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A Critical Review of the Antipsychotic Effects of Cannabidiol: 30 Years of a Translational Investigation

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Abstract: Δ^9-tetrahydrocannabinol (Δ^9-THC) is the main compound of the *Cannabis Sativa* responsible for most of the effects of the plant. Another major constituent is cannabidiol (CBD), formerly regarded to be devoid of pharmacological activity. However, laboratory rodents and human studies have shown that this cannabinoid is able to prevent psychotic-like symptoms induced by high doses of Δ^9-THC. Subsequent studies have demonstrated that CBD has antipsychotic effects as observed using animal models and in healthy volunteers. Thus, this article provides a critical review of the research evaluating antipsychotic potential of this cannabinoid. CBD appears to have pharmacological profile similar to that of atypical antipsychotic drugs as seem using behavioral and neurochemical techniques in animal models. Additionally, CBD prevented human experimental psychosis and was effective in open case reports and clinical trials in patients with schizophrenia with a remarkable safety profile. Moreover, fMRI results strongly suggest that the antipsychotic effects of CBD in relation to the psychotomimetic effects of Δ^9-THC involve the striatum and temporal cortex that have been traditionally associated with psychosis. Although the mechanisms of the antipsychotic properties are still not fully understood, we propose a hypothesis that could have a heuristic value to inspire new studies. These results support the idea that CBD may be a future therapeutic option in psychosis, in general and in schizophrenia, in particular.

Keywords: Cannabidiol, CBD, cannabis, antipsychotic, psychosis.

INTRODUCTION

The first evidence that cannabidiol (CBD), a non-psychoactive component of *Cannabis sativa*, could have antipsychotic properties was published in 1982 [1]. This initial study investigated the interaction between Δ^9-tetrahydrocannabinol (Δ^9-THC), the main active constituent of the plant, and CBD in health volunteers. The co-administration of the two cannabinoids induced less anxiety and psychotomimetic symptoms than Δ^9-THC alone. At that time it was suggested that CBD attenuation of Δ^9-THC effects depended on a pharmacodynamic rather than pharmacokinetic interaction, since it had been shown that, at the CBD dose used, the drug did not change Δ^9-THC levels in blood [2]. The possible antipsychotic effect of CBD received further support later that year with the report of a higher frequency of acute psychotic episodes in patients admitted in psychiatric hospital after the use of a variety of cannabis virtually devoid of CBD [3]. These initial results led to a series of studies that have established, from laboratory bench to patients, a clear link between CBD and antipsychotic activity. Therefore, the present article provides a critical review of the research evaluating antipsychotic potential of this cannabinoid.

EVIDENCE FROM ANIMAL MODELS

A summary of studies that have investigated the antipsychotic effects of CBD in animal models is shown in Table **1**.

CBD produced effects similar to haloperidol, a typical antipsychotic drug, in apomorphine–induced stereotyped behavior and hyperlocomotion induced by both D-amphetamine and ketamine [4, 5]. Unlike haloperidol, CBD increased prolactin levels only at doses higher than those needed to block stereotyped behavior and did not cause catalepsy even at very high doses [4]. This profile is similar to clozapine, an atypical antipsychotic drug [5]. Some discrepancies, however, have been observed in hyperlocomotion tests. Unlike ketamine, the increase in locomotor behavior induced by the more potent non-competitive antagonist of glutamate NMDA-receptors MK-801 was not attenuated by CBD [9]. Also, Long *et al*, [8] failed to find a decrease in amphetamine-induced hyperlocomotion by acute doses of CBD, although chronic treatment with this drug was effective. Differences in rodent strains, CBD administration regime and the drug used to induce hyperlocomotion could help to explain these discrepancies.

Contradictory results were also observed regarding the effects of CBD in disruption of the prepulse inhibition (PPI) by MK-801. A study in mice found a significant reversal of PPI disruption [6] while in rats this effect was not observed [9]. An increase in PPI response was also observed with acute and chronic administration of CBD in mice [8]. Although this result is not indicative of an antipsychotic action, it suggests an effect that goes to the opposite direction from that produced by drugs that induce psychotic symptoms. In addition, CBD was effective in attenuating social withdrawal induced by Δ^9-THC in rats [7], but only partially effective to produce this same effect induced by MK-801 in mice [9]. As pointed out above, differences in rodent species could be one of the reasons for these contradictory results.

Taken together, and even considering some conflicting results, preclinical data indicate that CBD does possess antipsychotic properties, having a profile compatible with atypical antipsychotics. Consistent with this suggestion, studies investigating changes in the expression of the proto-oncogene c-Fos showed that both CBD and clozapine, but not haloperidol, are able to increase this expression in the prefrontal cortex, while only haloperidol enhanced c-Fos expression in the dorsal striatum [10, 11].

SAFETY STUDIES

Safety and side effect studies of CBD were required before human administration. Extensive *in vivo* and *in vitro* reports of

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Table 1. Antipsychotic Effects of CBD in Animal Models

Reference	Animal	Model	Drug (dose-mg/kg)	Dose with significant results (mg)
Zuardi *et al*. [4]	Rats	Apomorphine stereotypy	CBD (15, 30, 60)	60
			Haloperidol (0.125, 0.25, 0.5)	0.5
		Prolactin levels	CBD (15,30,60,120,240)	240
			Haloperidol (0.06, 0.125,0.25, 0.5)	0.125, 0.25, 0.5
		Catalepsy	CBD (60,120,240, 480)	-
			Haloperidol (0.125,0.25, 0.5, 1.0)	0.25, 0.5, 1.0
Moreira & Guimarães [5]	Mice	Amphetamine hyperlocomotion	CBD (15, 30, 60)	30, 60
			Haloperidol (0.15, 0.3, 0.6)	0.15, 0.3, 0.6
			Clozapine (1.25, 2.5, 5.0)	5
		Ketamine hyperlocomotion	CBD (15, 30, 60)	30 (<0.1)
			Haloperidol (0.15, 0.3, 0.6)	0.3, 0.6
			Clozapine (1.25, 2.5, 5.0)	1.25, 2.5, 5
		Catalepsy	CBD (15, 30, 60)	-
			Haloperidol (0.15, 0.3, 0.6)	0.15, 0.3, 0.6
			Clozapine (1.25, 2.5, 5.0)	-
Long *et al*. [6]	Mice	MK-801 – PPI disruption	CBD (5)	5
			Clozapine (4)	4
Malone *et al*. [7]	Rats	Δ^9-THC- social withdrawal	CBD (5, 20)	20
Long *et al*. [8]	Mice	Dexamphetamine hyperlocomotion	CBD (1, 50)	-
			Chronic (21 days) CBD (1, 5, 10, 50)	50
		PPI - increase	CBD (1, 5, 10, 50)	1, 5, 50
			Chronic (18 days) CBD (1, 5, 10, 50)	1
Gururajan *et al*. [9]	Rats	MK-801 – PPI disruption	CBD (3, 10, 30)	-
			Clozapine (1, 3, 10)	-
		MK-801 – hyperlocomotion	CBD (3, 10, 30)	-
			Clozapine (1, 3, 10)	3, 10
		MK-801 – social withdrawal	CBD (3, 10, 30)	3, 10 (partially)
			Clozapine (1, 3, 10)	1

CBD administration across a wide range of concentrations, did not detect important side or toxic effects [12]. In addition, the acute administration of this cannabinoid by different routes did not induce any significant toxic effect in humans. Moreover, chronic administration of CBD for one month to healthy volunteers (daily doses ranging from 10 to 400 mg), did not induce any significant abnormalities in neurological, psychiatric or clinical exams [13]. The same positive profile has been observed in patients with Huntington's disease (daily fixed doses of 700 mg) [14]. Also, chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans. Although some studies reported that CBD can induce some minor side effects, including inhibition of hepatic drug metabolism, the available clinical data suggest that CBD can be safely administered over a wide dose range confirming results from animal studies [12],

EVIDENCE FROM STUDIES WITH HEALTHY VOLUNTEERS

A summary of studies that have investigated the antipsychotic effects of CBD in humans is shown in Table **2**.

Table 2 - Antipsychotic Effects of CBD in Human Studies

Reference	Sample	Type of Study	Drug (dose-mg/route)	Main Finding
Healthy subjects				
Zuardi *et al.* 1982 [1]	8 healthy volunteers	Co-administration of CBD and Δ^9-THC	0.5 mg/kg Δ^9-THC, 1 mg/kg CBD, a mixture containing 0.5 mg/kg Δ^9-THC and 1 mg/kg CBD and placebo, oral	The co-administration of CBD and Δ^9-THC induced less psychotomimetic symptoms than Δ^9-THC alone
Bhattacharyya *et al*, 2010 [15]	6 healthy volunteers	Co-administration of CBD and -Δ^9-THC	5mg CBD, or placebo administered immediately before 1.25 Δ^9-THC, both IV	Positive psychotic symptoms induced by Δ^9-THC were reduced by CBD
Leweke *et al*, 2000 [17]	9 healthy volunteers	Co-administration of CBD and nabilone, cross-over, double blind, controlled with placebo	200 mg CBD and 1mg nabilone, oral	CBD attenuated the impairment effects induced by nabilone
Morgan and Curran, 2008 [18]	140 drug users and non-users subjects	Δ^9-THC/CBD ratios in hair samples (20 with Δ^9-THC only the hair; 27 with Δ^9-THC + CBD; and 85 with no cannabinoids in hair)	Smoked cannabis in naturalistic settings	Subjects with Δ^9-THC only showed higher levels of positive psychotic symptoms than the groups with Δ^9-THC + CBD or non cannabinoids in hair
Morgan *et al*, 2010 [20]	134 acutely intoxicated cannabis users	Users were tested 7 days apart on measures of memory and psychotomimetic symptoms, once while they were drug free and once while acutely intoxicated	Intoxicated by their own chosen smoked cannabis	Subjects who smoked cannabis high in CBD showed no memory impairment, whereas the ones who smoked cannabis low in CBD presented marked impairment in prose recall of individuals. CBD content did not affect psychotomimetic symptoms, which were elevated in both groups when intoxicated.
Morgan *et al*, 2011 [19]	120 current cannabis smokers (66 daily users and 54 recreational users)	Δ^9-THC/CBD ratios in hair samples. Subjects were classified according to the presence or absence of CBD and high versus low levels of Δ^9-THC	Acute effects of smoked cannabis in naturalistic settings	CBD had a protective effect on positive psychotic symptoms and in the recognition memory impairment related to Δ^9-THC daily use, in subjects with high levels of Δ^9-THC.
Hallak *et al*, 2010 [22]	10 healthy volunteers	Ketamine model of psychosis	600 mg, oral	CBD increased psychomotor activation and reduced depersonalization symptoms
Clinical Trials				
Zuardi *et al*, 1995 [24]	19-year old female patient with schizophrenia	Open trial, four weeks of CBD	Up to 1500mg, oral	CBD reduced BPRS psychotic scores
Zuardi *et al*, 2006 [25]	Three treatment-resistant patients with schizophrenia	Open trial, 30 days of CBD	Up to 1280mg, oral	One patient had partial improvement; another a slight and the third no response.
Zuardi *et al*, 2009 [26]	Six Parkinson´s Disease (PD) with psychotic symptoms	Open trial, four weeks of CBD plus the usual antiparkinsonian drug	150 to 400mg/day, oral	BPRS and PPQ were significantly reduced.

(Table 2) Contd....

Reference	Sample	Type of Study	Drug (dose-mg/route)	Main Finding
Leweke *et al*, 2012 [27]	42 patients with schizophrenia or schizophreniform disorder	Double-blind, CBD vs amisulpride, four weeks	800 mg/day, oral	BPRS and PANSS decreased significantly under both treatments, with no difference between them. Less side-effect under CBD.
Leweke *et al*, 2011 [28]	29 First-episode onset schizophrenia	Double-blind, CBD vs placebo, for 14 days with each condition, cross-over	600 mg/day, oral	10 drop-outs in the placebo and one in the CBD treatment group. Eighteen patients completed the 28 days of treatment with a significant reduction in psychotic symptoms during CBD treatment when compared with baseline.
Neuroimaging Studies				
Bhattacharyya *et al*, 2010 [15]	15 healthy controls	Double-blind randomized, cross-over, fMRI, CBD vs Δ^9-THC vs placebo. verbal memory task, a response inhibition task, a sensory processing task, and when viewing fearful faces.	600 mg, oral	CBD and Δ^9-THC presented opposite effects: On activation relative to placebo in the striatum during verbal recall In the hippocampus during the response inhibition task In the amygdala when subjects viewed fearful faces In the superior temporal cortex when subjects listened to speech In the occipital cortex during visual processing
Fusar-Poli *et al*, 2009 [29]	15 healthy controls	Subjects were studied on 3 separate occasions in a double-blind randomized, cross-over, fMRI, CBD vs Δ^9-THC vs placebo. Viewing faces that implicitly elicited different levels of anxiety	600mg, oral	Δ^9-THC increased anxiety, intoxication, sedation, and psychotic symptoms, whereas there was a trend for a reduction in anxiety with CBD. Number of SCR fluctuations increased with Δ^9-THC but decreased with CBD CBD attenuated the BOLD signal in the amygdala and the ACC and PCC Δ^9-THC mainly modulated activation in frontal and parietal areas.
Bhattacharyya *et al*, 2009 [30]	15 healthy controls	Subjects were studied on 3 separate occasions in a double-blind randomized, cross-over, fMRI, CBD vs Δ^9-THC vs placebo. Verbal paired associate learning task.	600mg, oral	Δ^9-THC augmented activation in the parahippocampal gyrus across repeated encoding blocks. Δ^9-THC attenuated the time-dependent change in ventrostriatal activation during retrieval of word pairs, which was directly correlated with concurrently induced psychotic symptoms. CBD had no such effects.
Bhattacharyya *et al*, 2011 [31]	15 healthy controls	Subjects were studied on 3 separate occasions in a double-blind randomized, cross-over, fMRI, CBD vs Δ^9-THC vs placebo. Novelty salience detection paradigm	600 mg, oral	Δ^9-THC attenuated the dorsal striatum and hippocampus activation, but augmented in the prefrontal cortex. Δ^9-THC in the dorsal striatum was negatively correlated with both the severity of the psychotic symptoms it induced, and its effect on response latency. CBD on task-related activation was in the opposite direction to those of dΔ^9-THC: relative to placebo. CBD augmented striatal and hippocampal activation, but attenuated prefrontal activation.

(Table 2) Contd....

Reference	Sample	Type of Study	Drug (dose-mg/route)	Main Finding
Borgwardt *et al*, 2008 [32]	15 healthy controls	Subjects were studied on 3 separate occasions in a double-blind randomized, cross-over, fMRI, CBD vs Δ^9-THC vs placebo. Motor inhibition task (GO/No-Go)	600 mg, oral	Δ^9-THC attenuated activation in the right inferior frontal and the ACC gyrus, whereas CBD deactivated the left temporal cortex and insula.
Winton-Brown *et al*, 2011 [33]	15 healthy controls	Subjects were studied on 3 separate occasions in a double-blind randomized, cross-over, fMRI, CBD vs Δ^9-THC vs placebo. Visual and auditory processing task (listened passively to words read and viewed a radial visual checkerboard)	600 mg, oral	Δ^9-THC deactivated bilateral temporal cortices during auditory processing, and increased and decreased activation in different visual areas during visual processing. CBD was associated activated the right temporal cortex during auditory processing, Δ^9-THC and CBD had opposite effects in the right posterior superior temporal gyrus, the right-sided homolog to Wernicke's area.

That first report showing that CBD is able to reduce psychotic symptoms induced by Δ^9-THC [1] has been recently replicated using specific scales for assessing the severity of psychotic symptoms [15]. In this study six health volunteers, in a pseudorandomized, double blind, within-subject design, received CBD or placebo intravenously (IV) five minutes before Δ^9-THC administered by the same route. Positive psychotic symptoms induced by Δ^9-THC at 30 minutes after the administration were significantly lower under CBD than placebo pretreatment.

Another model used to evaluate possible antipsychotic effects of new drugs is the perception of binocular depth inversion. In this model, patients with schizophrenia and healthy volunteers treated with psychotomimetic drugs have difficulty in perceiving an illusory change in convexity induced by inversion of familiar pictures from one eye to the other [16]. CBD was able to attenuate the impairment effect induced by nabilone, a synthetic analogue of Δ^9-THC, in this model, suggesting an antipsychotic-like activity of this compound [17].

An indirect evidence of an antipsychotic effect of CBD was provided by a study who analyzed the ratio of Δ^9-THC/CBD in hair samples of subjects screened for cannabis use. The subjects were allocated into three groups: only Δ^9-THC, Δ^9-THC plus CBD and no cannabinoids in hair. The group with only Δ^9-THC in hair showed higher levels of positive schizophrenia-like symptoms than the groups with Δ^9-THC plus CBD or non cannabinoids in hair. This result suggests that the presence of CBD in the strain of cannabis smoked has a protective action against the psychotic symptoms induced by Δ^9-THC [18]. Recently these findings were replicated in recreational users with higher levels of Δ^9-THC in their hair. This study also indicated that CBD had a protective effect on recognition memory impairment related to Δ^9-THC daily use, in subjects with high levels of Δ^9-THC [19]. Another naturalistic study of the same group compared individuals acutely intoxicated by samples of cannabis with high and low CBD content. They observed that CBD was protective against memory impairment induced by Δ9-THC. In this study, however, the presence of CBD did not change the increase in psychotomimetic symptoms induced by the latter drug [20]. The lack of protective effect of CBD on THC-induced psychotomimetic symptoms could be related to a smaller CBD /THC ratio, compared to the other studies mentioned earlier, where this effect was observed [1, 15].

An additional procedure that has been used to induce psychotic symptoms in healthy volunteers is the administration of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine [21]. In this model, which is based on the glutamatergic hypothesis of schizophrenia, CBD increased psychomotor activation [21], but reduced depersonalization symptoms [22, 23]. Although these results suggest a complex interaction between the glutamate and cannabinoid systems, the latter effect has been previously described with CBD/Δ^9-THC interaction [1] and reinforces a possible antipsychotic effect of CBD.

EVIDENCE FROM CLINICAL TRIALS

For ethical reasons, the first clinical trials with CBD were open-labeled and with a small number of patients. The first one was a case-study with a 19-year old female patient with schizophrenia. The rationale of the trial was the presence of serious side effects the patient was experiencing with previous antipsychotic drugs. After hospitalization and a wash-out period of four days the patient was treated for four weeks with increasing doses of CBD up to 1,500 mg/day. Then this treatment was replaced by placebo for four days followed by haloperidol treatment at increasing doses up to 12.5 mg/day. CBD treatment significantly reduced the scores of the Brief Psychiatric Rating Scales (BPRS). Unfortunately, symptoms worsened when CBD was suspended. Haloperidol decreased BPRS scores, but not beyond the levels reached with CBD [24].

The next open-label clinical trial was made with three male patients with treatment resistant schizophrenia (22 to 23 years old). The protocol included: a first five days period with placebo followed by CBD, from day 6 to 35, placebo for another five days and olanzapine for at least 15 days. CBD and olanzapine doses were increased from 40 mg/day to 1,280 mg/day and from 10 to 20

mg/day, respectively. Under CBD treatment one patient had a partial improvement, another a slight improvement and the third did not respond at all. A worsening of symptoms was observed with CBD interruption in all three patients. Among the three patients, one improved more with olanzapine than with CBD, the other responded only to clozapine and the third did not respond even to clozapine [25].

An open trial with CBD was also performed in six out-patients with Parkinson´s disease (PD) treated with dopaminergic drugs that presented psychotic symptoms. They were administered a flexible oral dose of CBD (150 to 400mg/day) for four weeks, in addition to their usual treatment. The scores of BPRS and Parkinson Psychosis Questionnaire were significantly decreased under CBD treatment. No worsening of motor function or other adverse effects was observed during CBD treatment [26].

The first double-blind controlled clinical trial of CBD in psychotic patients compared its effects with those of amisulpride on 42 acute paranoid schizophrenia or schizophreniform psychosis individuals treated during four-weeks. The scores of BPRS and Positive and Negative Syndrome Scale (PANSS) decreased significantly under both treatments with no differences between them. The side effects (extra pyramidal symptoms, increase in prolactin levels and weight gain) were significantly less observed with CBD than amisulpride [27].

The same research group reported another clinical trial with antipsychotic-naïve, first-episode schizophrenic patients, comparing treatment with CBD or placebo for 14 days in a cross-over condition. There were ten drop-out patients in the placebo and one in the CBD treatment groups. Eighteen patients completed the 28 days of treatment with a significant reduction in psychotic symptoms during CBD treatment when compared with baseline [28].

Taken together, these studies strongly suggest that CBD induces therapeutic effect in psychotic symptoms. However, as will be discussed in the next session, its mechanisms are still unclear.

MODULATION OF REGIONAL BRAIN ACTIVITY BY CBD

Studies aimed at investigating at the same time CBD effects on behavior and regional brain activity could provide an initial clue about its mechanisms and place of action. Functional magnetic resonance imaging (fMRI) was used to study the effects of Δ^9-THC (10 mg) and CBD (600 mg) on activation of several cerebral regions of 15 healthy volunteers during tasks related to modulation of specific brain regions. It was observed that Δ^9-THC and CBD caused opposite effects, relative to the placebo condition, on activation of several cerebral areas, including the striatum, anterior cingulated, prefrontal cortex, parahippocampal gyrus, amygdala, right posterior superior temporal gyrus, middle occipital gyrus and cerebellum [15, 29-33].

The Δ^9-THC dose used in these fMRI studies (10 mg) was able to induce anxiety and psychotic symptoms. Since in the study mentioned earlier [15] the transient psychotic symptoms induced by IV Δ^9-THC (1.25 mg) were attenuated by IV CBD (5mg), it is possible to postulate that the opposing effects of the two cannabinoids on brain activation could be related to their antagonism and to the antipsychotic effect of CBD.

For example, the severity of psychotic symptoms induced by Δ^9-THC was correlated with a decrease in activation of the ventral striatum and anterior cingulated gyrus during word recall of a verbal paired associate learning task [30]; dorsal striatum during "Oddball" stimuli processing [31], and right temporal lobe during auditory processing [33]. As showed in (Fig. **1**), CBD and Δ^9-THC produced opposite effects on activation compared to placebo during specific tasks in the three areas where a correlation was found between the latter drug and psychotic symptoms. CBD was able to increase activation of the ventral striatum during word retrieval, dorsal striatum during visual "Oddball" salience processing and right temporal lobe during auditory processing [15, 31, 33]. Considering that the ventral striatum is an important structure involved in the pathogenesis of schizophrenia [34], these results could reflect a possible brain site where CBD acts to attenuate psychotic-like effects induced by Δ^9-THC [15].

Similar results were observed in the dorsal striatum during the response to "Oddball" relative to "Standard" stimuli [31]. In this study it was observed that under Δ^9-THC effect the "Standard" visual stimuli become more salient. The enhancement of salience of non-salient stimuli seems to be related to psychotic symptoms [35]. There was a significant correlation between the effects of Δ^9-THC on attenuation of activation and its effects on increased salience to non-salient stimuli and positive psychotic symptoms in both the right and left caudate. In the left caudate the effects of CBD were opposite to those of Δ^9-THC, suggesting another possible brain site where CBD exerts its antipsychotic action [31]. The classical division of the striatum into dorsal and ventral has been proposed to be less appropriated than a dorsolateral-to-ventromedial distinction, since the dorsal and ventral division showed many overlap in cognitive functions and similarities in cytology and inputs-outputs [36]. In this view, the dopaminergic mesolimbic pathway represents an input to the medial caudate and nucleus accumbens from the ventral tegmental area and medial substantia nigra. This pathway is involved in reward-based associative learning and salience [34]. Thus, the BOLD responses observed with cannabinoids in dorsal

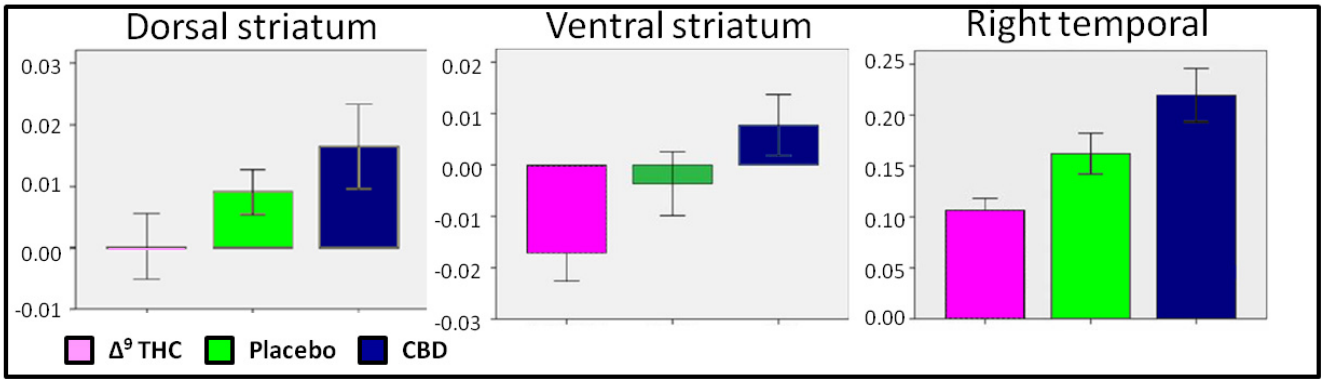

Fig. (1). Bar graph (mean± SEM) of fMRI activation results on: left caudate during visual oddball salience processing; ventral striatum during word retrieval; right temporal cortex during auditory processing. Opposite effects of THC and CBD relative to placebo were observed in these brain areas, in which there was a significant correlation, during specific tasks, between psychotic symptoms and Δ^9-THC attenuation of fMRI activation. Figure based in results showed in references 12, 28 and 29.

and ventral striatum could be related to the same mesolimbic pathway.

The attenuation effect of Δ^9-THC on right temporal lobe activation relative to placebo, during auditory processing, was also associated with an increase in psychotic symptoms [30]. The temporal lobe has been related to psychotic disorder, particularly with auditory hallucinations [37]. The right temporal lobe is thought to have a role in perceiving subordinate meaning of ambiguous words or the comprehension of figurative language [38, 39]. Patients with schizophrenia show impairments in comprehension of figurative language [40]. Again, the opposite effect of CBD and Δ^9-THC in this brain region could also be related to the opposed effects of the two cannabinoids in psychotic symptoms.

In summary, these fMRI results strongly suggest that the antipsychotic effects of CBD, at least in relation to the psychotomimetic effects of Δ^9-THC, involve two brain areas, the striatum and temporal cortex, that have been traditionally associated with psychosis.

MOLECULAR BASIS OF THE ANTIPSYCHOTIC EFFECT OF CBD

Several mechanisms of action have been associated to CBD effects. Most of the studies that have investigated these mechanisms, however, have been performed *in vitro* and their relevance for the *in vivo* effects of this drug is still uncertain. For example, in spite of its low affinity for CB1 receptor (CB1R), CBD is capable of antagonizing CB1R agonists at reasonable low concentrations [41]. Although this would decrease endocannabinoid-mediated neurotransmission, CBD can also inhibit anandamide uptake and metabolism [42], enhancing, rather than decreasing, endocannabinoid tonus.

Since the acute administration of Δ^9 THC, an exogenous CB1R agonist, can induce psychotic symptoms in healthy volunteers [43, 44] and a transient exacerbation of psychosis in patients with schizophrenia [45], it is possible to attribute the antipsychotic action of CBD to an antagonism of CB1R. Arguing against this possibility however, is a double-blind, controlled trial with a high number of patients with schizophrenia in which SR141716, a CB1R antagonist, failed to show any antipsychotic effect [46]. Moreover, Δ^9 THC is as a partial agonist of CB1R with less efficacy than anandamide (AEA) and even less than 2-arachidonoylglycerol (2-AG). Hence, depending on several factors such as the density and coupling efficiency of the receptor [47], the fire rate of neurons [48] or agonist concentration [49], Δ^9 THC can either facilitate or decrease endocannabinoid-mediated neurotransmission. Therefore, one alternative hypothesis is that the antipsychotic effect of CBD depends on increased anandamide availability resulting from the blockade of its uptake and metabolism. Higher concentrations of anandamide in cerebrospinal fluid (CSF) of patients with schizophrenia in comparison to healthy controls and patients with affective disorder and dementia have been described [50]. These concentrations were negatively correlated with psychotic symptoms, suggesting that the anandamide increase involves a negative feedback response to counterbalance psychotic symptoms [51]. This suggestion was reinforced by the observation that patients in the initial prodromal states of psychosis had higher levels of anandamide in CSF than health controls. Moreover, this study also found a trend for a longer interval to reach the full-psychotic picture in patients with more elevated anandamide levels [52]. In the double-blind study that showed a therapeutic effect of CBD in patients with schizophrenia it was also observed that this compound induced a significant increase in anandamide levels in the CSF and that this elevation was associated with clinical improvement [28].

If anandamide participates in the antipsychotic effect of CBD, the neuronal circuitry involved is far from being understood. Several brain areas, including the ventral tegmental area (VTA), the nucleus accumbens, the ventral pallidum, the mediodorsal thalamic nucleus and the prefrontal cortex, have been associated with the pathophysiology of schizophrenia [53]. Studies with animal models of psychosis in rodents suggest that a "supersensitive" response of dopaminergic receptors in the nucleus accumbens induces an inhibition of local GABA neurons with a reduction of GABA release from terminals in the ventral pallidum [54]. Actually, the medium-spiny GABAergic neurons constitute about 95% of the neurons of nucleus accumbens. These cells, which are inhibited by activation of D2-like receptors [55, 56], send inhibitory GABAergic projections to the ventral pallidum [57, 58]. Thus, dopamine release in the nucleus accumbens by projections from the ventral tegmental area (VTA) could reduce the inhibition of ventral pallidum GABAergic neurons, resulting in increased activity of the pallidum-mediodorsal thalamus. As a consequence, there would be a decrease in glutamatergic inputs from this area to the prefrontal cortex, impairing locomotor activity and working memory [59]. Endocannabinoids could regulate this system. They are synthesized "on demand" in post-synaptic neurons, acting pre-synaptic terminals and negatively regulating the release of neurotransmitters, particularly GABA and glutamate [60]. In the basal ganglia CB1 receptors are located mainly in axon terminals of GABAergic rather than glutamatergic neurons [61]. Thus, an increase in anandamide levels induced by CBD could attenuate GABA release from ventral pallidum neurons, restoring the normal function of this system in psychotic patients. An illustration of this hypothesis is presented in (Fig. **2**).

CBD can also increase adult neurogenesis in mice and that this effect has been shown to be dependent on the CB1 receptors [62]. Decrease in hippocampal neurogenesis was observed in schizophrenic but not in unipolar depression patients compared with control subjects [63]. Based on this observation and in the common neuropathological hippocampal findings in those patients, it was proposed that altered adult neurogenesis could contribute to cognitive deficits and other symptoms of schizophrenia [64].

In addition to the mechanisms discussed above, CBD can produce several other effects (for a review, see 65) that could also be involved to be responsible for its antipsychotic properties, including interaction with 5HT1A and TRPV1 receptors and anti-inflammatory/neuroprotective effects [66, 67].

CBD can act as a serotonin 1A receptor (5HT1A) agonist [42, 67] and recent studies have indicated that its acute anxiolytic and antidepressant-like effects are dependent on this mechanism [68-70]. Although the role of 5-HT1A-mediated neurotransmission in schizophrenia is unclear, aripiprazole, an atypical antipsychotic, acts as a partial agonist at this receptor, an effect that could, together with its actions on D2 and 5-HT2A receptors, contribute to therapeutic effects of this drug [71].

However, studies with rodents show that the dose range for the anxiolytic effects of CBD (5-20 mg/kg in rats, [72, 73] is smaller than that effective in animal models aimed at detecting antipsychotic effects (60-120 mg/kg) [4]. Moreover, the dose-response curve for the anxiolytic effect is bell-shaped, with larger doses being ineffective [72, 73].

In addition to 5HT1A, CBD can also activate Transient Receptor Vanilloid-1 (TRPV1) receptors [42, 67]. These receptors are expressed in several brain areas related to psychosis such as the prefrontal cortex, amygdala and hippocampus [74]. Their putative endogenous agonists are lipid compounds that have been named endovanilloids (EVs), the most studied being anandamide [75]. Activation of pre-synaptic TRPV1 receptors, contrary to CB1 receptors, can facilitate glutamate release [76]. These opposite effects have been related to the bell-shaped dose responses curves observed both with anandamide and CBD [77]. As described above, antipsychotic-like doses of CBD in rats (120 mg/kg) was able to increase neuronal activation (measure by cFos immunohistochemistry) in the medial prefrontal cortex, and effect that is not observed when anxiolytic (10 mg/kg) doses were used [78]. As depicted in (Fig. **2**), then, facilitating of glutamate-mediated activation of the prefrontal

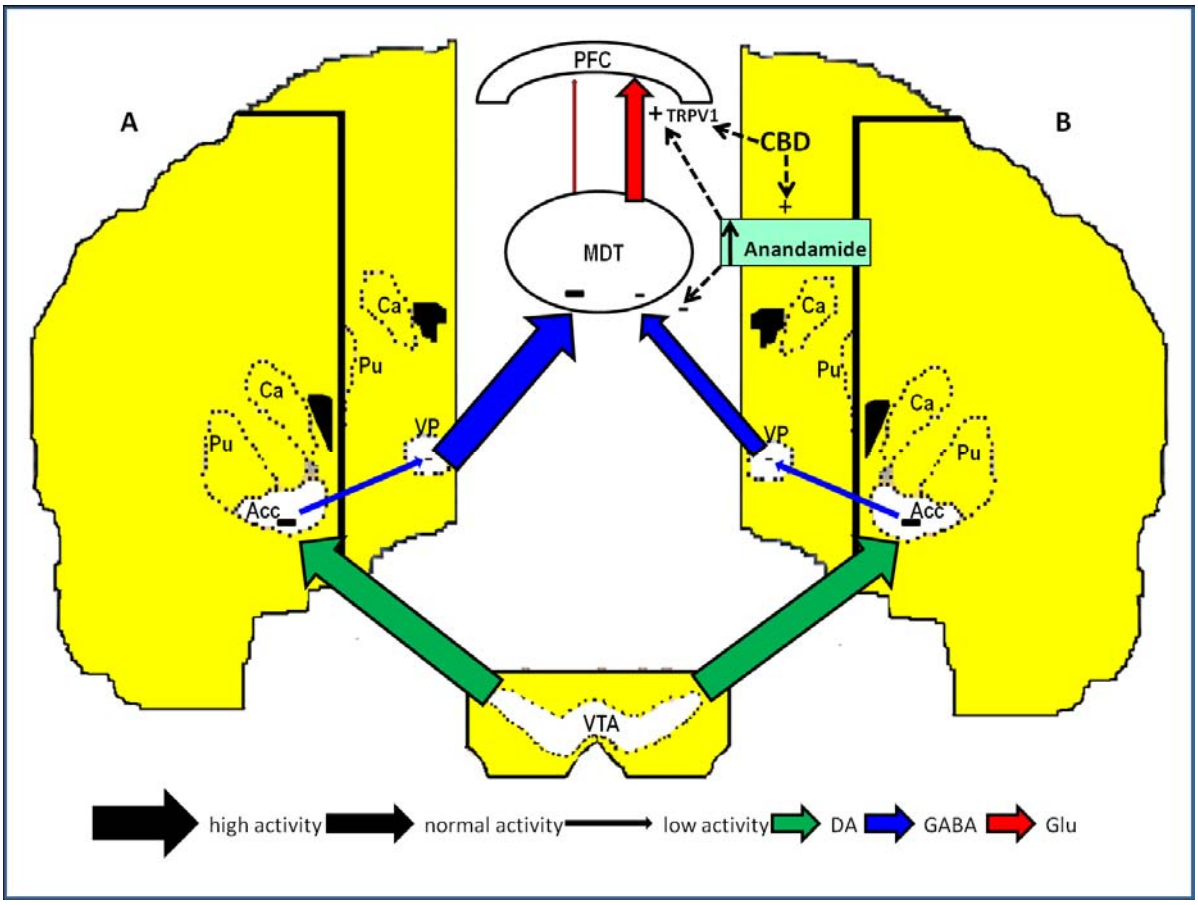

Fig. (2). Illustration of a hypothetical neural circuit involved in the antipsychotic effect of CBD. (**A**)- Changes in the ventral tegmental area (VTA) – nucleus accumbens (Acc) – ventral pallidum (VP) – mediodorsal thalamus (MDT) –prefrontal cortex (PFC) sub-circuit mediating psychotic symptoms. (**B**) – Normalization of these changes by the CBD action counterbalancing the decrease of the glutamate activity in the frontal cortex, directly through TRPV1 agonism and indirectly by the increase in anandamide-mediated CB1 activation, causing decrease in GABA release.

cortex by direct and indirect (enhancing anandamide levels) mechanisms could also be related to CBD effects. Supporting this possibility, the antipsychotic-like effects of CBD on MK-801 (a glutamate non-competitive antagonist)-induced disruption of PPI was prevented by a TRPV1 antagonist [6].

Recent studies have shown that minocycline, a broad-spectrum tetracycline antibiotic, has therapeutic effect in schizophrenia as an add-on treatment. The mechanisms of this effect are still unclear, but could be related to the anti-inflammatory and neuroprotective actions of this drug [79-81]. Since CBD is also a potent anti-inflammatory, antioxidant and neuroprotective compound [66], it is possible that these effects are involved in its antipsychotic action.

CONCLUSIONS

Taken together, the results discussed above clearly indicate that CBD behaves in preclinical and clinical studies as an atypical antipsychotic, improving psychotic-like symptoms in doses that do not impair motor function. The mechanisms of these properties, however, are still not completely understood. One possibility, put forward in the present review (Fig. **2**), is that they depend on direct (TRPV1 agonism) and indirect (increase in anandamide-mediated CB1 activation, causing a decrease in GABA release) facilitation of glutamate activity in the prefrontal cortex. Even considering that it is an oversimplification, since it does not take into account other possible CBD mechanisms, we hope the hypothesis will have enough heuristic value to inspire new studies. Considering the need for new and effective antipsychotic and the remarkable safety profile of this compound, these studies will be most welcome.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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