COULD CANNABIDIOL BE THE ANSWER FOR DRUG ADDICTION? A SYSTEMATIC REVIEW OF CANNABIDIOL IN ADDICTIVE BEHAVIOURS.

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2015-2016 COURSE
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ABSTRACT

Cannabis sativa preparations have been used since antiquity for medicinal purposes. This plant contains more than 60 phytochemicals, being the phytocannabinoids (pCBs) some of them. Despite of the psychoactive properties produced by Δ²-tetrahydrocannabinol (THC), current research is focused on cannabidiol (CBD), a nonpsychoactive compound. Even though, the mechanism of action of CBD is not clearly understood, it seems to interact with CB1 receptors (CB1R) from the endocannabinoid system (eCB) among many other neurotransmitter systems. Altogether, pre-clinical studies have reported many therapeutic actions of CBD, which improves the treatment of schizophrenia, depression, anxiety, inflammatory and carcinogenic diseases. Furthermore, a cannabis whole extract medicine, Sativex®, has just been approved for multiple sclerosis. Besides of this range of effects, the goal of this systematic review is to summarize the therapeutic efficacy of CBD for the treatment of drug addiction. Taken together, the main results of pre-clinical and clinical studies, provide evidence for the therapeutic properties of CBD on opioid, psychostimulants, cannabis and nicotine addiction in humans. Notwithstanding, the efficacy of CBD as a treatment of addictive behaviours has not yet been proved completely and some investigations are still needed.

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INTRODUCTION

For thousands of years, Cannabis sativa has been an important crop among the cultures throughout the history acquiring commercial, medicinal and spiritual values. Cannabis plants are believed to have appeared in Central Asia with origins between 5000 to 3000 BC (Zuardi 2006) due to cultural and archaeological evidences and widespread across Europe and Egypt. Cannabis sativa grows as male or female plant and in rare cases as hermaphrodite. The three classes of cannabis have very similar genetic properties and differentiates only by certain factors, such as the content of the psychoactive substance called Δ9-tetrahydrocannabinol (THC) and by the type and size of their fibers (Rodríguez 2012). Besides this, only the female variant contain enough THC to produce the psychoactive effects and its content in the plant is variable: some of these plants can have a very low THC content (about 1.5%), while others, especially which are grown for this purpose, can have up to 20% of this substance. (Baker et al. 1984).

According to the parts of the plant that can be used to take profit of, it can get different types of drug. Marijuana, which has a tea-like appearance and greenish colour, is obtained from the buds and leaves of the cannabis plant. Marijuana is relatively dry and has a very characteristic smell and also its THC content is variable (Rodríguez 2012). Preferably marijuana is consumed smoked due to rapid effects. Hashish is a resinous form extracted from the female hemp plant. Hashish has more THC than marijuana, usually between 5 and 12% of this substance. This yellowish green, sticky mass, which can be solid or crumbly has a very distinctive smell (Rodríguez 2012).

The first recorded use of Cannabis as a medicinal occurred in 2737 BC when Chinese had discovered the effectiveness in the treatment of pain (Li and Lin 1974). Also popular knowledge attributes analgesic, muscle relaxants, anti-depressant, hypnotic, immunosuppressive, anti-inflammatory, anxiolytic, antidepressant, antiemetic, appetite stimulants and expectorant among many others properties (Zuardi 2006). This medical interests began to increase at 1960 when many epidemiologic studies related marijuana consumption to learning and memory problems (Zuardi 2006). In spite of this, the multiple physiological implications of its components lead to academic researchers being focused on this plant and the separation of its molecular compounds.

Many separation techniques showed that the Cannabis plant and its products consist of an enormous variety of chemicals. It has been identified more than 480 compounds which includes mono and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogen compounds and amino acids (Brenneisen 2007). Regardless, Cannabis contains more than 66 different chemicals, which are unique to the plant and called
Mallén A.

cannabinoids. The term “cannabinoids” represents a group of C₂₁ terpenophenolic compounds which are also called *phytocannabinoids* (pCBs) (Brenneisen 2007). Although pCBs are divided into 10 groups, the two major constituents are: THC, the psychoactive substance which mediated the rewarding processes, and the cannabidiol (CBD). CBD, in contrast of THC, seems to lack hedonic properties and reinforcing effect (Morgan 2010).

These findings have major therapeutic and public health implications. It is well known that for recreational uses, the consumption of cannabis strains which have high THC but low CBD doses has been widespread. It may endanger users leading to detrimental psycotrophic effects of THC so many legal restrictions have been stablished to avoid it (Swift et al 2013). Therefore, the uses of plant strains with balanced THC to CBD concentrations that maximize therapeutic endpoints, could be a wise public health strategy for marijuana consumers and also for locations where cannabis are legal (Todd et al 2016).

For these reasons the current researches focus on obtain different chemovariants of cannabis which contain 1:1 ratio of THC to CBD in order to decrease the unwanted effects of THC (Allsop et al. 2014). One of these cannabis extract which has been approved as a medicinal drug for the treatment of pain and spasticity of multiple sclerosis is Sativex® (Barnes 2006; Perras 2005).

Therefore, the aim of this review consist on update the therapeutic applications and neuropharmacologycal knowledge of CBD mainly focusing on the role that this cannabinoid plays in the modulation of the addictive properties of drugs of abuse.

OVERVIEW OF ENDOCANNABINOID SYSTEM

The endocannabinoid (eCB) system is a physiological machinery which comprises neuromodulatory lipid ligands (endocannabinoids), as well as metabolic enzymes for the synthesis and degradation of its ligands, and G protein-coupled receptors (Parsons and Hurd 2015). Moreover, exogenous cannabinoids as phytocannabinoids (e.g., THC and CBD) and synthetic cannabinoids, could produce their effects via the activation of cannabinoids receptors (Ulugöl 2014).

There are two major types of cannabinoid receptors which have been characterized and cloned: the cannabinoid 1 receptors (CB1R) and cannabinoid 2 receptors (CB2R). The
CB1R are most abundantly expressed in the central nervous system (CNS), most densely in regions which are involved in reward, addiction and cognitive functions including the amygdala, cingulate cortex, prefrontal cortex (PFC), ventral pallidum, caudate putamen, nucleus accumbens (NAc), ventral tegmental area (VTA) and lateral hypothalamus (Glass et al. 1997). In addition, CB1R are also found in basal ganglia, cerebellum, periaqueductal grey, rostral ventromedial medulla and peripheral tissues (e.g., autonomic nervous system, immune cells and testis) (Brenneisen 2007; Ulugöl 2014). Furthermore, CB1R are generally located pre-synaptically on the axons and terminals of neurons. CB1R activation mediates the inhibition of neurotransmitter release (e.g., γ-aminobutyric acid (GABA) and glutamate) by the inhibition of adenylate cyclase, blockade of voltage-dependent calcium channels, and by the activation of potassium channels and mitogen-activated protein kinase (Figure 1) (Pertwee 2001; Ulugöl 2014).

These actions produce widespread effects on neural signalling across many neurotransmitter systems (Parsons and Hurd 2015).

By other hand, CB2R are expressed mainly outside the CNS in immune cells and tissues associated with immune function. Even though, recent evidence suggests that CB2R are also expressed in neurons and microglia of human brain. In conclusion CB1R and CB2R

![Transduction mechanisms of CB1 receptor and their localisation](Ulugöl 2014).
are coupled to similar transduction mechanisms, primarily through G\textsubscript{i}/G\textsubscript{o} proteins (Parsons and Hurd 2015).

Another well-characterized components of eCB system, are the eCB ligands: N-arachidonylethanolamide (anandamide (AEA)) and 2-arachidonoylglycerol (2-AG) (**Figure 2**). These lipid ligands, are not stored in vesicles but are synthesized by membrane precursors on demand, and release immediately via Ca\textsuperscript{2+} mechanisms (Parsons and Hurd 2015). On the one hand, AEA is derived from the phospholipid precursor N-arachidonoyl-phosphatidylethanolamine (NAPE) and the precise formation mechanisms are not known (Matyas et al. 2008). On the other hand, 2-AG derives primarily from the hydrolytic metabolism of 1,2-diacylglycerol (DAG) by the sn-1-selective DAG lipases (DAGLs) DAGL\textalpha and DAGL\textbeta. Even though, whereas AEA is primarily catabolized by fatty acid amide hydrolase 1 (FAAH1), the 2-AG is catabolized by monoacylglycerol lipase (MAGL) and, to a lesser extent, by \(\alpha,\beta\)-hydrolase 6 (ABHD6), cyclooxygenase 2 (COX2) and FAAH1 (Matyas et al. 2008; Parsons and Hurd 2015).

In addition, the mainly catabolic enzymes FAAH1 and MAGL have different location. While MAGL is localized predominantly in presynaptic neurons, the FAAH1 remains into postsynaptic terminals (**Figure 2**). Moreover, 2-AG and AEA both leads to an agonist activity at CB1R and CB2R (Parsons and Hurd 2015).

**Figure 2.** Endocannabinoids AEA and 2-AG byosynthesis and inactivation (Ulugöl 2014).
More importantly, the eCB system provides a means for verifying whether cannabinoids are acting directly or indirectly to produce their wide range of pharmacological effects (Brenneisen 2007) and it is important to characterize the mechanism of action of CBD.

**CANNABIDIOL: MECHANISM OF ACTION**

As mentioned above, CBD is a non-psychotomimetic phytocannabinoid derived from Cannabis *sativa*. This compound was isolated in 1940 (Adams et al. 1940), but its correct structure was first elucidated in 1963. Seven CBD-type cannabinoids with C1 to C5 side chains have been described, being essentials to CBD synthesis in Cannabis *sativa* plant (Figure 3) (Brenneisen 2007; Mechoulam and Shvo 1963).

![Cannabinoids](image.png)

**Figure 3. Seven CBD-type cannabinoids** (Brenneisen 2002).

Even though the structure similarity, the mechanisms of action and interactions of CBD are different than others pCBs. Specifically in contrast to THC, this compound lacks of psychoactive properties (Katsidoni et al. 2013). CBD targeting to CB1R and CB2R is not able to produce directly and has lower affinity. Also, many studies have demonstrated the ability of CBD to modulate the inhibitory effect of the CB1R agonist R-(+)-WIN55212 on electrically evoked contractions of the mouse isolated vas deferens (Pertwee 1997;
Schlicker and Kathman 2001). Furthermore, some studies have demonstrated that CBD does not stimulate the dopaminergic neurons of VTA and keep the basal levels of dopamine in the NAc (French et al. 1997). These studies have supported the idea that CBD may reduce unwanted effects of THC attenuating anxiety, tachycardia, impairment of short-term memory and antinociception (Hampson and Deadwyler 1999; Karniol 1973) when is administrated with THC (Russo 2011). In addition, CBD seems to reduce the addictive behaviours in rats which diferents drugs were administrated (Prud’homme et al. 2015).

Moreover current studies have reported clear neuropharmacological interactions between CBD and THC. These studies have revealed great complexity in these interactions which are influenced by many factors as dose, dose ratio of THC to CBD and the interval between THC and CBD injection (Zuardi et al. 2012). However such interactions have not been fully understood, while a number of animal trials reproduce the CBD inhibition of THC effects in humans, opposed other studies have suggested that CBD potentiated the action of THC (Arnold et al. 2012).

Otherwise CBD is known to interact with many non-endocannabinoid signaling systems such as the opioid receptors (Pertwee et al. 2002), dopamine receptor (D2) (Pandolfo et al 2011; Bloom and Hillard 1985), the transient channel receptor 1 (TPRV1) (De Petrocellis et al. 2008), serotonin receptors (5-HT1A, 5-HT2A, 5-HT3) (Russo et al. 2005), the nuclear receptor and peroxisome proliferator activated receptor (PPAR)-c, among others. CBD does not bind to the orthosteric CB1R binding site (Morales et al. 2016); however, it has been shown to display antagonism of CB1R agonists in vitro. More recently, current studies provided evidences that CBD act as a negative allosteric modulator of THC and 2-AG by CB1R internalization, β-arrestin recruitment, and phospholipase C and ERK1/2 phosphorylation (Thomas et al. 2007; Laprairie et al. 2015). These results may explain some of the in vivo effects of this promising non-psychoactive compound providing novel insights in the intriguing pharmacology of CBD. Likewise, CBD can behave as an inverse agonist at the human CB2R (Thomas et al. 2007).

Therefore the mechanism of interaction between CBD and THC requires clarification, and no human or animal studies have addressed the question of which brain circuits are activated during such an interaction. Nevertheless, the implications of CBD in these signalling pathways open therapeutic actions in vivo.
THERAPEUTIC ACTIONS OF CANNABIDIOL

Despite of the higher numbers of implications of CBD and the emerging evidences of its diversity of receptors targets, a few clinical studies are achieved and they are still needed to evaluate the clinical potential of CBD in diverse fields. Nevertheless, the combination of THC with CBC in approximate 1:1 ratio, has allow to license the first medicinal whole cannabis-based extract as a buccal spray, Sativex® (Zlebnik and Cheer 2016). It has been approved as a prescription drug in Canada for use in neuropathic pain and spasticity, and has found to be effective on reducing these symptoms in multiple sclerosis (MS) (Barnes 2006). Moreover, early clinical trials has developed Epidiolex®, a pharmacotherapy for the treatment of pediatric epilepsy (Devinsky et al. 2014).

Rigorous pre-clinical studies has shown CBD to have a range of effects that may be therapeutically useful, including anti-seizure, antioxidant, neuroprotective, anti-inflammatory, analgesic, anti-tumour, anti-psychotic, anti-anxiety, anti-depressant properties (Table 1) and also it may be involved in the treatment of addictions, which studies are the main of this review and it will presented later.

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<td>Anti-tumour</td>
<td>-Interfering with tumour neovascularization, cancer cell migration, adhesion, invasion and metastasization which involves endogen cannabinoids.</td>
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Table 1. A few currently pre-clinical studies of therapeutic applications of CBD

ROLE OF CBD IN DRUG ADDICTION

Overview of drug addiction

Drug addiction is a chronically relapsing disorder characterized by the compulsive desire to seek and use drugs with impaired control over consumption despite negative consequences (Prud’homme et al. 2015). Addictive disorders can go through various stages, each of which can be characterized by specific neurobiological states (Figure 4). Firstly, the substance consumption produces psychoactive and addictive effects acting on neural regions that control pleasure and motivation, the reward system (Nestler 2006). In this acute phase of addiction, the motivational stimulus produced by the consumption of drugs causes a reinforcement, which leads to a voluntary acts in order to obtain pleasurable sensations (positive reinforcement) or avoid the unpleasant sensations (negative reinforcement) (Schultz et al. 1997; Bobes and Calafat 2000).

Altogether, this state is characterized by the mesolimbic system. This neural pathway is the primarily involved in positive reinforcement of drug seeking and originates from the dopaminergic neurons in the VTA of the midbrain and projects to limbic structures, most prominently the NAc (Figure 5) (Bobes and Calafat 2000). Increases in NAc dopamine are theorized to mediate the primary positive reinforcement of each drugs of abuse (Oleson and Cheer 2012).

Figure 4. Cycle of addiction.
When drug intake is produced recurrently, occurs the chronical stage, which leads to dependence and tolerance phenomenon. The tolerance consists on decreases of typically effects of each drug or the maintenance of these effects when a substance is intake recurrently or even when its consumption is increased (Bobes and Calafat 2000). Furthermore, when the interruption of substance use occurs, produces an early abstinence state. The withdrawal phase may include symptoms that vary according the type of drug (Galenter and Kleber 2008) which includes both physical symptoms (e.g., diarrhea, nausea, vomiting, tremor, palpitations, sweating and difficulty breathing) produced by opiates and alcohol, and emotional symptoms (e.g., anxiety, restlessness, irritability, insomnia, fatigue, depression and dysphoria) produced by cocaine, nicotine and marijuana (Galenter and Kleber 2008; Bobes and Calafat 2000). This negative affective state produced in drug abstinence, is associated with a decrease in mesolimbic dopamine function in contrast of the positive reinforcement and it might leads to compulsive drugs seeking (Oleson and Cheer 2012).

Finally, in the long-term, addiction becomes characterized by recurrent episodes of craving and this repetitive urges to consume the drug, can persist even after sustained periods of withdrawal, often resulting in relapse (Rohsenow et al. 2007). The exposure to environmental cues previously associated with drug-taking elicits craving and several studies have showed that learning and contextual memory play a critical role in establishing conditioned responses in drug addiction (Nestler 2005).

**Figure 5.** Schematic representation of simplified mesolimbic system and main projections from the VTA to NAc in the rodent brain (Russo and Nestler 2013).
The endocannabinoid system as a modulator of addictive properties

The eCB system has been the subject of growing interest in the treatment of drug addiction because of its influence on the acquisition and maintenance of drug-seeking behaviours through its role in reward and plasticity (Gardner 2015).

As different studies related, the physiological and emotional effects of drug addiction, are produced by modulation of different neurotransmissions systems such as dopamine, opioid, serotonin and norepinephrine (Hurd et al 2015). Likewise, the eCB has tight neurobiological interactions with these neurotransmission systems, specifically the interactions of TPRV1 (which binds the endogenous AEA) and CB1R (Prud’homme et al. 2015). The CB1R are co-localized with opioid µ receptors in striatal output projection neurons of the NAc, which mediate the actions of opioid drugs and modulates reward and habit formation relevant to addiction (Rodríguez et al. 2001).

Similarly, CB1R are described to be absent in dopaminergic neurons from VTA (Matsuda et al. 1990) and are also localized in different interneurons of this mesolimbic circuitry. In this way, such drugs as THC or opioids, appear to increase the activity of DA neurons in the VTA via the activation of CB1R or µ-opioid receptors respectively (Lupica et al. 2004). These receptors which are located on GABAergic axon terminals, lead to the inhibition of GABA release on DA neurons. This inhibition of inhibitory neurotransmitter release referred as disinhibition, is a common mechanism in local circuit interaction (Johnson and North 1992; Lupica et al. 2004). In contrast, psychostimulants like cocaine or amphetamine, are referred to increase the DA levels in the NAc via the inhibition of DA transporters so the CB1R implication, seems to be absent (Lupica et al. 2004).

In addition, drugs that activate CB1Rs increase the motivational and reinforcing effects and facilitates the rewarding effects (Figure 6), as indexed by animal models of drug addiction (Parsons and Hurd 2015).
Figure 6. A Neuronal synapsis and eCB influences at VTA involved in motivational reinforcement effects of addiction process.

(A) The VTA dopamine neurons which projects to NAc, are interconnected in complex circuits that involve excitatory (primarily glutamatergic) and inhibitory (primarily GABAergic) projections. In the baseline conditions, these VTA-DA neurons are inhibited via GABA receptors on these neurons due to greater involvement of GABAergic in front of glutamatergic projections.

(B) When drug acute cue is administrated, DA neurons fire in high-frequency bursts and increases intracellular calcium levels which activates eCB enzymes. It allows to synthetized 2-AG and releases into extrasynaptic space, where retrogradely activates Gi/o-CB1R on GABAergic interneurons leading to a suppression of GABA release that contributes to a disinhibition of the DA neuron and originates the reinforcement effects (Adapted from: Oleson and Cheer 2012).
Role of CBD in cannabis addictive behaviours

Acute and chronic unfavourable effects of Cannabis sativa are produced by action of THC in CB1R (Rodríguez de Fonseca et al. 1997). Animal studies showed that chronic exposition of THC leads to a straight connection between dopaminergic systems and cannabinoid endogenous system. Moreover, among the compounds that interacts with CB1R, the THC activates CB1Rs increasing the motivational and reinforcing effects as many studies have showed (Morgan et al. 2013; Ren et al. 2009).

In addition, the effect of CBD on THC drug discrimination (DD) in rats, was assessed. After inducing THC DD, the several combinations of THC and CBD at different doses were tested. The results showed that CBD and THC injection did not alter the DD at any dose, compared to THC alone (Vann et al. 2008).

On top of that, human studies of CBD on all three phases of cannabis addiction were found. One experimental trial investigates the role of CBD in withdrawal symptoms on a 19-year-old female with cannabis dependence (Crippa et al. 2013). CBD was administrated for 11 days and the uses of daily assessments tests (e.g., Withdrawal Discomfort Score), showed a rapid decrease in these symptoms (Crippa et al. 2013). The same study showed beneficial impact on relapse phase, leading to a lower frequency of recurrent episodes on crabbing cannabis; one or twice days in a week versus 7 days in a week (Crippa et al. 2013).

Box 1 | Definition of mainly procedures for drug addiction evaluation

- **Microdialysis**: this procedure consist on the sampling of fluid from determined brain regions. The fluid can be analysed to measure the levels of neurotransmitters or other neurochemicals.
- **Intra cranial self-stimulation (ICSS)**: method that consist to introduce a micro-electrode in a discrete brain area and allows a rat to press a lever which produces a brief electrical current. This technique is used to detect drug-induced changes in the sensitivity of reward system and measures the reinforcing effects.
- **Conditioned place preference (CPP)**: This procedure involves using a chamber with two distinctive compartments: the effect of a drug is associated in one by previous drug-administration, and no effect can be evaluated in the other one, where a vehicle is administrated. This method allows to assess the craving effects of drugs and long-term properties of addiction.
Furthermore, the impact of CBD on the reinforcing effects of THC was also studied. Two groups were formed based on levels of CBD:THC low, versus high ratio on smoked cannabis (Morgan et al. 2010). Cannabis users were evaluated by attentional bias, which consist on measure the deviation of users attention via attentional tests (e.g., Wechsler Adult Reading Test) and by rating of pleasantness. The results showed that high CBD:THC ratio was associated with lower rating of pleasantness and low deviation on attentional bias (Morgan et al. 2010).

**Role of CBD in opioid addictive behaviour**

Multiple studies have already examined the effects of CBD on heroin or morphine’s brain reward function on rats and humans. Current animal studies show that repeated CBD administration do not alter heroin self-administration in a short-term, but clearly inhibits cue-induced heroin seeking behaviours (Hurd et al. 2015). This suggests that CBD has the ability to inhibit relapse behaviour even after a period of abstinence (Hurd et al. 2015).

The mechanisms by which CBD mediates the long-term effects of heroin seeking behaviour are not known but it is thought that CBD normalizes the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor GluR1(AMPA) and CB1R in NAc (Ren et al. 2009). The GluR1 receptors are known to contribute to neuroplasticity under craving behaviour, and currently are being tested as treatment target of addiction (Knackstedt and Kalivas 2009).

Other preclinical studies evaluated the abstinence scores in morphine withdrawal precipitated by naloxone in rats, and evidenced that CBD reduced morphine withdrawal symptoms like wet shakes or diarrhea (Hine et al. 1975). Moreover, through the use of ICSS it was examined the effect of morphine’s brain reward function and the results showed that CBD inhibited the decrease of morphine ICSS threshold and its reward effect (Katsidoni et al. 2013).

Based on animal data supporting the effect of CBD on opioid-seeking behaviour, a pilot human clinical study has carried out (Figure 7), and the results confirm the preliminary findings in rodents (Hurd et al. 2015). Overall, CBD has found to have an important impact on all three phases of opioid addiction although are needed more studies to detail the effects on rewarding phases.
Few animal studies were found for the implication of CBD on each phases of psychostimulant addiction and no human studies were found for it. Firstly, the effect of CBD on cocaine’s brain reward function has shown to fail to inhibit a decrease in the ICSS threshold induced by cocaine (Katsidoni et al. 2013).

In addition, the impact of CBD on cocaine- and amphetamine-induced conditioned place preference (CPP) on rats was assessed (Parker et al. 2004). After the group of rats were exposed to these psychostimulant drugs, it divided onto two groups in which CBD or vehicle (VEH) were administrated. Then, the extinction trial and CPP were induced. The results (Figure 8) suggests that CBD potentiated the extinction of cocaine- and amphetamine-induced place preference learning and the disruption of contextual drug-associated memories, showing the impact on relapse phases (Parker et al. 2004).

Even though CBD studies may suggest great impact on psychostimulants addictive behaviours during the relapse phase and it does not seems to appear on rewarding effects, one recent study contradicts it. The potential antipsychotic-like properties of CBD within the mesolimbic system is reported by the attenuation of amphetamine-induced psychomotor sensitization in rats (Renard et al. 2016). Furthermore, these effects are produced by modulation of the phosphorylation states of mTOR/p70S6K signalling downstream pathways in NAc shell. Apparently, intra-NAc shell CBD, increases phosphorylation of mTOR and p70S6K, which act as a critical regulators of synaptic plasticity, memory and neuronal morphology (Jernigan et al. 2011).
normalize amphetamine-induced dysregulation of mesolimbic DA neuron activity states and also suggests a great impact on schizophrenia-like neuropsychopathology (Renard et al. 2016).

Role of CBD in others addictive behaviours (e.g., nicotine and alcohol)

Only one clinical study has achieved in order to know the effect of CBD on tobacco addiction. The study initiated with 24 smokers who wanted to stop smoking and subdivided into two groups who received either one a CBD inhaler and the other one a placebo inhaler (Morgan et al. 2013). The use of inhalers was produced when the subjects felt the necessity of smoke cigarettes, and it was measured once daily for one week. Nicotine-craving behaviour was measured at the baseline and the end of the week and the results showed a significant reduction of smoked cigarettes in subjects that inhaled the CBD during the treatment (Figure 8) (Morgan et al. 2013).
Similarly, only one clinical study in humans has emulated the involvement of CBD in alcohol addiction. It shows the effects of CBD on acute consumption of alcohol in 10 subjects after administration of alcohol alone or in combination with CBD and there was no difference in into each group (Consroe et al. 1979).

CONCLUSIONS

Recreational uses in society and medicinal aspects of cannabinoids are known since long period of time in history, but truly we are starting to learn and search out about it. One of these cannabinoids located in Cannabis sativa plants, which seems to lack of psychoactive properties, is CBD. The various therapeutic effects of CBD are produced in part by its interaction with eCB system. The eCB system is a very complex one and regulates numerous processes via CB1R and CB2R, in parallel with other well-known systems such as the dopaminergic. It is known that CBD modulates the endocannabinoid receptors, but these interactions, however, are still not completely understood. So despite the unknown mechanisms that mediate the CBD actions, it has been seen to be implicated in the treatment of addiction. Addiction process is mediated by the activation of reward circuits in brain in acute phases and by dependence phenomenon in a long-term stages which leads to drug seeking behaviours and relapse state. In order to solve this problem, pre-clinical and clinical studies have investigated the effects of CBD in rewarding, withdrawal and relapse phases of addiction originated by several drugs. Animal studies have shown the possible effects of CBD on opioid, psychostimulants, and cannabis addiction, while human studies presented some preliminary evidence of beneficial impact of CBD on nicotine, cannabis and opioid dependence. Overall, some of these studies are far from being conclusive, and well-designed trials are necessary at this point to determine this properties and improve clinical outcomes on humans.

ACKNOWLEDGEMENTS

The preparation of this review was supported by Universitat Pompeu Fabra (UPF) under the supervision and dedication of Fernando Berrendero, researcher from neuropharmacology laboratory of the Department of Experimental and Health Sciences (DCEXS).
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