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| **Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors** |
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| Presenter: Wei-Jie Chen | Date/Time: 2024/10/24, 16:10 -17:00 |
| Commentator: Dr. Ya-Hsin Hsiao | Location: Room 601, Med College Building |

**Background:**

Decreased dendritic spine density in the cortex is a hallmark of several neuropsychiatric diseases, and the ability to promote cortical neuron growth has been hypothesized to underlie the rapid and sustained therapeutic effects of psychedelics. Activation of 5-hydroxytryptamine (serotonin) 2A receptors (5-HT2ARs) is essential for psychedelic-induced cortical plasticity, but it is currently unclear why some 5-HT2AR agonists promote neuroplasticity, whereas others do not.

**Objective:**

Previous research indicated that serotonin and psychedelics can both activate 5-HT2AR, but only specific psychedelics can promote neuroplasticity. Unlike psychedelics, the physicochemical properties of serotonin prevent it from entering cells by passively diffusing across nonpolar membranes. Therefore, the authors aimed to determine whether the differences in 5-HT2AR cell signaling could be attributed to location bias.

**Results:**

After administering various serotonin structural analogs and psychedelics to mice, the data showed that increased methylation corresponded with a more significant neuroplasticity effect, confirming the relationship between the drug's lipophilicity and its ability to enhance neural plasticity. The G protein-coupled receptor β2AR is known to be expressed on the cell membrane. To explore its correlation and colocalization with 5-HT2AR, the authors overexpressed both receptors in primary neurons and HEK293T cells, finding a weaker correlation between them in primary neurons. However, there was a high colocalization, indicating that a portion of 5-HT2AR is expressed intracellularly. Furthermore, electroporation or direct activation of intracellular 5-HT2AR via serotonin transporter (SERT) with serotonin can induce neuroplasticity. In a mouse model with SERT overexpression, stimulation of endogenous 5-HT release by para-chloroamphetamine hydrochloride promoted neuroplasticity and exhibited antidepressant effects in novelty-induced locomotion and forced swim tests.

**Conclusion:**

This study demonstrates that psychedelics promote neuroplasticity through the activation of intracellular 5-HT2AR, which in turn generates antidepressant effects.