Mechanisms of Antidepressant Action of Psilocybin: Role of 5-HT2B-5-HT1A Receptor Dimerization and GSK-3β Activation in an Animal Model of Treatment-Resistant Depression

Psychedelics, and psilocybin in particular, have been under intense investigation as potential antidepressants, with some reports indicating that they could be both fast-acting and effective in cases where treatments with currently available drugs fail. Despite multiple reports corroborating their potential, their use remains limited only to early-stage clinical trials, as strong concerns remain about whether the potential benefits outweigh the risks associated with their psychomimetic effects.

Recent reports show that the psychomimetic and antidepressant effects may involve independent and separate mechanisms. In particular, it was shown that antagonists of serotonin 5-HT2A receptors block the psychomimetic effects of psilocybin while the antidepressant actions remain intact. Thus, hypothetically it is possible to develop a treatment with a novel, selective drug or a combination of drugs that would mimic the antidepressant action of psilocybin while avoiding the psychomimetic effects. The issue, however, is that the mechanism of psilocybin's antidepressant effects, is unknown and currently highly debated.

Our concept assumes **that the antidepressant effect of psilocybin in treatment-resistant depression is due to increased activity of the 5-HT1A receptor through its direct interaction (dimerization) with the 5-HT2B receptor.** We hypothesize that the 5-HT2B and 5-HT1A receptors form dimers, and upon binding psilocybin, the complex is stabilized on the cell membrane, preventing 5-HT1A internalization and increasing its availability to serotonin. This mechanism somewhat resembles the action of some tricyclic antidepressants, and moreover, the impact on 5-HT1A internalization could potentially explain the faster onset of antidepressant effects. Increased 5-HT1A activity may influence phosphorylation at Ser9 and block the activity of glycogen synthase kinase-3β (GSK-3β). Since GSK-3β inhibition is associated with improved neurotransmitter function, promotion of neuroplasticity, and neuron survival, this could be one of the key and universal final antidepressant effects for all drugs.

There is data indicating the existence of 5-HT2B-5-HT1A dimers; therefore, we plan to confirm their presence in the brain *in vivo* and demonstrate that this mechanism is necessary for the antidepressant effects of psilocybin in a model of treatment-resistant depression in Wistar Kyoto (WKY) rats.

Understanding the antidepressant action of psilocybin in treatment-resistant depression could pave the way for new drug targets and therapeutic approaches. Furthermore, this study will expand our knowledge of the pathophysiology of depression, particularly in the context of treatment resistance depression.