Studies into Psilocybin: The Potential of Hallucinogens for Depression

Reported by Vanessa Reyes Lopez December 2nd, 2024.

Introduction

Depression affects 28 million adults in the United States and only half of adults receive treatment.[1,2] Depression is caused by the imbalance or lack of important neurotransmitters, like serotonin, dopamine, glutamate, and noradrenaline in the brain.[3] Current antidepressants aim to help intake more neurotransmitters in different modes of action. Yet, antidepressants struggle to help people as half of adults do not respond to current antidepressants and build resistance.[4] A potential solution is the usage of Psilocybin, a tryptamine serotonergic psychoactive natural product. Psilocin, the active form of Psilocybin, acts as a agonist for serotonin receptor and shows improvement and decrease in severity of depression of subjects as early as one dose.[5] There has been renewed interest in psilocybin for alternative antidepressant and therapy due to its low toxicity and low risk for addiction, but also for its fast-acting effects. This seminar will highlight the main findings of the potential of Psilocybin for depression.

Clinical trials in comparison to Escitalopram

In phase 2 clinical trials, Psilocybin showed to have a profound antidepressant effect along with positive change in the brain network integration.[6] All patients started with taking a Beck Depression Inventory (BDI) to measure severity of depression and fMRI to analyze brain flow before and after taking Psilocybin or Escitalopram, a selective-serotonin reuptake inhibitor (SSRIs) antidepressant. Through fMRI, brain modularity is calculated and used to track how depression affects the neural networks and was hypothesize that a decrease in brain modularity will relate to decrease depression severity.[7] In the Escitalopram trial group, there was a decrease in depression, however there was no change in the brain modularity 6-week post-treatment analysis. Psilocybin demonstrates that it has antidepressant effects and can help brain connectivity when compared to Escitalopram.

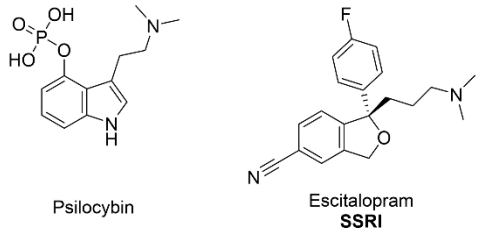

Figure 1. Structures of Psilocybin (left) and Escitalopram (right)

Structure-Activity Relationship

It has been previously reported that stimulation at the serotonin receptor 5-HT_{2A} is responsible for psychedelic effects.[8] Yet, there is a curiosity surrounding the importance of the substituents of the indole ring and the degree of N-methylation, and especially if that affects the interaction with other serotonin receptors.[9] Through radioligand binding assay, varying the substituents and degree of N-methylations does have significance for human and mice receptors binding. The head-twitch response (HTR) is the standard assay to detect psychedelic effect in mice if serotonin 5-HT_{2A} receptors is activated, and it showed that only tertiary amines produce an increase of head twitch response.[10] Quaternary ammonium substituents do not have an affinity for the serotonin receptors nor exhibit any psychedelic effect. Secondary amines do have a mild affinity, yet weakly showcased psychedelic effect.

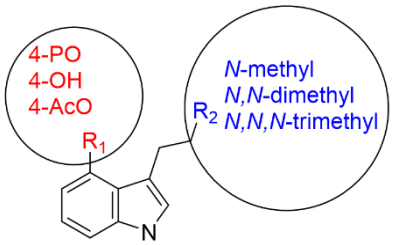

Figure 2. Structure of Psilocybin Analogs

Road to non-hallucinogenic derivatives

Despite Psilocybin having an exciting potential for depression, the long psychedelic effect limits its application for a greater population. At this current stage, psilocybin research is focused on finding the exact mode of action, but there are few looking into either minimizing or abolishing the hallucinogenic experience. One way to answer this issue is to alter the pharmacokinetics of psilocin by creating a structurally different prodrug that will still metabolize to psilocin.[11] Using subcellular fraction from human liver and intestinal tissue, most synthesized novel prodrugs (NPDs) were able to metabolize to the active form of psilocin and interestingly had different half-life. The derivative side chains that work best tend to be aromatic and aliphatic, and those that had a modified indole-NH generated no psilocin. Measuring psilocin in plasma also showed that different NPD derivatives stayed in plasma less than psilocybin metabolized psilocin. The structures of prodrugs ESO1 and TO1 demonstrated to produce similar amounts of psilocin and shorten psilocin exposure when compared to psilocybin, and whole high potential for future investigation as an alternative to psilocybin.

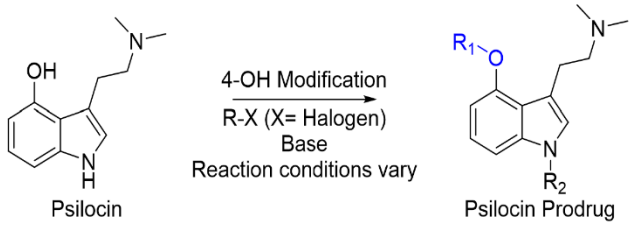

Figure 3. General scheme for 4-OH modified NPDs

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