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Psychedelics

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Exploring the therapeutic potential of psychedelics: Fear extinction mechanisms and amygdala modulation

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Classical psychedelics are increasingly receiving attention as potential therapeutic agents for treating post-traumatic stress disorder (PTSD). Research has explored various classical psychedelics in the context of fear learning, recall, and extinction in rodents. We provide an overview of the reported effects of these substances on behavioral responses to learned fear. The amygdala complex, a key brain region involved in fear learning and extinction, plays a central role in these processes. We discuss how psychedelics interact with various cell types in the amygdala and propose which neural circuits may be essential for the observed fear-suppressing effects following psychedelic administration in rodents. The rodent amygdala has functional homology with the human amygdala. Thus, insights gained from preclinical studies can inform the design and implementation of clinical trials for psychedelic-assisted psychotherapy for PTSD. Finally, we stress the importance of considering compound-specific pharmacology and the acute duration of action as key factors in guiding the future direction of this field.

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Introduction

Fear and anxiety-related disorders, such as posttraumatic stress disorder (PTSD), specific phobias, and generalized anxiety disorder, present significant challenges for both patients and clinicians. Despite advancements in traditional therapeutic approaches, such as cognitive-behavioral therapy and exposure therapy, a substantial proportion of individuals with these disorders continue to experience persistent symptoms and impaired quality of life (1, 2). The mechanisms underlying the therapeutic effects of exposure therapy have been explored in rodent models utilizing classical fear conditioning and extinction paradigms (3). The neural substrates implicated in fear extinction in rodents are comparable to those recruited during exposure therapy in humans (4). In recent years, there has been a resurgence of interest in the therapeutic potential of psychedelic substances, such as psilocybin and 3,4-methylenedioxy methamphetamine (MDMA), for the treatment of fear and anxiety-based disorders (5). Clinical trials assessing the efficacy of MDMA-assisted psychotherapy for the treatment of PTSD have shown promising results (6, 7), and trials for psilocybin-assisted therapy for the same indication are ongoing. A prevailing view is that psychedelics induce enduring therapeutic effects by enhancing structural plasticity of cortical neurons (8–10). This viewpoint stems from observations that a single dose of a psychedelic induces both sustained changes in cortical dendritic spine density and sustained antidepressant-like effects in rodent models of despair. In this perspective article, we propose that the fear-associated environmental cues may activate excitatory principal neurons in the amygdala, while psychedelics acutely suppress fear responses by enhancing GABAergic inhibition of these principal neurons. The opposing effects on neuronal activity in the amygdala may provide a basis for understanding psychedelic-assisted treatment for fear-based disorders.

Classical Psychedelics Acutely Suppress Learned Fear Responses

Classical psychedelics induce a characteristic 5-HT_{2A} receptor–dependent head twitch response in rodents (11, 12) that correlates with hallucinogenic potency in humans (13). Indeed, the 5-HT_{2A} receptor antagonist ketanserin dose-dependently blocks subjective psychedelic effects in humans (14). It has been postulated that the therapeutic effects of classical psychedelics rely on prolonged neuroplastic changes in the cortex after the acute drug effects have worn off (8, 9, 15–17). In the case of fear extinction learning, the preclinical data have not directly supported this model of action. Studies in mice have demonstrated that classical psychedelics reduce freezing responses to conditioned auditory fear cues (18–24). However, fear suppression to conditioned cues wanes as the acute effects of classical psychedelics subside (20). In contrast, the height of psychedelic-induced structural plasticity in the cortex is apparent long after the drug has worn off (1–3 days) (9). Thus, psychedelics induce an acute suppression of learned fear that is unlikely to depend on structural neuronal plasticity.

The magnitude of psychedelic-induced fear suppression appears to rely on drug dosage, and timing of the dose, while sustained effects appear to rely on the specific fear extinction paradigm psychedelic treatment is paired with (See Table 1 for summary). Notably, studies that paired psychedelic treatment with fewer conditioned fear cue presentations ($\leq$12), or a single 3-min tone showed enhanced extinction retention the following day (21, 22), while studies that paired a higher number of fear cues (20–40 tones) with psychedelic treatment showed no difference in extinction retention between treatment and control groups 24 h later (19, 20). A larger number of cue presentations strengthens fear extinction within the session but also normalizes freezing levels between drug treatment groups by the end of the extinction session. Thus, the timing, dose, and number of cue presentations during psychedelic-paired fear extinction likely determine whether reductions in cue-induced freezing are observed at later timepoints.

Regardless of the fear extinction protocol that is used, the acute fear-suppressing effect of classical psychedelics likely depends on 5-HT_{2A} receptor agonism as full knockout of the receptor prevented the acute fear-suppressing effect of the full 5-$HT_{2A/2C}$ agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) (19), and systemic injection of the selective 5-HT_{2A} antagonist volinanserin (also known as MDL 100907 or M100907) prevented the acute fear-suppressing effects of psilocybin and 4-(2-((2-hydroxybenzyl)amino)ethyl)-2,5-dimethoxybenzonitrile (25CN-NBOH) (18). Overall, these data suggest that 5-HT_{2A} receptor agonism is required for the acute fear-suppressing effects of classical psychedelic drugs, but the enduring effects on fear behavior are highly dependent on the specific extinction paradigm psychedelic treatment is paired with.

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Table 1. Overview of the doses, timing, and fear-suppressing effects of various classical psychedelics

Compound	Mechanism	Dose and Timing	Effect on Conditioned Fear
Psilocybin/Psilocin	Non-selective 5-HT receptor agonist, low 5-HT_{2B} receptor affinity (25)	2 mg/kg, 30 min before contextual test	Suppression of freezing to context (18)
		0.1, 0.5, and 2.5 mg/kg; 30 min before cue presentation	0.5 and 2.5 mg/kg caused suppression of cued freezing (23)
N,N-DMT	Non-selective 5-HT receptor agonist (25)	10 mg/kg, 1 h before cue presentation	Suppression of cued freezing (22)
DOI	Selective 5-HT_2 agonist (26)	2 mg/kg, 30 min before cue presentation	Suppression of cued freezing
		2 mg/kg, 2 h after conditioning, 24 hours before cue presentation	Weak suppression of contextual freezing (27)
		2 mg/kg, 24 h before fear conditioning, 48 h before cue presentation	Weak suppression of contextual freezing (27)
TCB-2	High affinity 5-HT_{2A} agonist, off target binding sites unknown (28)	1 mg/kg, Immediately after trace fear conditioning	Enhanced cued freezing during recall 24 h later (24)
		1 mg/kg, 30 min before cue presentation	Suppressed cued freezing (24)
		1 mg/kg, 30 min before context test	Suppressed contextual freezing (18)
4-OH-DiPT	Modestly selective for 5-$HT_{2A/B}$ receptors over 5-HT_{2C} and 5-HT_1 receptor family (20)	3 mg/kg, 30 min before extinction	No suppression of cued free (20)
		3 mg/kg, 5 min before extinction	Suppression of cued freezing (20)
25CN-NBOH	High-affinity 5-HT_{2A} receptor agonist, moderate selectivity over 5-$HT_{2B/C}$ receptors (29)	3 mg/kg, 30 min before contextual test	Suppression of freezing to context (18)

The Amygdala Plays a Crucial Role in the Fear-Suppressing Effect of Psychedelics

The locus whereby 5-HT_{2A} agonism suppresses conditioned fear is an area of ongoing investigation. Fear extinction is a complex behavior which involves processing salient stimuli, responding to expected stimuli outcomes, and adjusting responses to these outcomes over time (30). The hippocampus, amygdala complex, and prefrontal cortex (PFC) play distinct roles in the extinction of fear (31); in-depth reviews can be found elsewhere (32–34). The 5-HT_{2A} receptor is expressed in all these regions (35–37), and its collective activation at each region in vivo likely contributes to the acute fear-suppressing effect of systemically administered classical psychedelics. However, local infusion of DOI into the amygdala complex, and not the medial PFC most closely resembles its fear-suppressing effect after systemic injection (19). This suggests that activation of the 5-HT_{2A} receptor in one or more amygdala nuclei is necessary for the acute fear-suppressing effects of classical psychedelic drugs in rodents.

The amygdala complex is commonly broken into the central (CeA) and basolateral complex. The basolateral complex is further divided into the lateral amygdala (LA), basolateral amygdala (BLA), and basomedial amygdala (BMA) (38). CeA, LA, BMA, and BLA have anterior-posterior heterogeneity and contain subregions with distinct functions (38). The LA is positioned immediately dorsal to the BLA and has high expression of *Htr2a* mRNA (20). During auditory fear conditioning, synaptic inputs from auditory and somatosensory cortex converge onto LA neurons and induce synaptic strengthening (39). The depolarization of LA neurons induced by glutamate release from cortical input neurons (40–42) causes calcium influx through NMDA receptors, AMPA receptor surface trafficking, and sustained synaptic potentiation (43, 44). Local infusion of the NMDA antagonist APV into the amygdala during fear conditioning impairs cue-outcome association (45). Thus, simultaneous excitation from auditory and somatosensory inputs to lateral amygdala principal neurons led to NMDA-dependent synaptic strengthening and fear learning. Activation of the 5-HT_{2A} receptor in LA neurons during fear conditioning could induce depolarization and calcium influx through Gq-protein dissociation (46). It is plausible that depolarization via 5-HT_{2A} receptor activation could lower the threshold for Hebbian-based forms of plasticity that occur between LA neurons and their somatosensory and auditory inputs during fear learning. Strengthened inputs to LA neurons could potentially result in heighted fear responses during a recall event the following day. This idea has not been directly tested yet, but may be difficult to distinguish from 5-HT_{2A}–mediated enhancement of memory consolidation after fear conditioning procedures. For example, the administration of TCB-2 shortly after fear conditioning led to enhancement of fear learning the following day (24). On the other hand, administration of DOI prior to cued fear recall suppresses freezing, yet, increases expression of the immediate early gene c-Fos in the LA (19). Thus, psychedelic-induced activation of LA neurons, might enhance or disrupt conditioned fear responses depending on the administration timepoint.

The BLA is directly below the LA and is comprised of ~80% excitatory neurons and ~20% inhibitory GABAergic neurons (20). While the BLA contains slightly more GABA neurons than the LA (47), the expression of 5-HT_{2A} receptor mRNA is substantially lower in the BLA compared to the LA, and has higher localization to inhibitory neurons (20). Notably, not all GABA neurons expressed *Htr2a* mRNA in the above study. However, RNA-sequencing has characterized the expression of *Htr2a* mRNA across the mouse brain in great detail including BLA inhibitory neuronal subtypes (48). The BLA contains four major populations of interneurons which express either parvalbumin (PV^+), somatostatin (SST^+), vasoactive intestinal polypeptide (VIP^+), or cholecystokinin (CCK^+) and have differential roles in fear encoding and expression (49). The specific subpopulation of inhibitory BLA neurons which express 5-HT_{2A} receptor protein is unclear. Studies show conflicting results, 5-HT_{2A} receptor expression has been shown to be restricted to only PV^+ (50), both PV^+ and SST^+ (37), or widespread expression including excitatory neurons, although most accounts show expression localized to post synaptic soma and dendritic sites (51). Ex vivo slice electrophysiology experiments provide some clues as to which BLA interneuron population expresses the $5HT_{2A}$ receptor. Bath application of serotonin enhances the frequency and amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) in BLA neurons, an effect which can be blocked by the selective 5-HT_{2A} receptor antagonist volinanserin (50, 52). The increase in sIPSC frequency and amplitude is likely due to enhanced action potential firing from one of the local interneuron populations as focal application of the 5-HT_{2A} receptor agonists 4-OH-DIPT or α-methyl-5-hydroxytryptamine leads to interneuron depolarization and action potential firing (20, 53). Psychedelics likely exert comparable interneuron-mediated inhibition in vivo as the number of BLA neurons expressing the immediate early gene c-Fos were

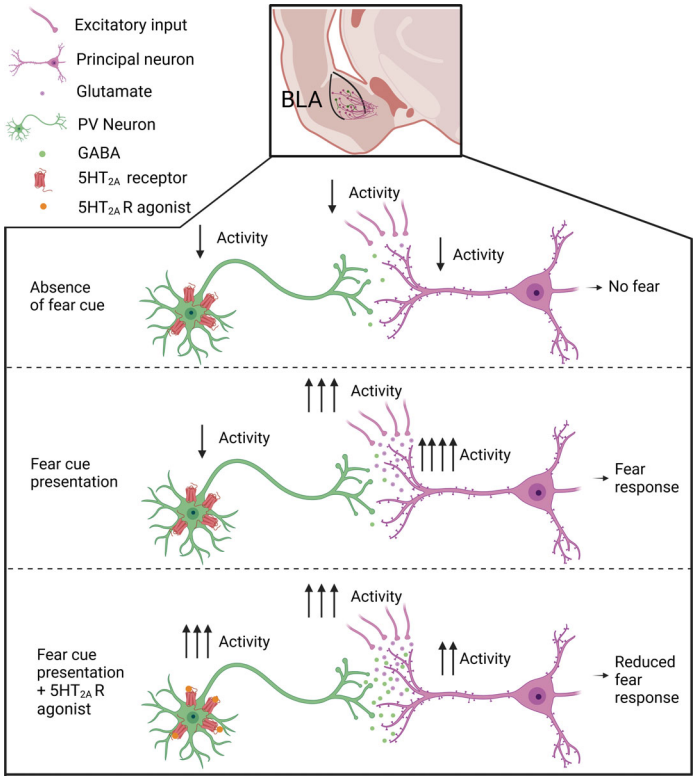

Figure 1. Schematic of a theoretical mechanism for psychedelic-induced fear suppression. Activation of excitatory inputs to BLA principal neurons drives fear responses during cue presentation. 5-HT_{2A} receptor agonists activate PV neurons which release GABA to inhibit principal neuron activity and reduce fear responses to cues. Created with BioRender.

decreased in psilocybin-treated mice compared to saline-treated controls (54). Moreover, ex vivo activation of Gq-DREADDs expressed on BLA PV^+ neurons mimics the 5-HT_{2A} receptor–mediated enhancement of sIPSCs in BLA neurons (52). Thus, 5-HT_{2A} receptor–mediated activation of PV neurons likely causes inhibition of BLA principal neurons.

Modulation of PV^+ neuron activity in the BLA during fear conditioning or extinction leads to distinct outcomes in fear expression. Gq-mediated activation of BLA PV^+ interneurons during fear conditioning enhances fear expression one day later (52). While optogenetic activation of PV^+ neurons during fear extinction suppresses freezing (55) and chemogenetic inhibition of BLA parvalbumin neurons enhances freezing in mice that have undergone extinction (56). Agonism or antagonism of the 5-HT_{2A} receptor at similar timepoints induces a comparable pattern of behavior as BLA PV^+ neuron activation or inhibition, respectively (Fig. 1). Administration of the potent 5-HT_{2A} receptor agonist TCB-2 shortly after fear conditioning led to enhanced fear expression one day later, yet administration of TCB-2 prior to fear extinction suppressed cue-induced freezing (24). Systemic administration of the selective 5-HT_{2A} receptor antagonist volinanserin at the same timepoints in the above study showed opposite effects on fear expression, suggesting the behavioral effects of TCB-2 in this paradigm were dependent on 5-HT_{2A} receptor activation (24). One caveat is that while TCB-2 is a highly potent 5-HT_{2A} receptor agonist, its selectivity has not been established (57). Taken together, these studies indicate that the acute effect of 5-HT_{2A} receptor activation leads to PV interneuron-mediated inhibition of excitatory BLA neurons and may differentially augment fearful responses depending on the administration timepoint. Future experiments should directly test this potential mechanism in vivo.

The CeA has also been reported to express the 5-HT_{2A} receptor on SST^+ interneurons (58). Chemogenetic inhibition of 5-$HT_{2A}{}^+$ CeA neurons reduces freezing to learned fear cues, while chemogenetic activation had no effect on freezing to learned fear cues (58). However, the same study found that activation of 5-$HT_{2A}{}^+$ CeA neurons reduced freezing to innate fear (58), which might contribute to the acute anxiolytic-like effect of the potent 5-HT_{2A} receptor agonist DOI in the elevated zero maze and elevated plus maze (19). Interestingly, systemic administration of psilocin, the active metabolite of psilocybin, led to an acute increase in CeA activity in both male and female rats, while it enhanced stimulus-specific CeA reactivity solely in females, rather than males (59). This raises the possibility that the CeA may contribute to some of the sex differences in fear and avoidance behaviors observed after administration of psychedelics in rodents (20, 60, 61).

Fear Induces Amygdala Activation in Rodents and Humans

Fear extinction requires altering the perceived threat of a stimulus, a concept not directly measurable in rodents. Human trials are ultimately required to understand how psychedelics alter the perception of threat. The neurobiological mechanisms underlying fear responses are relatively well conserved across mammalian species. RNA-sequencing experiments show that humans and mice contain similar proportions of excitatory and inhibitory neurons in the amygdala (62). Functional studies in rodents and humans have demonstrated the critical role of the amygdala in fear processing and fear-related behaviors. For example, lesion studies in rats have shown that damage to the amygdala impairs the acquisition of conditioned fear (63). Excitatory BLA neurons are activated by fear cue presentation in rats, and optogenetic inhibition of the same neurons impairs cue-induced freezing during extinction (55). Moreover, functional imaging in humans revealed increased amygdala activity in response to fear conditioning (64). While in vivo field potential recordings of the amygdala in awake humans demonstrated increased activity upon the presentation of fearful faces (65). In contrast, reductions in amygdala activity are associated with the early phase of fear extinction in humans (66), and humans with bilateral amygdala lesions do not display typical fear responses (67). Thus, fear learning, and expression require excitatory amygdala activity in both rodents and humans.

Implications for the Treatment of PTSD

Functional magnetic resonance imaging has shown that acute psilocybin administration to human subjects reduced amygdala reactivity to both negative and neutral stimuli compared to placebo administration (68). In the same study, the reduction in blood oxygen level-dependent signal in the right amygdala was correlated with elevated mood 210 min after psilocybin administration (68). Hyperactivity of the amygdala is implicated in PTSD (69, 70). Thus, classical psychedelics and exposure therapy may work synergistically to dampen amygdala activity and reduce PTSD symptoms. Clinical trials investigating the efficacy of psilocybin for treating PTSD are ongoing (NCT05243329, NCT05312151, NCT05554094) and some clinical trials integrate exposure therapy into their design (71). It is critical that future clinical trials investigate how modulating the number of trauma exposures or type of psychotherapy accompanied by psychedelic administration influences long-term outcomes in patients with PTSD. It has been suggested that the psychological insight gained from the psychedelic-assisted treatment can improve an individual's ability to respond to subsequent stressors more adaptively (72), which is consistent with the findings that the intensity of the acute psychedelic experience is associated with improved metrics of mental health (73). Thus, the type of therapy administered, and intensity of psychedelic effects will ultimately inform the long-term behavioral changes induced by psychedelic assisted psychotherapy for fear-based disorders.

Pharmacological Considerations

Agonism of the 5-HT_{2A} receptor is responsible for the acute illusory and sensory effects of psychedelic drugs, However, nearly all psychedelic drugs have activity at other receptors which augments their activity at the level of neural circuits and systems. The differential effects of serotonin receptors on anxiety and fear are reviewed elsewhere (74). It was recently shown that several commonly studied classical psychedelics such as N,N-DMT, 5-MeO-DMT, psilocin, and lysergic acid diethylamide have higher efficacy at the Gi/o-coupled 5-HT_{1A} receptor compared to the 5HT_{2A}

receptor (75). The 5-HT_{1A} receptor is expressed on the presynaptic terminals of excitatory dorsal raphe serotonergic neurons that project to the amygdala (74). 5-HT_{1A} receptor knockout mice display anxiety-like behavior (76) and elevated freezing responses immediately after foot shock (77). However, global 5-HT_{1A} receptor knockout does not significantly alter cue-induced freezing during extinction (78). Bilateral microinjection of the 5-HT_{1A} agonist flesinoxan into the amygdala of rats reduced freezing to conditioned fear cues (79). It is unknown whether knockout of the 5-HT_{1A} receptor alters the acute fear-suppressing effect of classical psychedelics. However, 5-HT_{1A} receptor agonists such as buspirone are used clinically for the treatment of generalized anxiety disorder (80). Thus, it is possible that 5-HT_{1A} agonism may contribute to some of the therapeutic effects of psychedelics on anxiety and fear expression.

The 4–8 h duration of acute psychedelic effects from psilocybin will be costly for patients and difficult to implement as a treatment for PTSD. While psychedelic-assisted psychotherapy may be a promising treatment for PTSD and other fear-based disorders, short-acting psychedelics such as 4-OH-DiPT, N, N-DMT, and 5-MeO-DMT may be more practical in this regard. A striking case study observed robust symptom reduction in a patient with PTSD following a single dose of 5-MeO-DMT (81). Consecutive treatment with Ibogaine and 5-MeO-DMT reduced self-reported PTSD symptoms in veterans and led to sustained clinical benefits up to 6 months later (82). The psychoactive effects from 5-MeO-DMT inhalation can begin within 1–50 s (83), with a total duration of up to ~30 min (84). However, 5-MeO-DMT has a high incidence of flashbacks (also termed reactivation) (85). Instances of traumatic memories resurfacing during or shortly after psychedelic-assisted therapy have been documented (86, 87), which may be more prevalent with 5-MeO-DMT compared to other psychedelic compounds. 4-OH-DiPT a short-acting tryptamine derivative with high affinity for the 5-HT_{2A} receptor (25) and has been shown to suppress learned fear responses mice (20). A 4-OH-DiPT prodrug is currently under investigation for postpartum depression (U.S. Patent No. 11,292,765). 4-OH-DiPT has modest selectivity for 5-HT_{2A} receptor over the 5-HT_{2C} receptor but demonstrates near full agonism at the 5-HT_{2B} receptor (20). Chronic agonism at the 5-HT_{2B} receptor is associated with cardiac valvulopathy (88). While this is less of a concern with single or infrequent doses used in single sessions of psychedelic-assisted psychotherapy, compounds with reduced 5-HT_{2B} receptor agonism could mitigate the risk of developing cardiac valvulopathy. MDMA, which has been shown to reduce the affective symptoms of PTSD (6), blocks reuptake of serotonin and indirectly agonizes the 5-HT_{2B} receptor (89). The incidence of cardiac valvulopathy is higher in MDMA users compared to non-users (90). The development of short-acting psychedelics that lack 5-HT_{2B} receptor agonism may be highly valuable clinical tools.

Overall, the long duration of acute psychedelic effects from compounds like psilocybin may make them difficult to scale as widespread PTSD treatments. Short-acting psychedelics may be promising alternatives. Special consideration should be given to the specific receptors each psychedelic drug activates in addition to the 5-HT_{2A} receptor. Ongoing investigation into their safety and efficacy in psychedelic-assisted psychotherapy for PTSD is warranted.

Conclusion

Despite advancements in traditional therapeutic approaches fear and anxiety-based disorders remain challenging to treat. While exposure therapy has been effective in many cases of PTSD, the resurgence of interest in psychedelic substances offers promising avenues for treatment. Classical psychedelics have been shown to acutely suppress fear responses in rodent models of fear, suggesting potential therapeutic applications for fear-related disorders. Understanding the neural mechanisms underlying these effects, particularly in regions such as the amygdala, is crucial for developing effective psychedelic-assisted psychotherapy treatments. Additional consideration for the pharmacological profile of psychedelics, their duration of action, and the therapeutic context in which they are administered is essential for optimizing treatment strategies. Short-acting psychedelics may be promising alternatives treatments for PTSD. Further research into their safety and efficacy is needed to address the persistent challenges posed by fear-based disorders.

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