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Cannabidiol and the corticoraphe circuit in post-traumatic stress disorder

Claire Alexander, Maryam Vasefi *

Department of Biology, Lamar University, Beaumont, TX 77710, USA

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ABSTRACT

Post-Traumatic Stress Disorder (PTSD), characterized by re-experiencing, avoidance, negative affect, and impaired memory processing, may develop after traumatic events. PTSD is complicated by impaired plasticity and medial prefrontal cortex (mPFC) activity, hyperactivity of the amygdala, and impaired fear extinction. Cannabidiol (CBD) is a promising candidate for treatment due to its multimodal action that enhances plasticity and calms hyperexcitability. CBD's mechanism in the mPFC of PTSD patients has been explored extensively, but literature on the mechanism in the dorsal raphe nucleus (DRN) is lacking. Following the PRISMA guidelines, we examined current literature regarding CBD in PTSD and overlapping symptomologies to propose a mechanism by which CBD treats PTSD via corticoraphe circuit. Acute CBD inhibits excess 5-HT release from DRN to amygdala and releases anandamide (AEA) onto amygdala inputs. By first reducing amygdala and DRN hyperactivity, CBD begins to ameliorate activity disparity between mPFC and amygdala. Chronic CBD recruits the mPFC, creating harmonious corticoraphe signaling. DRN releases enough 5-HT to ameliorate mPFC hypoactivity, while the mPFC continuously excites DRN 5-HT neurons via glutamate. Meanwhile, AEA regulates corticoraphe activity to stabilize signaling. AEA prevents DRN GABAergic interneurons from inhibiting 5-HT release so the DRN can assist the mPFC in overcoming its hypoactivity. DRN-mediated restoration of mPFC activity underlies CBD's mechanism on fear extinction and learning of stress coping.

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating stressor and trauma-related disorder associated with exposure to traumatic events (Bitencourt and Takahashi, 2018; Elms et al., 2019; Xiang et al., 2017; Lacivita et al., 2012; Ursano et al., 2009). Symptoms include intrusive memories and re-experiencing, avoidance, and negative cognitions (Reisman, 2016; American Psychiatric Association, 2013). PTSD is often comorbid with substance abuse disorders, anxiety disorders, and depression (American Psychiatric Association, 2013). Trauma exposure impairs physiological and psychological habituation to stress (Hill et al., 2018; Lissek and van Meurs, 2015). Trauma exposure facilitates formation and consolidation of an associative fear memory (Elms et al., 2019; Parsons and Ressler, 2013), while frequent exposure to a fear-related cue facilitates reconsolidation of the traumatic memory, impairing fear extinction (Hill et al., 2018). Thus, the individual is unable to retain the extinction memory that should have eventually replaced the fear memory (Fenster et al., 2018). Persistent negative cognitions impair suppression of intrusive memories (Catarino et al., 2015; Meiser-Stedman et al., 2009), while frequent flashbacks and avoidance behaviors in turn worsen the negative cognitions, leading to anxiety and depression symptoms (Hill et al., 2018).

Treatments for PTSD are still limited, and there are currently 2 pharmacological treatments approved by the United States Food and Drug Administration (FDA) to treat PTSD: the selective serotonin reuptake inhibitors (SSRIs) Sertraline (Zoloft) and Paroxetine (Paxil) (Reisman (2016); Jeffreys (2016)). Other pharmaceuticals, such as other SSRIs, selective norepinephrine reuptake inhibitors (SNRIs), and classic antidepressants, are commonly prescribed off-label (Reisman (2016); Elms et al., 2019). SSRIs are first line treatments for PTSD, but are often

Abbreviations: 2-AG, 2-arachidonoylglycerol; 5-HT, Serotonin; 5-HT1AR, 5-HT Receptor Type 1A; 5-HT2AR, 5-HT Receptor Type 2 A; AEA, Anandamide; CB1R, Cannabinoid Receptor Type 1; CB2R, Cannabinoid Receptor Type 2; CBD, Cannabidiol; COVID-19, SARS-CoV-2; DRN, Dorsal Raphe Nucleus; ERK1/2, Extracellular Signal-Related Kinases Type 1 or Type 2; FAAH, Fatty Acid Amide Hydrolase; fMRI, Functional Magnetic Resonance Imaging; GABA, Gamma-Aminobutyric Acid; GPCRs, G-Protein Coupled Receptors; mPFC, Medial Prefrontal Cortex; NMDAR, N-Methyl-D-aspartate Receptors; PET, Positron Emission Tomography; PFC, Prefrontal Cortex; PTSD, Post-Traumatic Stress Disorder; SSRI, Selective Serotonin Reuptake Inhibitor; SSNRI, Selective Norepinephrine Reuptake Inhibitor; TRPV1, Transient Receptor Potential Vanilloid 1 Channels.

* Corresponding author.
E-mail addresses: ealexander5@lamar.edu (C. Alexander), svasefi@lamar.edu (M. Vasefi).

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abandoned due to unpleasant side effects and delayed onset of observable effects (Soares and Campos, 2017; Roy-Byrne et al., 2006; Hammack et al., 2012; Vaswani et al., 2003). Moreover, only 60% of PTSD patients reported some symptom improvement from Paroxetine and Sertraline, while an underwhelming 20–30% of PTSD patients reported complete abrogation of symptoms from these SSRIs (Kelmendi et al., 2016; Reisman (2016); Berger et al., 2009). Some patients have reported self-medication with cannabis, citing improved sleep and reduced anxiety (Bitencourt and Takahashi, 2018; Russo et al., 2007; Hill et al., 2018; Betthauser et al., 2015; Bonn-Miller et al., 2007; Bremner et al., 1996). High-dose THC use is associated with anxiety and memory impairment, but studies have implicated CBD as a promising non-psychoactive alternative to address PTSD-related endocannabinoid deficits (Bitencourt and Takahashi, 2018; Di Marzo (2009); Castillo et al., 2012). CBD may also be superior to SSRIs due to its multimodal action that produces rapid, long-lasting effects, potentiates fear extinction, impairs fear memory consolidation, and facilitates neurogenesis (Campos et al., 2012; Stern et al., 2012; Bitencourt et al., 2008; Norris et al., 2016; Fogaça et al., 2018; Morena et al., 2016). Chronic CBD has an anxiolytic effect in rodent chronic unpredictable stress (CUS) models, an antidepressant effect in forced swim test (FST) models, and an anti-aggressive effect in socially isolated rodents (DeGregorio et al., 2019; Campos et al., 2013; Zanelati et al., 2010; Hartmann et al., 2019; Ferris et al., 2008).

The mechanism of CBD is still debated, but several studies have investigated its activity in structures affected by PTSD, including the hippocampus, amygdala, and prefrontal cortex (PFC). Thus, treatments must seek to improve functional deficits in these and other structures like the DRN. The corticoraphe circuit is a monosynaptic circuit between the mPFC and DRN that is implicated in psychiatric disorders (Grizzell et al., 2020; Geddes et al., 2016). Furthermore, the identification of CB1R in these structures (Häring et al., 2015) suggests that collaborative endocannabinoid, 5-HT, and glutamatergic signaling may regulate the stress response. Thus, this literature review aims to deduce CBD's mechanism of action within the corticoraphe circuit of PTSD patients. Chronic CBD administration in the circuit should produce anxiolytic and antidepressant effects by augmenting mPFC control over the amygdala, thereby facilitating fear extinction and re-establishing fear network balance (Campos et al., 2013; Sales et al., 2019). To our knowledge, this is the first review connecting the role of the corticoraphe circuit in CBD treatment of PTSD. While some studies have investigated CBD injection into the PFC to treat PTSD, we have yet to identify a review addressing the role that CBD administration into the DRN would have on the corticoraphe circuit. In this review, we address recent literature regarding CBD effects in the PFC and DRN separately, then describe current literature on corticoraphe administration of CBD in models and pathologies related to PTSD. Finally, we propose some of the mechanisms by which CBD can alleviate PTSD symptoms within the circuit, hoping to support the necessity of future research into this circuitry for PTSD treatments. This review attempts to answer whether CBD administration to the DRN could, in turn, restore inhibitory control to the mPFC. We propose differing acute and chronic mechanisms of CBD that ultimately achieve this goal. In short, the acute mechanism of CBD reduces excitability of the amygdala and DRN, to allow chronically administered CBD to shift inhibitory control back to the mPFC, critically ameliorating the core symptoms of PTSD.

2. Methods

2.1. Study selection and data extraction

For data gathering purpose the PRISMA guidelines was used. Data was collected using the PubMed, Science Direct, and Google Scholar databases until February 2021. A relevant list of research articles, review articles, and clinical studies were used to study the effects of cannabidiol on corticoraphe circuit in Post-Traumatic Stress Disorder (PTSD). The inclusion criteria required that articles must discuss any of the following: components of the corticoraphe circuit, CBD and its mechanism of action, endocannabinoids mechanism, structural and functional changes in PTSD, and the mechanism of action of CBD in the corticoraphe circuit in disorders and symptoms related to PTSD. Some n = 11,099 articles were identified during an initial search on these databases, then n = 100 full-text articles were screened according to their abstract if the content was relevant to the purpose of the review. A final screening resulted in n = 52 papers relating to the action of CBD in PTSD and the corticoraphe circuit. Data in this review was collected from studies relevant to our objective and the language was limited to English. (Fig. 1).

3. Fear network dysregulation in PTSD

PTSD is associated with significant structural and functional changes in the amygdala, hippocampus, PFC, and DRN (Fig. 2) (Harnett et al., 2020; Worley et al., 2018; Liu et al., 2012). Upon exposure to trauma reminders, amygdala activity reaches a level that cannot be effectively controlled by inhibitory input from the hypoactive mPFC (van Rooij and Jovanovic, 2019; Liberzon et al., 1999; Milad et al., 2009; Rauch et al., 2000; Stevens et al., 2013, 2017; Hill et al., 2018; Morena et al., 2016; Logue et al., 2018; Etkin and Wager, 2007; Clausen et al., 2017). fMRI studies confirmed hyperactivity and reduced amygdala volume in PTSD, while PET studies suggested that enhanced glutamate receptor availability increases amygdalar excitability (Harnett et al., 2020; Ganzel et al., 2008; Rogers et al., 2009; Holmes et al., 2017). Amygdala hyperactivity and mPFC hypoactivity underlie hypervigilance and re-experiencing (Fenster et al., 2018). The amygdala and hippocampus mediate acquisition and consolidation of contextual fear memory during traumatic events, while the amygdala and vmPFC mediate fear extinction (Kida (2019); Mamiya et al., 2009). However, fMRI studies revealed disengagement and hypoactivity of the vmPFC and mPFC during extinction learning and recall in PTSD (van Rooij and Jovanovic, 2019; Rougemont-Bücking et al., 2011; Garfinkel et al., 2014; Milad et al., 2009; Jovanovic et al., 2013; Aupperle et al., 2016; Falconer et al., 2008), supporting the significance of vmPFC and mPFC participation in improvement of PTSD-related memory deficits. Moreover, PTSD is associated with reduced gray matter of the ventromedial and dorsomedial prefrontal cortex (Harnett et al., 2020; Bing et al., 2013; Li et al., 2014; Rauch et al., 2003; Woodward et al., 2006; Wrocklage et al., 2017; Yamasue et al., 2003). Thus, our review considers the amygdala relevant to CBD's corticoraphe mechanism. Also, reduced hippocampal volume and excitotoxicity-induced damage to hippocampal neurons contribute to hippocampal hypoactivity and impaired memory processing (Harnett et al., 2020; Logue et al., 2018; Karl et al., 2006; Kühn and Gallinat, 2013; Rosso et al., 2017; Lowy et al., 1995; Choi et al., 1988; Mark et al., 2001). Finally, data on structural and functional changes of the DRN in humans with PTSD has not yet been identified, however enhanced DRN 5-HT excitability was observed in rodents exposed to inescapable stress (Worley et al., 2018; Greenwood et al., 2003), while rodents exposed to single prolonged stress had reduced gray matter volume of the pons (Liu et al., 2012). These behavioral paradigms are frequently used to study symptoms of PTSD in rodents (Worley et al., 2018; Liu et al., 2012).

4. The corticoraphe circuit

4.1. Corticoraphe circuit in PTSD

The corticoraphe circuit consists of the glutamatergic projections from the mPFC to DRN 5-HT and GABAergic interneurons, and the 5-HT projections from DRN to the mPFC (Grizzell et al., 2020; Ren et al., 2018; Zhou et al., 2017; Geddes et al., 2016). The DRN, implicated in anxiety and depressive behaviors (Hammack et al., 2012; Lowry et al., 2005; Amat et al., 1998a, 1998b; Prakash et al., 2020), is a major source of 5-HT, abundantly expresses 5-HT1AR, and sends projections to areas

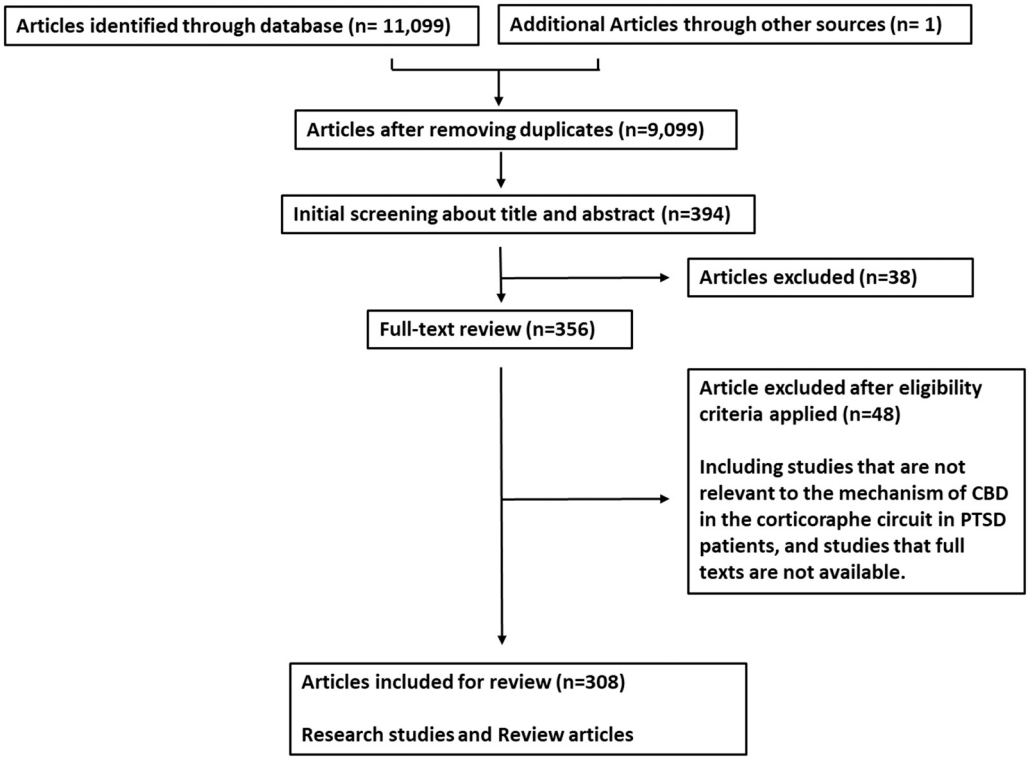

Fig. 1. Flow chart of article screening and selection process.

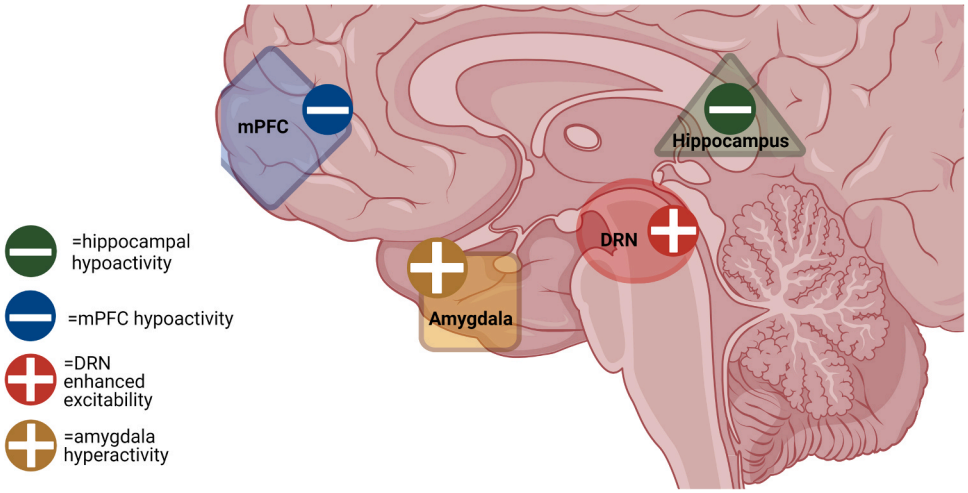

Fig. 2. Dysfunction of the fear network and corticoraphe circuit in PTSD. Regarding functional change in PTSD, the amygdala becomes hyperactive while the hippocampus and mPFC become hypoactive, and DRN may become more excitable. In general, PTSD appears to be associated with reduced volumes of the amygdala, ventromedial PFC (vmPFC) and dorsomedial PFC (dmPFC), and hippocampus. One study has suggested reduced DRN volume in rats due to stress-induced apoptosis. "Created with BioRender.com"

including amygdala, mPFC, and hippocampus (Ren et al., 2018; Zhou et al., 2017; Gagnon and Parent, 2014; Celada et al., 2013; Charnay and Leger, 2010). DRN 5-HT neurons can express $GABA_A$ and $GABA_B$ receptors and receive input from local GABAergic interneurons and external GABA projections (Hernández-Vázquez et al., 2019; Gao et al., 1993; Abellán et al., 2000; Serrats et al., 2003; Pollak Dorocic et al., 2014; Weissbourd et al., 2014). Furthermore, the DRN sends GABAergic innervation to the mPFC (Hernández-Vázquez et al., 2019; Bang and Commons, 2012; Puig et al., 2005). These projections must also be controlled by CBD and endocannabinoids to limit inhibitory input to the mPFC. Excitatory input from the mPFC terminals to the GABAergic interneurons of the DRN inhibits 5-HT release (Geddes et al., 2016), while the 5-HT neurons from the dorsal and median raphe nuclei innervate GABAergic neurons in the vmPFC, amygdala, and hippocampus (Kelmendi et al., 2016; Neumeister, 2013a, 2013b). Some NMDAR-expressing 5-HT neurons in intrafasicular DRN innervate the mPFC but are highly sensitive to chronic unpredictable stress (Natarajan et al., 2017; Grahn et al., 1999; Hale and Lowry, 2011; Littrell (2012); Paul and Lowry, 2013).

As previously stated, many symptoms of PTSD, such as enhanced anxiety and impaired extinction memory consolidation, stem from vmPFC hypoactivity, contributing to an underwhelming inhibitory control response to amygdala activation. vmPFC hypoactivity is related to reduced glutamatergic activity in PTSD patients (Harnett et al., 2020; Yang et al., 2015), suggesting impaired plasticity and impaired extinction learning. Specifically, elevated plus maze, tail shock, and forced swim test studies suggested that stressor controllability facilitates learning of stress resilience by recruiting the vmPFC-DRN circuit, while uncontrollable/inescapable stressors impair stress coping and plasticity in the vmPFC (Grizzell et al., 2020; Maier and Watkins, 2005; Maier

et al., 2006; Worley et al., 2018; Faye et al., 2020; Baratta et al., 2009a, 2009b, 2019; Warden et al., 2012). Traumatic stress enhances DRN excitability by downregulating 5-HT1A autoreceptor expression (Worley et al., 2018; Amat et al., 2005; Rozeske et al., 2011) and reducing vmPFC engagement (Grizzell et al., 2020; Cooper et al., 2008). Thus, the amygdala can easily recruit the DRN, allowing both structures to provide excitatory input to each other, and impairing fear extinction by increasing the activity disparity that the mPFC must overcome to control amygdala activity. Plus, rodents with impaired PFC-DRN connectivity showed impaired stressor control following replacement of inescapable stressors with escapable stressors (Taylor et al., 2014; Amat et al., 2005; Hammack et al., 2012; Robbins (2005)). Activation of caudal DRN 5-HT neurons potentiated 5-HT release and enhanced anxiety-like behavior in learned helplessness models exposed to inescapable shock (Hammack et al., 2012; Lowry et al., 2005; Amat et al., 1998a, 1998b). Thus, PTSD treatments must reduce DRN and amygdala excitability before mPFC control is restored.

4.2. Net effects of corticoraphe dysregulation: amygdala

The basal amygdala, basolateral amygdala, and central amygdala receive abundant input from the caudal and dorsal raphe nuclei (Sengupta and Holmes, 2019; Ren et al., 2018; Retson and van Bockstaele, 2013; Gagnon and Parent, 2014). In turn, the amygdala sends abundant GABAergic and glutamatergic input to modulate the DRN (Zhou et al., 2017). In PTSD, the excitability of both the amygdala and DRN increases, perpetuating the reconsolidation of fear memories (Harnett et al., 2020; Worley et al., 2018; Grizzell et al., 2020; Sengupta and Holmes, 2019). Relevant to PTSD, the DRN mediates acquisition and expression of social defeat behaviors, and its 5-HT projections to the amygdala participate in anxiety-like behaviors (Grizzell et al., 2020; Cooper et al., 2008; Ren et al., 2018). DRN-mediated excitation of basal amygdala glutamatergic neurons in animals during fear conditioning favored acquisition of associative fear memory over encoding of fear extinction (Sengupta and Holmes, 2019; Akirav et al., 2006; Anglada-Figueroa and Quirk, 2005; Herry et al., 2008; Namburi et al., 2015; Sierra-Mercado et al., 2011). Furthermore, DRN 5-HT neurons may release excess 5-HT into the basolateral amygdala following inescapable stress (Worley et al., 2018; Christianson et al., 2010), enhancing basolateral amygdala participation in fear memory acquisiton and association between threatening stimuli and danger (Harnett et al., 2020; Campeau and Davis, 1995; Fanselow and Kim, 1994; LeDoux et al., 1990). The central amygdala assigns salience to emotionally aversive stimuli and relays associative fear information to the hypothalamus and brainstem (Retson and van Bockstaele, 2013). Taken together, these data suggest that new PTSD treatments must target DRN 5-HT1AR to reduce DRN 5-HT projection-mediated excitation of the basal amygdala and basolateral amygdala, thereby reducing the participation of these structures in generation of associative fear memory and anxiety. Moreover, by targeting DRN 5-HT projections to central amygdala, new treatments could reduce physical manifestations of PTSD such as enhanced freezing/startling responses (Harnett et al., 2020; Avery et al., 2014; Cheng et al., 2003, 2006; Dong et al., 2001; Helmstetter (1992); Helmstetter and Bellgowan, 1993; Knight et al., 2005; LaBar et al., 1998; Maren (2001); Ono et al., 1985; Pitkänen et al., 1997; Veening et al., 1984; Weller and Smith, 1982; Wilensky et al., 2006).

4.3. Relevance of corticoraphe and fear network dysfunction to PTSD symptoms

Many of the defining PTSD symptoms are related to fear memory, the encoding of a fear response and the strong re-experiencing of the traumatic event as a maladaptive defense mechanism (Bitencourt and Takahashi, 2018; Fenster et al., 2018). Symptom provocation studies, in which humans with PTSD are exposed to reminders related to their trauma during an fMRI study, suggested that intrusive memories, which tend to culminate in re-experiencing of the traumatic events, are associated with hypoactivity of the mPFC, resulting failure of the mPFC to inhibit amygdala-hippocampal crosstalk in generation of the traumatic fear memory (Fenster et al., 2018; Bremner et al., 1999a, 1999b; Lanius et al., 2010; Liberzon et al., 1999; Osuch et al., 2001; Pissiota et al., 2002; Rauch et al., 1996; Shin et al., 1999; Zubieta et al., 1999; Milad et al., 2009). Since the mPFC has failed to control amygdala activity, the amygdala has greater freedom to re-consolidate the traumatic fear memory via crosstalk with the hippocampus, thus strengthening the fear memory (Kida (2019); Mamiya et al., 2009; Fenster et al., 2018). The chronic stress associated with PTSD culminates in hippocampal hypoactivity due to glutamate-induced excitotoxicity and death of the hippocampal neurons, resulting in declarative memory deficits and dysfunctional threat expectations, thereby compounding the difficulty with fear extinction learning (Harnett et al., 2020; Bremner et al., 2004; Rabinak et al., 2017; Tischler et al., 2006; Carrión et al., 2010; Hayes et al., 2011; Milad et al., 2009). Proper mPFC-amygdala connectivity is required to favor strengthening of the extinction memory over strengthening of fear memory, but a traumatized individual's ability to retain the extinction memory is impaired with each re-exposure to reminders, in which the traumatic memory is reconsolidated by enhanced amygdala-hippocampal crosstalk (Kida (2019); Mamiya et al., 2009).

Moreover, chronic stress due to PTSD further impairs fear extinction ability by reducing activity of the PFC, as indicated by reduced biomarker Glx (ratio of glutamate to glutamine) levels in the vmPFC of PTSD patients (Harnett et al., 2020; Yang et al., 2015). As previously stated, the necessity of the vmPFC and mPFC to extinction learning was supported by a series of fMRI studies revealing decreased participation of both structures during extinction learning and recall (van Rooij and Jovanovic, 2019; Rougemont-Bücking et al., 2011; Garfinkel et al., 2014; Milad et al., 2009; Jovanovic et al., 2013; Aupperle et al., 2016; Falconer et al., 2008). The vmPFC and mPFC are also critically involved in inhibitory control over amygdala-mediated emotional reactivity (van Rooij and Jovanovic, 2019; Stevens et al., 2013). Moreover, studies have already demonstrated that the corticoraphe circuit is necessary for learning of stress resilience, which is crucial for greater stress coping ability upon later stressor exposure (Worley et al., 2018; Grizzell et al., 2020). Tail shock-exposed hamsters who did not demonstrate PTSD-like behavior had greater DRN-vmPFC engagement during the traumatic event, allowing for learning of stress resilience, while those with reduced vmPFC activity and increased DRN activity became more susceptible to stress upon later tail shock (Grizzell et al., 2020; Baratta et al., 2009a, 2009b, 2019; Maier and Seligman, 2016; Amat et al., 2008). Given the frequent strengthening of traumatic memories upon trauma reminder exposure, paired with the hypervigilance symptoms that contribute to a constant anxious state, there is significant impairment of synaptic plasticity in PTSD patients, that in healthy individuals with normal levels of mPFC activity, would normally strengthen extinction memory following trauma exposure. Thus, the corticoraphe circuit is also crucial in prevention of PTSD development following trauma exposure, as a treatment that can first stabilize DRN activity would lead to downstream improvement of the memory impairments that underlie PTSD symptoms. This DRN-vmPFC circuit was critically involved in learning of stress resilience in hamsters and rodents (Grizzell et al., 2020; Worley et al., 2018), suggesting that new treatments for PTSD should aim to normalize corticoraphe signaling.

Separately from the DRN-mPFC circuit, the DRN-basal amygdala circuit plays a crucial role in generation of associative fear memory (Sengupta and Holmes, 2019), while the DRN-central amygdala circuit participates in anxiety-like behavior (Ren et al., 2018). Since the DRN 5-HT projections to the basal amygdala participate in reconsolidation of fear memories, they contribute to impaired fear extinction in PTSD (Sengupta and Holmes, 2019). As such, reduction of DRN and amygdala excitability will begin to reduce the tendency to favor fear memory reconsolidation, as the reduction of such amygdala activity slowly reduces the activity disparity that the mPFC must overcome to exert its

inhibitory control over the amygdala and favor consolidation of fear extinction. In order for new PTSD treatments to effectively treat the core symptoms of PTSD, the circuitry involved in fear memory must first be targeted. Moreover, the treatment must have a rapid mechanism that can control DRN excitability and re-route its excitatory projections to favor greater connectivity with the hypoactive mPFC over the enhanced DRN-amygdala connectivity observed in trauma-exposed animals. After the activity of circuitry mediating generation and reconsolidation of fear memory is normalized, the new PTSD treatment must next be able to potentiate fear extinction ability by re-establishing proper mPFC-amygdala signaling, in which the mPFC is able to properly exert inhibitory control over the amygdala.

5. Neurotransmitters

5.1. Serotonin

5-HT receptors are abundantly expressed in the DRN, hippocampus, amygdala, striatum, substantia nigra, and frontal cortex (Charnay and Leger, 2010). 5-HT1AR and 5-HT2AR are often implicated in PTSD (Xiang et al., 2017). In healthy individuals, 5-HT1AR expression is most abundant in the raphe nuclei, hippocampus, septum, and cerebral cortex (Lewis et al., 2020; Glikmann-Johnston et al., 2015; Ito et al., 1999; Kia et al., 1996; Hall et al., 1997; Weissmann-Nanopoulos et al., 1985; Li et al., 2006; Knapp and Kornetsky, 2009; Depoortère et al., 2010). 5-HT1AR activation reduces depressive-and anxiety-like behavior by inhibiting ERK1/2 to reduce 5-HT2AR signaling (Xiang et al., 2017; Franklin and Carrasco, 2013; Kurrasch-Orbaugh et al., 2003; Ursano et al., 2009; Wang et al., 2009), while 5-HT2AR activation potentiates 5-HT release and desensitizes 5-HT1AR via ERK1/2 phosphorylation (Xiang et al., 2017; Pilar-Cuellar et al., 2012; Xie et al., 2012; van Praag (2004); Canli et al., 2005; Liu et al., 2013). Reports on 5-HTR expressional changes in PTSD are mixed. Xiang et al. (2017) found increased 5-HT2AR in traumatized rodents, while trauma type may have varying effects on 5-HT1AR expression depending on region (Lewis et al., 2020; Luo et al., 2011; López et al., 1999; Flügge (1995); Norris et al., 2016; Sullivan et al., 2013). A PET study found the highest 5-HT1AR binding in the raphe nuclei, but 5-HT1AR binding in the amygdala, vmPFC, and mPFC of PTSD patients was also significant (Sullivan et al., 2013), and single prolonged stress (SPS) induced 5-HT1AR upregulation in the DRN of rats (Liu et al., 2012; Luo et al., 2011).

5.2. Endocannabinoids

Endocannabinoids, including AEA and 2-AG, are lipid-based neuromodulators synthesized on-demand in post-synaptic neurons that bind to CB1R/CB2R, reducing neurotransmitter release (Bassir Nia et al., 2019; Hillard (2014); Cravatt and Lichtman, 2003; Morena et al., 2016; Howlett et al., 2002; Kano et al., 2009). FAAH inhibits AEA signaling via hydrolysis, while Monoacylglycerol Lipase terminates the 2-AG signal (Morena et al., 2016; Cravatt et al., 2001; Dinh et al., 2002; Gulyas et al., 2004). CB1R, FAAH, and AEA are found in the basolateral amygdala, hippocampus, PFC, and DRN (Burstein et al., 2018; Breivogel and Sim-Selley, 2009; Papagianni and Stevenson, 2019; Russo (2018); Scherma et al., 2018). However, PTSD patients show deficits in CB1R expression and AEA levels in many regions due to elevated FAAH (Neumeister, 2013a, 2013b). CB1R expression increases in the amygdala, hippocampus, and corticostriatal pathway as a possible compensatory mechanism for AEA depletion in PTSD, though one study suggested varying AEA levels (Kelmendi et al., 2016; Neumeister, 2013a, 2013b; Bitencourt and Takahashi, 2018; Hauer et al., 2013; Hill et al., 2013a; Loflin et al., 2017; Papagianni and Stevenson, 2019). These deficits may underlie some PTSD symptoms, as anxiety-like behavior was observed in CB1R knockout rodents (Häring et al., 2015). Like 5-HT1AR, trauma type and brain region differentially affect CB1R expression. Specifically, maternal deprivation-exposed rats had reduced CB1R function in the PFC, while chronic unpredictable stress-exposed rats had increased PFC CB1R expression but decreased expression in the hippocampus and hypothalamus, and single prolonged stress exposure enhanced CB1R expression in amygdala, hippocampus, and PFC (Bassir Nia et al., 2019; Llorente-Berzal et al., 2013; Hill et al., 2005; Zer-Aviv and Akirav, 2016). Long-term restoration of AEA in PTSD animals facilitates short-term fear extinction and reduces fear-related behavior (Kelmendi et al., 2016; Gunduz-Cinar et al., 2013; Pamplona et al., 2008). Lentiviral infection and forced swim test exposure had anxiogenic effects due to reduced AEA in the vmPFC (Worley et al., 2018; Rubino et al., 2008a). Finally, neuroimaging studies observed improved fear extinction, and reduced anxiety and amygdalar activity in healthy patients with a mutation impairing FAAH activity (Bassir Nia et al., 2019; Gunduz-Cinar et al., 2013; Hariri et al., 2009; Mayo et al., 2018).

6. CBD mechanism of action

CBD is a partial agonist of 5-HT1AR and an agonist of Transient Receptor Potential Vanilloid 1 Channels (TRPV1) but has low affinity for CB1R (Bitencourt and Takahashi, 2018; Russo et al., 2005; DeGregorio et al., 2019; Bisogno et al., 2001; Hassan et al., 2014; Iannotti et al., 2014; Norris et al., 2016; Thomas et al., 2007). CBD rapidly treats PTSD symptoms not only by activating 5-HT1AR to modulate 5-HT signaling, but can also modulate endocannabinoid signaling by inhibiting FAAH activity and consequently enhancing CB1R activation via AEA (Papagianni and Stevenson, 2019; Batista et al., 2015). CBD is highly lipophilic, allowing it to easily diffuse into the cytosol (Branca et al., 2019; Bruni et al., 2018). Under normal conditions, binding of AEA to a fatty acid binding protein (FABP) would allow the FABP to transfer AEA to FAAH for enzymatic degradation, but by occupying this same binding site on the FABP, CBD prevents AEA degradation and thereby potentiates AEA signaling (Papagianni and Stevenson, 2019; Gunduz-Cinar (2021); Elmes et al., 2015). By this mechanism, CBD indirectly potentiates CB1R signaling (Papagianni and Stevenson, 2019; Bitencourt and Takahashi, 2018). The utility of 5-HT1AR agonism in PTSD treatment is supported by increased anxiety-like behaviors following 5-HT1AR deletion in mice (Kelmendi et al., 2016; Ramboz et al., 1998). Finally, lack of observable 2-AG alterations in PTSD patients (Neumeister, 2013a, 2013b), supports the need for AEA-targeted PTSD treatments.

6.1. Acute mechanism

Previous studies have suggested that CBD may alleviate PTSD symptoms by reducing hyperactivity of the amygdala (Bitencourt and Takahashi, 2018; Passie et al., 2012). Since DRN-amygdala signaling facilitates fear memory acquisition (Sengupta and Holmes, 2019), and DRN-basolateral amygdala 5-HT projections are required for consolidation of fear memory in chronically stressed rodents (Baratta et al., 2016; Michelsen et al., 2007; Vertes (1991); Hale et al., 2012; Cools et al., 2008; Kennett et al., 1997), CBD must first limit activity of this circuit. Also, glutamate receptor antagonist administration to the amygdala reduced startle responses in single prolonged stress-exposed animals (Harnett et al., 2020; Walker and Davis, 1997). Likewise, CBD may reduce startle responses via AEA-mediated inhibition of glutamate release from amygdala neurons.

We propose two acute effects of CBD (see Fig. 3) which limit fear network excitability. First, CBD activates 5-HT1AR on DRN 5-HT projections to the amygdala, limiting excitation of the amygdala by 5-HT. Likewise, CBD potentiates endocannabinoid signaling at the synapse between amygdala input (glutamate, for example) and a DRN 5-HT neuron to reduce DRN excitability. This mechanism ultimately reduces anxiety during re-experiencing and, second, begins to restore some inhibitory control to the mPFC by reducing the activity disparity. Specifically, since enhanced DRN-basal amygdala excitation during fear conditioning favored associative fear memory acquisition in animals

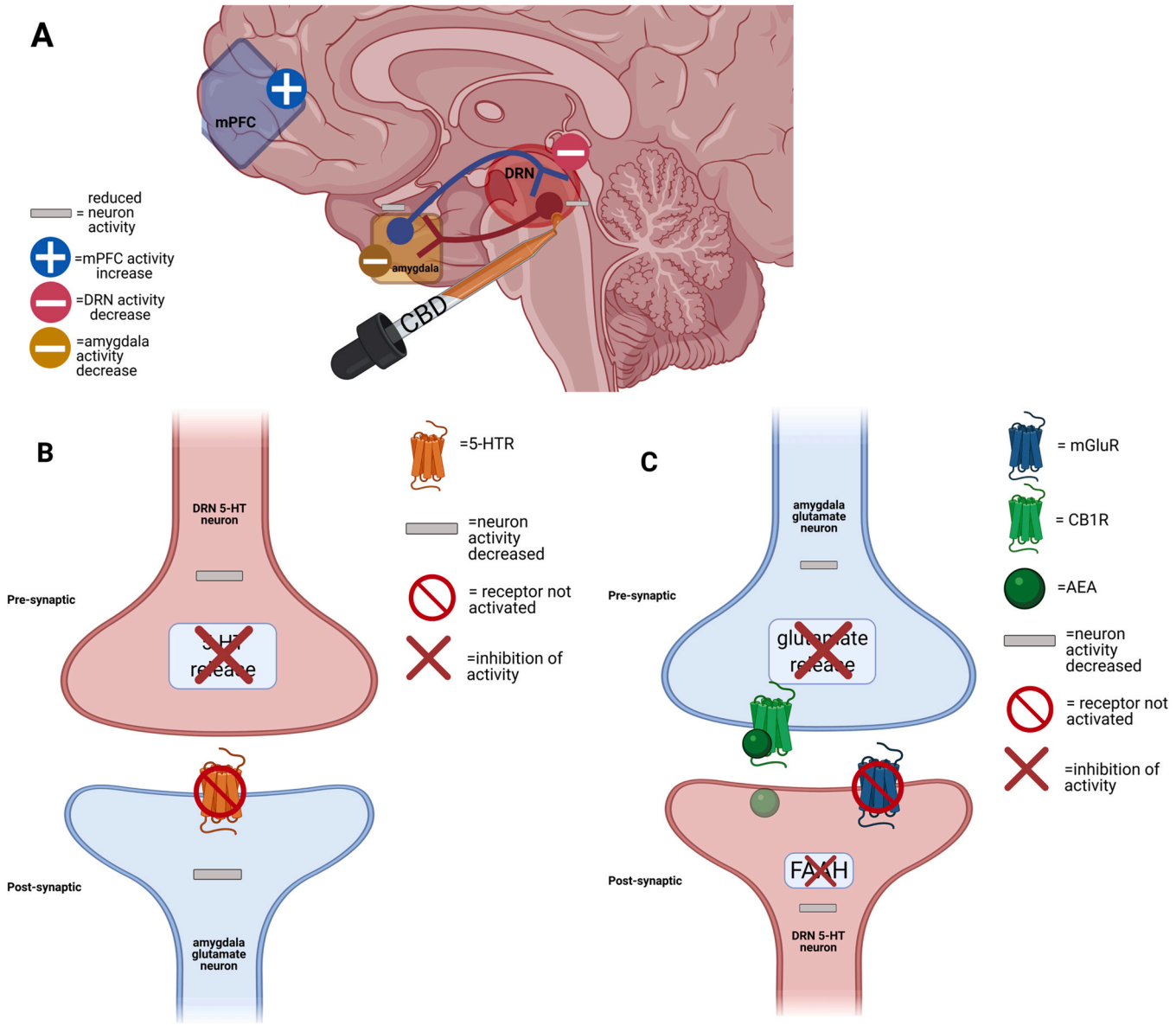

Fig. 3. A) A graphical summary of the literature addressing acute CBD effects. CBD administration to 5-HT1AR temporarily inhibits 5-HT release from DRN neurons, reducing DRN hyperactivity and reducing excitation of the amygdala. This reduces the activity disparity between the amygdala and mPFC. B) Acute CBD activates 5-HT1AR on DRN 5-HT neurons, reducing 5-HT release to the amygdala. C) In DRN, CBD inhibits FAAH in 5-HT neurons. AEA is released from DRN 5-HT neurons to amygdala input, inhibiting neurotransmitter release. "Created with BioRender.com"

(Sengupta and Holmes, 2019; Akirav et al., 2006; Anglada-Figueroa and Quirk, 2005; Herry et al., 2008; Namburi et al., 2015; Sierra-Mercado et al., 2011), CBD acutely reduces consolidation of associative fear memory via 5-HT1AR-mediated inhibition of DRN release of 5-HT onto basal amygdala neurons. As previously mentioned, the basolateral amygdala also participates in acquisition of associative fear memory (Harnett et al., 2020; Campeau and Davis, 1995; Fanselow and Kim, 1994; LeDoux et al., 1990), thus CBD could also acutely reverse associative fear memory generation by silencing DRN-basolateral amygdala circuitry. These inhibitory effects of CBD on DRN-basal amygdala and DRN-basolateral amygdala projections may inhibit acquisition and reconsolidation of associative fear memory (Sengupta and Holmes, 2019), which would be useful to uncouple specific trauma reminders or "triggers" such as emergency sirens from the traumatic memory. In addition, since the DRN-central amygdala circuitry generates anxiety-like behavior (Ren et al., 2018), CBD will also acutely reduce anxiety-like behaviors by inhibiting release of excitatory 5-HT from the DRN neurons into the central amygdala.

Second, AEA release from DRN 5-HT neurons may begin to maintain normal activity within the DRN, while also preventing DRN GABAergic interneurons from exerting excess control over DRN 5-HT neurons to drive the DRN into hypoactivity. Furthermore, in addition to reduced release of 5-HT from DRN neurons synapsing to amygdala glutamatergic neurons, CBD-mediated release of AEA from DRN 5-HT neurons that receive input from the amygdala is also critical to rapidly reduce DRN excitability during anxiety and fear responses. The reduction of fear responses is likely related to diminished reconsolidation of the fear memory, which is dependent on CBD-mediated AEA signaling and activation of CB1R in fear network regions including the amygdala and hippocampus (Stern et al., 2012; Lin et al., 2006; Kobilo et al., 2007; de Oliveira Alvares et al., 2008; Suzuki et al., 2008). Therefore, CBD acutely reduces strain on the mPFC and begins to enhance ease of fear network inhibiton via activation of 5-HT1AR. Specifically, the disparity in amygdala-mPFC activity levels is reduced by decreased 5-HT release,

so the mPFC can exert greater control over the amygdala. Meanwhile, enhanced AEA signaling begins to restore proper activity levels to the DRN and amygdala via CB1R activation. By altering signaling and activity within the DRN-amygdala circuit, CBD begins to unfavor fear memory consolidation and reconsolidation by the amygdala, paving the way for enhanced favoring of fear extinction following chronic CBD administration.

6.2. CBD in the corticoraphe circuit

Since literature addressing CBD effects in the DRN of PTSD models is still somewhat lacking, we must deduce our mechanism from studies of 5-HT1AR agonism and endocannabinoid signaling in the DRN of related models. For instance, 5-HT1AR agonism in the DRN of inescapable stress-exposed rodents inhibited neuron firing and reduced acquisition and expression of learned helplessness by reducing excess 5-HT release from the DRN (Worley et al., 2018; Kirby et al., 2003; Maier et al., 1995). Both the acute and chronic effects of CBD involve the DRN, but the chronic effect specifically recruits DRN-mPFC circuitry to treat PTSD (see Fig. 4). While the acute effect of CBD is critical for reducing anxiety and limiting expression of fear memory, the chronic effect of CBD is crucial for permanently restoring inhibitory control to the mPFC and for favoring of extinction memory consolidation over fear memory reconsolidation. In the DRN, CBD acutely reduced 5-HT neuron firing rate, but the anxiolytic effect of CBD arose from delayed potentiation of 5-HT release via 5-HT1A autoreceptor desensitization following chronic

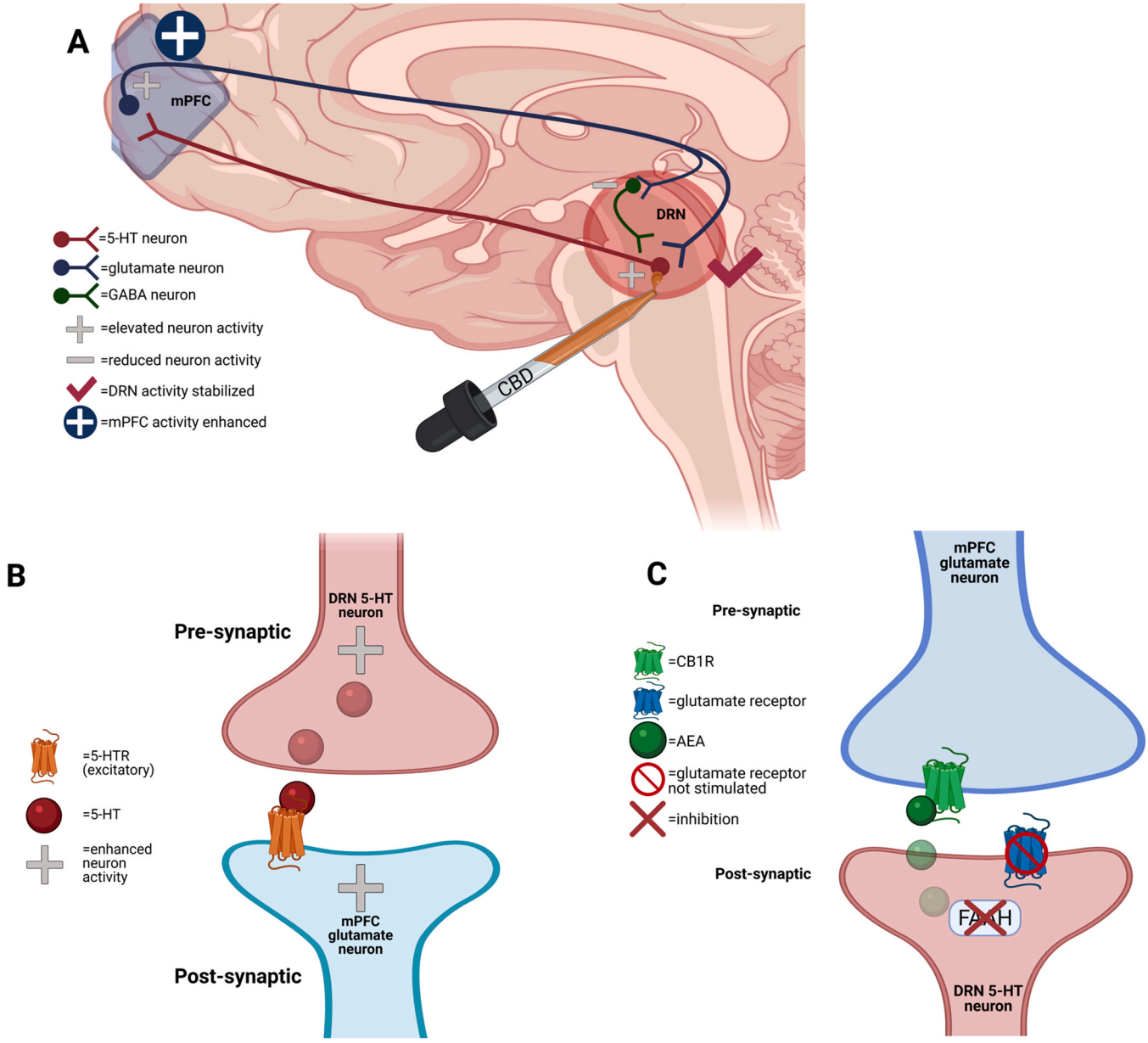

Fig. 4. A) Graphical representation of literature presented. DRN 5-HT and mPFC glutamate synapses are favored by chronic CBD, restoring mPFC activity via the DRN. DRN 5-HT neurons release more 5-HT to excite the mPFC. In turn, mPFC glutamate neurons consistently excite DRN 5-HT neurons, with AEA regulating circuitry to maintain corticoraphe stability. AEA is consistently released from DRN 5-HT neurons to GABAergic interneurons to maintain 5-HT release to mPFC. Also, AEA can control mPFC-mediated DRN excitation. This treats PTSD by restoring mPFC inhibitory control to allow fear extinction. B) CBD chronic mechanism at the DRN 5-HT and mPFC glutamate synapse potentiates mPFC activity to restore its inhibitory control and ultimately favor fear extinction and stress coping. C) If mPFC glutamate input to the DRN 5-HT neuron provides excess excitation to the DRN, AEA can regulate glutamate release to prevent DRN hyperactivity. This AEA availability is due to chronic CBD administration to DRN. "Created with BioRender.com"

CBD administration to the DRN (DeGregorio et al., 2019; Blier and DeMontigny, 1983). Thus, the DRN may also restore mPFC activity in PTSD-afflicted brains via enhanced 5-HT release.

The DRN expresses CB1R, AEA, 2-AG, and FAAH (Bambico et al., 2010; Egertova et al., 1998; Haring et al., 2007; Moldrich and Wenger, 2000). Administration of FAAH inhibitor URB597 into the DRN potentiated both 5-HT neuron firing and AEA agonism of CB1R (Bambico et al., 2010; Burstein et al., 2018; Gobbi et al., 2005). Given that depression is a very common symptom of PTSD, this data, in addition to the finding that CB1R knockout in the DRN enhances anxiety-like behaviors (Häring et al., 2015), suggests that AEA levels may be decreased in the DRN of PTSD patients. However, future studies should seek to confirm whether traumatic stress produces a significant decrease in DRN AEA levels. vmPFC glutamatergic and GABAergic interneurons express CB1R, thus vmPFC hypoactivity could also be ameliorated by AEA-mediated inhibition of GABA release (Worley et al., 2018; Marsicano and Lutz, 1999; Moldrich and Wenger, 2000; Katona and Freund, 2012; Kim and Alger, 2010; Xia et al., 2016). mPFC glutamate terminals innervating DRN 5-HT and GABAergic interneurons express CB1R (Geddes et al., 2016; Häring et al., 2015; Gobbi et al., 2005; Bambico et al., 2007; Haj-Dahmane and Shen, 2009). Furthermore, endocannabinoid deficiencies are a proposed contributor to the maladaptive stress responses in PTSD (Bitencourt and Takahashi, 2018; Hill et al., 2018). Finally, CB1R-mediated signaling favors mPFC glutamate-DRN 5-HT synaptic activity over mPFC glutamate-DRN GABAergic synaptic activity (Geddes et al., 2016; Häring et al., 2015; Haj-Dahmane and Shen, 2005, 2009), suggesting that endocannabinoids are required to maintain stable 5-HT signaling in the corticoraphe circuit to ultimately restore mPFC activity. CB1R knockout in mPFC glutamatergic-DRN 5-HT synapses followed by stress exposure likely facilitates the anxiety-like behavior observed in PTSD (Häring et al., 2015; Geddes et al., 2016; Worley et al., 2018). On the other hand, given the fMRI observations of reduced biomarker Glx (glutamate/glutamine concentration) in the vmPFC (Harnett et al., 2020; Yang et al., 2015), we surmise that GABAergic interneurons may hold greater influence on mPFC activity in the PTSD brain compared to a healthy brain. As such, CBD-induced elevation of AEA release from DRN 5-HT neurons to the mPFC, paired with chronic CBD-induced release of 5-HT from DRN 5-HT neurons to a mPFC glutamatergic neuron, will provide much needed stimulation to these neurons, thereby beginning to restore some plasticity to excitatory synapses in the mPFC.

In a clinical trial, healthy volunteers were administered PF-04457845 (FAAH inhibitor), and showed improved baseline AEA levels, reduced negative affect, and enhanced extinction memory 1 day after stressor exposure (Mayo et al., 2020). Since FAAH inhibitors restore proper mPFC-amygdala activity in healthy individuals (Mayo et al., 2020; Gray et al., 2015; McLaughlin et al., 2014; Morena et al., 2016), CBD likely facilitates fear extinction in PTSD patients via a similar mechanism, though the extinction-potentiating effects may require a greater timecourse due to the large activity disparity between the amygdala and mPFC in PTSD patients. In addition, CBD must also establish a consistent favoring of fear extinction over fear consolidation. Preclinical studies support this favoring of fear extinction as intra-mPFC infusion of CBD before fear conditioning inhibited acquisition of associative fear memory and disrupted associative fear memory consolidation when administered to the mPFC 5 h after fear conditioning (Rossignoli et al., 2017; Lemos et al., 2010, Do Monte et al., 2013). CBD also impaired the reconsolidation of both new and old contextual fear memories in Wistar rats via CB1R (Stern et al., 2012), suggesting that FAAH inhibition is also a critical component of the fear-attenuating mechanism of CBD. This mechanism of CBD is consistent with results from a study employing OL-135 (an FAAH inhibitor), as FAAH inhibition also disrupts consolidation of contextual fear memory following fear conditioning (Burman et al., 2016). These data support the efficacy of CBD in normalizing fear network and corticoraphe circuit activity, and importantly, in favoring fear extinction over fear memory consolidation to ameliorate PTSD symptoms. However, one study suggested an anxiolytic effect rather than fear extinction-potentiating effect of CBD in predator scent stress models (Shallcross et al., 2019).

Taken together, these data suggest the following chronic mechanism of CBD in PTSD treatment. First, since an anxiolytic effect of CBD was observed following desensitization of 5-HT1AR (DeGregorio et al., 2019), we propose that the primary chronic effect of CBD in treating PTSD favors excitation of the mPFC glutamatergic neurons by release of 5-HT from DRN neurons. AEA release from DRN 5-HT neurons to GABAergic interneurons in the DRN ensures that the corticoraphe circuitry will favor mPFC excitation (Worley et al., 2018; Kim and Alger, 2010; Xia et al., 2016), and as such, chronic CBD will also maintain a required level of AEA to regulate DRN GABAergic interneuron signaling. However, if chronic CBD allows DRN 5-HT neurons to release excess 5-HT, they can be controlled by DRN GABAergic interneurons that express 5-HT2AR and 5-HT2CR with great affinity for high concentrations of 5-HT (Hernández-Vázquez et al., 2019; Liu et al., 2000; Roberts et al., 2004; Serrats et al., 2005; Broadbelt et al., 2010). CBD also binds to 5-HT1AR on DRN GABAergic interneurons of rat social defeat models of depression (Linge et al., 2016; Challis et al., 2013). These data suggest that CBD can restore normal activity levels to the mPFC by engaging proper 5-HT and endocannabinoid signaling in the corticoraphe circuit. Thus, chronically administered CBD exerts its therapeutic effect on memory deficits in PTSD by stabilizing DRN-mPFC signaling. Specifically, since adequate activity of the vmPFC and mPFC is required to maintain proper connectivity with the amygdala during learning of fear extinction (Kida (2019); Mamiya et al., 2009), chronically administered CBD can shift the balance toward favoring of extinction memory by favoring DRN-mediated excitation of the hypoactive mPFC instead of the already hyperactive amygdala. Most importantly, this shift slowly un-favors reconsolidation of fear memory via crosstalk between the hyperactive amygdala and the stress-impaired hippocampus (Bitencourt and Takahashi, 2018; Shin et al., 2006; Patel et al., 2012; Etkin and Wager, 2007). Moreover, CBD-mediated restoration of adequate vmPFC and mPFC engagement will also equip the patient with greater inhibitory control over emotional reactivity from the amygdala during stress (van Rooij and Jovanovic, 2019; Stevens et al., 2013), thereby maintaining a chronic anxiolytic effect to reduce hypervigilance in the patient's daily life. Finally, since endocannabinoids have been proposed to critically potentiate corticoraphe circuit-mediated improvement of learning of resilience to stress (Worley et al., 2018), we suggest that CBD administration to this circuit could produce a similar effect to treat PTSD via elevation of AEA.

Our corticoraphe mechanism of CBD slightly differs from Linge et al. (2016) proposal. First, DRN 5-HT1AR binding is enhanced in PTSD (Sullivan et al., 2013), and the amygdala likely favors excitation and maintenance of 5-HT neurons rather than GABAergic interneurons of the DRN. Furthermore, DRN hyperactivity in traumatized rodents (Worley et al., 2018; Amat et al., 2005; Rozeske et al., 2011) suggests that 5-HT neurons may also be thriving and favored in humans, while enhanced 5-HT1AR binding (Sullivan et al., 2013) and high AEA levels (Neumeister, 2013a, 2013b) in the DRN of PTSD patients suggest that CBD would optimally target human DRN 5-HT neurons.

7. Discussion

The objective of this review was to explore the mechanism of CBD in the corticoraphe circuit of PTSD patients. This circuit was selected for three reasons: first, endocannabinoid and 5-HT signaling has been observed in this circuit (Geddes et al., 2016; Häring et al., 2015), implicating participation in CBD's mechanism. Second, the concurrent mPFC hypoactivity in PTSD patients (Harnett et al., 2020; Fenster et al., 2018; Grizzell et al., 2020; Cooper et al., 2008), and the recently documented DRN hyperactivity and downregulation of 5-HT1A autoreceptor expression (Worley et al., 2018; Amat et al., 2005; Rozeske et al., 2011) suggested that this circuitry requires endocannabinoid-mediated

regulation to achieve stability. Third, DRN 5-HT neurons abundantly innervate other structures (Charnay and Leger, 2010), and CBD administration to either the DRN or mPFC impaired anxiety and fear memory consolidation, respectively (DeGregorio et al., 2019; Rossignoli et al., 2017). Thus, we expect that CBD will exert both effects via the corticoraphe circuit in PTSD patients. In short, we first concluded that the DRN is the missing puzzle piece in CBD's treatment of PTSD patients. Since mPFC hypoactivity underlies susceptibility to re-experiencing and impaired fear extinction (Fenster et al., 2018), the mechanism of CBD should aim to normalize mPFC activity. In the mPFC of depressed rodents, CBD-induced elevation of 5-HT release relieved plasticity deficits and exerted antidepressant effects (Silote et al., 2019; Sales et al., 2019; Linge et al., 2016). This suggests that enhanced 5-HT release from DRN 5-HT input following chronic CBD will compensate for lost mPFC excitement in PTSD. Reduced glutamatergic activity in the mPFC also underlies reduced plasticity and impaired extinction learning (Harnett et al., 2020; Yang et al., 2015), supporting the need for external excitation sources.

Linge et al. (2016) suggested that CBD exerts antidepressant effects via corticoraphe circuit, but their proposal excluded endocannabinoid regulation because AM251 (CB1R antagonist) did not appear to alter these effects. However, altered AEA levels within the mPFC and DRN, combined with altered CB1R expression and 5-HT signaling, suggests that endocannabinoids are required in the corticoraphe circuit of PTSD patients to regulate CBD's 5-HT-enhancing effect. Plus, results in olfactory bulbectomy (OBX) models of major depressive disorder may vary from that of various PTSD models. FAAH inhibitors enhanced fear extinction by elevating AEA levels in mPFC of healthy participants (Mayo et al., 2020). CB1R have been identified on GABAergic interneurons and glutamatergic neurons in the vmPFC (Worley et al., 2018; Marsicano and Lutz, 1999; Moldrich and Wenger, 2000; Katona and Freund, 2012; Kim and Alger, 2010; Xia et al., 2016). Furthermore, CB1R are expressed in the DRN on 5-HT neurons, GABAergic interneurons, and glutamate terminals from the mPFC (Häring et al., 2015; Geddes et al., 2016). mPFC projections to the DRN may favor AEA release onto GABAergic interneurons to facilitate consistent 5-HT signaling, though 5-HT in the DRN could also recruit GABAergic regulation when needed (Worley et al., 2018; Häring et al., 2015; Geddes et al., 2016; Hernández-Vázquez et al., 2019). Taken together, these data suggest that endocannabinoids and 5-HT signaling collaboratively regulate corticoraphe circuit activity following chronic CBD treatment in PTSD.

CBD is non-anxiogenic, safe, and non-addictive (Bitencourt and Takahashi, 2018; Campos et al., 2012) and has few significant side effects. In one clinical trial, PTSD patients were administered 22–28 mg oral CBD capsules and reported improved sleep quality and reduced nightmares on a PTSD Checklist for DSM-V (PCL5) questionnaire of PTSD symptoms (Elms et al., 2019). Reported side effects included fatigue, daytime fogginess, impaired concentration, and gastrointestinal bloating and pain (Elms et al., 2019). CBD also reduced anxiety in simulated public speaking tests (Campos et al., 2012; Bergamaschi et al., 2011; Zuardi et al., 1993). Finally, healthy volunteers in another trial inhaled 32 mg of CBD following fear conditioning and showed enhanced extinction memory consolidation during fear extinction tasks (Elms et al., 2019; Das et al., 2013).

The COVD-19 pandemic and concurrent crises of 2020 have raised concern about an influx of PTSD diagnoses in healthcare workers, frontline workers, and COVID-19 victims (O'Sullivan et al., 2021; Dutheil et al., 2021) due to chronic stress and traumatic stress. The relevant dysregulations observed in PTSD rodent models may be applicable to humans. Specifically, endocannabinoid changes and CBD effects in chronic unpredictable stress models may be generalized to frontline workers, while findings in single prolonged stress models likely also occur in individuals traumatized by COVID-19 infection or other recent disasters. CBD may also reverse social isolation-induced impairments, as seen in socially isolated rodents (Hartmann et al., 2019; Ferris et al., 2008).

Finally, CBD could possibly serve as a useful adjunct to normal psychological therapy for PTSD patients. Repeated exposure to fear-related cues allows the fear memory to temporarily enter a labile state in which the memory can be slightly altered prior to reconsolidation (Kida (2019); Nader et al., 2000a, 2000b; Bitencourt and Takahashi, 2018), thus CBD administration during mild exposure therapies like CBT could hasten the fear extinction-potentiating effect of the therapy. Moreover, the authors of the aforementioned FAAH inhibitor study suggested that the ability of FAAH inhibition to enhance fear extinction recall may serve as a useful adjunctive treatment for prolonged exposure therapy in PTSD patients (Mayo et al., 2020). This suggests that the FAAH-inhibiting effect of CBD may also present similar potentiating effects on extinction recall in PTSD patients receiving co-treatment with exposure therapy. Other evidence for the utility of CBD in combination with exposure therapy can be derived from separate disorders, such as social anxiety disorder. Specifically, CBD administration to patients with social anxiety prior to simulated public speaking tasks significantly reduced self-reports of anxiety, enhanced cognitive function during speech, and improved self-reported assessment of speech performance (Bergamaschi et al., 2011). This suggests that CBD co-administration with other types of exposure-related therapy such as cognitive behavior therapy (CBT) and eye movement desensitization and reprocessing therapy (EMDR) could also be useful to treatment of PTSD, though specialists may not approve use of CBD or other cannabinoid-related substances before EMDR therapy, due to the potential for CBD to manipulate memory retrieval and reconsolidation (Bitencourt and Takahashi, 2018; Stern et al., 2012; Lemos et al., 2010). Regardless, the improved self-reported assessments by these anxious patients, even while exposed to their fear (public speaking) (Bergamaschi et al., 2011), suggests that a future study investigating the effects of CBD pretreatment before exposure-based therapies may be of great utility to expand treatment regimens for PTSD patients.

Interestingly, CBD and PTSD-specific psychotherapies such as EMDR may have some mechanistic overlap in ameliorating affected brain regions. Specifically, just as CBD may improve functional deficits of the amygdala, hippocampus, and vmPFC and mPFC, a fMRI study revealed that EMDR therapy also enhanced fear extinction by improving functional connectivity of the amygdala, hippocampus, vmPFC, and mPFC in PTSD patients (Rousseau et al., 2019). EMDR therapy is designed to facilitate proper reconsolidation of traumatic memories by mimicking the eye movements produced during rapid eye movement (REM) sleep, which is often compromised in PTSD patients (Rousseau et al., 2019; Shapiro and Maxfield, 2002; Bisson et al., 2007; Germain et al., 2008, 2013). Thus, CBD could possibly potentiate fear extinction by a mechanism that partially mimics first line psychological therapies (Bitencourt and Takahashi, 2018; Bitencourt et al., 2008; Do Monte et al., 2013). Taken together, these data suggest that CBD could possibly be an effective adjunctive treatment to exposure-based psychotherapies in PTSD.

8. Conclusion

The acute effect of CBD administration to the DRN should have the following outcomes: first, the 5-HT neurons in the hyperactive DRN will temporarily reduce excitatory 5-HT release within the DRN and from the DRN 5-HT projections to the amygdala due to CBD agonism of 5-HT1AR on 5-HT neurons. This effect would prevent the amygdala from over-exciting the DRN, and the DRN from potentiating amygdala excitability, especially during re-experiencing. Second, CBD facilitates release of AEA from DRN 5-HT neurons to the amygdala, thereby limiting amygdala excitement of the DRN. Third, AEA release from DRN 5-HT neurons to GABAergic projections from the DRN to mPFC would also acutely reduce GABA inhibition of mPFC activity. In short, the acute effect of CBD is concentrated to the DRN, as CBD mediated regulation of DRN activity would help stabilize the activity of the mPFC and amygdala.

Chronic CBD will treat PTSD by restoring stability to the corticoraphe circuit. In other words, chronic CBD administration will restore mPFC activity via enhanced release of 5-HT by DRN neurons. This mechanism of CBD was observed in rodent models of depression (Silote et al., 2019; Linge et al., 2016), however this mechanism slightly differs for PTSD. Due to enhanced endocannabinoid signaling, we suggest that cortico-raphe signaling will be stabilized by AEA regulation of 5-HT release in the DRN when needed. CBD will potentiate fear extinction via a DRN mechanism, as it will reduce amygdala hyperactivity and restore mPFC activity, so that they may appropriately participate in fear extinction.

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CRediT authorship contribution statement

Maryam Vasefi: Contributed to conception, Design, Supervision, Revision of the study. **Claire Alexander:** Wrote the first draft of the manuscript.

Conflicts of Interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethical Statement

The authors declare no competing financial interests.

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