Psychedelics for mental health: a biochemical perspective

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Psychedelics, such as psilocybin, mescaline and lysergic acid diethylamide (LSD), are psychoactive substances that induce alterations in cognition, perception and sensory processing. Studies in rodent models and healthy human volunteers highlight the serotonin 5-HT$_{2A}$ receptor's pivotal role in mediating hallucinogenic effects. More recent findings indicate that psychedelics induce lasting effects on neuroplasticity in preclinical models and are currently undergoing testing for their potential therapeutic effects on psychiatric conditions, including depression and anxiety. Critical questions persist, such as the necessity of the 'trip' for therapeutic benefits or the obstacles in establishing valid placebo groups in psychedelic studies. Despite challenges, this information supports the therapeutic potential of psychedelic compounds in addressing mental disorders. However, more direct and mechanistic based preclinical studies are required to assess the extent to which this association is causal.

Psychedelics, also known as classical hallucinogens, including psilocybin, mescaline and lysergic acid diethylamide (LSD), have been utilized for spiritual and recreational purposes throughout human history. Despite their profound impact on cognitive and perceptual processes, recent questions centre on whether psychedelics can effectively treat psychiatric conditions such as severe depression, anxiety and substance use disorders. As one example, individuals with treatment-resistant depression have shown positive responses to a single administration of psilocybin, the psychedelic compound in magic mushrooms. This therapeutic effect persists for weeks to months, raising fundamental questions about the unique mechanisms underlying psychedelics' impact on mental health.

Preclinical assays in rodent models and brain imaging techniques in healthy volunteers identified the serotonin 5-HT$_{2A}$ receptor as a key player in mediating the hallucinogenic effects of psychedelics. Preventing activation of this monoaminergic G protein-coupled receptor (GPCR), either genetically in knockout mice or pharmacologically with 5-HT$_{2A}$ receptor antagonists, diminishes the hallucinogenic properties, emphasizing its role in the pharmacological action of psychedelics. Another intriguing question pertains to the therapeutic effects of psychedelics, and this introduces the concept of neuroplasticity, which refers to the adaptive capacity of the brain to undergo structural and functional changes.

In neuroscience, plasticity is known as the capacity of neurons to change their connections and behaviour in response to new information such as sensory stimulation, development or damage. Neuroplasticity is when the brain is rewired to function in a way that is different from how it did before. Interestingly, recent observations in rodent models suggest that a single administration of psychedelics induces long-lasting effects on neuroplasticity, particularly in the frontal cortex, a brain region involved in cognition, sensory processing and mood. These plasticity changes observed upon psychedelic administration include synaptic plasticity shown as a greater magnitude of long-term potentiation which is a measure of synaptic strength, structural plasticity with an increase in frontal cortex dendritic spine density and epigenetic plasticity indicated by lasting changes in covalent histone modifications linked with rearrangements of chromatin organization. The translational validity of these preclinical findings is supported by studies that indicate therapeutically relevant lasting effects in individuals with psychiatric conditions, particularly depression upon one or two administrations of the psychedelic psilocybin in conjunction with psychological support.

While these findings are promising, critical questions remain unanswered. The first is whether the hallucinogenic effects of psychedelics are completely independent of the cell signalling mechanisms that lead to an increase in neural plasticity (Figure 1). In other words, would it be possible to identify new serotonin 5-HT$_{2A}$ receptor agonists that still promote structural and functional neural plasticity but do not induce hallucinations? Recent studies in rodent models with non-psychedelic 5-HT$_{2A}$ receptor agonists such as lisuride or 2-Br-LSD are encouraging, but this still leaves open an important question: Is the 'trip' necessary for the therapeutic benefits induced by psychedelics, or the mystical experience under the effects of psilocybin a prerequisite to decrease levels of depression, anxiety or addiction? Addressing these questions is essential

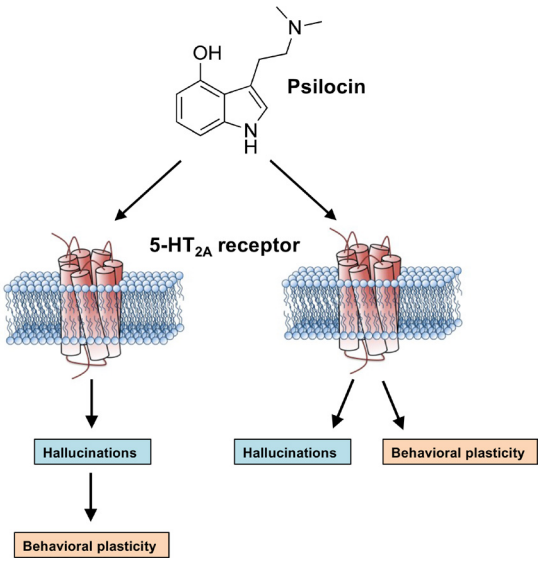

Figure 1. Psychedelics, such as psilocin (the active metabolite of psilocybin) or LSD, are well known for their hallucinogenic properties. Recent basic, translational and clinical research is beginning to indicate that these psychoactive compounds may also yield fast-acting and long-lasting benefits in individuals with severe psychiatric disorders, particularly depression. It remains unknown whether it is possible to pharmacologically separate their psychedelic properties from therapeutically relevant behavioural plasticity effects.

because psychedelics themselves are not very expensive, but to reduce the risk associated with these substances, patients need to do so in a clinic with psychological support from specially trained therapists.

Establishing control groups in psychedelic studies, where the placebo effect is challenging to maintain considering their intrinsic hallucinogenic properties, adds complexity to understanding the direct therapeutic impact of psychedelics. The absence of a valid placebo group across clinical studies examining the therapeutic impacts of psychedelics in individuals with psychiatric conditions, particularly depression, in conjunction with the influence of expectancy effects and the inclination of certain participants to undergo a psychedelic experience, introduces an unresolved complication into the effects of psychedelics by themselves on therapeutic outcomes. This important contribution of the placebo effect has been recently corroborated by studies showing that the dissociative drug ketamine delivered during surgical anaesthesia had no greater effect than placebo in reducing depressive symptoms in individuals with major depression. Do classical psychedelics such as psilocybin, dissociative drugs such as ketamine and entactogens such as MDMA behave as a 'magic bullet' targeting a wide variety of, in principle, unassociated psychiatric conditions such as depression, anxiety, tobacco and alcohol use disorder, anorexia nervosa, autism or post-traumatic stress disorder, among many others, or is there a shared neural mechanism behind these therapeutic effects?

In the field of psychiatry, there is a notable absence of requisite for advanced biochemical tools for diagnostic purposes and treatment decision-making. Unlike other medical fields, psychiatry relies on patient interviews, behavioural observations and trial-and-error approaches with medications due to the lack of objective measures like blood tests. This deficit in objective diagnostic tools underscores a significant gap in psychiatric research, raising compelling questions within the biomedical field. Particularly, the exploration of neurobiological underpinnings of psychiatric disorders remains an intriguing and unresolved avenue of investigation. Collaborative efforts across basic, preclinical, and clinical research domains offer a potential avenue to unravel the intricate biochemical and therapeutic properties of psychedelics. Despite the challenges, these inquiries hold promise for advancing mental health treatment paradigms in the coming years. ■

Further Reading

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Author information

Javier González-Maeso obtained his PhD in pharmacology at the University of the Basque Country in Bilbao, Spain. During his postdoctoral training at Mount Sinai School of Medicine in New York City, he identified a neuroreceptor involved in the behavioural effects of psychedelics such as LSD. He is currently a Professor of Physiology and Biophysics at Virginia Commonwealth University. His research is focused on understanding the structure, function and regulation of neurotransmitter receptors, with the goal of translating this knowledge into strategies to treat psychiatric disorders including schizophrenia and depression.