

Research round-up

Highlights from the psychedelics lab. By Michael Eisenstein

Identifying predictors of bad trips

The psychedelic experience can range from the sublime to the terrifying, depending on the conditions in which the drug was consumed and the individual taking it. For such drugs to become a viable therapeutic option, clinicians will need guidelines to help distinguish between people who are likely to benefit and those for whom treatment is more likely to yield discomfort than relief.

Patterns of drug response identified in past psychedelic clinical trials could be a helpful starting point, and researchers at Central Michigan University in Mount Pleasant and Ohio State University in Columbus have carried out a systematic review of previous trials. They examined 14 studies of psychedelic drugs, including psilocybin, LSD and ayahuasca, in search of factors associated with negative drug experiences.

Their analysis identified several patterns. Some were physiological: for example, neurological features associated with increased ability to respond to the mood-altering neurotransmitter serotonin were associated with a more powerful drug experience. Mental state seemed to be a particularly important predictor: people who entered the experience with an open-minded and accepting perspective were more likely to have a positive outcome than were those with feelings of apprehension or uncertainty. Older individuals and those



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Jars of chopped psilocybin mushrooms are sometimes seen in science labs, such as this one in Canada.

with a history of previous psychedelic use also tended to have a less-intense and more-positive clinical experience.

The authors caution that these findings came from a limited number of small studies with relatively homogeneous patient populations, and many lacked a control group. Nevertheless, they offer useful starting points for thinking about patient selection, and could guide both future trial design and the development of more-effective conditions for psychedelic treatment.

ACS Pharmacol. Transl. Sci. **4**, 424–435 (2021)

Depression therapy without hallucination

As the evidence accumulates that the psychedelic drug psilocybin can potentially provide potent and durable

relief for people with depression (see page S87), questions remain about whether the drug's consciousness-altering effects are essential to this recovery. Findings from researchers at the University of Maryland in Baltimore suggest that it might be possible to decouple these two aspects of the response to psilocybin treatment.

This drug's various effects in the brain are predominantly linked to its ability to activate a number of different serotonin receptors belonging to the 5-HT receptor family. One of these, the 5-HT_{2A} receptor, is especially important in the context of the drug's hallucinogenic and other perceptual effects. A selective 5-HT_{2A} receptor antagonist known as ketanserin therefore allowed the researchers to assess how psilocybin's effects in mice are altered by switching off this component of the serotonergic machinery.

Psilocybin on its own proved

effective at mitigating the depression-like characteristics normally observed in mice subjected to a stress-inducing experimental system. The drug also produces a distinctive head-twitch behaviour that is widely used as an analogue of the complex perceptual effects of psychedelics in humans.

Pretreatment with ketanserin greatly reduced head twitching, and also counteracted certain distinctive changes in the oscillatory patterns of neural-circuit activity in the hippocampus and other brain regions that are normally triggered by psilocybin. However, the mice still derived equivalent relief from the depression-associated behaviours seen in untreated control animals.

Importantly, ketanserin also did not seem to impede the psilocybin-induced formation of new synapses, which is thought to be a component

of its putative therapeutic effects. These results suggest that it might be possible to make psilocybin therapy more accessible and palatable by mitigating the broader mind-altering effects of the drug.

Proc. Natl Acad. Sci. USA **118**, e2022489118 (2021)

Do psychedelics raise mental-health risk?

The potent cognitive and perceptual effects of psychedelics have raised concerns that repeated use of these drugs might put young people at risk of developing psychotic disorders. Previous studies have yielded contradictory results, but findings from a team led by researchers at the Karolinska Institute in Stockholm reveal minimal evidence for such a connection.

The researchers point out that previous studies might have overlooked evidence of such a link because of their reliance on clinical diagnostic criteria. To remedy this blind spot, the Karolinska group instead devised an approach based on subtler, earlier manifestations of potentially abnormal cognitive characteristics.

The study began with a survey of 323 users of psychedelics and 709 non-users, who were recruited through various social-media platforms. As well as gathering demographic and drug-use data, the survey was designed to evaluate various indicators of schizotypy – cognitive traits associated with heightened risk of psychosis. The analysis revealed no significant relationship between schizotypy and the extent or frequency of using psychedelic drugs.

A direct evaluation of a subset of schizotypal traits in 39 subjects revealed only a small, marginally significant correlation of these traits with

psychedelic use. By contrast, such a correlation was readily apparent among users of stimulant drugs such as cocaine and methamphetamines.

Notably, psychedelic-drug users scored better than non-users in some metrics associated with reduced risk of schizotypy. For example, this group proved more capable of reassessing their initial interpretation of an experimental scenario when provided with new information that challenged their views. This finding could be relevant to the potential use of these drugs as a psychiatric intervention.

The researchers point out that it remains an open question whether the drugs might negatively affect the mental health of individuals who are especially prone to develop psychotic disorders owing to genetic or other factors. But they conclude that psychedelics do not seem to meaningfully heighten this risk for healthy young people.

Sci. Rep. **11**, 15058 (2021)

Epigenetic roots of long-lasting therapy

One of the more intriguing aspects of the putative therapeutic benefits of psychedelics for mental-health disorders is their longevity, because effects can persist for months after a single dose. Researchers at Virginia Commonwealth University, Virginia Tech and elsewhere have now identified some of the cellular and molecular changes in the brain that might contribute to these long-term outcomes.

The researchers gave mice a single dose of a psychedelic drug called DOI, and observed a clear reduction in behaviours associated with depression in these animals. The drug also had notable effects on synapse formation in the cerebral cortex, with increased formation of synapse-establishing dendritic

spines 24 hours after the drug was given. Importantly, this effect was not seen in genetically modified mice lacking the 5-HT_{2A} serotonin receptor, which is associated with the distinctive cognitive effects of DOI and many other psychedelic drugs.

DOI also produced robust changes in gene expression that persisted for days after the drug had been cleared from the animals' bodies. The authors did an epigenetic analysis of cortical neurons from these animals, and found many chemical modifications to the genomic DNA that can profoundly affect gene activity. They observed many DOI-associated alterations in the vicinity of gene-controlling enhancer sequences, and observed that these changes could still be detected a week after treatment. Similar epigenetic effects might underlie the long-term effect of psychedelic drugs in humans.

The data also offered a potential reason for caution. Several of the genes predicted to be affected by these epigenetic changes have established links to certain psychiatric conditions, including schizophrenia and attention-deficit hyperactivity disorder. These connections raise the question of whether people with such conditions might be at greater risk of adverse events following the use of psychedelics.

Cell Rep. **37**, 109836 (2021)

Designer drugs to treat depression

Psilocybin and LSD are among the many psychedelic drugs that exert their reality-warping effects by interacting with the 5-HT_{2A} receptor. After careful investigation of the structure of this receptor's interactions with these drugs and other molecular ligands, a multi-institutional team based in China has identified compounds that can

invoke the clinically beneficial effects of activating the 5-HT_{2A} receptor without inducing a hallucinogenic state.

Activating 5-HT_{2A} can initiate multiple downstream signalling pathways, with a variety of neurological consequences. After analysing high-resolution crystal structures of 5-HT_{2A} in complex with both psychedelic and non-psychedelic ligands, the authors focused on a specific part of the receptor called the extended binding pocket (EBP).

Serotonin, LSD and psilocybin all interact with the EBP, but subtle differences in that interaction seem to shape whether a psychedelic effect occurs. Specifically, interactions with the EBP that selectively induce strong activation of a protein called β -arrestin seem to correlate with an antidepressant but non-hallucinogenic effect. By contrast, ligands that strongly induce general receptor activation through what is known as the G-protein-mediated pathway produce the psychedelic experience typically associated with LSD or psilocybin.

The researchers used these insights to develop compounds that can achieve robust and selective activation of β -arrestin after interaction with the EBP. Two of these molecules showed promising results in animal studies, abolishing depression-associated behaviours in a mouse model with similar efficacy to LSD. But, unlike LSD, neither of the novel agents the researchers created produced a head-twitch response in treated animals – a behaviour that is widely viewed as an analogue for psychedelic effects.

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