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Neuroprotective Effects of Semaglutide in Endotoxemia Mouse Model

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ABSTRACT

Aims The present study aimed to examine the neuroprotective effects of semaglutide during endotoxemia and its role in modulating pro-inflammatory mediators.

Materials & Methods Twenty-four adult male Swiss albino mice, 8-12 weeks old, weighing 25-35g, were randomly divided into four equal groups (n=6), including sham (laparotomy without cecal ligation and puncture, sepsis (laparotomy with CLP), vehicle (equivalent volume of distilled water before CLP), and semaglutide (40µg/kg/day before CLP). The brain was used for tissue evaluation of TNF-α, IL-6, IL-1β, TLR4, and P-STAT3, as well as for histological examination.

Findings The tissue levels of TNF-α, IL-6 and IL-1β in the sham group were significantly lower than the sepsis and vehicle groups ($p<0.05$). In the semaglutide group, tissue levels of TNF-α, IL-6, and IL-1β were significantly lower than the sepsis and vehicle groups ($p<0.05$). The tissue levels of TLR4 and STAT3 in the sham group were significantly lower than the sepsis and vehicle groups ($p<0.05$). Also, tissue levels of TLR4 and STAT3 in the semaglutide group were significantly lower than the sepsis and vehicle groups ($p<0.05$). Histopathologically, semaglutide considerably reduced brain damage compared to the sepsis and vehicle groups.

Conclusion Semaglutide can reduce brain dysfunction during CLP-induced polymicrobial sepsis in male mice through its modulating effects on TLR4\STAT3 downstream signaling pathways and subsequently reducing inflammatory cytokines TNF-α, IL-6, and IL-1β.

Keywords Semaglutide; Endotoxemia; Sepsis

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Introduction

Endotoxemia means the presence of endotoxins in the blood, which are derived from gram-negative rod-shaped bacteria [1]. Sepsis is a systemic inflammatory response associated with infection, which in severe condition can lead to septic shock and multiple organ failure syndromes [2]. Sepsis is a global health problem. The World Health Organization estimates that sepsis affects more than thirty million people every year. It is responsible for more than six million deaths worldwide, one million of which are newborns [3]. Sepsis has been reported as the cause of more than 100 million individual deaths in 195 countries, accounting for 19.7% of all global deaths in 2017 [4]. In addition, septic shock is responsible for high mortality of 30-50% [5].

Sepsis causes cerebral dysfunction in the short and long term. In acute phase, it causes numerous clinical syndromes that are resulted in cognitive impairments, including Sepsis-Associated Encephalopathy (SAE), sickness behavior, delirium, cerebral ischemia, and hemorrhage [6]. Acute cognitive impairments, for unclear reasons, may continue for a long time, even after improvement of sepsis [7]. Sepsis induces disruption of the Blood–Brain Barrier (BBB), neuroinflammation, hypoperfusion, and accumulation of Amyloid β (Aβ) and tau protein in the brain [8].

Endotoxin acts as a potent stimulus for the release of pro-inflammatory cytokines, such as Tumor Necrosis Factor alpha (TNF-α), Interleukin-1β (IL-1β) and IL-6 [9]. Bacterial endotoxins could trigger STAT3's tyrosine phosphorylation [10]. Nuclear Factor kappa B (NF-κB) translocation is induced by activated STAT3, which then starts the production of cytokines [11]. Neurotransmitter alterations, synthesis of inflammatory cytokines, oxidative stress damage, mitochondrial dysfunction, and apoptosis are implicated in multifactorial pathophysiology of sepsis-associated encephalopathy [12]. However, the precise mechanisms involved are still unknown.

Toll-Like Receptors (TLRs) are type I transmembrane proteins. They are a panel of conserved Pattern-Recognition Receptors (PRR), activated by a variety of Pathogen-Associated Molecular Patterns (PAMPs), upregulate inflammatory-related genes and induce a complex intracellular signaling system, so, in higher animals, initiate an innate immune response and inflammation [13, 14]. TLR4 recognizes Lipopolysaccharide (LPS) and regulates the production of pro-inflammatory cytokines as TNF-α and IL-1β [15], as well as mediates infiltration and activation of inflammatory cells as a response to infectious pathogens [16].

Although no model reflects all the clinical complexities of sepsis, animal modeling is an appreciated method to study its underlying mechanisms to develop new therapeutic approaches [17]. The main animal model that used in sepsis research is the Cecal Ligation and Puncture (CLP) model. It induces lipopolysaccharide, which is the major component of gram-negative bacteria, which has been studied as a crucial modulator of the pathogenesis of bacterial infection and plays a crucial role in endotoxic shock [2, 18].

Currently, the management of acute sepsis-associated brain injury has focused on treating sepsis as the underlying disease, with no specific treatments to address brain dysfunction. Encouraging of the appropriate sepsis management can help prevent acute and long-term cognitive impairments that many patients experienced after sepsis [19].

Semaglutide is a human Glucagon-Like Peptide-1 (GLP-1) analog that has been researched for the treatment of obesity and type 2 diabetes [20]. Recently, semaglutide displayed a neuroprotective effect on several neurodegenerative diseases, suggesting that it may have a protective effect in Experimental Autoimmune Encephalopathy (EAE)-induced multiple sclerosis [21].

Semaglutide functions as a GLP-1 Receptor Agonists (GLP-1-RA) with four distinct mechanisms that regulate blood glucose and aid to lose weight loss. By encouraging insulin production from beta cells and inhibiting glucagon production from pancreatic alpha cells, semaglutide helps to enhance glycemic control. Semaglutide delays stomach emptiness to aid in weight loss, and because of its low molecular weight, it also increases satiety [20].

Semaglutide was created with the goal of creating a liraglutide analog with improved affinity for albumin binding to provide once-weekly dosage of a GLP-1 RA. It shares 94% of its sequence with native GLP-1, but there are three significant structural variations that allow for longer pharmacokinetics [20]:

1. The stability of the enzyme (DPP4) is increased by replacing Ala with Aib at position 8.
2. The C18 diacid chain and linker attachment at position 26 results in a strong albumin binding.
3. The incorrect site binding of C18 fatty acids is avoided by replacing Lys with Arg at position 34.

The aim of this study was to examine the neuroprotective effects of semaglutide during endotoxemia and its role in modulating pro-inflammatory mediators.

Materials and Methods

This study was done in Pharmacology and Therapeutics Department and Middle Euphrates Unit for Cancer Researches, Faculty of Medicine/University of Kufa, Iraq.

Design of the study

Twenty-four adult male Swiss albino mice, 8-12 weeks old, weighing 25-35g, were obtained from the College of Science, Baghdad University, Iraq. Mice were kept at a constant temperature of 25°C and humidity of 60-65%, with a 12h light: 12h dark cycle

in the animal house at the Collage of Science/University of Kufa.

Mice were randomly divided into four groups (6 mice in each group) as follows:

- Sham group: mice were anesthetized before laparotomy surgery without CLP.
- CLP group: mice underwent CLP (sepsis group)
- Vehicle group: mice were given an equal volume of Distilled Water (DW) by subcutaneous injection daily for 7 days before CLP.
- Semaglutide group: mice received 40µg/kg of Semaglutide (Novo Nordisk; Denmark), prepared by dilution with DW, subcutaneously once daily for 7 days before CLP [21].

Experimental procedure

Mice were anesthetized with 100mg/kg ketamine and 10mg xylazine intraperitoneally. The cecum was exposed through a 1.5cm midline incision after abdominal laparotomy. The cecum was then ligated right below the ileocecal valve and punctured twice with a G-20 needle before being returned to its anatomical location. After that, the abdomen was sutured with a 5.0 surgical suture. Mice were checked for various indicators of illness every 4h for 24h before being returned to their cages with unlimited food and drink. The surgical control group consisted of sham surgically operated mice (anesthesia and laparotomy without CLP) [22, 23].

Tissue preparation for TNF-α, IL1β, IL-6

Following 24 hours after CLP, mice were beheaded; brains were separated and rinsed in ice-cold phosphate buffer solution. They were maintained on ice and weighed before being sectioned into two major coronal slices, one of which was retained in 10% formalin for histological investigation. The final slice was combined in a 1:10 (w/v) ratio with ice cold 0.01M phosphate-buffered saline (PH 7.4) with 0.5% cocktail protease inhibitor, and then processed with an ultrasonic liquid processor. The homogenates were then centrifuged at 15,000g for 30 minutes at 4°C, and the supernatants were removed and kept at -80°C for detection of additional markers using the ELISA (Enzyme-Linked Immunosorbent Assay) method [24].

The formalin-fixed slices were processed to embed paraffin wax before being longitudinally cut into 5µm pieces. Then Hematoxylin and Eosin stain was used to stain the sections for histopathological examination [25].

A professional pathologist performed the histological examination (who was not aware of the study's design or the classification of each animal). The way to score brain damage is as follows [26]:

1) When there are no morphological signs of damage, the score is 0 (normal).
2) If there is edema, eosinophilic dark (pyknotic) neurons or dark shrinking cerebral purkenje cells, the score is 1 (slight).
3) If there are at least two small hemorrhages, the score is 2 (moderate).
4) If there are clear infarct foci (local necrosis), the score is 3 (severe).

Statistical analysis

SPSS 26 software was used for statistical analysis. The normality of the data was checked by the Kolmogorov-Smirnov and Shapiro-Wilk tests. One way ANOVA test was applied for normally distributed data (parametric data).

Findings

Pro-inflammatory markers (TNF-α, IL-6, IL-1β)

The brain levels of TNF-α, IL-6, and IL-1β were significantly higher in the sepsis and vehicle groups compared to the sham group ($p<0.05$). However, the brain levels of TNF-α, IL-6, and IL-1β in the treated group were lower (Table 1).

TLR4\STAT3 expression

The expression of TLR4\STAT3 in brain tissue in the sham group was significantly lower than that in both sepsis and vehicle groups ($p<0.05$). On the other hand, the brain tissue level of TLR4\STAT3 of the semaglutide-treated group was significantly ($p<0.05$) lower than those levels in both the sepsis and vehicle groups (Table 1).

Table 1) Mean levels of brain tissue inflammatory markers in the four experimental groups

Inflammatory markers	Sham group	CLP (sepsis) group	Vehicle group	Semaglutide group	p-value
IL-6 (pg/ml)	183.11±4.30	219.27±6.30	212.96±1.80	194.5±2.20	0.0001* 0.2** 0.0001***
IL-1β (ng/L)	662.25±49.05	924.75±25.90	886±34.90	689.5±24.46	0.0001* 0.4** 0.0001***
TNF-α (ng/L)	176.61±3.02	241.56±13.70	259.61±4.60	30.02± 3.26	0.0001* 0.080** 0.0001***
P-STAT3 (ng/ml)	34.6±1.50	72.8± 3.20	77.11±8.60	60.38±1.80	0.0001* 0.4** 0.03***
TLR4 (ng/ml)	3.33±0.60	7.64± 0.42	6.86±0.40	4.95±0.30	0.0001* 0.2** 0.0001***

* Comparison between the sham group and CLP group
** Comparison between the vehicle group and CLP group
*** Comparison between the semaglutide group and CLP group

Histopathological examination

Normal brain tissue was observed in the sham group. The cross section of brain tissue of sepsis and vehicle groups showed abnormal brain structure, including cerebrum with interstitial edema and presence of glial cells with pyknotic nuclei (Figure 1).

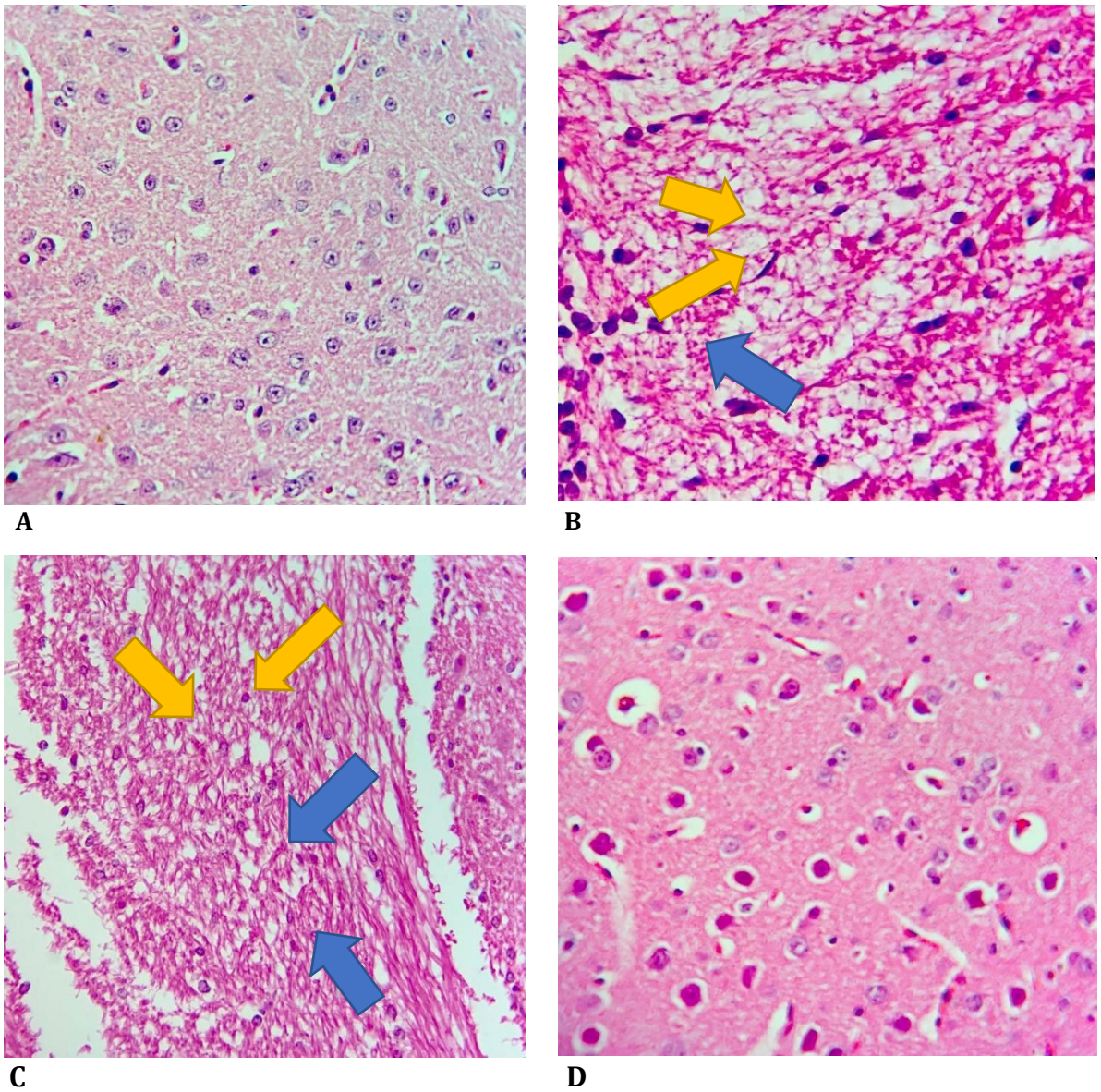

Figure 1) Histopathological examination of brain section. The section stained with haematoxylin and eosin (×400).
A) Sham group: The cross section of the brain showed normal histology (Normal cerebrum).
B) Sepsis group: The cross section of the brain tissue showed sepsis score 1 changes, including cerebrum with interstitial edema (yellow arrows) and the presence of glial cells with pyknotic nuclei (blue arrows).
C) Vehicle group: The cross section of the brain tissue showed sepsis score 1 changes, including cerebrum with interstitial edema (yellow arrows) and the presence of glial cells with pyknotic nuclei (blue arrows).
D) Semaglutide group: The cross section of brain tissue showed sepsis score 0 changes, including normal cerebrum.

Discussion

Sepsis is a generalized inflammatory response, which involves organ systems remote from the locus of the initial infectious insult [27].

Many organ dysfunctions, particularly in the brain, make sepsis more complicated. The fact that this brain dysfunction can occur in people with no known etiological agents suggests that it is not linked to a direct Central Nervous System (CNS) infection but rather to mediators generated during sepsis. This brain dysfunction often manifests as changes in consciousness (known as encephalopathy), which can range from confusion and delirium to coma. Otherwise, focal neurologic symptoms may be evident, and a localized brain lesion, often ischemic in nature, should be considered [28].

The term "brain dysfunction" was used by the authors because "encephalopathy" is too limited. Recent evidence of long-term cognitive deterioration following sepsis supports its use. It is a common belief that encephalopathy can be reversed. Increased mortality, morbidity, and long-term

cognitive impairment are all linked to Sepsis-Induced Brain Dysfunction (SIBD) [29]. Its importance for detection and therapy is based on this. In order to create specialized therapy strategies, an understanding of its pathophysiology is necessary. Neurological tests must be carried out every day to detect brain dysfunction [30], and it must direct the indications for additional research.

This experimental study reported that there is a significant elevation in TNF-α, IL-6, and IL-1β in brain tissues in both control and vehicle groups (p=0.0001) compared to the sham group after sepsis. These findings are in agreement with other studies. Sepsis-induced central nervous system dysfunction is related with the local production of pro- and anti-inflammatory cytokines, altered cerebral microcirculation, neurotransmitter imbalance, apoptosis, and cognitive impairment. It is well established that IL-1β is one of the first cytokines to undergo modification, and after 24h of CLP, the level of IL-1β was highly elevated [31]. CLP surgery dramatically increased the levels of IL-1β, IL-6, and TNF-α in plasma compared with those in the sham group [32]. The levels of TNF-α, IL-1β, and IL-6 were significantly elevated after CLP operation at 24h [33].

The results of this study showed that semaglutide-treated group had considerably lower brain tissue levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) than those in the sepsis and vehicle groups. This finding means that the semaglutide has a neuroprotective impact on the brain tissue after sepsis induction on mice model. This conclusion is consistent with those of previous research. One study showed that semaglutide pretreatment significantly reduced IL-1β, TNF-α, and IL-6 production [34]. Another study showed that semaglutide significantly reduced the expression of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) [35].

This experimental study reported that a significant increase in the expression of TLR4 in brain tissues was observed in both the control and vehicle groups (p<0.05) compared to the sham group after sepsis. This finding is in agreement with other studies. Mouse's brain tissue, when subjected to CLP-induce neuroinflammation, activates microglia (the major active immune cells in the central nervous system). When microglia are activated, TLR4 mRNA expression or protein levels increase in the brain [36].

This experimental study reported that the expression of P-STAT3 in brain tissues was significantly increased in both the control and vehicle groups (p<0.0001) compared to the sham group after sepsis. This finding is in agreement with other studies. An experimental study reported that p-STAT3 levels increased in the CLP group [37].

This experimental study showed that semaglutide treated groups had significant lower brain tissue levels of TLR4 compared to the sepsis and vehicle groups. Our findings are consistent with other studies showing that semaglutide reduces pro-inflammatory TLR4 activity [38].

The present study showed that semaglutide treated group had significant lower brain tissue levels of STAT-3 compared to the sepsis and vehicle groups. One study showed that semaglutide significantly down-regulated transcription factor 3 (STAT3) [39].

The present study showed that the sepsis and vehicle groups had significantly higher degrees of brain tissue injury compared to the sham group.

Histopathological findings in the sepsis and vehicle groups showed cerebrum with interstitial edema and the presence of glial cells with pyknotic nuclei, activation of astrocyte and microglia (increased cellularity). This finding is consistent with other experimental research. In Altaş *et al.*'s study, shrunken neurons and eosinophilic cell bodies were observed in the ischemia Repurfusion Injury (I/R) group. Additional findings included disruption of certain microvessels, meningeal congestion, bleeding, edema, and pyknotic nuclei [40].

The brain's tissues obtained from mice treated with semaglutide showed significantly less cellular injury at the same time. This result indicated that semaglutide can protect against sepsis and prevent brain dysfunction. This finding is in agreement with other experimental studies.

An experimental study indicated that semaglutide has a neuroprotective effect in EAE-induced multiple sclerosisin mice (Experimental Autoimmune Encephalomyelitis or EAE is a mouse model for multiple sclerosis) [21].

Another study demonstrated that semaglutide treatment for a mouse model is neuroprotective, ameliorates neuroinflammation and reduces cell death pathways, resulting in significant improvements in locomotor function and lifespan [41].

Semaglutide was used in a dose of 40μg/kg for one week. So, future studies may be justified with different doses and longer duration. The protective effect on brain, which revealed in the current study, was mediated by TLR4, NF-κB, and P-STAT3 cascades. So additional researches for other probable signaling pathways are desired. Future studies must investigate diabetic patients with sepsis and treated by this drug.

Conclusion

Semaglutide can reduce brain dysfunction during CLP-induced polymicrobial sepsis in male mice through its modulating effects on TLR4\STAT3 downstream signaling pathways and subsequently reducing inflammatory cytokines TNF-α, IL-6, and IL-1β.

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Ethical Permission: This study was approved by Bioethics Committee center in the University of Kufa and its representative in Faculty of Medicine. Whole procedures were done according to recommendations of this Committee (No. 7925 in 30/3/2022).

Conflict of Interests: All authors declare that there is no conflict of interest in the study.

Authors' Contribution: Shnaien AA (First Author), Introduction Writer/Main Researcher/Discussion Writer (50%); Mohammad AR (Second Author), Methodologist/Assistant Researcher/Statistical Analyst (30%); Hassan ES (Third Author), Assistant Researcher/Discussion Writer (20%)

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