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The Effect of Cannabidiol on Myokine, Cerebral and Cardiac Response in Rats with Sepsis Induced by Cecal Ligation and Punture Method

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ABSTRACT

Background: The aim of this study was to investigate the effects of Cannabidiol on myokine (Irisin), cerebral (BDNF) and cardiac (cTnI) responses in sepsis-induced rats by Cecal Ligation Perforation (CLP) method.

Methods: In this study, 40 adult male Wistar albino rats, aged between 8-10 weeks, were used. 5 groups were created, with 8 rats in each group: Control (C), Sham (S), CLP, CLP+CBD 2.5 mg/kg, CLP+CBD 5 mg/kg group. Rats in groups C and Sham were sacrificed at the end of the 10th hour and intracardiac blood was taken immediately afterwards. In groups CLP, CLP+2.5 mg/kg, CLP+5 mg/kg, intra-abdominal sepsis was induced and at the end of the 10th hour after sepsis occurred with CLP application, rats were sacrificed and intracardiac blood was taken immediately afterwards. İrisin, BDNF and cTnI levels in the serum samples were measured by ELISA method.

Result: In the present study, mean serum irisin, BDNF and levels were determined to be at the lowest level in the CLP group, while cTnI levels were at the highest level ($p<0.01$). In CLP groups, serum irisin and BDNF levels increased due to CBD addition and the most significant decrease in cTnI levels occurred in 5 mg/kg CBD groups. As a result, it was concluded that CLP may be safe and beneficial when administered at a dose of 5 mg/kg in sepsis-induced rats.

Key words: Brain-derived neurotrophic factor, Cannabidiol, Cardiac troponin I, Cecal ligation perforation, Irisin, Rat, Sepsis.

INTRODUCTION

Sepsis accounts for 11 million deaths worldwide and the rise of multidrug-resistant organisms has increased the urgency surrounding the management of multidrug-resistant sepsis and is of critical concern to health authorities (Kumar *et al*., 2024). Sepsis is an important health problem with a variable incidence and consequences over time, characterized by high mortality and multiple organ failure caused by an irregular systemic inflammatory response to infection (Hotchkiss *et al*., 2016). Severe sepsis, complications of septic shock, multiorgan failure and hemostatic disorders leading to disseminated intravascular coagulation are formed (Gando *et al*., 2020). Adipokines and cytokines have important roles in the etiopathogenesis of sepsis due to their role in metabolic processes (Bayraktar, 2020). Irisin is an exercise-induced adipomyokine that is the product of cleavage of a type I membrane protein called fibronectin type III domain-containing protein 5 (FNDC5/FRCP2/PeP) (Boström *et al*., 2012). Irisin participates in hepatic glucose and lipid metabolism and converts white adipose tissue cells into brown adipose tissue cells, thus regulating glucose homeostasis by providing energy expenditure and also has a role in reducing oxidative stress in hepatocytes (Mo *et al*., 2016). Irisin has a role in thermogenesis, muscle cell glucose uptake and reduction of insulin resistance, muscle growth, neural and osteoblast differentiation through its effect on browning of white adipose tissue (Perakakis *et al*., 2017; Avgerinos *et al*., 2023). One of the organs affected by sepsis is the brain. Sepsis causes disruption of the blood-brain barrier, neuroinflammation and cerebral dysfunction with the accumulation of amyloid β and tau protein in the brain (Sekine *et al*., 2022). Brain-derived neurotrophic Factor (BDNF) is an important neurotrophic factor that plays a role in neurons' growth, survival and plasticity (Yu *et al*., 2021). BDNF plays an important role in sepsis-associated brain dysfunction and the development of long-term cognitive impairment (Pisani *et al*., 2023).Cardiac dysfunction is an important outcome that can develop as a result of sepsis and affects mortality

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with multiple organ failure (Zanotti-Cavazzoni and Hollenberg, 2009; Zaky *et al*.,2014). Cardiac adrenergic signaling is impaired in septic patients, further worsening cardiac function (El Shahat *et al*., 2018). Cardiac troponin I (cTnI) is a highly specific cardiac biomarker used to evaluate myocardial damage and diseases due to its release into plasma from cardiac myocytes in cases of heart attack and cardiac damage (Wu *et al*., 1996).

Sepsis is a medical emergency that requires rapid diagnosis and treatment because it can lead to severe septic shock. Medicinal and aromatic plants occupy an important place in traditional and complementary medicine due to the valuable phytochemicals they contain, which are used for therapeutic and preventive purposes in diseases. Cannabinoids are phytochemical compounds derived from the cannabis plant (Cannabis Sativa). The two most important cannabinoids are ∆9-tetrahydrocannabinol (∆9-THC) and cannabinoid (CBD), the latter being the main non-psychotropic cannabinoid and used in many pathological conditions, including neuropsychiatric disorders (Zuardi *et al*., 2006) and brain inflammatory diseases (Klein, 2005). CBD is reported to protect against sepsis-related heart and kidney damage by suppressing the cytokine storm (Maayah *et al*., 2024). The CLP rat model is highly preferred because it creates a clinical picture similar to the human sepsis model. In the literature research conducted, there was no study examining the Effect of CBD on myokine, cerebral and cardiac response in rats with sepsis caused by the CLP method. In this study, the effect of different doses (2.5 and 5 mg/kg) of CBD on myokine (irisin), cerebral (BDNF) and cardiac (cTnI) response was investigated in rats with sepsis caused by the CLP method.

MATERIALS AND METHODS

The study used 40 male Wistar rats, 12 weeks old and weighing an average of 200-240 grams, as animal material. Before starting the study, the Ethics Committee's approval was obtained from the Research Center Ethics Committee (Decision No: 2024/86-2). In the study, a polymicrobial sepsis model with cecal ligation perforation (CLP) was applied to the rats. All rats were given 25 mg/kg thiopental intraperitoneally. After the subjects were fixed in the supine position, the abdominal area was shaved 37 and wiped with povidone-iodine twice. Aseptic conditions were provided by covering with a sterile drape. The abdomen was opened with a 2 cm midline incision. The cecum was found and explored. The ileocecal valve was ligated with 3/0 silk from the distal and the anterior surface of the cecum was punctured twice with a 22 G needle. After observing the feces output, the abdomen was closed in two layers with 3/0 silk and a continuous suture. In the sham operation group, the cecum was found and explored. Afterward, the abdomen was closed in two layers without any further procedure. The composition of the experimental diet used in the study is shown in Table 1 and the chemical composition of Cannabidiol extract oil is shown in Table 2. The experimental protocol was formed as follows:

Control group (C) (n=8)

A group of clinically healthy rats without any problems and without any treatment.

Sham group (n=8)

Rats that underwent only laparotomy without cecal ligation and puncture (CLP).

CLP group (Sepsis group) (n=8)

CLP was performed on the subject to create intra-abdominal sepsis. After sepsis was created, the rats were sacrificed at the end of the 10th hour and intracardiac blood was taken immediately afterwards.

CLP + CBD 2.5 mg/kg group (n=8)

After cecal ligation and puncture (CLP), rats were injected intraperitoneally (i.p) with 2.5 mg/kg Cannabidiol (CBD) and sepsis was induced with CLP.

CLP+ CBD 5 mg/kg group (n=8)

After CLP rats were injected i.p with 5 mg/kg Cannabidiol (CBD) and sepsis was induced with CLP.

Collection of serum samples

Rats in groups C and Sham were sacrificed at the end of the 10th hour and intracardiac blood was taken immediately afterwards. In groups CLP, CLP+2.5 mg/kg, CLP+5 mg/kg, intra-abdominal sepsis was induced and at the end of the 10th hour after sepsis occurred with CLP application, rats were sacrificed and intracardiac blood was taken immediately afterwards**.** Blood samples were collected in tubes without anticoagulant and centrifuged in a

Table 1: Composition of experimental diet (%).

Ingredients	Quantity %
Maize	60.22
Soybean meal	15.01
Groundnut cake	6.04
Wheat offal	5.00
Bonemeal	3.50
Limestone	9.45
Salt	0.23
Methionine	0.19
Lysine	0.10
Premix	0.26
Total	100
ME (kcal/kg)	2672.70
Crude protein (%)	17.00
Crude fibre (%)	3.21
Ether extract (%)	3.02
Calcium (%)	4.70
Phosphorus (%)	0.89

refrigerated centrifuge (NF 1200R, NÜVE, Türkiye) for 10 minutes at 3000 rpm in the laboratory and the resulting sera were separated.

Measurement of serum irisin, BDNF and cTnI level

In measuring serum irisin, BDNF and cTnI levels obtained in the study, ELISA kit type-specific for rat irisin ELISA kit (Sinogeneclon, Cat. No SG-20179, CHINA), ELISA kit type-specific for rat BDNF Elisa Kit (SinoGeneclon, Cat. No: SG-20200, CHINA) and cTnI ELISA kit (BT LAB, Cat. No SG-20697, CHINA) an intra-assay coefficient of 8.0% and an inter-assay coefficient of 10.0% was utilized under the manufacturer's protocol.Serum irisin, BDNF and cTnI were measured using ELISA (RandD Systems, Minneapolis, MN, USA) and parameters were read with ELISA reader (Mindray MR- 96 A, CHINA). The results were evaluated by reading absorption values at 450 nm using the procedure reported in the kit.

Statistical analysis

Statistical data analyses were performed with SPSS version 15 (IBM, USA). Normality and homogeneity tests of the data were performed with Kolmogorov-Smirnov, Shapiro-Wilk and Levene's tests. Differences between groups were analyzed with the nonparametric Kruskal Wallis Test. The interaction between groups and time for repeated measurements (0 and 21 days) was analyzed with the general linear model (GLM). The significance level in the analysis results was accepted as $p<0.05$.

RESULTS AND DISCUSSION

Sepsis is a worldwide public health problem that poses a significant economic burden to the healthcare system due to its high morbidity and mortality rates. Sepsis is a life-threatening organ dysfunction characterized by an abnormal inflammatory response caused by a dysregulated host response to infection (Rudd *et al*., 2020). Irisin is a novel adipo-myokine with metabolic regulatory functions and it has anti-inflammatory, antioxidant and anti-apoptotic effects that may protect against sepsis-induced organ damage in experimental studies (Karampela *et al*., 2024). Serum irisin levels are decreased in patients with sepsis and negatively correlate with disease severity (Wei *et al*., 2020). In the rats constituting the study group, the mean serum irisin levels in the C, S, CLP, CLP+2.5 mg/kg, CLP+5 mg/kg groups at the 10th hour of the study were found to be 1.64, 1.27, 1.24, 1.32 and 1.43 ng/ml, respectively (Table 3). Our study's results are consistent with studies reporting that serum irisin levels decrease in sepsis (Wei *et al*., 2020;Wang *et al*., 2022; Wang *et al*., 2024). Although it is the first study to examine the effects of different doses of CBD, which is reported to have metabolic regulating and anti-inflammatory effects, on serum irisin levels in rats with sepsis induced by CLP, the studies are limited and are consistent with similar research results reporting that mean serum irisin levels increase with the therapeutic use of CBD or irisin hormone in rats with sepsis (Wei *et al*., 2020; Wang *et al*., 2022).We think that the reason for this situation is that CBD increases serum irisin levels, which has metabolism-regulating and anti-inflammatory effects and has anti-inflammatory, antioxidant and anti-apoptotic effects that may protect against sepsis-induced organ damage.

BDNF is a neurotrophic factor that affects neuronal proliferation and differentiation. In sepsis, p75 neurotrophin receptors are affected, leading to cognitive impairment (Ji *et al*., 2024). BDNF reduces septic myocardial dysfunction in rats *via* eNOS/NO pathway (Zeng *et al*., 2017). CBD has a neuroprotective effect by increasing the anti-inflammatory process and decreasing oxidative stress by affecting neurotrophin expression (Gava *et al*., 2024).In the rats constituting the study group, at the 10th hour of the study, the mean serum BDNF levels in the C, S, CLP, CLP+2.5 mg/kg, CLP+5 mg/kg groups were found to be 22.33, 16.56, 15.78, 17.11 and 18.08 ng/ml, respectively (Table 3). The lowest mean serum BDNF level was determined in the CLP groups due to increased inflammation-related damage in the brain caused by sepsis. Similarly, the most significant decrease in the CLP groups due to CBD administration was determined in the CLP+5 mg/kg groups, which has been reported to have anti-inflammatory and neuroprotective effects in sepsis groups ($p<0.01$). Gava *et al.* (2024) reported that CLP caused an increase in brain damage and that CBD had neuroprotective effects on memory impairment and neurotrophins, as well as against neuroinflammation and oxidative stress, mediated by PPARγ activation. Our study's results are consistent with studies reporting that serum BDNF levels decrease in sepsis (Zeng *et al*., 2017, Gava *et al*., 2024). CBD administration, which is reported to have neuroprotective and anti-inflammatory effects, is consistent with the results of studies reporting that serum BDNF levels increase in rats with CLP-induced sepsis (Gava *et al*., 2024). We think

Table 2: Composition of Cannabidiol oil extract.

Ingredients	wt %
CBD	92.99
Δ^9-THC*	0.16
CBC	<0.01
CBG	4,72
Δ^8-THC	<0.01
CBDv	0.34
THCv	<0.01
CBN	<0.01
CBL	<0.01

CBD: Cannabidiol, Δ^9 -THC: (-)-Δ-9-tetrahydrocannabinol ((-)-Δ-9-THC), CBC: Cannabichromene, CBG: Cannabigerol, Δ^8 -THC: Δ-8-Tetrahydrocannabinol, CBDV: Cannabidivarin, THCv: Tetrahydrocannabivarin, CBN: Cannabinol, CBL: Cannabidiol; wt% (weight of solute/ weight of solvent*100 = Per cent of solute in the solution).

Table 3. Mean serum irisin, BDNF and cTnI values (ng/ml) and statistical comparisons (Mean±SD) of the study groups.

Groups	İrisin (ng/ml)		BDNF (ng/ml)		cTnI (ng/ml)	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Control	1,64	0.04	22,33	1,23	0.43	0.13
Sham	1,27	0.10	16,56	1,47	0.93	0.11
CLP	1,24	0.05	15,78	1,23	0.98	0.21
CLP2.5	1,32	0.06	17,11	1,18	0.91	0.22
CLP5.0	1,43	0.03	18,08	,56	0.78	0.11
Diet	<0.01		<0.01		<0.01	

*BDNF: Brain-Derived Neurotrophic Factor, cTnI: Cardiac Troponin I, Control (C), Sham (Rats that underwent only laparotomy without cecal ligation and puncture (CLP)), CLP (CLP was performed on the subject to create intra-abdominal sepsis), CLP + CBD 2.5 mg/kg (After cecal ligation and puncture (CLP), rats were injected intraperitoneally (i.p) with 2.5 mg/kg Cannabidiol (CBD) and sepsis was induced with CLP), CLP+ CBD 5 mg/kg (After CLP rats were injected i.p with 5 mg/kg Cannabidiol (CBD) and sepsis was induced with CLP).

that the reason for this situation is that CBD increases BDNF expression due to its neuroprotective effect against neuroinflammation and oxidative stress in the brain in sepsis.

Cardiac dysfunction in sepsis is characterized by decreased contractility, impaired ventricular response to fluid therapy and sometimes ventricular dilatation (Kakihana *et al*., 2016). Sepsis-induced myocardial dysfunction increases mortality in sepsis, but the underlying mechanisms remain unclear.In the rats constituting the study group, at the 10th hour of the study, the mean serum BDNF levels in the C, S, CLP, CLP+2.5 mg/kg, CLP+5 mg/kg groups were found to be 0.43, 0.93, 0.98, 0.91 and 0.78 ng/ml, respectively (Table 3).The highest mean serum cTnI level was determined in CLP groups due to increased cardiac damage due to sepsis. Similarly, the most significant decrease in CLP groups due to CBD administration was determined in CLP+5 mg/kg groups, which has been reported to have a cardioprotective effect in sepsis groups ($p<0.01$). The results of our study are consistent with the results of studies reporting that serum cTnI levels increase in sepsis (Zhang *et al*., 2015; Wang *et al*., 2021; Zhang *et al*., 2021). CBD administration, which is reported to have cardioprotective effects, is consistent with the results of studies reporting that serum cTnI levels decrease in rats with CLP-induced sepsis (More *et al*., 2024). We think that this is due to the cardioprotective effect of CBD.

CONCLUSION

Sepsis is an acute organ dysfunction that develops as a result of a dysregulated host response to an infection. Irisin, with its metabolic regulatory function, has anti-inflammatory, antioxidant and anti-apoptotic effects that may protect against sepsis-induced organ damage, BDNF, neuroprotective effects on brain damage in sepsis and cTnI is a marker of cardiac damage. It is thought that examining irisin, BDNF and cTnI levels in sepsis management would be beneficial. As a result, it was concluded that CBD, which has been reported to have anti-inflammatory, neuroprotective and cardioprotective effects, may be safe and beneficial when applied at a dose of 5 mg/kg in sepsis groups.

Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments Central Research were approved by the Committee of Experimental Animal Care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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