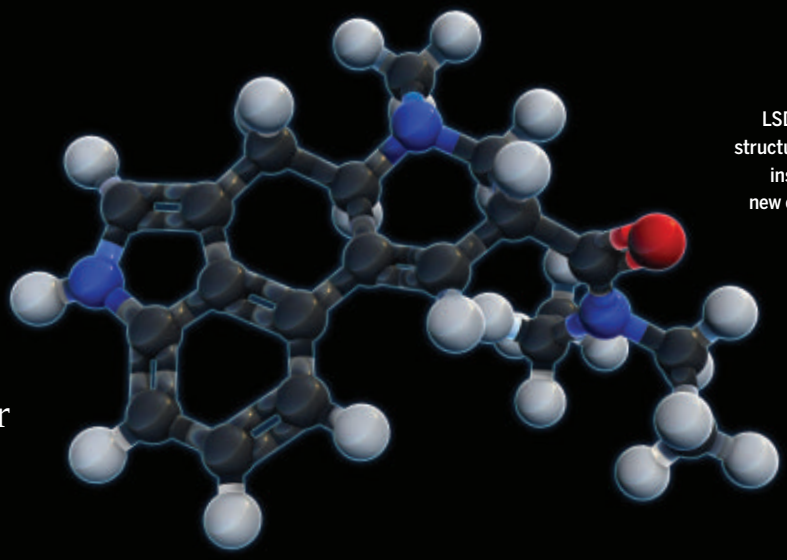
PHARMACOLOGY

Psychedelics without hallucinations?

Chemical relatives of LSD appear to treat depression in mice

By **Robert F. Service**



LSD's chemical structure provided inspiration for new compounds.

More than 50 years after the Summer of Love, psychedelics are again the rage. This time the love comes from doctors beginning to embrace psychedelics such as LSD and psilocybin to treat depression, substance abuse, and other serious mental health conditions. But because the drugs cause hallucinations, their medical use requires intensive monitoring by clinicians. That drives up treatment costs, making psychedelics impractical for widespread therapeutic use.

In recent years, researchers have begun to tweak psychedelics' chemical structures, aiming to make analogs that retain medical usefulness but don't cause hallucinations. Now, researchers report in *Science* (p. 403) they've teased apart the molecular interactions responsible for psychedelics' antidepressive effects from those that cause hallucinations. They used that knowledge to make new compounds that appear to activate brain cellular circuits that help relieve depression without triggering a closely related pathway involved in hallucinations. So far, the compounds have only been studied in mice. But if such psychedelic analogs work in humans, they could spawn new families of pharmaceuticals.

"This work is going to generate a lot of interest," says Bryan Roth, a pharmacologist at the University of North Carolina School of Medicine, whose lab is also seeking nonhallucinogenic psychedelic analogs.

The need is profound. Mental or neurological disorders are estimated to affect roughly one-quarter of U.S. adults every year, and therapies often don't work. LSD, psilocybin (the main ingredient in magic mushrooms), and other psychedelics might do better. Studies have shown a single dose of psilocybin can offer relief from depression for months at a time, and last year, a clinical trial of 3,4-methylenedioxymethamphetamine, or ecstasy, showed it can alleviate posttraumatic stress disorder (*Science*, 21 May 2021, p. 774).

How these hallucinogens exert their effects remains something of a mystery. In the brain, LSD, psilocybin, and other psychedelic compounds bind to a class of receptors for the neurotransmitter serotonin, known as 5-HT_{2A}R. The receptors, a type of cell membrane protein called a G-protein coupled receptor (GPCR), trigger two effects: They initiate a host of cellular responses, and they recruit other proteins called beta-arrestins that modulate GPCR activity.

Previous work in people showed hallucinogens strongly activate both the GPCR and beta-arrestin pathways. In 2017, Sheng Wang, then a postdoc in Roth's lab, took first steps toward showing why. He produced an x-ray crystal structure—basically an atomic-scale map—of LSD bound to a serotonin receptor closely related to 5-HT_{2A}R. It revealed that LSD nestles into a pocket within the receptor called the orthosteric binding pocket (OBP).

Now, Wang, at the Shanghai Institute of Biochemistry and Cell Biology, and his colleagues have produced six new crystal structures of compounds including LSD, psilocin (the active metabolite of psilocybin), serotonin, and lisuride, a nonhallucinogenic psychedelic analog, bound to 5-HT_{2A}R itself. Some of the compounds, they found, touched not only OBP, but a neighboring cavity known as the extended binding pocket (EBP).

To make sense of the binding patterns, the researchers turned to behavioral studies with mice injected with the different drugs. The team watched for freezing responses and head twitches, mouse behaviors strongly associated with depression and hallucination in humans, respectively. The results suggested compounds including serotonin that evoke more beta-arrestin activity and less GPCR activity were associated with antidepressive activity without hallucinations. And those compounds interacted more with the EBP than the OBP.

So, Wang and his colleagues designed structural cousins of LSD they thought would favor binding to the EBP. They then repeated the behavioral tests on mice given these compounds and found that two of them, dubbed IHCH-7079 and IHCH-7806, did not trigger head twitches but did reduce the freezing behavior, much as effective antidepressants do.

IHCH-7079 and -7806 aren't the first compounds to show potential as therapeutic nonhallucinogenic analogs of psychedelics. Lisuride, which is used to treat Parkinson's disease and migraines, was first marketed in the 1970s. But the compound interacts with many receptors in the brain besides 5-HT_{2A}R and, as a result, has side effects including nausea and low blood pressure.

In 2020, researchers led by David Olson, a chemist at the University of California, Davis, reported in *Nature* that a nonhallucinogenic analog of the psychedelic compound ibogaine called tabernanthalog showed antidepressive effects in rodents. Last year in *Cell*, Olson's team reported related nonhallucinogenic compounds that appear more potent than tabernanthalog. Delix Therapeutics, a company Olson co-founded, is working to commercialize his compounds and related nonhallucinogenic experimental drugs as treatments for depression and other conditions. Brigitte Robertson, the company's chief medical officer, says she expects it to begin its first clinical trials later this year.

If any of the new compounds work to improve mental health as effectively and as quickly as psychedelics seem to, "it would change the world of psychiatric care," she says. But even if these first compounds don't pass muster, the new structural insights into how these compounds work give medicinal chemists a road map for taking the hallucinations out of the healing. ■

IMAGE: EVAN OTO/SCIENCE SOURCE