SEROTONERGIC PSYCHOPLASTOGEN MICRO-DOSING: A NOVEL APPROACH TO TREATMENT RESISTANT DEPRESSION AND POST-TRAUMATIC STRESS DISORDER

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This paper will discuss serotonin (5-hydroxytryptamine, 5-HT), the location of 5-hydroxytryptamine 2A receptors (5-HT2ARs), and the applicability of lipophilic drug profiles to serotonergic signaling cascades. The author will explain how findings of Vargas et al. (2023) suggest serotonergic psychoplastogens lysergic acid diethylamide (LSD), N, N-dimethyltryptamine (DMT), and psilocybin as possible future psychopharmaceutical agents for treatment resistant depression (TRD) and post-traumatic stress disorder (PTSD).

Background

5-HT2AR Binding, Cellular Location, and Substrates

5-HT2ARs are found throughout the body, particularly in the brain and intestines. They are concentrated in brain regions responsible for mood and cognition (amygdala, anterior and posterior cingulate cortices, hippocampus, and prefrontal cortex; Guimaraes dos Santos et al. 2021). 5-HT2ARs bind to serotonin on post-synaptic neurons. When 5-HT is released by a pre-synaptic neuron into the synapse, the post-synaptic neuron 5-HT2AR is triggered, causing a cascade of monoamine release (Stahl, Grady, & Muntner, 2021). Elsewhere in the body, 5-HT is responsible for controlling gut motility. Imbalances in 5-HT levels can increase inflammation and make a person more sensitive to visceral pain.

5-HT2ARs are transmembrane proteins normally located in the dendrites of the neurons. Though 5-HT is critically important to human functioning, its chances of being produced by a neuron is 1:1M, as it is manufactured in a special collection of neurons in the brain called the raphe nuclei (Boland & Verduin, 2022).

5-HT is derived from tryptophan, an essential amino acid acquired through foods such as kidney beans, nuts, and animal proteins (Friedman, 2018). Tryptophan is transported into a serotonergic neuron, where it is then converted by tryptophan hydroxylase (TRY-OH) to 5-hydroxytyptophan (5-HTP). Next, aromatic amino acid decarboxylase (AAADC) converts 5-HTP to 5-HT. The cell's synaptic vesicular transport system (VMAT2) captures 5-HT and stores it until ready for use (Stahl, Grady, & Muntner, 2021).

Serotonergic Psychoplastogens: LSD, DMT, and Psilocybin

Serotonergic psychoplastogens arise from both nature and chemical science and primarily bind to the 5-HT2A receptor. LSD is a globally distributed, semisynthetic substance derived from a rye fungus that yields lysergic acid. It is taken orally and binds to the 5-HT2AR. N, N-Dimethyltryptamine (DMT) is a synthetic substance with roots in the leaves of *Virola calophylla* from South America. It is used as snuff or injected intravenously and binds to both 5-HT2A and 5-HT2C receptors. Psilocybin is a natural product derived from psilocybin mushrooms in the southern United States, Mexico, and areas of South America. It is ingested orally and binds to 5-HT2A, 5-HT2C, 5-HT1A, and 5-HT1B receptors. (Boland & Verduin, 2022).

When 5-HT2ARs are activated in the ACC and PFC, c-fos and BDNF expression are stimulated (Guimaraes dos Santos et al. 2021). When c-fos is activated as a response to a stimulus, it leads to cell proliferation and differentiation (Velazquez et al. 2015).

Neuroplasticity Definition and Clinical Applications of Serotonergic Psychoplastogens

Neuroplasticity can be defined as the brain's ability to develop over time and to adapt to experiences (Puderbaugh & Emmady, 2023). It is responsible for learning and developing. However, behavior and thought patterns learned through dysfunctional cognitive cycling or trauma can be detrimental to a person's functioning and sense of wellbeing.

If researchers found that LSD, DMT, and psilocybin alter neuroplasticity, it could lead to micro dosing for treatment-resistant depression and post-traumatic stress disorder, along the lines of nasal esketamine.

Tryptophan Derivatives and Neuroplasticity

5-HT2AR Location Bias and 5-HT Functioning

Reduced complexity and fewer neural synapses may contribute to the brain dysregulation found in people with mental illnesses, such as depression. Vargas et al. (2023) proposed location bias as a possible etiological factor. 5-HT, unlike serotonergic psychoplastogens, does not readily enter cells. The researchers used chemical design and genetic manipulation to test the hypothesis that activation of a specific population of 5-HT2ARs inside neurons is necessary for 5-HT2AR ligands to induce changes in brain structure and produce antidepressant effects.

Vargas et al. (2023) found a positive correlation between lipophilicity and 5-HT, and 5-methoxytryptamine, and tryptamine's ability to promote neurogenesis. They hypothesized an intracellular pool of 5-HT2ARs might be responsible for some compounds' enhanced ability to promote neuroplasticity. They suggest 5-HT2AR is primarily located within organelles, such as the Golgi apparatus. This intracellular location of 5-HT2AR is important not only as a necessary component of neuroplastic and antidepressant processes, but because it also suggests an intracellular signaling role in 5-HT2AR function.

The idea of an intracellular 5-HT2AR pool increases the importance of membrane permeability in the ability of serotonergic psychoplastogenic substances to promote neuroplasticity. These findings by Vargas et al. (2023) suggest SERT transportation of serotonin into brain cells and activation of intracellular serotonin receptors may be necessary for serotonin to promote its effects.

Membrane permeability and intracellular signaling are important factors in 5-HT and serotonergic psychoplastogenic effectiveness.

Polar and Nonpolar Tryptophan Derivatives

Vargas et al. (2023) tested different derivatives of tryptophan with varying membrane permeability to understand the role of intracellular signaling in inducing cortical structural plasticity. 5-HT is unable to enter cells via passive diffusion because it is polar and only small, hydrophobic compounds diffuse through the phospholipid bilayer. This may explain the difference in cellular signaling between 5-HT and serotonergic psychoplastogens, as serotonergic psychoplastogens are able to utilize diffusion. This afforded the researchers an understanding as to why intracellular serotonergic psychoplastogens create sustained signaling and promote cortical structural plasticity that produces rapid therapeutic behavioral responses, while other compounds cannot.

Vargas et al. (2023) developed membrane-impermeable versions of serotonergic psychoplastogens and found they could only promote cell growth when applied together with electroporation, suggesting the compounds' inability to pass through cell membranes limited their effectiveness. They solidified this idea by testing both membrane-permeable and impermeable antagonists to determine where the serotonergic psychoplastogens were active within the cells.

Neuronal Growth, Dendritogenesis, and Spinogenesis

Compounds that increase dendritic crossings and spines include DMT, ketamine, 5-HT, 5-methoxytryptamine, tryptamine, and related compounds with different levels of methylation. Vargas et al. (2023) found increasing the methylation of the compounds led to a greater ability to promote the growth of brain cells, such that compounds with N,N-dimethyl groups showed the

strongest effect. Vargas et al. (2023) observed DMT could increase dendritogenesis and spinogenesis in both SERT-positive and SERT-negative neurons. However, a chemically modified, membrane-impermeable version of DMT was unable to exert effects, despite maintaining affinity for 5-H2AR. 5-HT was able to promote neuron growth only in SERT-positive neurons, suggesting that the import of 5-HT into the cell was necessary for its effects.

Antidepressant Effects

Serotonergic psychoplastogens should influence depressive symptoms. To test whether the antidepressant-like response of 5-HT and serotonergic psychoplastogens might be linked to neuroplasticity, Vargas et al. (2023), injected an adeno-associated virus attached to SERT into rodents and waited three weeks. The researchers observed rodents who expressed SERT were more active (decreased psychomotor retardation) after being injected with parachloroamphetamine (PCA, an amphetamine-derivative that releases 5-HT), which indicated intracellular 5-HT was a contributory factor.

5-HT2AR activation may utilize TrkB, mechanistic target of rapamycin (mTOR), and AMPA receptor signaling pathways to change the brain. Though they work on the same receptor, 5-HT and serotonergic psychoplastogens appear to work slightly differently from one another. Understanding the mechanism of action of serotonergic psychoplastogens and the importance of intracellular signaling of 5-HT2ARs in inducing cortical structural plasticity will help guide future research into antidepressant medications.

Both legal and illegal drugs, including serotonergic psychoplastogens and esketamine, have been identified as potential compounds that could influence depression. Based on the work of Vargas, et al. (2023), in small amounts under controlled circumstances, serotonergic psychoplastogens should have an effect on depression with a mechanism unlike antidepressants.

Traditional antidepressants like SSRIs can rescue deficits in dendritic arbor complexity and dendritic spine density, possibly through TrkB signaling. Citalopram was tested in the aforementioned experiments. The effects of serotonergic psychoplastogens are distinct from this process.

Testing in a rodent model of depression indicates effects proposed and tested by Vargas et al. (2023) demonstrate serotonergic-psychoplastogen-specific antidepressant effects and en vivo efficacy. Though their primary focus was understanding the cellular mechanisms and differences between 5-HT and serotonergic psychoplastogens in promoting cortical structural plasticity, the findings of Vargas et al. (2023) offer new frontiers in treating challenging mental health disorders like treatment-resistant depression and post-traumatic stress disorder.

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