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Cannabinoid Modulation of Fear Extinction Brain Circuits: A Novel Target to Advance Anxiety Treatment

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Abstract

Anxiety disorders, such as post-traumatic stress (PTSD), panic, and phobic disorders, can be conceptualized as a failure to inhibit inappropriate fear responses. A common, effective treatment strategy involves repeated presentations to the feared cue without any danger (extinction). However, extinction learning has a number of important limitations, and enhancing its effects, generalizability and durability via cognitive enhancers may improve its therapeutic impact. In this review we focus specifically on the role of the cannabinoid system in fear extinction learning and its retention. We address the following questions: What are the neural circuits mediating fear extinction?; Can we make fear extinction more effective?; Can cannabinoids facilitate fear extinction in humans?; How might the cannabinoid system effect fear extinction? Collectively, translational evidence suggest that enhancing cannabinoid transmission may facilitate extinction learning and its recall, and that the cannabinoid system is a potential pharmacological target for improving the active learning that occurs during exposure-based behavioral treatments prompting future research in terms of mechanisms research, novel treatment approaches (‘cognitive enhancers’), and pharmacotherapeutic drug discovery.

Keywords

Cannabinoid; fear extinction; cognitive enhancer; ventromedial prefrontal cortex; hippocampus; amygdala; anxiety

INTRODUCTION

Anxiety disorders, such as post-traumatic stress (PTSD), panic, and phobic disorders, can be conceptualized as a failure to inhibit inappropriate fear responses [1, 2]. Cognitive behavioral therapy (CBT) is a high efficacious, empirically-validated, first-line treatment for anxiety disorders [3]. One of the core features of CBT involves repeated presentations to the feared cue without any danger (clinically referred to as exposure treatment leading to

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CONFLICT OF INTEREST

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desensitization) of fear and subsequently diminishes emotional responsiveness to these cues [4]. Over time, in the absence of an aversive outcome, the patient begins to recognize what was previously anxiety-provoking no longer predicts a bad outcome and avoidance behaviors become less frequent. In the laboratory, Pavlovian fear conditioning and extinction are used to model this type of learning, during which a neutral cue (a conditioned stimulus, CS) is paired with an aversive event and this association is weakened by being exposed to the CS-alone, in the absence of the aversive consequence, and thus promotes 'fear extinction'.

One drawback of extinction is that it is a transient phenomenon and fear that becomes extinct can come back after time has elapsed (spontaneous recovery), as a result of a change in experimental context (renewal shift), or from an unsignaled presentation of the aversive unconditioned stimulus (US; reinstatement effect) [5–11]. Thus, the process of extinction is a thought of as new learning, and fear reduction results from inhibition rather than erasure of the original fear memory [11]. Fear extinction and its recall has become the prime translational neuroscience target for the treatment of anxiety disorders [12–14]. Enhancing the neural and neurochemical substrates of inhibitory fear learning could solve this challenge and improve treatment outcomes [12–14].

WHAT ARE THE NEURAL CIRCUITS MEDIATING FEAR EXTINCTION?

Convergent evidence from rat and human work have elucidated that discrete, yet interconnected, brain structures are important to facilitate the learning and recall of extinction (amygdala [AMYG], ventromedial prefrontal cortex [vmPFC], and hippocampus [HPC]) [9, 15–32]. At acquisition, sensory information about the CS and US converge at the AMYG and become associated (i.e. yielding the fear memory) and translated into conditioned responses of fear (CRs) [18, 19]; of note the AMYG may also be involved in extinction learning [20–22]. AMYG activation has been correlated with fear responses during conditioning in human subjects based on functional magnetic resonance imaging (fMRI) studies [23, 33, 34]. Prefrontal brain regions that interconnect with the AMYG, particularly the vmPFC, are important for consolidation and retrieval of extinction memories and consequent attenuation of fear CRs perhaps via inhibiting AMYG output neurons [23–29]. During extinction recall vmPFC and HPC activation, as well as, vmPFC thickness both correlate with magnitude of extinction retention [23, 30, 31, 35, 36]. Poor extinction retention and vmPFC-HPC dysfunction displayed by patients with anxiety disorders, such as PTSD, could undermine the efficacy of the therapeutic effects of exposure [37–42]. Despite having converging translational evidence from rodents to clinical patients of the critical neural mechanism underlying extinction recall and its retention, few strategies exist to augment the generalization and retention of extinction memory in the clinical setting in order to maximize treatment effects of exposure-based therapies.

CAN WE MAKE FEAR EXTINCTION MORE EFFECTIVE?

New evidence has shown that pharmacological agents known as "cognitive enhancers" can facilitate fear extinction in animals and exposure-based therapy in humans. Several signaling pathways within the brain, such as the GABAergic, glutamatergic, noradrenergic,

cholinergic, and cannabinoid systems, have been implicated as potential pharmacological targets to improve learning and recall of extinction in both rats and humans (for a review see Kaplan and Moore [43]). In this review we focus specifically on the fear extinguishing effects of cognitive enhancers that act on the cannabinoid system.

In the past decade rodent studies have implicated the cannabinoid (CB) system within extinction neural circuitry (e.g. AMYG, vmPFC, HPC) as important for regulating extinction learning and retention. In a seminal study, Marsicano and colleagues [44] found that mice with a genetic deletion of type 1 CB (CB1) receptors were strongly impaired in short-term and long-term extinction of auditory fear conditioning, without any observable deficits in fear memory acquisition and consolidation, and these impairments of extinction were not due to sensory-motor deficits or by increased anxiety. Moreover, wild-type mice treated with the CB1 antagonist, rimonabant [SR141716], displayed a similar phenotype to the CB1-deficient mice, further suggesting that CB1 receptors are critical for successful extinction of fear memories.

Similarly, local infusions of AM251, a CB1 antagonist, into brain regions important for extinction learning and memory, such as the dorsal HPC [45] or the infralimbic cortex (IL), a homologous structure to the human vmPFC [46], have been shown to block consolidation for fear that is contextually related to the extinction period and impair extinction of fear-potentiated startle, respectively. Several studies have corroborated and extended these findings by showing profound impairments in extinction retention when CB1 antagonists were given either prior to or immediately following extinction learning. Together, these studies suggest that CB1 receptor activation is an important mechanism for learning and retaining what is learned during the extinction period and for being able to retrieve what has been learned in the future [47–50].

Based on these findings it is not surprising that activation of CB1 receptors, via agonists (e.g., WIN 55,212–2, HU210, Δ9-tetrahydrocannabinol [THC]), and other drugs that enhance release of endogenous cannabinoids (eCBs) (e.g., AM404, an eCB reuptake inhibitor, and URB597, a fatty acid amide hydrolase (FAAH) inhibitor that blocks hydrolysis of anandamide) have also been shown to facilitate extinction learning [51, 52] and enhance the retention of extinction [45–47, 51, 52]; but see [47]). Chhatwal and colleagues [47] have shown that administration of AM404 given to rats prior to extinction learning led to dose-dependent enhancements in extinction and decreased the recovery of conditioned fear responses. Moreover, these enhancements in extinction with AM404 could be blocked with co-administration of a CB1 antagonist, further supporting that the enhancement of extinction is likely CB1-dependent [47].

Moreover, Lin and colleagues have found that local injections of WIN 55–212,2 [46, 53] or AM404 [46] into the IL cortex prior to training improves the extinction of fear-potentiated startle and local injections of HUB210 and/or WIN 55–212,2 into the AMYG during fear extinction blocks the return of extinguished fear-potentiated startle in rodents [54]. Similarly, extinction learning can be enhanced with local infusions of anandamide into the dorsal HPC [45]. Collectively, these animal studies suggest that the durability of learning and recall of

extinction can be facilitated by enhancing CB1 receptor activity in fear extinction brain circuits (AMYG, HPC, IL) and prompt us translate these findings into human studies.

WHAT EFFECTS DO CANNABINOIDS HAVE ON FEAR AND FEAR CIRCUITRY IN HUMANS?

Non-empirical reports from recreational marijuana users or other studies on drug effects of marijuana/THC suggest that agonists of the CB1 system can promote calmness and/or reductions in subjective anxiety [55–57]. An early placebo-controlled study demonstrated that nabilone, a synthetic THC, significantly diminished nervousness in patients with anxiety [58]. Consistent with this and evidence from rodents [59, 60], a study in humans conducted in our laboratory using fMRI found that an acute dose of THC (7.5 mg) significantly reduced AMYG responding to cues that convey the potential for threat (fearful and angry faces) without altering subjective levels of anxiety [61]. Moreover, the level of cannabis use has been inversely related to AMYG reactivity to threat signals [62]. However, it should be noted that others have reported that administration of THC, particularly at a higher dose (10 mg) *increases* AMYG activation [63], and modulates activation in frontal and parietal regions [64] while increasing levels of anxiety and autonomic arousal to fearful faces [63, 64]. These divergent findings highlight the complexity of THC's effect on fear responding, which may be bimodal such that low doses of THC may be anxiolytic [57] whereas high doses of THC are anxiogenic [55, 65, 66].

Besides THC, cannabidiol (CBD), a non-psychotomimetic compound also found in *Cannabis sativa*, has been shown to have anxiolytic effects [64, 67–69] and can reduce or reverse the negative symptoms induced by THC [63, 70]. CBD (600 mg) has been shown to attenuate AMYG and anterior cingulate cortex (ACC) activation and reduce forward connectivity between the ACC and AMYG to fearful faces, as well as reduce anxiety levels and autonomic arousal in healthy volunteers [63, 64, 67, 71]. Moreover, administration of CBD decreases subjective anxiety in patients with social anxiety disorder [72, 73]. Interestingly, converging evidence from rodent studies suggests CBD administration may be used to facilitate extinction of contextual fear memory [51] or prevent reconsolidation of contextual fear memories [74].

The above findings point to potential, and complex, effects that exogenous pharmacological modulation of cannabinoid receptors may have on anxiety and its underlying brain circuitry. One important contributor to these complex effects may be the differential sensitivity to the effects of THC and other cannabinoid modulators between individuals [75, 76]. Part of the individual differences may be driven by genetic variation [77, 78]. Studies using imaging genetics (coupling functional brain imaging with genotyping) in humans have shown that genetic variation in an FAAH inhibition (FAAH 385A), which would alter the extent of hydrolysis of anandamide and thereby increase endocannabinoid signaling, is associated with decreased AMYG reactivity to threatening faces [79, 80] and with reduced reactivity to stress [80], further supporting a role for the cannabinoid system in fear regulation. Collectively, these data demonstrate that modulation of the cannabinoid system would have down-stream effects on anxiety and neural substrates involved in processing social signals of

fear (e.g., AMYG reactivity to fearful faces) which are observable in humans. As noted above, emerging evidence from rodent studies show that these effects can be specifically linked to the extinction of previously acquired fear. However, until recently, it was not known if these effects can be translated to humans.

CAN CANNABINOIDS FACILITATE FEAR EXTINCTION IN HUMANS?

Until recently current knowledge about cannabinoids and fear extinction recall and the underlying neural and neurochemical substrates were limited to studies using animal models. Klumpers and colleagues [81] conducted a behavioral Pavlovian fear conditioning study using fear-potentiated startle, in healthy, marijuana-naïve, adult volunteers. The authors acutely challenged the volunteers with either oral dronabinol (synthetic THC) or placebo (PBO) during extinction learning to test the hypothesis that THC would increase retention of fear extinction. All subjects participated in partial discrimination fear conditioning, in which a neutral face CS was presented and co-terminated with an aversive US at a partial reinforcement rate of 75% (CS+). A second neutral face CS was presented during this period but never paired with the US (CS−). Extinction training occurred the following day, in which the CS+ and CS− were presented but the CS+ was presented in the absence of the US. Approximately 2 hours prior to extinction learning participants were administered an oral dose of THC (10 mg) or PBO. An extinction retention test was conducted, drug-free in all participants, approximately 48 hours after extinction learning and involved non-reinforced presentations of the CS+ and CS−. Contrary to their hypothesis, the authors did not find an effect of THC on fear extinction. During extinction learning THC did reduce SCRs to the CS+, however this effect was not maintained during the extinction retention test and THC had no effect on fear-potentiated startle either during extinction learning or during the retention test. Therefore the authors concluded that their findings suggested that facilitation of the CB1 system with THC does not affect long-term conditioned fear extinction in humans.

A recent study [82], conducted in our laboratory with a similar design produced findings not consistent with the above observations reported by Klumpers *et al.* [81]. Using a randomized, double-blind, placebo-controlled, between-subjects design, we tested healthy volunteers with a combined standard Pavlovian fear extinction paradigm and an acute pharmacological challenge with oral dronabinol (THC; 7.5 mg) or PBO. The THC/PBO administration occurred prior to extinction training and we tested extinction retention 24 hours after extinction training [82]. Via partial discrimination fear conditioning, participants were presented with two neutral CSs (CS+s; e.g., blue and yellow squares) that co-terminated with an aversive US at a partial reinforcement rate of 35%. A third CS (e.g. red square) was presented during fear conditioning but never paired with the US (CS−). On the following day, one of the CS+s was extinguished (CS+E) whereas the other CS+ was not (CS+U). Approximately 2 hours before extinction learning participants were administered an oral dose of THC (7.5 mg) or PBO. Approximately 24 hours after extinction learning we conducted an extinction memory recall test to the following conditions: CS+E, CS+U, and CS−. Here, we observed that participants who had previously received PBO displayed evidence of a return of fear after the passage of a day’s time to a CS that was previously extinguished, whereas THC attenuated this ‘spontaneous recovery’ of fear [82]. Our study

provided the first evidence to suggest that pharmacological enhancement of extinction learning is feasible in humans using cannabinoid agonists.

It is important to discuss the potential factors that may have contributed to the conflicting results from our study [82] and those from Klumpers *et al* [81]. For instance, Klumpers and colleagues administered a slightly higher dose of THC (10 mg) than we did (7.5 mg). We had previously used this lowest effective dose, which did generate behavioral and subjective effects [57, 61, 83]. This lower dose has also been shown to reduce response of the amygdala to facial cues that signal the potential for threat (fearful and angry faces) in healthy recreational marijuana users [61], whereas administration of a higher dose of oral THC (10 mg) has been shown to increase amygdala activation [63] and increase levels of anxiety and autonomic arousal to fearful faces [63, 64]; a future dose-response study comparing 7.5mg vs. 10mg is needed to clarify this open question. In addition, differential sensitivity to the effects of THC between individuals may also contribute these conflicting findings [75, 76]. Another major difference between the two studies is that we examined extinction retention 24 hours following training of extinction whereas Klumpers and colleagues examined retention of extinction 48 hours after that training. In their study, THC did reduce SCRs generated by the CS+ during the training of extinction, but this effect was not maintained at 48 hours post training (extinction retention test), therefore future studies are needed to determine if the effects that we observed on Day 2 would persist for a longer period of time beyond 24 hours. Lastly, sex differences, particularly related to hormone influences, could have also potentially affected the efficacy of THC on fear extinction. Previous studies have shown fear extinction can be facilitated by high estradiol levels [84, 85]. Female participants in our study completed the study sessions approximately 1 week before the onset of menses to ensure the examination occurred during periods when estrogen levels were low, whereas accounting for differences in hormonal levels within the menstrual cycle at the time of testing was not explicitly mentioned in the Klumpers *et al* [81] study. Although some of these differences in study design between the two studies may help explain the conflicting findings, these are the first and only two studies to investigate the role of the cannabinoid system in human fear extinction and future studies are necessary to replicate these observations. Together these studies couple the basic science of fear extinction learning and human neuropsychopharmacology to enhance fear inhibition and prompt more studies of this kind. Moreover, more studies are needed to help explain the brain and neurochemical mechanisms by which cannabinoid agonists mediate extinction learning and its retention.

HOW MIGHT THE CANNABINOID SYSTEM AFFECT FEAR EXTINCTION?

In the brain, endocannabinoids (eCBs) are released postsynaptically and diffuse back to presynaptic CB1 receptors, densely localized within AMYG, vmPFC, and HPC [86–89], thereby inhibiting presynaptic neurotransmitter release [90, 91]. It has been hypothesized that during extinction learning eCB activation of CB1 receptors within the AMYG decreases local GABAergic networks, which leads to a disinhibition of principal neurons and finally to the extinction of conditioned fear responses [44, 91]. Interestingly, intra-basolateral AMYG infusion of CB1 agonist enhances retention of inhibitory training (e.g., via memory consolidation) [92]. In addition, activation of CB1 receptors within the vmPFC during

extinction induces neuronal plasticity within the vmPFC, and thus enhances top-down inhibition on the AMYG [46]. In parallel, activation of HPC CB1 receptors increases glutamatergic neurotransmission, which may facilitate extinction memory formation over the long term [45].

Studies on the effect of cannabinoids on the underlying neural circuitry involved in the retention and recall of extinction memory in humans are ongoing in the lab, which combine fMRI with a similar Pavlovian fear conditioning-extinction paradigm as in our recent behavioral study [82] (mentioned above) to assess the effects of THC on extinction circuit function (e.g., vmPFC and HPC activation) when tested for recall and maintenance of extinction learning at 24 hours and 1 week after training, respectively. Preliminary fMRI results from our lab [93] suggest that THC administration during extinction learning subsequently increases vmPFC activation and functional coupling with the HPC to a previously extinguished CS (vs. a non-extinguished CS+) during recall of extinction memory compared to PBO (unpublished). Based on these preliminary results we would hypothesize that THC facilitates retention of extinction memory via increased recruitment of the vmPFC and HPC. Studies, such as this, are important proof-of-concept studies that translate animal to human studies and ultimately to clinical trials. This process will facilitate our knowledge of the role and neural mechanism of cannabinoids in extinction learning, and subsequently may lead to new pharmacologic strategies (e.g., cannabinoid-enhancing modulators) that can be combined with to improve exposure-based behavioral treatments.

SUMMARY

Although CBT is an effective first-line treatment for anxiety disorders, such as PTSD, some patients continue to have an anxiety disorder diagnosis, fail to achieve stringent criterion for good end-state functioning [94, 95], and some fail to complete treatment [96]. Even fewer respond to first-line pharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs) [97, 98]. The Institute of Medicine in 2007 concluded that little empirical evidence exists to support pharmacological treatment for PTSD; therefore new treatments are desperately needed [99].

As mentioned previously, basic science research has shown that activation of the cannabinoid system can improve the learning and retention of extinction, whereas inhibition of this system impairs fear extinction [44–47, 49–51, 53, 91, 100, 101]. Moreover, we provided the first evidence that THC when given prior to extinction training to previously conditioned fear can improve the recall of that extinction memory in humans [82] and have preliminary data to suggest that this effect may be due to increased recruitment of the vmPFC and HPC [93]. If activation or agonism of the CB1 receptor, thereby enhancing cannabinoid neurotransmission, can improve the recall of what is learned during extinction training, then the cannabinoid system may prove to be a promising neurochemical target. This target appears to be most relevant in the clinical setting where there is a need to maximize, retain and sustain treatment effects of exposure-based therapies.

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