
CANNABIDIOL AND ANXIETY-DEPRESSION

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

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Cannabidiol (CBD) is a major phytocannabinoid present in the *Cannabis sativa* plant. It lacks the psychotomimetic and other psychotropic effects that the main plant compound Δ^9 -tetrahydrocannabinol (THC) being able, on the contrary, to antagonize these effects. This property, together with its safety profile, was an initial stimulus for the investigation of CBD pharmacological properties. It is now clear that CBD has therapeutic potential over a wide range of non-psychiatric and psychiatric disorders such as anxiety, depression and psychosis. Although the pharmacological effects of CBD in different biological systems have been extensively investigated by *in vitro* studies, the mechanisms responsible for its therapeutic potential are still not clear. Here, we review recent *in vivo* studies indicating that these mechanisms are not unitary but rather depend on the behavioural response being measured. Acute anxiolytic and antidepressant-like effects seem to rely mainly on facilitation of 5-HT_{1A}-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex. Other effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, and facilitation of adult hippocampal neurogenesis could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD.

Recent comprehensive reviews suggest that this compound is one of the most promising candidates for a therapeutic tool in a wide range of disorders [3,4]. In the present paper, we will review the evidence that supports its use in psychiatric disorders and the proposal mechanisms that try to explain it.

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In vivo mechanisms of cannabidiol anxiolytic effects: 5-HT_{1A} receptors

Russo *et al.* [35] were the first to suggest that CBD could act as a 5HT_{1A} receptor agonist. They observed that, at μ M range, this drug displaces 8-OH-DPAT, a 5-HT_{1A} receptor agonist, from cloned human 5-HT_{1A} receptors expressed in cultured cells obtained from Chinese hamster ovary. *In vivo* experiments gave further support to the involvement of 5-HT_{1A} receptors in the effects of CBD [18–20,55]. For instance, the neuroprotective effects of CBD in hepatic encephalopathy or cerebral infarction are mediated by these receptors [55,56]. Regarding the behavioural studies, the effects of CBD in a PTSD model (predator exposure) were prevented by WAY100635, a 5HT_{1A} receptor antagonist [11]. This same antagonist prevented the anxiolytic- and panicolytic-like effects of CBD after injections into the DPAG [16,18], bed nucleus of the stria terminalis [19,20] and prefrontal cortex (M. V. Fogaça & F. S. Guimarães 2012, unpublished data; figure 1). In humans, although no study so far has investigated the involvement of 5-HT_{1A} mechanisms in CBD effects, the anxiolytic profile of this drug in the public speaking model was remarkably similar to the positive control ipsapirone, a 5HT_{1A} receptor partial agonist [24].

Other CBD effects also involve 5-HT_{1A} receptors. It decreases nausea and vomiting probably by an indirect agonism at these receptors. Although the mechanism of this indirect action is unclear, it may

involve interactions with allosteric sites or changes in different systems that would result in a facilitation of 5-HT_{1A}-mediated responses [57]. Adding to the evidence that the interaction of CBD with 5-HT_{1A} receptors could be complex, it was recently shown that this compound antagonizes food intake induced by 8-OH-DPAT [58]. Therefore, additional research is clearly needed to clarify how CBD facilitates 5-HT_{1A}-mediated neurotransmission.

***In vivo* mechanisms of cannabidiol effects: the endocannabinoid system**

CBD could facilitate eCB-mediated neurotransmission by blocking the metabolism and uptake of anandamide [33]. However, AM251, a CB₁ receptor antagonist, failed to prevent the anxiolytic effects of CBD injected into the DPAG observed in the elevated plus maze at the same dose that antagonized the anxiolytic effects of anandamide [18,59].

On the other hand, CB₁, but not 5-HT_{1A}, receptor antagonism was able to prevent CBD effects on both extinction and reconsolidation, indicating that its interference on aversive memories involves eCB-mediated mechanisms [15,23]. These results agree with the well-described facilitation of extinction by endogenous cannabinoids [60], suggesting that CBD interferes with aversive memories by facilitating the effects of eCBs [45].

Finally, AM251 blocked CBD effects in the marble burying model [14], whereas 5-HT_{1A}-receptor antagonism was ineffective. This result corroborates the proposal that anxiety and OCD models engage distinct brain mechanisms, with the marble burying behaviour being related to repetitive behaviours instead of anxiety [61].

How facilitation of eCB-mediated neurotransmission decreases repetitive behaviour is unknown, but may involve attenuation of glutamate-mediated neurotransmission. eCBs can reduce the release of several neurotransmitters, including glutamate [62], a major neurotransmitter of the cortico-striato-thalamo-cortical circuitry that has been implicated in the pathophysiology of OCD [63]. Anti-glutamatergic drugs such as riluzole and memantine decrease marble burying behaviour [64,65] and are proposed to be clinically useful for OCD treatment [66,67].

An indirect anti-glutamatergic action via increased eCB neurotransmission may also be involved in other central effects of CBD such as anticonvulsant [3], an effect that could also be related to indirect CB₁-mediated inhibition of glutamate release. Corroborating this proposal, anticonvulsant effects of other inhibitors of anandamide metabolism/uptake have recently been described [3]. Moreover, epileptic patients present a significant reduction in the fraction of CB₁-positive glutamatergic, but not GABAergic, axon terminals, probably resulting in increased neural excitability [68].

***In vivo* mechanisms of cannabidiol effects: adult hippocampal neurogenesis**

Impairment in adult hippocampal neurogenesis has been associated with the pathogenesis of anxiety disorders and depression [69] and at least some of the behavioural effects of prototype antidepressant drugs depend on facilitation of this process [70]. CBD can also increase adult hippocampal neurogenesis, as first demonstrated by Wolf *et al.* [71]. They also showed that the proneurogenic effect of CBD was absent in CB₁-knockout mice [71]. Because CBD is not a CB₁-receptor agonist, this result suggested that CBD effect was mediated by an indirect activation of these receptors, possibly by inhibition of anandamide metabolism/uptake [33]. Corroborating this latter possibility, recent results from our group showed that CBD increases proliferation of hippocampal progenitor cells in culture, an effect mimicked by CB₁ or CB₂ receptor agonists and prevented by antagonists of these receptors [72]. Moreover, CBD effects were also inhibited by overexpression of the FAAH, reinforcing the proposal of anandamide involvement. These results agree with those previously reported by Jiang *et al.* [73] showing that a synthetic CB₁ agonist is able to promote embryonic and adult hippocampus neurogenesis, an effect associated with the anxiolytic and antidepressant properties of the drug. Similar to prototype antidepressants, the anxiolytic effect of repeated administered CBD (30 mg/daily for 14 days) in mice submitted to a chronic unpredictable stress model disappeared when hippocampal neurogenesis was inhibited [72], suggesting a causal link between its proneurogenic and anxiolytic effect after repeated administration (figure 1).

Other mechanisms could also be involved in CBD effects on adult hippocampal neurogenesis—for example, activation of peroxisome proliferator-activated receptors. This particular mechanism seems to be important during neuroinflammation and neurodegenerative process related to β -amyloid protein deposits in CNS [51]. Although the pro-neurogenic effect of CBD has not yet been studied in rats, it could help us to explain the recent report that repeated CBD treatment enhances contextual fear conditioning [22]. Immature newborn neurons are selectively activated by this task [74], and neurogenesis suppression impairs contextual fear memory [75]. Considering the important role proposed for hippocampal neurogenesis in several brain functions [76,77], the effects and mechanisms of CBD on this process is another important research venue to be pursued.

Cannabidiol and the vanilloid system

CBD can activate transient receptor potential (TRP) channels [33]. These channels comprise a family of over 50 members and are present in different species, including yeast, worms, insects, fish and mammals [78]. The vanilloid receptor 1 or TRPV1 is one of the first identified members of the family, being a non-selective cation channel with a preference for calcium. It is activated by noxious stimuli, heat, protons (pH < 5.9) and various, mostly noxious, natural products such as capsaicin [79]. TRPV1 receptors are present in the brain, where anandamide has been proposed to act as an endogenous agonist or an endovanilloid [80]. These receptors can facilitate the release of glutamate [81], a neurotransmitter that induces defensive responses in brain areas such as the DPAG [82]. On the basis of these pieces of evidence, we hypothesized that TRPV1 activation could be at least partially responsible for the inverted U-shaped dose-response curves commonly observed with CBD. Accordingly, using intra-DPAG injections, we showed that local pretreatment with an ineffective dose of the TRPV1 antagonist capsazepine turned a higher, ineffective dose (60 nmol) of CBD into an anxiolytic one [83]. TRPV1 receptors are also involved in the bell-shaped dose responses curves of anandamide analogues [84,85].

In addition to TRPV1, CBD could also interfere with other members of the TRP family, activating TRPV2 and ankyrin type 1 (TRPA1) channels and antagonizing melastatin type 8 (TRPM8) channels [45,46]. The role played by these mechanisms on CBD behavioural effects, however, is unknown at the moment.

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Initial studies with laboratory animals suggested that CBD prevents some of the effects produced by THC [86]. Similar antagonism was also found in humans, where CBD attenuated the impairment of time production tasks and the euphoria induced by THC in healthy volunteers [87,88]. Confirming and extending these results, Zuardi *et al.* [31] demonstrated that CBD inhibits THC-induced anxiety and psychotic-like symptoms such as disconnected thoughts, perceptual disturbance, depersonalization and resistance to communication. In the same year, it was observed that patients admitted to a psychiatric hospital in South Africa after the use of a variety of *Cannabis* virtually devoid of CBD showed a much higher frequency of acute psychotic episodes than in other countries [89], suggesting that the presence of CBD in *Cannabis* samples protects users against the occurrence of THC-induced acute psychotic episodes. Because experimental evidence indicates that the antagonistic effect of CBD did not result from a pharmacokinetic interaction between the two cannabinoids [90], these initial observations led to the hypothesis that CBD could possess antipsychotic properties.

An initial study in rats investigated whether this compound could attenuate stereotypies induced by the dopaminergic agonist apomorphine. CBD effects were compared with those of haloperidol [91]. Both drugs reduced apomorphine-induced stereotyped behaviour in a dose-related manner. Even though they increased plasma levels of prolactin, CBD had much lower potency, with significant increases only seen after the doses of 120 and 240 mg kg⁻¹. Moreover, contrary to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg kg⁻¹. These results suggest that CBD exhibits a profile similar to atypical antipsychotic drugs. In another study, CBD was compared with haloperidol and clozapine, an atypical antipsychotic drug. The drug inhibited the hyperlocomotion induced by amphetamine and ketamine, an NMDA receptor antagonist, in mice [92]. As expected, while both haloperidol and clozapine

inhibited hyperlocomotion, only haloperidol induced catalepsy. These results extend CBD antipsychotic-like effects to a glutamate-based model. In agreement with these results, CBD, similar to clozapine, reversed the disruption of prepulse inhibition (PPI) in mice and the hyperactivity and reduction of social interaction in rats caused by MK-801, another NMDA receptor antagonist [93,94]. Typical antipsychotics, on the other hand, are usually unable to restore the deficits in PPI and social interaction induced by NMDA receptor antagonists [95,96].

Extending findings from studies using single drug administration, chronic treatment with CBD attenuated amphetamine-induced hyperlocomotion [97]. Preliminary results from our group indicate that this treatment regime is also able to decrease the impairments in PPI and object recognition induced by repeated administration of MK-801 (F. V. Gomes, E. A. Del Bel & F. S. Guimarães, unpublished data). Despite these findings, there are also negative results regarding the possible antipsychotic effects of CBD. Chronic treatment with this drug failed to change behavioural changes such as locomotor hyperactivity and PPI deficits observed in transmembrane domain neuregulin 1 mutant (Nrg1) mice, a proposed model for a schizophrenia susceptibility gene [98]. A summary of the studies investigating the antipsychotic-like effects of CBD in animal models can be seen in [table 3](#).

model	species	effective doses
studies with laboratory animals		
amphetamine-induced stereotyped behaviour	rat	50 mg/kg ⁻¹
↓ MK-801 and haloperidol induced hyperlocomotion	mouse	10–50 mg/kg ⁻¹
↓ MK-801 induced disruption of PPI	mouse	5 mg/kg ⁻¹
↓ amphetamine-induced hyperlocomotion	mouse	50 mg/kg ⁻¹ (chronic = 21 days)
↓ MK-801 induced social withdrawal and disruption of PPI	rat	5–20 mg/kg ⁻¹

Table 3.

Preclinical and clinical studies investigating the antipsychotic properties of CBD. ↓, antipsychotic-like effects; BPRS, brief psychiatric rating scale; CADSS, clinician administered dissociative states scale; PANSS, positive and negative syndrome ...

Cannabidiol and psychosis: clinical studies

The antipsychotic-effects of CBD have also been demonstrated in humans ([table 3](#)). In healthy volunteers, Leweke *et al.* [100] observed that the decrease of the perception of illusory image induced by nabilone, a synthetic cannabinoid drug with THC-like properties, was reduced by CBD. Another model used to evaluate antipsychotic-like activity of drugs in humans is the administration of sub-anaesthetic doses of ketamine. This drug induces psychotic symptoms that mimic both positive and negative symptoms of schizophrenia. An initial investigation in healthy subjects showed that CBD induced a non-significant trend to reduce ketamine-induced dissociative effects, but, at the same time, augmented the activating effects of ketamine [102]. Because only a single dose of CBD was used, additional studies are needed to characterize the effects of CBD in this model [102].

The therapeutic use of CBD in psychotic patients was tested for the first time in 1995. In an open, case-report study, a 19-year-old black schizophrenic female patient, who presented serious side effects after treatment with conventional antipsychotics, received increasing oral doses of CBD (up to 1500 mg d⁻¹) for four weeks [103]. A significant improvement with no side effects was observed in all items of the standard brief psychiatric rating scale (BPRS) during CBD treatment, with an efficacy similar to that of haloperidol. Symptom worsening was observed when the administration was interrupted. In another case study, CBD was administered to three 22- or 23-year-old male schizophrenic patients who had not responded to typical antipsychotic drugs for 30 days [104]. The dose of CBD was increased from 40 up to 1280 mg d⁻¹. One patient showed mild improvement, but only slight or no change was observed in the other two, suggesting that CBD may not be effective for the treatment of resistant schizophrenia. Moreover, CBD

had no beneficial effects on the performance of schizophrenic patients in the Stroop colour word test, which can be used to assess attentional processes frequently impaired in schizophrenia [106]. It is still unknown whether chronic administration of CBD could improve the cognitive deficits in the disorder. No significant side effects were observed during CBD treatment in these clinical studies, suggesting that CBD is safe and well tolerated in schizophrenic patients.

In an open-label study evaluating CBD effects on psychotic symptoms associated with L-dopa use in Parkinson's patients [105], the drug decreased scores of a questionnaire developed to assess psychotic symptoms in Parkinson's disease (Parkinson psychosis questionnaire), improved total BPRS scores as well as scores specifically related to positive and negative symptoms. Confirming the lack of motor effects observed in animal studies, CBD did not affect motor function. On the contrary, it decreased the total scores of the unified Parkinson's disease rating scale, suggesting an improvement of this function.

Overall, therefore, even if there are negative results, most clinical studies with normal subjects or schizophrenic patients suggest that CBD has antipsychotic properties. Corroborating this possibility, a four-week double-blind controlled clinical trial in 42 acute schizophrenic and schizophreniform psychosis patients comparing the effects of CBD with those of amisulpride, an atypical antipsychotic, showed that both treatments were equally effective in reducing acute psychotic symptoms after two and four weeks of treatment [34]. Moreover, compared with amisulpride, CBD caused a lower incidence of extrapyramidal symptoms and increases in prolactin and weight gain.

The presence of antipsychotic properties in CBD is also supported by convergent evidence linking the habitual use of *Cannabis* to the risk of developing schizophrenia or schizophrenia-like psychosis, especially in vulnerable subjects [107]. This effect has been attributed to THC. In agreement with the initial reports showing antagonism of THC-induced psychotomimetic effects [31,87,88], the presence of CBD in *Cannabis* strains has been shown to be protective against the occurrence of psychotic-like reactions and cognitive impairment [108–110]. In this context, Di Forti *et al.* [111] found that the use of *Cannabis* containing high THC- and low CBD concentration was associated with a higher risk of a first psychotic episode. Furthermore, the presence of CBD protects from *Cannabis*-associated decrease in hippocampal volume [112]. This neuroprotective effect of CBD has also been reported in the human basal ganglia, where there was a strong positive correlation between *N*-acetylaspartate/total creatine ratio and the amount of CBD (as measured by its presence in hair samples) in the putamen/globus pallidum of recreational *Cannabis* users. This finding could reflect a CBD-induced enhancement of neuronal and axonal integrity in these regions [113]. More recently, Bhattacharyya *et al.* [114], investigating the effects of THC and CBD during attentional salience processing, have also showed that these two cannabinoids produce opposite effects on prefrontal, striatal and hippocampal functions.

Brain sites and mechanisms of cannabidiol antipsychotic effects

Few studies in laboratory animals have investigated the possible brain sites and mechanisms of CBD antipsychotic effects. Consistent with the behavioural data described earlier, both CBD and clozapine, but not haloperidol, increased neuronal activation (measured by cFos-protein expression) in the prefrontal cortex. Probably reflecting its motor side effects, only haloperidol increased cFos in the dorsal striatum. CBD, and, in addition, increased cFos in the nucleus accumbens [115], an effect shared by typical and atypical antipsychotic drugs [116]. Intracerebroventricular administration of CBD (10 µg) also enhanced cFos expression in waking-related brain areas such as hypothalamus and dorsal raphe nucleus [117], but the relation between this finding and its antipsychotic properties is unclear.

A number of neuroimaging studies in healthy volunteers have compared the effects of CBD and high doses of THC. Consistent with the behavioural findings in humans and rodents, these drugs caused opposite effects on brain activity in the striatum, anterior cingulate, prefrontal cortex, parahippocampal gyrus, amygdala, right posterior superior temporal gyrus, middle occipital gyrus and cerebellum [27,101,114,118–120]. Behavioural measurements in these studies indicated that some of these changes (decreased activation of ventral and dorsal striatum, anterior cingulate gyrus, right temporal lobe) are associated with the psychotic-like effects of THC, suggesting that these regions could be possible brain sites of CBD action [121]. No study using direct injections into key brain regions associated with the

pathophysiology of schizophrenia, such as the prefrontal cortex and nucleus accumbens, has been performed so far to investigate CBD antipsychotic properties.

Regarding the pharmacological mechanisms, intracerebroventricular administration of CBD enhanced extracellular levels of dopamine in the nucleus accumbens [122]. A similar finding was found after microdialysis perfusion of CBD (30, 60 or 90 nM) into the rat lateral hypothalamus [117], a procedure that also enhanced alertness. It is unclear how this effect would relate to the antipsychotic properties of CBD because usual antipsychotic drugs act by antagonizing dopamine-2 receptors [123]. Moreover, studies with animal models that involve dopaminergic stimulation suggest that the antipsychotic-like doses of CBD (60–120 mg kg⁻¹) are higher than those needed to induce anxiolytic-like effects [7,91,92] and reverse behavioural deficits induced by the NMDA receptor antagonist MK-801 [93,94,99]. These findings indicate that the mechanisms of CBD effects on glutamate- or dopamine-based models could be at least partially distinct. This possibility needs to be further explored.

Recently, Leweke *et al.* [34] showed that schizophrenic patients treated with CBD present higher anandamide serum levels compared with those receiving the antipsychotic amisulpride. Moreover, in the CBD group, there was a significant association between anandamide levels and improvement of psychotic symptoms. In the same study, they confirmed, *in vitro*, that CBD inhibits FAAH activity in a concentration (10 μM) that does not interact with receptors (dopamine, GABA, serotonin and glutamate) commonly associated with schizophrenia. However, by indirectly activating CB1 receptors via increased levels of anandamide, CBD could potentially modulate neurotransmitters systems related to these receptors [121,124]. Moreover, as previously discussed, facilitation of CB1-mediated neurotransmission by CBD also increases adult hippocampal neurogenesis, a mechanism that could be related to the cognitive deficits found in schizophrenic patients [124].

As discussed already, CBD and anandamide can also activate TRPV1 channels. This mechanism, probably by facilitating the pre-synaptic release of glutamate [80], is involved in the ability of CBD to reverse the disruption of PPI induced by the NMDA receptor antagonist MK-801 [93].

Other mechanisms that could also help us to explain CBD anti-psychotic effects are facilitation of 5-HT1A-mediated neurotransmission, an effect shared by the atypical anti-psychotic aripiprazole, which acts as a partial agonist at these receptors, and anti-inflammatory/neuroprotective action [124].

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Cannabis sativa exerts significant effects upon humour, which include euphoria and mood elevation [125]. THC may account for most of these effects through activation of CB1 receptors. Considering these observations, as well as the effects of synthetic cannabinoids and drugs that increase eCB levels, a putative role for the eCB system in mood disorders has been proposed [126]. The effects of CBD, however, have been scarcely investigated (table 4). The fact that this compound, in addition to facilitating eCB activity [33], may facilitate the activation of 5-HT1A receptors [35] suggests that it might also have antidepressant-like properties. 5HT1A receptors modulate responses to stressful stimuli and are proposed to mediate the effects of antidepressant drugs [129].

model	species	effective doses	CBD-effects
constant stress	rat	10–100 mg kg ⁻¹	↓ antidepressant and behavioural effects of 5HT
PWT	mouse	100 mg kg ⁻¹	↓ immobility
TST	mouse	10–100 mg kg ⁻¹	no effect
PWT	mouse	10 mg kg ⁻¹	↓ immobility
chronic unpredictable stress	rat	10 mg kg ⁻¹ (daily, chronic treatment)	↓ the behavioural consequences of stress (i.e. hippocampal neurogenesis)

Table 4.

Antidepressant-like effects of CBD. Studies with laboratory animals. FST, forced swimming test; TST, tail suspension test.

Stress exposure is a key aetiological factor in depression [130] and animal models used to study antidepressant-like effects are generally based on acute responses to inescapable aversive stimuli, which are prevented by antidepressants [131]. Alternatively, considering the nature of depression as a chronic psychiatric disorder, some models investigate drug effects upon the diverse consequences of chronic stress, including anhedonia and changes in exploratory activity [132].

One of the first studies that indicate the presence of antidepressant-like properties in CBD focused on its ability to prevent the autonomic and behavioural consequences of inescapable stress [17]. Rats were submitted to restraint stress during 60 min, which increases heart rate and blood pressure and caused anxiogenic-like responses in rats exposed to the elevated plus maze 24 h later. CBD was injected 30 min before the stress at the doses of 1, 10 or 20 mg kg⁻¹. The doses of 10 and 20 mg kg⁻¹ attenuated the changes in autonomic parameters, whereas at 10 mg kg⁻¹ CBD also prevented the late anxiogenic-like effect of stress. There were no changes in motor activity or basal cardiovascular parameters, discarding any possible confounding factor [17]. Similar effects were observed after intra-cisterna magna administration of CBD [12], thus suggesting that these effects are centrally mediated.

Another behavioural model widely used to assess antidepressant-like effects, mainly due to its pharmacological predictability, is the forced swim test. In this assay, rats or mice exposed to inescapable swimming assume a posture of immobility, which is reversed by antidepressants [131]. We tested in mice the effects of CBD (3–100 mg kg⁻¹) injected 30 min prior to the test [128]. The drug produced an inverted U-shaped dose-response curve. At the dose of 30 mg kg⁻¹, it reduced immobility similar to the tricyclic antidepressant imipramine (30 mg kg⁻¹). Our behavioural findings in the forced swimming test were confirmed by another study, published in the same year. CBD was tested at the doses of 20, 100 and 200 mg kg⁻¹ [127], with the higher dose being effective. The drug had no effect, however, in the mouse tail suspension test. One drawback common to all these studies is that the animals received only acute injections. Depression, however, is a chronic disorder that requires long-lasting drug treatment [130]. CBD has been recently tested against the consequences of chronic unpredictable stress, which includes anhedonia and anxiety-like behaviour [130]. Chronic treatment with CBD was able to prevent these behavioural changes, an effect that depends on hippocampal neurogenesis, similar to antidepressant drugs [72]. This observation further strengthens the notion that this natural cannabinoid should be considered as a potential approach for the treatment of mood disorders.

Despite this body of evidence, no clinical study has investigated whether CBD can decrease depressive symptoms in patients. This compound has been tested, however, in patients suffering from bipolar disorders, a subtype of mood disorder, in whom it was not effective in treating manic episodes [133]. Actually, this is in line with animal models, in which CBD failed to prevent hyperactivity in rodents [134].

To summarize, although the data are scarce, preclinical studies so far do provide evidence that this compound could induce antidepressant-like effects. Clinical studies are important to confirm this possibility.

Mechanisms of cannabidiol antidepressant effects

Similar to findings with animal models of anxiety, the attenuation of the behavioural consequences of restraint stress and the antidepressant-like effects of CBD in the forced swimming test were attenuated by a 5-HT_{1A} receptor antagonist [17,128]. In the latter model, despite the association between increased expression of neurotrophic factors and antidepressant activity [130], CBD failed to modify brain-derived neurotrophic factor hippocampal levels [128].

As discussed earlier, CBD can also facilitate hippocampal neurogenesis, probably by facilitation of eCB neurotransmission [72]. The involvement of this mechanism on its antidepressant-like properties after repeated administration remains to be investigated.

CONCLUSIONS

CBD is a safe compound with a wide range of therapeutic applications, including the treatment of psychiatric disorders [3,4]. These findings make this drug an attractive candidate for future clinical use. Its therapeutic use, however, has some limiting factors. In addition to its low and variable oral bioavailability in humans [135], it causes bell-shaped dose-response curves and, judging from the studies with laboratory animals, possesses a narrow therapeutic dose range. A clear target of future research, therefore, is to try to develop compounds with similar safety and clinical profile but with larger effective dose ranges. To this aim, a better understanding of the mechanisms responsible for the unique properties of CBD is essential. The behaviour studies reviewed here clearly indicate that more than one mechanism is involved, depending on the effects being measured (anxiolytic, anti-compulsive, antidepressant or antipsychotic-like) and the drug regime (single versus repeated administration). Facilitation of 5-HT_{1A}-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex, seems responsible for CBD acute anxiolytic-like effects. Other CBD effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, facilitation of adult hippocampal neurogenesis and blockade of the anxiogenic consequences of chronic unpredictable stress could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD. In addition to these mechanisms, CBD can interfere in several other important biological processes (e.g. inhibition of adenosine uptake, inverse agonism at CB₂ receptor, CB₁ receptor antagonism, GPR55 antagonism, PPAR γ receptors agonism, intracellular (Ca²⁺) increase, etc.). Additional *in vivo* studies are clearly needed to investigate their possible involvement on CBD behavioural effects.