Changes of serum level of acetylcholinesterase enzyme in lipopolysaccharide-induced model of depression in mice

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Abstract
Background and Objective: Depression is a common disorder, especially in developed countries. Functional changes of cholinesterase are involved in pathogenesis of some brain disorders. Until now, exact association of these changes with depression has not been determined. This study was conducted to evaluate the changes of serum cholinesterase in lipopolysaccharide (LPS)-induced model of depression in male mice.

Materials and Methods: Male mice (n = 48) were divided into 2 groups of control and LPS. For induction of depression, LPS (0.5 mg/kg; i.p.) was injected 24 h before the experiments. Open field, forced swimming, and tail suspension tests were used for behavioral assessment. Finally, serum cholinesterase activity was determined using biochemical method.

Results: LPS injection significantly decreased travelled distance in open field test (p<0.05) and increased immobility duration in forced swimming and tail suspension tests (p<0.01). In addition, serum cholinesterase showed a significant decrease in LPS subgroups versus control (p<0.05).

Conclusion: Our data showed that LPS could induce a valid model of depression and changes of cholinesterase are in part involved in development of its complications.

Key words: Depression, Lipopolysaccharide, Cholinesterase.

1. Introduction
Depression is regarded the second most prevalent chronic disease worldwide that is expanding in the world while about half of the patients with depression are unaware of their disease, or their disease are diagnosed else. Depression occurs in children, adolescents, adults and in elderly as a combination of states of sadness, loneliness, irritability, absurdity, despair, confusion and shame and reveals some physical symptoms. Major depressive disorder is one of the most common psychiatric illnesses, leading to enormous personal and socioeconomic burdens (1-3). The Gram-negative bacterial lipopolysaccharide (LPS) plays a key role in host-pathogen interactions with the innate immune system. During infection, bacteria are exposed to a host environment that is typically dominated by inflammatory cells and soluble factors, including antibiotics, which provide cues about regulation of gene expression. Bacterial adaptive changes including modulation of LPS synthesis and structure are a conserved theme in infections, irrespective of the type or bacteria or the site of infection. In general, these changes result in immune system evasion, persisting inflammation and increased antimicrobial resistance (4).

Cholinesterase is an enzyme responsible for termination of excitatory transmission at cholinergic...
synapses by the hydrolyzing of a neurotransmitter. Nowadays, other functions of cholinesterase in the organism are considered, for example its role in regulation of apoptosis. Cholinergic nervous system as well as acetylcholinesterase activity is closely related to pathogenesis of cognitive deficits in brain disorders like Alzheimer disease (5). This study was conducted to evaluate the changes of serum cholinesterase in lipopolysaccharide (LPS)-induced model of depression in male mice.

2. Materials and Methods

Male NMRI mice m (n = 48; 20-25 g) were divided into 2 groups of control and LPS. For induction of depression, LPS (0.5 mg/kg; i.p.) was injected 24 h before the experiments. Open field, forced swimming, and tail suspension tests were used for behavioral assessment. Finally, serum cholinesterase was determined using biochemical method.

2.1. Forced swimming test

In the forced swimming experiment, mice were individually placed in an open cylindrical container (diameter: 10 cm, height: 25 cm) containing 18 cm of water at 25°C for 6 min. This depth forced the mice to swim without allowing their tails to touch the bottom of the container. Mice were forced to swim 15 min daily for 2 consecutive days. At the end of each session, the mice were removed from the water, and immediately and gently wiped dry (6, 7).

2.2. Open-field test (OFT)

The open field consisted of a square arena (40 × 60 × 50 cm) with clear Plexiglas walls inside an isolated room with dim illumination. Mice were placed in the center of the box and allowed to adjust to the environment for 5 min. Mice were videotaped using a camera fixed above the floor and analyzed with a video tracking system. The “center” field is defined as the central area of the open field, one-fourth of the total area. Each subject was placed in the center of the open field and its activity was measured for 6 min (6).

2.3. Tail suspension test

Mice were hung by their tail on the tail hanger using sticky tape for tail fixation, at approximately 1 cm from the end of the tail. The hanger was fixed to the black plastic box (35 cm × 35 cm × 40 cm) with the opening at the top front. The distance between the hanger and floor was approximately 40 cm. The mouse was suspended in the air by its tail and the immobility time was recorded over a period of 6 min. The duration of immobility was defined as the absence of all movements excluding those required for respiration (8).

2.4. Serum activity of butyrylcholinesterase (BChE)

The serum activity of this enzyme was determined on the basis of degradation of butyrylthiocholine iodide. The kinetics of the reaction was followed spectrophotometrically over 5 min at 412 nm.

2.5. Statistical analysis

The data were expressed as mean ± standard error of the mean (SEM). Statistical comparisons were performed via analysis of variance (ANOVA). If the ANOVA was significant, post hoc comparisons were conducted using Tukey’s test. In all cases, p < 0.05 was considered statistically significant.

3. Results

Locomotor activity was obtained by counting the crossed squares in an open field. In this respect, LPS-challenged group showed a reduction of this activity as compared to control group that was statistically significant (p<0.05) (Fig. 1).

Performance of animals in forced swimming test was checked out in control and LPS-challenged groups. In this respect, LPS group had a higher duration as compared to control group that was also statistically significant (p<0.01) (Fig. 2).

Performance of animals in tail suspension task was assessed in control and LPS-challenged groups. In this regard, LPS group had a higher duration as compared to control group that was also statistically significant (p<0.01) (Fig. 3).

In addition, we measured specific activity of butyryl cholinesterase (BCHE) in control and LPS-challenged groups. Our findings showed that activity of this enzyme is significantly lower in LPS group relative to control group (p<0.05) (Fig. 4).

![Fig. 1. Locomotor activity in control and LPS-challenged groups. * p<0.05 (versus control)](image-url)
4. Discussion

Lipopolysaccharide (LPS) that is the main component of the outer membrane of Gram-negative bacteria is strongly responsible for neuroinflammatory response, short-term sickness behavior, fever, locomotor abnormality, loss of appetite, anxiety, disturbed cognitive ability, and depression. An inflammatory signaling could lead to overproduction of reactive oxygen species (ROS) and is associated with stress and changes of cholinesterase activity (9, 10).

Systemic LPS exposure could be associated with an increase of hippocampal glial fibrillary acidic protein (GFAP) that is a specific marker of astrocytes (11, 12), leading to development of neuroinflammation. Increased expression of GFAP clearly indicates over-activity of astrocytes and development of astrogliosis in the brain that will be associated with cognitive and non-cognitive dysfunctions (13, 14). Part of motor deficits in LPS-challenged group in this study could be attributed to changes of GFAP expression in brain tissue. However, this important issue needs further assessment in future studies. In this study, we also assessed the role of cholinergic system and its alterations in pathogenesis of depressive-like behaviors subsequent to LPS challenge. In this regard, the enzyme BChE that has a role in learning and memory abilities (13, 15, 16) shows a lower activity in LPS group. In addition, inflammation due to LPS could affect BchE (17-20). Although contrasting reports exist on the effect of LPS-induced neuroinflammation on the activity of cholinesterases, some evidences have shown its increase (14, 19, 21) that is contrary to our findings. However, this issue also warrants conductance of more studies to be unraveled.

To conclude, the obtained data of this study showed that LPS could induce a valid model of depression and changes of cholinesterase are in part involved in development of its complications.

Acknowledgement

This research study was the result of M.Sc. thesis project that was approved and financially supported by Faculty of Advanced Sciences and Technology, Pharmaceutical Sciences Branch, Islamic Azad University (Tehran, Iran) in 2015.

References


