Effects of Oleuropein on Systemic Lipopolysaccharide-Induced Neuroinflammation in Rats

Sevim Şahin[1], Gülnur Esenülkü[2], Elif Şahin[3], Gülin Renda[4], Seren Gülşen Gürgen[5], Nihal Yıldız[1], Pınar Özkan Kart[1], Ahmet Alver[2], İsmail Abidin[6], Ali Cansu[1]

[1] Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey [2]Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey [3]Department of Medical Biochemistry, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey [4] Department of Pharmacognosy, Faculty of Pharmacy, Karadeniz Technical University, Trabzon, Turkey [5]Department of Histology and Embriyology, Celal Bayar University, Manisa, Turkey [6]Department of Biophysics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

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Introduction:

Infection-related neuroinflammatory response may contribute to the development of epilepsy and various neurodegenerative disorders (1). Astrocytes and microglia are actively involved in the development of neuroinflammation (2). IL-1b is a proinflammatory cytokine released from activated microglia and coordinates the systemic host defense response to pathogens (3,4). Nod-like receptor protein 3 (NLRP3) inflammasome; can be activated by a variety of stimuli such as crystals and endoplasmic reticulum (ER) stress, acting as a gate to produce mature IL-1β (5). While IL-17 plays a protective role against microorganisms with its proinflammatory activity, uncontrolled IL-17 activity is associated with immunopathological conditions such as autoimmune diseases and cancer development (6). IL-4, on the other hand, is one of the well-known anti-inflammatory cytokines (7).

Lipopolysaccharide (LPS), the major component of the gram-negative bacterial wall, causes neuroinflammation in animals (8,9). Oleuropein (OLE), whose effects on LPS-related neuroinflammation were examined in our study, is one of the primary phenolic compounds found in olive leaves. It is known to have biological effects such as antioxidant, anti-obesity and antimicrobial activity (10).

Objectives:

We evaluated the effects of oleuropein (OLE), a phenolic component of olive leaf, on LPS-related neuroinflammation.

Materials and methods:

Six-week-old, thirty-five male Wistar rats, were randomly divided into five groups: control, OLE, LPS, seven days OLE+LPS (OLP-7), single dose OLE+LPS (OLP-1). LPS and OLE were administered 2.5 mg/kg intraperitoneally, and 200 mg/kg/day by gavage, respectively. Animals were decapitated at 24th hour following LPS administration. In the hippocampus and cortex, CD11b and GFAP were studied to evaluate microglia and astrocyte activation by immunohistochemistry; NLRP3, an inflammasome component, proinflammatory cytokines IL-1b and IL-17a, and anti-inflammatory cytokine IL-4 were studied by ELISA method. The significance level was determined as p≤0.027 in the multiple test correction by the Benjamini-Hochberg method.

Results:

LPS increased CD11b and GFAP levels in the cortex and hippocampus (p<0.001), and IL-1b and IL-17a levels in the hippocampus (p=0.001, p=0.005). Before LPS, seven days or a single dose of OLE reduced GFAP and CD11b levels in the hippocampus, and CD11b levels in the cortex (p<0.001). GFAP level in the cortex decreased in the OLP-1 group (p<0.001). Compared to the LPS group, the OLP-7 group had higher cortex IL-4 level and lower hippocampal IL-17a level (p=0.009, p=0.004, respectively).

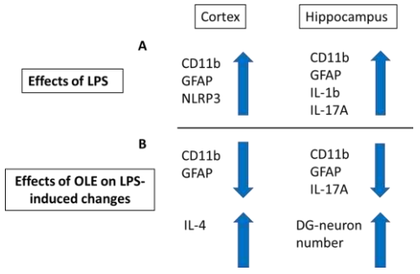

Figure 1. Effects of LPS (a) and pre-LPS administration of OLE (b) on findings in cortex and hippocampus.

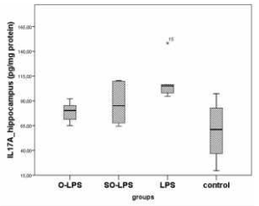

Figure 4: In the hippocampus, 7 days of OLE administration before LPS (O-LPS group) decreased the level of IL-17A, a proinflammatory cytokine, compared to the LPS group (p=0.009).

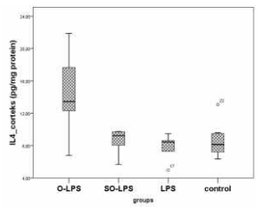

Figure 5: In the prefrontal cortex, 7 days of OLE administration before LPS (O-LPS group) increased the level of IL-4, an anti-inflammatory cytokine, compared to the LPS group (p=0.009).

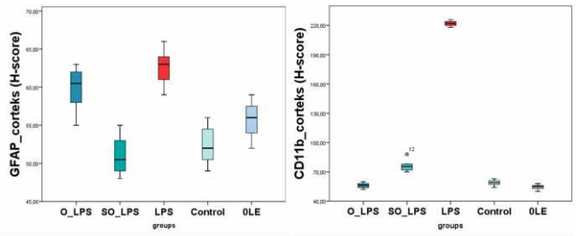

Figure 6. Cortex (prefrontal) GFAP and CD11b levels increased with LPS compared to control and OLE groups (p<0.001). While CD11b level decreased significantly in both animals given a single dose (SO-LPS group) or 7-day of OLE (O-LPS group) before LPS (p<0.001); GFAP level decreased significantly only in the SO-LPS group (p<0.001).

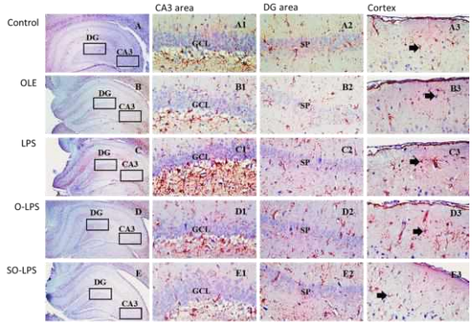

Figure 2. In the brain hippocampus and cortex, GFAP staining showed weak expression in OLE and control groups, but increased in the LPS group. Its expression was decreased in O-LPS and SO-LPS groups given LPS before OLE. (A,B, C,D,E) X40, (1,2,3) X400.

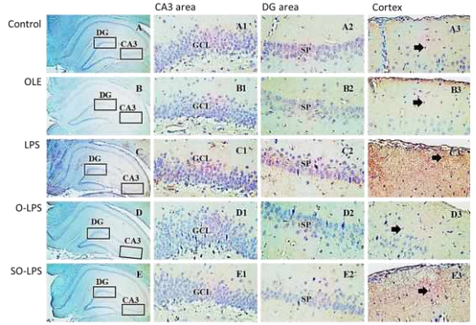

Figure 3. In the brain hippocampus and cortex, CD11b staining showed weak expression in OLE and control groups, but increased in the LPS group. Its expression was decreased in O-LPS and SO-LPS groups given LPS before OLE. (A,B, C,D,E) X40, (1,2,3) X400.

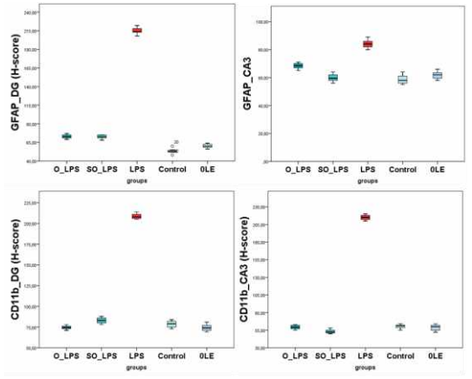

Figure 7. In the DG (dentate gyrus) and CA3 regions of the hippocampus, LPS increased GFAP and CD11b levels in comparison with the control and OLE groups (p<0.001); with 7 days or a single dose of OLE before LPS (O-LPS and SO-LPS groups, respectively), both of them decreased significantly (p<0.001).

Conclusions:

Oleuropein (OLE) has an anti-inflammatory effect by suppressing the astrocytes and microglia activation and by decreasing the IL-17a and increasing the IL-4 levels.

In our study, the suppressive effect of OLE on astrocytes and microglia in the cortex and hippocampus with a single dose administration before LPS suggests that it may have an effect in acute treatment. Especially, a single dose of OLE instead of long-term use, provided a significant improvement in the increased GFAP levels due to LPS.

In our study, the decrease in the increased IL-17A level in the hippocampus with OLE suggests that OLE may be beneficial in preventing autoimmune diseases that can be triggered by infection-related neuroinflammation. IL-17A is one of the cytokines thought to have a key role in autoimmune diseases such as MS and neurodegenerative diseases such as Alzheimer's disease (6).

References: 1. Tohidpour A, et al. Front Cell Infect Microbiol. 2017). 2. Sanz P, Garcia-Gimeno MA. Int JMol Sci. 2020;21(11):1–17. 3. Scheiblich H, et al. J Neurochem. 2017;143(5):534–50. 4. Basu A, et al. J Neurosci Res. 2004;78(2):151–6. 5. Zhao Z, et al. J Neuroinflammation. 2020;17(1):1–19. 6. Milovanovic J, et al. Front Immunol. 2020;11(June):1–15. 7. Lively S, Schlichter LC. Front Cell Neurosci. 2018;12(July):1–19. 8. Buttini M, et al. Neurochem Int. 1996;29(1):25–35. 9. Hoda Badr, et al. Bone. 2011;23(1):1–7. 10. Ryu SJ, et al. J Agric Food Chem. 2015;63(7):2098–105. 11. Huang YN, et al. J Neuroinflammation [Internet]. 2015;12(1):1–12.

Acknowledgements:

Contact: Sevim Şahin, Karadeniz Technical University, Turkey. e-mail: sevimsahin1@yahoo.com