Mechanism behind reductions in depression symptoms from LSD and mushrooms found

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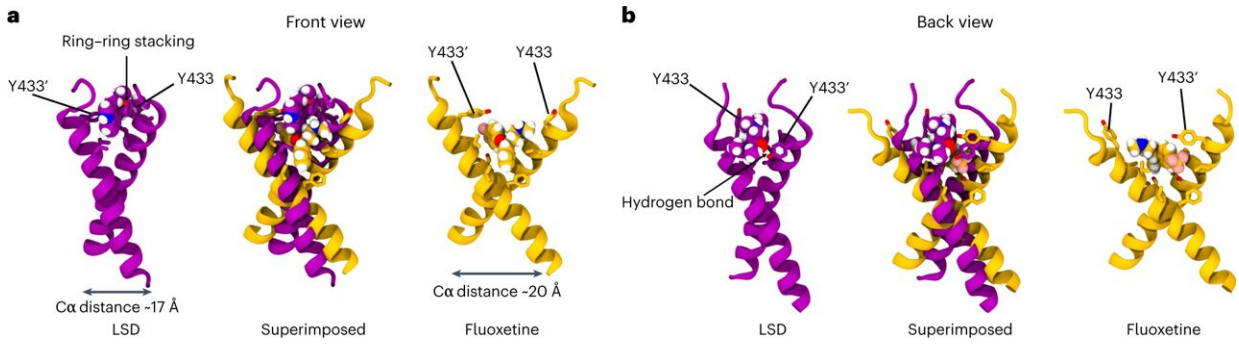

Different TrkB binding modes of LSD and fluoxetine. a,b, Representative snapshots of atomistic MD simulations showing the front (a) and back (b) views of the binding pockets for LSD (purple) and fluoxetine (yellow) in the extracellular-facing crevice of TrkB TMD dimers. Side chains of relevant binding site residues are displayed. Superimposed structures of TrkB optimally bound to LSD or fluoxetine reveal that, while some residues involved in binding are shared (Y433 and V437), the binding modes are different. Fluoxetine binds at a site deeper within the dimer, locking the TMD dimers in a more open cross-shaped conformation (distance between the center of mass L451–L453 Cα atoms of each monomer ~20 Å). In contrast, LSD binds closer to the N-terminus of the TrkB TMD and establishes more stable interactions with the dimer: a hydrogen bond between the oxygen atom of the diethylamide group of LSD and the Y433 residue of one monomer, and pi-stacking of the aromatic backbone of the drug with the Y433 residue of the second monomer, locking the TMD dimer in a tighter cross-shaped conformation (L451–L453 Cα distance ~17 Å) compared with fluoxetine. Drugs are shown in van der Waals representation. Oxygen, nitrogen and hydrogen atoms are shown in red, blue and white, respectively. Credit: *Nature Neuroscience* (2023). DOI:

10.1038/s41593-023-01316-5

An international team of biotechnologists and neuroscientists has found the mechanism responsible for reducing depression symptoms in patients given two kinds of hallucinogenic compounds. In their mouse study, reported in the journal *Nature Neuroscience*, the group isolated binding receptors involved in the types of neural plasticity associated with improvements in depression symptoms. The editors at *Nature Neuroscience* have published a Research Briefing in the same journal issue outlining the work done by the team on this new effort.

For several years, mental health specialists have known that psychedelic drugs like magic mushrooms and LSD can reduce symptoms in patients with chronic depression. But until now, it was not known how such compounds function. While most in the field suspected it was a chemical present in both kinds of compounds, others insisted it was the hallucinogenic trips associated with such drugs that brought relief. The researchers with this new effort have found that it is the former.

The research team added psilocin or LSD to cells in a petri dish in their lab and then looked at what occurred under a microscope. More specifically, they watched the interactions between chemicals in the compounds and receptor cells to see which might bind. After a trial-and-error process, they finally discovered that some of the chemicals were binding to the receptor TrkB—the same receptor targeted by drugs developed to treat depression—only they were creating bonds that were 1,000 times stronger. They also found that the result of such strong bonding was an increase in neuroplastic activity—the mechanism believed to be responsible for the reduction of depression symptoms.

Intrigued by their findings, the researchers gave doses of LSD or psilocin

to mice driven to depression by exposure to stressful situations. They then dissected their brains and found the same type of binding they had observed in the petri dishes. They also found that the antidepressant effects from the binding were independent of the effects of chemicals in the drugs that altered serotonin receptors, which are responsible for inducing psychedelic experiences and hallucinations. And that means that the team may have found a way to treat patients without inducing such experiences.

More information: Rafael Moliner et al, Psychedelics promote plasticity by directly binding to BDNF receptor TrkB, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01316-5

Research Briefing: Psychedelics bind to TrkB to induce neuroplasticity and antidepressant-like effects, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01317-4