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Abstract

Depression remains one the most commonly diagnosed mental health disorders in the United States. The Food and Drug Administration granted psilocybin breakthrough therapy status four years ago as a possible solution to this pervasive disorder. Since then, psilocybin, and hallucinogens in general, have produced promising results as alternatives to classical antidepressants. As more research confirms psilocybin's potential therapeutic effect, research surrounding the mechanistic action of these 5-HT_{2A} receptor agonists has increased as well. Hallucinogens have different downstream effects compared to non-hallucinogenic 5-HT_{2A} receptor agonists, including the formation of a 5-HT_{2A} receptor and metabotropic glutamate receptor complex. Psilocybin's unique synaptogenic effect may play a role in its therapeutic effect for major depressive disorder; however, the underlying mechanism by which synaptogenesis is induced upon psilocybin administration has not been explored. Psilocybin's distinctive upregulation of transcription factors, such as egr-2, c-fos, and brain-derived neurotrophic factors, and its connection with the TrkB signaling pathway, may be the answer to this unexplained mechanism.

Keywords: Psilocybin, Hallucinogens, Depression, Synaptogenesis, 5-HTR, mGLUR

1. Introduction

While originally discovered in blood *serum* for its effects as a vasoconstrictor (*tonic*) and its effects in the gut, serotonin's role as a neurotransmitter was not thoroughly confirmed for nearly another decade when the findings of experiments with lysergic acid diethylamide (LSD) on peripheral nervous systems (PNS) were synthesized with the early localization of serotonergic receptors in the midbrain. Serotonin (5-HT) and LSD were quickly recognized to have an intimate relationship, but the subtypes of 5-HT receptors in the brain were not categorized or localized until decades later. One receptor, 5-HT_{2A}R, was found to be tightly linked to hallucinogenic activity. Though it is debated, 5-HT_{2A}Rs are largely localized in the claustrum, cerebral cortex, olfactory tubercle, striatum, and nucleus accumbens.[1] This debate is due to the fact that radioligands are not entirely specific to individual subtypes of receptors, including 5-HTRs.[2] Thorough research returned no indications of any GFP-tagged 5-HT receptor studies looking at neuroanatomy, which may be explained by the multitude of differences in 5-HTR localization between model species and humans.

The first use for drugs targeting these receptors was recreational, as most were discovered as psychedelics or hallucinogens, producing consciousness-altering effects. The most prominent of these was lysergic acid diethylamide, or LSD, discovered in the 1900s by Swiss chemist

Albert Hoffman.[3] While not as similar structurally to 5-HT or Psilocybin, it still shares the indole and similarly positioned nitrogen that allows binding to the 5-HT_{2A}R, contributing to its similarity in hallucinogenic effect and usefulness in analogous psilocybin research.

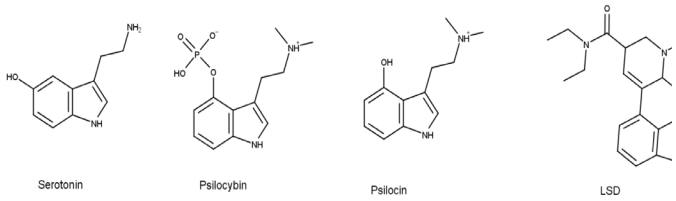

Figure 1. Comparison of Structures of Serotonin, Psilocybin, Psilocin, and LSD. Adapted from Bauer et al., 2019.[4] Molecular structure of Serotonin, Psilocybin, its metabolite Psilocin, and LSD.

Psilocybin (and its active metabolite, psilocin), however, is almost identical to 5-HT, featuring the same indole and distant NH_2 group, with the only changes being the 2 additional n-methyl groups and the electronegative hydroxyl group shifting over one carbon on the benzene ring. Research into psilocybin, like LSD and other hallucinogens, was hampered by its designation as a schedule 1 drug by the US government, tightening regulations, increasing stigmas, and overall decreasing interest in researching its potential therapeutic effects.

However, after decades of mixed opinions from the scientific community, hallucinogens are now widely accepted as potential therapies for all kinds of disorders, including substance abuse, anxiety, and depression, as will be discussed later.[5] In 2018, the FDA granted psilocybin breakthrough therapy status through COMPASS Pathways' ongoing work in phase 2 clinical trials to combat Treatment Resistant Depression.[6,7] In the United States, treatment resistant depression creates an annual burden of $43.8 billion dollars, with an estimated 12-month prevalence of 2.8 million in 2021. More recently, the FDA also granted breakthrough status to a therapy from the Usona Institute in phase 2 trials to treat Major Depressive Disorder (MDD), expanding patient scope by an estimated 3-10 times. Medication-treated MDD has a 12-month prevalence in the United States of 8.9 million adults, costing $92.7 billion annually.[6,8] Finding higher quality and more cost-effective treatments for these disorders would help millions of Americans and potentially tens to hundreds of millions of people internationally, as well as alleviate tens of billions of dollars in medical burdens in the US alone.

2. Relevance to Depression

Depressive symptoms have been linked to overactivity of the brain network responsible for introspection and self-referential thinking, called the default mode network, which is localized to the medial prefrontal cortex, bilateral angular gyri, and temporal poles. Depression is also found to involve an impairment of the executive network and salience network, which are associated with cognitive control and switching between internal and external attention.[9] The binding site of psychedelics such as psilocybin, 5-HT_{2A}R, has become an important focus in depression research as this receptor is found most densely in a "broad pattern of cortex that closely resembles a conjunction map of the default mode, executive and salience networks."[10]

In a clinical trial in which patients with treatment resistant depression were given an orally administered 10mg dose of psilocybin and then another 25mg dose a week later, depression symptoms as measured by Beck's depression inventory (BDI) decreased significantly. Starting from a BDI score of 34.81± 7.38, the mean was reduced by 21 points after one week and remained 14.19 points lower relative to the baseline at the six-month check in. This was a greater decrease than that observed among those who were given the selective serotonin reuptake inhibitor (SSRI) escitalopram daily for six weeks.[10] Another study which used the Quick Inventory of Depressive Symptomatology -Self Report (QIDS SR 16) showed no significant difference between scores of participants given psilocybin versus escitalopram after six weeks.[11] This discrepancy is most likely due to the difference in timing between the two

studies' assessments and possible differences between the two self-reporting scales for depression symptoms.

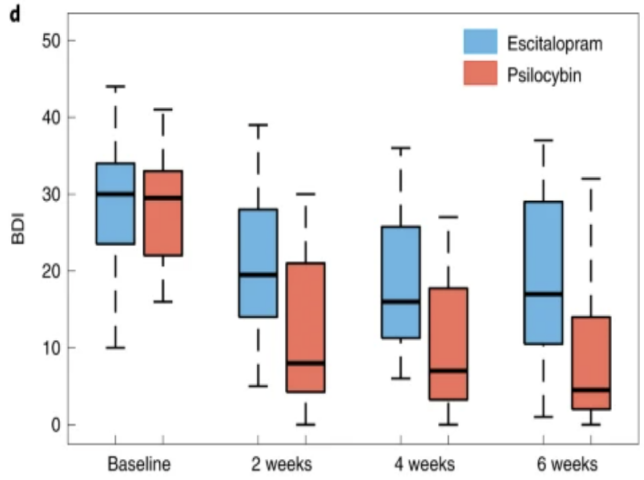

Figure 2. Beck's Depression Index Scores after treatment with psilocybin and escitalopram. DB-RCT BDI scores from each study arm and time point. Adapted from Daws et al., 2022.[10]

In addition to having an equal or greater effect on self-reported feelings of depression, as measured by BDI or QIDS SR 16, than treatment with the SSRI escitalopram, psilocybin also decreased brain modularity, a measure of how segregated brain networks are from one another. Lower modularity means more functional connectivity between networks and a reduction of within-network connectivity. After treatment with psilocybin, there was a significant decrease in the hyperconnectivity within the default mode network that characterizes depression. There was also a significant increase in connectivity between the default mode and executive networks as well as the default mode and the salience networks. The researchers hypothesized that this increase of integration among brain networks was responsible for the antidepressant effect of psilocybin, so they compared brain modulation, measured by fMRI, and BDI scores of each patient and found that they were significantly correlated at the six-month point.[10] Similarly, it has recently been shown that LSD, a hallucinogenic with a similar mechanism of action to psilocybin, is associated with a decrease in functional connectivity within the default mode network and an increase of functional connectivity between the default mode network and the executive network.[12]

3. Molecular Mechanisms of Hallucinogens

3.1 Interactions with the 5-HT$_{2A}$ Receptor

The clinical application of psilocybin as a treatment for depression is promising and has spurred investigations into how similar drugs function on a molecular level. Primarily, psilocybin and other hallucinogenic compounds function through their interactions with the 5-HT$_{2A}$ receptor. Psilocybin acts as a 5-HT$_{2A}$ receptor agonist, and the activation of this receptor can lead to hallucinogenesis in humans and experimental animals.[13] Although there are other 5-HT$_{2A}$ receptor agonists, many do not produce hallucinogenic effects (non-hallucinogenic compounds) indicating that hallucinogenic effects are caused by a specific signaling pathway.[13] Both hallucinogenic and non-hallucinogenic compounds activate phospholipase C-β, but research conducted by González-Maeso et al. indicates that the hallucinogenic pathway is unique due to co-activation of heterotrimeric $G_{q/11}$ and pertussis toxin-sensitive $G_{i/o}$ proteins.[13] Furthermore, expression of *c-fos*, *egr-2*, and *egr-1* is elevated by hallucinogenic compounds while non-hallucinogenic compounds only show *c-fos* elevation, allowing *erg-2* and *erg-1* to be used as a marker unique to 5-HT$_{2A}$R hallucinogens.[14]

Using the characteristic gene responses of *c-fos* and *egr-1/2,* González-Maeso et al. investigated how this hallucinogenic pathway worked. They found that when phospholipase C-β was inhibited by U73122, a gene response was not obtained by LSD or R-Lisuride, a non-hallucinogenic closely related to LSD (Figure 3A). Similarly, inhibition of Gi/o protein with pertussis toxin and inhibition of Src attenuated the gene response to LSD (Figure 3B). This indicates the importance of specific regulation of $G_{i/o}$ protein and Src in response to hallucinogenic compounds like LSD, emphasizing their role in hallucinogenesis as a

result of partial or complete agonism of the 5-HT_{2A} receptor.

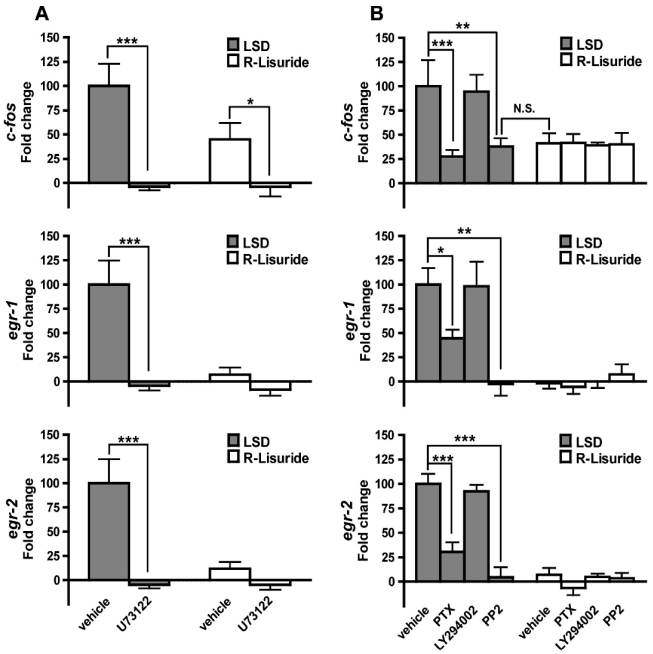

Figure 3. LSD-Specific Signaling in Primary Cortical Neurons. A) Cortical neurons treated with U73122, a PLC-β inhibitor, results in inhibition of gene expression in response to LSD. B) Gene induction pattern in response to LSD is attenuated by inhibition of $G_{i/o}$ protein with pertussis toxin and not affected by inhibition of PI-3-K with LY294002. LSD and R-lisuride are identical in the absence of Src activity via inhibition with PP2. Adapted from González-Maeso et al., 2007.[13]

Based on their research, González-Maeso et al. proposed a model that elucidates the molecular mechanism that results in the hallucinogenic response seen in psychedelics including LSD, psilocybin, and DOI. Although hallucinogenic and non-hallucinogenic compounds both interact with the 5-HT_{2A} receptor, the conformation stabilized by hallucinogens like LSD is unique and leads to a different pattern of cellular signaling. In this research, they also assessed how recovery of the 5-HT_{2A} receptor in specific neuron populations recovered the hallucinogenic response. Using *htr2A*$^{-/-}$ mice, they discovered that signaling and behavioral responses to hallucinogenic compounds were established when 5-HT_{2A} receptors were restored within the cortical neurons. They did not find that restoration in the thalamus or subcortical brain region were sufficient in re-establishing normal hallucinogenic responses, indicating that these areas are not required for hallucinogenic activity, but that the cortex is.[13] Overall, this outlines the molecular interactions with the 5-HT_{2A}R typical of hallucinogenic drugs like psilocybin, dependent on $G_{i/o}$ proteins, $G_{q/11}$ proteins, and Src.

3.2 5-HT_{2A}R and mGluR2 Complex Formation

Although 5-HT_{2A}R activation is an essential part of classical hallucinogenic function, discussion of the psychedelic mechanism would be incomplete without mentioning metabotropic glutamate receptors. These serotonergic receptors, 5-HT_{2A}R, and mGluRs are co-localized throughout the brain, specifically 5-HT_{2A}R and mGluR2.[15] Moreno et al. found that mGluR2 was essential to the hallucinogenic effects caused by 5-HT_{2A}R agonists. In this study, they injected (±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and lysergic acid diethylamide (LSD) (both of which are functionally similar to psilocybin in their hallucinogenic effects) into mGluR2 knockout (KO) mice. They found that the KO mice had a significantly reduced head twitch response (a common behavioral assay indicating hallucinogenic response upon 5-HT_{2A}R activation) in a 30 minute window compared to wild type mice as seen in Figure 4, indicating mGluR2 was necessary for hallucinogenic specific response within the mice.[16,17] In a more recent study by Benvenga et al., DOI administered to mGluR2 KO mice failed to produce a significant number of head twitches even at a dose tenfold higher than the normal, peak effective dose that produced head twitches in wild type or mGluR3 KO mice supporting Moreno's findings.[18]

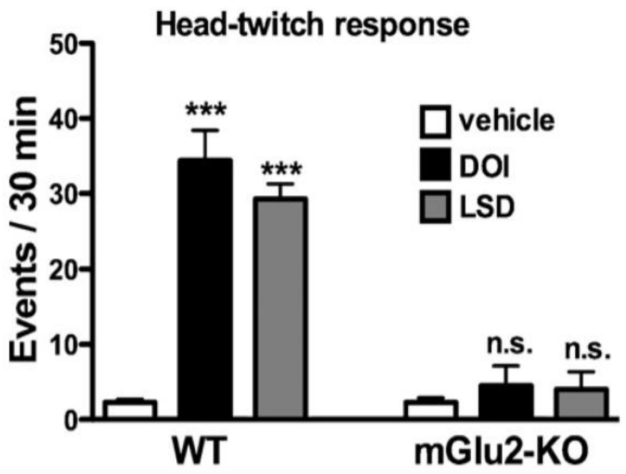

Figure 4. Behavioral response to hallucinogens DOI and LSD. Wild type and mGluR2-KO mice (n = 4–5 per treatment group) were injected with vehicle, DOI (2 mg/kg) or LSD (0.24 mg/kg), and the head-twitch response was scored 15 min after injection for 30 min. ***p < 0.001; Bonferroni's *post hoc* test of two-way ANOVA. Data are means ± S.E.M. Adapted from Moreno et al., 2011.[16]

These findings suggested that 5-HT_{2A}R relies on mGluR2 for its downstream effects upon activation. Per multiple co-immunoprecipitation based studies, it has been found that the two receptors form a heterocomplex.[19] More specifically, phosphorylation at serine 843, an event dependent on 5-HT_{2A}R activation, is a key modulator in mGlur2's functioning in $G_{i/o}$ and $G_{q/11}$ protein activation and subsequent signaling.[20,21]

$G_{q/11}$ activation leads to phosphatidylinositol 4,5-biphosphate hydrolysis and calcium release that promotes excitatory transmitter release. For example, extracellular glutamate levels in the somatosensory cortex of rats increases upon intracortical administration of DOI without any effect on GABA or glycine levels, thus increasing excitatory neurotransmission and activating NMDA receptors and AMPA receptors downstream (Figure 5).[22] However, this activation is not only linked to hallucinogenic "behavioral" effects (such as head twitching in rats and mice), but also, as mentioned earlier, to the release of the transcription factor *c-fos* and brain-derived neurotrophic factor (BDNF).[16,23] $G_{i/o}$'s activation is linked to increased *egr-2* expression, a transcription regulatory factor highly expressed in migrating neural crest cells, and is essential for normal differentiation and maintenance of myelinating Schwann cells, which have been found to remyelinate in the CNS under certain conditions.[24,25] The increased expression upon heterocomplex formation may be what underlies the increased synaptogenesis seen upon psilocybin administration in rats.

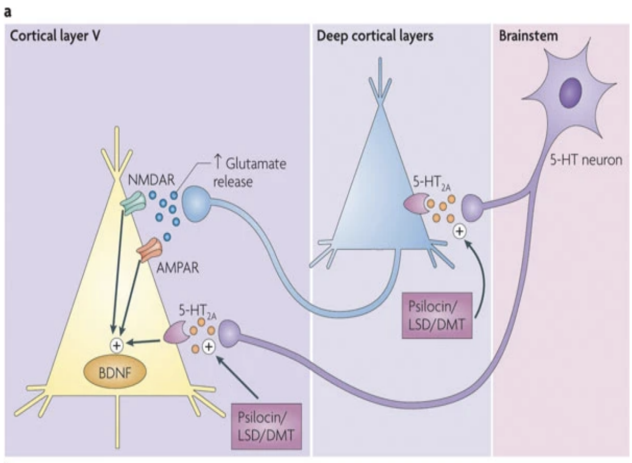

Figure 5. The figure shows a model in which hallucinogens, such as psilocin, lysergic acid diethylamide (LSD) and dimethyltryptamine (DMT), increase extracellular glutamate levels in the prefrontal cortex through stimulation of postsynaptic 5-HT_{2A} receptors that are located on large glutamatergic pyramidal cells in deep cortical layers (V and VI) projecting to layer V pyramidal neurons. This glutamate release leads to an activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (*N*-methyl-D-aspartate) receptors on cortical pyramidal neurons. In addition, hallucinogens directly activate 5-HT_{2A} receptors located on cortical pyramidal neurons. This activation is thought to ultimately lead to increased expression of BDNF. Adapted from Vollenweider et al., 2010.[26]

4. Synaptogenesis and Psilocybin

4.1 Synaptogenesis in the Pre-Frontal Cortex upon Psilocybin Administration

Depression is associated with synaptic atrophy of the pre-frontal cortex; however, psilocybin may provide a fix to such atrophy.[27] Shao et al. investigated how a single dose of psilocybin can lead to rapid and persistent growth of dendritic spines in the frontal cortex of mice (Cg1/M2), possibly reversing the synaptic atrophy associated with depression.[28] Dendritic spines are small protrusions from neuronal dendrites that receive input from an axon at the synapse. They are the primary site of glutamatergic and excitatory neurotransmission in the brain and serve to maximize contact between neurons.

Researchers dosed mice with 1mg/kg of psilocybin and analyzed the turnover of dendritic spines. Interestingly, dendritic spine formation increased significantly in both males and females, but the spine formation of females increased by nearly double that of males'.[28] Additionally, there was no significant change in the rate of spine elimination, suggesting a net-positive growth rate in both males and females. Due to the deficit of synapses in the pre-frontal cortex, spine formation could lead to new neural connections that may alleviate symptoms of depression. This is significant because if these results can be replicated in humans, it could provide a possible molecular explanation to the alleviation of depressive symptoms commonly associated with hallucinogenics.

The highest rate of dendritic spine formation occurred a day after administration; however, spine formation increased up to 7 days after administration suggesting that psilocybin has an extended ability to increase spine formation post-administration. To further investigate, researchers imaged the new spines that formed 34 days later and found approximately a third of psilocybin-provoked new spines persisted in growth (34% ± 10% for females and 37% ± 12% for males).[28] These findings are novel and significant, considering there has been no direct demonstration in the past of psilocybin-induced structural plasticity observed at the cellular level in mammalian brains.

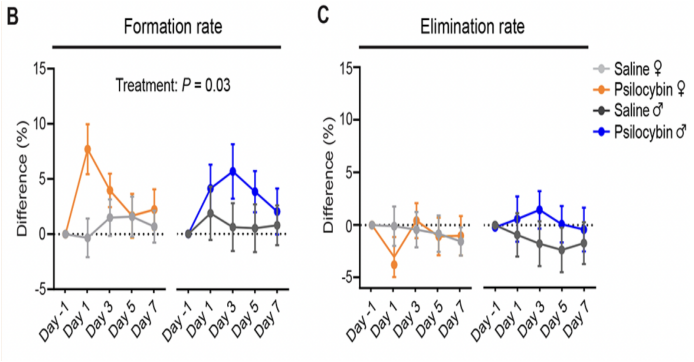

Figure 6. Dendritic Spine Formation Rate Persists For Up to 7 Days After Treatment with No Significant Net Change in Spine Elimination Rate. Mice (Cg1/M2) were dosed with 1mg/kg of psilocybin. After 7 days spine formation rate was greater in dosed mice compared to control mice. Spine formation rate was nearly double in females compared to males. Additionally, spine elimination rate did not significantly change. Adapted from Shao et al., 2021.[28]

Then, researchers attempted to replicate the above findings in a separate cohort of mice (ThyG1 mouse) and found similar results. By integrating data from these two cohorts, researchers were able to conclude that a single dose of psilocybin initiated dendritic spine growth in the medial frontal cortex of the mouse.[28]

Given that synaptic atrophy is associated with depression, these results have potential to revolutionize psilocybin's use as an antidepressant. However, many questions remain before psilocybin can become an approved treatment for depression. For example, female mice experienced a much higher spine formation than male mice in this experiment. Perhaps biological sex plays a role in the effectiveness of psilocybin on spine formation. Research on human models is essential to further understanding of how psilocybin affects depression at the molecular level and its potential effects as a depression treatment.

4.2 Hypothesis to Synaptogenesis Caused by Psilocybin

As previously mentioned, major depressive disorder has been linked to synaptogenesis disruption including loss of neurotrophic factor support.[29] Antidepressants have shown to increase synaptogenesis and plasticity; however, the underlying mechanisms by which this occurs has not been investigated, likely because it is a combination of complex and interconnected mechanisms. Psilocybin's analogous effect to antidepressants provides a new avenue to investigate the mechanisms that underlie synaptogenesis and plasticity upon serotonin receptor activation.

One such factor that may be involved is *egr-2*, specifically in its relation to hallucinogen generated synaptogenesis and plasticity. Moreno et. al. showed that mGluR2 KO mice did not express *egr-2*, indicating that this transcription factor relies on mGluR2 complex formation.[16] Very little research has been done on *egr-2* as more focus has been given to its other gene family members. These family members include *egr-1* which is implicated in synaptic homeostasis and plasticity and *egr-4* which has been found to modulate BDNF induction of potassium chloride cotransporter.[30,31] However, one group found that mutations in the *egr-2* gene are associated with hereditary myelinopathies.[32] Although *egr-2* has been found to be involved in the onset of myelination, its expression and effect on disrupted or damaged synapses had not been investigated, especially in its connection with hallucinogens or depression.

Along with *egr-2* expression being increased upon mGluR2 complex activation, *c-fos* expression was also increased. An important early response gene highly expressed within the prefrontal cortex, *c-fos* has been implicated in multiple important functions. For example, *c-fos* is essential for cell proliferation and differentiation, it is an activator of phospholipid synthesis during events that require biogenesis, and it modulates BDNF. In rats, *c-fos* and BDNF expression was found to be upregulated when administered antidepressants.

No one has investigated BDNF's expression upon mGluR2 complex activation despite the fact BDNF has been shown to encourage development and growth of new and existing neurons.[33] BDNF potently binds to TrkB, creating a BDNF-TrkB signaling pathway. The TrkB gene contains at least three different receptor subtypes: TK+, T1, and T2.[34] TrkB-T1 overexpression induces has been shown to promote elongation and an increase in the branch number of distal dendrites of cortical pyramidal neurons in slices.[35] Moreover, research has implicated the BDNF-TrkB pathway as playing a role in cell migration, outgrowth of neurites, synaptogenesis, cell survival and death, neuronal transmission, and synaptic plasticity in the CNS.[36] Referring back to Shao et al., (see under "synaptogenesis in the PFC") researchers observed "rapid and persistent growth" of dendritic spines in the frontal cortex of mice.[28] Shao et al. reported these observations but did not propose a molecular mechanism as to why this occurs. Upon further examination of new research and the results from Shao et al., it seems to be possible that the rapid and persistent growth of dendritic spines, as seen in Shao et al., could be caused by a complicated molecular pathway involving 5-HT_{2A}R-mGluR2 complex formation, *c-fos* and BDNF upregulation upon activation of this complex, and a BDNF-TrkB signaling pathway.

5. Conclusion and Thoughts for the Future

Psilocybin and other psychedelics are increasingly being explored for therapeutic purposes. Initial experiments show promising results for psilocybin in treating clinical depression, particularly treatment-resistant depression. Psychedelic applications could revolutionize depression treatments as experiments suggest the therapeutic effects of psilocybin may be prevalent after only one or two dosages, as opposed to the daily dosages required for many antidepressants. Furthermore, many antidepressants have unwanted side effects, such as drowsiness, that psychedelic therapy could avoid.

Psilocybin acts on the 5-HT_{2A}R. Hallucinogens stabilize a specific response at this receptor that results in a hallucinogenic specific response. Also vital to the molecular mechanism of psilocybin is the formation of a 5-HT_{2A}R and mGluR2 complex. Specifically, glutamate release activates downstream receptors, which in turn release transcription factor *c-fos* and BDNF. Furthermore, BDNF binds to Trk, resulting in the BDNF-TrkB signaling pathway which has a role in processes including synaptogenesis and synaptic plasticity.

Psilocybin has also been shown to increase synaptogenesis in the prefrontal cortex. This finding is particularly significant as synaptic atrophy in the prefrontal cortex is associated with depression. More experiments should be conducted to determine the precise connection between these findings, including how egr-2 may play a role, but existing research supports psilocybin's potential as an antidepressant.

Combining the research indicating the upregulation of *c-fos, egr-2*, and BDNF as a result of 5-HT_{2A}R activation by psilocybin and the synaptogenesis seen in the prefrontal cortex, we put forth a hypothesis to explain how these results may work in conjunction with each other. The upregulation of *c-fos, egr-2*, and BDNF (connecting with the BDNF-TrkB signaling pathway) may be the molecular mechanism underlying synaptogenesis. One way to elucidate this mechanism would be to administer psilocin and track *c-fos, egr-2* and BDNF's expression throughout the brain. A few questions appear from this line of investigation: Does expression of these growth and plasticity related factors appear more in the prefrontal cortex? Does this expression coincide with synaptic growth and Schwann Cell migration? How might these factors and growth be related to mGluR2 complex formation? Exploring questions like these are on the forefront of the emerging field of psychedelic medicine. In the future, psilocybin and other psychedelics like LSD and DOI may play a vital role in the treatment of depression, impacting the lives of many and spurring research into new therapeutic applications.

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