Psychedelics show promise for treating PTSD by suppressing learned fear responses

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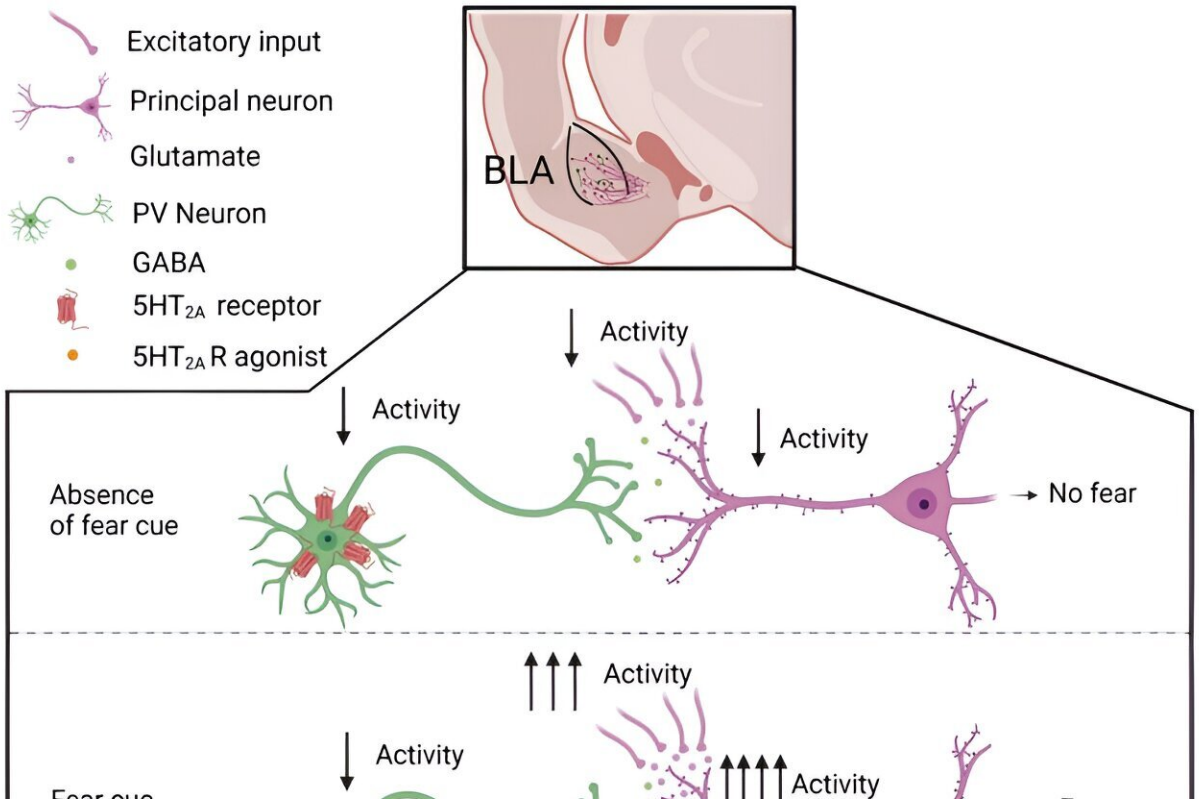

Schematic of a theoretical mechanism for psychedelic-induced fear suppression. Activation of excitatory inputs to BLA principal neurons drives fear responses during cue presentation. 5-HT_{2A} receptor agonists activate PV neurons which release GABA to inhibit principal neuron activity and reduce fear responses to cues. Created with BioRender.

Ongoing research is revealing how psychedelic drugs like psilocybin (the active ingredient in "magic mushrooms") and LSD may help treat post-traumatic stress disorder (PTSD) by suppressing learned fear responses.

In a new article published in the journal *Psychedelics*, researchers from the Medical College of Wisconsin provide an in-depth look at the neural mechanisms underlying psychedelics' acute fear-reducing effects in rodent models of PTSD.

The amygdala, an almond-shaped structure deep within the brain, plays a central role in fear learning and expression. Excitatory neurons in the lateral amygdala are activated by fearful stimuli, leading to a cascade of activity that drives fear responses. The new research proposes that psychedelic drugs suppress this fear-related activity by enhancing inhibitory signaling from GABAergic interneurons onto the excitatory neurons.

"Our hypothesis is that psychedelics acutely suppress learned fear responses by activating serotonin$_{2a}$ receptors on inhibitory neurons in the amygdala," said the lead author Thomas Kelly, an MD/Ph.D. candidate. "This leads to increased release of the inhibitory neurotransmitter GABA, which quiets the activity of excitatory neurons that normally drive fearful behaviors."

The finding that psychedelics' acute effects on fear require activation of serotonin $_{2a}$ receptors aligns with the receptor's established role in the drugs' hallucinogenic effects. However, the authors emphasize the importance of considering the broader pharmacological profile and duration of action of different psychedelic compounds.

For example, the drug MDMA, which has shown promise for treating PTSD in late-stage clinical trials, does not directly activate serotonin $_{2a}$ receptors. Instead, MDMA increases the release of serotonin, which then

activates various serotonin receptor subtypes. The research suggests that psychedelics with faster onset and shorter duration of acute effects may be advantageous for PTSD treatment compared to longer-acting drugs like LSD.

"The insights from preclinical studies can help guide the design of clinical trials and treatment protocols that optimize the therapeutic potential of psychedelics for PTSD," said senior author Dr. Qing-song Liu. "By understanding the mechanisms and time-course of psychedelics' effects on fear circuitry, we can better harness these compounds in a clinical setting."

Several clinical trials are currently investigating psilocybin-assisted therapy for PTSD, with some protocols incorporating drug administration in combination with exposure therapy to promote fear extinction learning. As this research progresses, the amygdala is emerging as a key locus of interest for understanding how psychedelics may extinguish fearful memories and provide a novel treatment approach for PTSD and other fear-related disorders.

More information: Thomas Kelly et al, Exploring the therapeutic potential of psychedelics: Fear extinction mechanisms and amygdala modulation, *Psychedelics*. DOI: 10.61373/pp024b.0019. pp.genomicpress.com/wp-content … P0019-Kelly-2024.pdf,

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