Creating non-hallucinogenic analogs of LSD and psilocybin to treat mental illnesses

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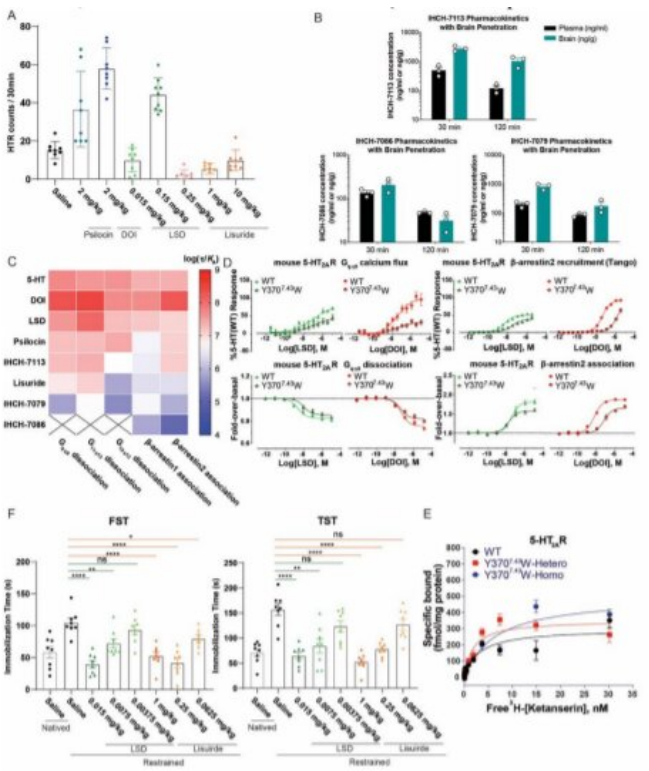

Effects of the psychedelics on animal behavior relevant to hallucination and depression. (A) Effect of LSD, lisuride, psilocin, and DOI on HTR behavior in mice (30- to 60-min time interval, Related Fig. S8A-D). (B) Metabolic rate and brain penetration of IHCH7079/7086/7113 in C57/BL6J mice (5 mg/kg intraperitoneally (ip); n = 3). (C) Heatmap illustration of transduction coefficients of psychedelics and non-hallucinogenic analogs at 5- HT_{2A}R (Related Fig. S10). (D) Mouse 5-HT_{2A}R-mediated ?-arrestin2 association and $G_{q-?9}$ dissociation activity of wild-type and $Y370^{7.43}W$ mutant with LSD and DOI. Error bars represent (n = 3). (E) Saturation curves of the specific [^{3}H]-ketanserin binding to membranes of frontal cortex from wild-type and $Y370^{7.43}W$ mutant mice (n = 3 B6D2F1 mice). The density of 5-HT_{2A}R is expressed as the asymptote value (B_{max} = 299.5 ± 34.47 for wild-type; 351.2 ± 24.94 for heterozygous; 494.1 ± 49.52 for homozygous) of the radioligand bound. The selective antagonistMDL100907 was used to exclude the non-5-HT_{2A}R binding. (F) Effects of LSD and lisuride on freezing behavior in Acute Restraint Stress (ARS)-induced “depression-like” mice. The freezing behavior of mice was tested by the forced swimming test (FST) and tail suspension test (TST). In (A) and (F), error bars represent SEM (n = 8 C57/BL6J or B6D2F1 mice), ns is not significant, *P

A combined team of researchers from the Shanghai Institute of Biochemistry and Cell Biology and ShanghaiTech University's, iHuman Institute has created non-hallucinogenic analogs of LSD and psilocybin for possible treatment of mental illnesses. In their paper published in the journal *Science*, the group describe the analogs they created and how they performed in mice.

In recent years, scientists have found that some hallucinogens, such as LSD and psilocybin, can provide relief for patients suffering from chronic depression and other mental illnesses like PTSD. And while many patients may enjoy the hallucinogenic experience, many do not. Scientists have therefore been taking a closer look at hallucinogens to find the mechanisms that provide relief to those suffering from depression—and if possible, to determine if the hallucinogenic effects of such drugs are necessary for treatment.

In this new effort, the researchers took a close look at both LSD and psilocybin using X-ray crystallography, and were able to determine their conformations when they become bound to the neural receptor 5-HT_{2A}R. They found that both molecules could bind to 5-HT_{2A}R in two ways, resulting in unique conformations. They then created compounds that would bind to 5-HT_{2A}R in the secondary type of binding they discovered.

The researchers administered the compounds to mice that were stressed to the point of depression by being hung from their tails or forced to swim for extended periods. To test whether the mice were experiencing hallucinogenic effects, they used the twitch test. Prior research has shown that when mice are given hallucinogens, their heads twitch in a unique way. And to test whether symptoms of depression eased, they observed whether the test mice engaged in activities they had stopped doing when depression set in. The researchers found no head twitching and a renewed interest in normal activities. They suggest their work represents a good starting point for the development of non-hallucinogenic analogs of common hallucinogenic drugs.

More information: Dongmei Cao et al, Structure-based discovery of nonhallucinogenic psychedelic analogs, *Science* (2022). DOI: 10.1126/science.abl8615