyosin receptor kinase B (TrkB) receptor binding (Moliner et al., 2023) (Fig. 1). LSD, a high-affinity 5-HT_{2A} agonist, binds to most 5-HT receptor subtypes (Nichols, 2004), multiple dopamine and adrenergic receptors (Ray, 2010; Lewis et al., 2023), and TrkB (Ly et al., 2018; Moliner et al., 2023); thus, these sites may serve a function in the overall positive effects of LSD on psychiatric disorders. While DMT, an indolamine-based psychedelic, appears to exert its effects through 5-HT_{1A} agonism in concert with 5-HT_{2A} (Halberstadt and Geyer, 2011), the phenethylamines (e.g., mescaline) show no affinity for 5-HT_{1A} (Nichols, 2004). Thus, a more rigorous description of the molecular pathways is needed to disentangle the therapeutic

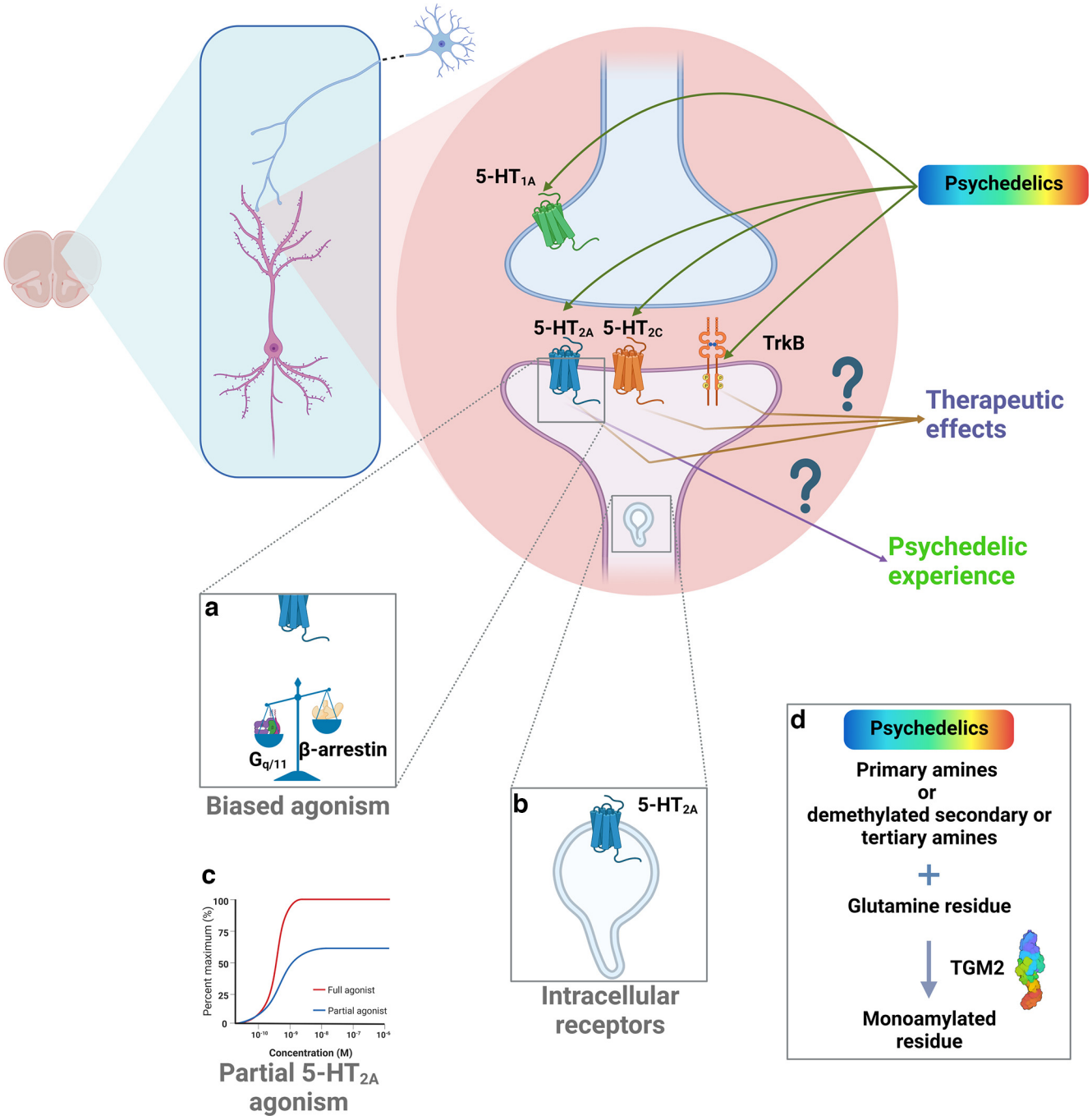

Figure 1. The multiple targets of serotonergic psychedelic drugs. Among the major anatomic targets for serotonergic psychedelics are cortical areas, such as the PFC, where serotonergic receptors are located in pyramidal neurons. Although activation of 5-HT$_{2A}$ receptors is an integral element of the hallucinogenic experience and may contribute to some of the proposed therapeutic effects of these class of drugs, other receptors of the same family (5-HT$_{2C}$ and 5-HT$_{1A}$) or even the TrkB receptor of the neurotrophin, BDNFs are involved in the therapeutic effects of psychedelic drugs. This suggests a potential to dissociate psychedelics from therapeutic effects. ***a***, Several psychedelic drugs may also induce their effects (psychedelic and or therapeutic) via a biased activation of signaling pathways (G-protein-mediated vs β-arrestin). ***b***, Alternatively, serotonergic psychedelics may target intracellular 5-HT$_{2A}$ receptors to induce therapeutic effects because of their lipophilicity, which allows them to traverse the cell membrane. ***c***, Some derivatives, such as 2-Br-LSD, also target 5-HT$_{2A}$ receptors as partial agonists, inducing synaptic plasticity but lacking hallucinogenic effects. ***d***, Finally, it is also conceivable that several psychedelics and entactogens can be a substrate for TGM2 to monoamylate glutamine restudies in proteins, such as Rac1 or histones, to alter cytoskeleton function or gene expression, respectively, in the induction of lasting therapeutic effects.

action from the various hallucinogenic effects (Ray, 2010; Lewis et al., 2023).

Serotonergic psychedelics are being investigated for the treatment of depressive disorders and other mood disorders (Davis et al., 2021; Daws et al., 2022; D'Souza et al., 2022; Goodwin et al., 2022, 2023; Zeifman et al., 2023). In preclinical studies, chronic stress (a risk factor for depression and other mood disorders) results in structural and functional atrophy, primarily in the prefrontal cortex (PFC) and hippocampus (Duman et al., 2016), and such effects are thought to be the basis of deficits of many mood disorders (Russo and Nestler, 2013). Current pharmaceutical treatments, such as monoamine reuptake inhibitors, promote positive neuroplastic changes but only following chronic treatment, and they suffer from high resistance in patient populations

(Zhdanava et al., 2021). These drawbacks have motivated preclinical and clinical research on more effective and faster-acting alternatives for mood disorders. Several studies have demonstrated that psychedelics can increase structural and functional neuroplasticity (Cameron et al., 2018; Ly et al., 2018; Shao et al., 2021; Vargas et al., 2023) in the PFC, hippocampus, and other brain regions involved in emotion (Vargas et al., 2021). Importantly, these compounds appear to be rapid-acting and effective in at least some treatment-resistant patients with major depressive disorder (Carhart-Harris et al., 2017; Palhano-Fontes et al., 2019; Davis et al., 2021; Daws et al., 2022; D'Souza et al., 2022; Goodwin et al., 2022, 2023; Zeifman et al., 2023).

Serotonergic psychedelics also show promise in reducing alcohol intake in heavy drinkers (Bogenschutz et al., 2022) and increasing smoking cessation (Johnson et al., 2017). Recently, data from the National Survey on Drug Use and Health found that psilocybin was associated with a 30% decrease in the odds of developing an opioid use disorder (OUD) (Jones et al., 2022), suggesting that serotonergic psychedelics may be efficacious in the treatment of the underlying addiction in many different SUDs. While the evidence is promising, little is known about the modulatory mechanisms of psychedelic serotonergic agonists on the mesocorticolimbic system, which is thought to drive the development of addiction-related behaviors.

Despite the promise of psychedelic-assisted treatments for several psychiatric illnesses, their widespread use, which requires close clinical supervision, represents an economic strain on health care systems. As it currently stands, psychedelic-assisted therapy costs several thousand dollars per session (Marseille et al., 2022; Chrysanthos, 2023), making this effective therapy inaccessible for a large portion of the patient population, especially those from lower socioeconomic areas. Furthermore, regulatory and legal barriers still exist, which makes treatment implementation problematic (Johnson et al., 2008). There are also concerns that the hallucinogenic action of serotonergic psychedelics could produce hallucinogen-persisting perception disorder (Ford et al., 2022) and irreversible psychotic episodes in susceptible populations, which has already led to routinely excluding patients with a family history of bipolar disorder or schizophrenia from participating in psychedelic clinical trials (Johnson et al., 2008). This underscores the importance of determining psychedelics' mechanism of action. Recent findings suggest that it may be possible to decouple the hallucinogenic and therapeutic effects of psychedelics. Thus, there is a growing interest in developing so-called "second-generation" psychedelic analogs with attenuated or absent hallucinogenic effects, which may have similar neuroplastic and behavioral effects to the classic psychedelics.

In this review and the Mini-Symposium at the Society for Neuroscience meetings in 2023, we will review some of the latest findings of serotonergic psychedelic drug actions and introduce the concept of nonhallucinogenic psychedelic analogs with therapeutic potential.

5-HT$_{2A}$ receptor: an integral part of the psychedelic experience

5-HT$_{2A}$ is the most abundant excitatory G-protein-coupled receptor (GPCR) of the 5-HT receptor family (Saha and González-Maeso, 2023). Like 5-HT$_{2B}$ and 5-HT$_{2C}$, 5-HT$_{2A}$ signals through Gq/11, activating a cytoplasmic protein phospholipase C (PLC), which cleaves the membrane phospholipid, phosphatidylinositol 4,5-bisphosphate, followed by generation of diacylglycerol and inositol triphosphate). Inositol triphosphate releases Ca^{2+} from intracellular stores (Saha and González-Maeso, 2023).

The PFC layer 5 pyramidal cells express high levels of the 5-HT$_{2A}$ receptor, making drugs that target this receptor, serotonergic psychedelics, ideal for the modulation of pyramidal cell excitability (Weber and Andrade, 2010). Treatment with serotonergic psychedelic compounds increases both the structural (dendritogenesis, spinogenesis, synaptogenesis) and functional plasticity of these cells (Ly et al., 2018; Cameron et al., 2021, 2023; Shao et al., 2021; Vargas et al., 2023).

The 5-HT$_{2A}$ receptor is an integral part of the psychedelic experience (Vollenweider et al., 1998; Kraehenmann et al., 2017), as cotreatment with the antagonist ketanserin blocks the perceptual effects of psychedelic compounds (psilocybin and LSD) in humans (Vollenweider et al., 1998; Kraehenmann et al., 2017). In mice, the head-twitch response, characterized by a rapid back-and-forth head movement, has predictive validity of the hallucinogenic potency of serotonergic psychedelics in humans (Halberstadt et al., 2020). The head-twitch response induced by several serotonergic psychedelics [DOI, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane DOB (DOB), psilocin, mescaline, LSD]; it is prevented by pretreatment with ketanserin, and abolished in 5-HT$_{2A}$-KO animals (González-Maeso et al., 2003, 2007).

While 5-HT$_{2A}$ receptor activation gives rise to the hallucinogenic part of the drug action, it remains unclear whether this is necessary for all the therapeutic effects of psychedelic-assisted therapy (Fig. 1). The emotional journey characteristic of the psychedelic experience correlates with the lasting therapeutic effects of these compounds (Yaden and Griffiths, 2021). There is also counterevidence: a case study reported an antidepressant effect of psilocybin in the absence of hallucinations while the patient was being cotreated with a 5-HT$_{2A}$ antagonist (Rosenblat et al., 2023). Furthermore, recent testing of "nonhallucinogenic" analogs of serotonergic psychedelic compounds, such as tabernanthalog, AAZ-A-154 (*R*)-70, lisuride, and 2-bromo-LSD (2-Br-LSD), further suggest that hallucinations may not be necessary for some therapeutic effects (Cameron et al., 2021; Kaplan et al., 2022; Lewis et al., 2023; Dong et al., 2021). However, if any of these nonhallucinogenic compounds has therapeutic effects on patient populations remains to be determined. Clinical trials with novel putative nonhallucinogenic analogs are underway (Delix Therapeutics, 2023). Furthermore, 2-Br-LSD has shown efficacy against cluster headaches (Karst et al., 2010), similar to LSD and psilocybin (Sewell et al., 2006).

There have been contrasting reports regarding the engagement of the 5-HT$_{2A}$ receptor for some cellular and behavioral effects of serotonergic psychedelics. Highly selective 5-HT$_{2A}$ agonists, such as 25CN-NBOH (Jensen et al., 2020), appear to increase cognitive flexibility in mice (Odland et al., 2021). Indeed, neuronal growth elicited by psychedelics (DOI, DMT, psilocybin, and LSD) and spine dynamics *in vivo* reveals that spine density is inhibited by pretreatment with the 5-HT$_{2A}$ antagonist, ketanserin (Ly et al., 2018; Cameron et al., 2021; Shao et al., 2021), but other aspects, such as spine size, are unaffected (Shao et al., 2021). Furthermore, the effects of psychedelics (DOI, psilocybin, LSD) in behavioral assays for antidepressant efficacy (e.g., forced swim test and sucrose preference test) or social behavior are blocked by 5-HT$_{2A}$ antagonists (De Gregorio et al., 2021; Cameron et al., 2023) in some studies, but not in others (Hesselgrave et al., 2021; Moliner et al., 2023).

Experiments using antagonists to study the 5-HT$_{2A}$ receptor require careful dose titration and determination of adequate treatment timing. In addition, ketanserin has off-target affinity at other targets (Henry et al., 1994; Casey et al., 2022), leading to conflicting results (Hesselgrave et al., 2021). Thus, further confirmation with other selective antagonists or using 5-HT$_{2A}$-KO mice provides a more precise approach to probing the mechanism of action of serotonergic psychedelic compounds.

For example, the effects of 5-methoxy-DMT (5-MeO-DMT) in the tail-suspension test were abolished in the 5-HT$_{2A}$-KO mice (Cameron et al., 2023). Furthermore, psilocybin restored the reward-seeking effects after chronic stress in the sucrose preference test in WT mice but not in 5-HT$_{2A}$-KO mice. In this same vein, other groups have also reported a blunted effect on fear extinction learning in 5-HT$_{2A}$-KO mice (de la Fuente Revenga et al., 2021). Finally, the neuroplastic growth and functional effects of psychedelic treatment are abolished in 5-HT$_{2A}$-KO mice (Cameron et al., 2023; Vargas et al., 2023). This supports the necessity of the 5-HT$_{2A}$ receptor in mediating some of the therapeutic and neuroplastic effects of serotonergic psychedelics. However, the constitutive 5-HT$_{2A}$-KO mice are less anxious than their WT littermates (Weisstaub et al., 2006), which may muddle the interpretation of some of the data. Thus, conditional KO mice would further validate the abovementioned findings while providing temporal and spatial resolution.

One alternative hypothesis posits that therapeutic and hallucinogenic effects diverge via functional selectivity at the 5-HT$_{2A}$, driving different downstream intracellular signaling cascades (Fig. 1*a*) (Kwan et al., 2022). It is also possible that signaling through dimers, such as a 5-HT$_{2A}$-mGluR$_2$ complex, underlie the divergent signals, although this has yet to show physiological validity in more complex *in vitro* and *in vivo* systems. Further work to elucidate the downstream signaling effects may be helpful to optimize further and disentangle the psychedelic effects from the hallucinogenic effects.

In addition to their action on membrane surface receptors, there is the intriguing possibility that serotonergic psychedelics may target an intracellular pool of 5-HT$_{2A}$ receptors (Fig. 1*b*) (Vargas et al., 2023). Indeed, serotonergic psychedelics are highly lipophilic compounds that can easily pass through cell membranes, and some of them (DMT and psilocin) target intracellular 5-HT$_{2A}$ receptors to induce neuronal growth (Vargas et al., 2023). It remains unknown whether the total volume of receptors targeted is sufficient to elicit growth or whether the internal receptors have different properties or signaling pathways leading to these effects.

Serotonergic psychedelics as treatment for OUD: role of 5-HT$_{2A}$ and 5-HT$_{1A}$

Serotonergic psychedelics are currently being investigated as novel SUD treatments (Johnson et al., 2017; Bogenschutz et al., 2022), with most studies focusing on reducing alcohol and nicotine use. The mystical experience and subjective effects through activation of 5-HT$_{2A}$ are thought to be attributed to the reduction in humans abusing substances. However, the activation of these receptors has been shown to modulate other neurotransmitter systems (e.g., dopaminergic pathways) that may be responsible for producing behavioral changes.

Indeed, excitatory pyramidal neurons from layers II/III and V/VI in both the mPFC (Goldman-Rakic, 1996; Jakab and Goldman-Rakic, 1998) and somatosensory cortex, where 5-HT$_{2A}$ receptors are expressed most abundantly, synapse onto medium spiny neurons in the NAc and other regions in the striatum to promote goal-directed actions (Nestler, 2001; Russo et al., 2010; Scofield et al., 2016). Studies using electrophysiology discovered that the prominent form of plasticity at corticostriatal synapses is NMDA glutamate receptor-dependent LTP, and further studies found positive reinforcement learning specifically engages the mPFC to striatum pathway (Reynolds et al., 2001; Ungless et al., 2001; Lüscher and Malenka, 2011). These pathways and the corresponding behaviors are implicated in SUDs.

The use of serotonergic agonists, such as 5-HT receptor-selective phenethylamines and psilocybin, is understudied regarding the adaptations produced in drug dependence. There is contradictory evidence on how 5-HT$_{2A}$ receptor stimulation in cortical neurons affects DA firing in the NAc and behaviors associated with drug reward and craving. The activation of 5-HT$_{2A}$ receptors on pyramidal neurons projecting to the NAc is thought to influence adaptive value applied to conditioned behavior and may play a significant role in relapse-related behaviors, such as avoiding uncomfortable physical or mental states associated with drug abstinence, reward-seeking, or being triggered by paired contexts (McFarland et al., 2003; Zhang et al., 2021). To this end, studies have assessed the role of 5-HT$_{2A}$ receptor activation in intracranial self-stimulation (Jaster et al., 2022), behavioral sensitization (Pang et al., 2016; Sierra et al., 2022), shifting to drug-dependent states (Vargas-Perez et al., 2017), and withdrawal (Pang et al., 2016).

The 5-HT$_{2A}$ receptor is involved in the acute effects of some, but not all, psychedelics in rodent models of intracranial self-stimulation. All structurally different psychedelics produced a depression in intracranial self-stimulation responses (Sakloth et al., 2019; Jaster et al., 2022), and the selective 5-HT$_{2A}$ receptor antagonist, volinanserin (MDL-100907), was only able to attenuate the effect of the phenethylamine psychedelic, DOI, but not the ergoline, LSD, or the tryptamine, psilocybin (Jaster et al., 2022). This suggests that less 5-HT$_{2A}$-selective psychedelics exert a mechanism outside the 5-HT$_{2A}$ receptor that contributes to psychedelic action in some models.

Most animal models of substance use tend to assess the acute effects of psychedelics on behavior rather than the sustained behavioral changes, although this is starting to change. One group assessed the effects of LSD on ethanol drinking behaviors up to 46 d following initial administration and found that LSD decreased overall ethanol consumption, and a higher dose produced a decrease in ethanol preference, with no changes in overall fluid intake (Alper et al., 2018). Another study evaluating psilocybin on ethanol consumption in male and female mice found a sex-dependent effect, in which male mice had decreased consumption and preference of alcohol following a single dose of psilocybin, and female mice displayed no changes in ethanol consumption or preference (Alper et al., 2023).

While the mechanisms behind psychedelics' potential therapeutic effects on addiction-related behaviors are still under investigation, feedback inhibition could be one such mechanism to explain how these compounds are modulating behavior, both independently or dependently on 5-HT$_{2A}$. It is known that drugs, such as selective serotonin reuptake inhibitors (SSRIs), increase the extracellular concentration of serotonin, leading to the activation of 5-HT$_{1A}$ receptors and immediate inhibition of serotonin neurons (Babb et al., 2018). Psychedelics also rapidly increase extracellular serotonin by activating 5-HT$_{2A}$ receptors, most likely producing a similar feedback inhibition. This feedback inhibition is perhaps influencing the incentive salience of drugs of abuse as coded by projections between the mPFC/somatosensory cortex and NAc. Considering that psilocin has an

affinity for both the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors (Fig. 1) (Halberstadt and Geyer, 2011), there might be some equilibrium between the two signaling pathways that are necessary for the potential therapeutic action of psychedelics in this context.

Another potential mechanism of action of serotonergic psychedelics on SUD could be the interaction of downstream signaling pathways or receptor crosstalk, which is currently under investigation. One example is the interaction between serotonin and opioid signaling, where opioid use indirectly alters NMDA signaling by acting on neighboring μ-opioid receptors (MORs), causing crosstalk between the downstream signaling pathways (Rodríguez-Muñoz et al., 2012; Chartoff and Connery, 2014). Evidence also shows that MOR and 5-HT$_{2A}$ receptors colocalize in several rodent brain regions, including the PFC and dorsal/ventral striatum. Further, in neurons expressing MOR and 5-HT$_{2A}$ receptor, upregulation of MOR levels was seen and blocked by selective inhibition of Gq proteins; and when treated with serotonin and morphine, there was desensitization, internalization, and downregulation of MOR (Lopez-Gimenez et al., 2008). A novel mechanism for serotonergic modulation of substance use, specifically opioids, is the activation of pyramidal neurons expressing 5-HT$_{2A}$ receptors in the PFC, which then send projections into the NAc, influencing the dopamine tone that is altered following prolonged drug use. Potential therapeutics using this mechanism would target the pathways involved in drug-liking, craving, and potentially withdrawal, instead of directly targeting the opioid receptors.

The question remains whether these psychedelics can produce therapeutic effects in other models of drug-related behaviors, and whether the combination of behavioral, pharmacological, and molecular techniques can provide insight into the specific receptor and cell targets modulating the underlying circuitry related to these behavioral phenotypes. To that end, the use of conditioned-place preference, reinstatement, and withdrawal assays in combination with FLP/Cre-mediated expression of 5-HT$_{2A}$ receptor in the cortico-accumbal pathway are being explored with structurally different psychedelics to identify critical targets and cell populations involved in their potential to unpair opioid-context interactions and reduce uncomfortable states. By identifying specific neuronal populations and their projections involved in these behaviors associated with opioid use and abuse, it could be possible to produce a novel treatment mechanism for OUD.

The nonhallucinogenic analog 2-Br-LSD also targets 5-HT$_{2A}$ receptors

Several nonhallucinogenic derivatives from serotonergic psychedelics have been investigated in preclinical models, and some are already in clinical testing. Lisuride, for example, is an ergoline on the market as a Parkinson's treatment. Although its mechanism of action for Parkinson's is thought to involve dopamine receptor activation (Horowski and Löschmann, 2019), lisuride binds to TrkB (Moliner et al., 2023), is a 5-HT$_{2A}$ partial agonist (López-Giménez and González-Maeso, 2018), and has recently shown antidepressant potential (Qu et al., 2023).

A newly synthesized analog of ibogaine, tabernanthalog, has been found to promote neuroplasticity in the PFC and reverse depression-like behavior following chronic stress in mice (Cameron et al., 2021). Furthermore, the same group developed the compound AAZ (Dong et al., 2021), which is a nonhallucinogenic analog developed for depression. Indeed, there are already putative nonhallucinogenic analogs in Phase I clinical trials (Delix Therapeutics, 2023).

Most recently, 2-Br-LSD has also been investigated. 2-Br-LSD is a partial 5-HT$_{2A}$ agonist that enhances PFC neuroplasticity and promotes the reversal of depression-like behavior in preclinical models but lacks hallucinogenic effects (Lewis et al., 2023). Synthesized alongside LSD by Albert Hoffman in the early 1960s, it was found to lack LSD's mind-altering side effects and was initially thought to be a 5-HT$_{2A}$ antagonist. Recently, it was shown to be a potential treatment for cluster headaches, a trait shared with other classical psychedelics (Karst et al., 2010). Thus, based on its close structural homology with LSD and apparent neuroactive potential, work began investigating its possible efficacy as a novel therapeutic for mood disorders.

2-Br-LSD shows an interesting receptor-binding profile; while it is a mild to potent agonist of many 5-HT receptors, including 5-HT$_{1B/1D/1F/2A/6}$, it also shows potent dopamine D$_2$ and D$_4$ receptor agonism (Lewis et al., 2023). However, 2-Br-LSD's receptor profile shows greater receptor selectivity activity than LSD (which showed agonism for all 5-HT receptors assayed). Most importantly, 2-Br-LSD did not show 5-HT$_{2B}$ agonism, a receptor linked to fibrotic cardiac valvulopathy (Rothman and Baumann, 2009), and thus represents a safer alternative to other psychedelic compounds in treating mood disorders. While LSD is a potent agonist of 5-HT$_{2A}$, 2-Br-LSD only partially activates this receptor; thus, it can partially antagonize it in the presence of serotonin (Fig. 1*c*). This may explain why it lacks hallucinogenic effects, although its therapeutic effects depend on 5-HT$_{2A}$ activity; a threshold of efficacy may exist below which pathways related to the side effects are not activated. Interestingly, chronic 2-Br-LSD treatment does not induce tolerance, an effect possibly mediated by weak recruitment of β-arrestin2, a pathway thought to underlie desensitization found with the classic psychedelics (Smith et al., 1999; Gresch et al., 2005).

Compared with the classic psychedelics, 2-Br-LSD shows similar 5-HT$_{2A}$ activation-dependent antidepressant and neuroplastic effects, as demonstrated with the selective 5-HT$_{2A}$ antagonist, volinanserin, *in vitro* and *in vivo*. In stress-naive mice, 2-Br-LSD increases the probability of active coping behavior in the forced swim test without increasing overall locomotor behavior (Lewis et al., 2023). Further, in chronically stressed mice, 2-Br-LSD reverses the effects of stress on center exploration in the open field assay and deficits in self-grooming in the splash test. Acute 2-Br-LSD treatment also induces cortical spinogenesis, both *in vitro* and *in vivo*, and increases dendritic arbor complexity of cortical neurons in culture, effects like that seen with ketamine treatment.

The fact that 2-Br-LSD is not hallucinogenic but shows similar neuroplastic and behavioral effects in mouse models may suggest that the mind-altering characteristic of psychedelics is not a necessary factor in their therapeutic potential. However, human trials will be necessary to demonstrate clinical efficacy. Further, 2-Br-LSD's receptor profile shows that not only is 5-HT$_{2A}$ agonism a necessary component of its mechanism of action, but also that it represents a possibly safer alternative to treatment with the classic psychedelics.

The 5-HT$_{2C}$ receptor as a therapeutic target for SUD

Along with the other 5-HT$_2$ family members, 5-HT$_{2C}$ is a GPCR that canonically couples to Gq/11 subtypes to signal, primarily leading to PLC activation, inositol triphosphate accumulation, intracellular calcium release, and protein kinase C activation (Kim et al., 2020). Previously, GPCRs are understood to couple to one specific canonical G protein subtype (Gq/11, Gi/o, G12/13, Gs/olf) as well as signal through G protein-independent

pathways, notably via β-arrestins (Lefkowitz and Whalen, 2004). However, accumulating evidence has revealed that many GPCRs exhibit varying degrees of promiscuous coupling, interacting with multiple G protein subtypes (Inoue et al., 2019; Sandhu et al., 2022). In particular, 5-HT$_{2C}$ has been demonstrated to activate Gi/o and G12/13 subtypes, which lead to distinct downstream signaling pathways (Alberts et al., 1999; Cussac et al., 2002; McGrew et al., 2002). The activation of these additional G proteins complicates our understanding of which 5-HT$_{2C}$ signaling pathways are ultimately responsible for therapeutic versus side effects, mainly as they apply to psychedelics and their emerging therapeutic properties.

The 5-HT$_{2C}$ receptor has emerged as a promising target for therapeutic effects (Palacios et al., 2017). The high sequence homology of 5-HT$_{2A}$ and 5-HT$_{2C}$ has posed a challenge in developing selective agonists for either receptor subtype (Cheng et al., 2016a,b; Palacios et al., 2017), and most clinically studied psychedelics, such as LSD, are nonselective agonists with the 5-HT$_2$ family and across other 5-HT receptors (Nichols, 2004; Lewis et al., 2023).

However, there has been progress in developing several selective 5-HT$_{2C}$ agonists, which have been investigated as potential therapeutics for the treatment of multiple psychiatric disorders, particularly impulse-related disorders, such as SUDs (Higgins et al., 2013; Campbell et al., 2021). A growing body of evidence supports the influence of 5-HT$_{2C}$ on impulse regulation, partly through the modulation of dopaminergic neurotransmission in the VTA (Bubar and Cunningham, 2007; Howell and Cunningham, 2015). 5-HT$_{2C}$ agonists have been shown to decrease substance use behaviors, including the self-administration of ethanol, cocaine, and nicotine in rodents (Grottick et al., 2000; Rocha et al., 2002; Tomkins et al., 2002; Howell and Cunningham, 2015). Additionally, there is abundant evidence that 5-HT$_{2C}$ mediates satiety and food intake. For example, 5-HT$_{2C}$ KO mice display hyperphagia and increased body mass, whereas 5-HT$_{2C}$ agonists suppress food intake (Tecott et al., 1995; Nonogaki et al., 1998; Vickers et al., 1999; Clifton et al., 2000; Grottick et al., 2000; Higgins et al., 2013). For this reason, lorcaserin (Belviq) was an FDA-approved 5-HT$_{2C}$ selective agonist implemented as a treatment for weight loss (Thomsen et al., 2008). Not surprisingly, lorcaserin and other 5-HT$_{2C}$ selective agonists can reduce alcohol drinking in rodent models in addition to anorectic effects (Rezvani et al., 2014; Tabbara et al., 2021; Fletcher et al., 2022). These studies have solidified the potential of 5-HT$_{2C}$ as a pertinent therapeutic drug target for both obesity and SUDs; but unfortunately, lorcaserin was recently withdrawn because of a higher frequency of cancer diagnoses in the lorcaserin-treated group relative to the placebo group (Mazza et al., 2023). Interestingly, psilocybin, which has equal 5-HT$_{2A}$ and 5-HT$_{2C}$ affinities, has shown promise in SUD treatment, while no difference in food intake was found in rodents (Fadahunsi et al., 2022). Thus, further studies into 5-HT$_{2C}$ signaling and how psychedelics signal at this receptor subtype are warranted.

In recent years, the concept of ligand bias for either G-protein-dependent or G-protein-independent signaling pathways has been identified as a means to achieve biased agonists endowed with greater therapeutic value over traditional balanced agonists (Kenakin, 2011; Tan et al., 2018). Therefore, the design of biased agonists and, ultimately, pathway-selective 5-HT$_{2C}$ agonists will likely uncover key signaling pathways necessary for treatments for SUDs, which could avoid many side effects associated with previous 5-HT$_{2C}$ selective agonists. Overall, investigating psychedelics' ability to engage noncanonical downstream signaling for other serotonin receptors, such as 5-HT$_{2C}$, is crucial for the potential development of more precise and effective therapeutics for mental health disorders.

BDNF and TrkB: key to psychedelic-induced neuroplasticity and therapeutic effects

BDNF is a member of the neurotrophin family of growth factors that regulate neurite outgrowth, synaptogenesis, and acts as a critical regulator of activity-dependent neuronal plasticity through its receptor TrkB (Park and Poo, 2013), BDNF binding leads to TrkB dimerization, autophosphorylation, and signaling through mitogen-activated protein kinase, phosphoinositol-3-kinase, and the PLC γ pathways (Park and Poo, 2013).

BDNF and TrkB are widely recognized as key components that mediate the therapeutic effects of pharmacologically diverse antidepressants (Castrén and Antila, 2017; Vollenweider and Preller, 2020). Recent studies have shown that commonly used antidepressants, such as slow-acting fluoxetine or fast-acting ketamine can directly bind to the transmembrane domain of TrkB, thereby allosterically promoting BDNF effects and producing plasticity- and antidepressant-related effects of antidepressants in mice (Casarotto et al., 2021; Kot et al., 2023).

A recent breakthrough discovery found that psychedelics with clinical potential, such as LSD and psilocin, bind to TrkB with 1000-fold higher affinities than other antidepressants (Moliner et al., 2023). It was shown that binding to TrkB mediates the plasticity and antidepressant-like effects of psychedelics. The binding of psychedelics to the transmembrane domain of TrkB dimers in a different site than BDNF was confirmed using several orthogonal methods: binding assays with radiolabeled LSD, mutagenesis studies, NMR spectroscopy, TrkB dimerization assays, microscale thermophoresis, and extensive molecular dynamics simulations in physiological membrane conditions. Interestingly, the binding pockets and TrkB conformational changes induced by serotonergic psychedelics are different from those seen for conventional antidepressants, which may help explain the faster and longer-lasting antidepressant actions of psychedelics.

Serotonergic psychedelics are not direct TrkB agonists, as extracellular BDNF is required for their effects on TrkB dimerization, spinogenesis, and dendritogenesis. Activity-dependent BDNF release in stimulated synapses selectively stabilizes active synapses at the expense of inactive ones (Park and Poo, 2013), which is critical for Hebbian-type plasticity. Direct agonists are expected to activate TrkB regardless of neuronal activity and BDNF presence in all synapses, worsening signal-to-noise ratios within neuronal networks. In contrast, psychedelics selectively promote, maintain, and strengthen activity-dependent plasticity in active synapses through a positive allosteric modulation of endogenous BDNF signaling.

A point mutation in the transmembrane domain of TrkB that impairs the binding of serotonergic psychedelics prevents induction of neuroplasticity and antidepressant-like behavioral responses to LSD and psilocybin, but does not influence the head-twitch response associated with 5-HT$_{2A}$ activity and hallucinations in humans (Halberstadt et al., 2020; Moliner et al., 2023). Moliner et al. (2023) also report that the relatively selective 5-HT$_{2A}$ antagonist volinanserin does not prevent psychedelics from promoting TrkB dimerization and neurotrophic signaling, spinogenesis, dendritogenesis, or antidepressant-like behavioral effects. These findings suggest that the TrkB-dependent effects of psychedelics on plasticity

can be detached from their hallucinogenic-like action via 5-HT_{2A} receptors.

However, several outstanding questions remain about the involvement of TrkB in the effects of serotonergic psychedelics. For example, the binding of tritiated LSD (Meibach et al., 1980) and the localization of TrkB (Yan et al., 1997) appear to be in different brain regions, indicating the need for additional studies to disentangle the contribution of TrkB and serotonin receptors to the psychedelic experience and the different therapeutic effects of these compounds.

In summary, TrkB is gathering increased attention as a common binding site for antidepressants and psychedelics that plays a key role in mediating their plasticity and therapeutic-like actions, independently of hallucinogenic effects.

Psychedelics as protein modifiers in neuronal function and plasticity

Biogenic amine neuromodulators, such as serotonin and dopamine, in addition to binding receptors, are chemically reactive and have been reported to bind to glutamine residues of diverse proteins covalently; this modification is referred to as monoaminylation (Muma and Mi, 2015; Farrelly et al., 2019; Lepack et al., 2020). The covalent addition of amines, such as serotonin and dopamine, to proteins is called transamidation (Lukasak et al., 2022) and is catalyzed by the enzyme transglutaminase 2 (TGM2). Transamidation of serotonin (serotonylation) or dopamine (dopaminylation) of key proteins underlies cytoskeletal rearrangement (Dai et al., 2008; Jones et al., 2009), transcriptional regulation (Farrelly et al., 2019; Lepack et al., 2020), and mitogenesis (Muma and Mi, 2015), processes linked to synapse formation and maturation.

Psychedelic drugs structurally resemble the neuromodulators serotonin and dopamine, produce profound states of altered consciousness, and show promise for treating mental health disorders (Kwan et al., 2022). Psychedelics are so potent, long-lasting, and varied in their effects on cognition and neuroplasticity that additional mechanisms beyond 5-HT_{2A} agonism seem likely. Psychedelics are more lipophilic than their endogenous counterparts, and their cellular entry is not restricted by the presence of specific transporters (Vargas et al., 2023). Therefore, in the context of monoaminylation, psychedelic drugs may serve as exogenous substrates for transamidation by TGM2 in place of endogenous amines. Prior evidence has demonstrated a role for TGM2-mediated transamidation in psychedelic-indced synaptogenesis, as the psychedelic phenethylamine DOI required TGM2 activity to promote the formation of new dendritic spines (Mi et al., 2017). DOI was shown to induce serotonylation of Rac Family Small GTPase 1 (Rac1), which functions in the assembly of the actin cytoskeleton, a process critical for neurite outgrowth (Dai et al., 2008). Serotonylation of Rac1 leads to its constitutive activation and results in a spine growth phenotype. Intriguingly, this activity also required 5-HT_{2A} agonism. As 5-HT_{2A} activity induces Ca^{2+} fluxes, and TGM2 is a Ca^{2+}-dependent enzyme, this sets up the hypothesis that 5-HT_{2A} and TGM2 work in conjunction to manifest the cellular effects of psychedelics.

Several psychedelic and entactogen compounds (e.g., mescaline, 4-bromo-2,5-dimethoxyphenethylamine) are primary amines and can, theoretically, undergo transamidation by TGM2 (Fig. 1*d*). Most others are secondary or tertiary amines and would require demethylation (Al-Kachak and Maze, 2023) to become TGM2 substrates (Fig. 1*d*). The demethylation of psychedelics has been shown to occur *in vivo* (e.g., tryptamine was identified as a direct and fairly rapid metabolite of DMT in brains) (Kargbo, 2022). Like serotonin, tryptamine is a suitable substrate for TGM2-mediated transamidation of proteins (Lukasak et al., 2022). Several drugs, administered as pro-drugs, require demethylation by CYP3A4 or other enzymes for activation (Ortiz de Montellano, 2013). It is plausible that some psychedelic drugs require similar demethylation for many effects. Interestingly, the commonly prescribed antidepressant medication sertraline functions as a CYP3A4 inhibitor in addition to an SSRI (Masubuchi and Kawaguchi, 2013; Ghosh et al., 2015). Sertraline has been shown to blunt the subjective effects of psychedelic drugs, while other SSRIs, such as escitalopram, which are not CYP3A4 inhibitors, have less impact on these effects (Bonson et al., 1996). This raises the possibility that the subjective and/or therapeutic effects of some psychedelic drugs could be mediated by metabolites, which appears to be the case for ketamine as well (Farmer et al., 2020).

Could the therapeutic effects of psychedelics be mediated, at least somewhat, through TGM2 activity? A landmark study showed that serotonylation of histone H3 promotes permissive expression of genes related to cellular differentiation and maintenance and was required for neurite outgrowth (Farrelly et al., 2019). Serotonylation of histone H3 in neurons of the dorsal raphe nucleus decreases with stress, and patients with major depressive disorder who were not taking antidepressants at the time of death display decreased histone serotonylation (Al-Kachak et al., 2023). In the same study, major depressive disorder patients that had been prescribed an antidepressant before the time of death had increased histone serotonylation, indicating there may be an interaction between SSRIs and histone serotonylation (Al-Kachak et al., 2023). Histone H3 serotonylation occurs at glutamine residue 5 (H3Q5ser) and leads to altered gene expression through the protein WD Repeat Domain 5, a chromatin modulator that reads H3Q5ser and activates transcription (Zhao et al., 2021). In humans, H3Q5ser appears upstream of, and frequently in combination with, histone H3 trimethylated lysine 4 (H3K4me3). H3K4me3 reader enzymes promiscuously bind H3K4me3Q5ser; Q5ser strongly inhibits H3K4 methylation erasers; these conditions favor gene expression in the presence of the H3K4me3Q5ser modification (Zheng et al., 2022). TGM2 is further capable of "writing" and "erasing" monoaminylation based on the concentrations of the amine substrates, lending to the idea that psychedelics could alter these histone marks (Zheng et al., 2022). Further investigation of histone monoaminylation will be required to determine whether this newly identified class of histone marks is part of the molecular underpinnings of depression, anxiety, etc., and if psychedelics impact this process, either by themselves being incorporated by TGM2, or by shifting the equilibrium of incorporated substrates.

Psychedelic drugs are also being trialed and showing great promise in SUDs (Noller et al., 2018; Meinhardt et al., 2021). *In vivo*, dopaminylation of histone H3 decreases with initial cocaine use and increases during withdrawal, regulating genes linked to cocaine seeking (Lepack et al., 2020). Withdrawal from heroin also increases H3 dopaminylation, resulting in transcriptional and behavioral changes (Fulton et al., 2022). Thus, it is possible that the success of psychedelics in this regimen also stems from the covalent modification of histones and other cellular targets.

Discussion

Psychedelics are gaining rapid momentum for treating neuropsychiatric disorders. Therefore, determining the molecular targets and signaling pathways of classical psychedelics is essential for understanding their effects on brain physiology and behavior

and their potential therapeutic targets. While it is well established that the principal molecular target of classical psychedelics to elicit hallucinations and subjective effects is the 5-HT_{2A} receptor widely expressed in cortical pyramidal neurons (González-Maeso et al., 2003; González-Maeso et al., 2007), there is an ongoing debate on whether 5-HT_{2A} agonism is necessary for the plasticity-inducing and therapeutic actions of psychedelics (Fig. 1). A growing body of evidence reinforces the idea that psychedelics display complex polypharmacological profiles that go beyond their 5-HT_{2A}-mediated hallucinogenic activity. Among their many targets, TrkB, 5-HT_{2C}, and 5-HT_{1A} are gathering increased attention as binding sites that play a key role in mediating psychedelics' plasticity and therapeutic actions, independently of hallucinogenic effects. It is possible, and likely, that psychedelics mediate their effects through several of these mechanisms. The spectrum of receptors activated by each compound may be key for optimizing use across different disorders. Furthermore, delineating the downstream effects of these targets may help optimize and refine the therapeutic effects for patients needing help. While technically challenging, there is also an increasing need to dissect circuit-level or brain-wide mechanisms of action of psychedelics, as they may provide further insight into how these compounds elicit their many complex and diverse actions.

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