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Translational Evidence for a Role of Endocannabinoids in the Etiology and Treatment of Posttraumatic Stress Disorder

Alexander Neumeister[1,2,*], **Jordan Seidel**[1], **Benjamin J. Ragen**[1], and **Robert H. Pietrzak**[3,4]

[1]Department of Psychiatry, New York University School of Medicine, New York, NY, USA.

[2]Department of Radiology, New York University School of Medicine, New York, NY, USA.

[3]United States Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, USA.

[4]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA.

Abstract

Introduction—Posttraumatic stress disorder (PTSD) is a prevalent, chronic, and disabling anxiety disorder that may develop following exposure to a traumatic event. Despite the public health significance of PTSD, relatively little is known about the etiology or pathophysiology of this disorder, and pharmacotherapy development to date has been largely opportunistic instead of mechanism-based. Recently, an accumulating body of evidence has implicated the endocannabinoid system in the etiology of PTSD, and targets within this system are believed to be suitable for treatment development.

Methods—Herein, we describe evidence from translational studies arguing for the relevance of the endocannabinoid system in the etiology of PTSD. We also show mechanisms relevant for treatment development.

Results—There is convincing evidence from multiple studies for reduced endocannabinoid availability in PTSD. Brain imaging studies show molecular adaptations with elevated cannabinoid type 1 (CB_1) receptor availability in PTSD which is linked to abnormal threat processing and anxious arousal symptoms.

Conclusion—Of particular relevance is evidence showing reduced levels of the endocannabinoid anandamide and compensatory increase of CB_1 receptor availability in PTSD,

*Corresponding author: Alexander Neumeister, M.D. Professor of Psychiatry and Radiology New York University School of Medicine Director, Molecular Imaging Program for Anxiety & Mood Disorders One Park Avenue, 8th floor, room 225 New York, NY 10016 Phone: 646-754-4827 alexander.neumeister@nyumc.org.

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and an association between increased CB_1 receptor availability in the amygdala and abnormal threat processing, as well as increased severity of hyperarousal, but not dysphoric symptomatology, in trauma survivors. Given that hyperarousal symptoms are the key drivers of more disabling aspects of PTSD such as emotional numbing or suicidality, novel, mechanism-based pharmacotherapies that target this particular symptom cluster in patients with PTSD may have utility in mitigating the chronicity and morbidity of the disorder.

Keywords

PTSD; endocannabinoids; 5-factor PTSD model; anxious arousal; treatment

Introduction

Posttraumatic stress disorder (PTSD) related to non-combat trauma is a major public health concern. According to U.S. population-based studies such as the National Comorbidity Survey (NCS) (Kessler et al., 1995), NCS-Replication (Kessler et al., 2005), and the National Epidemiologic Survey on Alcohol and Related Conditions (Pietrzak et al., 2011), the lifetime prevalence of PTSD ranges from 6.4% to 7.8%. PTSD is a chronic disorder, with population-based studies indicating that it can persist for up to 10 years, especially if left untreated (Kessler et al., 1995, Pietrzak et al., 2011). Conversely, PTSD is one of the most prevalent, chronic, and disabling psychiatric disorders in solders exposed to war. For example, a study of 18,305 U.S. Army personnel found that 23.6% of active component soldiers and 30.5% of National Guard soldiers screened positive for DSM-IV PTSD 12 months after returning from deployment to Iraq (Thomas et al., 2010). Despite the high prevalence of PTSD in combat veterans, however, most veterans with PTSD do not seek treatment or receive inadequate or inappropriate treatment (Hoge et al., 2008).

One of the biggest challenges to novel pharmacotherapy development in PTSD is that studies have largely failed to develop mechanism-based treatments that target heterogeneous aspects of this disorder. While PTSD is often characterized as a unitary disorder, a large body of evidence suggests that it is comprised of heterogeneous symptom clusters that have unique neurobiological correlates and may be differentially sensitive to treatment (Pietrzak et al., 2014, Pietrzak et al., 2013a, Pietrzak et al., 2013b). For example, several confirmatory factor analytic studies in both veterans (Tsai et al., 2012, Pietrzak et al., 2012, Harpaz-Rotem et al., 2014) and civilians (Armour et al., 2012, Elhai et al., 2011, Contractor et al., 2014) have revealed that PTSD is best characterized as being comprised of five distinct symptom clusters—re-experiencing, avoidance, emotional numbing, dysphoric arousal (e.g., sleep difficulties, concentration problems, anger/irritability), and anxious arousal (i.e., hypervigilance, exaggerated startle); this same symptom structure was recently confirmed using DSM-5 data (Tsai et al., in press). Our research team aimed to evaluate neurobiological and functional endophenotypic correlates of this novel dimensional model of PTSD (Pietrzak et al., 2014, Pietrzak et al., 2013a, Pietrzak et al., 2013b).

Besides psychotherapeutic interventions, there are only a few available pharmacotherapies for PTSD. These include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), both of which the Food and Drug

Administration (FDA) has approved for the treatment of PTSD and which have been demonstrated to provide some benefit in the management of PTSD symptoms (Brady et al., 2000, Marshall et al., 2001, Davidson et al., 2001, Davidson et al., 2006a, Davidson et al., 2006b, Ipser and Stein, 2012) However, meta-analyses (Stein et al., 2006) have concluded that effect sizes of these pharmacotherapies are small (i.e., mean total CAPS score for the medication group was 5.76 points lower than that observed for the placebo group); and that there may be relatively less benefit for subgroups of individuals with PTSD, such as those with complicated PTSD (Friedman et al., 2007). Commonly utilized pharmacotherapeutic augmentation strategies such as second-generation antipsychotic medications (e.g., risperidone), were also recently shown to be ineffective in treating PTSD (Krystal et al.). Neurobiological mechanisms relevant to etiology of PTSD and key aspects of the PTSD phenotype are linked to the mechanism of action of endocannabinoids and may provide a basis for novel treatment development, specifically for PTSD.

Is There a Role for Endocannabinoids in the Etiology of PTSD?

A number of translational approaches have yielded insights into model mechanisms of PTSD. Amongst those, fear conditioning experiments highlight the role of an amygdala-hippocampalcortico-striatal circuit as a key brain circuit responsible for processing and storing fear-related memories and for coordinating fear-related behaviors (Rogan et al., 1997, LeDoux, 2000, Rodrigues et al., 2004), leading to the hypothesis that PTSD is characterized by amygdala over-activity or hyper-responsiveness to threatening stimuli in humans (Grillon et al., 1996, Phelps and LeDoux, 2005, Rauch et al., 2006). Indeed, a convergence of findings from functional neuroimaging investigations in clinical populations supports a neurocircuitry model of PTSD characterized by abnormally elevated amygdala activity (subserving exaggerated acquisition of fear associations and expression of fear responses) coupled with deficient regulation by prefrontal cortical structures (mediating deficits in extinction and the capacity to suppress attention/response to trauma-related stimuli), as well as abnormal hippocampus (mediating deficits in appreciation of safe contexts and explicit learning/memory) and basal ganglia functions (moderating stimulant and conditioned reinforcement, affective and motor habits). Whereas the neurocircuitry of PTSD is well established and has been consistently reported in the literature, the neurochemistry that moderates the function of this circuit and its alterations relevant to the development of the PTSD phenotype remains incompletely understood.

Various lines of evidence suggest that the endocannabinoids, anandamide (AEA) and 2-arachidonolyflycerol (2-AG) which exert much of their actions through the two known CB receptors (CB_1, CB_2), play an important role in the development (Krebs-Kraft et al.) and function of the PTSD circuit, specifically in stress responses (Hill et al., Rademacher et al., 2008, Reich et al., 2009, Gorzalka et al., 2008, Hill et al., 2009, Hill et al., 2008b). CB_1 receptors are the most abundant G-protein-coupled receptors in the central nervous system (Glass et al., 1997, Herkenham et al., 1990) and are found in high concentrations in the aforementioned PTSD circuit. Genetic or pharmacological disruption of CB_1 receptor signaling results in anxiety phenotypes (Haller et al., 2002, Haller et al., 2004). Moreover, brain CB_1 receptor signaling controls extinction of aversive memories (Marsicano et al., 2002, Varvel et al., 2007, Chhatwal et al., 2005) and deficits in the learned inhibition of fear

characterize patients with PTSD. Therefore, impaired CB_1 receptor function is a potentially important mechanism in the etiology of PTSD (Figure 1.).

Recent animal studies (Hill et al., 2005) show that chronic stress is associated with significantly decreased AEA levels in the amygdala-hippocampal-cortico-striatal ciruit. Notably, this finding complements results from human studies in depression (Hill et al., 2008b) reporting that female outpatients with major depressive disorder have lower serum 2-AG levels than controls. The magnitude of the decrease was associated with the length and severity of the depressive episode. While AEA was not associated with major depression per se, an inverse relationship was found between serum AEA content and Hamilton anxiety ratings, suggesting that AEA tone may relate to the anxiety component of the depression phenotype. Interestingly, there is now substantial evidence from independent PTSD cohorts for lower endocannabinoid concentrations in human PTSD (Hill et al., 2013, Neumeister, 2013, Pietrzak et al., 2014), associated with upregulation of brain CB_1 receptors (Neumeister, 2013) as a molecular adaption to this reduced synaptic availability (Pietrzak et al., 2014). These data add to more recent studies demonstrating an association between trauma-related disorders such as PTSD, MDD, and GAD, and abnormal threat processing (Sveen et al., 2009, Lindstrom et al., 2011, Fani et al., 2012) by implicating the CB_1 receptor system as a key neurobiological mechanism of this endophenotype and its concomitant phenotypic expression of trauma-related threat symptomatology, particularly hyperarousal symptoms.

These results are consistent with the high rates of cannabis abuse among PTSD patients (Vetter et al., 2008, Cornelius et al.). They authenticate, at least in part, emerging evidence that synthetic cannabinoid receptor agonists (Fraser, 2009) or plant-derived cannabinoids such as marijuana (Passie et al., 2012) may possess some benefits in individuals with PTSD by helping relieve haunting nightmares and other threat-related symptoms of PTSD. However, such data do not allow the conclusion that self-medication with cannabis with its primary psychoactive constituent tetrahydrocannabinol should be recommended for the treatment of PTSD, as direct activation of CB_1 receptors with plant-derived cannabinoids over an extended period of time leads to down-regulation of CB_1 receptors (Hirvonen et al., Leweke and Koethe, 2008), which may in turn facilitate the emergence of a depression-like phenotype in certain individuals (Beyer et al., 2010) and increase risk of addiction (Klugmann et al.).

What is the Evidence for Gender Disparity of CB_1 Receptor Functions in PTSD?

Important sex-related differences exist in cannabinoid pharmacology (for review (Fattore and Fratta)) mediating the profound sex differences in the stress response on a systemic level (Hill et al., 2005). These studies directly implicate the CB_1 receptor (Reich et al., 2009) in modulating the functions of the brain PTSD circuit. Rodent studies report basal (non-stress) sex differences in hippocampal CB_1 receptor levels with males having higher CB_1 levels than females, but no differences in fatty acid amide hydrolase (FAAH), the main degradative enzyme for circulating endocannabinoids (Hill et al., 2005, Reich et al., 2009). Chronic stress produced an upregulation of FAAH levels, regardless of sex. Gender

disparities in CB_1 receptor regulation were observed at this step in the stress response such that chronic stress reliably produced a downregulation of CB_1 receptors in male animals (Hill et al., 2008a, Hill et al., 2005, Reich et al., 2009) and a robust upregulation of CB_1 receptors in female animals (Reich et al., 2009) which was associated with impaired CB_1 receptor-mediated eCB signaling (Suarez et al., 2009). Whereas there is evidence for developmental influence of sex hormones on eCB function (Hill et al., 2007), the observed CB_1 receptor changes were found in both intact and gonadectomized animals and are therefore not a result of circulating sex hormones or glucocorticoids (Reich et al., 2009).

These sex-related results from animal work accord with our recent brain imaging data using the CB_1 receptor radiotracer [^{11} C]OMAR and positron emission tomography demonstrating sex differences in CB_1 receptor regulation, with up-regulation of CB_1 receptors observed predominantly in women, particularly those with PTSD (Neumeister, 2013).

Such data can contribute to models aiming to understand why women are at greater risk for developing PTSD following exposure to various types of trauma than men even when sexual trauma—which is more common in women—is accounted for (Stein et al., 2000), and why women with PTSD have a higher disability burden and reduced quality of life compared to men (Dell'osso et al., Freedy et al., Irish et al., Luxton et al., Ditlevsen and Elklit, Bowler et al., Galovski et al., Breslau and Anthony, 2007, Breslau, 2002, McLean et al., Schnurr and Lunney, 2008). In addition, evidence for the influence of gender on endocannabinoid functioning should be considered in the correct interpretation of study results and the planning of treatment intervention trials involving both, men and women.

Potential Relevance of Fatty Acid Amid Hydrolase (FAAH) Inhibitors in the Treatment of PTSD

Although several psychotherapies are available to treat PTSD, novel pharmacotherapy development has lagged, and only recently have intensive pre-clinical and clinical studies yielded novel, potentially breakthrough discoveries that have the potential to introduce a new era of pharmacotherapies for PTSD. One noteworthy development in recent years has been the identification of the fatty acid amide hydrolase (FAAH) enzyme as a critical mediator of endocannabinoid metabolism and thus a potential target for novel pharmacotherapy development for PTSD and related disorders (Petrosino and Di Marzo, 2010, Gunduz-Cinar et al., 2013a).

FAAH inhibitors may help mitigate PTSD symptoms via multiple mechanisms: (1) restoring back to normal the low levels of anandamide (possibly through increased FAAH activity), which represent a vulnerability factor to developing PTSD and were found to be associated with increased anxiety and hyperarousal symptoms (Neumeister et al., 2013, Pietrzak et al., 2014, Hill et al., 2013); (2) suppression of amygdala hyperreactivity, thereby facilitating the mitigation of anxious arousal and more rapid habituation to threat (Gunduz-Cinar et al., 2013b); (3) restoration of the PTSD-characteristic hypothalamic-pituitary-adrenal (HPA)-axis dysregulation (Roberts et al., 2014); (4) promotion of sleep and suppression of rapid eye movement (REM) sleep (Garcia-Garcia et al., 2009), which can increase re-experiencing and hyperconsolidation of traumatic memories during sleep; (5) reduction of hyperarousal

and sympathetic tone via activation of CB_1 receptors on noradrenergic nerve terminals (Kirilly et al., 2013); and/or (6) by modulating other eCBs, such as palmitoylethanolamide or oleoylethanolamide, which are anti-inflammatory and analgesic, and regulate satiety, respectively. In addition to FAAH inhibitors potentially reducing PTSD symptoms, particularly hyperarousal, as well as depression symtpoms, they may also help mitigate altered pain sensitivity (Geuze et al., 2007), as well as low-grade inflammation (Lindqvist et al., 2014), which have been documented in PTSD. This broad spectrum of action could further enhance their utility in treating PTSD.

Although there is now preliminary evidence that orally absorbable Δ(9)-tetrahydrocannabinol (THC) may ameliorate symptoms of chronic PTSD (Roitman et al., 2014), several key questions remain unanswered: it is unclear what dose of THC may provide optimal treatment effects; what targets in the brain are engaged by THC besides direct CB_1 receptor activation; does THC affect specific PTSD circuits in the brain or are effects observed brain-wide and unspecific; and finally, the important question of abuse liability needs to be addressed before THC could become a relevant compound for treatment development.

In contrast, several lines of evidence demonstrate the superiority of a FAAH inhibitor over direct CB_1 receptor agonists for the treatment of PTSD. These include: (1) anandamide is a weak, partial CB_1 agonist, unlike Δ^9-THC, and has no reinforcing effects; (2) there are no cognitive impairments; (3) cardiovascular liabilities (tachycardia, orthostasis, syncope); or (4) hyperphagia are associated with FAAH inhibitor treatment; (5) the pharmacology of FAAH inhibitors can be localized to active pathways; and (6) FAAH inhibitors exhibit polypharmacology by influencing multiple endocannabinoids in their metabolism, possibly resulting in complementary positive effects in mitigating anxiety, as well as pain and inflammatory responses.

Conclusion

In conclusion, unlike prior pharmacotherapy studies in PTSD that have been largely opportunistic in nature, the upcoming generation of clinical trials to explore the utility of endocannabinoid-related compounds is based on a substantial body of preclinical and translational data that have directly implicated the endocannabinoid system in the pathophysiology of PTSD. We suggest that these trials employ a novel, theory-driven and empirically supported five-factor phenotypic model of PTSD symptomatology in evaluating treatment response. Unlike DSM-based approaches to classifying PTSD symptom dimensionality, this novel model, which suggests that the PTSD phenotype is best represented by five symptom dimensions—re-experiencing, avoidance, numbing, dysphoric arousal (e.g., sleep disturbance), and anxious arousal (e.g., exaggerated startle response)—has received extensive empirical support from a large body of confirmatory factor analytic studies of various trauma-exposed populations, including Veterans(Harpaz-Rotem et al., 2014). Accordingly, this approach will provide greater specificity in understanding how the novel compounds differentially modulate unique dimensions of the multi-faceted PTSD phenotype. This increased specificity in assessing treatment response in individuals with PTSD is particularly relevant to the mechanism of action of endocannabinoid drugs, i.e.

FAAH inhibition, which act primarily to modulate anxious arousal symptoms such as exaggerated startle and hypervigilance. Thus, we anticipate that results of these trials, while focused on evaluating the efficacy of endocannabinoid function modulating compounds in treating PTSD, will have potential relevance to a broad, transdiagnostic range of psychiatric syndromes characterized by elevated hyperarousal symptoms, such as generalized anxiety disorder, panic disorder, and major depressive disorder.

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Highlights

Endocannabinoids are involved in the etiology of PTSD

They are linked to anxious arousal symptoms

Enhancing endocannabinois function may specifically treat this symptom complex of PTSD

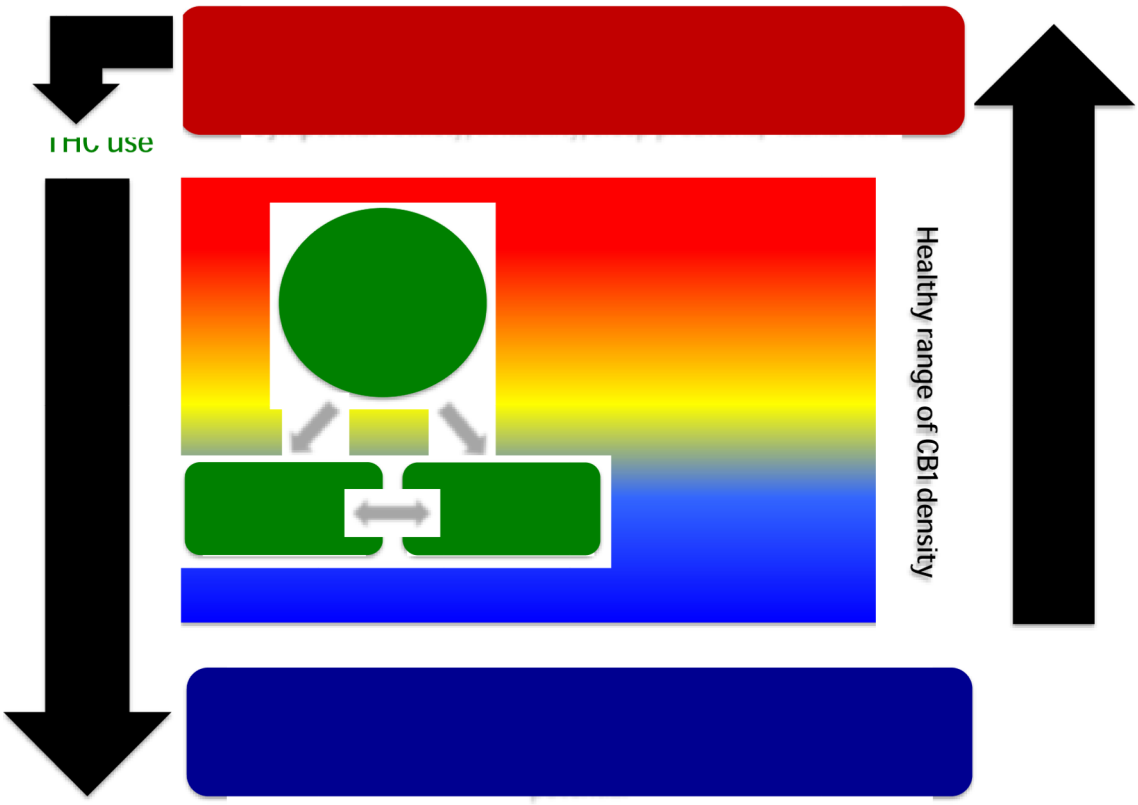

Figure 1.

Model of the role of endocannabinoids in the etiology of posttraumatic stress disorder (PTSD). The availability of anandamide (AEA) regulates the expression of cannabinoid (CB) type 1 (CB1) receptors. Male gender and age have been reported to be associated with lower CB1 receptor density in the human brain. While there is a range of healthy CB1 receptor availability, female gender and trauma exposure result in reduced AEA availability and consequent CB1 receptor upregulation, associated with increasing stress reactivity. Once a critical treshhold of CB1 receptor upregulation is reached, symptoms of PTSD emerge. Patients with PTSD show high rates of Δ(9)-tetrahydrocannabinol (THC) which results in a downregulation of CB1 receptors. Chronic THC exposure and low CB1 receptor availability cause anxiety, irritability, sleep problems and abuse liability.