Translational Research on the Effects of Treatment with Cannabidiol in Addictions

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Addiction is a behavioural disorder associated with proven deregulation of the functions of the CNS (in the dorsal striatum, globus pallidus, nucleus accumbens, hippocampus, thalamus, amygdala, orbitofrontal, and prefrontal cortex), which are also associated with functional changes in vital internal organs. In recent years, the application of cannabidiol (CBD), one of the cannabinoids without psychotropic activity, has become one of the options for the proposed treatment of addictions. The repeatedly described effects of cannabidiol, confirming the suppression of neurotoxic, behavioural, and other changes in both preclinical and clinical studies of addictions are considered to recommend further research for verification of the suitability of the indication of cannabidiol for the treatment of addictions.

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● 1 INTRODUCTION

Addictions, known as chronic (recurrent) behavioural disorders reinforced by a pleasant feeling ("reward"), are shown to be mediated by activation of the central dopaminergic neuronal pathway of the middle brain ("Reward Pathway") with deregulations proven in the dorsal striatum, globus pallidus, nucleus accumbens, hippocampus, thalamus, amygdala, orbitofrontal, and prefrontal cortex. These neurological changes alter behaviour, judgment, memory, learning, and stress management and thus addiction was called "Brain Disease" (Uhl et al., 2019). However, in addictions, other vital organs (the liver, lungs, cardiovascular system, and digestive tract) also react by changing their functions. More and more preclinical and clinical studies are being realized to find a strategy for the treatment of addictions and, of course, also the possibilities of addiction prevention. In recent years, the application of cannabidiol (CBD), the main non-psychoactive component of Cannabis sativa without the potential for addiction, has become one of the options for the proposed treatment of addictions (Parker et al., 2002; Izzo et al., 2009; Ren et al. 2009; Manzanares, 2019; Viudez-Martínez et al., 2019). In addition to the pharmacodynamic interactions of cannabidiol with the endocannabinoid system, its pharmacokinetic characteristics can also modulate the effects of drugs of abuse (Prud'homme et al., 2015; Zendulka et al., 2016; Lucas et al., 2018; Sulcova, 2019). The effects of cannabidiol confirming the suppression of neurotoxic, behavioural, and other changes in preclinical and clinical studies of addictions are considered a reason to recommend further research to verify the suitability of the indication of cannabidiol for the treatment of addictions.

● 2 METHODS

PubMed (https://pubmed.ncbi.nlm.nih.gov/), a free search engine containing citations for biomedical literature from MEDLINE, life sciences journals, and online books with the applied filters "Full text, books and documents, clinical study, review over the last 10 years", was used to gather the scientific evidence on the possible treatment of addictions by cannabidiol presented below. To qualify for inclusion, the studies must feature either a placebo condition or control conditions.

● 3 RESULTS

The intention of the author and expected goal of the publication of this paper is to provide a striking insight into the increasing number of highly relevant expert communications on the topic under discussion, i.e. the possible use of cannabidiol for the treatment of addictions. Therefore, the cited publications are also divided into messages on the positive results of A) preclinical and B) clinical studies, and at the same time they are purposefully arranged in the text for an easier overview of the historical development of the topic under discussion according to the years of their publication.

A. Examples of results from available experimental animal studies (1977–2021)

Repeated administration of CBD showed no potential for addiction when it failed to substitute for THC in pigeons trained to discriminate THC from the vehicle (Järbe et al., 1977).

A common effect characteristic of almost all drugs of abuse is increased dopamine release in the cells of the mesolimbic ventral tegmental area-nucleus accumbens pathway. While THC has been shown to increase the firing rate of these cells, CBD did not affect them (French et al., 1997).

A neuroprotective effect acting through a CB1 receptor-independent mechanism without the development of tolerance and signs of addiction was reported in mice (Hayakawa et al., 2007).

CBD at any of the doses tested appears not to cause rats trained to discriminate the drug from the vehicle to exhibit THC-like discriminative stimulus effects (Vann et al., 2008).

CBD reduced the heroin-seeking behaviour in rats and the result was interpreted as a sign of its potential for treatment of the effects of craving in drug addiction (Ren et al., 2009).

In Sprague-Dawley rats, a low dose of CBD (5 mg/kg) did not change the threshold frequency required for intracranial self-stimulation, while high doses (10 mg/kg and 20 mg/kg) elevated the threshold, which suggests diminution of their reward activity. Such effects were shown to be the opposite to those of drugs of abuse such as cocaine, methamphetamine, or opioids (Katsidoni et al., 2013).

Cannabidiol reduced the self-administration of methamphetamine in rats and behaviour associated with seeking this drug after its withdrawal (Hay et al., 2018).

CBD suppressed drug-seeking behaviour in mice trained for condition place preference (CPP) induced by cocaine (Calpe-López et al., 2019).

The repeatedly reported effects of CBD in the suppression of states of addiction are associated, according to the results of a preclinical pharmacological study, with the following mechanisms of its action: a) negative allosteric modulation of CB1 cannabinoid receptors; b) agonistic stimulation of cannabinoid CB2 receptors; c) potential stimulation of vanilloid receptors (TRPV1) and serotonergic 5HT1A receptors. These CBD receptor mechanisms may modulate the dopaminergic effects of drug abuse in the mesolimbic system, which is considered to be a major target of the suppressive effects of CBD on addiction (Galaj et al., 2020).

It was reported that CBD could act as a beneficial compound to treat states of illicit stimulant drugs of abuse as its intracerebroventricular microinjections suppressed the expression of methamphetamine-induced Condition Place Preference in rats (Anooshe et al., 2021).

B. Examples of results from available human studies (2012–2021)

CBD was well tolerated in a randomized, double-blind, crossover, placebo-controlled trial comparing the acute pharmacological influences of THC and CBD in healthy male volunteers. No differences were found between the effects of CBD and a placebo, while THC had marked acute behavioural and physiological effects (anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication with an increase in heart rate; Martin-Santos et al., 2012).

In a randomized double-blind placebo-controlled study evaluating the effects of inhaled CBD or placebo by smokers wishing to stop smoking cigarettes, the treatment significantly reduced the number of cigarettes smoked by ~40% and this effect persisted even after the withdrawal of CBD. Thus, the results of this clinical trial were presented as highlighting the potential of CBD for the treatment of nicotine dependence and to support data available from other preclinical studies suggesting a possibility of treatment with CBD in various states of addiction (Morgan et al., 2013).

CBD as an intervention in addictive behaviour measured in both preclinical and clinical studies highlighted its suggested therapeutic use in human addictions to cocaine, opioids, and psychostimulants, including cannabis and tobacco (Prud'homme et al., 2015).

High doses of CBD were reported to cause opposite effects to those of THC, and when given orally up to 800 mg did not produce abuse-related subjective effects reported from frequent marijuana smokers (Grotenhermen et al., 2016/2017).

CBD was repeatedly evaluated in frequent marijuana smokers as a placebo-like agent (Babalonis et al., 2017).

The effects of cannabidiol were reported to alleviate the symptoms of alcohol-induced liver damage, inflammatory response, metabolic deregulation, and steatosis (Yang et al., 2014; Wang et al., 2017).

Cannabidiol was reported to inhibit oxidative stress processes and increase autophagy, i.e. the lysosomal degradation of proteins, one of the mechanisms maintaining cellular homeostasis impaired by alcohol-induced steatosis (De Ternay et al., 2019; Turna et al., 2019).

Cannabidiol was reported to have the potential to protect not only the liver but also the brain and attenuate alcohol consumption (Nona et al., 2019).

Extensive analyses of the relationship between the protective effects of cannabidiol against changes caused by addiction to psychostimulants have shown beneficial effects such as a) suppression of the increased activity of the mesolimbic dopaminergic system in the "Reward Pathway" and other neurotransmitter systems; b) the reduction of neuroinflammatory responses; c) improvement in immune changes; d) improvement of cognitive functions (e.g. also erasing adverse memories related to drug use), and thus facilitation of the consolidation process (Calpe-López et al., 2019).

Cannabidiol was proposed as a treatment option for opioid use disorder as, in contrast to a placebo, it significantly reduced the signs of heroin withdrawal in a clinical double-blind randomized placebo-controlled trial (Hurd et al., 2019).

CBD was consistently shown to cause opposite effects to those of THC in clinical studies, and it was also repeatedly confirmed as a possible treatment for nicotine dependence (Blank et al., 2020).

In healthy volunteers, no evidence of withdrawal syndrome was found as a result of the abrupt discontinuation of treatment with cannabidiol (Taylor et al., 2020).

The repeatedly reported clinical effects of CBD in the suppression of states of addiction are associated, according to the results of a preclinical pharmacological study, with the following mechanisms of its action: a) negative allosteric modulation of CB1 cannabinoid receptors; b) agonistic stimulation of cannabinoid CB2 receptors; c) potential stimulation of vanilloid receptors (TRPV1) and serotonergic 5HT1A receptors. These receptor mechanisms of CBD may modulate the dopaminergic effects of drugs of abuse in the brain (Galaj & Xi, 2020).

The demonstrated beneficial efficacy of cannabidiol in states of addiction, in general, may also depend on some other factors, including the dosage or route of administration used, i.e. before, with, or after addiction (similar to schizophrenia, anxiety, mood disorders, sleep disorders, post-traumatic stress disorders, anorexia nervosa and eating disorders, dementia, epileptic syndromes; Fernández-Ruiz et al., 2020).

The efficacy of CBD in reducing craving and also preventing relapse was reported from a randomized double-blind placebo-controlled trial in people with cocaine use disorder (Mongeau-Pérusse et al., 2021). The authors recommend focusing further randomized clinical trials on the efficacy of CBD in the treatment of substance use disorders on the evaluation of the following biomarkers of efficacy: a) peripheral biomarkers of the endocannabinoid system, such as plasma cannabinoid levels; b) short-term parameters (craving); c) adherence to long-established abstinence, such as dose reduction or harm reduction.

● 4 CONCLUSION

The authors of the above-mentioned scientific papers recommend cannabidiol as an alternative treatment for mood disorders, including addictions. On the basis of all of the above-cited results of both preclinical and clinical studies, it can be concluded that the non-psychotropic cannabinoid cannabidiol (CBD) is expected to become a therapeutic agent for the treatment of substance use disorders and some of their comorbidities. Further large-scale studies must establish rules for clinical applicability.

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