Mechanisms of neuroplasticity induced by permeable serotonergics

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Abstract

Major depression affects about 280 million people worldwide and costs around 326 billion dollars per year in the United States, though the standard medications take 2-3 months to take effect, so faster and longer-lasting treatments are needed. Serotonergic psychedelics such as psilocybin, DMT or ayahuasca, LSD, and mescaline can reduce depression and anxiety symptoms after only one or two doses, with benefits that last from weeks to months. The persistence of psychedelic benefits points to real biological change, not just temporary drug action. Variants in the serotonin HTR2A gene can influence cortical serotonin 5-HT2A receptor density and may shape sensitivity. In cultured neurons, multiple psychedelic chemotypes and non-hallucinogenic analogs increase dendritic growth and synaptogenesis, while impermeable analogs fail unless forced into the cell, showing that intracellular permeability is required. In cortical circuits, 5-HT2A stimulation increases glutamatergic drive and AMPA signaling, triggers gene programs linked to plasticity, and supports extinction learning. Across species, these changes align with antidepressant and anxiolytic-like behaviors that can last days to weeks and may not require hallucinogenic effects. Here, I discuss genetics, cellular and systems research, animal behavior, and recent human data to explain how membrane-permeable serotonergics act as neuroplastogens, which help build out neural synapses. I propose a permeability plus mechanism model; The serotonergic mechanism must be both cell-permeable and engage 5-HT2A. A permeable psychedelic reaches intracellular 5-HT2A pools, then 5-HT2A activation quickly boosts plasticity related gene expression and causes structural change, 5-HT2A signaling raises BDNF and engages TrkB to support neuronal growth, and 5-HT2A activation in cortex increases glutamate and AMPA signaling that helps stabilize new synapses, together linking permeability, receptor engagement, and circuit activity to durable neuroplasticity.

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric conditions worldwide. It affects more than 280 million people across all age groups, though mostly among young adults and middle-aged people. In the United States alone, MDD carries an estimated economic cost of 326 billion dollars per year, including direct medical expenses, lost workplace productivity, and disability claims (Greenberg et al., 2021). Major depressive disorder reduces neural connections within the prefrontal and cingulate cortices as well as the hippocampus, reducing cognition, memory processes, and serotonin transmission. (Belleau et al., 2019).

Impaired serotonergic transmission in the prefrontal cortex causes MDD symptoms, including low mood and cognitive inflexibility, and serotonin insufficiency in the hippocampus has been

related to memory impairments and anxiety. Serotonin is produced in the raphe nuclei which are small groups of nerve cells situated in the brainstem. The long nerve fibers of these cells extend to the cortex, limbic system, and the spinal cord and the serotonin in these cells aids in the regulation of mood, memory, sleep and wake cycles, pain, and other daily activities (Walker & Tadi, 2023). Interference with serotonin transmission can have severe consequences on the mind and behavior, which suggests that serotonin targeting agents such as psychedelics could help.

Psychedelics are permeable serotonergic hallucinogens like psilocybin, DMT, LSD and mescaline. They primarily stimulate the serotonin 5-HT2A receptor. Lower doses (or “microdoses”) can elevate mood and enhance flexible thinking, whereas higher therapeutic doses induce the vivid perceptual shifts that are commonly referred to as a psychedelic trip. In addition to modern studies, most of these substances have been used in ritual and cultural practices, in which they were frequently attributed to learning, healing, or altered states of consciousness. Animal experiments also indicate that psychedelics activate cortical circuits in a manner that alters behavior and brain structure, indicating that their effects are based on neuroplastic processes and not simply subjective experience (Nichols, 2016). Psychedelics function as neuroplastogens, indicating that they exert neuroplasticity-promoting effects. They could reestablish synaptic and neuronal dysfunctions by inducing a plastic cellular state that promotes remodeling and a ‘reset’ of brain networks (Schmidt, 2023). Clinical studies report that one to two administrations of LSD, ayahuasca, or psilocybin can alleviate depressive, anxiety-related, and addictive symptoms in patients, with benefits lasting for 3 weeks to 6 months after the treatment/dose. The longevity of these improvements, even long after the drug's presence in the system, shows real and permanent biological adaptations with therapeutic outcomes, not just temporary drug effects (de Vos et al., 2021).

Section 1 - Serotonin

Genetic

The 5-HTR2A gene, which encodes the serotonin 2A receptor (5-HT2A), plays a key role in regulating serotonin signaling in the brain and is a target of many psychedelics. The most common variations in this gene in humans affect the expression of the 5-HT2A receptor in the cortex. There are some polymorphisms of this gene that affect function. For example, PET studies in healthy volunteers demonstrated that carriers of the T allele of the rs6313 (T102C) polymorphism of the 5-HTR2A gene have about 15% greater 5-HT2A binding potential in frontal and cingulate areas compared to the C-allele carriers. This genotype-based variation in receptor density might partially underlie individual differences in serotonergic psychedelics sensitivity in human subjects (Mueller et al., 2017).

In 5-HT2A knockout mice, using ketanserin (a 5-HT2A blocker), researchers showed that 5-HT2A activation is required for 5-MeO-DMT to produce neuroplastic and antidepressant-like effects in vivo and in vitro, and in mouse cortex and primary cortical cultures hallucinogens such as DOI (2,5-Dimethoxy-4-iodoamphetamine, a phenethylamine), LSD (Lysergic Acid Diethylamide, a lysergamide/ergoline), and psilocin (a tryptamine, the metabolite of psilocybin, found in 'magic mushrooms') drive immediate-early gene expression including Egr-1 (Early growth response 1), Egr-2 (Early growth response 2), and c-Fos (Fos protein), a transcript pattern that disappears in 5-HT2A knockout mice, which links psychedelic engagement of 5-HT2A to downstream neuroplasticity genes (Weiss et al., 2025). In humans, psychedelics engage 5-HT2A receptors and show concurrent neurotrophic signals: psilocybin produces dose-related 5-HT2A receptor occupancy in cortex (with subjective intensity tracking occupancy) and the 5-HT2A antagonist ketanserin reverses LSD's acute effects, while low doses of LSD raise plasma BDNF (brain-derived neurotrophic factor) 4-6h after dosing in healthy volunteers, supporting the 5-HT2A to genetic edits to neuroplasticity model (Madsen et al., 2019) (Hutten et al., 2020).

Receptor

In vitro, loss of dendritic and synaptic contacts is common in depression, though psychedelic drugs have been shown to enhance dendritic arborization and neurite outgrowth. In a study, cultured cortical neurons exposed to several psychedelics, with DMT (Dimethyltryptamine) and psilocin as tryptamines, DOI and MDMA (3,4-methylenedioxymethamphetamine) as amphetamines, and LSD as an ergoline. What happened was the psychedelics raised dendritic arbor complexity to the same level as the ketamine, which is used for treatment resistant depression. Analysis of the dendritic arborization in the cultured cortical neurons found a larger arbor area and more branch intersections, pointing to more branches and greater total arbor length (length of the neuron's dendritic tree). In the brain, more dendritic branching means more surface area for synaptic contacts, so neurons can receive input from more other neurons. This increases connectivity and neuronal network integration, supporting enhanced communication between cortical circuits that underlie learning, memory, and mood regulation. A structurally unrelated neuroplastogen, 7,8-dihydroxyflavone (a BDNF promoter), served as a non-hallucinogenic control and produced similar growth effects (Ly et al., 2018). This shows that compounds from many classes, not only hallucinogens, can strongly trigger neurite growth in vitro.

In another in vitro study, authors tested whether 2-Br-LSD (a non-hallucinogenic analog of LSD) could limit the loss of dendrites on neurons in cell cultures. Primary cortical neurons kept for three days in vitro (DIV3) received a 3 hour treatment with 100 nM 2-Br-LSD. By day six in vitro (DIV6), dendritic arbor complexity had climbed in a dose-dependent way, meaning that increasing doses of 2-Br-LSD increased dendritic arborization linearly. Counting how many times dendrites crossed a series of concentric circles centered on the cell body showed far more

branch intersections, with the strongest rise at 1 μM and 10 μM, doses also used when studying ketamine. These doses also increased total arbor length compared with control cells, showing that 2-Br-LSD can drive structural plasticity similar to fast-acting antidepressants (Lewis et al., 2023). In addition, cultured cortical neurons exposed to DMT (10 μM) or LSD (90 μM) after 24h had more dendritic branching and length than controls. The 5-HT2A blocker ketanserin eliminated these effects of growth, demonstrating that they are 5-HT2A receptor dependent. LSD was the most potent of the tested compounds to stimulate neurite growth (de Vos et al., 2021).

In mice, 5-MeO-DMT induces significant structural and functional neuroplasticity, but only if 5-HT2A receptors are present. Golgi-Cox staining, a classic method for visualizing the full shape of individual neurons and their dendritic spines, revealed that 5-MeO-DMT increases dendritic spine density in both male and female animals, an effect that disappears in 5-HT2A knockout mice. Ex vivo (brain slices) experiments showed that 5-HT2A activation is required for 5-MeO-DMT to produce lasting increases in both the frequency and amplitude of excitatory synaptic signals, linking receptor activation to stronger synaptic function (Vargas et al., 2023). Within the context of more general pathophysiology, MDD is characterized by a smaller hippocampal volume, which is caused by dendritic retraction and decreased spine density and impaired neurogenesis, with glutamatergic signaling and plasticity programs being upstream of structural change (Boku et al., 2018). The evidence points to psychedelics being capable of neuronal/interneuronal repair after MDD.

In mice, psilocybin also showed clear evidence of structural neuroplasticity. A single dose increased dendritic spine density and size in layer 5 pyramidal neurons of the frontal cortex. Spine density increased by ~7% and spine head width by 11% within 24h, and after 7 days, density was still increased by 12% and head width was still greater than baseline. Psilocybin also increased the rate of new spine formation, suggesting that the drug induces rapid and persistent synaptic remodeling that is consistent with long-term circuit strengthening (Shao et al., 2024). Similarly, in mice, a single dose of psilocybin increased dendritic spine density and size in the medial frontal cortex. Within 24 hours, spine density rose by ~7% and spine head width increased by 11%, and by day 7 spine density remained elevated by 12% with a 5% increase in spine head width. Psilocybin also raised the rate of new spine formation, showing that the drug produces rapid and lasting structural changes at the synaptic level (Shao et al., 2021). The outgrowth of new spines allows the neurons to become more active and receive more information, reversing the damage done through MDD on spine density.

Behavioral

In rats, ayahuasca, which is DMT with a monoamine oxidase inhibitor (aka MAOI, which prevents DMT from breaking down immediately), accelerated the extinction of conditioned fear

responses, and reduced anxiety. This pro-extinction effect, a form of “unlearning” a behavior, required simultaneous activation of infralimbic-cortex serotonergic 5-HT2A and 5-HT1A receptors, indicating that serotonergic signaling in this prefrontal subregion is essential for ayahuasca’s behavioral influence with reduction of fear and anxiety responses in the rats (Werle et al., 2024).

In a study in mice with 2-Br-LSD (non-hallucinogenic LSD analog), to analyze changes in stress levels, 2-Br-LSD reversing stress-related changes in mouse behavior was investigated. Female mice faced a five-week chronic variable stress schedule, then received either one post-stress dose of 2-Br-LSD (3 mg/kg, i.p.) or four lower doses (1 mg/kg, i.p., every 48 h) during the final eight days. Chronic stress has reduced the time animals spent in the center of the open-field test and cut self-grooming in the splash test, both markers of anxiety/depression. Both dosing plans restored center time and grooming to levels seen in unstressed controls, matching effects reported for ketamine and classical serotonergic psychedelics (Lewis et al., 2023) and reversing the effects of the chronic stress paradigm.

In a study in humans with LSD acting at the serotonin 5-HT2A receptor agonist (a double-blind, randomized, cross-over fMRI study), 20 healthy adults received 100 µg LSD or placebo before an emotion-processing task. Compared with placebo, LSD reduced reactivity to fearful faces in the left amygdala and in the right medial prefrontal cortex. The drop in left amygdala signal also tracked subjective drug intensity, with a negative correlation between amygdala BOLD (Blood Oxygen Level Dependent Imaging) and visual analog ratings of drug effects ($r = -0.46$, $P < 0.05$). Together, these results show 5-HT2A engagement alongside a measurable dampening of threat-related brain responses in humans (Mueller et al., 2017).

Section 2 - Glutamate

Genetic

In vitro, serotonergic psychedelics can strongly promote neuritogenesis and spinogenesis, as shown by experiments where administering DMT (10 µM) and LSD (90 µM) to cultured cortical rat neurons for 24h increased dendritic complexity, shown by both the number and total length of dendrites compared with vehicle-treated controls (Ly et al., 2018).

In rats and mice, a single systemic injection of LSD (0.20–1.0 mg/kg, i.p.) quickly raised cortical mRNA for the activity dependent plasticity genes c-Fos, Arc, SGK1, IκB-α, NOR1, and Egr2 within 1-2h, and the rise scaled with dose. None of these genes encode a glutamate receptor or transporter, instead, their induction reflects a strong glutamatergic drive that triggers the downstream transcriptional program required for structural plasticity via DNA transcription (de Vos et al., 2021). However, a single oral dose of LSD did not alter the mRNA expression of its

main target receptor (HTR2A) or the immediate-early genes EGR1-3 at 1.5h and 24h after dose compared with placebo in *healthy* human volunteers. The results of this study suggest that psychedelic exposure in non-clinical subjects fails to up-regulate major plasticity-related genes, and whether a repeated dosing could cause transcriptional responses in patient populations remains an open question. (Dolder et al., 2017).

In humans, genetic variation in the glutamate system also has an impact on the risk of depression. For example, certain polymorphisms of GRM1 (the metabotropic glutamate receptor 1) have been linked to depressive phenotypes. These variants were additionally shown to relate to altered hippocampal glutamate levels as determined by 1H-MRS, providing a mechanistic route between genotypic variation in glutamate signaling and susceptibility to depression. (Menke et al., 2012). Expanding on this genetic connection, there is a larger body of evidence that glutamatergic plasticity and stress biology are close to the center of MDD. Persistent stimulation of the hypothalamic-pituitary-adrenal axis with high glucocorticoids decreases hippocampal volume by shortening dendrites and losing spines (neuroplasticity hypothesis) and by decreasing neurogenesis in the dentate gyrus (neurogenesis hypothesis), which can be used to explain the latency of antidepressant response and suggests treatments that target plasticity-related pathways and not monoamines alone (Boku et al., 2018).
Receptor

In an in vitro study with human cortical organoids, 24 hours of exposure to 13 μM of 5-MeO-DMT (a more potent analog of DMT) up-regulated proteins involved in plasticity-related signaling, including parts of the NMDA and AMPA receptor pathways and also ephrin-B2, suggesting this psychedelic quickly engages molecular programs that support structural and functional neuroplasticity (de Vos et al., 2021). This finding suggests that 5-MeO-DMT can quickly activate glutamatergic and growth-related pathways, providing the molecular basis for long-term changes in synaptic strength and cortical circuitry.

In rodents, psychedelics signal post-synaptic 5-HT2A receptors on layer 5/6 cortical pyramidal neurons, and GABAergic interneurons, causing a net excitation of layer 5 pyramidal neurons in the neocortex, mainly the prefrontal cortex. Such increased activity increases extracellular glutamate, which in turn increases AMPA-receptor signaling, increasing neuroplasticity. This temporary increase in cortical glutamate is able to override the hypofrontality and synaptic downscaling of MDD and reinstate excitatory drive, enhance network connectivity, and reopen a plasticity window, which facilitates top-down control and learning (Calder & Hasler, 2023).

In humans, psilocybin acutely alters glutamate signaling across brain regions. Using 7-Tesla magnetic resonance spectroscopy (7T MRS), a neuroimaging method that measures concentrations of neurotransmitters and metabolites in vivo, researchers found increased glutamate in the medial prefrontal cortex (mPFC) and decreased glutamate in the hippocampus

after psilocybin. Changes in mPFC glutamate strongly predicted negatively experienced ego dissolution, while hippocampal decreases were linked to positively experienced ego dissolution. This shows that region-specific glutamate modulation may underlie key aspects of the psychedelic experience and contribute to therapeutic outcomes. This is because ego dissolution has been associated with greater psychological flexibility and less rigid self-focus, both of which are often impaired in MDD and whose restoration is associated with better therapeutic outcomes (Mason et al., 2020).

In vivo, LSD caused a massive increase in extracellular glutamate in the prefrontal cortex. In the study, microdialysis (a tiny implanted probe that samples extracellular fluid to measure neurotransmitters in the living brain) revealed that systemic LSD increased PFC glutamate through 5-HT2A receptors, and local reverse dialysis revealed a rapid increase that continued after infusion was stopped (Muschamp et al., 2004). This elevation recruited cortical UP states that are dependent on the NMDA (N-methyl D-Aspartate) receptor and are associated with synaptic plasticity in prefrontal circuits, including AMPA and NMDA driven synaptic strengthening and dendritic spine remodeling which together is neuroplasticity (Lambe & Aghajanian, 2006).
Behavioral

In wild-type mice, DOI (2,5-Dimethoxy-4-iodoamphetamine), psilocybin or lisuride administration (single dose) resulted in a potent, long-term (<=15 days) anxiolytic and antidepressant-like effect in the novelty-suppressed feeding, sucrose-preference and forced-swim tests. These effects were lost in DOI and lisuride in 5-HT2A knockout mice, but not in psilocybin, suggesting that 5-HT2A receptor agonists can produce long-lasting antidepressant-like effects with or without strict receptor dependence and independently of hallucinogenic effects (Sekssaoui et al., 2024).

In rats, chronic intermittent low doses of DMT produced robust antidepressant-like responses, with treatment significantly reducing immobility and increasing swimming behavior in the forced swim test. DMT, as a neuroplastogen, promotes the rapid growth of dendritic branches, spines, and synapses through activation of 5-HT2A receptors, which engage glutamatergic pathways linked to neuroplasticity. These findings are important because a single dose of DMT has been shown to alter rodent brain structure and behavior long after the drug has been cleared from the body, indicating that its behavioral effects reflect durable neuroadaptive changes rather than short-lived drug action (Cameron et al., 2019).

In wild-type (C57Bl/6J) male mice, stimulation of 5-HT2A receptors in the medial prefrontal cortex (mPFC) has been demonstrated to raise extracellular glutamate levels (Aghajanian & Marek 1999), thereby modulating subcortical neurotransmission and boosting dopamine neuron (DA) firing in the ventral tegmental area (VTA) (Vazquez-Borsetti et al. 2009). Because agents

that heighten DA availability are associated with fear extinction, it is plausible that psilocybin promotes this process by modulating 5-HT, DA, and glutamatergic signaling pathways in the PFC, amygdala, and hippocampus (HPC). At the same time, DA signaling in mesolimbic circuits (the brain's reward pathway from the midbrain to the nucleus accumbens that helps us learn what to seek and repeat) is involved in liking and wanting and in reinforcement learning that supports the formation and maintenance of addiction, so any DA-mediated facilitation of extinction by psilocybin should be considered in the context of its engagement of reward circuitry. (Catlow et al., 2013).

In alcohol-dependent rats, psilocybin reduced alcohol drinking, with a single dose of 1 or 2.5 mg/kg significantly lowering alcohol consumption compared with controls. This effect was linked with the glutamate system, as psilocybin fixed (re-upped) mGluR2 receptor levels that had been damaged (reduced) by chronic alcohol exposure. Supporting this mechanism, a virus-mediated rescue of mGluR2 expression in post-dependent rats also decreased excessive alcohol intake, showing that normalization of mGluR2 (which can be done with psychedelics) is sufficient to reduce alcohol-seeking behavior (Domanegg et al., 2023).

Section 3 - BDNF

Genetic

DOI induces a specific transcriptional program in cultured cortical neurons, and this program is regulated by intracellular kinase signaling. It increases expression of the neuron growth markers arc, BDNF and egr-2 through pathways that activate cells through MAPK (MAP activated by potassium) and CaMKII (Calcium, M, potassium), although the induction of c-Fos (an intracellular activity marker) is dependent upon CaMKII activation alone whereas egr-1 is dependent upon MAPK activation alone. This trend indicates that DOI can use different kinase cascades to up-regulate plasticity-related genes to facilitate structural remodeling (Hatzipantelis & Olson, 2024). In vitro, psilocin quickly triggered a neuroplastogenic state in human iPSC-derived cortical neurons: increased BDNF, a transcriptional program oriented toward plasticity, and increased neuronal excitability. Such molecular changes are reflected in the long-term changes in structure and functionality, such as the enhanced synapse formation and stronger network activity-which is consistent with the hypothesis that psychedelics can rewire broken neuronal networks by facilitating plasticity (Schmidt et al., 2025). In mice subjected to fear conditioning, hippocampal BDNF protein levels dropped significantly. A single psilocybin injection reversed the effects of the fear, restoring BDNF to baseline by day 7 (Du et al., 2023).

In healthy adults, a single dose of 25 mg of psilocybin in a placebo-controlled study increased TrkB phosphorylation in peripheral leukocytes by approximately 20% six hours after administration, evidence that psilocybin can acutely increase BDNF TrkB signaling in humans.

However, since the levels of peripheral BDNF are merely a substitute of brain BDNF (the blood–brain barrier restricts correspondence), human studies produce mixed results. A single trial found that ayahuasca increased circulating BDNF in both healthy and depressed subjects (Palhano-Fontes et al., 2019), but another trial did not find this effect (Rocha et al., 2021). Similarly, studies of LSD have reported increases or no effect in turn, and two studies of psilocybin in healthy volunteers had opposite results, with one failing to report any increase in plasma BDNF (Becker et al., 2022) and the other reporting a large increase (Holze et al., 2022) (Calder & Hasler, 2023).

Receptor

In Vitro, LSD and psilocin bind to the BDNF receptor TrkB, at its transmembrane domain, with nanomolar affinity (LSD Kd 0.9 nM, psilocin Ki 7 nM) approximately 1000 times more strongly than other well-known antidepressants such as fluoxetine or ketamine. This binding is eliminated by mutation of key transmembrane residues (Y433F or V437A) indicating that the psychedelic pocket partially overlaps the other antidepressant binding site. Binding itself does not activate TrkB but in the presence of BDNF, it prolongs TrkB dimers at the surface, enhances the phosphorylation of receptors and activates the ERK and mTOR pathways that stimulate spine and dendrite growth (Moliner et al., 2023). In this way, LSD and psilocin act as adjuncts to BDNF, boosting its efficacy at the TrkB receptor.

Animal data suggests that almost all antidepressants including classic psychedelics enhance neuroplasticity, which is believed to be the mechanism behind their clinical effects. In the core of this plasticity is BDNF signaling and its receptor TrkB. In mice with the Y433F mutation (which disrupts the TrkB transmembrane binding site), psychedelics such as LSD and psilocin show greater potency in driving neuroplasticity, in comparison with standard antidepressants like fluoxetine and ketamine. BDNF-dependent plasticity fails to respond from antidepressants but still show effects from psychedelics, indicating a direct action at TrkB. Binding studies confirm this, showing that psychedelics attach to TrkB with almost 1,000 times higher affinity than fluoxetine or ketamine (Hatzipantelis & Olson, 2024) (Moliner et al., 2023). Mice with the Y433F mutation fail to exhibit BDNF-induced plasticity, and antidepressant-like effects, whereas 5-HT2A blocker-treated animals retain them, establishing that LSD and psilocin are agonists of TrkB, not serotonin signaling. (Hatzipantelis & Olson, 2024). Also, psychedelic actions are increasingly associated with BDNF-TrkB signaling that is activated downstream of 5-HT2A receptor activation (Moliner et al., 2023).

Behavioral

In mice exposed to fear conditioning, psilocybin significantly enhanced extinction learning to the point where the animal forgot conditioned fear responses. At the same time, psilocybin prevented the conditioning-induced decrease in hippocampal dendritic complexity and spine density as well as the decrease in protein levels of BDNF and mTOR. These findings provide a

molecular and structural correlate of the behavioral improvements seen in fear extinction, and demonstrate that psilocybin supports recovery through a restoration of BDNF signaling and hippocampal plasticity (Du et al., 2023).

In primates (common marmosets), the AG (ayahuasca group) showed higher cortisol reactivity and fecal cortisol levels than the IG (no intervention group), while both measures were like the FG (family control group). Depression in this model was measured through anhedonia, using sucrose intake as a behavioral marker, since depressed animals consume less sucrose due to reduced ability to experience pleasure. Animals in the AG displayed no signs of anhedonia, maintaining normal sucrose intake, while the IG showed reduced intake consistent with depressive-like states. The AG also showed no increase in chronic stress-related behaviors, which were observed in the IG. These findings suggest that ayahuasca helped prevent or reverse depressive-like symptoms in stressed animals, supporting resilient responses and reducing the onset of behavioral and physiological markers of depression. Overall, the results support further investigation into the potential preventive use of psychedelics against stress-related psychopathologies (de Meiroz Grilo et al., 2022).

In humans (healthy controls and patients), ayahuasca increased serum BDNF at 48h post-dose (D2) in comparison to placebo. Only the patient group showed a significant inverse relationship between the levels of BDNF and depression scores which means that the antidepressant effect of ayahuasca possibly happens, at least in part, due to the increase in BDNF signaling (de Almeida et al., 2019).

Permeability

The neuroplasticity-promoting effects of psychedelics require membrane permeability. Although the activation of the 5-HT2A receptor is necessary, it is not sufficient alone, as demonstrated by the absence of neuronal growth when impermeable analogs of DMT or psilocin were tested. These impermeable compounds did not induce dendritic growth but maintained normal receptor affinity and only when electroporation was used to get them into the cell, did they induce dendritic growth. This was also the case with serotonin, which is impermeable and could only promote growth following electroporation or when entry was promoted by the serotonin transporter (SERT). This implies that lipophilicity (ability to enter a cell) is important in predicting neuroplastogenic potential, as it enables a compound to penetrate the neuronal membrane. The mechanism can be the activation of an intracellular pool of 5-HT2A receptors in cortical neurons that link to downstream signaling pathways including TrkB, mTOR and AMPA receptor signaling, which ultimately leads to dendritic and synaptic remodeling. The knockout mouse studies validate that these effects are 5-HT2A receptor-dependent, proving that psychedelic-induced neuroplasticity is membrane permeability-dependent and receptor-dependent (Vargas et al., 2023).

Discussion

Depression features loss of dendrites, weak synapses, and rigid circuits. Standard antidepressants (SSRIs and SNRIs) act slowly and often do not repair these changes. Serotonergic psychedelics can open a short plasticity window that supports lasting repair. Genetics points to variable sensitivity, since HTR2A variants change cortical 5-HT2A levels. At the receptor level, psychedelics increase dendritic branching and synapse formation, and these effects drop when 5-HT2A is blocked or removed, as shown in mouse studies where 5-MeO-DMT raised dendritic spine density, but this effect disappeared in 5-HT2A knockout animals. In cortical cultures, DMT and LSD similarly expanded dendritic arbors, effects that were abolished by the 5-HT2A blocker ketanserin (de Vos et al., 2021). Permeability is required, impermeable analogs with intact affinity do not grow neurons unless they are forced into the cell.

In living cortex, 5-HT2A activation increases glutamate, strengthens AMPA signaling, and promotes synaptogenesis and synapse maintenance. This is supported by rodent experiments, in which LSD rapidly increases immediate-early gene expression associated with glutamatergic drive (de Vos et al., 2021), and by human 7T MRS studies, in which psilocybin increased glutamate in medial prefrontal cortex in a way that correlated with ego dissolution (Mason et al., 2020). At the same time, BDNF is up-regulated and TrkB is activated, which supports protein synthesis, spine stability and network remodeling. For instance, psilocybin reversed the loss of BDNF following fear conditioning in mice, and in humans (Du et al., 2023), ayahuasca increased circulating BDNF that was inversely correlated with depression scores (de Almeida et al., 2019).

The neurological changes due to serotonergic psychedelics are reflected in behavior. In rodents, psychedelics accelerate fear extinction, reverse the effects of stress and reduce excessive drug seeking. For example, in alcohol-dependent rats, psilocybin decreased drinking after acute administration, restoring mGluR2 receptor levels that had been reduced by chronic alcohol exposure (Domanegg et al., 2023). Viral rescue of mGluR2 alone recapitulated this effect, showing that normalization of glutamatergic signaling is sufficient to reduce alcohol-seeking behavior. These data show cellular plasticity leading to meaningful behavioral recovery. In humans, psychedelics reduce threat responses in the amygdala and medial prefrontal cortex (Mueller et al., 2017), enhance mood and flexibility, and in some studies increase circulating markers of plasticity (Hutten et al., 2020). Often, the benefits last for months even after the drug is stopped.

Conclusion

I propose a permeability plus mechanism model. The serotonergic drug must be both cell-permeable and engage 5-HT2A. A permeable psychedelic reaches intracellular 5-HT2A

pools, 5-HT2A activation quickly boosts plasticity-related gene expression and drives structural change, 5-HT2A signaling raises BDNF and engages TrkB to support growth, and 5-HT2A activation in cortex increases glutamate and AMPA signaling that helps stabilize new synapses, together linking permeability, receptor engagement, and circuit activity to durable neuroplasticity.

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