Battling stress-related psychiatric disorders using cannabis extract CBD

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Date: 20-08-2019

Abstract

Cannabis is often used for stress relieve, raising the question whether cannabis can be used as a treatment in stress-related psychiatric disorders. Cannabis exerts its effects via the endocannabinoid system (ECS), which both affects and is affected by the major stress response system. Even though medical cannabis reduces feelings of anxiety and stress in patients, it comes with severe adverse effects, making its therapeutic potential in stress-related psychiatric disorders questionable. Therefore, research has focussed on the non-intoxicating compound of cannabis, cannabidiol (CBD). As CBD exerts a great variety of effects, the therapeutic potential and drawbacks of CBD are discussed in relation to stress-related psychiatric disorders. Clinical studies in patients diagnosed with anxiety disorders, schizophrenia and major depression were reviewed. It was concluded that CBD has therapeutic potential in patients with anxiety disorders and schizophrenia. For major depression, preclinical animal studies showed anti-depressant like effects of CBD. However, placebo-controlled randomised clinical trials have not (yet) supported this. Placebo-controlled clinical trials assessing chronic CBD treatment and CBD as adjunctive therapy in psychiatric conditions are needed to enhance knowledge on CBDs safety.

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Introduction

Cannabis has been used as a recreational drug since ancient times. Cannabis comes from the plant *Cannabis sativa* and consists of more than 100 pharmacologically active phytocannabinoids. It is often consumed for its relaxing and mood-elevating effects (Green et al., 2003). It induces a psychoactive, mildly euphoric, relaxing intoxication, often called 'high', which results in slight changes in psychomotor and cognitive function (Baker et al.,2003; Kumar et al., 2001). As cannabis consumption reduces feelings of anxiety and stress in medical cannabis patients (Webb and Webb, 2014), cannabis might be useful in treating stress-related psychiatric disorders such as major depression and anxiety disorders.

To determine whether cannabis could be useful in treating stress-related psychiatric disorders, the first part of this essay will look into the working mechanisms of cannabis and how this interacts with stress. Moreover, the side effects of cannabis will be discussed.

To investigate how cannabis is able to reduce feelings of anxiety and stress, it is important to understand how cannabis affects the human brain. The main psychoactive compound of cannabis, delta-9-tetrahydrocannabinol (THC), exerts (most of) its effects through the endocannabinoid system (ECS). The ECS comprises of cannabinoid receptors (CB1 and CB2), endogenous ligands, called endocannabinoids (eCBS), and the enzymes for eCBS biosynthesis and inactivation. The ECS functions to gate and regulate neurotransmitter release, as activation of the CB1 and CB2 receptors results in a reduced cell firing rate and neurotransmitter release (Schlicker & Kathmann, 2001). Therefore, the ECS is greatly important in fine tuning the strength of a particular synapse (Freund et al., 2003). During development, the eCB system plays a critical role in neural growth and connectivity. Moreover, the ECS has profound effects on mood and behaviour (Wyrosfsky et al., 2019)

The ECS is an interesting system due to the ubiquitous nature of endocannabinoid signalling and CB1 receptor expression throughout the brain. CB1 receptors can be mainly found in the limbic system, amygdala, prefrontal cortex, hippocampus and periaqueductal gray matter (Herkenham et al., 1991; Tsou et al., 1998). CB2 receptors are mostly distributed in peripheral immune cells. The CB1 receptors are located primarily on GABAergic and glutamatergic neuronal presynaptic terminals, where they restrict neurotransmitter release and modulate neuronal firing. When the CB1 receptor is activated, it suppresses the release of neurotransmitters in two ways (Figure 1). Firstly, activation inhibits the voltage-gated Ca^{2+} channels, reducing presynaptic Ca^{2+} influx. Secondly, activation inhibits adenylyl cyclase (AC) and the subsequent cAMP/protein kinase A pathway, which is involved in long term depression (LTD) (Castillo et al., 2012). Whereas ion channel modulation allows eCBS to very rapidly down-regulate neuronal circuits, it is the kinases that mediate the long-lasting effects of eCBS (Volkow et al., 2017).

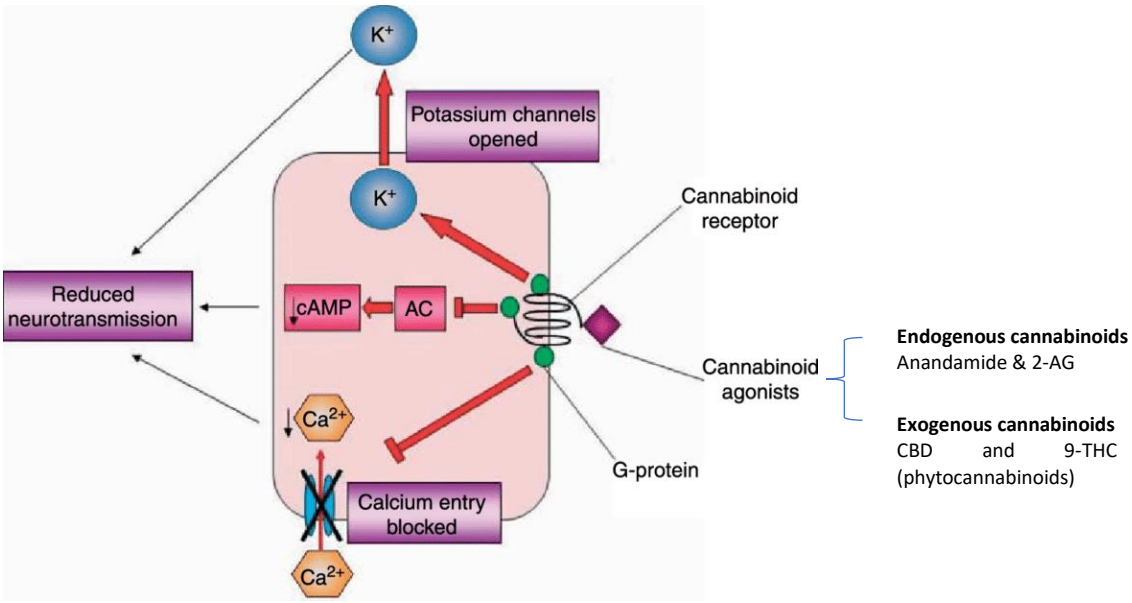

Figure 1 Cannabinoid-mediated signaling Binding of either endogenous or exogenous cannabinoids to the cannabinoid receptor inhibits voltage-gated Ca^{2+} channels, decreasing Ca^{2+} influx. Moreover, activation of the receptor inhibits andenylyl cyclase, resulting in a decreased cAMP/PKA pathway. This results in a reduced neurotransmission. (adapted from Butler and Korbonits, 2009)

ECS signalling is highly dependent on the state of synaptic activity. Network activity tightly controls the synthesis and degradation of eCBS. This is because eCBS are synthesised and secreted on demand, instead of stored in vesicles. They are post-synaptically synthesised in a calcium-dependent manner following cell depolarisation. Therefore, eCBS are not typical neurotransmitters. The two main eCBS are N-arachidonylethanolamine (AEA)

and 2-arachidonylglycerol (2-AG). Since the cannabinoid receptors are localised in the pre-synapse, eCBS act in a retrograde fashion on the receptors (Wilson and Nicoll, 2002).

2-AG is primarily synthesised from 1,2-diacylglycerol (DAG) by diacylglycerol lipase-α (Daglα). AEA is derived mainly form N-arachidonoyl-phosphatidylethanolamine (NAPE), which is hydrolysed by NAPE- specific phospholipase D (Nape-PLD) (Piomelli, 2003; Zou & Kumar, 2018). 2-AG is degraded by MAGL, whereas AEA is degraded by FAAH (figure 2). Moreover, postsynaptic cyclo-oxygenase 2 (COX-2) can terminate eCB signaling by turning 2-AG and AEA into prostraglandins (Hermanson et al., 2013).

The basal level of 2-AG is 1000 times higher than the level of AEA in the brain (Zou & Kumar, 2018). 2-AG acts as a full agonist at the CB1 receptor located at the presynaptic terminal, but can also activate CB1 receptors located at astrocytes, leading to the release of glutamate (Zou & Kumar, 2018).

AEA inhibits Ca^{2+} channels and is able to negatively regulate 2-AG biosynthesis in the striatum (Maccarrone et al., 2008). AEA plays a major role in mood regulation, cognition and behaviour (Di Marzo & Petrosino, 2007). AEA has lower affinity for the cannabinoid receptors than 2-AG has, but acts as a full agonist on a totally different receptor; the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor.

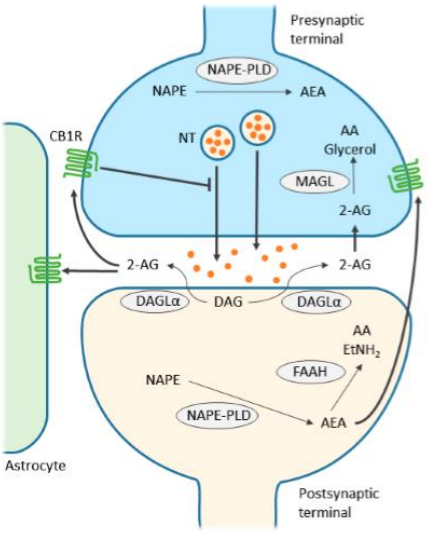

Figure 2 Schematic overview of endocannabinoid synaptic transmission Upon neuronal activation, eCBs are produced in the postsynaptic terminals. 2-AG is synthesised from DAG by DAGLα and AEA is synthesised from NAPE by NAPE-PLD. The eCBs, mainly 2-AG, retrogradely activate CB1 receptors at the presynaptic terminals, resulting in a reduced neurotransmitter release. (Zou & Kumar, 2018)

TRPV1 is predominantly expressed in sensory neurons (Caterina et al., 1997), and is thought to play a crucial role in synaptic transmission and nociception (Caterina et al., 2000). AEA acting on TRPV1 mediates a postsynaptic form of LTD (Castillo et al., 2012). In the central nervous system, TRPV1 receptors are expressed in brain regions related to the control of the stress response, including the mPFC, hippocampus, hypothalamus, locus coeruleus and PAG (Mezey et al., 2000).

There is growing evidence that even more different receptors are targeted by eCBS. One of these receptors is the orphan receptor, GPR55 (Ryberg et al., 2007). Ryberg et al. revealed that CB1 and CB2 receptor agonists, like AEA and 2-AG, can specifically bind to human GPR55. Therefore it is thought that AEA and 2-AG are not only endogenous ligands for the CB1 and CB2 receptors, but also for GPR55. Remarkably, 2-AG shows a 170 times greater potency as an agonist at GPR55 than at the CB1 or CB2 receptors. GPR55 mRNA is expressed in the adrenal tissue, frontal cortex and striatum in mice. Moreover, GPR55 is expressed in tissue that is involved in regulating energy intake and expenditure.

The ECS is involved in many physiological regulation pathways in the human body and as the CB1 receptor is the most abundant G-protein-coupled receptor in the mammalian brain, it is highly probable that the eCB signalling system interacts with even more receptors and pathways, yet to be discovered.

The main psychoactive compound of cannabis, THC, acts as an agonist on the CB1 receptor (Pertwee, 2018). By blocking the CB1 receptor with SR141716 , acute effects of THC are blocked in vitro and in animals (Huestis et al., 2001). This suggests that cannabis (mainly) exerts its effects via the CB1 receptor. Therefore, cannabis is able to modulate the ECS, thereby altering, among others, neurotransmitter release and synaptic strength.

It is well established that the ECS plays a role in the regulation of mood and the stress response. Dysregulation of the eCB system can even result in the development of stress-induced psychiatric disorders (Parolaro et al., 2010; Wyrofsky et al., 2015). As cannabis is able to alter the ECS, this might influence mood and stress responsiveness. Endocannabinoid signalling is widely distributed throughout corticolimbic circuits that are linked to the stress response. Both AEA and 2-AG are synthesized in the hypothalamus, amygdala, hippocampus and prefrontal cortex (Malcher-Lopes et al., 2006; Herkenham et al., 1991). In the upcoming chapter, it will be explained how the ECS affects the stress response and vice versa.

The HPA-axis

Stress can be defined as any stimulus that presents a challenge to homeostasis. In other words, stress is a real or perceived threat to someone's well being (Hill et al., 2010). The main neuroendocrine response to stress is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. This starts with the release of corticotropin-releasing hormone (CRH) by the paraventricular nucleus (PVN) of the hypothalamus (Swanson and Sawchenko, 1980). CRH will then be transported to the anterior pituitary gland, where it promotes the release of adrenocorticotropic hormone (ACTH). The release of ACTH results in the release of glucocorticoid hormones (called cortisol in humans) into the bloodstream. The release of glucocorticoids during stress can be beneficial, as it, for example, mobilises energy stores (Herman et al., 2005). This is important for the organism to be able to respond appropriate to the stressful situation. Elevated levels of glucocorticoids suppress the HPA axis activity by means of negative feedback inhibition of the HPA axis. Additionally, the amygdala, extended amygdala (including the bed nucleus of the stria terminalis), the hippocampus and prefrontal cortex also respond to stress and influence behaviour and HPA responses.

The LC-NE pathway

Besides the activity of the HPA-axis following stress exposure, the connection of the central noradrenergic (NE) system to the source of NE, the locus coeruleus (LC) plays an important role in the response to stress. The LC-NE system is regulated by both CRF as well as the eCB system and is thought to play a major role in the pathophysiology of stress-related disorders. Following chronic stress, the LC-NE pathway can get dysregulated. CRF released from the amygdala and PVN target the LC (Valentino and Van Bockstaele, 2008). LC-NE neurons express CRF receptor 1 and the release of CRF increases the firing of these neurons (Reyes et al., 2008). Chronic CRF release and stimulation of LC-NE neurons increases anxiety and depressive-like behaviours (Valentino and Van Bockstaele, 2008). Therefore, dysregulation of the LC-NE system might play a big role in the development of stress-related psychiatric disorders. However, in this essay, the focus will be on the endocrine stress response that is regulated by the HPA-axis and how this response is both affecting and affected by the eCB signaling system.

Acute stress & the ECS

Regarding the effects of acute stress on eCB signaling, the majority of studies suggest that 2-AG levels increase as a result of stress in the mPFC, hippocampus and hypothalamus (Hill et al., 2011b; Wang et al., 2012b; Evanson et al., 2010). It has been suggested that this increase is the result of increased corticosterone levels. This is supported by the studies of Atsak et al (2012a) and Hill et al. (2010a), which reported that administration of corticosterone increases 2-AG signaling in the hippocampus and hypothalamus. AEA levels have been found to be reduced in the amygdala and hippocampus, in both mice and rats, following acute stress (Hill et al., 2009c; Wang et al., 2012b). This has been attributed to CRH, which is released in response to stress. It is thought that CRH increases FAAH activity, which leads to an increased AEA hydrolysis (Hill et al., 2009c). However, in human

studies circulating levels of AEA were found to be elevated instead of decreased following stress (Dlugos et al., 2012) Moreover, significant differences have been reported in the temporal dynamics of AEA and 2-AG. Whereas AEA shows a rapid decrease following stress exposure, 2-AG levels show a prominent delay, which is related to the corticosterone levels going up (Morena et al., 2016).

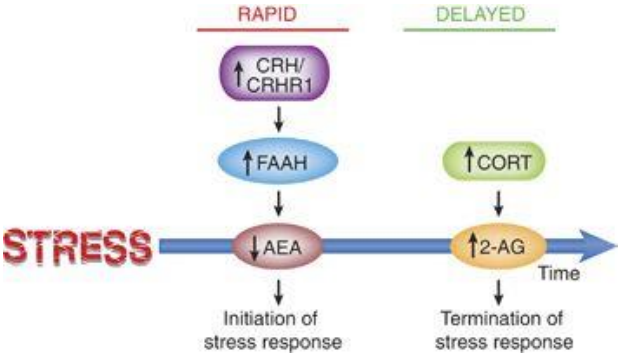

Figure 3 Rapid and delayed changes in AEA and 2-AG levels following stress Acute stress exposure rapidly increases CRH in the basolateral amygdala. This activates the CRHR1 receptors, which increases the activity of FAAH, thereby decreasing AEA levels. This results in the activation of the HPA-axis and induces stress-related behavioural responses. The delayed increase of corticosterone levels induces 2-AG release in the mPFC and PVN. What follows is a termination of the stress response, as the increased 2-AG signalling induces a negative feedback inhibition of the HPA-axis. (Morena et al., 2016)

Chronic stress & the ECS

As this essay focuses on stress-related psychiatric disorders, of particular interest is the effect of chronic stress exposure on the endocannabinoid signaling. Several studies have investigated the effects of chronic stress exposure on the receptors and eCBs involved in the ECS. Regarding AEA and 2-AG levels, the effects just described following acute stress exposure become amplified following chronic exposure to the same stressor (Morena et al., 2016). Interestingly, chronic stress also greatly affects the CB1 receptor. Multiple studies have reported that following chronic stress exposure, the ability of CB1 receptors to inhibit neurotransmitter release is drastically impaired in the striatum and hypothalamus (Rossi et al., 2008; Wamsteeker et al., 2010; Wang et al., 2010). In other words, following chronic stress, CB1 receptor signalling in limbic structures is less functional.

The ECS & HPA-axis activity

Important to emphasize is that, besides that the HPA-axis affects eCB signalling, this also works the other way around. It is well-established that cannabis consumption, which activates the eCB singalling system, has stress-reducing effects in human. This implicates that the eCB signalling system might have direct effects on HPA-axis activity. Several research groups have focused on this and found that by promoting the neurotransmission of eCBs, stress-induced HPA-axis activity may be inhibited (Patel et al., 2004). Moreover, blocking of and damage to the CB1 receptor signalling pathway results in an increase in HPA axis activity under basal and stress states (Hill et al., 2006a). In other words, the activity of eCB signalling results in a dampened HPA-axis response. Therefore, when CB1 receptor signalling is impaired following chronic stress, the eCB signalling system has a reduced ability to buffer against the effects of stress. This could potentially lead to the development of adverse responses, such as anxiety and anhedonia, which are classically linked to the onset of psychiatric conditions (Morena et al., 2016).

To enhance understanding of how the ECS can have a therapeutic role in stress-related disorders, it is of great importance to also understand how these changes in eCB signaling pathways following stress affect the human body and behaviour. Under conditions of chronic stress, the reduction in AEA manifests in an anxiety state, the activation of the HPA-axis and the impairment in fear extinction (Hill et al., 2009; Patel et al., 2005). Moreover, it could play a role in the development of anhedonia and hyperalgesia (Morena et al., 2016). Good news is that by inhibiting FAAH, many of the effects of acute and chronic stress can be reversed. For 2-AG, an enhanced 2-AG signaling seems to be important for terminating the stress response (Morena et al., 2016).

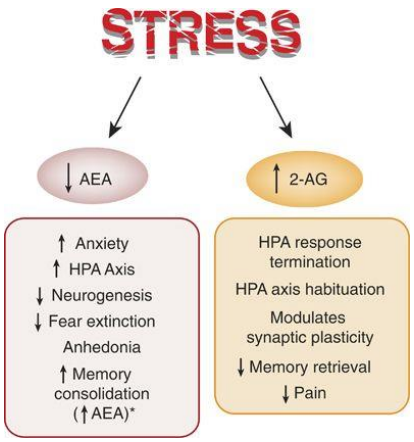

Figure 4 Illustration of behavioural consequences following changes in AEA and 2-AG levels following stress Following acute and chronic stress, levels of 2-AG increase, whereas levels of AEA decrease. The decline in AEA contributes to an anxiety state, the activation of the HPA-axis and reduced neurogenesis and fear extinction. The increase in 2-AG terminates the HPA-axis response. (Morena et al., 2016)

In conclusion, there seems to be a protective role for the ECS against the development of psychiatric disorders. An increased eCB signalling dampens the HPA-axis activity. An impaired capacity to modulate stress reactivity is relevant for psychiatric disorders such as schizophrenia, depression and anxiety disorders. The role of the ECS in downregulating hypersensitized stress systems may be the key to understanding its therapeutic potential in a host of psychiatric disorders. Altering the eCB tone might be helpful in reducing the stress response and may be effective in preventing the occurrence of stress-related diseases (Akirav., 2011)

Now that the effect of cannabis on the ECS and the interaction between the ECS and HPA-axis has been discussed, we get back to the question of how cannabis can reduce stress. Cannabis seems to have therapeutic potential in stress-related psychiatric disorders as it can dampen HPA-axis activity by increasing CB1 receptor signalling. Unfortunately, cannabis use can have major side effects. Cannabis can induce anxiety, panic and paranoia and, in rare cases, can even lead to acute psychosis (Kumar et al., 2001). Moreover, cannabis increases heart rate, lowers blood pressure due to vasodilation and stimulates appetite (Kumar et al., 2001). So even though cannabis might be beneficial in treating stress-related psychiatric disorders, it exerts major adverse effects, making its therapeutic potential questionable.

Even though THC has been acknowledged to reduce stress, it also seems to be responsible for the major adverse effects of cannabis. Nowadays, a certain extract of the cannabis plant has been thought to have great therapeutic potential, while lacking the major adverse effects linked to cannabis. Cannabidiol, also known as CBD, is the non-intoxicating compound of the cannabis plant. Together with THC, it is the most abundant phytocannabinoid of cannabis and it constitutes up to 40% of the cannabis extracts. By using CBD instead of cannabis, the feeling of being high is eliminated as THC, the intoxicating compound of cannabis, is not present. However, CBD seems to be still promoting relaxation and stress reduction, and therefore, an increasing number of people are using it, hoping to unwind and reduce stress and to fall asleep more easily.

CBD has become crazy popular among the general public and nowadays, it can be bought without prescription, for example, in the form of oil solutions or oral capsules, in almost all pharmacies. For the CBD oil solutions, the concentrated solvent extract made from the cannabis flower and leaves is dissolved in an edible oil such as sunflower, hemp or olive oil with concentrations typically ranging from 2-10% of CBD. Because of its lipophilic nature, CBD can easily pass the blood brain barrier. The terminal half-life of CBD is 9 hours. CBD oil can be efficiently dosed by counting the number of drops consumed.

One of the big questions regarding CBD oil is whether it should be seen as a medicinal drug or as a food supplement. There is one very important difference between medicinal drugs and food supplements. Whereas drugs are considered unsafe until proven safe, food supplements are considered safe until proven differently (Hazekamp., 2018). As CBD has not yet seen enough clinical testing and the working mechanisms of CBD are still largely unknown, it is being sold as a supplement.

The use of CBD for medical purposes all started with treating epilepsy in young children. A well-known case is Charlotte Figi, who suffered from Dravet's Syndrome- a very rare form of childhood epilepsy (Maa et al., 2014). She had several seizures a day, even while being on heavy medications. Doctors made clear that all clinical treatment options had been exhausted and so the family had the feeling they had nothing to lose, when they first tried treating her with cannabis oil. This cannabis oil was quite unique, it contained way more CBD than it contained THC. The result was miraculous, going from 300 seizures a week to no seizures in the entire first week. After this first dosage, Charlotte seized less and less frequent. More cases like this are known, but unfortunately not all children suffering from epilepsy were lucky to experience such-life changing results. However, as clinical studies have supported the therapeutic potential of CBD, a FDA-approved drug for rare forms of epilepsy, Epidiolex, is on the market.

More and more promises abound on the internet regarding its therapeutic potential; numerous articles state that CBD can be used to relieve symptoms of anxiety, insomnia, chronic pain, inflammatory diseases, cancer, diabetes, arthritis, menstrual cramps, dry skin, psychosis, Alzheimer's disease, anger, depression, Chron's disease, addiction, migraine and the general feeling of being stressed. Even though not all of these claims have been supported by clinical data, this does not stop people from trying CBD themselves. More often than not, people are unfamiliar with the working mechanisms of CBD. Moreover, downsides of using CBD are unknown, often thinking that CBD can not be dangerous as it can be bought without prescription. Therefore, I feel that it is important to shed light on the working mechanisms and downsides of CBD oil to enhance the awareness of the users.

The second part of this essay aims to create an overview of clinical research that has been done on CBD as a therapeutic treatment for stress- and anxiety-related disorders, hoping to reveal whether CBD could be a potential treatment. Furthermore, this essay will try to answer the question whether self-medication with CBD

oil is worth trying or should be warned against and what is important to know, if you decide to use CBD oil yourself.

Working mechanisms of CBD

While the other compounds of the *Cannabis Sativa* plant interact with the two cannabinoid receptors, CBD has very little direct effect on both. Despite this, CBD is capable of antagonising CB1 and CB2 receptor agonists (Bergamaschi et al., 2011) The study of Laprairie et al. (2015) showed that CBD acts as a non-competitive, negative allosteric modulator of the CB1 receptor. This means that CBD can alter the potency and efficacy of the orthosteric ligand, but cannot activate the receptor by itself. It was revealed that CBD treatment reduces CB1 orthosteric ligand (for example THC and 2-AG) efficacy (Laprairie et al., 2015). This finding helps to explain how CBD can protect against some of the negative effects of THC (Englund et al., 2013). However, at very high concentrations (>10 µM), CBD exerts CB1 receptor agonist-like activity *in vitro* (McPartland et al., 2014). Therefore, it is unclear how the effect of CBD on the CB1 receptor contributes to CBDs therapeutic potential, especially in stress-related psychiatric disorders. Therefore, of great interest are the very many other, indirect effects CBD exerts.

Russo et al. (2005) revealed that CBD can facilitate 5-HT1A mediated neurotransmission, as it acts as an agonist at these receptors (Russo et al., 2005). Interestingly, this mechanism has been suggested to play an important role in CBDs regulation in the acute autonomic response to stress in rats (Resstel et al., 2009). Moreover, CBD is an agonist of the TRPV1 receptor. Stimulation of this receptor induces vasodilation and inflammation. Following CBD binding to this receptor, quick desensitisation occurs, leading to the depletion of sensory nociceptors (Bisogno et al., 2001). On top of this, CBD can antagonise the GPR55 receptor. GPR55 was found to promote cancer cell proliferation via the ERK pathway, both in cell cultures and in xenografted mice (Andradas et al., 2010). As CBD antagonises the GPR55 receptor, CBD might have therapeutic potential in cancer.

CBD also seems to have an anti-inflammatory and neuroprotective role via various receptors, like the adenosine and the ppar-ϒ receptors. The adenosine A2A receptors have been shown to be able to downregulate overreactive immune cells (Ohta & Sitkovsky, 2001). As CBD can enhance adenosine signalling by inhibiting its uptake, CBD can reduce inflammation (Carrier et al., 2006). Esposito et al (2011) revealed that CBD can reduce β-amyloid-induced neuroinflammation and promote hippocampal neurogenesis through ppar-ϒ involvement (Esposito et al., 2011). Moreover, CBD can be neuroprotective in pathological conditions involving mitochondrial dysfunction and Ca^{2+} dysregulation. By restoring Ca^{2+} homeostasis, apoptotic signalling might be prevented (Ryan et al., 2009).

In the scope of this essay, it is particularly important how CBD can have therapeutic potential in stress-related psychiatric disorders, such as schizophrenia, anxiety disorders and major depression. Several lines of evidence have described that CBD exerts antipsychotic properties. This effect has been attributed to its effects on several different pathways. By blocking the reuptake and the FAAH-mediated hydrolysis of AEA (Pisanti et al., 2017), CBD increases the endocannabinoids level in postsynaptic neurons. This, in turn, may regulate presynaptic release of GABA and glutamate, but also stabilise dopamine neurotransmission (Gururajan & Malone, 2016). Moreover, CBD also directly influences dopamine neurotransmission by being a partial agonist on the dopamine D2 receptors (Seeman, 2016). Furthermore, the activation of the TRPV1 receptor has been thought to have an antipsychotic effect, as this facilitates pre-synaptic glutamate release (Campos et al., 2012).

Moreover, it has been suggested that CBD exerts anxiolytic effects. This has been linked to the agonistic activity CBD exerts on serotonin type 1A receptors (Soares & Campos, 2017), both in the dorsal periaqueductal grey and in the medial prefrontal cortex (Campos et al., 2012). It has even been suggested that CBD activates this serotonin receptor in the same way that serotonin activates it (Russo et al., 2005). Another acute anxiolytic effect that CBD has, is modifying the cerebral blood flow in brain regions that are involved in anxiety, like the amygdala, hippocampus, hypothalamus and cingulate cortex (Soares & Campos, 2017). This has been supported by the study of Crippa et al. (2011) in which cerebral SPECT has been performed in patients with social anxiety disorder

(SAD) before and after acute CBD or placebo intake. It was found that, in the patients that administered CBD, regional cerebral blood flow was reduced in the left parahippocampal gyrus, hippocampus and inferior temporal gyrus, while blood flow was increased in the right posterior cingulate gyrus (Crippa et al., 2011).

CBD has also been thought to exert an anti-depressant effect, which has been, at least partly, attributed to its effect on BDNF levels. In depressed humans, decreased levels of brain-derived neurotrophic factor (BDNF) have been found (Nestler et al., 2002). Common antidepressants increase brain-derived neurotrophic factor (BDNF) (McArthur & Borsini, 2006) and brain infusion of BDNF in rats produces antidepressant-like effects (Siuciak et al., 1997; McArthur & Borsini, 2006). This suggests an anti-depressant effect of BDNF. Interestingly, the study of Réus et al. (2011) revealed an increase in BDNF levels in rats that were treated with CBD, implicating an anti-depressant effect of CBD in rats. The study of Sales et al. (2018) supported this, as a single administration of CBD (10 mg/ kg bodyweight) induced acute and sustained antidepressant-like effects in the forced swimming test in mice (Sales et al., 2018). Important to note is that this effect is depending on intact TrKB and mTOR signalling pathways in the central nervous system, as antagonising or inhibiting these pathways eliminated the behavioural effects of CBD. Interestingly, acutely increased BDNF levels were reported in the hippocampus and prefrontal cortex. Furthermore, the number of dendritic spines in the medial prefrontal cortex were increased (Sales et al., 2018).

In conclusion, CBD seems to exert beneficial effects, including antipsychotic, anxiolytic and anti-depressant effects, via a great variety of different working mechanisms. An overview of the receptors that are affected by CBD and the general effects exerted by CBD, that were discussed in this chapter, can be found in table 1. As the working mechanisms discussed in this chapter have mostly been studied *in vitro* or in animal models, the next chapter will focus on whether CBD seems to be an effective treatment in patients diagnosed with stress-related psychiatric disorders.

1A. Overview of the effects of CBD on receptors

CB1 receptor	Negative allosteric modulator	In vitro, < 1 µM (Laprairie et al., 2015)
CB1 receptor	Agonist-like activity	In vitro, > 10 µM (McPartland et al., 2014)
5-HT1A receptor	Agonist	In vitro, 16 and 32 µM (Russo et al., 2005)
TRPV1 receptor	Agonist	In vitro, 3, 10 and 30 µM (F et al., 2014)
GPR55 receptor	Antagonist	In vitro, 10 µM (Ryberg et al., 2009)
Dopamine D2 receptor	Partial agonist	Dissociation constant: 11 nm at D2High receptors and 2800 nm at dopamine D2Low receptors (Seeman, 2016)
PPAR-Ɣ receptor	Agonist	In vitro→ 1-100 nM In vivo → 10 mg/kg (Esposito et al., 2011)

1B. Overview general effects of CBD

Regulates intracellular Ca^{2+} levels
Inhibits AEA reuptake
Inhibits adenosine uptake
Modifies cerebral blood flow
Increase BDNF levels

Chronic stress, which often leads to HPA-axis dysfunction, seems to play a critical role in the manifestation of several psychiatric disorders. The psychiatric disorders that will be discussed here, anxiety disorder, schizophrenia and major depression, have all been linked to chronic stress exposure and dysregulation of the HPA-axis. In anxiety disorders, a relation has been found between scores the severity of the anxiety, rated by anxiety scales, and cortisol levels (Kallen et al., 2008). In first episode, drug naïve schizophrenia patients, evidence for basal overactivity of the HPA-axis was found. Schizophrenia patients showed higher ACTH and cortisol levels that control subjects (Ryan et al., 2004). In depressed patients, CRH immunoreactivity is up-regulated in the CSF (Widerlov et al., 1988) and in severe cases of depression elevated basal cortisol levels in both the CSF and the blood are found (Holsboer, 2000). In conclusion, dysregulation of the HPA-axis seems to play an important role in these psychiatric disorders.

In this chapter, the therapeutic potential of CBD will be discussed in patients with anxiety disorders, schizophrenia or major depression. An overwhelming amount of studies have focussed on the effects of CBD treatment in animal models mimicking these psychiatric disorders. As this might not be fully translatable to the effects CBD treatment might have in human patients, the coming chapter will (mostly) focus on the effects of CBD administration in patients diagnosed with either anxiety disorder, schizophrenia or depression, that have been studied in randomised placebo-controlled clinical studies.

Anxiety Disorders

Anxiety disorders are chronic, disabling conditions, including several syndromes such as generalized anxiety disorder (GAD), panic disorder (PD) and social anxiety disorder (SAD). Antidepressants and benzodiazepines are the main pharmacological treatments (Scherma et al., 2018). However, there is a strong need for alternative treatments, as 40-60% of the patients do not attain total relief (Bandelow et al., 2008).

It is well-acknowledged that cannabis consumption can affect anxiety, with low doses being anxiolytic (Turna et al., 2017). As discussed in the previous chapter, mounting evidence indicates that the cannabis extract CBD possesses anxiolytic properties. Animal studies discovered that acute systemic administration of CBD produces a bell-shaped dose-response curve in rats, being anxiolytic at low and intermediate doses (Guimarães et al., 1990). In human studies, healthy subjects exposed to anxiety-provoking situations also benefitted from the anxiolytic properties of CBD (Crippa et al., 2004).

Multiple studies have been done in subjects diagnosed with social anxiety disorder (SAD). In the study of Bergamaschi et al. (2011), the anxiolytic effects of CBD were tested in subjects submitted to the Simulation Public Speaking Test. 24 treatment-naive subjects with generalised SAD were randomly assigned to either the group receiving CBD (600 mg dissolved in corn oil) or placebo. 12 healthy control subjects also participated in the test. State-anxiety levels and other subjective states were determined through the Visual Analogue Mood Scale (VAMS). Moreover, skin conductance, blood pressure and heart rate were measured. No psychological differences were observed between the groups in the initial levels of reported anxiety, discomfort, cognitive impairment and sedation. This study revealed that during the speech phase, SAD subjects that received CBD reported significant lower levels of anxiety, cognitive impairment and discomfort than SAD placebo subjects did (Figure 5). This effect of CBD on anxiety, cognitive impairment and discomfort was only detectable during the speech phase.

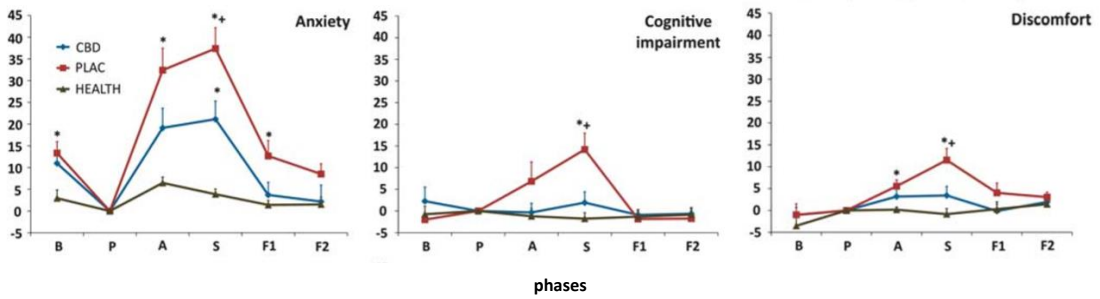

Figure 5: Changes in the Visual Analogue Mood Scale factors induced by the simulated public speaking test. Anxiety, cognitive impairment and discomfort were measured in 12 social anxiety patient who received cannabidiol (CBD), 12 social anxiety patients who received placebo and 12 healthy control. The experimental session consisted of basal (b), pre-test (p), anticipation (a), speech performance (s), post-speech measures 1 (F1) and post-speech measures 2 (F2). Mean with SEM are shown. * means significant difference from healthy control, + means significant difference from social anxiety patients who received CBD. (Bergamaschi et al., 2011)

The study of Crippa et al. (2004) evaluated the capacity of 400 mg oral CBD to reduce anxiety induced by neuroimaging procedures, analysing cerebral blood flow in 10 healthy men. This was a double-blind placebo controlled study in which subjects were assessed on two different occasions, 1 week apart. During the first session, subjects were either given CBD or placebo. In the second session, the other drug was administered. Single-photon emission computerised tomography (SPECT) imaging was done 110 min after drug ingestion. Moreover, subjective ratings on the VAMS 30 min before drug ingestion, at the time of drug ingestion and 60 and 75 min after drug ingestion were determined. It was found that CBD significantly decreased subjective anxiety and increased sedation, while the placebo did not induce significant changes (Crippa et al., 2004).

Crippa et al. (2011) also performed a double-blind placebo-controlled trial in 10 male patients that were diagnosed with social anxiety disorder. The participants took either 400 mg of CBD dissolved in corn oil or placebo. The participants evaluated anxiety by the VAMS 30 min before intake, at drug intake, 60 min and 75 min after intake and after SPECT scanning. They found that CBD reduced subjective anxiety in all endpoints after drug intake.

In conclusion, in all three randomised double-blind placebo-controlled trials, CBD exerted an anxiolytic effect. Unfortunately, the studies only had a limited number of participants and the primary measures used were evaluated using the subjective VAMS. Moreover, no dose-response correlation between anxiety measurements and CBD plasma levels was established and no long-term effects of CBD on anxiety were investigated.

Schizophrenia

Schizophrenia (SZ), a complex neuropsychiatric disorder, is characterised by symptoms including hallucinations, delusions and deficits in cognitive filtering (Swerdlow & Light, 2016). Disturbances in the brains dopamine signaling pathways are thought to play a major role in the pathology of this disease. Especially dopamine D2 receptors are important and therefore, all currently effective antipsychotic drugs for schizophrenia target the dopamine D2 receptors. Interestingly, in animal models, the pharmacological profile of atypical antipsychotic drugs was revealed to be similar to that of CBD (Zuardi et al., 1991; Moreira & Guimarães, 2005). As CBD is thought to exert anti-psychotic effects, its therapeutic potential in schizophrenia patients will be discussed next.

At this point, several double-blind RCTs have been performed to assess the effects of CBD, either compared to placebo or to antipsychotic drugs. Leweke et al. (2013) performed a double-blind RCT study, comparing the efficiency of CBD with placebo. The sample consisted of 29 patients presenting first-episode paranoid schizophrenia. In this study, a CBD powder of 600mg was dissolved in oil formulation. Patients administered either CBD or placebo for 14 days and were then switched to the other treatment. The authors reported that

CBD significantly improved positive symptoms when compared to baseline. However, no statistical difference was found by the Positive and Negative Syndrome Scale (PANSS) between CBD and placebo-treated groups. Important to note is that this study has several limitations that should be taken into account. The sample size was small, the duration of the treatments was short and, because of the crossover strategy that was used, possible carry-over effects are present.

Besides comparing CBD to placebo, a double-blind RCT was performed by Leweke et al. (2012) to assess the effects of CBD compared to Amisulpride, a common atypical antipsychotic. Either CBD or Amisulpride was given for 28 days in a sample of 42 patients with acute schizophrenia. The symptoms were assessed by the PANSS and Brief Psychiatric Rating Scale (BPRS) at days 14 and 28. A comparable reduction of psychotic symptoms was revealed with both treatments (Figure 6).

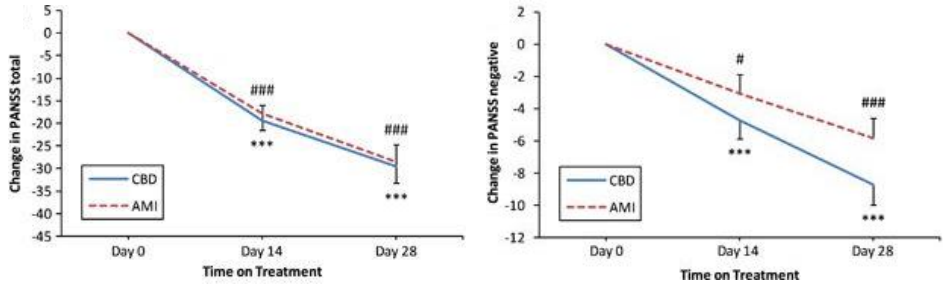

Figure 6: Changes from baseline in Positive and Negative Symptoms Scale (PANNS) in patients with acute schizophrenia, either treated with CBD or with Amisulpride. PANSS total scores and PANSS negative scores are shown. * is statistical significance of CBD treatment compared to baseline. # is statistical significance of amisulpride treatment compared to baseline.

The use of antipsychotic drugs often is associated with side effects, which influence long-term treatment fidelity. Interestingly, CBD showed to produce fewer motor disturbances, less weight gain and lower prolactin increase, which is a predictor of sexual dysfunction, compared to amisulpride treatment (Leweke et al., 2012). Moreover, levels of anandamide and FAAH hydrolase substrates were increased in the group treated by CBD. Unfortunately, the authors reported that in this study the underpowered sample makes that results should be regarded with consideration (Leweke et al., 2012).

But also multiple studies have reported that CBD was ineffective to treat psychotic symptoms in SZ outpatients (Zuardi et al., 2006; Boggs et al., 2018). The study of Zuardi et al. (2006) assessed the efficacy and safety of CBD monotherapy in three patients with treatment-resistant schizophrenia (TRS). Patients were given placebo during the first 5 days, followed by an oral dose of 40 mg up to 1280 mg/day during day 6 to 35. After this, CBD treatment was discontinued and replaced by placebo for 5 days, which was then switched to olanzapine for over 15 days. One of the three patients showed mild improvement, but the other two patients did not show any improvement during CBD treatment. This preliminary data implicates that CBD monotherapy may not be effective for TRS. However, treating with olanzapine was also not very effective, showing mild/ no symptom improvements. Notably, all patients tolerated CBD very well and no side effects were reported (Zuardi et al., 2006). As the duration of CBD treatment was short, most antipsychotics are also not effective in treating negative symptoms within 4 weeks, it could be that CBD monotherapy is effective when continued for a longer period of time. Moreover, the findings of this study do not exclude that CBD could be effective in treating non-refractory schizophrenia patients.

In conclusion, CBD seems to exert anti-psychotic effects in schizophrenia patients, comparable to common atypical antipsychotics. As CBD seems to be well-tolerated in schizophrenia patients and produces less severe side-effects, it seems to have great therapeutic potential in schizophrenia. Important to note is that clinical studies have not well-documented the effects of CBD as adjunctive therapy in schizophrenia and long-term effects of CBD treatment have also not been assessed yet.

Major depression

Major depression is one of the most common stress-related psychiatric disorders. It is characterised by episodes of depressed mood, feelings of worthlessness, high anxiety, memory impairment, the inability to experience pleasure (anhedonia) and a decreased interest in pleasurable activities (de Mello Schier et al., 2014). For centuries, cannabis has been used recreationally for its mood elevating and euphoric effects (Williamson & Evans, 2000). This lead to the idea that the ECS might be involved in the development of depression, but even more interesting, to the idea that by targeting the ECS, symptoms of major depression could be alleviated.

In rats, CBD in 30 mg/ kg dosage shows similar effects compared to imipramine, which is a tricyclic antidepressant. This dosage seemed to produce a bigger anti-depressant effect than the dosages 15 mg/kg and 60 mg/kg. Moreover, in the animals treated with CBD a similar increase was found in BDNF levels compared to the rats treated with imipramine (Réus et al.,2011) The study of El-Alfy et al. (2010) found the same antidepressant- like effect in a dose-dependent manner. Sartim et al. (2016) found that in rats, CBD administration into the vmPFC produces antidepressant-like effects in the forced swimming test. This effect was blocked by the pretreatment with the 5-HT1a receptor antagonist WAY100635 (Sartim et al., 2016), which implicates that the antidepressant-like effect of CBD is indeed mediated via the 5-HT1a receptor. However, it is not clear if 5-HT1a participation in CBD effects is a consequence of increased serotonin availability or direct receptor activation by CBD itself (Sales et al., 2018).

Multiple preclinical studies have demonstrated that administration of CBD induces antidepressant-like effects in animal models. Unfortunately, CBD efficiency has not been assessed compared to placebo, in people diagnosed with major depression. Even a literature search for case studies on CBD as treatment for major depression showed no results. Despite the data showing antidepressant-like effects of CBD in animal models of depression, there is no evidence on whether CBD would have therapeutic potential in patients diagnosed with major depression. As preclinical studies assessing CBD suggest antidepressant-like effects, performing clinical studies, assessing CBDs effects compared to both placebo and common anti-depressants, is of great importance to determine whether CBD treatment could be beneficial for major depression.

Safety and side effects of CBD

Although CBD does not produce the same major adverse effects as cannabis does, also CBD has some limitations and drawbacks that have to be taken into account.

First, as CBD affects many different pathways, it is not improbable that CBD interacts with other drugs that are, likely, co-administered in patients with psychiatric disorders. CBD interacts with general (drug)- metabolising enzymes, for example from the cytochrome P450 family. CBD is metabolised, among others, via the P4503A4 enzyme. Various drugs affect this enzyme by either inducing or inhibiting it. This leads to a reduced bioavailability or a slower CBD degradation, respectively. The latter results in higher CBD doses that are longer pharmaceutically active (Iffland & Grotenhermen, 2017). On the other hand, CBD is able to inactivate human P450 3A4 (Jaeger et al., 1996). As this could mean that the co-administered drug degrades slower, this could be an advantage as well as a disadvantage. This is a serious matter that should be taken into account when CBD is being co-administrated with other drugs, especially since 60% of clinically prescribed drugs are metabolised via P4503A4 (Guengerich, 1995; Bergamaschi et al., 2011). Therefore, in the case of patients diagnosed with psychiatric disorders, it is always advisable to discuss administration of CBD as adjunctive treatment with a healthcare professional.

Moreover, as the production of CBD is not yet carefully regulated, the quality of CBD products varies enormously. Over-the-counter CBD products could contain way more of the compound THC than is desired and advertised with. The presence of THC in CBD products has also been discussed in the Dutch television programme 'Radar'. A sample of CBD oils was tested for the concentration of CBD and THC. It was found that several of the tested oils contained less CBD than stated on the label and also some of the oils failed to contain less than 0.05% THC, the maximum allowed concentration of THC in CBD oils (Hazekamp, 2018). As THC does have an intoxicating effect, increasing feelings of anxiety and impairing cognition, the presence of THC in CBD products is a serious matter, especially in psychiatric patients.

Dosage

Unfortunately, no official recommendations have been done regarding the dose of CBD that should be taken for a specific condition. This results in recommendations on CBD dosage done by people with limited pharmacological and physiological knowledge. Moreover, it is often said that in humans, each body reacts differently to CBD. Therefore, there is no such thing as a one size fits all dosage for CBD. The bioavailability, severity of the condition and weight of the user are all aspects that influence the effects CBD administration might have. The factor bioavailability is clearly illustrated by the study of Deiana et al. (2012). When orally administering 120 mg/kg CBD in mice, plasma levels reached 2.2 µg/mL CBD. When orally administering 10mg/ kg CBD to humans, blood levels of 0.01 µg/mL CBD were found. This corresponds to blood levels of 0.12 µg/mL when 120 mg/ kg CBD was given to humans. This shows that when mice and humans are given the same CBD dose, in the mouse organism way more of the compound becomes available than in human. This is a highly important finding, as an enormous amount of studies on therapeutic effects of CBD have been done in animal models. This suggests that effects of CBD found in animal studies might be attributed to the higher bioavailability in animals than in humans, suggesting that the revealed effects might actually be smaller in humans. In general, it is advised to start with a low dose and gradually increase until symptoms for which CBD is taken, alleviate. The lowest dose that provides the desired benefits is seen as the ideal CBD dosage.

Side effects

As there are no clear unequivocal recommendations regarding CBD dosage, possible side-effects of CBD administration become even more important. In animal studies, CBD treatment of up to 14 days (3-30 mg/kg bodyweight) did not affect important physiological measures like blood pressure, heart rate, body temperature, glucose levels, pH, pCO2, Po2 and haematocrit (Bergamaschi et al., 2011). In human, treatment with up to 600 mg CBD also did not affect physiological measures like blood pressure and heart rate, nor performance on a verbal paired-associate learning test (Bergamaschi et al., 2011). A lack of CBD side effects was observed during studies whose primary objectives were not to evaluate CBD's safety, but to study cannabinoid activity. Moreover, Bergamaschi et al. (2011) presented an extensive list of studies that reported on CBD safety. CBD administration did not induce side effects across a wide range of dosages, up to 1500 mg/day (orally), including acute and chronic dose regimens. Tolerance to CBD did not develop and no psychomotor slowing, negative mood effects or vital sign abnormalities were reported (Bergamaschi et al., 2011). In conclusion, based on the available studies on safety and side-effect of CBD use, no serious side-effects have been reported following CBD administration.

However, some important facets regarding CBD have not been studied yet. For example, it is (largely) unknown how CBD affects neurotransmitter levels and hormone systems. There seems to be a bidirectional interaction between eCBs and gonadal hormones (Gorzalka & Dang, 2012). Therefore, it might be the case that CBD affects still unknown pathways, like the hormone systems, which in turn influence psychiatric conditions and the ability of CBD to treat them.

Furthermore, CBD safety has been tested in CBD monotherapy. Especially in the scope of this essay, it is of great importance to test how CBD interacts with common medicine used to treat stress-related psychiatric disorders. Moreover, side-effects and safety of longer chronic CBD administration have not been addressed (Iffland and Grotenhermen, 2017).

Conclusion

In this essay it was discussed how the ECS and the HPA-axis (bidirectionally) influence each other. The ECS seems to be an important regulatory system in the brain, providing a buffer against many of the effects of stress. Therefore, altering the eCB tone, resulting in a dampened HPA-axis, might prevent the development of stress-related disorders like anxiety disorders, schizophrenia and major depression.

The use of cannabis as a treatment for stress-related psychiatric disorders was discussed. However, as cannabis is known to have severe adverse effects, its therapeutic potential is questionable. Interestingly, over the last years a lot of research has focussed on a certain cannabis extract; CBD. CBD not only alters the eCB tone, but also exerts its effects via other pathways. To evaluate whether CBD could be a promising drug for stress-related disorders, the clinical studies that have been performed using CBD have been reviewed here.

In patients diagnosed with social anxiety disorder, CBD seems to exert beneficial effects. During a stressful situation, CBD is able to significantly decrease anxiety, cognitive impairment and discomfort. In acute schizophrenia, CBD showed to be similarly effective to common anti-psychotics (amisulpride). Interestingly, CBD showed less severe side effects compared to amisulpride, suggesting CBD treatment might be favourable over amisulpride treatment in patients diagnosed with schizophrenia. In major depression, preclinical studies done in animal models of depression showed promising results, however, no clinical studies are performed that support that CBD can be used to treat people diagnosed with major depression.

It should be noted that these conclusions are based on just a limited number of clinical trials. As most of the clinical trials performed to date only involved a small number of subjects, some of the studies lack the power to reliably draw conclusions from the data. Another drawback is that most studies have used subjective measures for the evaluation of the primary variable tested. However, as CBD treatment is assessed in psychiatric disorders, this is difficult to overcome.

Even though clinical studies seem to support the anxiolytic and antipsychotic properties ascribed to CBD, several important aspects of CBD as a treatment in psychiatric disorders have not been well-studied yet. One of these aspects is chronic administration of CBD. Most of the studies testing CBD in psychiatric condition only have a duration of several weeks. Therefore, to gain more knowledge on CBDs safety, longitudinal studies assessing chronic CBD administration have to be performed.

Even though several studies have suggested that CBD is well tolerated and safe in humans at high doses, in vitro and in vivo studies also showed (potential) drug metabolism interactions. This is a major disadvantage in assessing whether CBD can be used as a treatment for stress-related psychiatric disorders. As it is extremely likely that people coping with severe psychiatric disorders are already taking medical drugs for their condition, CBD would most probably be used as an adjunctive treatment. This stresses the need for more research focussed on how CBD interacts with the metabolism of psychiatric treatments. Moreover, it is highly advised not to quit taking prescribed medicine and replace them with CBD.

Although the clinical trials that have been discussed here showed the therapeutic potential of CBD in treating anxiety disorders and schizophrenia, more clinical studies are needed. As often the clinical studies showed little power, it is important to test CBDs efficacy and safety in more subjects diagnosed with a stress-related psychiatric disorder. Moreover, treating with different dosages of CBD is particularly important to enhance insight in CBDs safety, but also to decide on advisable dosages for the specific disorder.

As a final note, it is highly advisable to discuss with a healthcare professional or clinician whether self-medication with CBD would be a wise idea. Especially, when talking about the use of CBD as a monotherapy when coping with a psychiatric disorder, professional judgement is needed per individual case. As long as the working

mechanisms of CBD are not fully elucidated, careful monitoring of CBD use in humans, especially when using CBD for treating psychiatric disorders, is of great importance.

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