Pain

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Psilocybin reduces comorbid chronic pain and depression in mice

Chronic pain often co-occurs with depression and anxiety, creating a debilitating comorbidity that intensifies pain perception, reduces treatment adherence and worsens clinical outcomes. These overlapping conditions share dysregulated neural circuits within the medial prefrontal cortex, anterior cingulate cortex (ACC), amygdala and insula—regions central to both pain and affective processing. Psilocybin, a naturally occurring indole alkaloid, has recently gained attention for its potential antidepressant and anxiolytic effects. Although psilocybin has been shown to modulate ACC activity, its effectiveness in treating chronic pain is still understudied.

In a study in *Nature Neuroscience*, researchers investigated whether a single dose of psilocybin could alleviate both chronic pain and associated mood disturbances in mouse models of neuropathic and inflammatory pain. Wild-type C57BL/6J mice underwent either spared nerve injury (SNI) or complete Freund's adjuvant (CFA) injection to induce persistent pain-like states. Behavioral analyses using the elevated plus maze, open field test, light/dark box, forced swim test and tail suspension test revealed that psilocybin treatment reduced mechanical hypersensitivity and restored normal anxiety- and depression-like behaviors. Psilocin acts as a partial agonist at serotonergic receptors (5-HT2A, 5-HT1A, and 5-HT2C), modulating neural activity in key cortical and limbic regions. Local administration of psilocin directly into the ACC was sufficient to reverse SNI-induced allodynia and anxiodepressive phenotypes, suggesting that psilocin's primary site of action is within this integrative pain–emotion hub. Electrophysiological recordings showed that psilocin normalized the hyperactivity of ACC pyramidal neurons characteristic of chronic pain states. Mechanistically, both 5-HT2A and 5-HT1A receptor signaling were required for psilocybin's restorative effects, as pharmacologic activation of either receptor alone only partially replicated its efficacy.

These findings reveal that psilocybin acts through dual serotonergic modulation within cortical circuits governing pain and mood, offering a potential mechanistic framework for treating chronic pain comorbid with depression and anxiety. Therefore, psilocybin can be a potential candidate for rapid, durable relief of both sensory and affective components of chronic pain.

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Original reference: Hammo, A., Wisser, S. & Cichon, J. *Nat. Neurosci*. **28**, 2285–2295 (2025)