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Biochemical Mechanisms Underlying Psychedelic-Induced Neuroplasticity

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Abstract

In addition to producing profound subjective effects following acute administration, psychedelic compounds can induce beneficial behavioral changes relevant to the treatment of neuropsychiatric disorders that last long after the compounds have been cleared from the body. One hypothesis with the potential to explain the remarkable enduring effects of psychedelics is related to their abilities to promote structural and functional neuroplasticity in the prefrontal cortex (PFC). A hallmark of many stress-related neuropsychiatric diseases—including depression, post-traumatic stress disorder (PTSD), and addiction—is the atrophy of neurons in the PFC. Psychedelics appear to be particularly effective catalysts for the growth of these key neurons, ultimately leading to restoration of synaptic connectivity in this critical brain region. Furthermore, evidence suggests that the hallucinogenic effects of psychedelics are not directly linked to their ability to promote structural and functional neuroplasticity. If we are to develop improved alternatives to psychedelics for treating neuropsychiatric diseases, we must fully characterize the molecular mechanisms that give rise to psychedelic-induced neuroplasticity. Here, I review our current understanding of the biochemical signaling pathways activated by psychedelics and related neuroplasticity-promoting molecules, with an emphasis on key unanswered questions.

Graphical Abstract

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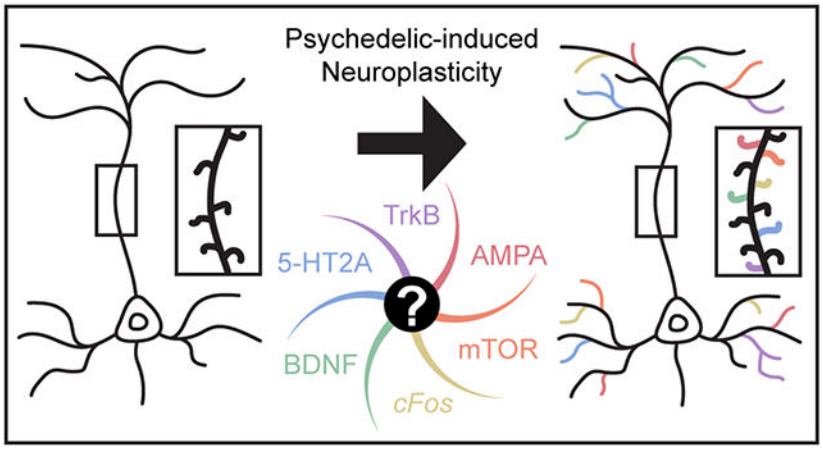
Disclosure

David E. Olson is a co-founder and the chief innovation officer of Delix Therapeutics, Inc.



Keywords

Psychedelic; psilocybin; LSD; DMT; neuroplasticity; spinogenesis; synaptogenesis; dendritogenesis; mTOR; TrkB; BDNF; psychLight; TBG

Increasing preclinical[1,2,3,4,5,6,7] and clinical[8,9,10,11,12,13] evidence suggests that psychedelics produce therapeutic effects relevant to treating neuropsychiatric diseases like depression, PTSD, and substance use disorder (SUD). [14,15,16,17,18,19,20] Moreover, these effects exhibit rapid onset (within 24 h), occur after only a single or a few doses, and last long after the compounds have been cleared from the body. The sustained behavioral effects of psychedelics are truly remarkable and differentiate these compounds from traditional neurotherapeutics that must be administered daily. Currently, it is unclear exactly how psychedelics produce such long-lasting effects. One hypothesis is that psychedelics induce mystical-type experiences that can facilitate interactions with therapists, enable patients to gain insight into their disorders, and perhaps even enhance the placebo effect.[21,22,23,24] Another non-mutually exclusive explanation involves the ability of psychedelics to promote structural and functional neuroplasticity in the prefrontal cortex (PFC) enabling pathological circuits controlling mood, fear, and reward to be repaired.[25,26,27,28]

Cortical atrophy and dysfunction underlie many stress-related neuropsychiatric diseases including depression, PTSD, and SUD.[29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44] Thus, compounds capable of rapidly and robustly re-growing atrophied neurons in the PFC have broad therapeutic potential. Our group has hypothesized that compound-induced cortical neuron growth might explain why psychedelics produce therapeutic effects across several distinct neuropsychiatric diseases,[45] giving them the semblance of panaceas. Psychedelics belong to a broader class of compounds known as psychoplastogens (Figure 1),[46] and unlike other small molecules capable of promoting induced plasticity (iPlasticity)[47] such as fluoxetine, psychoplastogens produce robust, and lasting changes in cortical neuron growth following a single administration. The list of known psychoplastogens continues to grow and includes classic serotonergic hallucinogens such as lysergic acid diethylamide (LSD), psilocin, *N,N*-dimethyltryptmaine (DMT), and 2,5-dimethoxy-4-iodoamphetamine (DOI),[6,7,48] entactogens like 3,4-methylenedioxymethamphetamine (MDMA),[48] oneirogens

like ibogaine,[49] deliriants like scopolamine,[50] and dissociatives like ketamine.[51,52,53] Moreover, several non-hallucinogenic psychoplastogens, such as tabernanthalog (TBG) have recently been identified,[49,54,55] suggesting that it may be possible to decouple the hallucinogenic effects of psychedelics from their sustained beneficial effects on behavior,[56,57,58] though this hypothesis requires further testing in humans.

Penzes and co-workers were the first to demonstrate that serotonergic psychedelics can impact structural neuroplasticity.[59] Using cultured cortical neurons, they demonstrated that DOI transiently increased dendritic spine size 30 mins after treatment, but that spine size returned to baseline after an hour. Muma and co-workers later demonstrated that DOI-induced changes in spine morphology involve 5-HT2A/5-HT2C-mediated activation of transglutaminase, Rac1, and Cdc42.[60] In addition to promoting changes in spine morphology, Shiga and co-workers demonstrated that DOI increases spine density in embryonic rat cortical cultures treated for 24 h.[61] They also showed that activation of 5-HT2 receptors by DOI increases the size of cortical neuron dendritic growth cones in vitro.[62]

All of the early work studying the effects of psychedelics on structural plasticity had been performed with DOI, leaving open the possibility that the effects of DOI on neuronal structure could be an inherent property of the amphetamine scaffold rather than a general attribute of psychedelics. To address this question, our group directly compared the psychoplastogenic effects of psychedelics from the amphetamine, tryptamine, and ergoline families.[48] We found that psychedelic compounds across diverse chemical space could all robustly promote neuritogenesis, spinogenesis, and synaptogenesis in rat embryonic cortical cultures,[48] and that these changes can be induced by only transient stimulation (~1 h).[63] Interestingly, unlike DOI, D-amphetamine was unable to promote neuritogenesis,[48] demonstrating that the psychoplastogenic effects of DOI were due to its pharmacological properties rather than its core chemical structure. In vivo, D-amphetamine has been shown to promote growth in the medial PFC, though it decreases spine density in the orbital PFC and has no effect on neuronal growth in the parietal and occipital cortices.[64,65,66] Moreover, these effects were observed after chronic dosing, which might yield different results than acute treatment. Like D-amphetamine, we found that serotonin did not promote the growth of cultured cortical neurons,[48] suggesting that psychedelics have a unique ability to promote structural neuroplasticity.

In addition to producing psychoplastogenic effects in vitro, psychedelics also impact neuronal structure in vivo and across species (i.e, rodents and Drosophila).[48] We found that a single administration of DMT to rats led to increased dendritic spine density measured in the PFC long after the compound had been cleared from the body. Moreover, this change in structural plasticity was accompanied by functional changes as well, including sustained increases in the amplitude and frequency of spontaneous excitatory postsynaptic currents (sEPSCs).[48] In collaboration with Yi Zuo and co-workers, we performed two-photon imaging in live mice to demonstrate that both hallucinogenic (i.e., DOI) and non-hallucinogenic (i.e., TBG) psychoplastogens increase the rate of spine formation, but not elimination, over the course of 24 h.[49] Furthermore, a single dose of TBG partially rescued dendritic spine loss induced by unpredictable mild stress and completely normalized the activity of cortical neurons.[67] Following these studies, Kwan and co-workers reported that

a single administration of psilocybin increases cortical spine density for at least a month in mice, with females responding more robustly than males.[6] Using a recently developed PET ligand, Knudsen and co-workers demonstrated the psilocybin increases cortical density of the presynaptic marker synaptic vesicle glycoprotein 2A (SV2A).[68] Taken together, these long-lasting changes in neuronal structure and function could potentially explain why psychoplastogens produce sustained behavioral effects after a single dose.

Like psychedelics, several non-serotonergic psychoplastogens, including ketamine and scopolamine, increase dendritic spine density in the PFC[50,51,52] and promote dendritogenesis in cortical cultures.[48,63] Recently, an elegant study by Liston and co-workers demonstrated a causal relationship between ketamine-induced spine growth in the PFC and the long-lasting antidepressant-like behavioral effects of the drug.[53] While it is reasonable to hypothesize that spine growth in the PFC also underlies the long-lasting antidepressant-like effects of psychedelics in rodents, an experiment testing this hypothesis has not yet been performed. Interestingly, the effects of ketamine on spine density and antidepressant-like behavior last for approximately one week,[69] while the effects of psilocybin appear to be significantly more enduring.[2,6] Though all psychoplastogens appear to engage similar downstream biochemical signaling pathways leading to neuronal growth, their primary molecular targets can be distinct.[26,70] For example, ketamine and scopolamine target NMDA and muscarinic receptors, respectively, while serotonergic psychedelics exert their primary effects through activation of 5-HT2A receptors.

Serotonergic psychedelics exhibit complex polypharmacology[71] with many of these compounds targeting several GPCRs implicated in structural neuroplasticity including 5-HT6 and 5-HT7 receptors.[72,73,74,75,76] In fact, the unique polypharmacology of psychedelics might contribute to their psychoplastogenic and/or therapeutic effects.[77] However, the one commonality shared by all classic serotonergic psychedelics is high affinity for 5-HT2 receptors.[78,79] There are three 5-HT2 receptor subtypes—5-HT2A, 5-HT2B, and 5-HT2C—with 5-HT2A and 5-HT2C receptors being highly expressed in the brain. The exact contributions of 5-HT2A and 5-HT2C receptors to the effects of psychedelics have yet to be fully elucidated, though increasing evidence suggest that 5-HT2A receptor activation plays a critical role in both the hallucinogenic and psychoplastogenic effects of these compounds.

Glennon and co-workers found that the affinities of psychedelics for 5-HT2 receptors correlate very well with their human hallucinogenic potencies,[80] and that 5-HT2A/5-HT2C antagonists can block the discriminative stimulus properties of psychedelics in rodents, suggesting that 5-HT2B activation does not play a role in their subjective effects.[81] Blocking 5-HT2 receptors in humans with the antagonist ketanserin eliminates hallucinations produced by both psilocybin[82] and LSD,[83,84] and the intensity of the hallucinogenic experience correlates with 5-HT2 receptor occupancy.[85]

Given the high sequence homology between 5-HT2A and 5-HT2C receptors, it has been challenging to identify selective pharmacological tools to disentangle their respective contributions to psychedelic-induced effects, though some evidence suggests that the 5-HT2A receptor affinities of antagonists correlate better with their abilities to block the discriminative stimulus properties of psychedelics than do their 5-HT2C receptor

affinities.[86] Given the selectivity issues associated with pharmacological probes, genetic tools have proven extremely valuable. Genetic knockout (KO) of 5-HT2A receptors completely abolishes psychedelic-induced head-twitch response (HTR) behavior in mice,[87] while 5-HT2C receptor KO only leads to a ~50% reduction.[88] Potency in the HTR assay correlates exceptionally well with human hallucinogenic potency across a wide range of psychedelic compounds.[89,90]

Like their hallucinogenic effects, the psychoplastogenic effects of psychedelics appear to be mediated by 5-HT2A receptors. While ketanserin completely blocks the ability of psychedelics to promote dendritogenesis, spinogenesis, and synaptogenesis in cortical cultures,[48] ketanserin pretreatment only leads to a partial block of psilocybin-induced structural plasticity in vivo.[6] The inability of ketanserin to completely block the effects of psilocybin in vivo is likely due to pharmacokinetic considerations, as ketanserin is known to exhibit poor brain penetration[91] and only occupies ~30% of cortical 5-HT2A receptors when administered to rats at 1 mg/kg.[92] Our group has found that the passive diffusion of ketanserin across non-polar membranes is surprisingly poor, as measured via a PAMPA assay (unpublished results). To avoid the issues associated with 5-HT2 antagonists, González-Maeso and co-workers recently used 5-HT2A receptor KO mice to demonstrate that these receptors are critical for the increases in spine density observed following DOI administration.[7] While evidence strongly suggests that 5-HT2A receptors mediate the psychoplastogenic effects of psychedelics, it is still unclear why serotonin cannot produce similar effects on structural plasticity.[48]

Though the sequences of 5-HT2A receptors are very similar across species, there are several key differences between the human and rodent receptors that lead to functional differences. In humans, residue 242 is a serine, while it is an alanine in rodents. In the human receptor, this particular serine can form a hydrogen bond with certain ligands, drastically impacting their binding potencies and kinetics.[93,94,95] Additionally, the rat and human 5-HT2A receptors exhibit differences in recycling and internalization, which have been linked to their divergent C-terminal sequences.[96] These important differences should be taken into consideration when evaluating psychoplastogenic effects across species.

Exactly how 5-HT2A receptor stimulation leads to structural plasticity remains a mystery, though several clues have emerged. Like ketamine and scopolamine,[50,51] psychedelics seem to require TrkB, AMPA receptor, and mTOR signaling to produce psychoplastogenic effects[48,63,97] with mTOR being a critical downstream kinase responsible for producing plasticity-related proteins.[98] Using shotgun proteomics, Rehen and co-workers found that 5-MeO-DMT modulated levels of proteins associated with structural neuroplasticity in cerebral organoids.[99]

The prevailing hypothesis is that both ketamine and psychedelics induce a glutamate burst[100,101,102,103] leading to AMPA receptor activation and subsequent secretion of brain-derived neurotrophic factor (BDNF).[104,105] Secreted BDNF then binds to TrkB resulting in mTOR activation. As mTOR activation is known to increase the production of BDNF,[106] and BDNF can facilitate nonexocytotic glutamate release,[107] the pathway can stay activated for some time though this autoregulatory feedback loop.[63]

While psychoplastogens appear to catalyze neuronal growth processes involving AMPA receptors, TrkB, and mTOR, several questions remain. Activation of AMPA receptors seems to be necessary for psychoplastogen-induced neuronal growth, but it is unclear if a large glutamate burst is essential. Psychedelic- and ketamine-induced glutamate release in the cortex has been hypothesized to result in hallucinogenic effects through increased cortical excitation.[108] Given that non-hallucinogenic analogs of psychedelics can produce similar psychoplastogenic effects,[49,54,55] it is unclear if a large glutamate burst is critical to turn on biochemical pathways leading to sustained neuronal growth. Moreover, several alternative mechanisms do not invoke a glutamate burst to explain the effects of ketamine on pyramidal neuron structure and function. Monteggia and co-workers have hypothesized that ketamine might promote neuronal growth through homeostatic synaptic upscaling,[109,110] while Kwan and co-workers suggest that ketamine might increase pyramidal neuron excitability by blocking NMDA receptors on GABAergic neurons within cortical microcircuits.[26]

Several studies have demonstrated that BDNF plays a critical role in mediating the effects of ketamine and scopolamine. The antidepressant effects of ketamine are absent when the drug is administered to inducible *BDNF* KO mice[111] or Val66Met mutant mice.[112] Similarly, infusion of an anti-BDNF antibody into the PFC can block the antidepressant-like effects of scopolamine.[113] While it is largely assumed that BDNF is essential to the psychoplastogenic effects of serotonergic psychedelics, similar mechanistic studies have not yet been performed.

Though a causal link between BDNF and psychedelic-induced neuroplasticity has not yet been definitively established, psychedelics do increase *BDNF* gene expression in the cortex, and this effect is blocked by pretreatment with a 5-HT2A receptor antagonist.[114] Psychedelics also increase the expression of immediate early genes (IEGs) associated with neuroplasticity such as *c-Fos*, *arc*, *egr-1*, and *egr-2,* among others, and these increases in expression are abolished by 5-HT2A receptor antagonists or in 5-HT2A receptor KO mice.[87, 115,116,117,118,119,120,121,122,123,124,125,126] Using selective inhibitors, Vaidya and co-workers found that psychedelic-induced expression of plasticity-related genes required activation of both CaMKII and MAPK pathways.[127] Even though psychedelics produce profound, long-lasting changes in behavior, they induce differential expression of relatively few genes.[7,128,129] Interestingly, a recent study suggests that a single administration of DOI leads to sustained epigenomic changes in the frontal cortex of mice, and that these changes were primarily found at enhancer regions of genes implicated in neuroplasticity.[7] Given that the antidepressant-like effects of serotonergic psychedelics appear to be more sustained than those of ketamine,[2] it would be interesting to directly compare the long-lasting epigenomic profiles of these classes of psychoplastogens.

Canonical G protein signaling pathways are believed to be responsible for some, but not all, of the gene expression changes observed after treatment with psychedelics.[87,120,127] The 5-HT2A receptor typically couples to G_q,[130] and thus, stimulation of 5-HT2A receptors can lead to activation of phospholipase C (PLC), the production of inositol triphosphate (IP_3), and an increase in intracellular calcium.[131,132,133] Psychedelics such as LSD, DOI, and 5-MeO-DMT act as partial agonists of this pathway, as do several non-hallucinogenic 5-HT2A ligands such as lisuride, 6-F-DET, and TBG.[49,134,135,136,137,138] Increased *c-Fos*

expression following treatment with either hallucinogenic or non-hallucinogenic agonists of the 5-HT2A receptor is abolished in 5-HT2A receptor KO neurons or by pretreatment with a PLC inhibitor.[87,120,127] However, the contribution of G_q signaling to the behavioral effects of psychedelics is unclear given that non-hallucinogenic 5-HT2A receptor ligands can activate G_q, and DOI still produces a robust HTR in G_q KO mice.[139] Moreover, it is currently unknown what role, if any, canonical G_q activation plays in the psychoplastogenic effects of psychedelics. Full agonists like serotonin do not necessarily promote plasticity, and partial agonists like LSD can induce large increases in structural plasticity.[48]

In addition to activating PLC, psychedelics have also been shown to increase arachidonic acid release through activation of phospholipase A_2 (PLA_2),[140,141] While this pathway is quite opaque compared to the pathway leading to PLC activation, it appears that it may require $G_{i/o}$, $G_{\beta\gamma}$, and $G_{12/13}$ in NIH3T3–5HT2A cells.[142] Cellular context seems to be critical for determining which signaling pathways psychedelics can activate, as Roth and co-workers recently used TRUPATH[143] to demonstrate that LSD selectively activates G_q, G_{11}, and G_{15} in HEK293T cells while Gonzalez-Maeso, Meana, and co-workers have shown that psychedelics can activate G_i in neurons.[87,144] Given that non-hallucinogenic 5-HT2A agonists do not appear to be capable of activating G_i, yet they can promote neuroplasticity, it is unclear what role G_i signaling plays in the psychoplastogenic effects of psychedelics.

Stimulation of 5-HT2A receptors can activate a variety of other downstream effectors known to be involved in cell growth including, but not limited to, ERK,[142,145] JAK2,[146] and GSK3β,[147] though no studies to date have assessed the roles of these key proteins in the psychoplastogenic effects of psychedelics. Similarly, β-arrestin activation can play important roles in the downstream effects of 5-HT2A ligands,[148,149,150,151,152] but we currently do not know if β-arrestin is involved in psychedelic-induced structural neuroplasticity.

Given that the potencies and efficacies of 5-HT2A ligands for activating various 5-HT2A-dependent signaling cascades do not correlate well with either their hallucinogenic or psychoplastogenic effects, we were interested in developing a direct fluorescence readout of 5-HT2A receptor conformation. To achieve this goal, we fused a circularly permuted green fluorescent protein to the third intracellular loop of the 5-HT2A receptor.[55] Activation and inactivation of the sensor increases and decreases fluorescence intensity, respectively. Interestingly, when the sensor is expressed in HEK293T cells, its activation correlates very well with human hallucinogenic potency. Moreover, non-hallucinogenic agonists of the PLC pathway like lisuride, TBG, and 6-F-DET act as inverse agonists of this sensor. Given its ability to predict hallucinogenic potential across a wide range of structurally diverse compounds, we started calling this sensor psychLight.[55] While psychLight is quite good at predicting hallucinogenicity, the current version of the sensor cannot predict psychoplastogenicity.

Ultimately, the integration of various 5-HT2A receptor signaling pathways can lead to compound-specific changes in the phosphoproteome and/or transcriptome. Several efforts have attempted to distinguish between hallucinogenic and non-hallucinogenic 5-HT2A receptor agonists by comparing their phosphoproteomic[145,153] or transcriptomic signatures.[87,120] While these initial results are promising, the effects of many more

compounds from diverse chemical classes need to be assessed before any claims can be made about a particular phosphorylation or gene expression pattern being a hallmark of one group of compounds over another. Similar efforts should be undertaken to compare proteomic, phosphoproteomic, and transcriptomic signatures of psychoplastogens against their structurally related non-psychoplastogenic congeners.

Though we know relatively little about how 5-HT2A receptor signaling converges on activation of TrkB, AMPA receptors, and mTOR to promote neuronal growth, it is clear that ligands for this receptor can exhibit a high degree of functional selectivity or biased agonism.[87,154,155,148,156,157] The 5-HT2A receptor interacts with a number of scaffolding proteins[158] and forms heterodimeric complexes with metabotropic glutamate,[155] dopamine,[159] cannabinoid,[160] and serotonin[161] receptors that can alter its signaling profile, though the in vivo functional relevance of these heterodimers is highly debated.[162] The 5-HT2A-mGlu2 heterodimer[155,163,164,165] has received a lot of attention given that it seems to be selectively activated by hallucinogens.[155] It is interesting to note that DOI-induced *BDNF* expression in the cortex can be modulated by mGlu2 receptor ligands.[166] Thus, it is possible that psychedelics induce glutamate release through a presynaptic mechanism[167,168] involving a putative 5-HT2A-mGlu2 heterodimer. In theory, this glutamate burst could activate AMPA receptors leading to upregulation of BDNF/TrkB signaling. However, the role of a 5-HT2A-mGlu2 heterodimer in the psychoplastogenic effects of psychedelics is still unclear given that non-hallucinogenic ligands do not appear to activate this heterodimer and yet several non-hallucinogenic psychoplastogens have recently been discovered.

Because it is still unknown which 5-HT2A receptor signaling pathways are most critical to promoting neuronal growth (Figure 2), we focused our medicinal chemistry efforts on using phenotypic screening in neuronal cultures to identify non-hallucinogenic psychoplastogens.[49,54,55] These compounds are structural analogs of psychedelics that do not induce a HTR, but are still capable of producing robust psychoplastogenic effects and sustained therapeutic behavioral responses after a single administration. Currently, tabernanthalog (TBG) is the most studied non-hallucinogenic psychoplastogen having demonstrated the ability to repair neural circuitry damaged by chronic stress[67] and to produce long-lasting behavioral effects relevant to treating both depression and addiction.[49,169] Efforts to design new non-hallucinogenic psychoplastogens have relied heavily on structure-activity relationship studies, but with the advent of high resolution structures of the 5-HT2A receptor in both active and inactive states,[95,170] rational design of improved psychedelic-related therapeutics might be possible in the near future.

CONCLUSION

Biochemical signaling resulting from 5-HT2A receptor activation is complex and depends on both the nature of the ligand and the cellular environment. In order to understand which pathways lead to psychedelic-induced neuroplasticity, we need to use a variety of pharmacological ad genetic tools to block these pathways in neurons. Additionally, the development of high-throughput assays to assess psychoplastogenic effects will be essential for correlating psychoplastogenic potencies and efficacies with those of more traditional assays relevant to 5-HT2A receptor signaling. While we know that 5-HT2

receptors appear to be essential for the psychoplastogenic effects of psychedelics, several key questions remain. Does the genetic localization of 5-HT2 receptors impart a level of cell-type selectivity in the psychoplastogenic effects of psychedelics? Do psychedelics induce growth of non-neuronal cells expressing 5-HT2 receptors? These are some of the many questions that need to be answered if we are to engineer better neuroplasticity-promoting therapeutics based on psychedelics. For other perspectives on psychedelic-induced neuroplasticity and the molecular mechanisms of psychedelics, please see several excellent recent reviews.[25,71,171,172]

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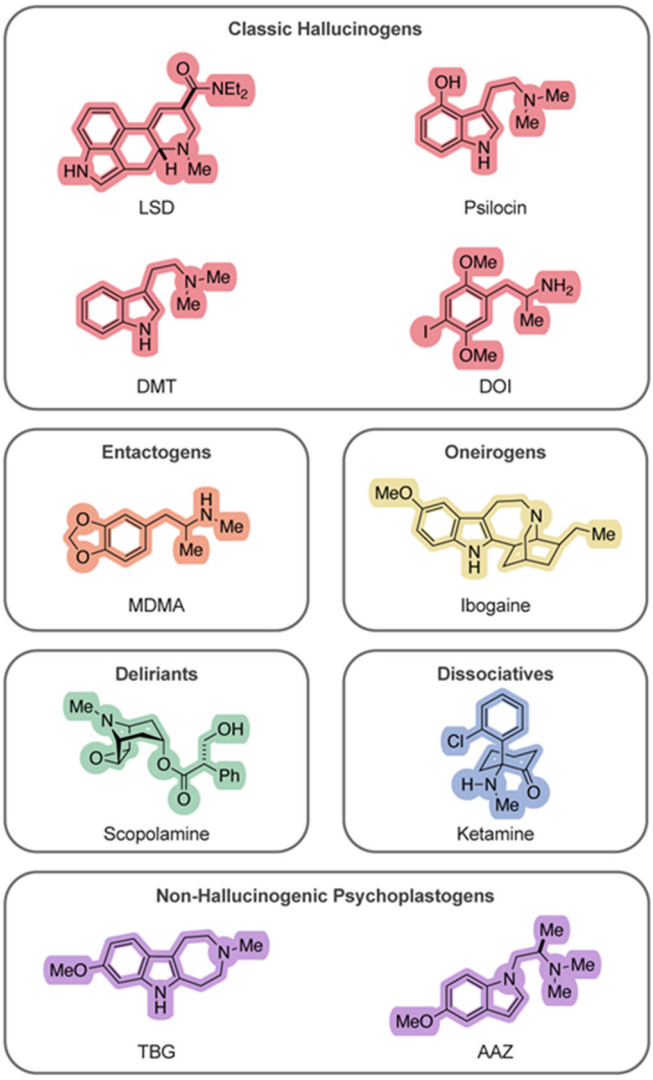

Figure 1.
Chemical structures of psychoplastogens from various pharmacological classes

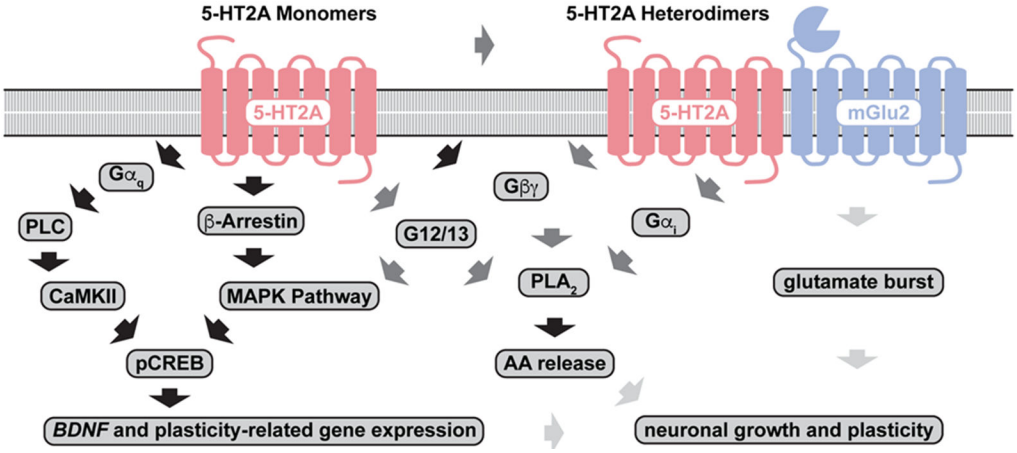

Figure 2.

Biochemical pathways activated by psychedelics. Pathways with with strong, moderate, and weak supporting evidence are indicated with black, dark grey, and light grey arrows, respectively.