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Cannabidiol mitigates cognitive impairment from LPS-induced neuroinflammation in mice

Sultan MENTE [1], Elif Beyzanur POLAT[1], Hümeysa Kiyak-Kırmacı[2], Büşra ERTAŞ [1*]

1 Department of Pharmacology, Faculty of Pharmacy, Marmara University, Istanbul, Türkiye.
2 Department of Pharmacology, Faculty of Pharmacy, University of Health Sciences, Istanbul, Türkiye
* Corresponding Author. E-mail: busra.ertas@marmara.edu.tr (B..E.); Tel. +90- 0216 777 52 00.

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ABSTRACT: Cannabidiol (CBD) is a non-psychoactive substance derived from the *Cannabis sativa* plant, with anti-inflammatory and antioxidant effects. Neuroinflammation is a pathological process triggered by multiple mechanisms in the brain and progresses in a spiral manner, commonly encountered in the pathology of many neurodegenerative diseases. The effects of neuroinflammation on memory problems that begin in the early stages of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are discussed. In recent years, the search for effective drugs for these paradoxical pathologies has continued. Thus, our study aimed to evaluate the effect of CBD on learning and memory performance in a mouse model of lipopolysaccharide (LPS)-induced neuroinflammation. An in vivo neuroinflammation model was performed by administering LPS (2mg/kg; ip) to C57BL/6J mice on days 1 and 3. Mice that were given CBD treatment for 21 days were subjected to neurobehavioral tests on the last 4 days. In the open field test, no difference was observed between the groups in terms of spontaneous movements and anxiety. In the novel object recognition test, the movement time to recognise the new object was longer in the CBD treatment group than in the LPS group. Finally, in the passive avoidance test, the delay in moving to the dark compartment was longer in the CBD-treated group than in the LPS group. As a result, the cognitive functions impaired by LPS administration can be improved with CBD treatment, and the study will be carried forward by supporting these behavioural results with neurobiochemical results.

KEYWORDS: Cannabidiol; neuroinflammation; lipopolysaccharide; cognitive decline; neurobehavioral test.

1. INTRODUCTION

The central nervous system (CNS) has components that cooperate in response to unusual stimuli. In addition to neuronal cells, the brain also contains microglia and astrocytes that play the role of macrophages. Microglial activation creates immune responses and plays a role in preventing damage that can be caused by toxic substances and inflammatory events in normal physiological conditions. The inadequacy of the response against inflammation adds to the pathologies of neurodegenerative diseases and causing the damage to become more complex. In Alzheimer's disease and Parkinson's disease, inadequate defence against inflammation results in the deterioration of neuronal structures, the rupture of synaptic connections, the death of neuronal cells, and is associated with the emergence of consequences that affect the daily lives of patients decades later. Therefore, supporting inflammatory responses is considered as a treatment option to prevent memory-related consequences of neurodegenerative diseases [1].

Cannabidiol (CBD) is one of the primary phytocannabinoids derived from *Cannabis sativa*, distinguished by its non-psychoactive profile, in contrast to Δ9-tetrahydrocannabinol (THC), which exerts euphoric effects through high-affinity binding to CB1 receptors [2]. While CBD does not induce psychoactive responses, it has attracted increasing scientific interest for its neuroprotective, anti-inflammatory, and antioxidant properties. In models of neuroinflammation, such as lipopolysaccharide (LPS)-induced paradigms, CBD has been shown to modulate multiple molecular targets and signaling pathways [3]. Notably, it suppresses nuclear factor-kappa B (NF-κB) activation, reduces pro-inflammatory cytokine release (e.g., TNF-α, IL-1β, IL-6), and regulates microglial activation, thereby attenuating the neuroinflammatory response [4]. Additional mechanisms include modulation of adenosine A2A receptors, interaction with transient receptor potential vanilloid 1 (TRPV1) channels, and reduction of oxidative stress via preservation of intracellular glutathione

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levels and stabilization of mitochondrial function. In LPS-induced models, several studies have also demonstrated that CBD enhances BDNF-TrkB signaling, inhibits GSK3β activity, and reduces phosphorylated tau accumulation-suggesting its potential in mitigating neurodegenerative processes [5]. Thus CBD is increasingly recognized as a promising therapeutic agent for the treatment of neuroinflammation and its associated cognitive impairments.

LPS, a major component of the outer membrane of gram-negative bacteria, increases cytokine expression in the brain via microglial activation. In addition, numerous studies have reported deterioration in learning-memory performance in LPS-induced in vivo neuroinflammation models [6]. Based on these data, we aimed to investigate the changes in cognitive performance in the LPS-induced mice model treated with CBD.

2. RESULTS

2.1. Open Field Test

As seen in Figure 1, the time spent in the center zone, the latency to enter center, the number of groomings and rearings did not show any significant difference between the groups.

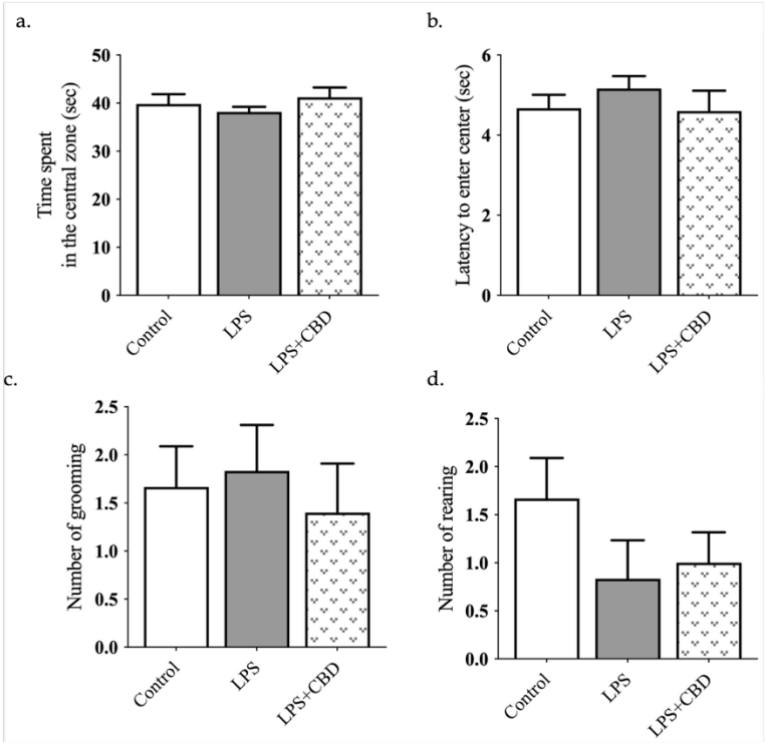

Figure 1. Effect of CBD treatment on the locomotor movements of LPS-induced mice in the open field test. a) time spent in the central zone, b) Latency to enter the centre, c) number of grooming, and d) number of rearing.

2.2. Novel Object Recognition Test

In the NORT test, DI value was significantly decreased ($p < 0.001$) in the LPS-treated group compared to the control group, while the DI value was significantly increased ($p < 0.001$) in the CBD-treated group compared to the LPS-induced group (Figure 2).

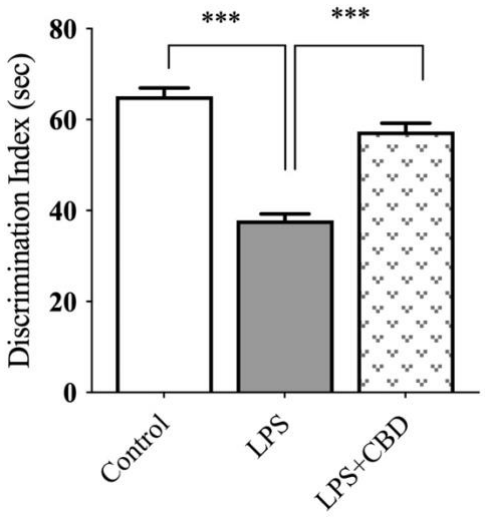

Figure 2. Effect of CBD treatment on the discrimination index of LPS-induced mice in the novel object recognition test

2.3. Passive Avoidance Test

As shown in Figure 3, the step-through latency to the dark compartment was markedly ($p < 0.001$) reduced in the LPS group compared to the control group. On the other hand, this latency was significantly longer in the CBD-treated group than in the LPS group.

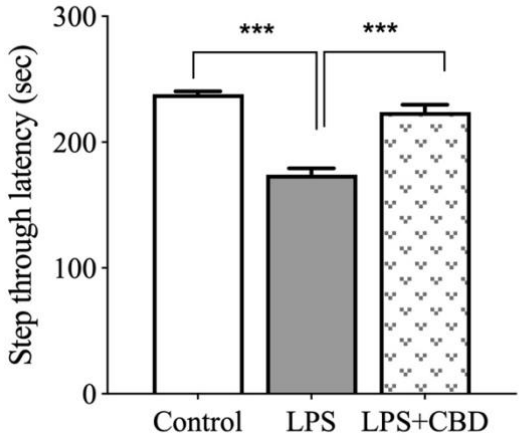

Figure 3. Effect of CBD treatment on the step-through latency of LPS-induced mice in the passive avoidance test

3. DISCUSSION

Uncontrolled neuroinflammation is increasingly recognized as a key contributor to the onset and progression of neurodegenerative disorders. In particular, elevated levels of pro-inflammatory cytokines and persistent activation of microglia have been associated with early-stage cognitive deficits, including impairments in learning and memory. Experimental and clinical evidence suggests that such inflammatory processes not only exacerbate neuronal damage but also interfere with synaptic plasticity mechanisms critical for memory formation. Understanding and targeting these inflammatory pathways is therefore essential for the development of therapeutic strategies aimed at preventing or delaying neurodegeneration-related cognitive dysfunction.

This study provides an insight into the neuroprotective properties of CBD through its ameliorating effect on LPS-induced impaired cognitive functions. Firstly, OFT and NORT tests were performed to evaluate both anxiety levels and spontaneous movements as well as short-term memory functions, respectively. In OFT, the time spent in the central zone, the first time entered the central zone, the number of rearings and the

number of ornamentations did not differ between the groups. To evaluate both anxiety levels and spontaneous movements and short-term memory functions, OFT and NORT tests were performed, respectively. In OFT, the time spent in the central zone, the first time entered the central zone, the number of rearing and the number of grooming did not differ between the groups. Accumulated data showed that hypolocomotion can be observed in LPS administration [7, 8]. However, the lack of difference compared to the control group can be interpreted as tolerance to the hypolocomotion effects of LPS over time. On the other hand, previous studies have shown that CBD application does not cause any impairment in spontaneous movements in other in vivo models, which is consistent with the results of our study. The functionality of short-term memory requires the coordination of different regions of the brain [9]. Neuronal connectivity in the prefrontal cortex and hippocampus provides short-term learning-memory integration [10]. The lack of significant change in novel object exploration times in mice and rats in LPS-induced in vivo models may be related to the inflammatory process in the brain regions. In our study, the decrease in DI in the LPS group compared to the control indicates LPS-induced short-term memory impairments. On the other hand, the increase in DI shown by CBD treatment may have a neuroprotective effect against LPS-induced inflammation. In the PAT, LPS-induced neuroinflammation has been shown to impair memory functions, as evidenced by decreased latency times in rodents. This cognitive decline is associated with increased levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), and activation of microglial cells in the hippocampus [11]. Our study demonstrates that CBD treatment ameliorates these deficits, restoring latency times in the PAT to levels comparable to control groups. This effect is consistent with previous findings where CBD administration improved memory performance and reduced IL-1β serum levels in LPS-treated rats [12]. The neuroprotective effects of CBD are attributed to its anti-inflammatory properties, including the inhibition of pro-inflammatory cytokine production and modulation of microglial activation. These results suggest that CBD has potential therapeutic value in mitigating cognitive impairments associated with neuroinflammatory conditions.

4. CONCLUSION

The present study shows that cannabidiol has a neuroprotective effect in improving LPS-induced impaired short-term memory and cognitive performance. These effects may be due to the prevention of LPS's stimulation of the proinflammatory pathway by microglial activation and cannabidiol's antioxidant and anti-inflammatory effects. However, further studies are needed to elucidate the relationship between this effect of cannabidiol and changes in neuronal structures.

5. MATERIALS AND METHODS

5.1. Animals

Twenty-one adult 8-week-old male albino mice (23-25 g) of the C57BL/6J male mice strain were purchased from Experimental Animal Application and Research Laboratory at Medeniyet University (DEHAL). Animals were housed in a pathogen-free facility and optimum laboratory conditions appropriate to their physiological characteristics before and after the study began: under a controlled temperature (22–23 °C), on 12-h light/dark cycles, and were supplied with standard chow and tap water ad libitum. To ensure that the drug administration and behavioural studies were appropriate for the animal's welfare, the researcher performed the handling procedure one week before the experiment. All protocols in this study were approved by the Animal Ethics Committee of the Medeniyet University (Protocol No:70)

5.2. Experimental design for drug treatment

The mice groups randomly divided into three groups: Control group, LPS group, and LPS + CBD group. All mice except of control group were injected with 2 mg/kg LPS (dissolved with saline) intraperitoneally (i.p) on 1th and 3rd days. The CBD-treated group received 10 mg/kg CBD (dissolved with vehicle –(%10 ethanol + %10 Tween80 + %80 saline)) via i.p for 21 consecutive days. The control group was treated with the same vehicle solution. Neurobehavioral assessments were recorded at 17, 18, 19, and 20. days. After these tests, mice were anaesthetised and sacrificed via cervical dislocation.

5.3. Open Field Test

OFT allows the evaluation of spontaneous locomotor movements, exploratory behaviours and anxiety level. The animals were placed in a box measuring 40x40x40 cm, and whose bottom was divided into 4

horizontal and vertical lines. The movements of all animals were recorded with a video camera for 3 min and scored. After each animal, the box was cleaned with ethanol and prepared for the next animal. The time spent in the centre period, the first time passing to the centre, and the number of rearings and ornamentations for each group were recorded [13].

5.4. Novel Object Recognition Test

The NORT, which evaluates short-term memory and learning ability, was performed on the 18th day of the study. It is based on analysing the reconnaissance movements to distinguish two different objects from each other in a certain period . Initially, the animals' approach and interest movements on the objects in a box containing two identical objects (A+A) were monitored for 3 minutes. After 1 hour, one object was replaced with another of a different color and shape (A+B) and the same movements were monitored and recorded for 3 minutes. The total time spent with these different objects was recorded as Ta and Tb, and the difference score index was calculated according to the following formula: Discrimination Index: $(tA1 - tA1)/(tA1 + tB1)$ [13]

5.5. Passive Avoidance Test

The PAT test was divided into two stages. In the training phase, mice were placed in the lighted compartment of the passive avoidance apparatus. Mice that passed from the sensor door to the dark compartment were given an electric shock (0.8 mA, 3 seconds) after the door was closed. In this phase, all mice were given 300 seconds for the first transition to the dark compartment. After 24 hours, mice were placed in the bright compartment in the test phase. The delay in transition to the dark compartment of mice that were not given an electric shock was recorded [13].

5.6. Statistical Analyses

All data were analysed with GraphPad Prism 9.0 software using one-way ANOVA for multiple comparisons. Post hoc analyses were performed with Tukey's multiple-comparison test with significance set at * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. Data are presented as the mean ± S.E.M.

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