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REVIEW PAPER

Mechanisms of action of cannabidiol (CBD) in anxiety disorders in animals*

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Abstract

Anxiety disorders are among the most commonly observed behavioral problems in pets, especially in dogs and cats. Animal owners are looking for multiple solutions, including traditional pharmacotherapy, e.g. the use of benzodiazepines or serotonin reuptake inhibitors. However, alternative therapies are increasingly being reached for, including naturally derived compounds such as cannabidiol (CBD). CBD, a non-psychoactive compound derived from *Cannabis sativa*, which is gaining interest as a potential therapeutic agent for treating anxiety disorders in animals. This review examines the mechanisms of action of CBD, with a focus on its effects on serotonin (5-HT1A) receptors, cannabinoid receptors (CB_1 and CB_2), the GABA-ergic system and neurogenesis in the hippocampus. Evidence from preclinical studies indicates that CBD modulates these systems to exhibit anti-anxiety effects by reducing stress reactions and improving adaptation to anxiety stimuli. In addition, the safety profile of CBD is discussed, including such side effects as sedation, gastrointestinal distress and interactions with other drugs. Although CBD has a high safety profile at moderate doses, there is a need for further research to determine its long-term effects and optimal therapeutic regimens. The review confirms the potential of CBD as an innovative anti-anxiety agent for the treatment of anxiety disorders in animals, while emphasizing the need for continued research into its mechanisms of action and safety.

Keywords: cannabis sativa, CBD, anxiety, behavioral problems

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INTRODUCTION

Anxiety disorders are among the most commonly observed behavioral problems in pets, especially in dogs and cats (Barcelos et al. 2024). They appear as a response to a variety of environmental triggers, such as noise, separation from the owner, or changes in the environment, and manifest themselves as separation anxiety, phobias, social anxiety, noise anxiety or travel anxiety (Morag 2015). Key symptoms include excessive excitability, difficulty calming down, aggression, running away or avoiding certain situations. In addition, changes in behavior, such as excessive vocalization, excessive salivation, or destruction of property, can be significant indicators of the presence of an anxiety disorder (Tiira et al. 2016, Salonen et al. 2020). Moreover, chronic stress associated with behavioral disorders of any animal also significantly affects the body, causing impaired growth, reproductive problems, immune dysfunction or shortened life expectancy (Kiełbik, Witkowska-Piłaszewicz 2024). Anxiety symptoms can significantly reduce the quality of life for both animals and their caregivers, leading to increased interest in therapeutic methods that are effective and well tolerated by animals (Barcelos et al. 2024). Traditional pharmacotherapy, including the use of benzodiazepines or serotonin reuptake inhibitors (SSRIs), is used to treat anxiety disorders in animals. However, its use is often associated with side effects such as sedation, appetite changes and even addiction (Garakani et al. 2020). As a result, alternative therapies, including naturally derived compounds such as cannabidiol (CBD), are receiving increasing attention.

CBD is one of the main phytochemical compounds found in hemp (*Cannabis sativa* L.) and exhibits a number of pharmacological properties, including anti-anxiety effects (Campos et al. 2012). It was isolated as early as 1940; however, its structure was not elucidated until more than 20 years later (Adams et al. 1940, Michoulam et al. 1963). Importantly, CBD is non-psychoactive and has a good safety profile, making it a potentially attractive therapeutic agent for anxiety disorders in animals (Khan et al. 2016). Numerous preclinical studies in animal models have shown that CBD can affect the endocannabinoid system and a number of neurotransmitters, such as serotonin and gamma-aminobutyric acid (GABA), which are involved in regulating anxiety reactions (Mauryna, Velmurugan 2018).

Previous studies indicate that CBD can alleviate anxiety symptoms in animals, but many aspects of its effects remain unclear. With the growing interest in CBD as a potential therapeutic agent for animals with anxiety disorders, it is necessary to systematically review and analyze the available preclinical studies.

Mechanisms of action of CBD – serotonin receptors (5-HT1A)

One of the key mechanisms of action of CBD is the modulation of serotonin receptors, especially 5-HT1A receptors, which play an important role in

the regulation of mood, anxiety and stress responses (Melas et al. 2021). 5-HT1A receptors are mainly located in brain structures associated with emotional control, such as the prefrontal cortex (Lat. *cortex prefrontalis*), hippocampus (Lat. *hippocampus*) and amygdala (Lat. *corpus amygdaloideum*), and play a role in inhibiting the release of serotonin, which acts as a neuromediator responsible for regulating emotional states (Garcia-Garcia et al. 2013).

The action of CBD as a partial agonist of 5-HT1A receptors can lead to increased activity of serotonergic neurons, resulting in modulation of serotonin neurotransmission (Garcia-Garcia et al. 2013). This mechanism is important in the context of treating anxiety disorders, as increased serotonin availability at synapses is crucial for regulating mood and anxiety reactions (Yarar 2021).

Although the interaction of CBD with 5-HT1A receptors has been confirmed in various animal models, there are significant interspecies differences in the expression and distribution of serotonin receptors (Hannon et al. 2002), which may affect the therapeutic efficacy of CBD. In rats, 5-HT1A receptors are located in similar brain regions as in humans, i.e. as autoreceptors in the sutural nuclei and in structures such as the hippocampus, prefrontal cortex and amygdala; however, their density and function may differ from humans (Akimova et al. 2009). In mice, it has been observed that the absence of 5-HT1A receptors leads to increased stress reactivity and depressive symptoms. The distribution of these receptors is similar to that in rats, but subtle differences in their expression may affect the results of preclinical studies (Park et al. 1998, Lesch 2001). Studies in rhesus monkeys have shown that 5-HT1A receptor agonists can modulate the effects induced by 5-HT2A receptor activation differently compared to rats, suggesting important differences in the neurobiology of the serotonergic system between these species (Li et al. 2010). In animal models such as rats and mice, CBD has demonstrated anti-anxiety effects through activation of 5-HT1A receptors in anxiety-related brain structures such as the hippocampus and prefrontal cortex (Melas et al. 2021, Schouten et al. 2024). Data on CBD's effects on 5-HT1A receptors in primates are limited. However, given the differences in serotonergic system modulation between monkeys and rodents, CBD's effects may differ in this species (Li et al. 2010). This suggests the need for further research to optimize doses and administration regimens.

Mechanisms of action of CBD – CB_1 and CB_2 receptors

CBD exhibits anti-anxiety effects whose mechanism involves, in part, modulation of the endocannabinoid system (ECS). This system, crucial for the regulation of emotions, stress reactions and neurophysiological homeostasis, includes cannabinoid receptors CB_1 and CB_2 and endogenous ligands such as anandamide (AEA) and 2-arachidonylglycerol (2-AG). However, the effects of CBD on ECS are different from those of Δ9-tetrahydrocannabinol

(THC), such as a relatively weak affinity for CB_1 and CB_2 receptors, CBD acts indirectly by regulating the activity of CB_1 and CB_2 receptors without directly activating them (Mauryna, Velmurugan 2018, Gingrich et al. 2023).

CB_1 receptors are widespread in the central nervous system, especially in brain structures associated with emotion regulation, such as the prefrontal cortex, hippocampus, amygdala and nucleus accumbens (Lat. *nucleus accumbens septi*). CBD's indirect effect is to inhibit the anandamide-degrading enzyme fatty acid amide hydrolase (FAAH), leading to an increase in anandamide concentration at synapses. Anandamide, which is an endogenous CB_1 agonist, exerts sedative and anti-anxiety effects by inhibiting excessive neuronal activity, resulting in a decreased response to stressful stimuli. Thus, CBD can regulate the anxiety response by increasing anandamide levels, leading to the activation of CB1 receptors and, consequently, the modulation of anxiety-related neurophysiological responses (Yarar 2021).

CB_2 receptors are mainly distributed on cells of the immune system and are found to a lesser extent in the central nervous system. They are thought to play a key role in regulating immune responses and neuroinflammatory processes, which may have a role in modulating anxiety symptoms. CBD acts as a partial agonist of CB_2 receptors, leading to its immunomodulatory and anti-inflammatory properties (Svizenska et al. 2008). In preclinical studies, CBD has been shown to reduce neuroinflammatory responses, which may be associated with the pathophysiology of anxiety disorders, by decreasing the production of pro-inflammatory cytokines such as TNF-*α* and IL-6 (Elsaid et al. 2019, Tito et al. 2021). CBD's action on CB_2 receptors may also affect oxidative stress and inflammation in the brain, promoting neuroprotection and improving neuronal function. The reduction of neuroinflammatory processes through CB_2 receptors is relevant to anti-anxiety effects, as the reduction of oxidative stress and inflammation in brain structures involved in emotion regulation may result in improved adaptability of the body to stressors (Paloczi et al. 2019, Kopustinskiene et al. 2022, Pagan et al. 2023).

Mechanisms of action of CBD – effects on the GABA system

The gamma-aminobutyric acid (GABA) system is crucial for regulating neuronal excitability and the balance between excitation and inhibition in the central nervous system (CNS). It influences the neurophysiological aspects of anxiety, stress and emotional disorders (Zhang et al. 2021). CBD, as one of the main phytocannabinoids present in cannabis, exhibits anti-anxiety effects partly through modulation of GABAergic system activity. These observations are based on the results of preclinical studies, which suggest that CBD may indirectly affect GABA neurotransmission, in particular by modifying $GABA_A$ receptor signaling and at the presynaptic level (Voicu et al. 2023). For example, studies on mice by Dearborn et al. (2022) showed that chronic administration of CBD increased the expression of $GABA_A$ receptor subunits in the cerebral cortex of mice with CLN1 disease (infantile

neuronal ceroid lipofuscinosis), which correlated with a reduction in the frequency of epileptic seizures. This suggests that CBD may modulate the GABAergic system by regulating the expression of $GABA_A$ receptors. In addition, a study analyzing the effects of CBD on GABAergic neurotransmission in the spinal cord (lat. *medulla spinalis*) of mice showed that CBD increases GABAergic conduction, which may explain its potential analgesic effects in models of neuropathic pain (Wang et al. 2023). Studies on the effects of CBD on GABAergic conduction in the rat hippocampus showed that CBD increased the frequency and amplitude of spontaneous inhibitory currents (sIPSCs) in CA_1 pyramidal neurons, indicating that synaptic inhibition is enhanced by modulating the activity of GABAergic interneurons (Hoffman, Lupica, 2000).

$GABA_A$ receptors, which are major inhibitory receptors in the brain, play an important role in regulating mood and anxiety (Kalueff et al. 2007, Nuss 2015). This action is thought to be related to CBD's interaction with binding sites on $GABA_A$ receptors or their subunits, which may increase the flow of chloride ions into the cell, producing a hyperpolarizing effect and inhibiting excessive neuronal activity (Kumar et al. 2002, Ng et al. 2024). CBD, through its effects on other neurotransmitter systems such as the serotonin and endocannabinoid systems, can indirectly regulate the synthesis and release of GABA (Martinez Naya et al. 2023).

Mechanisms of action of CBD – increased neurogenesis in the hippocampus

The hippocampus is a key brain structure responsible for memory processes, neuronal plasticity and emotion regulation (Leuner, Gould 2010, Shi et al. 2023). Its proper functioning is particularly important in the context of anxiety disorders, as it is responsible for adaptation to stressors and modulation of anxiety responses. Neurogenesis in the hippocampus, the process of creating new neurons, is considered one of the brain's adaptive mechanisms, and it is crucial in the context of alleviating anxiety symptoms (Shi et al. 2023). CBD, by interacting with receptors of the endocannabinoid system and serotonin receptors, can modulate neurogenesis in the hippocampus (Fogaça et al. 2013, 2018), making it a potential therapeutic tool for treating anxiety disorders in animals.

Preclinical studies show that CBD can stimulate neurogenesis within the hippocampus, particularly in the dentate gyrus *(*Lat. *gyrus dentatus)*, where the processes of neuronal proliferation and differentiation occur intensively throughout life (Valeri, Mazzon 2021). CBD indirectly increases progenitor cell proliferation by modulating endocannabinoids, such as anandamide, which affects the activity of CB_1 and CB_2 receptors (Galve-Roperh et al. 2013).

Increased neurogenesis in the hippocampus is one of the mechanisms through which CBD can affect the reduction of anxiety symptoms in animals (Wolf et al. 2010).

Pharmacokinetic and side effects and safety of CBD

CBD's therapeutic properties depend on its pharmacokinetics, which varies between animal species. These differences affect the efficacy, safety and potential side effects associated with its use. Absorption, distribution, metabolism and excretion should be considered in the context of pharmacokinetics.

Absorption: Studies indicate that the bioavailability of CBD after oral administration in dogs is low, at around 13-19%. The low bioavailability is related to the first-pass effect through the liver and the limited solubility of CBD in water (di Salvo et al. 2023). In rats, the bioavailability of CBD after oral administration is low at 2.8%, which may be due to similar metabolic mechanisms as in other species (Gingrich et al. 2023).

Distribution: CBD, as a lipophilic compound, is widely distributed in the bodies of various species (Chayasirisobhon 2020). Specific differences in tissue composition and blood supply can affect CBD concentrations in individual organs (Child, Tallon 2022).

Metabolism: CBD metabolism occurs mainly in the liver by cytochrome P450 enzymes such as CYP3A and CYP2C (Chayasirisobhon 2020). The activity of these enzymes varies between species, which affects the rate of metabolism and the formation of active metabolites (Nishimuta et al. 2013). Cats, for example, have reduced activity of certain liver enzymes, which can lead to slower metabolism of CBD and longer duration of its effects (Deabold et al. 2019).

Excretion: Excretion of CBD metabolites occurs mainly through feces and urine (Chayasirisobhon 2020). In dogs, the half-life ranges from 3 to 9 h after administration (Samara et al. 1990, Bartner et al. 2018, Gamble et al. 2018, Deabold et al. 2020). Data in cats are limited, but indicate that the half-life is shorter than in dogs at 1.5 h (Deabold et al. 2020). In rats, the half-life is relatively short, which may require more frequent dosing in preclinical studies (Deiana et al. 2012).

The use of CBD for the treatment of anxiety disorders in animals, despite its growing popularity and documented therapeutic potential, is associated with some side effects and risks. The safety and tolerability of CBD in animals are the subject of intensive research, but significant knowledge gaps remain regarding its long-term effects and potential side effects, especially with chronic use.

The most commonly reported side effects include sedation, decreased appetite, transient diarrhea and vomiting (Huestis et al. 2019). Sedative effects are likely due to CBD's interaction with $GABA_A$ receptors and serotonin 5-HT1A receptors, which are responsible for relaxation and sedative effects (Garcia-Garcia et al. 2013, Voicu et al. 2023). The observed decreased appetite and digestive disturbances, on the other hand, may be due to CBD's effects on intestinal motility and its interaction with serotonin receptors in the gastrointestinal tract (Maselli, Camilleri 2021).

CBD is mainly metabolized by cytochrome P450 enzymes, particularly by the CYP3A4 and CYP2C19 isoenzymes. Therefore, CBD can affect the metabolism of other substances and lead to drug interactions that are important for the safety of therapy, especially in animals using other drugs. It has been shown that CBD can inhibit the activity of these isoenzymes, leading to increased blood concentrations of certain drugs and potentially exacerbating their effects or toxicity. In the context of anxiety disorders in animals, it is important to understand the interaction of CBD with commonly used psychotropic drugs, such as benzodiazepines or selective serotonin reuptake inhibitors (SSRIs) (Iffland, Grotenhermen 2017).

In addition, some studies in animal models suggest that high doses of CBD may be associated with a risk of hepatotoxicity. Studies in dogs have shown that the use of high doses of CBD can lead to an increase in liver enzymes, suggesting a burden on the liver (Chen, Kim 2024). Although these data are inconclusive and further research in this area is needed, the potential risk of liver damage warrants special attention with long-term high-dose CBD therapy in animals.

CONCLUSIONS

CBD, a non-psychoactive phytocannabinoid, is gaining increasing interest as a potential therapeutic agent for the treatment of anxiety disorders, both in humans and animals. The studies presented here have shown that CBD exhibits anti-anxiety effects through multidirectional mechanisms, including modulation of serotonin receptors, cannabinoid receptors, and effects on the GABAergic system, key to regulating emotions and stress responses. Importantly, CBD may also increase neurogenesis in the hippocampus, which plays an important role in the body's adaptation to stressful stimuli and regulation of long-term anxiety responses. These effects may be particularly important in the treatment of chronic anxiety disorders, where adaptation to stressors plays a key role. CBD's effects on neurogenesis, mediated by endocannabinoid and serotonin receptors, indicate its potential as a substance that promotes neuronal plasticity and adaptive brain mechanisms. Further research is needed, however, to define more specifically the relationships between dosage, neurogenesis effects and therapeutic efficacy in the context of different animal species so as to optimize and ensure safety of CBD use in anxiety disorders.

Author contributions

P.M.O. – methodology, software, conceptualization, investigation, visualization, writing – original draft preparation, writing – review & editing. The authors has read and agreed to the published version of the manuscript.

Conflicts of interest

The author ensures that she has neither professional nor financial connections related to the manuscript sent to the Editorial Board.

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