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HOT TOPICS

# The evolution of the psychedelic revolution

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Atrophy of pyramidal neurons in the prefrontal cortex (PFC) is a hallmark of stress-related neuropsychiatric diseases such as depression, post-traumatic stress disorder (PTSD), and addiction. Given the critical role of the PFC in top-down control of mood, fear, and reward, strategies aiming to restore PFC structure and function have the potential to be disease-modifying and broadly efficacious. Psychoplastogens are a class of compounds that can rapidly rectify pathological changes in PFC circuitry after a single administration, with ketamine and serotonergic psychedelics being prime examples [1]. The rapid and sustained therapeutic effects of psychoplastogens clearly differentiate them from traditional antidepressants.

While their therapeutic properties are exciting, first-generation psychoplastogens like ketamine, psilocin, and 3,4-methylenedioxymethamphetamine (MDMA) suffer from safety issues such as abuse potential, cardiotoxicity, and/or psychostimulant properties. Moreover, the hallucinogenic/dissociative effects of first-generation psychoplastogens drastically limit the scalability of these treatments by necessitating in-clinic administration. While the role of mystical-type experiences in the therapeutic properties of first-generation psychoplastogens is the subject of intense debate, mounting evidence suggests that beneficial psychoplastogenic effects can be achieved without inducing hallucinations [2].

Through rational chemical design, our group engineered the first analogs of psychedelics that increase cortical neuron growth at nanomolar concentrations, yet do not induce behavioral effects characteristic of hallucinogens [3]. Shortly after this initial report, we disclosed the development of tabernanthalog (TBG), a structural analog of 5-MeO-DMT and ibogaine with an improved safety profile including lower cardiotoxicity and reduced hallucinogenic potential [4]. Despite not eliciting a head-twitch response—a behavior characteristic of serotonergic hallucinogens—TBG produces effects on neuronal structure comparable to psychedelics. In cortical neuron cultures, TBG increases both dendritogenesis and spinogenesis, and two-photon imaging studies revealed that TBG promotes spine growth in vivo to a similar extent as the hallucinogenic drug 2,5-dimethoxy-4-iodoamphetamine (DOI) [4].

Like psychedelic compounds, TBG appears to have broad therapeutic potential, presumably due to its ability to impact the structure/function of pyramidal neurons in the PFC. A single administration of TBG produces a rapid antidepressant response as well as antiaddictive effects in alcohol and heroin self-administration assays that last long after TBG has been cleared from the body. Most impressively, a single dose of TBG rescues stress-induced deficits in dendritic spine density, cortical neuron calcium dynamics, parvalbumin-positive interneuron function, and behavioral effects related to anxiety, sensory processing, and cognitive flexibility [5].

To facilitate drug discovery efforts aimed at identifying safer analogs of psychedelics like TBG, we recently engineered psychLight, a biosensor based on the 5-HT2A receptor capable of predicting hallucinogenic potential [6]. Using psychLight, we identified AAZ as a new psychoplastogen that, like TBG, produces sustained therapeutic effects after a single administration and has low hallucinogenic potential [6]. Using psychoplastogens to rewire pathological neural circuitry represents a paradigm shift in neuropsychiatry, though first-generation compounds like ketamine and psychedelics will inevitably be limited in scope. Ultimately, we need to identify medicines capable of producing long-lasting beneficial changes in neural circuits without abuse potential and cardiotoxicity if we hope to develop scalable solutions for the large number of people impacted by neuropsychiatric diseases.

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The authors both contributed to the writing and editing of this manuscript.

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## ADDITIONAL INFORMATION

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