Scientists create 'non-psychedelic' compound with same anti-depressant effect

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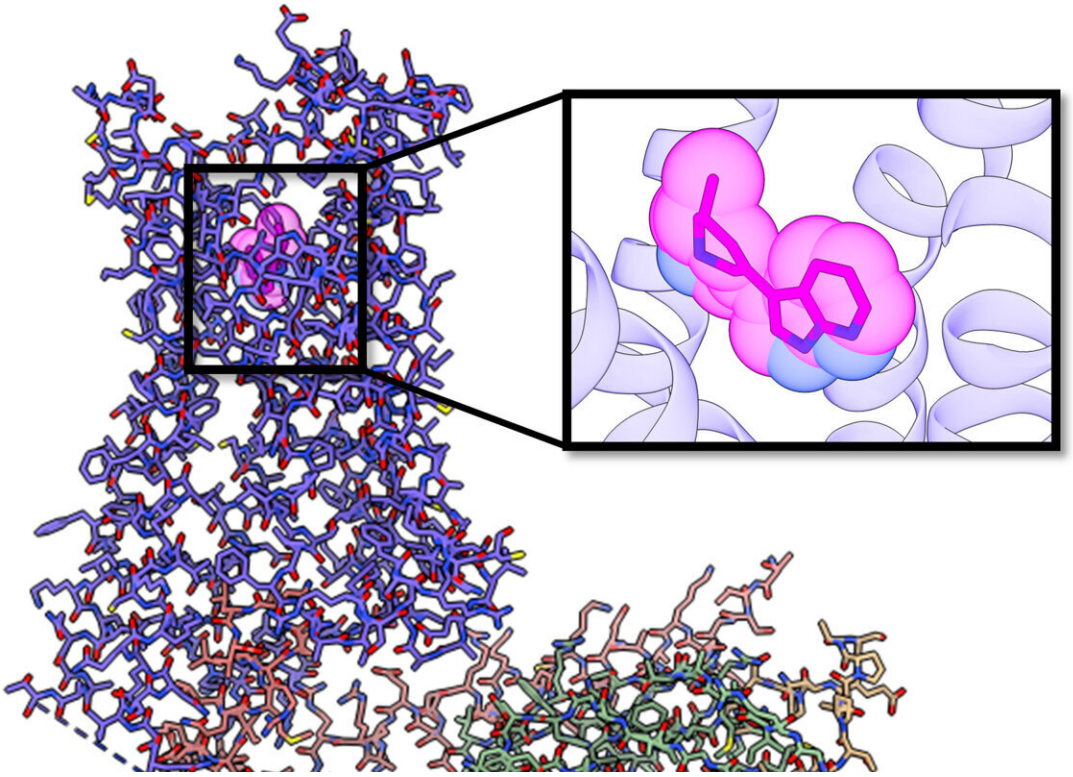

Representation of the serotonin 2A Receptor (5HT2AR) signaling protein complex bound with the novel compound R-69 (in subset, magenta). Credit: Roth Lab, UNC School of Medicine

While illegal for recreational use, psychedelic drugs are showing great promise as treatments for severe depression and anxiety, as well as

alcohol addiction and other conditions. Some advocates and scientists believe the actual psychedelic trip—hallucinations and profound emotional experiences—is what leads to long-lasting therapeutic effects. Other scientists speculate that if the "trip" could be eliminated from such drugs, then only the therapeutic effects might remain. Researchers at UNC-Chapel Hill, UC San Francisco, Yale, Duke, and Stanford have taken a major step toward answering that question.

Published in *Nature*, this research in animal models show it's possible to create a compound that hits the same exact target as psychedelic drugs hit—the 5-HT2A serotonin receptors on the surface of specific neurons—but does not cause the same psychedelic effects when given to mice. The new compound triggers the same anti-depressant action that researchers have long observed in mice treated with SSRI drugs over the past two decades, with just two differences: the anti-depressant action of the new compound was immediate and long-lasting after just one dose.

"We were very surprised the compound had any anti-depressant activity similar to ketamine and psilocybin, both rapidly acting antidepressant psychedelic drugs," said co-senior author Bryan L. Roth, MD, Ph.D., the Michael Hooker Distinguished Professor of Pharmacology at the UNC School of Medicine and director of the NIMH Psychoactive Drug Screening Program. "We were basically running a chemistry experiment to see if we could create a compound to activate 5-HT2A. Once we achieved that, we decided to run experiments in mice."

The compound is patented by Yale, UNC-Chapel Hill, and UCSF and licensed to Onsero, a company created to fine-tune experimental compounds before they can be further tested in clinical trials.

"We don't know if we'll see the same effects in people," Roth said. "But we hope to find out. It would be a game changer to create a one-dose, long-acting therapy to help people with treatment-resistant depression

and other conditions."

The case for psychedelics

When someone eats a magic mushroom, the active ingredient pscilocin—which is derived from psilocybin—binds tightly to the 5-HT2A serotonin receptors on the surface of neurons. The receptor is activated for a long time, triggering a cascade of chemical signals inside cells. These cells then communicate to other cells throughout the brain, sending the person on a long, strange hallucinogenic trip for hours. For those who are treatment-resistant, psychedelic drugs can immediately alleviate depression, and the effect lasts for many months.

Ketamine, used medically as an anesthetic, also has become a tool against severe depression. In 2019, the FDA approved a prescription version of ketamine called esketamine (Spravato), administered through a nasal spray. Use of this drug requires supervision of a medical professional and is expensive. Ayahuasca—a brew that includes two psychoactive plants—also shows anti-depressant effects in uncontrolled clinical studies. It's illegal in the United States, as is one of its active ingredients—N, N-Dimethyltryptamine, also known as DMT.

Roth said it would be difficult to scale up these drugs to help the millions of people in need as these drugs and others can drastically change brain chemistry, to say the least, and, like LSD, carry risks. An individual's experience can be harrowing, despite coming out the other side feeling "cured" of depression, severe anxiety, or addiction.

A class of anti-depressant drugs called selective serotonin reuptake inhibitors (SSRIs) modulate serotonin signaling indirectly and not in the same way as psychedelic drugs do. SSRIs also enhance serotonin levels in cells throughout the body, which is likely one reason why these drugs can cause a wide swath of unpleasant side effects. Although SSRIs lead

to the immediate increase in serotonin in the brain, people who take these drugs do not typically report feeling the anti-depressant until weeks later.

"So, there's more going on than simply raising serotonin levels to treat depression," said Roth, who spent two decades seeing psychiatric patients. "SSRIs cause changes in the brain that lead to anti-depressive action. We don't know what's going on, exactly. But I know many people who have had their lives transformed by SSRIs and psychotherapy."

The idea, then, is simple: what if scientists could create a compound that selectively hits the 5-HT2A receptor but activates it in a way that alters brain chemistry to treat depression, leaving the trippy pathway alone while avoiding the side effects associated with SSRIs.

The full project took seven years, beginning when Roth's lab solved the complex chemical structure of serotonin receptors, including what they look like when a psychedelic compound is tightly bound to them. This, alone, took years.

In 2020, the Defense Advanced Research Projects Agency (DARPA) in the Department of Defense funded Roth and colleagues $26.9 million to create new medications that effectively and rapidly treat depression, anxiety, and substance abuse without major side effects. Roth secured this high-risk, high-reward project through his UNC lab's expertise, experience, and collaborations with experts in the field, including co-senior authors on the *Nature* paper Brian Shoichet, Ph.D., at the UC-San Francisco and others at Duke, Icahn School of Medicine at Mount Sinai, and Stanford.

Years of collaborative science

An expert in combinatorial chemistry, Jonathan Ellman, Ph.D., the

Eugene Higgins Professor of Chemistry and professor of pharmacology at Yale co-first author Danielle Confair, Ph.D., now a senior scientist at AstraZeneca, led work to a develop a sequence of reactions that, with different starting materials, could theoretically lead to the creation of billions of new compounds with slightly different chemical structures. For this study, Ellman and Confair focused on chemical reactions for the synthesis of tetrahydropyridines, or THPs, which occur in nature and are the basic building blocks of many compounds, including medications.

Then Shoichet and UCSF co-first author Anat Levit, Ph.D. and co-senior author John Irwin, Ph.D., used computational simulations to home in on specific THP-based virtual compounds most likely to only bind to 5-HT2A in specific ways on certain neurons, not unlike how psilocybin binds to these receptors, but just differently enough to potentially avoid the dramatic psychedelic effect.

"For us, the project began as an opportunity to expand the new virtual libraries with 75 million tricked-out molecules from the Ellman lab," Shoichet said. "It was only when we started to see the unusual signaling from the new compounds and their amazing permeability into the brain that we as a team started to think these compounds might have interesting effects in vivo."

Then Roth's UNC lab, led by co-first author Kuglae Kim, Ph.D., selected and tested several actual compounds to see how they bind to the serotonin receptors in cell cultures. This part also took years. Receptors are complex and delicate bunches of perfectly situated proteins. To be able to observe a compound's effect on them is a laborious process involving various experimental techniques, including X-ray crystallography.

With each experiment, Roth and UNC colleagues learned more nuances about the compound's relationship to 5-HT2A. Shoichet's team then used

that knowledge to tweak their computational chemical design to create yet another virtual compound that Roth's lab created in the real world.

This iterative process yielded a few compounds promising enough for Roth's lab to test in a mouse model, essentially to see if the compounds bound to 5-HT2A in an animal as it did in a lab dish.

"What we saw was completely unexpected," Roth said. "Not only did the compound bind the 5-HT2A serotonin receptor like we thought it would, but it had the same anti-depressant drug action as does ketamine but not the same hallucinogenic drug action."

While researchers can't know for sure if the mice were not depressed or hallucinating, they can study drug action—the biological effect in mice and then observe behaviors. For decades, researchers have used standard tests—forced swim test, tail suspension tests, novel suppressed feeding—when testing the action of compounds. Likewise, researchers have used standard mouse models of psychoactive drug action, models that have been validated over decades. Mice behave in specific ways, when given a hallucinogenic drug, sort of like humans behave in certain ways when tripping.

When the Duke lab of William Wetsel, Ph.D., gave mice the new compound, the research team observed the same anti-depressant drug action without the same psychoactive drug action.

"It was more than a little remarkable to us is that this compound was effective in all mouse models after a single dose, and the effect was long lasting, similar to psilocybin," Roth said. "We were lucky. And we know we're not finished."

Whether this drug or others like it can truly provide a one-dose, long-lasting anti-depressant effect for people with treatment-resistant

depression, severe anxiety, and other conditions is yet to be determined. But this research shows that it might be possible.

More information: Brian Shoichet, Bespoke library docking for 5-HT2A receptor agonists with anti-depressant activity, *Nature* (2022). DOI: 10.1038/s41586-022-05258-z

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