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The therapeutic potential of cannabidiol in neuropsychiatric and neurodegenerative disorders

Sâmia Joca[1] and Francisco S. Guimarães[2]

[1]Department of Biomedicine, Aarhus University, Aarhus, Denmark and [2]Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil

Editorial

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Corresponding author:
Sâmia Joca; Email: sjoca@biomed.au.dk

This Special Issue of Acta Neuropsychiatrica focuses on the role of cannabinoids in psychiatry (Wegener, 2024). In this context, it is relevant to highlight the studies on cannabidiol (CBD), a prominent non-psychoactive constituent of '*Cannabis sativa*', which has garnered significant attention over the past decade for its wide-ranging therapeutic potential. Unlike delta-9-tetrahydrocannabinol, which is responsible for the psychotomimetic effects of cannabis, CBD offers a unique pharmacological profile that has made it a subject of interest in treating neuropsychiatric and neurodegenerative disorders. As cannabis products gain mainstream acceptance, with increasing legalisation for both medicinal and recreational use, the need to separate and understand the benefits of its individual components has never been greater.

Cannabidiol's influence on memory processes: implications for addiction treatment

Addiction is often sustained by the reinforcement of reward-contextual memories, where environmental cues are strongly associated with drug use, thus driving relapse. A study in the current issue investigated the effects of CBD on reward memories induced by cocaine in male and female mice and revealed that CBD can effectively weaken these contextual associations. This finding has implications for addiction treatment, particularly in preventing relapse triggered by environmental cues. The study demonstrated that male and female mice exhibited a reduced preference for drug-paired environments when administered CBD, suggesting that CBD may attenuate the salience of drug-associated memories (Brianis *et al.*, 2024). From a broader perspective, other research has shown that the endocannabinoid system, of which CBD is a modulator, plays a crucial role in memory consolidation and extinction. By influencing endocannabinoid signalling, CBD could promote the extinction of harmful memories linked to substance abuse. In humans, this could mean that CBD may help individuals with substance use disorders to 'forget' or diminish the impact of the cues that lead them to relapse. Some literature further suggests that CBD might enhance cognitive flexibility, allowing individuals to break free from the rigid thought patterns that often underlie addiction behaviours (Mechoulam & Parker, 2013).

Neuroprotection and disease modulation: CBD in neurodegenerative disorders

Neurodegenerative diseases with impaired motor function, such as Parkinson's and Alzheimer's, involve the progressive loss of neurones, often accompanied by neuro-inflammation and oxidative stress. These conditions lack curative treatments, making CBD's neuroprotective properties an exciting area of study. In a preclinical model of parkinsonism, CBD demonstrated not only the ability to alleviate non-motor symptoms but also to promote neurogenesis – specifically the maturation of newborn neurons in the hippocampus, a region critical for memory and learning. Using bilateral injections of the neurotoxin 6-hydroxy-dopamine (6-OH-DA) into the substantia nigra pars compact as a model of Parkinson's disease, De Mattos and colleagues (2024) showed that repeated post-lesion CBD daily treatment for 13 days decreased mortality rate, dopamine neurone loss in SNpc, and the expression of neuroinflammatory markers in the striatum (de Mattos *et al.*, 2024). CBD also attenuated motor (locomotor activity) and non-motor (memory deficits in the novel object recognition test and increased immobility in the forced swimming test) changes. These effects were associated with a facilitation of hippocampal adult neurogenesis.

These studies suggest the potential of CBD as a therapeutic agent for diseases marked by inflammation and neuronal loss. Literature on neurodegeneration supports the idea that CBD's neuroprotective effects may be mediated through several mechanisms. One of the most notable is its ability to modulate oxidative stress. Reactive oxygen species (ROS) are a hallmark of neurodegenerative diseases, and CBD has been shown to reduce ROS production and enhance mitochondrial function, which is crucial for cellular health. By mitigating oxidative damage,

CBD may slow the progression of neuronal death, offering hope for conditions like Alzheimer's, where oxidative stress and inflammation are major pathological factors (Esposito *et al.*, 2006).

In another study, also studying motor function Abiola Kajero and colleagues (2024) show that repeated treatment with a low dose (5 mg/kg P.O.) of CBD decreased the vacuous chewing movements observed in rats after 21 days of haloperidol i.p. injections. However, a smaller improvement was observed when a much higher dose of haloperidol decanoate (50 mg/kg IM) was administered monthly over 90 days. The result reinforces the proposal that CBD could help prevent TD development associated with repeated first-generation antipsychotic treatment (Kajero *et al.*, 2024).

Molecular mechanisms: insights into CBD's modulation of adenosine receptor signaling

At the molecular level, CBD's interaction with various receptor systems is essential to understanding its diverse effects. In this issue, we show the ability of CBD to modulate adenosine A2A receptors. Adenosine receptors are involved in various physiological processes, including sleep regulation, neuroprotection, and inflammation. The study directly investigates the effects of CBD on adenosine A2A receptors (A2AR). Using HEK-293T cells transfected with the cDNA encoding the human A2AR and Gαs protein, it was shown that CBD does not bind orthosterically to these receptors but, instead, negatively modulates their function by reducing the receptor's signalling capacity by inhibiting its coupling with Gαs proteins. This negative modulation of A2A receptor activity suggests that CBD may help balance neurotransmitter systems, particularly in disorders characterised by receptor hyperactivity, such as Parkinson's disease (Sanchez-Fernandez *et al.*, 2024). Since A2A receptors have been implicated in several disorders and physiological processes, these results could help explain some of CBD's complex pharmacological effects.

This finding is particularly relevant for conditions involving neuroinflammation and overactivation of the adenosine system. In animal models, blocking A2A receptors has been shown to reduce neuroinflammation and protect against neurodegeneration. CBD's ability to modulate A2A receptor activity without directly blocking it suggests a novel mechanism for reducing inflammation and providing neuroprotection, with fewer side effects than traditional A2A antagonists (Pandolfo *et al.*, 2011).

Effect on psychiatric comorbid diabetes mellitus (DM)

The study of psychiatric comorbidities associated with diabetes mellitus (DM) is a significant but sometimes overlooked problem. Based on reports that DM can precipitate the development of post-traumatic stress disorder, Chaves and colleagues (2024) investigated if the CBD would interfere with fear consolidation in male rats subjected to a type-1 DM model (streptozotocin injection). They showed that a single CBD administration impaired contextual fear consolidation, an effect that persisted for one week. This effect was associated with reducing the Arc protein, a product of an immediate early gene necessary for memory consolidation, in the dorsal hippocampus (Chaves *et al.*, 2024).

Future directions and clinical implications

The clinical translation of CBD remains a challenge due to its complex pharmacology and interactions with multiple systems. While the preclinical evidence is compelling, human trials are still needed to fully understand the dosage, efficacy, and long-term safety of CBD in treating these disorders. Nonetheless, as also observed with papers in this issue of Acta Neuropsychiatrica, there are links to several promising therapeutic avenues for CBD, particularly in treating neuropsychiatric disorders like schizophrenia and anxiety, as well as neurodegenerative diseases like Parkinson's and Alzheimer's.

Conclusion

CBD's multi-targeted effects – ranging from memory modulation and antipsychotic properties to neuroprotection and receptor signalling – highlight its therapeutic versatility. The absence of significant psychotomimmetic or addictive properties makes CBD an attractive candidate for clinical use. However, the integration of CBD into mainstream medicine requires more rigorous clinical studies.

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