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HOT TOPICS

Schrooms against booze: Potential of mycotherapy for the treatment of AUD

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Alcohol use disorder (AUD) is highly prevalent, causes an immense burden of disease, and presents largely unmet clinical needs. The condition is characterized by a relapsing course of harmful alcohol consumption, excessively biased choices towards alcohol over healthy activities, and an apparent resistance to change this dysfunctional behavior, making treatment development very demanding [1]. Existing pharmacotherapies have limited efficacy and medication development is stagnant for many years now. The current 'psychedelic renaissance' rekindled some optimism, initially inspired by promising anecdotical accounts of lasting improvements after a single or a few therapeutic sessions, and now reinforced by the emergence of governmentally funded clinical trials in some countries. These trials are focusing mostly on treatment efficacy, but rarely address any mechanism of action that are crucial for treatment development.

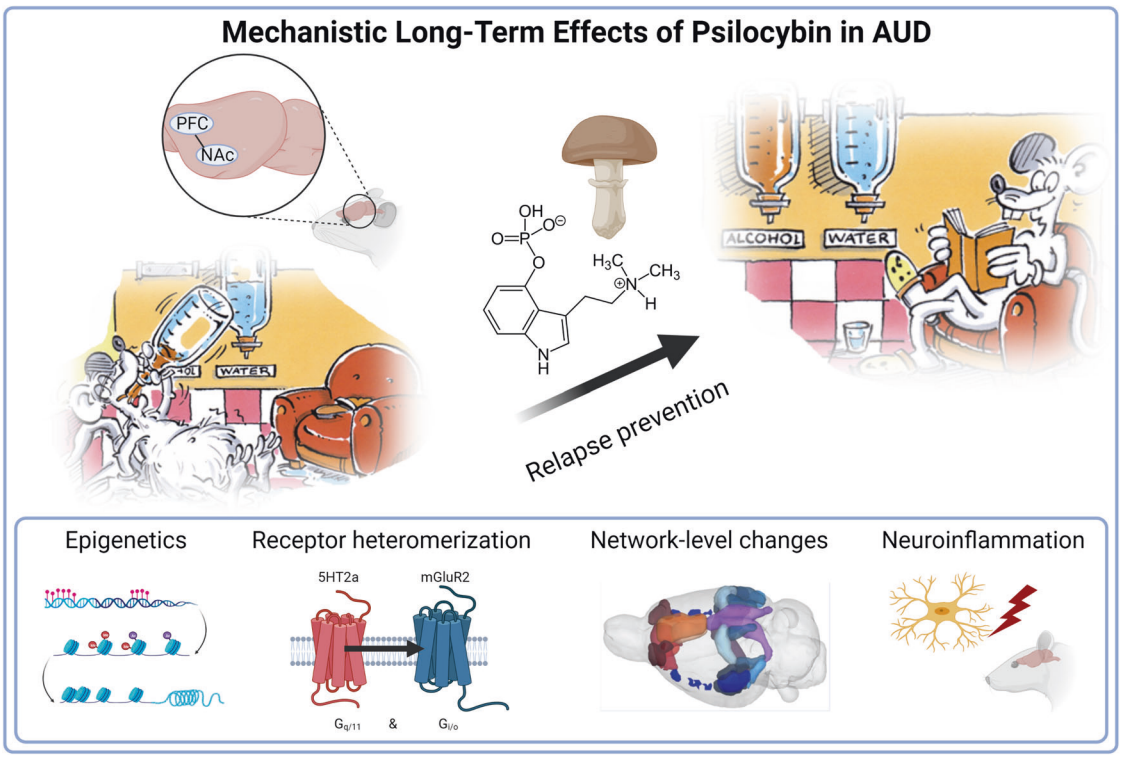

Fig. 1 Potential mechanisms of action of the fungal bioactive psilocybin in AUD. Psilocybin's cellular and systemic effects may range from unlocking a transcriptional blockade via epigenetic reprogramming, direct interactions on the receptor level e.g., through stable 5HT2A/mGluR2 heterodimerization, interference with altered brain networks to reactivate glutamatergic signaling in the mPFC or may impact on the alcohol or withdrawal induced microglia response (Figure modified from Meinhardt & Sommer 2015 [https://doi.org/10.1111/adb.12187] and created with www.biorender.com).

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Whilst the range of acute effects in perception, emotion, cognition, and sense of self distortion produced by psychedelic drugs such as LSD (lysergic acid dethylamide), ayahuasca, or psilocybin are primarily through actions on serotonin 2A receptors (5HT2A), these substances seem to have much wider ramifications on the brain and insights into these non-canonical actions may strongly benefit from animal studies. Considering AUD, we previously demonstrated a profound downregulation of class II metabotropic glutamate receptor (mGluR2) in the medial prefrontal cortex (mPFC) of AUD patients and rodent models thereof [2]. This molecular deficit represents a common pathological mechanism for excessive alcohol seeking—a model of craving—and impaired cognitive flexibility as recently established by bidirectional manipulation of mGluR2 expression in the rat mPFC. Interestingly, diminished prefrontal mGluR2 expression was reactivated by psilocybin via 5HT2A [3], thereby identifying a mechanism for the psychoplastic effects of the drug and offering a potential way to restore mPFC structure and function with a disease-modifying impact on AUD. Future research is needed to address how long such psychoplastic effect may last, and to determine its precise molecular mechanism.

Potential candidate mechanisms may function through epigenetic, receptor, or synaptic mechanisms, or via systemic changes of brain networks (Fig. 1). Acutely, psilocybin profoundly affects synapse formation and plasticity [4]. Beyond neurons, 5HT2A is also expressed in microglia, which thus can be targeted by psilocybin. We recently discovered a novel pathological process in AUD patients and animals models that is driven by a microglia reaction and results in increased brain diffusivity and likely impairs synptic remodeling [5]. Whether the beneficial effects of psilocybin in AUD are mediated through neuronal or microglia located 5HT2A or are due to off-target effects remains to be established. Given that alcohol is acting on a systemic level, therapeutic advances are likely to require a systems perspective and multi-level approach. Besides cellular mechanisms, future research should consider the circuity and network effects of alcohol and psychedelics by comparative PET or fMRI studies in humans and animals [3, 6]. The here proposed mechanisms promise exciting new venues for preclinical and translational research on the effects of psychedelic substances in the context of AUD treatment development.

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AUTHOR CONTRIBUTIONS

MWM and WHS wrote the paper.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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