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Mitigation of post-traumatic stress symptoms by *Cannabis* resin: A review of the clinical and neurobiological evidence

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It is known from clinical studies that some patients attempt to cope with the symptoms of post-traumatic stress disorder (PTSD) by using recreational drugs. This review presents a case report of a 19-year-old male patient with a spectrum of severe PTSD symptoms, such as intense flashbacks, panic attacks, and self-mutilation, who discovered that some of his major symptoms were dramatically reduced by smoking cannabis resin. The major part of this review is concerned with the clinical and preclinical neurobiological evidence in order to offer a potential explanation of these effects on symptom reduction in PTSD. This review shows that recent studies provided supporting evidence that PTSD patients may be able to cope with their symptoms by using cannabis products. Cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and to feel less anxious and less involved with flashback memories. The presence of endocannabinoid signalling systems within stress-sensitive nuclei of the hypothalamus, as well as upstream limbic structures (amygdala), point to the significance of this system for the regulation of neuroendocrine and behavioural responses to stress. Evidence is increasingly accumulating that cannabinoids might play a role in fear extinction and antidepressive effects. It is concluded that further studies are warranted in order to evaluate the therapeutic potential of cannabinoids in PTSD. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction: PTSD and cannabinoids

Clinical evidence obtained from clinical studies shows that people suffering from post-traumatic stress disorder (PTSD) may use recreational drugs to cope with their symptoms.[1] Some specific psychopharmacological effects of cannabis, such as sedation, relaxation, reduction of anxiety and sleep-induction, may explain its use as an attempt to cope with some PTSD symptoms.[1–4] Cannabis products have been used medicinally in Asia and Europe as sedatives or calmatives, including the Western medical tradition up to the early twentieth century.[5] Cannabis was also listed in the United States Pharmacopeia and Formulary until its removal in 1941.[6] Many patients with PTSD may actually cope with their symptoms in this way, as stated by the discoverer of Δ^9-tetrahydrocannabinol (THC)[7] who reported that use of cannabis led to improved sleep, significant reduction of nightmares and sleep interruption.[8] Marijuana use has emerged as one of the most commonly used illicit substance in treatment-seeking adolescents[9] and it has been suggested that cannabis use is significantly more common among adolescents with PTSD than in those without this condition.[10] More recently, some studies and surveys found even stronger evidence that cannabinoids are used in a larger population of patients with PTSD for coping with their symptoms.[11–15] Bonn-Miller *et al.*[11] examined cannabis use in PTSD patients and the interaction of PTSD-related sleep disorders, symptom severity, and motivations for use. These authors found a strong correlation between the severity of PTSD-related sleep disturbances and the amount of cannabis use. These results have to be taken with caution, because the evidence for sleep-enhancing effects of cannabis resin and marijuana is equivocal (see subsection on sleep-enhancing effects). An effect on sleep may also result from the decrease of symptoms of over-arousal, which would be consistent with findings involving self-medicating populations of PTSD patients.[1,2,13] Bujarski *et al.*[13] also studied alternative motives for use and demonstrated that in adolescents with PTSD the coping motive was the primary cause for use and all other motives examined, i.e. 'social', 'enhancement' or 'conformity', were close to zero. These results were limited to a population of PTSD patients seeking treatment for substance abuse, and therefore, generalizability seems limited. Another study reported a strong correlation between PTSD symptom severity and the amount of cannabis use[14,15] and discussed the self-medication hypothesis as a possible

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explanation.[14] An additional interesting finding was that the starting point of using cannabis correlated with the onset of PTSD symptoms in more than half of the sample.[15] These authors speculated that cannabis use was used to help alleviate aversive mood states, but this hypothesis was not confirmed by another more limited and smaller study carried out by Bujarski *et al.*[13]

Another specific study involving combat veterans who displayed severe PTSD pathology examined the symptom clusters individually by *post hoc* analyses in a correlation analysis of psychopathological relapse causes four months after treatment. Main causal factors for relapse were found in avoidance and numbing symptom clusters. A further more specific analysis suggested a unique predictive effect for the PTSD numbing symptom cluster, but not for the avoidance symptom cluster, which indicated that primarily numbing symptoms may be a risk factor for increased cannabis use in patients with PTSD.[12] Another interesting finding of this study was the fact that changes in PTSD symptom severity were not incrementally predictive of any non-cannabis substance use and the authors discussed this in context of limitations of their study. However, this may point towards some specific effects of cannabis on some major symptoms of PTSD. It has to be mentioned that all these studies used a cross-sectional methodology and so their results cannot solve questions regarding temporal and causal directionality underlying the observed effects.

Most of the studies mentioned here appear to have implications for clinical practice. It is implicated that more attention has to be paid to the comorbidity of cannabis users and the background of their motives for use, especially in those with cannabis dependency syndromes. Their treatment has to pay more attention to these comorbidities and at best offer a combined treatment for addictive behaviour and PTSD.

Recently, a study protocol which was introduced for consideration by the US regulatory agencies for the study of cannabis resin for the treatment of PTSD was rejected, but permits were provided for the use of medical marijuana in PTSD in two states of the USA (Delaware and New Mexico).[16]

There is some robust evidence from clinical and preclinical studies that the endocannabinoid system (eCB) may be involved in the pathogenesis of several psychopathological symptoms.[17,18] It was recently concluded that the endocannabinoid system is implicated in homoeostatic cortical excitation and inhibition as well as in emotional homoeostasis.[19] There is also growing evidence for antidepressant and anxiolytic effects of the major cannabis ingredients THC and cannabidiol (CBD).[20] This review aims to consider whether neurochemical alterations as well as changes in neurobiological functioning might underlie these effects.

A clinical case report

From about the age four, the patient was a victim of long-time sadistic sexual abuse by his father and paternal uncle, which continued until age 15 when he attempted to commit suicide for the second time following the first suicide attempt two years earlier. Since then, this patient has been closely followed in outpatient psychiatric clinics. Because he was not diagnosed with PTSD at first, he did not receive treatments specific to PTSD for years. We first saw the patient in April 2004 when he was admitted to an acute psychiatric ward of our department for safety and stabilization during a crisis with severe, uncontrolled flashbacks, panic attacks, and impulses for self-mutilation. His physical examination was without abnormalities and drug testing was negative. Usually, he was treated during/after these states with sublingual lorazepam up to 10 mg/day. In a typical and severe flashback episode, this patient appeared in a dissociative state with complete loss of self-control. He would cry intensely, fall down, thrash about uncontrollably, and did not appear to have any cognitive or emotional control over re-experiencing past trauma. Immediately after such episodes, the patient would experience severe urges for self-mutilation. Such urges had resulted in severe self-injury in the past (mainly lacerations from cutting with knives). After a few days of treatment and stabilization he was referred back to the inpatient psychotherapy treatment centre, and following a few weeks of suffering from the same range of symptoms, his condition improved dramatically. This improvement, which surprisingly stabilized over the next months, could not be explained by any other means by the staff of the inpatient treatment center. The patient was re-admitted to our clinic in November 2004 with similar symptoms but this time he told the psychiatric team he could now control himself much more before and during the upcoming flashbacks. Drug testing was negative with the exception of THC. When he was asked what his idea was about the improvement of his condition, he confessed that he had learned to smoke cannabis resin from some other inpatients. He had discovered that he could prevent dissociative states by smoking cannabis when he first felt reactivation and intensification of traumatic memories experienced as flashbacks. Although he still experienced flashback phenomena after the use of cannabis, he would smoke cannabis to alter their course and intensity. The patient described that cannabis use would assist him with the increased ability to maintain cognitive control. Though it did not eliminate traumatic images, cannabis allowed the patient to view them on an 'inner screen' from a distance. It should be mentioned that this patient never underwent specific PTSD-screening procedures for the treatment of intrusive flashback memories.[21] The urge for self-mutilation was also reduced when he smoked cannabis immediately after experiencing flashbacks. Sometimes he could not only prevent the urge to self-mutilate afterwards but could often feel cheerful instead. The patient stated that he found cannabis more useful than lorazepam because it worked better at targeting the very symptoms that were otherwise intensely painful and contributed to his self-injury and because he noticed that this occasional use of cannabis did not affect vigilance when compared to lorazepam. This was confirmed by his therapists and the fact that there had been no need for treatment of self-mutilation since he had started using cannabis in these critical states. His therapists at the inpatient psychotherapy treatment centre were not aware of his use of cannabis but noticed and charted the patient´s improved self-control and stability. It is evident from the case history that the patient experienced reduced stress, less involvement with flashbacks and a significant decrease of anxiety. In the following paragraphs, some key issues will be discussed that might be relevant for the mitigating effects of acute PTSD symptoms experienced by this patient. It is worth noting that the cannabis used was cannabis resin from turkey which is known to contain THC and a nearly equivalent amount of CBD.[22]

The pathophysiology of PTSD

PTSD is a serious disorder that is usually induced by one or more traumatic events. These events are typically characterized by their overwhelming character which have an impact on the organism

or psyche that renders the person unable to handle the impact at the moment of occurrence. A typical example is rape and a significant number of people who have experienced one or more such traumatogenic situations will develop symptoms of PTSD. These usually consist of a heightened level of general central nervous system (CNS) arousal, sleep disturbances, nightmares, psychological instability, depression, anxiety, avoidance behaviour, emotional numbing, and repeated intrusions of parts of the experience into consciousness ('flashbacks').[23]

On the neurophysiological level, patients with PTSD develop a hyperactivity of the amygdala[24] which is a central part of the fear network which is involved in the assessment of threat-related stimuli.[25,26] In these patients, the amygdala is especially hyper-responsive to the presentation of trauma-relevant stimuli.[27] Morphological studies were inconclusive in regards to structural changes in the amygdala,[28] but the amygdala appears to be implicated in extinction learning. The hippocampus is involved in learning and explicit (declarative) memory, working memory,[29] episodic memory,[30] and has also a role in the regulation of stress.[31] A decreased hippocampal volume of gray matter is a regular finding in chronic PTSD patients and there is evidence that elevated blood flow in the hippocampus is related to episodic, spatial and contextual memory and emotional responses. Activity in parahippocampal structures can be triggered by symptom provocation tests like trauma-relevant imagery.[32]

In contrast to over-activation of the amygdala, hippocampus and parahippocampal structures, and the anterior cingulate cortex (ACC), show decreased activity in acute[32] and chronic PTSD.[28,33] On the other hand, a sub-region of the ACC, the dorsal ACC (dACC), which is involved in emotional regulation, recall of emotional experiences and processing of emotional responses,[34] is over-activated in PTSD during symptom provocation tests (e.g. playing combat sounds to war-related traumatized PTSD patients).[35] In a study using [^{15}O]H_2O-PET, the exposure to traumatic imagery, which induces flashback-like memory, activated the medial posterior orbitofrontal cortex, the insular cortex, the anterior temporal pole, and the medial temporal cortex.[27,36] A deactivation of the rostral ACC was also observed.[37] The ACC is part of the medial prefrontal cortex and is also involved in the process of fear extinction conditioning.[38,39] The insular region mediates somatosensory processes, feelings and recall of emotional events such as emotional memory. A comparison between acute and chronic PTSD showed that acute PTSD displayed a more extended and unstable pattern of activation while chronic conditions included more circumscribed and stable neurofunctional abnormalities.[36] Flashback memories are typically induced by inner or outer stimuli which activate the amygdala and induce the retrieval of 'unmetabolized', but instead hypermnestically stored, memories from the hippocampus. Another important structure for the maintenance of PTSD is the ventromedial prefrontal cortex, which plays a major role in extinction learning ('forgetting') by interacting with the amygdala in a reciprocal fashion, i.e. leading to inverse correlation during emotional activity. This happens via inputs to inhibitory GABAergic cells that block information flow from the amygdala's lateral to central nucleus[40] and also regulates the hippocampus in regard to extinction recall.[41,42] The medial prefrontal cortex appears to be hypoactive in PTSD.[33,43]

From the evidence cited, the hypothesis was formed that a major cause for the persistent inappropriate fear responses and the diminished extinction of conditioned fear in PTSD patients may include under-activation of the ACC and the medial prefrontal cortex which may help to explain the emotional dysregulation observed in these patients. Learned fear associated with PTSD can persist for tens of years. Therapeutic interventions for PTSD include extinction learning and psychotherapeutic approaches for PTSD aim to strengthen the function of the medial prefrontal cortex to enhance the capability of extinction learning and to break the cycle of an over-activated fear system (amygdala, hippocampus, parahippocampal structures) while under-activating ACC and medial prefrontal cortex. Animal experiments have shown that extinction learning and recall involve different cellular mechanisms and possibly different brain regions.[44]

Possible mechanisms involved in the effects of cannabinoids in PTSD

The endocannabinoid system

The plant *Cannabis sativa* has been used by humans for thousands of years because of its psychoactive properties. The major psychoactive ingredient of cannabis is THC, which exerts effects in the brain by binding to a G-protein-coupled receptor known as the cannabinoid CB_1 receptor.[45] Two putative endocannabinoid ligands, arachidonylethanolamide (anandamide, AEA) and 2-arachidonylglycerol (2-AG), have been identified as major endogenous transmitters of the endocannabinoid system (eCB). The eCB system is distributed throughout the brain and regulates synaptic release of excitatory and inhibitory neurotransmitters. A key role of the eCB system is the activation of the CB_1 receptor which is widely represented in the brain showing a 10-fold higher distribution level in comparison with opioid receptor levels. Endocannabinoids such as AEA and 2-AG that interact with these receptors are post-synaptically synthesized signalling molecules and are not stored in vesicles. Instead, they appear to be generated on demand and liberated to act in a retrograde fashion on presynaptically localized CB_1 receptors.[46] Recent research revealed that the eCB system is homoeostatic in that it prevents extreme cortical excitation and inhibition and that it may be dysfunctional in some mental disorders. eCB signalling is widely distributed throughout corticolimbic circuits that are linked to the stress response. The general level of cortical excitability is determined by the neurotransmitter systems using GABA and glutamate. Stress, especially linked to some severe psychiatric disorders like PTSD, may produce an imbalance in the eCB system. This system serves as a modulator, comparable to a 'dimmer switch' that helps to prevent excessive excitatory or inhibitory activity.[18] Since the discovery of the endocannabinoid system a growing body of psychiatric research has emerged focusing on the role of this system involved in major psychiatric disorders like schizophrenia, bipolar disorder, major depression and anxiety disorders.[47] For example, the CB_1 receptor antagonist rimonabant was reported to cause depression and anxiety in a significant proportion of psychiatrically normal subjects.[48]

Cannabis and exocannabinoids

Three major exocannabinoids are THC, CBD and cannabinol (CBN) and represent the main constituents found in cannabis resin.[49] THC is the major psychoactive constituent and is responsible for the mood and consciousness-changing effects.[50] Reports concerning anxiolytic properties are inconsistent, and in some subjects, anxiogenic effects can be generated instead.[51,52]

Besides THC, CBD is the main non-psychoactive phytocannabinoid found in *C. sativa* which can constitute up to 40% of its

extract. CBD has anxiolytic, anti-psychotic and anti-convulsant effects and antagonizes the intoxicant and psychotomimetic actions of THC and has opposite effects on regional cerebral blood flow (rCBF) when compared to THC.[53,54] Recent reviews indicate that CBD is a promising candidate for the treatment of some neuropsychiatric disorders.[55–57] CBD also facilitates extinction in a contextual aversive conditioning model following intracerebral ventricular administration.

Cannabis and anxiety

It has been argued that the neuronal circuitry underlying fear conditioning has similarities to that responsible for fear-related clinical conditions, such as PTSD.[25] Moreover, behavioural therapies for PTSD/anxiety, including systematic desensitization and therapies relying on imagery, also share features of fear extinction. Although high doses of intravenous THC may appear to increase anxiety in humans,[58] low doses attenuate anxiety-related responses in animal models.[59] It was also shown that anxiety disorders may make people more vulnerable to cannabis abuse and dependence.[60–62] This vulnerability may depend on an increased sensitivity towards anxiety and the probability that these individuals may cope with their aversive anxiety by using cannabis was found to be higher.[63] Cannabis dependence increases the risk for panic disorders, but the causal direction was not definitely disentangled.[64] It is discussed in how far a 'repeated affect-relevant learning with aversive interoceptive cues' through the use of cannabis may be a key risk mechanism for maintaining cannabis dependency and relapse after treatment.[64]

There appears to be a lack of clinical investigation regarding eCB-activity and anxiety but preclinical and clinical data strongly suggest that anxiety is associated with a decreased endocannabinoid tone leading to excessive cortical excitation, particularly in stressful situations. The influence on anxiety is thought to be mainly mediated by CB_1 receptors, but also possibly by CB_2 receptor and G-protein coupled receptor activation which appears to involve decreased anxiety in a variety of rodent assays such as the elevated plus maze test. The fact that these effects are partially inconsistent may depend on a number of factors including regional endogenous tone, type of test, and dosage.[65] Mice, when exposed to a stressful environment, display a stronger anxiety response than their CB_1 knockout counterparts.[66,67] In addition, anxiolytic actions of benzodiazepines were observed to be absent in CB_1 receptor-knockout mice which presented increased anxiety-like behaviours. Thus, it was concluded that the CB_1 receptor played a pivotal role in the anxiolytic action of benzodiazepines.[68,69] Anxiolytic effects of CBD have also been demonstrated after microinjection into the dorsolateral periaqueductal gray, bed nucleus of the stria terminalis and prelimbic medial prefrontal cortex.[70–72] Additionaly, the CB_1 receptor antagonist rimonabant causes depression and anxiety in a significant proportion of psychiatrically healthy normal subjects.[48] Clinical studies have shown that CBD displayed anxiolytic properties, for example in subjects who showed anxiety of speaking in public.[73] In agreement with these findings, neuroimaging studies showed that CBD facilitated a change in brain activity in regions related to emotional responses. It impairs connectivity between the prefrontal and subcortical regions and attenuates responses to fearful faces in the maygdala and cingulate cortex[74] and furthermore decreases activation in the left amygdala-hippocampal complex and left posterior cingulate gyrus.[75]

Effects on hippocampus and memory

Endocannabinoids exert an amnesic effect and may be crucial for the extinction of aversive memories,[76,77] while blockage or knockout of the CB_1 receptor induce deficits of the extinction processes and supersensitivity to stress[78] by decreasing GABAergic function.[67] The mechanisms by which cannabinoids alter perception and memory have not been exactly elucidated. *In-vivo* recordings of populations and single neurons have shown that THC disrupts the synchrony of action potentials between hippocampal neurons with only marginal effects on average firing rates.[79] The hippocampal formation has an unusually high density of CB_1 receptors[80] and these are involved in both glutamatergic and GABAergic presynaptic processes.[81] CB_1 receptors are present on certain peri-terminal axons at astonishingly high densities,[82] enabling endogenous and exogenous cannabinoids to potently inhibit action potential-evoked GABA and glutamate release by means of CB_1 receptor-mediated inhibition of N-type presynaptic calcium channels. Thus, cannabinoids can dramatically depress fast synaptic communication in the hippocampal network leading to a functional decoupling of neurons. Robbe and co-workers[79] found that administering THC depressed hippocampal and neocortical electroencephalograms in rats at multiple frequencies. The effects of cannabinoids on gamma oscillations are especially important, because neurons form *ad hoc* assemblies defined by synchronous action potential firing.[83] These assemblies are thought to be tasked with the representation, storage and retrieval of information and memories. Hippocampal theta- and gamma oscillations are thought to be critical in working memory, the encoding of episodic memory, and in the coordination of neuronal discharges across regions.[84] Exogenous cannabinoids disrupt the induction of hippocampal long-term potentiation (LTP) and impede on behavioural learning, potentially including strength of association between stimuli and fear or anxiety. By reducing synchronous firing, exogenous cannabinoids may reduce the associational activation of synapses that induces LTP.[85] It has to be discussed in how far cannabinoids mediate disorganization of synchronized cell assemblies, and by doing so, leading to decreased hippocampus-dependent memory performance. A major implication of these data is that the synchrony of spike timing in neuronal assemblies is a necessary component of proper hippocampal function and that THC may reduce anxiety by reducing activation of hippocampal networks that retrieve fear-related memories, as when triggered by associated stimuli.

Involvement of endocannabinoids in fear extinction

A large body of work has established that a small region of the brain, i.e. the amygdala, is crucial in acquiring and, possibly, storing the memory of conditioned fear.[26] Endocannabinoids exert an amnesic effect and are crucial for the extinction (forgetting) of aversive memories[76,77] while blockage of the CB_1 receptor induces deficits on the extinction of aversive memories and supersensitivity to stress.[78] Extinction or reduction of fear responses (i.e. required by trauma) may be generated on a neurobiological level through synaptic plasticity mediated by NMDA receptors[86] but other mechanisms of extinction may also be involved.[87] Marsicano and colleagues[76] proposed a mechanism of extinction involving the eCB and CB_1 receptors which are some of the most abundant neuromodulatory receptors in the CNS and are expressed at high levels in the limbic system, cerebellum and basal ganglia.[88,89] The main psychopharmacological effects of exogenous cannabinoids

(sedation and changes in memory) have been correlated with the presence of CB_1 receptors in the limbic system and striatum.

Endocannabinoids also play a role in inhibiting neurotransmitter release. The research carried out by Marciano *et al.*[76] demonstrated the impact of endocannabinoids on learning and plasticity. It was shown that CB_1 receptor knock-out mice could learn and later recall association of a tone with a foot shock but were unable to extinguish the memory, i.e. their emotional response to the tone. These authors found that during the extinction period, the levels of endogenous AEA and 2-AG were raised in the basolateral amygdala in mutant and normal mice which implied a role for endocannabinoids in the extinction of conditioned fear. CBD also facilitated extinction in a contextual aversive conditioning model after intracerebral ventricular administration.[54]

Effects of endo- and exocannabinoids via stress-related hormonal systems

Stress can be defined as confrontation with stimuli that presents a challenge to homoeostasis, typically a perceived stress to the well-being of the organism. In humans, acute and chronic stressful situations correspond with the secretion of glucocorticoid hormones. The paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH) and the anterior pituary gland releases the adrenocorticotropic hormone (ACTH) into general circulation. Subsequently, glucocorticoid hormones, such as cortisol (from the adrenal cortex), are released to mobilize energy stores and to induce a range of effects on cardiovascular, immune, metabolic, and neural systems that facilitate optimal responses to aversive stimuli.[90] Although this may have adaptive functions in the short term, in cases of repeated stress exposure, prolonged glucocorticoid secretion can produce deleterious effects on metabolic, immune, cardiovascular and neurobiological functions.

Both hippocampus and PFC exert inhibiting effects on the hypothalamic-pituitary-adrenal (HPA) axis whereas antidepressive agents can normalize its hyperactivity. Furthermore, it has been shown that eCB signalling responds to and regulates the activity of the HPA axis which governs their secretion of stress hormones.[91] The eCB system, maintaining homoeostais of the stress system, can activate as well as terminate the HPA axis response to acute and repeated stress. Accumulating evidence indicates that the eCB tone provides a steady-state inhibition of the HPA axis activity.[92] Prominent in these behavioural stress responses is the interaction between eCBs and the HPA-axis. Data indicate that glucocorticoids induce eCB signalling through a rapid non-genomic process in CRH neurons of the PVN.[93] This induction of eCB signalling inhibits glutamatergic inputs to CRH neurons and thus decreases the excitatory drive to the HPA axis.[92] Glucocorticoids are self-regulated through negative feedback and eCB mediates glucocorticoid fast feedback mechanisms. Fast feedback inhibition of HPA axis stress responses by direct glucocorticoid action at the PVN of the hypothalamic rapidly inhibits restraint-induced ACTH and corticosterone release consistent with feedback actions at the cell membrane.[94] It was demonstrated that following repeated exposure to stress AEA is persistently decreased throughout the corticolimbic stress circuit whereas 2-AG is elevated (exclusively in the amygdala) in a stress-dependent manner.[95] This divergent regulation of AEA and 2-AG contributes to distinct forms of HPA axis habituation. Inhibition of AEA hydrolysis or intra-amygdala administration of a CB_1 receptor antagonist before the final stress exposure prevented the repeated stress-induced development of basal hypersecretion of corticosterone.[91] Thus, there is evidence for both GABAergic and CRH-mediated mechanisms involved in the anxiolytic effects of THC.

Reduction of anxiety and amygdala reactivity and the eCB system

The amygdala has been identified as one of the primary limbic structures involved in activating the HPA axis in response to stressful stimuli. There is also accumulating evidence that glucocorticoid-mediated induction of eCB signalling is also a relevant feature, because glucocorticoids enhance the long-term consolidation of emotionally arousing experiences.[92] Presence of eCB signalling within stress-sensitive nuclei of the hypothalamus as well as upstream limbic structures, such as the amygdala, suggests a role in regulating the stress response. Administration of CB_1 antagonists into the basolateral nucleus of the amygdala (BLA) blocks the ability of corticosterone to facilitate aversive memory consolidation[96] which highlights an important role of the eCB system in this complex adaptive process. During extinction training, but not initial fear conditioning, eCB levels in the amygdala, but not in the prefrontal cortex, were elevated. Mice lacking the CB_1 receptor exhibit prolonged expressions of fear behaviours during extinction training.[76] In mice exposed to brief inescapable electric foot shock subsequently presented a neutral tone, the CB1 receptor-deficient mice failed to suppress the conditioned fear response when the shock was stopped and showed persistent fear on on repeated tone exposures.[97] From these studies it was concluded, that 'the feardampening effects of eCBs become evident only in highly aversive situations and are independent of CRH and corticosterone action'.[97] The dampening of anxiety and over-arousal, especially in regard to inducing flashback memory appears significantly reduced in the case described in the beginning of this review.

During the adaption to stress and aversive stimuli the amygdala shows no change in 2-AG in response to acute stress.[98–100] However, following repeated stress/aversive stimuli a 2-AG increase was progressively observed[99] followed by decrease after 1 h and complete reversal within 24 h of exposure.[101] As far as habituation to homotypical stress is concerned, this reaction pattern is critically involved in the habituation of the HPA axis. Accordingly, the increase of 2-AG correlates directly with HPA axis suppression and the local administration of a CB_1 receptor antagonist into the BLA reversed the expression of stress habituation.[101] Transient augmentation of 2-AG signalling upon repeated stressor exposure dampens excitatory inputs to the BLA by decreasing outflow of the amygdala, which would include stimulation of the HPA axis.[101] This would be consistent with corticosterone inhibition of glutamatergic inputs to the BLA through an eCB-mediated mechanism but only in animals with history of previous stress exposure.[102] BLA administration of CB_1 antagonists blocks the ability of systemically administered corticosterone to facilitate aversive memory consolidation.[96] Glucocorticoids recruit eCB signalling in the BLA to modulate aversive memory consolidation. The amygdala's GABAergic system is known to modulate memory storage[103] and activation of CB_1 receptors decreases GABA release via rapid inhibition of Ca^{2+} entry into the terminals.[104] A recent fMRI neuro-imaging study in humans demonstrated that THC discretely attenuated localized limbic (amygdala) reactivity to threatening stimuli without affecting performance on other complex tasks.[105] Interestingly, these results resemble those shown with lorazepam.[106]

Cannabinoids decrease CRH levels in the central nucleus of the amygdala and decreased CRH levels are associated with decreased aversive stress responses in animals[107] and humans.[108] It was also demonstrated by Marciano *et al.*[76] that basolateral amygdala neurons present in normal mouse brains are capable of releasing GABA when stimulated under low-frequency conditions. This can lead to a long-term reduction in the release of GABA which in turn leads to less inhibition of the connecting pyramidal neurons. This long-term depression (LTD), a type of synaptic plasticity, was completely blocked by the CB_1 receptor antagonist rimonabant (SR141617) and absent in CB_1-deficient mice.[109] This finding implies a reduction of GABA release in the basolateral amygdala, thereby helping to extinguish the fear-conditioned response or reduction of anxiety.[58] CBD has been shown to attenuate neurophysiological responses to fearful faces in the amygdala as shown by fMRI[74] and, in addition, reduced activation in the left amygdala-hippocampal complex and left posterior cingulate cortex.[75]

Antidepressant effects of cannabinoids

Another significant set of symptoms observed in PTSD patients include depressive mood and stressful sleep disorders. Several lines of evidence suggest that cannabis may have antidepressant effects. Nevertheless, no clinical trials have been published to date on the use of cannabinoids for the treatment of affective disorders although anecdotal reports have described antidepressant properties of cannabis.[8] Some methodological limitations present in the very few human studies currently available make interpretation difficult. Antidepressive agents increase monoamine neurotransmitters such as serotonin and noradrenaline[110] and normalize the hyperactivity of the HPA axis, which also involves the eCB system. In a study designed to look for possible uses of cannabis resin as an antidepressant in recreational users[111] it was concluded that patients may be found who use marijuana for self-treatment of depressive symptoms. Degenhardt *et al*. argued that there was little evidence for an increased risk of later cannabis use among people with depression, and hence little support for the self-medication hypothesis.[112]

Several authors have reported altered endocannabinoid levels involved in the precipitation of depression.[113] The pharmacological enhancement of endocannabinoid activity at the CB_1 receptor level appears to exert an antidepressant-like effect in some animal models of depression. CB_1 agonists significantly increase the firing activity of neurons in the dorsal raphe, thus enhancing serotonin neurotransmission.[114,115] Stimulation of CB_1 activity was shown to increase firing in the locus coeruleus as well as the release of norepinephrine (NE) in the prefrontal cortex (PFC)[115,116] which implies antidepressant activity. Additional evidence comes from co-treatment with α- and β-adrenergic receptor antagonists that were found to attenuate antidepressive effects induced by chronic administration with CB_1 receptor agonist.[117] Moreover, it appears that CB_1 receptors modulate the effect of the selective serotonin reuptake inhibitor citalopram on extracellular serotonin levels in the rat prefrontal cortex.[118]

Sleep-enhancing effects of cannabinoids

It is well known that PTSD includes a pathologically hyperarousal syndrome which leads to serious sleep problems, especially with sleep onset and increased numbers of awakenings during the night. *C. sativa* has been utilized for the treatment of pain and sleep disorders since ancient times. Early studies reported an earlier sleep onset, decreased REM sleep and an increase in stage 4 sleep with the ingestion of THC in healthy subjects. Both drugs reduced eye movement density with some tolerance developing to this effect.[119–121] Marijuana effects on sleep were virtually identical to those produced by the same doses of THC.[120,121] However, an issue that requires further clarification in this context is that it was unknown whether these preparations contained CBD. Controlled studies have demonstrated that with orally administered dosage levels of 10, 20 or 30 mg THC the time needed for mild insomniacs to find sleep was minimized. Twenty mg THC were most effective and reduced the time of falling asleep by 62 min (placebo: 180 min *vs* 118 min). Higher doses did not improve this any further.

A more recent study which examined the relationship of THC (15 mg p.o.) and a combination of THC and CBD (5 mg or 15 mg p.o. of each substance) on sleep in a cross-over design found a very differentiated impact on sleep patterns. According to this study, no significant effects of pure THC on the sleep measures were observed, but a decrease of rapid eye movement (REM) sleep periods and REM duration as well as a decrease of stage 3 sleep was found instead. On the other hand, the combination of THC and CBD led to highly significant decreases of REM sleep (placebo: 84.75 min; THC 15 mg and CBD 15 mg: 61.88 min) at higher dosage levels, but at the same time, an increase of duration of wakefulness (placebo: 17.06 min; THC 15 mg and CBD 15 mg: 41.06 min) was also observed. No difference in latency of sleep onset and number of awakenings with any of the substances or combinations was found compared to placebo.[122] The authors noted the occurrence of sleepiness on the next morning following THC (15 mg) administration but also when the higher combined dose was given. When evaluating the psychomotor and memory performance on the next day clinically significant effects of the drugs were not detected. Surprisingly, in rats the endocannabinoid anandamide did not block the effects of CBD.[123,124] The mechanism of action of CBD on sleep modulation remains to be elicited[125] but it was speculated that CBD may modulate wakefulness by via an activation of neurons in the hypothalamus and the dorsal raphe nucleus.[124] Anandamide was observed to decrease wakefulness in addition to increases in slow wave sleep and REM sleep in rats.[124] When the action of anandamide was blocked by the CB_1 receptor antagonist SR 141716A, i.e. 15 min prior to anandamide administration, these anandamide-induced changes in sleep were not observed, hence providing indication that the CB_1 receptor was a major target for the sleep-inducing actions of anandamide.[125]

According to the study of Cousens and DiMascio[126] there was a decrease in the number of sleep interruptions, especially in the first third of the night which suggested that the hypnotic actions of THC were relatively short-lived. Some subjects complained in the morning about a mild to moderate feeling of being hungover or being stoned, but subjects who received the 20 mg dose did not observe any interference with their daily work function.[126] More recent studies showed THC and cannabis to be effective in sleep disorders and that they were well tolerated[127] and a low nabilone (THC) dose given once per day at bedtime was suggested as a possible alternative to amitriptyline.[128] No tolerance on pain or sleep, nor a need for dosage increases have been observed.[3] When intracerebroventricular administrations of CBD (10 μg/5 μL) were employed in rats during the lights-on sleeping period, an increased wakefulness and a decreased REM sleep was observed although sleep changes during the dark phase were not observed.[124] The decrease of REM sleep in humans may contribute to the fact that most individuals report a less frequent occurrence of dreams,

especially nightmares. The main conclusion from experiments carried out in humans with cannabis resin/marijuana, which includes a mix of cannabinoids (usually mainly THC and CBD), is that increases in sleep appear to be consistent features.[119,129–131]

An unexplained fact is the significant increase of 'strange dreams' for more than two weeks during withdrawal from heavy cannabis smoking,[132] which does not appear to depend on REM rebound. In a study examining regular cannabis users during a few days abstinence period, participants had a mild to moderate degree of decreased sleep efficiency, total sleep time, percent time spent in Stage 1 and Stage 2 sleep, REM latency and subjective sleep quality, as well as increased sleep latency and time spent in REM sleep when compared to these patterns when using cannabis.[133] In rats, which were sleep deprived for 24 h, it was demonstrated that the usually seen REM rebound was very much reduced when the CB_1 receptor antagonist SR 141716A was given before sleep.[134] However, a reduction in REM sleep observed with cannabis does not seem to be a consistent finding,[135,136] which may point towards different possible implications. It may lead to decreased periods of wakefulness and nightmares, although less REM sleep is also discussed to alter affect regulation and memory-related processes[137–139] and that it may also play a role in depression.[140]

Discussion

It seems obvious from more recent studies of clinical and non-clinical populations that cannabis is used by a significant number of PTSD patients in the attempt to cope with their symptoms.[10–15] It appears that through different levels of actions (physiological, transmitter and molecular) eCBs are involved in the etiological mechanisms of certain mental disorders. The field of research investigating the eCB system is growing rapidly. The effects of cannabinoids, even if in some important aspects not well researched in humans, are complex and include effects on mood, stress and distress mechanisms, mainly involving the HPA axis and its regulation via fast feedback/presynaptic mechanisms. Endocannabinoid systems also show direct effects on major limbic and paralimbic structures, especially in fear conditioning, habituation and extinction. Therefore, it appears that modulation of the eCB system might be a rewarding target for psychopharmacological drug development. It might even be possible that some cannabinoids may offer potential to compete with commonly employed antidepressive agents, at least in some respects (Table 1).

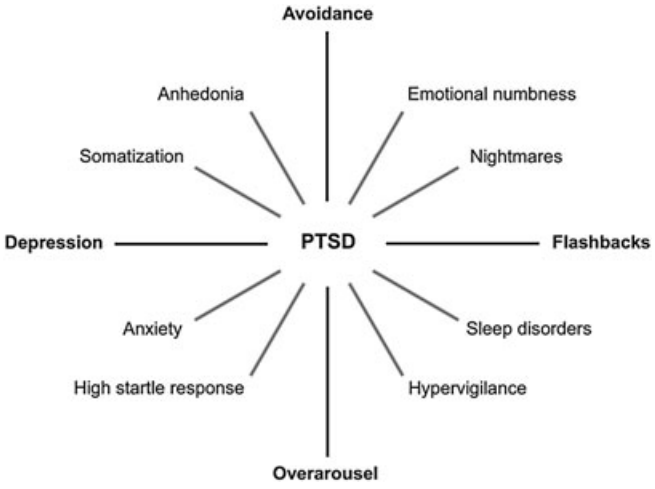

Figure 1. Symptom clusters typically involved in PTSD.

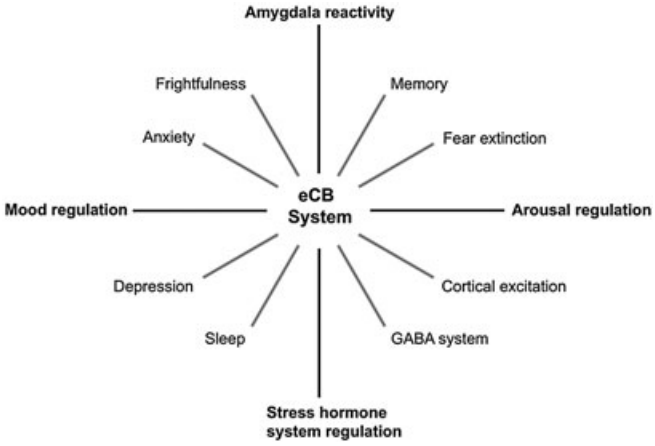

Figure 2. Involvement of the endocannabinoid system in neurobiological systems.

If one looks at the symptoms specific for PTSD (Figure 1) it also appears that effects at multiple levels that involve eCB signalling may be helpful when coping with symptoms of PTSD (Figure 2). Reduction of over-arousal, nightmares, sleep disorder, flashbacks as well as antidepressant and anxiolytic effects, may be achieved.

Table 1. Effects of Cannabis (THC, CBD) and antidepressants on symptoms of PTSD based on data given in cited references and clinical experience. + = effective; ++ = very effective

Symptom	Cannabis resin (THC + CBD)	Antidepressants (SSRI-type)	Antidepressants (Trimipramine/Amitriptyline-type)
Overarousal	+		+
Flashbacks	++ (frequency and intensity)	+	
Nightmares	++ (less REM)		+ (mirtazapine)
Anxiety	+	+	
Depression	+	++	++
Sleep disorders			
Sleep onset	++		++ (mirtazapine, amitriptyline)
Awakenings during night	++		+

Multiple effects associated with cannabis resin appear to act synergistically to reduce some symptoms of PTSD and might offer potentials for new psychopharmacological treatments. Therefore, PTSD subjects may opt to self-medicate by using cannabis.

In the case report presented in this review, the patient displayed a grave pathology involving anxiety, dissociation and heavy flashbacks as a consequence of PTSD. When he began to use cannabis he observed that he could handle his symptoms much better and that he was able to refrain from getting too involved with the flashbacks. The patient described this as being able to look at them from a distance, i.e. 'from outside'. His anxiety was also much more manageable, and as a consequence, he was able to handle the situation much better while exercising greater control. In the case where he was able to detect an upcoming flashback early enough he was able to stop the flashback from appearing by smoking cannabis resin. One possible explanation might include a reduced involvement of the amygdala (and hippocampus) in an overreaction that would otherwise produce panic and an overwhelming altered state of dissociation, including intrusive flashback memory. The patient found himself in control and was able to reduce his suffering.

It should be noted that although cannabis has been used as a psychopharmacological agent for centuries deleterious effects are commonly observed in some individuals, including dependence and worsening of life conditions associated with regular cannabis use. Even if excluded from the DSM-IV-TR, there is growing evidence that a significant cannabis withdrawal syndrome (mild to moderate symptoms of sleep difficulty, strange dreams, irritability, restlessness) may appear after longer time of daily smoking of cannabis in 60-75% of the users, but its clinical significance is still debated.[132]

It has been hypothesized that PTSD is maintained by amygdala hyperreactivity[141] and that cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and to feel less anxious and less involved with flashback memories. The presence of endocannabinoid signalling systems within stress-sensitive nuclei of the hypothalamus, as well as upstream limbic structures (amygdala), point to the significance of this system for the regulation of neuroendocrine and behavioural responses to stress. The eCB system is involved in activation and termination of the HPA axis reactions to acute and chronic stress.

Conclusions

This review provides an overview of accumulating clinical and preclinical evidence that cannabinoids may mitigate some major symptoms associated with PTSD. A case study was presented of a patient with severe PTSD symptoms, who learned to smoke cannabis resin in order to cope with grave PTSD symptoms and who benefitted enormously from doing so. The accumulating evidence points towards diverse actions where the endocannabinoid system is involved in different neurobiological systems critical for the complex pathogenesis of PTSD. Findings from studies suggest that by altering fear conditioning, memory systems, general CNS arousal, mood, and sleep, exogenous cannabinoids may hold potential for the treatment of people with PTSD.[17] While it seems clear that that consumption of cannabis products may not be well tolerated in all individuals, more research is needed to reach definite conclusions about a therapeutic potential of cannabinoids in PTSD.

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