

The Anxiolytic Effects of Cannabidiol (CBD)

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SUMMARY POINTS

- The present chapter focused on evidences related to the antianxiety effects of cannabidiol (CBD).
- CBD anxiolytic effects are dose-dependent, in a bell shaped dose–response curves manner.
- CBD antianxiety effects were demonstrated and replicated in several animal models of anxiety.
- CBD also promotes antianxiety effects in humans.
- CBD may affect the function of brain structures related to the control of anxiety-like states in laboratory animals and humans.
- The specific pharmacological mechanism that would explain CBD antianxiety effects remains to be determined, but may involve the modulation of CB1 and 5HT1A receptors functions.

KEY FACTS OF CANNABIDIOL ANTIANXIETY PROPERTIES

- Cannabidiol was isolated from *Cannabis sativa* in 1940, but its chemical structure was elucidated in 1963.
- Cannabidiol can be obtained as extract from the plant, by standard chemical techniques, or as a pure synthetic compound.

- In the early 1980s, the first evidence of CBD's anxiolytic effect in laboratory animals emerged, and independent groups replicated this effect several times.
- Elevated plus maze is based on the innate avoidance of rodents to unprotected and elevated places.
- Social anxiety disorder is characterized by the intense anxiety and fear of humiliation or embarrassment in social situations.

LIST OF ABBREVIATIONS

AM251	<i>N</i> -(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide
BNST	Bed nucleus stria terminalis
CB₁	Cannabinoid receptor 1
CB₂	Cannabinoid receptor 2
CBD	Cannabidiol
CFC	Contextual fear conditioning
DPAG	Dorsal periaqueductal gray
eCB	Endocannabinoid
EPM	Elevated plus maze
ETM	Elevated T-maze
GPR55	Orphan cannabinoid receptor
GTPγS	Guanosine-50-O-(3-thiotriphosphate)
5-HT_{1A}	Serotonergic receptor 1A

OCD	Obsessive-compulsive disorder
PL	Prelimbic frontal cortex
PTSD	Posttraumatic stress disorder
rCBF	Regional blood flow
SAD	Social anxiety disorder
SPECT	Single-photon emission computed tomography
SPST	Simulation of the public speaking test
THC	Δ^9 -Tetrahydrocannabinol
TRP	Transient receptor potential
TRPV₁	Transient receptor potential vanilloid 1 (vanilloid receptor 1)
TRPV₂	Transient receptor potential vanilloid 2 (vanilloid receptor 2)
VAMS	Visual analog mood scales

INTRODUCTION

The literature on the relationship between *Cannabis* and anxiety is contradictory. While users report decreased anxiety as motivation for their use, the most common adverse effect of acute cannabis use is the reaction of intense anxiety or panic (Crippa et al., 2009). The dose-dependent biphasic effect of THC on anxiety (Viveros, Marco, & File, 2005) could partially justify this observation, but another possibility is the effect of other cannabinoids present in the plant. In the early 1970s, a Brazilian group gave the first evidences that other cannabinoids interfere with the effects of Δ^9 -tetrahydrocannabinol (THC) in animals (Karniol & Carlini, 1972), particularly cannabidiol (CBD), a compound until then considered inactive (Karniol & Carlini, 1973).

These results led to studies of interaction between THC and CBD, in humans. In the first of these studies, healthy volunteers were submitted to cognitive tests, physiologic measures, and interview. Strong feelings of anxiety were reported after the ingestion of 30 mg of THC, while the subjects that received this THC dose with 60 mg of CBD showed less anxiety (Karniol, Shirakawa, Kasinski, Pfeferman, & Carlini, 1974). Confirming this result, a study with appropriate rating scales detected a statistically significant reduction in the elevation of anxiety scores induced by THC (0.5 mg/kg), when associated with CBD (1 mg/kg) (Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982). A possible anxiolytic effect of CBD, suggested by these interaction studies, started a line of research in animals and humans.

CBD EFFECTS IN ANIMAL MODELS OF ANXIETY

The antianxiety properties of CBD have been extensively studied in the last 3 decades. However, the initial studies in animal models found controversial results.

In the early 1980s, Silveira Filho and Tufik (1981), using a model based on conflict responses, failed to demonstrate any anxiolytic-like effect of CBD, at a dose of 100 mg/kg i.p. On the other hand, lower doses of CBD (10 mg/kg) were able to attenuate conditioned emotional responses in rats (Zuardi & Karniol, 1983).

Guimarães, Chiaretti, Graeff, and Zuardi (1990), subsequently explained these apparent contradictory results. Using the elevated plus maze (EPM), an ethologically based animal model of anxiety, and testing a large range of CBD doses (2.5–20 mg/kg), they showed that CBD does produce antianxiety effects in laboratory animals in a dose-dependent manner, but with an inverted U-shaped dose-response curve (Guimarães et al., 1990). These findings were later replicated by Guimarães and coworkers, as well as other groups, not only in ethologically based tests, but also in conflict and aversive conditioning models of anxiety (Table e13.1).

More recently, the investigation of the antianxiety properties of CBD were extended to animal models related to specific types of anxiety disorders. For instance, some studies suggest that CBD may be useful in trauma-related anxiety disorders (Bitencourt et al., 2008; Campos et al., 2013a; Stern et al., 2012). CBD repeated treatment attenuated the long-lasting behavioral consequences evoked by predator threats, in a proposed animal model of posttraumatic stress disorder (PTSD; Campos et al., 2013a). Moreover, CBD accelerates extinction, and impairs fear memory reconsolidation, two processes that have been associated with PTSD. Recently, a putative antipanic action of CBD was also described. CBD acute and chronic treatment reduce the defensive responses in two different models of panic disorder, the elevated T-maze (ETM) and the electrical stimulation of the dorsal portions of the periaqueductal gray matter (Campos et al., 2013b; Soares et al., 2010). Chronic treatment with a low dose of CBD (5 mg/kg) decreases the escape latency in the ETM, similar to the antidepressant Fluoxetine (Campos et al., 2013b). In addition, CBD reduces marble-burying behaviors, suggesting that this compound could be effective in obsessive-compulsive disorder (OCD; Casarotto et al., 2010; Nardo et al., 2014).

Considering the close relationship between stressful experiences and the precipitation of anxiety disorders symptoms, the effects of CBD during stress responses have also been studied. CBD prevents the autonomic and behavioral consequences of inescapable stress (Resstel et al., 2006). Moreover, Campos et al. (2013a) showed that chronic administration of CBD (30 mg/kg/daily for 14 days) prevented the anxiogenic effect of chronic unpredictable stress in mice tested in the elevated plus maze, and novelty suppressed feeding tests.

TABLE e13.1 Animal and Human Studies of Cannabidiol on Anxiety

Study	Model	Route	Dose	Anxiolytic effect
Animals				
Silveira Filho and Tufik (1981)	Geller–Seifter conflict test	Intraperitoneal	100 mg/kg	No
Zuardi and Karniol (1983)	Conditioned emotional response paradigm	Intraperitoneal	10 mg/kg	+
Onaivi, Green, and Martin (1990)	Elevated plus maze test	Intraperitoneal	0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 50.0, and 100.0	+
Guimarães et al. (1990)	Elevated plus maze test	Intraperitoneal	2.5, 5.0, 10.0, and 20.0 mg/kg	+
Moreira, Aguiar, and Guimarães (2006)	Vogel’s conflict test	Intraperitoneal	2.5, 5.0, and 10.0 mg/kg	+
Resstel, Joca, Moreira, Correa, and Guimarães (2006)	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
	Elevated plus maze	Intraperitoneal	?	+
Campos and Guimarães (2008)	Elevated plus maze test and Vogel’s conflict test	Intradorsal periaqueductal gray	15–60 nmol/0.2 µL	+
Bitencourt, Pamplona, and Takahashi (2008)	Contextual fear conditioning	i.c.v.	2.0 µg/µL	+
Campos and Guimarães (2009)	Elevated plus maze test	Intradorsal periaqueductal gray	30 or 60 nmol	+
Resstel et al. (2009)	Restraint stress	Intraperitoneal	1, 10, and 20 mg/kg	+
Soares et al. (2010)	Elevated T maze	Intradorsal periaqueductal gray	15, 30, or 60 nmol	+
Lemos, Resstel, and Guimarães (2010)	Contextual fear conditioning	Intraperitoneal and direct microinjection into the PL and IL prefrontal cortex	10 mg/kg (i.p.) and 15–60 nmol	+
Casarotto, Gomes, Resstel, and Guimarães (2010)	Marble-burying test	Intraperitoneal	15, 30, and 60 mg/kg	+
Gomes et al. (2011)	Elevated plus maze/Vogel’s conflict test	Intrabed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Gomes, Resstel, and Guimarães (2011)	Contextual fear conditioning	Intrabed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Deiana et al. (2012)	Marble-burying test	Intraperitoneal and oral	120 mg/kg	+
Uribe-Mariño et al. (2012)	Prey–predator paradigm	Intraperitoneal	0.3, 3.0, and 30 mg/kg	+
Hsiao, Yi, Li, and Chang (2012)	Open field/elevated plus maze	Intracental amygdala	0.5–1 µg/µL	+
Stern, Gazarini, Takahashi, Guimarães, and Bertoglio (2012)	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
Campos, Moreira, Gomes, Del Bel, and Guimarães (2012)	Prey–pradator paradigm	Intraperitoneal	5 mg/kg	+
Do Monte, Souza, Bitencourt, Kroon, and Takahashi (2013)	Contextual fear conditioning	Intra-PL prefrontal cortex	0.1–0.4 µg/0.2 µL	+
Campos et al. (2013a)	Elevated T maze	Intraperitoneal	5–20 mg/kg	+
Campos et al. (2013b)	Chronic unpredictable stress/novelty suppressed feeding/elevated plus maze	Intraperitoneal	30 mg/kg	+

(Continued)

TABLE e13.1 Animal and Human Studies of Cannabidiol on Anxiety (*cont.*)

Study	Model	Route	Dose	Anxiolytic effect
Nardo, Casarotto, Gomes, and Guimarães (2014)	Marble-burying test	Intraperitoneal	15 mg/kg	+
Fogaça, Reis, Campos, and Guimarães (2014)	Elevated plus maze/ contextual fear conditioning/restraint stress + elevated plus maze	Intra-PL prefrontal cortex	15–30 nmol/0.2 µL	+/- Depending on stressful experience
Humans				
Zuardi et al. (1982)	Decreased STAI scores elevation induced by THC (healthy volunteers)	Oral	1 mg/kg	+
Zuardi, Cosme, Graeff, and Guimarães (1993)	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	Oral	300 mg	+
Crippa et al. (2004)	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	Oral	400 mg	+
Fusar-Poli et al. (2009)	Decreased skin conductance fluctuation in task with fearful faces during an fMRI procedure (healthy volunteers)	Oral	600 mg	+
Crippa et al. (2011)	Decreased VAS factor anxiety scores before SPECT procedure (social phobia patients)	Oral	400 mg	+
Bergamaschi et al. (2011)	Decreased VAS factor anxiety scores after public speaking (social phobia patients)	Oral	600 mg	+

+, Anxiolytic effect; -, anxiogenic effect; no, no effects on anxiety.

Adapted from Schier et al. (2012).

ANXIOLYTIC EFFECTS OF CBD IN HUMANS

The first study evaluating the anxiolytic effect of CBD in humans was conducted on healthy volunteers submitted to a simulation of the public speaking test (SPST) (Zuardi et al., 1993). In a double-blind protocol, CBD (300 mg), ipsapirone (5 mg), diazepam (10 mg), or placebo were administered per os, 1 h and 30 min before the SPST. CBD, ipsapirone, and diazepam reduced significantly the anxiety induced by SPST.

Another double-blind, crossover trial study with healthy volunteers investigated CBD effects on regional blood flow (rCBF), using single-photon emission computed tomography (SPECT). It was observed that CBD (400 mg per os) attenuated the anxiety induced

by the procedure related to the exam (insertion of the venous cannula, tracer injection, and scanning procedure) (Crippa et al., 2004). Using a similar protocol to study the effect of CBD on rCBF of patients with social anxiety disorder (SAD), the same reductions of anxiety induced by the protocol was observed (Crippa et al., 2011).

The effects of one dose of CBD was studied in patients with SAD submitted on SPST, since the fear of speaking in public is one of the most prevalent symptoms of this disorder. As expected, the SAD group presented significantly higher anxiety level than health volunteers, during the SPST. Previous administration of CBD (600 mg, per os) reduced significantly the anxiety level of SAD group, during the public speaking (Bergamaschi et al., 2011).

These studies suggest that the acute administration of CBD in humans has an anxiolytic action in normal volunteers and patients with SAD. Studies of chronic administration of CBD in anxiety disorder are needed.

MECHANISMS OF CBD EFFECTS

Human Studies

In a study in which we investigated the central effects of CBD on rCBF in healthy volunteers, using SPECT, the anxiety induced by the experiment was reduced in the subjects who received CBD (Crippa et al., 2004). The volunteers received either CBD (400 mg) or placebo, in a crossed double-blind design, in two experimental sessions, one week apart. CBD significantly decreased subjective anxiety, as measured by rating scales (VAMS), while brain activity was changed in limbic and paralimbic areas, specifically increased in the left parahippocampal gyrus, and decreased in the left amygdala-hippocampus complex, including the fusiform gyrus (Fig. e13.1A). Interestingly, the pattern of SPECT results of this study was consistent with an anxiolytic action, as observed in other functional imaging studies using classical anxiolytic drugs such as benzodiazepines. The SPECT neuroimaging technique was also used later to investigate the neural anxiolytic correlates of CBD in a sample of drug-naïve patients with SAD (Crippa et al., 2011). A single dose of CBD 400 mg was able to reduce subjective anxiety measures, and SPECT showed changes in the same regions previously identified in healthy volunteers, but mainly in the opposite direction of activation (Fig. e13.1B). fMRI (functional magnetic resonance imaging), a neuroimaging method that allows the acquisition

of larger series of images with a much better temporal and spatial resolution, was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy volunteers (Fusar-Poli et al., 2009). This study showed that 600 mg of CBD attenuated fMRI responses during the recognition of fearful facial expressions, in the amygdala and the anterior cingulate, which are brain areas related to anxiety and emotion. Moreover, the authors found that this attenuation pattern correlated with skin conductance responses to the stimuli. The same group further reported that the antianxiety action of CBD is mediated by altering the subcortical prefrontal connectivity via amygdala and anterior cingulate (Fusar-Poli et al., 2010).

Animal Studies (Intracerebral Injection)

Although the anxiolytic effects of systemically administered CBD have been extensively reported since the beginning of the 1980s, the neurobiological substrates involved in behavioral actions of this phytocannabinoid only began to be investigated in the last decade (Table e13.1). In 2008, Campos and Guimarães showed for the first time that direct brain administration of CBD into the dorsal portions of the periaqueductal gray (DPAG) promotes anxiolytic-like effects in the EPM, and in Vogel's conflict test (Campos & Guimarães, 2008, 2009). These findings were later replicated by Soares et al. (2010), using two other different models of anxiety-like behaviors, the ETM and the electrical stimulation of the DPAG.

Investigating the effects of systemic administration of CBD (10 mg/kg) in animals exposed to a fear-conditioned environment, Lemos et al. (2010) showed that this drug decreases cFos expression, a marker of neuronal activation, in brain areas related to conditioned fear responses, the ventral medial prefrontal cortex and bed nucleus stria terminalis (BNST). Following these results, we showed that CBD direct injection into BNST produces antianxiety effect in rats tested in EPM, in Vogel's conflict, and contextual fear conditioning (CFC) models (Gomes et al., 2011, 2012). A more complex panorama, however, was found in the ventral medial prefrontal cortex. Whereas direct injections of CBD (30 nmol) into the prelimbic frontal cortex (PL) decreased freezing response in the contextual fear conditioning model (an antianxiety effect), it facilitated these responses when injected into the infralimbic cortex (IL) (Lemos et al., 2010). Recently, Fogaça et al. (2014) confirmed the anxiolytic-like effect of intra-PL administration of CBD. However, the same treatment was anxiogenic in animals tested in the EPM. To explain these contradictory results, the authors suggested that in the PL region of the prefrontal cortex the antianxiety effects of CBD depend on the level of previous stressful experiences. Corroborating this possibility, CBD produces anxiolytic effects in the EPM when

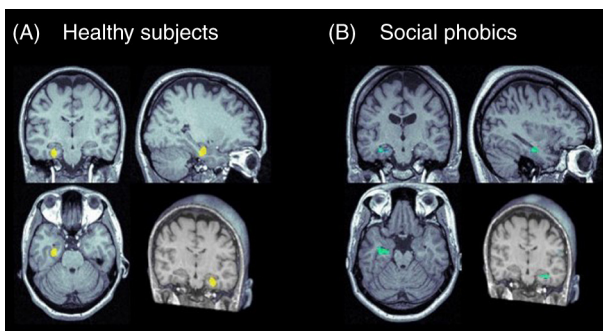


FIGURE e13.1 (A) The brain focus (yellow) of significantly increased rCBF in healthy subjects ($n = 10$) during CBD (400 mg) versus placebo on sagittal, coronal, axial sections (left side), and coronal sections (right side) located in the left hippocampal area; (B) the brain focus (blue) of significantly decreased rCBF in social anxiety disorder subjects ($n = 10$) during CBD (400 mg) versus placebo on sagittal, coronal, axial sections (left side) and coronal sections (right side) located in the left hippocampal area. Part A, adapted from Crippa et al. (2004); part B, adapted from Crippa et al. (2011).

injected into the PL of animals that have been previously (24 h) exposed to a stressful event (2 h restraint) (Fogaça et al., 2014). Intracerebral ventricular administration of CBD also facilitated extinction in a contextual aversive conditioning model (Bitencourt et al., 2008). Moreover, repeated microinjections of CBD into the IL subregion of the prefrontal cortex also facilitated fear extinction (Do Monte et al., 2013). In the amygdala, a brain structure similarly related to the control of anxiety-like behaviors, inconsistent effects have been found in the basolateral as well as in the medial amygdala nuclei (Campos et al., and Lisboa and Guimarães, unpublished results). There is a report, however, of anxiolytic-like effects of CBD after injection into the central nucleus in rats tested in the EPM and open field (Hsiao et al., 2012).

PHARMACOLOGICAL MECHANISMS OF THE ANXIOLYTIC EFFECTS OF CBD

While several pieces of the evidence reviewed earlier indicate that CBD could be a promising new anti-anxiety treatment, its specific mechanism of action remains to be fully determined. CBD seems to exert its anxiolytic effects by interacting with several systems in a wide range of drug concentrations (Campos, Ferreira, & Guimarães, 2012a; Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009). Moreover, the common bell-shaped dose-response curves produced by this compound further complicate the elucidation of its mechanisms (Campos and Guimarães, 2008, 2013a; Guimarães et al., 1990; Izzo et al., 2009).

CBD is proposed to directly interact with several receptors, including CB₁, CB₂, GPR55, TRPV1, and 5-HT1A (Bisogno et al., 2001; Campos et al., 2008; Russo, Burnett, Hall, & Parker, 2005; Ryberg et al., 2007; Thomas et al., 2007). It also interferes with the uptake and degradation system of endocannabinoids signaling (Bisogno et al., 2001; Campos et al., 2013b). However, the relevance of each of these mechanisms for the anti-anxiety effects of CBD still remains unclear.

Of particular importance, several studies have now established that the complex interaction between CBD and 5-HT1A receptors may explain some of its anxiolytic actions. Russo et al. (2005) published the first report that proposed this interaction. Using Chinese hamster ovary cultured cells overexpressing 5-HT1A, they observed that CBD, at micromolar range, displaces OH-DPAT, a selective 5-HT1A receptor agonist (Russo et al., 2005). In the same year, Mishima et al. (2005) suggested that the pharmacological mechanism of CBD-induced neuroprotection during cerebral infarction in rats involved 5-HT1A receptors activation. Regarding CBD's anti-anxiety effects, Campos and Guimarães (2008) were the first to demonstrate that the anxiolytic effects of CBD injected

into the DPAG depends on facilitation of 5-HT1A receptor signaling, rather than CB₁ receptors activation. The ability of systemically injected CBD in attenuating acute autonomic responses evoked by restraint stress is also mediated by 5-HT1A receptors. Moreover, the 5-HT1A receptor antagonist WAY-100635 also prevented the panicolytic-like effects of intra-DPAG injections of CBD, in rats tested in the DPAG-electrically induced escape responses (Campos & Guimarães, 2008; Soares et al., 2010). Activation of 5-HT1A receptors by CBD in other brain structures related to the control of anxiety-like behaviors, such as the BNST and PL, also decreases anxiety-related behaviors (Gomes et al., 2011, 2012; Fogaça et al., 2014). Although the involvement of 5-HT1A receptors in the clinical effects of CBD has not been directly tested, the study by Zuardi et al. (1993) showed that CBD induces anxiolytic effects in a simulated public speaking model that closely resemble those induced by the 5-HT1A receptor partial agonist ipsapirone.

Despite these pieces of evidence associating acute CBD anxiolytic effects with facilitation of 5-HT1A-mediated neurotransmission, the molecular mechanism of this interaction is still unclear. It does not seem to involve blockade of 5-HT reuptake, as recently demonstrated, after acute and repeated CBD treatment, by Campos et al. (2013b). This same study failed to show any changes in 5-HT1A mRNA expression in the DPAG, after chronic CBD administration. It was recently shown, however, that CBD, although failing to displace the binding of 8-OH-DPAT, even at high concentrations, could enhance the ability of this 5-HT1A agonist to stimulate [³⁵S] GTPγS binding at relatively low concentrations (100 nM) (Rock et al., 2012). Although these results have not been fully explained, they suggest that CBD modulation of 5-HT1A receptors is complex, and could involve allosteric interactions.

Not all CBD effects in anxiety-related behaviors, however, can be explained by interaction with 5-HT1A receptors. Another important mechanism that might contribute to CBD anxiolytic effects involves a complex action of this cannabinoid on the endocannabinoid (eCB) system. CBD could facilitate eCB signaling by blocking the metabolism and uptake of anandamide (Bisogno et al., 2001; Campos et al., 2013b). Although, in the DPAG, AM251 (a CB₁ receptor antagonist) failed to interfere in the anxiolytic effects of locally injected CBD, this drug was able to prevent CBD effects on processes related to aversive memories, such as extinction and reconsolidation (Bitencourt et al., 2008; Do Monte et al., 2013; Stern et al., 2012). In addition, AM251, but not a 5-HT1A-receptor antagonist, prevented CBD effects in the marble-burying model (Casarotto et al., 2010). Endocannabinoids can reduce the release of several neurotransmitters, including glutamate, a neurotransmitter closely involved in anxiety responses (Guimarães, Carobrez, De Aguiar, &

Graeff, 1991). An indirect antiglutamatergic action via increased eCB neurotransmission could contribute to the antianxiety effects of CBD.

Another effect of CBD that seems to involve the eCB system is its ability to increase hippocampal adult neurogenesis. Impairment in adult hippocampal neurogenesis has been associated to the pathogenesis of anxiety disorders and depression, and at least some of the behavior effects of antidepressant drugs, such as fluoxetine, depend on facilitation of this process (Samuels & Hen, 2011). CBD facilitation of adult hippocampus has been demonstrated by at least three independent works (Campos et al., 2013b; Esposito et al., 2011; Wolf et al., 2010). Wolf et al. (2010) showed that the proneurogenic effect of CBD was absent in CB₁-knockout mice. CBD has very low affinity for CB₁-receptor, thus this result might be reflecting its ability to inhibit anandamide metabolism/uptake (Bisogno et al., 2001). Corroborating this latter possibility, our group has recently shown that CBD increases *in vivo* and *in vitro* cell proliferation by activation of CB₁ and CB₂ receptors (Campos et al., 2013b). In this study, CBD effects were prevented by the overexpression of the fatty acid amide hydrolase, the enzyme responsible for anandamide degradation. Moreover, the anxiolytic effect of repeated administered CBD (30 mg/daily for 14 days) in mice submitted to a chronic unpredictable stress model was abolished in the absence of hippocampal neurogenesis. This behavior profile and neurogenic is similar to that observed with classic antidepressant drugs, and suggests a causal link between the proneurogenic and anxiolytic CBD effects.

Other mechanisms could also be involved in CBD effects on adult hippocampal neurogenesis, for instance the activation of peroxisome proliferator-activated receptors. This particular mechanism seems to be important during neuroinflammation and neurodegenerative processes related to β -amyloid protein deposits in the central nervous system (Esposito et al., 2011).

CBD can also act as an agonist of transient receptor potential (TRP) channels. These channels include over 50 members, and are present in different species, including yeast, worms, insects, fish, and mammals. The vanilloid receptor 1 or TRPV1 is one of the first identified members of the family, and are expressed in the brain, where anandamide has been proposed as an endogenous agonist, or endovanilloid. These receptors facilitate the release of glutamate, a neurotransmitter that, as described earlier, facilitates anxiety-like behaviors (Guimarães et al., 1991). Campos and Guimarães (2009) suggested that TRPV1 activation could explain, at least partially, the inverted U-shaped dose–response curves commonly observed in experiments conducted with CBD. They showed that intra-DPAG injections of an ineffective dose of the TRPV1 antagonist capsazepine turned a higher, ineffective dose (60 nmol) of CBD, into an anxiolytic one

(Campos & Guimarães, 2009). TRPV1 blocked is also involved in the bell-shaped dose–responses curves produced by anandamide analogues (Casarotto et al., 2012).

In addition to TRPV1, CBD could also interfere with other members of the TR family, activating TRPV2 and ankyrin type 1 (TRPA1) channels, and antagonizing melastatin type 8 (TRPM8) channels (Qin et al., 2008). The contribution of these mechanisms to CBD's anxiolytic effects has not been tested yet.

In addition to the activation of a classic pharmacological receptor, CBD pharmacological mechanisms could also involve intracellular pathways. The role played by these mechanisms on CBD antianxiety effects also remains to be further investigated.

CONCLUSIONS

Taken together, the results from laboratory animals, healthy volunteers, and patients with anxiety disorders support the idea that CBD clearly presents antianxiety properties. This cannabinoid does not present psychoactive effects, does not affect cognition, has an adequate safety profile (Bergamaschi et al., 2011), good tolerability, positive results in trials with humans, and a broad spectrum of pharmacological actions. Moreover, since this compound does not induce dependence, tolerance, and abstinence symptoms, it may be a good alternative to the benzodiazepines. Therefore, CBD appears to be the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice. However, future double-blind controlled studies should test this possibility in clinical trials, including patients with the diverse anxiety disorders, especially panic, obsessive-compulsive, social anxiety, and posttraumatic stress disorder. Additionally, as the actions of CBD usually present a bell-shaped pattern, the adequate therapeutic dose window for each anxiety disorder should be determined. In respect to the mechanism underlying its antianxiety effects, the most consistent evidence points to the involvement of the serotonergic system, probably through direct action on 5-HT_{1A} receptors, although other systems, such as the eCB itself, may also be involved. Thus, further investigation is necessary to clarify these issues, especially if we consider that CBD is a drug with a wide spectrum of effects in the nervous system.

MINI-DICTIONARY

Bell-shape dose–response-curve Drug-response curve produced by drugs that have the ability of promoting different or opposite responses at low or high concentrations.

Cannabinoids A term that refers a heterogeneous group of compounds that modulates cannabinoid receptors functions, classified into three main groups: endogenous, synthetic, and phytocannabinoids.

Chronic unpredictable stress A model applied to produce sustained stress response in rodents that aims to simulate the variability of stressful stimulus to which humans are exposed in daily life.

Elevated plus maze A wide applied animal model of anxiety, composed by two open arms opposed to two enclosed arms elevated to the floor.

Fear conditioning Behavioral paradigm where animals exposed to an aversive stimulus (eg, foot shocks) learn to predict an unpleasant event.

Functional magnetic resonance imaging A noninvasive technique largely used to detect brain activity by detecting changes in blood flow, and oxygen consumption in the brain tissue.

Intracerebral injection Technique that involves stereotaxic surgery to inject a drug directly into a specific brain structure, in laboratory animals.

Simulated public speaking A model with clinical validity that induces anxiety by exposing healthy volunteers to a simulation of a public speech.

Single photon emission computed tomography A clinical image technique that uses gamma rays emission, and a radioactive material as a tracer, to analyze blood flow in target tissues and organs.

Vogel's conflict test A model used for the screening of antianxiety drugs in which water-deprived rodents are exposed to a conflict: decide to drink water from the spout of a bottle that is connected to a shock generator.

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