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Emerging evidence for the antidepressant effect of cannabidiol and the underlying molecular mechanisms

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ABSTRACT

Significant limitations with the currently available antidepressant treatment strategies have inspired research on finding new and more efficient drugs to treat depression. Cannabidiol (CBD) is a non-psychotomimetic component of *Cannabis sativa*, and emerges in this regard as a promising compound. In 2010, we were the first laboratory to demonstrate that CBD is effective in animal models of predictive of antidepressant effect, a finding now confirmed by several other groups. Recent evidence suggests that CBD promotes both a rapid and a sustained antidepressant effect in animal models.

CBD has a complex pharmacology, with the ability to interact with multiple neurotransmitter systems involved in depression, including the serotonergic, glutamatergic, and endocannabinoid systems. Moreover, CBD induces cellular and molecular changes in brain regions related to depression neurobiology, such as increased Brain Derived Neurotrophic Factor (BDNF) levels and synaptogenesis in the medial prefrontal cortex, as well as it increases neurogenesis in the hippocampus. This review presents a comprehensive critical overview of the current literature related to the antidepressant effects of CBD, with focus at the possible mechanisms. Finally, challenges and perspectives for future research are discussed.

1. Introduction

Major depressive Disorder (MDD) is a disabling psychiatric disorder characterized by depressed mood or anhedonia for at least two weeks, accompanied by sleep and eating dysregulation, psychomotor changes, feeling of guilt, and in more severe cases, suicidal thoughts (APA, 2013). The World Health Organization (WHO) estimates that depression affects 322 million people worldwide (WHO et al., 2017), with a life-time prevalence of 20% (Hasin et al., 2018; Kessler and Bromet, 2013). It contributes to 2.5% of the global burden of disease, corresponding to more than 70 million disability-adjusted life years, emerging as a leading cause of disability worldwide (GBD, 2016, 2017). Moreover, MDD is associated with an increased risk of all-cause mortality, and a reduced life expectancy (Chang et al., 2011; Laursen et al., 2016). As a consequence, MDD has a considerable socioeconomic impact. According to the European Brain Council (Gustavsson et al., 2011), the total estimated cost with brain disorders in Europe, considering direct and indirect medical expenses, was approximately US$ 904.9 billion in 2010, with MDD representing the most costly (approximately US$ 128.6 million) (Gustavsson et al., 2011). An analysis of global return of investment estimated that the global economy loses about US$1 trillion every year in productivity due to depression and anxiety and that the appropriate treatment of depression would result in an economic gain of US$230 billion (Chisholm et al., 2016).

Despite the availability of many clinically effective antidepressants (Cipriani et al., 2018), we still face a lot of challenges regarding optimal treatment of depression. For example, antidepressants take several weeks (4 to 6 weeks) to promote significant mood-improving effects (Cipriani et al., 2018), and around 40–45% of the patients are partial or non-responders (Keks et al., 2007). In addition, all current clinically available antidepressants affect almost only monoaminergic neurotransmission, including many new drugs with similar pharmacology. Therefore, patients with depression could benefit from better and more effective medication with new mechanisms of action. These facts have initiated the search for new non-monoamine-based compounds, which potentially could overcome the limitations of antidepressants in use

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Interestingly, drugs with multimodal mechanism of action beyond monoaminergic neurotransmission have attracted considerable interest as putative treatment options in depression (Ceskova and Silhan, 2018). In this context, cannabidiol (CBD) represents a new promising molecule due to its broad-spectrum pharmacological profile. CBD is the second most abundant phytocannabinoid constituent in the plant *Cannabis sativa*, after Δ^9-tetrahydrocannabinol (Δ9-THC). Contrasting with Δ9-THC effects, it is not toxic in humans and animals (Russo and Marcu, 2017). CBD has a complex pharmacology, which may contribute to its large-spectrum therapeutic profile in different psychiatric disorders, including the ability to reduce psychotic, anxiety, and withdrawal symptoms (Mandolini et al., 2018). A potential antidepressant effect of CBD was first reported by our group in 2010 (Zanelati et al., 2010), initiating a new area of investigation about the therapeutic potential of this drug in depression. Although studies investigating the effects of CBD in animal models of depression are surprisingly few, the evidence reviewed here suggests that CBD could have potential for being a new treatment option in MDD.

2. Overview of depression neurobiology and potential treatment targets

Environmental and genetic factors play a significant role in the development of depression (Kendler KS, Gardner CO, 2006; Wichers et al., 2007). It has been long recognized that stress, including childhood adversity and adult negative life events, is a major factor predisposing individuals to depression (Kendler et al., 1999; Kendler and Gardner, 2016; Wichers et al., 2007). Genetic factors are proposed to influence individual sensitivity to stress, hindering them more susceptible or resilient to adverse life events (Caspi et al., 2003; Kendler KS, Gardner CO, 2006; Wichers et al., 2009). Accordingly, animal models involving stress exposure and genetic manipulations have been increasingly used to investigate the neurobiological mechanisms of behavioral dysfunctions associated with depression (for review, McArthur and Borsini, 2006; Söderlund and Lindskog, 2018).

Almost all known antidepressants act by increasing monoamines levels, primarily serotonin and noradrenaline, in the brain. This fact has given support for the so-called monoaminergic hypothesis of depression (Coppen et al., 1973; Pare and Sandler, 1959; Schildkraut, 1965). This hypothesis has been further encouraged over the years by cumulative evidence of impaired serotonergic neurotransmission in limbic brain regions of animals exposed to unpredictable stressful situations or in depressed patients (Albert and Benkelfat, 2013; Paul and Lowry, 2013). Accordingly, drugs that inhibit monoamine uptake or metabolism, or activate 5-HT1 A receptors, facilitate adaptation to stress and are effective antidepressants in humans (Cipriani et al., 2018; Hamon and Blier, 2013). Seminal works from the 90 s confirmed that the therapeutic effects of antidepressant drugs are, in fact, dependent on brain monoamine levels. Depletion of serotonin and noradrenaline abolished the antidepressant effect of selective serotonin (SSRIs) and noradrenaline (SNaRIs) reuptake inhibitors, respectively, in previously remitted patients (Delgado et al., 1990; Heninger et al., 1996).

However, despite the evidence about the involvement of monoamines in antidepressant mood-improving effects, the clinical observation that it takes 2–4 weeks of continuous treatment to achieve the therapeutic effect indicated that additional molecular mechanisms might participate in depression resolution (Blier and El-Mansari, 2013). It has been consistently shown that chronic antidepressant treatment, regardless of their pharmacological class, increases brain neuroplasticity in brain regions related to stress and depression depression neurobiology (Kraus et al., 2017). For instance, chronic antidepressant treatment increases the levels of brain-derived neurotrophic factor (BDNF) in prefrontal cortex (PFC) and hippocampus (Castrén and Rantamäki, 2010a). BDNF is a neurotrophin with crucial importance for synaptogenesis, cell proliferation, and repair in developing and adult central nervous system (CNS) (Castrén and Rantamäki, 2010a). Accordingly, increased synaptogenesis and hippocampal neurogenesis are also observed after chronic antidepressant treatment (Bambico and Belzung, 2013; Dwyer and Duman, 2013). More importantly, antidepressants attenuate the impaired neuroplasticity found in the brains of stressed animals and depressed individuals (Castrén and Rantamäki, 2010b). A causal link between increased neuroplasticity and antidepressant effect has been suggested based on the experimental observation that blocking BDNF signaling (Adachi et al., 2008) or inhibiting neurogenesis (Tanti and Belzung, 2013) also prevents the behavioral effect of antidepressant drugs.

Evidence about new fast-acting antidepressant and their mechanism of action has given further support to the involvement of neuroplasticity mechanisms in depression neurobiology and treatment. The groundbreaking discovery in this field was the observation that ketamine induces rapid and sustained antidepressant effect in animal models and in humans, including treatment-resistant patients (Autry et al., 2012; Berman et al., 2000; Diazgranados et al., 2010; Kishimoto et al., 2016; Li et al., 2010; Maeng et al., 2008; Zarate et al., 2006). The mechanism of action of ketamine is not fully elucidated, but probably involves multiple targets. It acts as a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors (Kohrs and Durieux, 1998; White et al., 1982) but can facilitate the effects of AMPA (Maeng et al., 2008) and serotonergic receptors (5-HT1 A and 5-HT1B; Du Jardin et al., 2018; Fukumoto et al., 2017), among others (Fukumoto et al., 2017; Haj-Mirzaian et al., 2014; Martin and Smith, 1982; Moaddel et al., 2013). The increase in BDNF-TrkB-mTOR signaling (Autry et al., 2012; Li et al., 2010), and subsequent increased synaptic plasticity in the PFC and hippocampus (Li et al., 2010; Park et al., 2014), has been particularly associated with ketamine rapid mood effects. Thanks to ketamine´s unique effects, the glutamatergic neurotransmission and modulation of synaptic plasticity have been the focus of intensive investigation into the neurobiology of depression and the development of new antidepressants with a faster onset of action (Gerhard and Duman, 2018; Zanos et al., 2018).

3. Cannabidiol: potential pharmacological targets of relevance to depression

The *Cannabis sativa* plant have been the focus of human interest for thousands of years. Medicinal preparations from its flowers and resin were used in China around ˜2,700 BC. However, it was only in the 19th century that medical cannabis was introduced into Western medicine through the work of William O'Shaughnessy. Initially, it was indicated for a wide range of medical conditions, until concerns about increased violence, crime, and other socially deviant behaviors following recreational use led to its criminalization in many countries (Small, 2015). After that, research on cannabis advanced slowly due to several factors including the lack of knowledge of its basic chemistry. The development of isolation techniques in the 40´s made it possible to successfully separate and identify the multiple chemical compounds constituting the plant preparations, initiating a new era on cannabis research (for a comprehensive review see e.g. Di Marzo, 2006).

CBD was first isolated in 1940 from cannabis extracts by Adam and colleagues (Adams and Hunt, 1940), but it was not until 1963 that its chemical structure was fully elucidated by Mechoulam and Shvo (Mechoulam and Shvo, 1963). Shortly thereafter, another abundant endocannabinoid, Δ9-THC, was isolated and its chemical structure clarified (Gaoni and Mechoulam, 1964). Currently, more than 100 phytocannabinoids have been identified in the cannabis plant (Small, 2015). While Δ9-THC was recognized as the primary psychoactive compound responsible for marijuana effects, namely euphoria, altered sensory perception, and relaxation, CBD was shown to be non-psychostimulant, with the suggestion that it was an inactive substance (Zuardi, 2008). However, later studies have confirmed this assumption to be wrong, and several studies demonstrated that CBD causes multiple

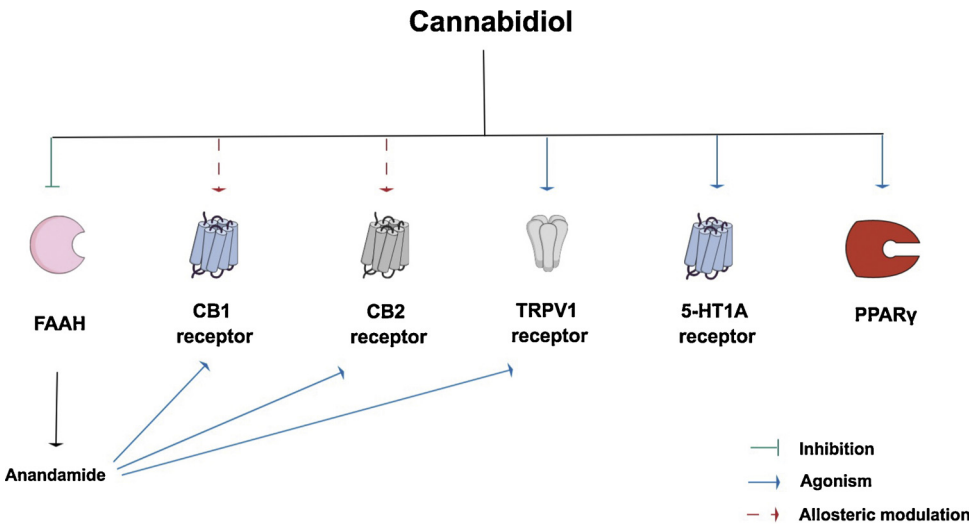

Fig. 1. Main pharmacological targets for cannabidiol investigated in *in vitro* and *in vivo* experiments. Despite having low affinity for CB1 and CB2 receptors, CBD can act as an allosteric modulator at these receptors. CBD inhibits the enzymatic degradation and uptake of anandamide, thus increasing anandamide levels and facilitating endocannabinoid signaling through CB1, CB2, and the vanilloid receptor 1 (TRPV1). Evidence also indicates that CBD can directly bind to 5-HT1 A receptors and PPARγ receptors. A complete overview of CBD mechanisms is presented on Table 1.

effects in the CNS. Interestingly, CBD attenutes the subjective rates of intoxication (Robson, 2011; Schoedel et al., 2011), the anxiogenic (Zuardi et al., 1982), and the psychotomimetic effects induced by Δ9-THC in healthy individuals (Martin-Santos et al., 2012). Furthermore, CBD show promising therapeutic effects on several psychiatric conditions, such as, anxiety (José Alexandre S. Crippa et al., 2011; Guimarães et al., 1990; Moreira et al., 2006; Antonio W. Zuardi et al., 2017), psychosis (Iseger and Bossong, 2015; Moreira and Guimarães, 2005), epilepsy (Crippa et al., 2016; Do Val-da Silva et al., 2017; Gobira et al., 2015), and movement disorders (Peres et al., 2018). The therapeutic potential of CBD in these conditions are reviewed elsewhere, and lies beyond the scope of the present review (Crippa et al., 2018; Mandolini et al., 2018).

The mechanism of action underlying the effects of CBD seems to be complex and involves multiple targets (Izzo et al., 2009) – see Fig. 1).

For example, CBD modulates the endocannabinoid system. The endocannabinoid system consists of the cannabinoid receptors (CB1 and CB2), endogenous ligands (mainly anandamide, AEA, and 2-arachidonoyl glycerol), and processes responsible for endocannabinoid biosynthesis, cellular uptake, and metabolism (Pertwee, 2015). *In vitro* studies show that, despite having a low affinity for cannabinoid receptors, CBD could act as an antagonist on CB1 (Thomas et al., 2007). This may be related to the ability of CBD to act as a negative allosteric modulator on both CB1 and CB2 receptors (Laprairie et al., 2015; Martínez-Pinilla et al., 2017). On the other hand, CBD inhibits the enzymatic degradation and uptake of anandamide (Bisogno et al., 2001), thus facilitating endocannabinoid signaling through CB1, CB2, and the vanilloid receptor 1 (TRPV1) (Pertwee, 2008; Pertwee and Ross, 2002). In fact, increased anandamide levels seems to mediate some of the effects of CBD (Leweke et al., 2012), and increased levels of anandamide produces some effects similar to those seen following administration of CBD administration (Gobbi et al., 2005; Sartim et al., 2016). Moreover, CBD has been reported to directly activate TRPV1 receptors (Bisogno et al., 2001), and some of its action can be blocked by selective TRPV1 antagonists (Campos and Guimarães, 2009).

In addition to the endocannabinoid and endovanniloid system, CBD also acts on the serotonergic system. Preclinical studies show that CBD can facilitate 5-HT1 A-mediated neurotransmission (Russo et al., 2005), and several behavioral effects of CBD seems to be mediated by 5-HT1 A receptors (Campos et al., 2012; Fogaça et al., 2014; Gomes et al., 2011; Sartim et al., 2016; Zanelati et al., 2010). Besides the serotonergic system, CBD can also modulate numerous other different transmitter systems and targets summarized in Table 1.

Interestingly, many of the pharmacological processes known to be modulated by CBD are also dysfunctional targets described to contribute to MDD and/or the behavioral/therapeutic effect of antidepressant drugs (Table 1). Of particular interest is that impaired 5-HT1 A signaling is observed in stressed animals and depression (reviewed by Kaufman et al., 2016). Activation of 5-HT1 A receptors, on the other hand, is a widely proposed mechanism involved in the behavioral effect of antidepressant drugs (for a complete review, see (Blier and El-Mansari, 2013; Carr and Lucki, 2011). Moreover, increasing anandamide levels through inhibition of its uptake or methabolism also promote antidepressant-like effects in preclinical studies (Gorzalka and Hill, 2011; Hillard and Liu, 2014; Micale et al., 2013). These pharmacological pieces of evidence support the assumption of a strong potential antidepressant effect of CBD, which will be discussed in more detail below.

4. Antidepressant effects of CBD

4.1. Evidence from animal models

Considering that CBD was effective in animal models of anxiety by facilitating 5-HT1 A neurotransmission (Campos and Guimarães, 2008), our group (Resstel et al., 2009) first explored the possibility that CBD could also attenuate stress-induced emotional consequences by promoting behavioral adaptation. Indeed, the results showed that systemic CBD injection before an exposure to restraint stress attenuated the anxiogenic and cardiovascular effects observed in rats submitted to the elevated plus-maze 24 h later. As expected, CBD effects were blocked by pretreatment with the 5-HT1 A antagonist WAY100635. Since conventional antidepressant drugs and 5-HT1 A agonists can also attenuate the delayed emotional consequences induced by restraint stress (Guimarães et al., 1993; Kennett et al., 1985; Padovan and Guimarães, 2000), it was hypothesized that CBD could be useful for treating psychiatric disorders that involve impairment of stress-coping mechanisms, such as depression (Resstel et al., 2009). Stress-coping can be defined as the behavioral and physiological efforts developed by the animal with the aim to reduce the deleterious effects produced by stress and, thus, promote adaptation (Commons et al., 2017; de Kloet and Molendijk, 2016). Impaired coping strategies have been associated to the development of psychiatric diseases, including depression (Commons et al., 2017).

Based on those initial findings, our group investigated the effects induced by acute systemic CBD administration to Swiss mice submitted to the forced swimming test (FST), a widely used test predictive of antidepressant effects (Nestler and Hyman, 2010; Porsolt et al., 1978, 1977). The results revealed that CBD induces dose-dependent antidepressant-like effects (with the effective dose 30 $mg.kg^{-1}$), which were blocked by prior administration of the 5-HT1 A antagonist

Table 1
Main pharmacological targets for cannabidiol with relevance for depression neurobiology and treatment.

Biological System	Target	Potential effect	References
eCBD	CB1 allosteric receptor	Antidepressant	(Parolaro et al., 2010; Thomas et al., 2007).
	CB2 allosteric receptor	antidepressant	(Parolaro et al., 2010; Thomas et al., 2007).
	FAAH inhibitor	↑ AEA: antidepressant	(Bisogno et al., 2001; Campos et al., 2013; Leweke et al., 2012; Parolaro et al., 2010; Petrosino et al., 2018).
	AEA uptake inhibitor	↑ AEA: antidepressant	(Bisogno et al., 2001; Campos et al., 2013; Leweke et al., 2012; Parolaro et al., 2010; Petrosino et al., 2018).
	TRPV1 agonist	Mixed (antidepressant and depressant)	(Bisogno et al., 2001; De Gregorio et al., 2018; Fonseca et al., 2018; Petrosino et al., 2018; Poleszak et al., 2018).
	TRPA1 agonist	ND	(De Moura et al., 2014; De Petrocellis et al., 2008).
	TRPM8 antagonist	ND	(De Petrocellis et al., 2008).
	TRPV2 agonist	ND	(Cherif et al., 2015; Eubler et al., 2018; Nabissi et al., 2015; Qin et al., 2008; Robbins et al., 2012).
	GPR55 antagonist	ND	(Cherif et al., 2015; Hill et al., 2018; Hurst et al., 2017; Walsh et al., 2015).
Serotonin	5-HT1 A agonist	antidepressant	(Campos et al., 2012; De Gregorio et al., 2018; Fogaça et al., 2014; Gomes et al., 2011; Hind et al., 2016; Myers et al., 2018; Resstel et al., 2009; Russo et al., 2005; Sartim et al., 2016; Zanelati et al., 2010; Żmudzka et al., 2018).
	5-HT2A agonist	mixed	(Long et al., 2012; Pelz et al., 2017; Russo et al., 2005; Żmudzka et al., 2018).
	5-HT3 agonist	prodepressant	(Xiong et al., 2012; Żmudzka et al., 2018).
	Tryptophan degradation inhibitor	Antidepressant?	(Jenny et al., 2009; Stahl and Felker, 2008).
Opioid	Mu-opioid ligand	antidepressant	(Callaghan et al., 2018; Rodríguez-Muñoz et al., 2012; Viudez-Martínez et al., 2018).
	Sigma-opioid ligand		(Callaghan et al., 2018; Rodríguez-Muñoz et al., 2012).
Adenosine	Adenosine uptake inhibitor and indirect A2A agonist	?	(Carrier et al., 2006; Cheffer et al., 2018; Liou et al., 2008; Mecha et al., 2013; Mijangos-Moreno et al., 2014; Nazario et al., 2015; Oláh et al., 2014).
Other	PPARγ agonist	Antidepressant?	(Hind et al., 2016; Vallée et al., 2017).
	GABAA positive allosteric modulator	Antidepressant?	(Almeida et al., 2018; Long et al., 2012; Meltzer-Brody et al., 2018).
	α7 nicotinic acetylcholine antagonist	?	(Mahgoub et al., 2013; Zhao et al., 2017).
	Regulator of intracellular calcium	?	(Drysdale et al., 2006; Nanou and Catterall, 2018).
	iNOS inhibitor	antidepressant	(Esposito et al., 2006; Joca et al., 2015; Montezuma et al., 2012).
	NF-κB inhibitor	antidepressant	(Décarie-Spain et al., 2018; Esposito et al., 2006; Fulenwider et al., 2018).
	COX-1 and 2 inductor	?	(Müller, 2013; Wheal et al., 2014).

WAY100635 (Zanelati et al., 2010). This study, besides suggesting for the first time an antidepressant-like effect of CBD, also showed that the effect of CBD depends on 5-HT1 A receptor activation. A subsequent study by El-Alfy and colleagues (2010) corroborated these original findings, showing that a single systemic administration of CBD had an antidepressant-like effect in Swiss mice submitted to both the FST and the tail suspension test (TST, another test predictive of antidepressant effects), although at much higher doses (200 $mg.kg^{-1}$).

Importantly, CBD has also been shown effective after repeated treatment, as seen in Swiss albino mice assessed with the TST, where daily injections of CBD in 3 and 30 $mg.kg^{-1}$ doses during 15 days had an antidepressant-like effect (Schiavon et al., 2016). The effects do not seem to be species specific, as similar results also were observed in male Wistar rats submitted to the FST, where both acute and chronic (14d) treatment with CBD (30 $mg.Kg^{-1}$) were effective (Réus et al., 2011). The latter study specifically reported that CBD increased swimming in the FST, which is the behavior in the FST believed to be related to increased serotonergic tonus in the brain (Cryan et al., 2002), thus supporting the possible involvement of the serotonergic neurotransmission in the behavioral effects of CBD. Consistently, co-administration of CBD augmented the antidepressant-like effects of fluoxetine, but not of desipramine, in the FST (Sales et al., 2018a). This study therefore also suggests that CBD may be useful to potentiate the therapeutic effects of clinically available serotonergic antidepressant drugs.

Although the FST and TST have relatively good predictive validity as behavioral paradigms to detect antidepressant effect, they were predominantly developed and validated upon monoaminergic antidepressants, which raises important concerns regarding generalizability, face, and construct validity (Abelaira et al., 2013; Cryan et al., 2002). Studies using other animal models of depression have confirmed the antidepressant properties of CBD, thus strengthening its potential antidepressant effect. Noteworthy, acute CBD (30 $mg.Kg^{-1}$) was effective in the rat learned helplessness model (LH, (Sales et al., 2018b) and in C57BL6 J mice submitted to the olfactory bulbectomy model (OBM; 50 $mg.Kg^{-1}$, Linge et al., 2016). CBD also showed antidepressant and prohedonic effects in genetic rat models based on selective breeding, such as the Flinders Sensitive Line (Sales et al., 2018b) and the Wistar-Kyoto rats (Shoval et al., 2016). Furthermore, chronic CBD treatment (30 $mg.Kg^{-1}$,14d) promoted stress-coping behavior in C57BL6 J mice submitted to chronic unpredictable stress, an effect involving endocannabinoids and neuroplastic mechanisms, as will be further discussed ahead. Table 2 summarizes and gives a complete overview of the preclinical CBD antidepressant-like effects.

Surprisingly, CBD produced an acute antidepressant effect in the OBM and the LH, which are models usually not sensitive to acute monoaminergic treatment (Linge et al., 2016; Sales et al., 2018b), thus suggesting that it might be a fast-acting antidepressant compound. Furthermore, the effects induced by CBD lasted for up to one week after a single injection, both in mice and rats (Sales et al., 2018b), indicating a sustained effect. Altogether, these results suggest that CBD has a similar pharmacological profile to ketamine, with rapid and lasting effects (Li et al., 2010). However, additional studies investigating the effects of CBD across different laboratories, experimental conditions, and using other animal models with good face and predictive validity, are needed to strength this possibility.

Based on the above findings, presented in full in Table 2, it is possible to conclude that CBD induce antidepresssant-like effects in different preclinical models, using distinct rodent species and strains of mice and rats. Moreover, both acute and chronic CBD treatment is effective, at the range of doses of 3–30 $mg.Kg^{-1}$ in mice and 30–60 $mg.Kg^{-1}$ in rats. More recently, it was also shown that subchronic, but not acute, treatment with CBD attenuates the behavioral dysfunctions associated with depression in diabetic rats (de Morais et al., 2018). Although all the studies mentioned above have been conducted in male rodents, new evidence suggests that CBD effects may be influenced by the gender, being inneffective in female FSL rats

Table 2
Evidence about CBD Effects in mordels predictive of antidepressant effects.

Reference	Animal	Age	Origin	Dose	Route	Test	Effect	Suggested mechanism of Action
Zanelati et, 2010	Male Swiss mice	n.s.	Natural	30 mg/kg	i.p.	FST	Antidepressant effect	Activation of 5-HT1 A receptor
				3, 10 and 100 mg/kg	i.p.	FST	No effect	Unaltered hippocampal BDNF levels
El-Alfy et al., 2010	Male Swiss Webster mice	8 weeks	Natural	200 mg/kg i.p.	i.p.	FST	Antidepressant effect	n.s.
	Male Swiss Webster mice	8 weeks		20 and 100 mg/kg i.p.	i.p.	FST	No effect	n.s.
	Male DBA/2	8 weeks		20, 100 and 200 mg/kg i.p.	i.p.	TST	No effect	n.s.
Réus et al., 2011	Male Wistar rats	8 weeks	n.s.	30 mg/kg (Acute)	i.p.	FST	Antidepressant effect	No change in BDNF levels in neither PFC, HPC and amygdala
				15 and 60 mg/kg (Acute)	i.p.	FST	No effect	
				30 mg/kg (Chronic - 14 days)	i.p.	FST	Antidepressant effect	Increase BDNF in amygdala (15 mg/Kg)
				15 and 60 mg/kg (Chronic - 14 days)	i.p.	FST	No effect	
Campos et al., 2013	Male C57BL/6 J mice (CUS)	12 weeks	Natural	30 mg/kg (Chronic - 14 days)	i.p.	EPM and NSF	Anti-stress effect	Increase number cells immunoreactive BrdU, NeuN and DCX in HPC Blocked by CB1 antagonist (AM251) Increase AEA level in HPC No change in 2 A G and PEA in HPC
	HiB5 cells	–	Natural	100 nM	culture medium	Immunofluorescence microscopy	Neural progenitor proliferation	Blocked by CB1 (SR141716) and CB2 antagonists (SR144528) Independent of 5-HT1 A receptor antagonism Dependent of FAAH and MAGL inhibition Blocked by overexpression of FAAH
						Flow citometry	Increase neural progenitor cell in S phase cells	Blocked by CB1 (SR141716) and CB2 antagonists (SR144528)
Schiavon et al., 2016	Male Swiss albino mice	5-6 weeks	Natural	3 and 10 mg/kg (Acute)	i.p.	TST	Antidepressant effect	n.s.
				30 mg/kg (Acute)	i.p.	TST	No effect	n.s.
				3 and 30 mg/kg (Repeated - 15 days)	i.p.	TST	Antidepressant effect	Increase number cells immunoractive Ki-67, BrdU and DCX in SGZ and SVZ (3 mg/Kg). Decrease number cells immunoractive Ki-67, BrdU and DCX in SGZ and SVZ (30 mg/kg).
Linge et al., 2016	Male C57BL6 mice (Olfatory bulbectomy)	12 weeks	Natural	50 mg/kg (Acute)	i.p.	OFT	Antidepressant effect	Increase 5-HT and glutamate in vmPFC dependent of 5-HT1 A receptor Attenuated by 5-HT1 A antagonist (WAY100635) Independent of CB1 receptor antagonism (AM251)
				50 mg/kg (Repeated- 7 days)	i.p.	OFT	Antidepressant effect	Increase 5-HT and glutamate in vmPFC
						SPT	Prohedonic effect	Restored of functionally 5-HT1 A receptor (CA1 and CA2 hippocampus, DRN, amygdala)
Shoval et al., 2016	Wistar-Kyoto rats	13 weeks	Natural	30 mg/kg	oral (food pellet)	SPT	Prohedonic effect	n.s.
				15 and 45 mg/kg	oral (food pellet)	SPT	No effect	n.s.
Sartim et al., 2016	Male Wistar rats	n.s.	Natural	10, 30 and 60 nmol/0.2 ul/side	intra-PL mPFC	FST	Antidepressant effect	Blocked by 5-HT1 A (WAY100635) and CB1 antagonist (AM251)
				45 and 60 nmol/0.2 ul/side	intra-IL mPFC	FST	Antidepressant effect	Blocked by 5-HT1 A antagonist (WAY100635)
				30 nmol/0.2 ul/side	intra-IL mPFC	FST	No effect	n.s.
Breuer et al., 2016*.	Male Swiss mice	n.s.	Natural	HUF101: 3 mg/kg	i.p.	FST	Antidepressant effect	n.s.
				HUF101: 1 and 10 mg/kg	i.p.	FST	No effect	n.s.
				HUF103: 3 and 10 mg/kg	i.p.	FST	Antidepressant effect	n.s.
				HUF103: 1 mg/kg	i.p.	FST	No effect	n.s.

(*continued on next page*)

Table 2 (*continued*)

Reference	Animal	Age	Origin	Dose	Route	Test	Effect	Suggested mechanism of Action
Fogaça et al., 2018	Male C57BL6 mice (CUS)	8-9 weeks	Natural	30 mg/kg (Chronic - 14 days)	i.p.	EPM and NSF	Anti-stress effect	Activation of CB1 and CB2 receptors Increase number cells immunoractive DCX and BrudU/NeuN in SGZ of DG Decrease FAAH expression in HPC Increase GSK-3β expression in HPC No change in p-Akt in HPC Increase number of dendritic spine and branchs in HPC Increase PSD-95, Synapsin Ia/b and GluR1 in HPC
Sartim et al., 2018	Male Swiss mice	7-8 weeks	Natural	10 nmol/0.2 ul/side	intra-dHPC	FST	Antidepressant effect	Blocked by mTOR antagonism (rapamycin) or TrkB antagonism (k252a)
				30 and 60 nmol/0.2 ul/side	intra-dHPC	FST	No effect	
				10 mg/kg	i.p.	FST	Antidepressant effect	Blocked by mTOR antagonism (rapamycin) or TrkB antagonism (k252a) Increase release BDNF HPC.
Sales et al., 2018a	Male Swiss mice	8 weeks	Natural	10 mg/kg	i.p.	FST	Rapid antidepressant effect	Blocked by mTOR antagonism (rapamycin) or TrkB antagonism (k252a) Increase BDNF levels in PFC and HPC. Increase PSD95 and Synaptophysin PFC, not inHPC Increase number of dendritic spine in PL and IL mPFC.
				10 mg/kg	i.p.	FST	Sustained antidepressant effect	No alteration on BDNF in PFC and HPC.
				7 and 30 mg/kg	i.p.	FST	No effect	n.s.
				300 nmol/ul	i.c.v.	FST	Antidepressant effect	n.s.
				50 and 150 nmol/ul	i.c.v.	FST	No effect	n.s.
	Male Wistar rats	n.s.	Natural	30 mg/kg	i.p.	LH	Rapid antidepressant effect	n.s.
				10 mg/kg	i.p.	LH	No effect	n.s.
	Male FSL and FRL rats	n.s.	Natural	10 and 30 mg/Kg	i.p.	FST	Rapid antidepressant effect	n.s.
Sales et al., 2018b	Male Swiss mice	8 weeks	Natural	10 mg/kg	i.p.	FST	Antidepressant effect	Blocked by 5-HT depletion (PCPA), but not NA depletion
				3 and 7 mg/kg	i.p.	FST	No effect	n.s.
De Morais et al., 2018	Male Wistar rats	n.s.	n.s.	30 mg/kg (Acute)	i.p.	FST	Antidepressant effect	n.s.
	Male Wistar rats (diabetic)	n.s.		0.3, 3, 10, 30 and 60 mg/Kg (Acute)	i.p.	FST	No effect	n.s.
				30 mg/Kg (Subchronic)	i.p.	FST	Antidepressant effect	n.s.
				0.3, 3, 10 and 60 mg/Kg (Subchronic)	i.p.	FST	No effect	n.s.

Abbreviations: 2 A G- Arachidonoylglycerol; 5-HT- Serotonin; 5-HT1 A - Serotonin receptor type 1 A; AEA - Anandamide; BDNF- Brain-derived nurotrophic factor; BrdU - 5- bromo-2′-deoxyuridine; CB1 - Cannabinoid receptor type 1; CB2- Cannabinoid receptor type 2; DCX - Doublecortin; EPM- Elevated plus maze; FAAH - Fatty acid amide hydrolase; FRL rats - Flinders Resistant Line; FSL rats - Flinders Sensitive Line; FST- Forced swimming test; GSK-3β- Glycogen synthase kinase 3β; HPC - Hippocampus; i.c.v - intracerebroventrcular; i.p. - intraperiatoneal; intra-dHPC- Intra-dorsal hippocampus; intra-IL mPFC- infralimbic medial prefrontal cortex: intra-PL mPFC- prelimbic medial prefrontal cortex; LH - Learned helplessness; MAGL - Monoacylglycerol lipase; mTOR - Mammalian target of Rapamycin; n.s. - not specified; NSF - Novelty supressed feeding; OFT - Open field test; p-Akt- Phospho protein kinase B; PEA - Palmitoylethanolamide; PFC - Prefronal cortex; PSD-95- Post-synaptic density 95; SPT - Sucrose preference test; SGZ - Subgranular zone; TST - Tail suspension test; TrkB - Tropomyosin receptor kinase B. * Fluorinate cannabidiol.

(Shbiro et al., 2019). However, this study tested only one dose of CBD (30 mg/kg), thus requiring additional investigation to raise further conclusions on that topic.

4.2. Human evidence

The effects of cannabinoids on depressive disorders have been a matter of debate for very long, and the evidence is still inconclusive, with reports of both beneficial and detrimental effects (National Academy of Sciences, 2017). However, it has been argued that some of the mood-improving effects related to cannabis use could be associated to the CBD content (Ashton et al., 2005), although THC has also shown antidepressant effects in sub-euphoric doses in humans (Ashton et al., 2005; Gruber et al., 1996) and laboratory animal (El-Alfy et al., 2010; Häring et al., 2013). Nevertheless, valid randomized data about CBD effects on depressed humans are scarce, and no clinical trial in depression has been published so far. However, a recently published study assessed 1483 individuals who have used CBD for treating several medical conditions (Corroon and Phillips, 2018). Of those, around 400 patients reported the use of CBD to achieve mood-improving effects, with 250 patients reporting CBD worked “very well by itself”. In the same study, the most common side-effects reported were dry mouth, hunger, and euphoria, which most likely could be related to TCH. Since the study did not discriminate the different sources of CBD (natural vs. synthetic), it is not possible to exclude a possible role of THC in these observations. Moreover, another limitation is the study sample, which could potentially bias the results due to the involvement of patients which have improved after CBD use. Therefore, controlled clinical trials assessing CBD effects in depressed patients are clearly needed. Currently, two ongoing randomized placebo-controlled trials of adjunctive CBD in bipolar depression are being carried out in Brazil and Germany. They are expected to end by 2020 (EUCTR, 2018; NCT, 2017). Whether any potential findings in these studies may be relevant also to unipolar depression would be of significant interest.

5. Potential mechanisms involved in CBD antidepressant effects

5.1. Neurochemical mechanisms

Although CBD modulates several targets involved in the neurobiology of depression, as outlined in Table 1, only a few of these mechanisms have so far been explored *in vivo*.

The involvement of the serotonergic neurotransmission in the antidepressant-like effect of CBD comprise the best investigated neurochemical mechanism to date. Initially, as mentioned above, Zanelati and co-workers showed that CBD-induced stress-coping behavior in the forced swimming, a finding depending on activation of 5HT1 A receptors (Zanelati et al., 2010). Interestingly, CBD induced antidepressant-like effects upon direct administration into the ventromedial prefrontal cortex (vmPFC), an effect which is in line with findings from systemic administration, since it could also be blocked by pretreatment with the 5-HT1 A receptor antagonist WAY100635 (Sartim et al., 2016). This finding further substantiates the importance of 5-HT1 A mediated signaling in the antidepressant effects of CBD, in addition to be the first study to indicate a possible site of action of this drug. This is consistent with previous studies which have shown that 5-HT1 A activation into the PFC promotes stress-coping and persistent antidepressant effects (Fukumoto et al., 2017). Interestingly, in the study by Sartim and colleagues, pretreatment with a CB1 antagonist also blocked CBD effects in the FST (Sartim et al., 2016). Since, as discussed above, this drug has low affinity for CB1 receptors, but may increase AEA levels by inhibiting its reuptake (Bisogno et al., 2001), the effects of CBD could be related to increased levels of AEA in the vmPFC. Accordingly, challenging the vmPFC with an injection of exogenous AEA induced antidepressant effect similar to that observed following CBD administration, an effect also was blocked by the 5-HT1 A antagonist WAY100635 (Sartim et al., 2016). Importantly, this study supports the hypothesis that CBD could increase the levels of AEA in the vmPFC, with subsequent local CB1 activation. This mechanism would disinhibit the serotonergic neurotransmission, favorouring 5-HT1 A receptor-mediated effects. Corroborating this proposal, intra-vmPFC administration of the anandamide hydrolysis inhibitor, URB597, induced active coping behavior in the FST associated to an increased firing rate of serotonergic neurons within the dorsal raphe nucleus, suggesting that CB1 signaling in the vmPFC promotes antidepressant-like effects through regulation of serotonergic neurotransmission (McLaughlin et al., 2012). In line with this evidence, depletion of brain serotonin, but not noradrenalin, abolished CBD effects in the FST (Sales et al., 2018a).

Further supporting this proposal, Linge and colleagues reported that the behavioral dysfunction induced by chronic olfactory bulbectomy was reversed by CBD, an effect which was associated with an increase in extracellular serotonin and glutamate levels in the vmPFC. In the same study, chronic CBD treatment reversed the detrimental effects of olfactory bulbectomy on 5-HT1 A signaling in the DRN, hippocampus, amygdala, and vmPFC (Linge et al., 2016). The effect of CBD was counteracted by prior blockade of 5-HT1 A receptors, but not by a CB1 antagonist. It was hypothesized that increased serotonergic drive into the vmPFC could result from activation of 5-HT1 A onto GABAergic interneurons, subsequently favoring glutamate release and stimulation of the DRN (Linge et al., 2016). This hypothesis, however, warrants further investigation.

Evidence indicates that, depending on the behavioral test and treatment duration, 5-HT1 A or CB1 signaling would prevail to mediate CBD effects. For instance, in the CMS, the stress-coping effects of chronic CBD treatment are associated with increased anandamide levels in the hippocampus and are sensitive to CB1 antagonists (Campos et al., 2013). More recently, in a similar protocol, the same group showed that chronic CBD injections (14d, 30 mg/kg) promoted stress-coping behavior that was blocked by CB_1 or CB_2antagonist but not by a $5HT_{1A}$ antagonist.

Despite its promiscuous pharmacology, the involvement of additional targets in CBD antidepressant effects, other than 5-HT1 A and CB1-CB2 receptors, have not been consistently explored to date. Notably, CBD has anti-inflammatory and immunomodulatory activity, reducing the production of inflammatory cytokines in response to a great variety of stimulus (Fernández-Ruiz et al., 2013; Ruiz-Valdepeñas et al., 2011). In this context, studies have shown that CBD decreases glial reactivity facing challenging situations (Kozela et al., 2011; Mecha et al., 2013) and part of the CBD effects seems to be mediated by activation of PPARγ receptors (Esposito et al., 2011; Gomes et al., 2015). However, the participation of immunomodulatory mechanisms in CBD-induced antidepressant effects remains to be investigated.

5.2. Neuroplastic mechanisms

A complete overview of CBD effects on neuroplasticity has been discussed elsewhere (Campos et al., 2017) and is beyond the scope of the present review. Briefly, there are convincing evidence that CBD modulates neuroplasticity processes, especially neurogenesis and synaptogenesis, which are often disrupted in chronically stressed animals and MDD. Early studies indicated that chronic CBD treatment increases hippocampal neurogenesis in a CB1-dependent mechanism, as the neurogenesis was absent in $CB1^{-/-}$ animals (Wolf et al., 2010). In support of that finding, Campos and colleagues (2013) reported the ability of chronic CBD treatment (14d) to attenuate the anxiogenic effects induced by CMS, which furthermore depended on adult hippocampal neurogenesis. In the same study, CBD treatment increased AEA levels in the hippocampus, and the proneurogenic effect of CBD was blocked by concomitant treatment with a CB1 or CB2 antagonist, suggesting involvement of cannabinoid receptors in CBD-induced neuroplasticity effects. Interestingly, CBD effect on neurogenesis was further confirmed in an *in vitro* experiment, where CBD increased proliferation

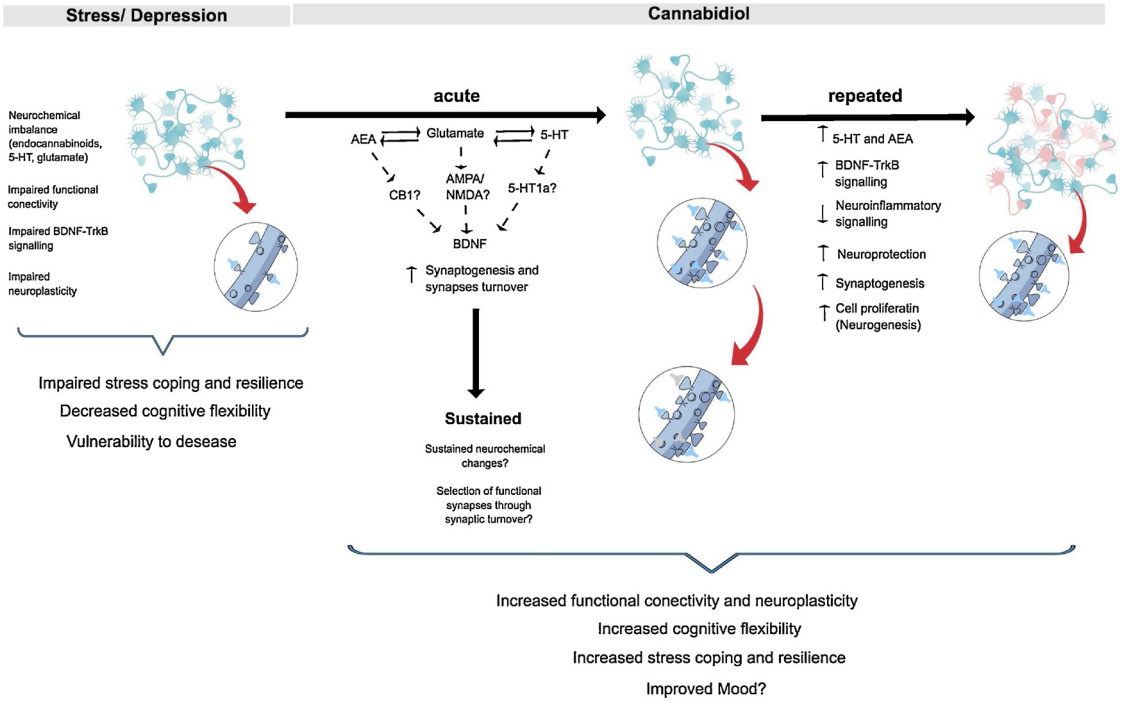

Fig. 2. Potential neurochemical and neuroplasticity mechanisms involved in CBD antidepressant effect. Stress and depression are often associated with neurochemical imbalance and impaired neuroplasticity (reduced synaptogenesis and/or neurogenesis) in limbic brain regions, primarily PFC and hippocampus. In this scenario, the acute antidepressant effect of CBD would be associated with rapid changes in neurotransmitter levels, including serotonin and endocannabinoids, in these brain regions. These could trigger rapid increase in BDNF and promote synaptogenesis. Upon repeated treatment, additional neurochemical and neuroplasticity mechanisms would take place promoting stress coping behavior and resilience to chronic stress. AEA: anandamide. References: Campos et al., 2013; Linge et al., 2016; Fogaça et al., 2018; Sales et al., 2018a, 2018b.

of HiB5 cells (Campos et al., 2013; Fogaça et al., 2018). This proliferative effect was abolished by CB1 and CB2, but not by 5-HT1 A antagonists. Therefore, it can be hypothesized that chronic CBD treatment increases AEA signaling in the hippocampus, which in turn, via CB1 and CB2 receptors, could promote synaptogenesis and neurogenesis to facilitate behavioral adaptation to chronic stress. In a subsequent in vivo study, the authors showed that chronic CBD treatment decreased FAAH expression in the hippocampus (Fogaça et al., 2018), which may contribute to the understanding of the increased AEA levels previously reported in the hippocampus of CBD treated animals (Campos et al., 2013). In this study CBD not only increased neurogenesis, but also augmented the expression of synaptic proteins, and prevented the stress-induced dendritic remodeling in mice hippocampus. All these effects were abrogated by co-treatment with CB1 and CB2 antagonists (Fogaça et al., 2018). These results fits well with reports showing that sustained increased in endocannabinoid signaling promotes hippocampal neurogenesis in preclinical models through CB1 and CB2 receptors and induces antidepressant-like effects (Bambico et al., 2016; Bambico and Gobbi, 2008; Fogaca et al., 2013; Zhang et al., 2015).

However, the participation of neurogenesis on the behavioral effects of CBD seems to be rather complicated and might depend on treatment duration and the behavioral paradigm used. For example, Schiavon and colleagues (2016) confirmed that acute (single ip injection, 3 and 30 mg.Kg^{-1}) and chronic (15d, 3, 30 mg.Kg^{-1}) treatment with CBD causes antidepressant-like effect in the tail suspension test. However, chronic treatment produced paradoxical effects. It increased neurogenesis at 3 mg.Kg^{-1}, but decreased it at 30 mg.Kg^{-1} dose. These results suggest that CBD might be able to induce antidepressant-like effects even under conditions of decreased hippocampal neurogenesis. Testing the neurogenesis involvement on CBD effects in different behavioral paradigms would help to clarify these results.

Recently, new information on the molecular mechanisms involved in CBD-induced antidepressant effects, particularly in its rapid effects, has been obtained (Sales et al., 2018b). Acute CBD administration increased BDNF levels in the PFC and hippocampus of mice 30 min after the administration of the drug. Moreover, increased expression of the synaptic proteins synaptophysin and PSD95, as well as increased dendritic spines density, was observed in the mPFC at this moment, but not 7 days later (Sales et al., 2018a). Since intracerebroventricular administration of the Trk receptor blocker K252a prevented CBD-induced behavioral effects, the rapid increase in BDNF signaling, particularly in the PFC, could trigger the synaptic changes mediating the effects of CBD (Sales et al., 2018b). Furthermore, inhibition of TrkB and mTOR signaling in the hippocampus also blocked the behavioral effects of CBD in the FST (Sartim et al., 2018). Together, these studies suggest that rapid synaptic changes in these brain regions, which are associated with depression, could contribute to the behavioral effects of CBD. However, none of these studies investigated if the plasticity changes induced by CBD were absent following inhibition of Trk-mTOR signaling. Moreover, the mechanisms underlying the increased BDNF signaling in CBD treated animals also warrants further investigation. As both 5-HT1 A (Jiang et al., 2016; Zhou et al., 2014) and endocannabinoid (Bambico et al., 2016) signaling can modulate BDNF levels in limbic brain regions, it can be hypothesized that both systems participate in the acute effects of CBD. Possible mechanisms involved in CBD antidepressant effects can be seen in Fig. 2. This proposal, however, needs to be further investigated. Similarly, other molecular targets of CBD should also be investigated as potential modulators of the neuroplasticity events observed following administration of CBD, either acutely or after repeated treatment.

6. Conclusion

The knowledge acquired during the past decades provides evidence that CBD has antidepressant-like profile in different animal models.

Given the very substantial large unmet clinical needs, the characterization of CBD as a possible therapeutic agent for affective disorders is of significant interest. It may be a useful and tolerable intervention strategy, alone or in combination with already established antidepressant strategies. In addition, identification of the mechanisms underlying the effects of CBD may pave the way for identification of novel targets and drug classes for the treatment of MDD.

7. Perspectives

CBD is now been approved in several countries for the treatment of severe forms of epilepsy in children and multiple sclerosis (together with THC). A significant number of clinical and preclinical studies indicates that it may also be useful for the treatment of several psychiatric and non-psychiatric disorders (Crippa et al., 2018; Pisanti et al., 2017), major depression being one of them. The side-effects described for CBD include tiredness, diarrhea, and changes in appetite/weight (Iffland and Grotenhermen, 2017), which compare favorably with other antidepressants available. However, the effects induced by chronic CBD treatment are not yet fully known, and more studies are needed to evaluate its tolerability and safety after long term use. How a single compound can show such a wide-range of therapeutic potential with a favorable safety profile (Bergamaschi et al., 2011) remains a mystery that is far from being solved. Hopefully, the recent increased scientific interest on CBD will enable additional research and shed new light into this problem. Meanwhile, it is urgent to carry out clinical trials to assess the position of CBD among our therapeutic options for major depression.

Disclosures

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