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Original Article

Hippocampal damage in sepsis induced by lipopolysaccharide: The neuroprotective effects of pregabalin in a rat model

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Abstract

Aim: An excessive immune response to bacterial infections can lead to sepsis, a condition with a high mortality rate. Lipopolysaccharide (LPS)-induced inflammation and oxidative stress cause hippocampal injury. We aimed to investigate the antioxidant, anti-inflammatory and neurogenic effects of pregabalin (PG) against hippocampal injury induced by LPS.

Material and Methods: Twenty-four rats were divided into three different groups (Control, LPS (5 mg/kg), and LPS+PG (30 mg/kg)). Six hours after LPS administration, animals were sacrificed, and the hippocampus tissue was gathered for biochemical, histopathological, and immunohistochemical research.

Results: Biochemical and immunohistochemical analyses revealed the increased levels of total oxidant status (TOS), oxidative stress index (OSI), tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and decreased expressions of total antioxidant status (TAS), brain-derived neurotrophic factor (BDNF), and sirtuin-1 (SIRT-1) in LPS group. In addition, histopathological analyses detected degenerative neurons, hyperemia, and edema.

Conclusion: PG treatment reversed biochemical and immunohistochemical parameters and improved hyperemia, edema, and degenerative changes. In conclusion, PG increased BDNF and SIRT-1 levels by inhibiting inflammation and oxidative stress.

Keywords: BDNF; hippocampus; pregabalin; sepsis; SIRT-1

INTRODUCTION

Sepsis is a life-threatening condition of organ failure that decreases physical and cognitive functions and occurs due to the host's irregular response to infection (1). Despite the advances in understanding the pathogenesis of sepsis in recent years, sepsis and its related diseases are a serious reason for death. Encephalopathy, delirium, cognitive impairment and brain dysfunction are common complications of sepsis. (2). Inflammation and impaired mitochondrial functions in neurodegenerative diseases are also associated with oxidative stress due to the overproduction of reactive oxygen (ROS) species (3). Lipopolysaccharide (LPS) is a gram-negative bacterial endotoxin that is widely used to induce neuroinflammation. LPS increases the release of various inflammatory mediators and cytokines, causing neuroinflammation (4). Early prevention of inflammation in the central nervous system and control of oxidative stress can reduce the ratio of neurological diseases (5).

In the early stage of the inflammation process, tumor necrosis factor-α (TNF-α) regulates the development of early host response, while interleukin-1β (IL-1β) regulates cell migration and the release of other mediators (6). The neuroprotective role of sirtuin-1 (SIRT-1) has been shown in diverse central nervous system diseases, particularly, Alzheimer's and Parkinson's diseases (7). Brain-derived neurotrophic factor (BDNF) has multiple effects on neuronal development and facilitates neuronal transmission by providing synaptic flexibility. Synapse loss in the human brain tissue causes neurodegenerative diseases (8). The increase in ROS causes oxidative damage in the cell and deterioration in cell integrity. Proper regulation of harmful oxidative products such as ROS in the cell can prevent neurodegenerative diseases (9).

Pregabalin (PG) is not only an antiepileptic drug, but also a drug used in the treatment of different symptoms, including neuropathic pain (10). PG binds to the α2-δ subunits of voltage-dependent calcium channels at

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the presynaptic end, causing conformational changes in the calcium channel structure and reducing calcium entry into the cell (11). Thus, it reduces the release of e excitatory neurotransmitters such as glutamate, noradrenaline, P-substance and calcitonin gene-related peptide in overstimulated neurons and allows the cell to return to its normal physiological state (12). Studies have shown that pregabalin has have neuroprotective effects. It has been found that it significantly reduced hippocampal and cerebellum damage in aged rats caused by lipopolysaccharide (13). Gabapentin has been found to exhibit neuroprotective effects similar to methylprednisolone in experimental spinal cord injury (14). It is shown that in animals with multiple sclerosis, pregabalin mainly affects neuronal calcium channel trafficking, thereby reducing calcium-mediated cytotoxicity and neuronal damage (11).

Little is known about the antioxidant and neuroprotective impacts of pregabalin on the hippocampus in LPS-induced experimental sepsis model. Therefore, the purpose of this research is to analyze the therapeutic effects of pregabalin on the hippocampus in a sepsis model by evaluating biochemical and histopathological findings.

MATERIALS and METHODS

Experimental procedure

The research procedures were approved by the Local Ethics Committee of Animal Experiments, of Mehmet Akif Ersoy University (Ethic No: 661, 26/08/2020). The experiment was carried out in accordance with the animal research principles of the National Institute of Health.

Twenty-four male Wistar albino rats (300-350 g) were used in the study. Each rat was fed a normal commercial chow (Korkuteli Yem, Antalya, Turkey), with food and water present ad libitum, and was housed in a controlled environment (12 h light / dark cycle, temperature 22 ± 2ºC, and humidity 55-60%). Housing, feeding, and care conditions of the animals were similar in all groups. All animals that completed the experimental period were included in the study.

Twenty-four male Wistar albino animals were randomly divided into three different groups (n=8): control, LPS and LPS+PG. Animals in the control group were given a single dose of 0.1 ml saline, which was administered orally and intraperitoneally. Animals in LPS group were given 0.1 ml saline (a single dose, orally, 1 h before LPS injection) and 5 mg/kg dose of LPS (a single dose, i.p.) (LPS: Sigma-Aldrich, Steinheim am Albuch, Germany) (15). Animals in LPS+PG group were given 5 mg/kg of LPS (a single dose, i.p) and 30 mg/kg of PG (a single dose, orally) (PG: Lyrica, Pfizer, Turkey) (13). The pregabalin dose was determined based on previous neuroprotective studies.

Pregabalin was administered as a single dose one hour before LPS. Six hours after LPS application, all rats were sacrificed via ketamine-xylazine anesthesia (90 mg/kg ketamine (Alfamine, Alfasan IBV) and 10 mg/kg xylazine (Alfazin, Alfasan IBV). The right hemisphere was placed in 10% formaldehyde for histopathological analysis of the hippocampus. Later, the hippocampus tissue from the left hemisphere was precisely extracted, homogenized, and stored for biochemical analysis.

Biochemistry

The hippocampal tissue was analyzed for oxidative stress. Initially, hippocampal tissues were placed in phosphate buffer (pH 7.4) and shredded with a homogenizer (IKA Ultra-Turrax T25 Basic; Labortechnic, Staufen, Germany) and a sonicator (UW-2070 Bandelin Electronic, Germany). Then, the specimens were centrifuged at 4000 rpm for 10 min at +4oC for oxidant-antioxidant analysis. An automated colorimetric method developed by Erel was used for measuring the total antioxidant status. Antioxidant capacity in the specimens reduces dark blue-green 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS radical) radical to colorless decreased ABTS. Tissue Total antioxidant status (TAS) levels of the tissues were presented as µmol Trolox equiv/l and µmol H_2O_2 equiv/l (16). Total oxidant status (TOS) of the hippocampal tissue was defined using an automated colorimetric method. Oxidants in the specimens oxidize the ferrous ion-o-dianisidine complex to ferric ion, and in this case, glycerol in the environment accelerates this reaction and triples its speed. Ferric ions form a colored complex with xylenol orange in the acidic environment. The color density proportional to the number, of oxidants present in the sample was analyzed using a spectrophotometer. The absorbance change of the specimens was determined at 660 nm using a spectrophotometer. The results were presented as µmol H_2O_2 equiv/l (17). The values of oxidative stress index (OSI) in the samples were expressed as a percentage of TOS levels to TAS ratio (16).

Histopathology

Hippocampus specimens were gathered during the autopsy and constant in 10% buffered formalin. After the routine processing by an automatic tissue processor equipment (Leica ASP300S, Wetzlar, Germany), tissues were embedded in paraffin and sectioned at five µm thickness by a Leica RM2155 rotary microtome. Subsequently, the sections were stained with Hematoxylin-Eosin (H&E), coated with a mounting medium and analyzed under a light microscope.

Immunohistochemistry

The sections mounted onto polylysine-coated slides were immunostained with IL-1β [anti-IL1 beta antibody (ab9722)], TNF-α [anti-TNF alpha antibody (ab6671)], BDNF [Anti-BDNF Picoband antibody (PB9075), Boster,] and SIRT-1 [Anti-SIRT-1 antibody [E104] ab32441)] by the streptavidin biotin technique. All primary antibodies were used at 1/100 dilution. Then, the samples were incubated with primary antibodies for 60 minutes, followed by immunohistochemistry using biotinylated secondary antibody and streptavidin-alkaline phosphatase conjugate. EXPOSE Mouse and Rabbit Specific HRP/DAB Detection IHC kit (ab80436) was used as secondary antibody. Diaminobenzidine (DAB) was used as the

chromogen. For negative controls the primary antiserum step was omitted. All examinations were performed on blinded samples. To evaluate the severity of the immunohistochemical reaction of cells with markers, semiquantitative analysis was performed using a grading score ranging from (0) to (3) as follows: (0-) = negative, (1) = focal weak staining, (2) = diffuse weak staining, (3) = diffuse strong staining. For evaluation, 10 different areas under 40X objective magnification in each section were examined. Morphometric analyses and microphotography were performed using the Database Manual Cell Sens Life Science Imaging Software System (Olympus Co., Tokyo, Japan).

Statistical Analysis

Statistical evaluation of the data were done using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov Smirnov and Shapiro-Wilk tests were used for normal distribution of data. Levene test was used for the homogeneity of variance. Data were presented as mean ± standard deviations. P<0.05 was considered statistically significant. ANOVA (post hoc Duncan test) tests were used to comparison immunohistochemical scores and biochemical findings between the groups.

RESULTS

Biochemistry

TAS levels were significantly decreased in LPS group compared to the control group (p=0.011) and significantly increased in LPS+PG group compared to LPS group (p=0.005). TOS and OSI levels were significantly increased in LPS group compared to the control group (p = 0.001 and p < 0.001, respectively). TOS and OSI levels were significantly decreased in LPS+PG group compared to LPS group (p = 0.003 and p < 0.001, respectively). Biochemical data are shown in Table 1.

Table 1. Oxidative stress markers of hippocampus tissue

Groups	TAS (mmolTroloxequivalents/L)		TOS (mmolH_2O_2 Equiv./L)		OSI	
	Mean±SD	P value	Mean±SD	P value	Mean±SD	P value
Control	1.40±0.03	NS	7.15±2.42	NS	5.06±1.63	NS
LPS	1.29±0.06*	**0.011**	15.05±3.79*	**0.001**	11.65±3.10*	**0.019**
LPS+PG	1.42±0.09**	**0.005**	9.56±2.24**	**0.003**	6.72±1.46**	**0.042**

Data were expressed as means± SD. The relationships between groups were evaluated by Bonnferroni one-way ANOVA. *p < 0.05 compared with control group, **p < 0.05 compared with LPS group. NS: Not siginificant. TAS: Total anti-oxidative status; TOS: Total oxidative status, OSI: Oxidative stres index

Table 2. Statistical analysis of immunohistochemically positive cell numbers

Markers	Control group	LPS group	LPS+PG group	P value
BDNF	2.00±0.30^a	0.28±0.18^b	1.42±0.36^a	**0.001**
SIRT-1	2.14±0.14^a	0.28±0.18^b	1.00±0.30^c	**0.001**
IL-1β	0.14±0.14^a	1.71±0.28^b	0.42±0.20^a	**0.001**
TNF-α	0.00±0.00^a	1.00±0.30^b	0.14±0.14^a	**0.001**

* Statistical analysis of the scores were assessed by ANOVA. Differences between the groups were analyzed by Duncan tests, values represent mean ± standard deviation (SD). ** The differences between the means of groups carrying different letters in the same column are statistically significant (P < 0.001).

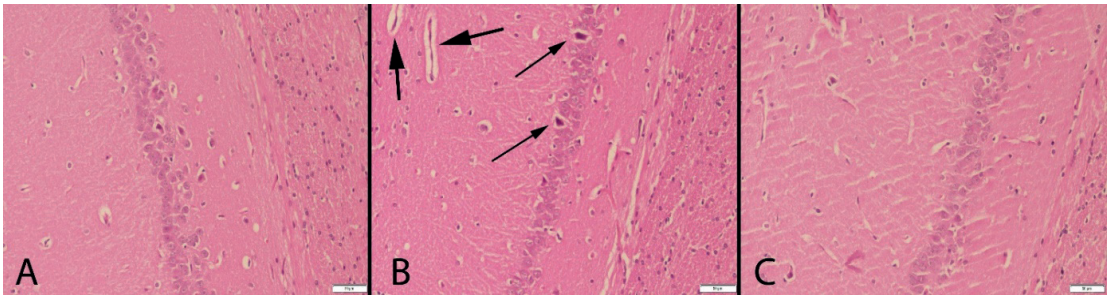

Figure 1. Hippocampus microarchitecture between the groups. (A) Normal hippocampus histology in control group; (B) numerous degenerated neurons (thin arrows) and marked edema around the vessels (thick arrows) in the LPS group; (C) marked amelioration in the LPS+PG group, H&E, Bars=50µm

Histopathology

The control group revealed normal tissue structure of the hippocampus. Degenerative neurons, hyperemia and edema were common findings in LPS-administered group. PG treatment caused marked mitigation in LPS+PG group (Figure 1).

Immunohistochemistry

Immunohistochemical examination of the control group showed marked BDNF and SIRT-1 expressions. LPS caused a significant decrease or a complete absence of BDNF and SIRT-1 expressions, but PG ameliorated the expressions (Figure 2,3).

Immunohistochemical examination of the hippocampus revealed a marked increase in IL-1β and TNF-α expressions in LPS group, however, PG treatment improved these expressions in LPS+PG group (Figure 4,5). The results of immunohistochemistry are shown in Table 2.

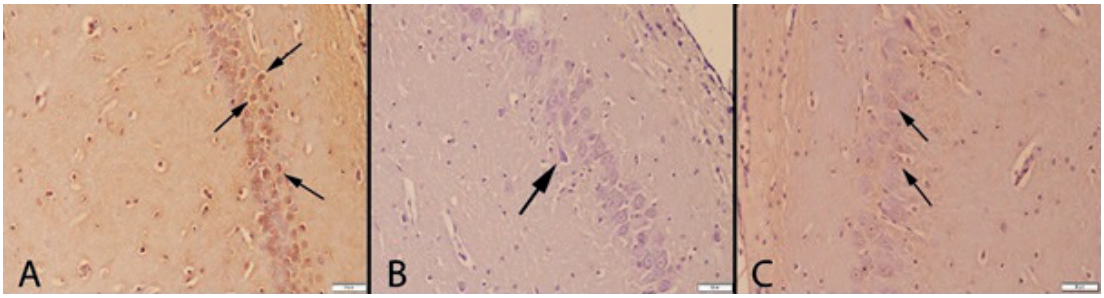

Figure 2. BDNF expression among the groups. (A) Evident expression in hippocampal neurons (arrows) in the control group; (B) negative immunoexpression and degenerated neurons (thick arrow) in the LPS group; (C) increased expression (arrows) in LPS+PG group, Streptavidin biotin peroxidase method, Bars=50μm

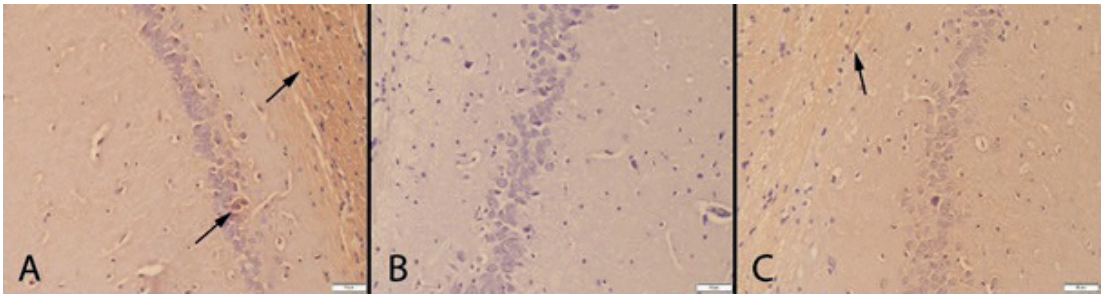

Figure 3. SIRT-1 expression between the groups. (A) Marked expression (arrows) in control group; (B) no immunoexpression in LPS group; (C) increased expression (arrows) in LPS+PG group, Streptavidin biotin peroxidase method, Bars=50μm

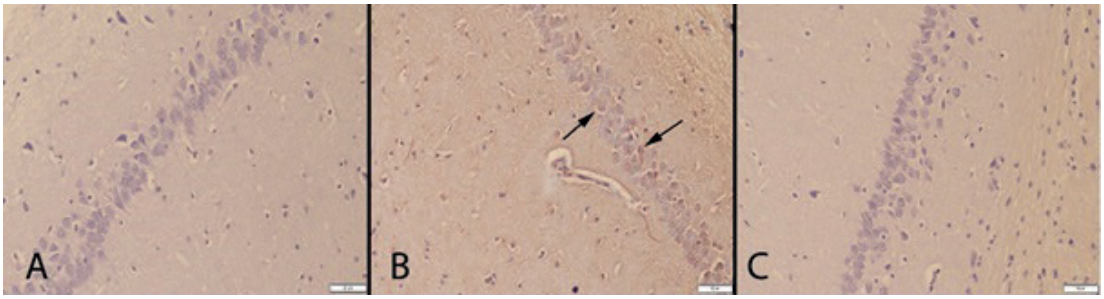

Figure 4. IL-1β expressions among the groups. (A) Negative expression in the control group; (B) increased expression in neurons (arrows) in the LPS group; (C) no expression in the LPS+PG group, Streptavidin biotin peroxidase method, Bars=50μm

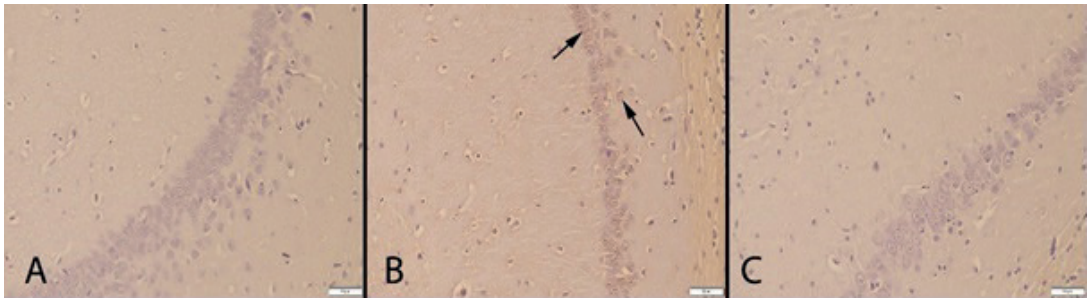

Figure 5. TNF-α expressions between the groups. (A) Negative expression in the control group; (B) increased expression in neurons (arrows) in the LPS group; (C) no expression in the LPS+PG group, Streptavidin biotin peroxidase method, Bars=50μm

DISCUSSION

PG is a pharmacological agent preferred in the therapy of epilepsy and neuropathic pain. Previous studies have shown that PG acts by reducing neurotransmitter release in the case of overstimulation of the nervous system (18). We tried to investigate whether PG has a therapeutic effect on the hippocampus, especially in the case of sepsis.

Reactive species play a vital role in normal physiological processes. However, when an excessive production of ROS cannot be controlled by the body's antioxidant enzyme systems, it causes damage to the cellular organization, lipids, proteins, and genetic materials (3). Moreover, it causes the oxidation of mitochondrial proteins, lipids and DNA. This mechanism is thought to be one of the major causes of oxidative stress (19). Previous experimental researches have described the link between oxidative stress and sepsis. In this regard, Ning et al. (2) investigated the neurodegenerative damage and neuroapoptosis in the brain of septic mice caused by LPS; Barichello et al. (20) demonstrated that a short-term oxidative damage could participate in the development of central nervous system symptoms during sepsis development or even septic encephalopathy. Sadraie et al. (5) investigated the impacts of berberine on LPS-induced learning and memory loss, and showed that LPS causes oxidative stress by increasing malondialdehyde levels on the hippocampus. In our study, TAS was decreased and TOS and OSI index were increased in LPS group. PG treatment reversed these negative effects and protected the hippocampus from oxidative stress by increasing the level of TAS. Similarly, Aslankoc et al. (13) showed the anti-inflammatory and antioxidative effects of PG on hippocampal and cerebellum damage.

Histopathology of the hippocampus revealed that degeneration, hyperemia and edema were common in hippocampal neuron cells in LPS group. Pretreatment of rats with PG before LPS significantly ameliorated neuronal injury and rearranged the histopathological model outside mild neuronal necrosis. El-Shoura et al. (21) detected neuronal necrosis, neurophagia, and local gliosis in LPS-stimulated sections of the rat brain.

TNF-α plays a major role in sepsis and endotoxic shock caused by gram-negative bacteria (22). Inflammatory cytokines such as TNF-α, IL-1β, IL-6 are the last general pathway in the physiopathology of brain damage in sepsis-associated encephalopathy. Zhu et al. (23) showed that the expressions of proinflammatory cytokines such as TNF-α and IL-1β were increased in hippocampal neurons stimulated by LPS. In a research investigating the impacts of acetaminophen on lipopolysaccharide-induced cognitive impairment, researchers suggested that TNF-α, IL-1β and IL-6 expressions rose in the mouse brain 6 hours after LPS administration (24). Similarly, our results showed that the expressions of IL-1β and TNF-α were increased in the hippocampus in LPS-induced sepsis model. PG treatment showed a regulatory and anti-inflammatory function by decreasing L1- β and TNF-α expressions.

BDNF plays many functional roles in the brain, including synaptic activity, neurogenesis, and the survival of neurons (25). Previous studies have shown that there was no significant reduction in hippocampal BDNF following LPS administration, but LPS did produce cognitive abnormalities without affecting BDNF expression (5, 26). One study showed a decreased hippocampal BDNF expression in an intranigral lipopolysaccharide-induced anxiety and depression model (27). In another study investigating the effect of nicotine on LPS-induced cognitive dysfunction in the rat hippocampus stimulated by LPS, the researchers showed that LPS reduced BDNF expression in the hippocampus (28). Considering our results, we found a significant decline in hippocampal BDNF expression following LPS administration, while PG treatment significantly increased it. We think that the reason for these differences is the experimental procedure and the dose of LPS.

SIRT-1 regulates NF-κB-induced inflammatory response and neurogenesis. In addition, it increases antioxidant enzyme activities to protect tissues against stress factors (15). In several previous studies, LPS administration has been shown to reduce SIRT-1 expression in LPS-induced experimental depression models (29,30). Similary, Savran et al. (31) showed that decreased SIRT-1 levels with LPS administration in all the brain and cerebellum tissues. We in the present research, showed decreased SIRT-1 levels with LPS adminisration in the hippocampus tissue, and PG treatment reversed these changes in the hippocampus.

CONCLUSION

The results of this research have shown that LPS induced inflammation, oxidative stress, and neurodegeneration in the hippocampal tissue. We hypothesized that PG treatment could reverse LPS-induced hippocampal damage. Our research has proved that, PG treatment increased TAS levels, BDNF and SIRT-1 expressions, and decreased TNF-α and IL-1β levels. In future sepsis studies, PG may be considered a protective agent in neuronal damage caused by increased inflammation and oxidative stress.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: Mehmet Akif Ersoy University, Ethic No: 661, 26/08/2020. .

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