The neurons that mediate a psychedelic's long-term antidepressive effects

Psilocybin, a classic psychedelic, has therapeutic potential for psychiatric disorders. A specific brain circuit and receptor have now been found to be required for psilocybin's long-term effects on neural plasticity and depression-related behaviour.

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The question

Psychedelics are powerful compounds that alter perception, cognition and mood, and they have sparked intense scientific and public interest for their potential as treatments for mental-health problems. Psilocybin — the active ingredient in 'magic mushrooms' — is the psychedelic with the most promising results in clinical research, showing benefits that last for weeks in people with depression, after just one or two doses[1,2].

Despite that potential, the biological mechanisms that drive these long-lasting effects remain unclear. Our previous work revealed that a single dose of psilocybin triggers rapid and persistent remodelling of neuronal connections in the mouse brain[3]. This was an exciting result because this drug-evoked neural plasticity could hold the key to the enduring therapeutic effects[4]. But exactly how does this rewiring occur? Which specific brain circuits and protein receptors are responsible? To answer these questions, we investigated the role of different neural populations and a key receptor of the neuromodulator molecule serotonin in mediating psilocybin's effects on neural plasticity and depression-related behaviour.

The solution

We knew that psilocybin acts on excitatory neurons (those that increase activity in downstream neurons) in the medial frontal cortex of the mouse brain[4]. However, there are two main subtypes of excitatory neuron in this region: pyramidal tract (PT) neurons and intratelencephalic (IT) neurons. By using viral and genetic techniques, we selectively targeted these subtypes to examine their roles in driving behavioural changes in mice treated with psilocybin. When PT neurons (but not IT neurons) in the frontal cortex were inactivated, psilocybin still produced immediate behavioural effects but failed to reverse the long-term negative impact of stress in mice. In line with this, we found that psilocybin preferentially increases calcium signalling and firing activity in PT neurons. Therefore, PT neurons in the frontal cortex are crucial components of the brain circuit for mediating psilocybin's long-term behavioural effects.

Next, we tried to identify the receptor responsible for psilocybin's effects. It is well known that the serotonin 2A receptor drives the hallucinogenic effects of classic psychedelics in humans[5], but its role in the long-term effects of psilocybin is less clear. Through international collaboration, we genetically modified mice so that the serotonin 2A receptor could be deleted from specific brain regions and cell types. This precise approach enabled us to test the receptor's function without disrupting early brain development or affecting other receptors. We found that without the serotonin 2A receptor in the frontal cortex, psilocybin could not ameliorate the deleterious effects of stress. Furthermore, the serotonin 2A receptor was required for the psilocybin-evoked structural adaptations of PT neurons (Fig. 1). These results demonstrate that the serotonin 2A receptor, which drives the intense subjective experience, is essential for psilocybin's long-term behavioural effects in mice.

The implications

Understanding how the brain responds to psychedelics can help to optimize their use as therapeutics. Although the immediate and long-term effects of psilocybin both rely on the serotonin 2A receptor, they depend on different brain circuits. This suggests that delivering the drug specifically to particular brain regions could tap into the long-term therapeutic effects without causing the 'trip'. Moreover, finding ways to modulate the activity of PT neurons could further boost neural plasticity in response to psychedelics.

Clinical trials will be needed to confirm how the findings relate to human experiences and depression treatment. The PT neurons in the frontal cortex receive inputs from other neocortical areas and send outputs to many distant regions, some of which are also probably involved in psilocybin's long-lasting action, but their contributions still need to be explored. We are currently studying how the different inputs and outputs of PT neurons are modified by psilocybin. By gaining such biological insights, we hope to lay the groundwork for more precise and effective treatments for mental-health conditions.

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EXPERT OPINION

"This interesting report on prefrontal cell populations affected by psilocybin is wonderfully prepared, making a technically challenging study look relatively straightforward. The authors find that psilocybin substantially increases the activity of a subset of PT neurons and promotes the growth of synaptic connections by both PT and IT cell populations. The results are timely, given the current interest in psychedelics, and get at the fundamental mechanisms underlying psilocybin's effects." (CC BY 4.0)

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FIGURE

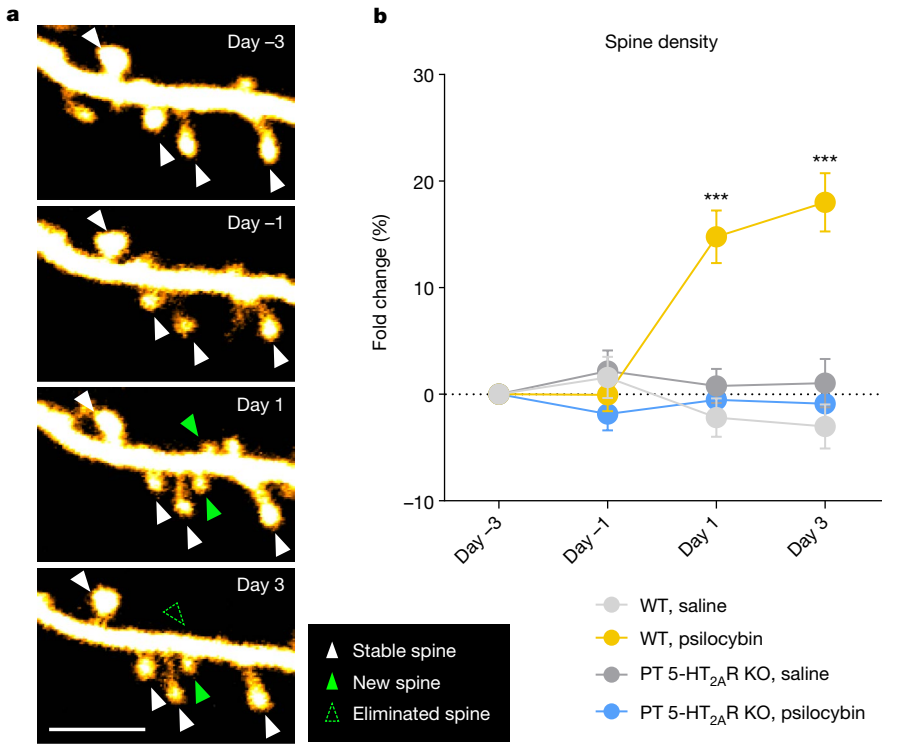

Figure 1 | Serotonin 2A receptors in PT neurons are needed for psilocybin-induced structural neural plasticity. The PT and IT neuronal cells of the frontal cortex of the mouse brain engage in different brain circuits. **a**, A dendrite (a neuronal-cell protrusion that receives inputs) of a PT neuron before (days −3 and −1) and after psilocybin treatment. Psilocybin causes a remodelling of the PT neuron's spines, which are the structures that form the basis of synaptic connections. **b**, Changes in spine density, expressed as fold change from the baseline of the first imaging session (day −3), in wild-type (WT) mice treated with saline (as a control) or psilocybin, and in mice in which a subset of receptors sensitive to the neuromodulator serotonin (5-HT_{2A}R) were selectively deleted ('knocked out'; KO) from PT neurons treated with saline or psilocybin. ***$P < 0.001$.

BEHIND THE PAPER

We initially thought that IT neurons would be more responsive than PT neurons to psilocybin, because IT neurons seem to have more serotonin 2A receptors. We were therefore surprised to find from the inactivation experiments that PT neurons were the ones needed for psilocybin's long-lasting effects on stress-related behaviours. Even so, both PT and IT neurons underwent structural remodelling after psilocybin administration, so IT neurons might still have a role in other behavioural effects of the drug. These unexpected results remind us just how complex the brain's circuitry really is. Neurons do not work in isolation. They have intricate interactions, making it difficult to predict exactly how a drug will affect the system. **L.-X.S.** and **A.C.K.**

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