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Full Length Research Paper

Systemic taurine prevents brain from lipopolysaccharide-induced lipid peroxidation in rats

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Lipopolysaccharide (LPS), the major component of the outer membran of Gram-negative bacteria, can reproduce neuroinflammation and leads to oxidative stress in brain. Because taurine exhibits antioxidative properties, in this study, we aimed to evaluate the protective effects of taurine at the subtoxic dose of lipopolysaccharide-induced lipid peroxidation and oxidative stress. We measured malondialdehyde (MDA), gluthathione (GSH) and nitrite + nitrate (NOx) levels of different brain regions in rats after the i.p administration of LPS and taurine. Wistar male rats (220 to 300 g) were divided into five groups: 1. Control; 2. Saline + LPS (500 µg/kg, i.p.); 3. LPS (500 µg/kg, i.p.) + LPS (500 µg/kg, i.p.); 4. LPS (500 µg/kg, i.p.) + taurine (500 mg/kg, i.p.); 5. Taurine (500 mg/kg, i.p.). i.p. LPS was administred 6 h before sacrification. Taurine was administered after 3 h of LPS injection and the animals sacrified after 3 h of taurine administration. Hippocampus, temporal cortex, frontal cortex, parietal cortex, basal forebrain, cerebellum and brain stem were dissected. MDA, GSH and NOx levels were assayed spectrophotometrically. MDA levels were found increased significantly in all mentioned brain regions after i.p. LPS ($p<0.05$) except basal forebrain. In LPS + taurine group, we found significantly decreased MDA levels in all mentioned brain regions except an insignificant decrease in cerebellum after i.p. LPS administaration. These results demonstrate that taurine administration with LPS protects brain against LPS-induced lipid peroxidation and oxidative stress.

Key words: Lipopolysaccaride, taurine, lipid peroxidation, nitric oxide, brain.

INTRODUCTION

Neuroinflammation is substantially mediated by activation of microglia and plays a pivotal role in the pathogenesis of Alzheimer's disease (AD). Chronic neuroinflammation has been reproduced in rats by infusion of lipopolysaccharide (LPS) into the fourth ventricle. LPS activates microglia to initiate a series of inflammation induced changes within the hippocampus and entorhinal cortex (Min et al., 2009). LPS, the major component of the outer membrane of Gram-negative bacteria, is known to trigger a powerful immune response (Fidalgo et al., 2011). Furthermore, it was also reported that intraperitoneal injection of LPS induces cognitive impairment in mice. Noble et al. (2007) reported that acute systemic inflammation induces central mitochondrial damage and amnesic deficit in adult Swiss mice and also it was reported that intraperitoneal injections of LPS cause AD-like neuronal degeneration (Lee et al., 2008)

LPS also is suggested to increase inducible nitric oxide synthase (iNOS) activation and thereby nitric oxide (NO) production. NO acts as an intracellular signaling molecule and a neurotoxin depending on its concentration (Garthwaite, 1991). It can damage DNA and irreversibly modify proteins such as tyrosine nitration or thiol oxidation, which are common pathogenic mechanisms in several neurodegenerative diseases (Noble et al., 2007). LPS could exert a detrimental effect by inducing brain injury through a mechanism involving increased reactive oxygen species (ROS) and NO production associated with cyclooxygenase-2 (COX-2) expression and lipid peroxidation, GSH depletion and mitochondrial impairment (Noble et al., 2007). In the LPS- induced inflammation model, microglial NADPH oxidase and/or

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iNOS have been reported to be centrally involved in triggering oxidative stress and mediating neurotoxicity (Armito and Bing., 2003; Chung et al., 2010).

ROS , such as O_2^- and O_2^- -derived oxidants, can cross cell membranes and induce neuronal death by causing oxidative damage to cellular components, such as proteins (Chung, 2010; Cadet and Brannock, 1998). Nitric oxide as a free radical and an agent that gives rise to highly toxic oxidants (peroxynitrite, nitric dioxide, nitron ion) becomes a cause of neuronal damage and death in some brain lesions such as Parkinson and Alzheimer Disease, and Huntington's chorea (DiGirolamo et al., 2003). Considerable evidence exists that the brains of individuals with Alzheimer's disease are subjected to elevated levels of oxidative stress, particularly in regions exhibiting pathological damage (Rupniak et al., 2000). A major contributor to this oxidative stress appears to be the inflammatory process. Activation of rodent microglial cells by LPS or beta amyloid peptide results in a marked up-regulation of iNOS and corresponding nitric oxide production. The reaction of NO with superoxide leads to the generation of the highly reactive and damaging peroxinitrite free radical species (Rupniak et al., 2000).

Taurine (2-aminoethylsulphonic acid), a non-protein amino acid, is present in most animal tissues. Its highest concentrations are found in skeletal muscles, heart, brain, and retina. Taurine exhibits antioxidative properties, regulates intracellular Ca^{2+} concentration, acts as a neuromediator and neuromodulator, is responsible for osmoregulation, is involved in cholic acid production, and modulates inflammatory reactions (Oja and Saransaari, 2007; Saransaari and Oja, 2000).

In the light of literature, and because taurine exhibits antioxidative properties, in this study we aimed to evaluate the protective effects of taurine at the subtoxic dose of LPS-induced lipid peroxidation and oxidative stress in different regions of rat brain.

MATERIALS AND METHODS

Animals

The rats used in the present study were males of the Wistar albino strain weighing 220 to 300 g. The rats were housed in cages (four/cage) until treatments with *ad libitum* food and water and maintained on a 12-h light:dark cycle with lights on from 08:00 to 20:00 h, at 20±22°C room temperature. All animal manipulations were carried out according to the Ethical Comittee for the use and care of laboratory animals of Gazi University, Faculty of Medicine. All efforts were made to minimize animal suffering and to reduce the number of animals used.

In the study, 30 rats were randomized into five groups: 1. Control (n=6); 2. Saline + LPS (500 µg/kg, i.p.) (n=6); 3. LPS (500 µg/kg, i.p.) + LPS (500 µg/kg, i.p.) (n=6); 4. LPS (500 µg/kg, i.p.) + Taurine (500 mg/kg, i.p.) (n=6); 5. Taurine (500 mg/kg, i.p) (n=6). Saline was injected 6 h before sacrification to the control group. In Group 2; i.p. saline was injected and then after 7 days i.p. LPS was injected. Then rats were sacrified 6 h after i.p. LPS injection. In Group 3, i.p. LPS was injected and after 7 days the same dose of i.p. LPS was injected. Then rats were sacrified 6 h after i.p. LPS injection. In Group 4, taurine was administered after 3 h of LPS injection and then the rats were sacrified after 6 h of LPS injection. In Group 5, taurine alone administered intraperitoneally 3 h prior to sacrification. The rats were decapitated and brains were rapidly removed on ice. Hippocampus, temporal cortex, frontal cortex, parietal cortex, basal forebrain, cerebellum and brain stem were dissected and frozen in liquid nitrogen and then stored at -80°C until use. On the day of experiment, tissues were placed in appropriate buffer and homogenised. MDA, GSH and NOx levels were assayed spectrophotometrically.

TBARS assay

Lipid peroxidation was estimated by the thiobarbituric acid (TBARS) test for MDA as described previously (Casini et al., 1986). Tissue samples were homogenized in nine volumes of 10% trichloroacetic acid (TCA) and centrifuged at 3000 *g* for 10 min. Ten microliters of butylated hydroxytoluen and 750 µl of 0.67% (m/v) thiobarbituric acid was added to 750 µl of supernatant. The mixture was boiled for 10 min for color development and then centrifuged. The absorbance of the samples was measured at 535 nm.

NOx assay

Nitrite plus nitrate (NOx) which are the last and stabile products of nitric oxide were determined in tissue samples spectrophotometrically as described previously (Taskiran et al., 1997). Tissue samples were homogenized in five volumes of phosphate buffer (pH 7.5) and centrifuged at 2000 xg for 5 min. The supernatant (0.5 ml) was added to a mixture of 0.25 ml of 0.3 M NaOH. After incubation for 5 min at room temperature, 0.25 ml of 5% (w/v) $ZnSO_4$ was added for deproteinization. This mixture was then centrifuged at 3000 g for 20 min and the supernatants used for the assay. NOx levels were analyzed mixing Griess reagent (1 part of 0.1% naphthylenediamine dihydrochloride in bidistilled water plus 1 part of 1% sulfanilamide in 5% HCl) and supernatant. After 30 min, the absorbance at 540 nm was determined. Assays were also performed with nitrite and nitrate standart solutions. Tissue NOx levels were expressed as micromoles per gram wet weight.

GSH assay

The GSH levels were determined by modified Elman method (Aykaç et al., 1985). Tissue samples were homogenized in nine volumes of 10% TCA and centrifuged at 3000 g for 10 min. Two milliliters of 0.3 M Na_2HPO_4 and 0.25 ml dithiobisnitrobenzoate (0.4 mg/ml 1% sodium citrate) was added to 0.5 ml supernatant. The mixture was incubated at room temperature for 10 min. The GSH level is determined by measuring the absorption at 412 nm.

Statistical analysis

All data are expressed as means ± SEM. Comparisons of means between groups were performed by one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test. In all data analysis, p values of 0.05 or less were considered significant.

RESULTS

MDA, NOx and GSH levels levels are shown respectively in Figures 1 to 3.

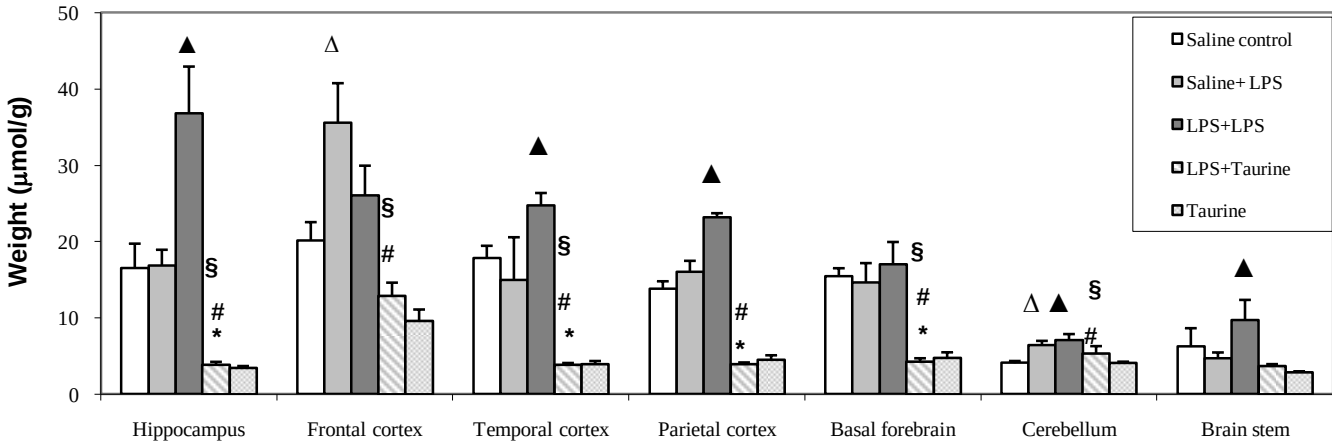

Figure 1. MDA levels in different brain regions. Δ, Denotes significant difference between control and Saline+LPS group ($p<0.05$). ▲, Significant difference between control and LPS+LPS group ($p<0.05$). *, Significant difference between control and LPS+Tau group ($p<0.05$). #, Significant difference between saline+LPS and LPS+Tau group. ($p<0.05$), Significant difference between LPS+LPS and LPS+Tau group ($p<0.05$).

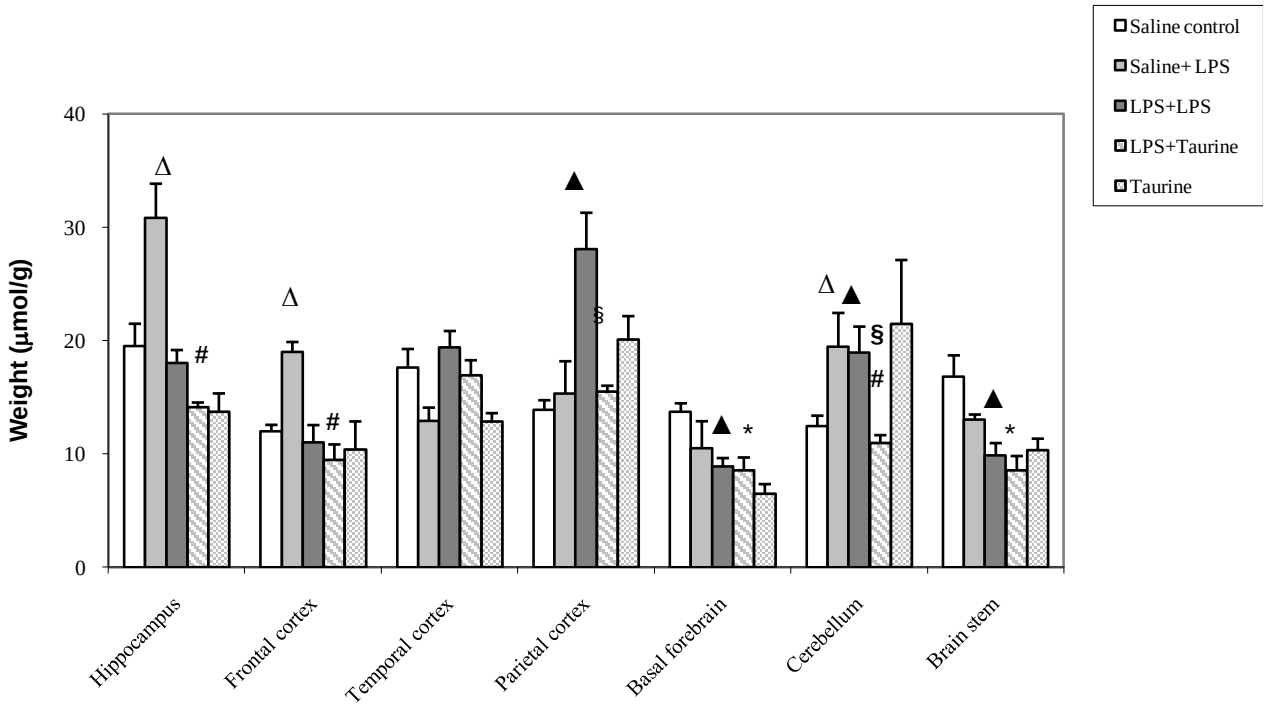

Figure 2. NOx levels in different brain regions. Δ, Significant difference between control and Saline+LPS group ($p<0.05$). ▲, Significant difference between control and LPS+LPS group ($p<0.05$). *, Significant difference between control and LPS+Tau group ($p<0.05$). #, significant difference between Saline+LPS and LPS+Tau group. ($p<0.05$), significant difference between LPS+LPS and LPS+Tau group ($p<0.05$).

Saline + LPS group

MDA levels were found significantly increased in frontal cortex and cerebellum when compared with control group ($p<0.05$). Therefore, i.p. LPS can not exert an effect on lipid peroxidation in other brain regions in 6 h. We found increased NOx levels in hippocampus, frontal cortex and cerebellum. Intraperitoneal LPS injection has acute effect on NOx levels in hippocampus, frontal cortex and cerebellum ($p<0.05$). GSH levels increased significantly in hippocampus, but decreased in basal forebrain and cerebellum ($p<0.05$).

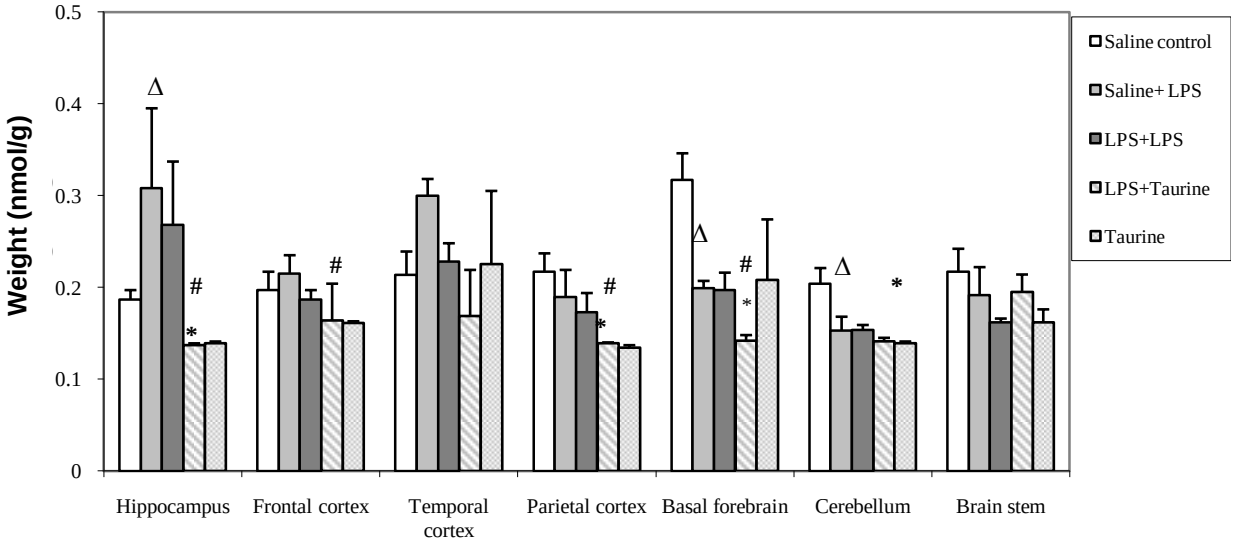

Figure 3. GSH levels in different brain regions. ∆, Significant difference between control and saline+LPS group (p<0.05). ▲, Significant difference between control and LPS+LPS group (p<0.05). *, Significant difference between control and LPS+Tau group (p<0.05). #, Significant difference between Saline+LPS and LPS+Tau group. (p<0.05). Significant difference between LPS+LPS and LPS+Tau group (p<0.05).

LPS + LPS group

MDA levels were found increased significantly in hippocampus, temporal cortex, parietal cortex and cerebellum when compared with control group (p<0.05). Therefore, increased levels of MDA suggest that LPS-induced lipid peroxidation lasts 1 week or more in these brain regions. NOx levels were found increased in parietal cortex and cerebellum (p<0.05). In hippocampus not NOx, but MDA levels were elevated, and GSH levels stayed elevated insignificantly compared with the saline control group.

This result suggests that NO-mediated oxidative stress occurs due to LPS administration in 6 h in hippocampus and also GSH levels were found elevated (p<0.05). GSH levels were found increased in hippocampus, however basal forebrain GSH levels were found decreased. It appears that hippocampus tends to protect itself against LPS-induced lipid peroxidation by increasing GSH levels.

The evidence suggesting that basal forebrain cholinergic system degeneration appears early in Parkinson disease (Bohen and Albin, 2011). In the present study, results show that basal forebrain, may be much more prone to LPS-induced GSH depletion. In the present study, it seems that basal forebrain is lack of compansation mechanism against lipid peroxidation. It is known that in Parkinson disease, antioxidant enzymes such as SOD, GPx and GRx activities are affected and cellular depletion of antioxidant enzymes are observed. Likely as basal forebrain, we found decreased GSH levels in cerebellum and parietal cortex compared with control group. Oxidative stress via GSH depletion might also accelerate the build-up of defective proteins leading to cell death of substantia nigra dopaminergic neurons by impairing the ubiquitin-proteosome pathway of protein degradation (Bharat et al., 2002).

LPS + taurine group

MDA levels were found decreased in all brain regions compared with the saline+LPS (p<0.05) or LPS+LPS groups (p<0.05). NOx levels decreased significantly in hippocampus, frontal cortex and cerebellum compared with the saline+LPS, and also NOx levels decreased significantly in parietal cortex and cerebellum compared to LPS+LPS group (p<0.05). Therefore, these results demonstrate that taurine administration with LPS protects brain against LPS-induced lipid peroxidation and oxidative stress, due to increased ROS. It seems that LPS administration induced elevated NOx levels in hippocampus, temporal cortex, parietal cortex and frontal cortex. In LPS+taurine group, GSH levels decreased in hippocampus, temporal cortex, parietal cortex, frontal cortex and basal forebrain significantly (p<0.05) compared with the saline+LPS or LPS+LPS.

When taurine was administered alone

MDA decreased significantly in hippocampus, temporal cortex, parietal cortex, frontal cortex and basal forebrain compared with the control group (p<0.05). Taurine alone significantly decreased NOx levels in hippocampus, basal forebrain and brain stem compared with the control group (p<0.05). And GSH levels in hippocampus, parietal cortex

and cerebellum was significantly decreased ($p<0.05$).

DISCUSSION

The mammalian brain is particularly prone to oxidative damage (Halliwell and Gutteridge, 1999). Inflammatory processes are widely considered as an important mechanism leading to oxidative stress by impairing the balance between oxidants and antioxidants in the nervous tissue. Many neuropathologies like neurodegenerative disorders, multiple sclerosis, brain ischaemia, infections, traumatic injury and intoxications are associated with neuroinflammation and oxidative stress (Röhl et al., 2010). Cytokines released by activated astrocytes can also induce microglial iNOS and prime microglia to generate more radicals upon activation. On the other side, reactive astrocytes may enhance their antioxidative status in response to mild oxidative stress, which in turn may result in neuroprotection (Röhl et al., 2010). Peripheral administration of LPS initiates an inflammatory response, which is mediated by proinflammatory cytokine and free radical generation such as NO. iNOS was suggested to be the main source of NO during inflammatory reaction and induced by various doses of endotoxin (Watts et al., 2004). GSH is vital in maintaining the cellular redox state. As reduction equivalent, it is involved in peroxide elimination by the GPx reaction and it directly scavenges reactive oxygen and nitrogen species (Dringen et al., 2000). It has been shown by Kovac et al. (2011) that LPS induces nitric oxide production via MAPK pathways in mouse brain pericytes. Also they demonstrated LPS stimulates cytokine and chemokine release by primary mouse pericytes. LPS strongly induces production of NO and nitrosative stress in brain pericytes (Kovac et al., 2011). There are *in vitro* studies in literature that had showed LPS induced lipid peroxidation, replenish antioxidant system, enzymatic or nonenzymatic. However, there are not enough *in vivo* results about lipid peroxidation alterations due to LPS in which different parts of brain regions as we investigated in this study.

For a long time, it has been accepted that the brain has an immune-privileged status and is protected by the blood–brain barrier against circulating LPS and cytokines; however, according to recent data, systemic inflammation affects the brain (Konsman et al., 2002). It has been suggested that cytokines produced in the periphery activate the immune system in the central nervous system (Konsman et al., 2002). The results indicate that synthesis of NO_x by both the inducible and constitutive NOS isoforms contribute to the activation of apoptotic pathways in the brain during systemic inflammation (Czapski et al., 2007).

Because LPS -induced alterations in the brain is dependent on the dose of LPS, there can be seen different responses in different brain regions. The dose of LPS which was used in this study did not lead to sickness behaviour and fever in rats, but increased MDA and NOx levels in hippocampus, the region of brain that is responsible for spatial memory. And also this increment was alleviated by single taurine administration.

Prior to this study, in other laboratories, it was shown that the administration of LPS increased nitrite in brain and liver by 26.8 and 37.1%, respectively; decreased GSH in brain and liver by 21.6 and 31.1%, respectively; increased brain TNF-α by 340.4% after intraperitoneal administration of lipopolysaccharide (LPS; 100 µg/kg) in mice (Abdel-Salam et al., 2011).

In this study, the fact that decreased levels of MDA and NOx due to taurine administration appear because of the antioxidant effect of the taurine. However, in living organism, under physiologic conditions optimum NO concentrations are required. When NO levels decrease below the physiologic concentrations, cognitive deficits are seen (Yamada and Noda, 1995; Southam and Garthwaite, 1993).

Enhanced taurine release from brain tissue has also been observed under various pathological conditions in which NO is reported to be involved, such as seizures, ischemia, and hypoglycemic coma (Bockelmann et al., 1998). As the taurine release might be regulated via the NO cascade, it could be expected that an effect on taurine release would give a hint for the further search of a mechanism of action. GSH has similar roles in the nervous system. In particular, the antioxidant/free radical scavenger role in neural tissue may be crucial for many of the same reasons (Janaky et al., 1999).

Glutathione (GSH) is an important soluble antioxidant present at high concentrations in the brain (Dringen et al., 2000). Thus, the increases in GPx and GR activities suggested a compensatory response to increase in oxidative stress which was indicated by the elevated lipid peroxide levels (Zhu et al., 2007). Conversely; in an *in vitro* study it has been shown that LPS treatment decreased GSH levels in astrocytes in mesencephalic cultures in a dose-dependent manner (Bharath et al., 2002).

Taurine, a sulfur-containing β-amino acid, is present in high concentrations in mammalian plasma and cells, and plays an important role in several essential biological processes such as development of CNS, osmoregulation, and neuromodulation (Oja and Saransaari, 2007; Saransaari and Oja, 2000). In addition, it is also known to exert a neuroprotective effect against excitotoxic agents and oxidative stress. It was reported that the uptake of taurine by brain cells increased in inflammatory conditions. The release of taurine in brain is significantly enhanced under neuronal cell-damaging conditions including exposure to free radicals. In addition, NO appears to regulate the release of excitotoxic glutamate and neuroprotective taurine (Saransaari and Oja, 2000). In the present study, in LPS+taurine group; taurine administration decreased Nox levels in hippocampus,

parietal cortex, frontal cortex, cerebellum compared with LPS administered groups. Taurin significantly reduced NOx levels that were elevated after LPS administration. We suggest that taking taurine in healthy state, may proceed to abnormalities in oxidant and antioxidant substances in brain. According to the results of the present study, when oxidative stress and lipid peroxidation induces due to LPS administration then taurine may show a preventive effect on these paradigms in rat brain.

In the present study, i.p. injection of 500 µg LPS induced significant increase in MDA levels in the brain areas especially which have relationship with spatial learning and memory, and working memory respectively, in hippocampus and frontal cortex. Also we observed that nonenzymatic antioxidant GSH levels increased significantly in hippocampus after LPS injection. Also in our results, it is clear that single intraperitoneal injection of taurine achieved to decrease MDA levels significantly especially in hippocampus, frontal cortex, temporal cortex, parietal cortex, basal forebrain, cerebellum and brain stem in LPS administrated groups. The organism can give different responses in *in vivo* conditions. *In vivo* conditions could effect LPS-induced responses which were given in *in vitro* experimental conditions. In this study, single systemic injection of a subtoxic dose of LPS induced a significant increase in MDA levels especially in hippocampus, frontal cortex, temporal cortex, parietal cortex, cerebellum and brain stem. Because LPS can be used to mimic pathophysiological neuroinflammatory responses, and can be used to mimic neuroinflammatory aspects of Alzheimer's disease, antioxidant GSH may play a compansatory role in brain to reverse LPS-induced lipid peroxidation and oxidative stress. The results of this study demonstrate that dose of LPS used in this study induced mild oxidative stress. According to the results of this study, elevated GSH levels despite hippocampus-specific MDA and NOx increase, suggests a probable mechanism to overcome oxidative stress. Therefore, in view of the results of this study, we suggest that taurine can be a promising treatment agent for increased lipid peroxidation in brain due to LPS after multiple focus investigations.

REFERENCES

Abdel-Salam OM, Salem NA, Hussein JS (2011). Effect of Aspartame on Oxidative Stress and Monoamine Neurotransmitter Levels in Lipopolysaccharide-Treated Mice., however in this study we demonstrated region specific alterations of brain response due to LPS administration. Neurotox Res. Aug 6 [Epub ahead of print]

Armito T, Bing G (2003). Up-regulation of inducible nitric oxide in the substantia nigra by lipopolysaccaride causes microglial activation and neurodegeneration, Neurobiol. Dis.,(12): 35-45.

Aykaç AG, Uysal M, Yalcın AS (1985). The effect of chronic ethanol ingestion on hepatic lipid peroxide, glutathione, glutathione peroxidase and glutathione transferase in rats. Toxicology, 36: 71–76.

Bharath S, Hsu M, Kaur D, Rajagopalan S, Andersen JK (2002). Glutathione, Iron and Parkinson's Disease. Biochem. Pharmacol., 64: 1037-1048.

Bockelmann R, Reiser M, Wolf G (1998). Potassium-Stimulated Taurine Release and Nitric Oxide Synthase Activity During Quinolinic Acid Lesion of the Rat Striatum. Neurochem. Res., 4(23): 469-475.

Bohen NI, Albin RL (2011). The cholinergic system and Parkinson Disease. Behav. Brain Res., 10;221(2): 564-573

Cadet JL, Brannock C (1998). Free radicals and the pathobiology of brain dopamine systems. Neurochem. Int., 32: 117-131.

Casini A, Ferrali M. Pompella A (1986). Lipid peroxidation and cellular damage in extrahepatic tissue of bromobenzene intoxicated mice. Am. J. Pathol., 123: 520–531.

Chung ES, Chung YC, Bok E, Baik HH (2010) Fluoxetine prevents LPS-induced degeneration of nigral dopaminergic neurons by inhibiting microglia-mediated oxidative stres. Brain Res., 1363: 143-150.

Czapski GA, Cakala M, Chalimoniuk M, Gajkowska B, Strosznajder JB (2007). Role of Nitric Oxide in the Brain during Lipopolysaccharide-Evoked Systemic Inflammation. J. Neurosci. Res., 85: 1694–1703.

DiGirolamo G, Farina M, Riberio ML, Ogando D, Aisemberg J, Santos AR, Marti ML, Franchi AM (2003). Effects of cyclooxygenase inhibitor pretreatment on nitric oxide. British, J. Pharmacol., 139: 1164-1170.

Dringen R, Gutterer JM, Hirrlinger J (2000). Glutathione metabolism in brain metabolic interaction between astrocytes and neurons in the defense against reactive oxygen species. Eur. J. Biochem., 267: 4912–4916.

Fidalgo AR, Cibelli M, White JPM, Nagy I, Mazec M, Ma D (2011). Systemic inflammation enhances surgery-induced cognitive dysfunction in mice. Neurosci. Lett., 498: 63–66

Garthwaite J (1991). Glutamate, nitric oxide and cell-cell signalling in the nervous system. TINS, 14 (2): 60-67.

Halliwell B, Gutteridge JM (1999). Free Radicals in Biology and Medicine. 3rd Edition. Oxford Science Publications. www.pdfgeni.com/book/free-radicals-biology-medicine-pdf.html

Janaky R, Ogita K, Pasqualotto BA, Bains JS, Oja SS, Yoneda Y, Shaw CA (1999). Glutathione and Signal Transduction in the Mammalian CNS. J. Neurochem., 73 (3): 889-902.

Konsman JP, Parnet P, Dantzer R, Larsen KE (2002). Cytokine-induced sickness behaviour: mechanisms and implications. Trends. Neurosci., 25(3): 154-159.

Kovac A, Erickson MA, Banks WA (2011). Brain microvascular pericytes are immunoactive in culture: cytokine, chemokine, nitric oxide, and LRP-1 expression in response to lipopolisacccharide. J. Neuroinflamm., 8:139.

Lee JW, Lee YK, Yuk DY, Choi DY, Ban SB, Oh KW, Hong JT (2008). Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J. Neuroinflamm., 5: 37.

Min SS, Quan HY, Ma J, Han J, Jeon HB, Seol GH (2009). Chronic brain inflammation impairs two forms of long-term potentiation in the rat hippocampal CA1 area. Neurosci. Lett., 456: 20–24.

Noble F, Rubira E, Boulanouar M, Palmier B, Plotkine M, Warnet JM, Marchand-Leroux C, Massicot F (2007). Acute systemic inflammation induces central mitochondrial damage and mnesic deficit in adult Swiss mice. Neurosci. Lett., 424: 106-110.

Oja SS, Saransaari P (2007). Pharmacology of taurine. Proc. West Pharmacol. Soc., 50: 8-15.

Röhl C, Armbrust E, Herbst E, Jess A, Gülden M, Maser E, Rimbach G, Bösch-Saadatmandi C (2010). Mechanisms Involved in the Modulation of Astroglial Resistance to Oxidative Stress Induced by Activated Microglia: Antioxidative Systems, Peroxide Elimination, Radical Generation, Lipid Peroxidation. Neurotox. Res., 17: 317–331.

Röhl C, Armbrust E, Kolbe K, Lucius R, Maser E, Venz S, Gülden M (2010). Activated microglia modulate astroglial enzymes involved in oxidative and inflammatory stress and increase the resistance of astrocytes to oxidative stress *in vitro*. Glia, 56(10):1114–1126

Rupniak HT, Joy KA, Atkin C, Brown G, Barnes JC, Doctrow SR, Malfroy B, Wong T, Anderson IK, Molloy CR, Mills GI, Soden P (2000). Oxidative neuropathology and putative chemical entities for Alzheimer's disease: neuroprotective effects of salen-manganese catalytic antioxidants. Neurotox. Res., (2):167-178.

Saransaari P, Oja SS (2000). Taurine and neural cell damage. Amino Acids, 19: 509–526.

Southam E, Garthwaite J (1993). The nitric oxide-cyclic GMP signalling pathway in rat brain. Neuropharmacology, 32 (11): 1267-1277.

Taskiran D, Kutay FZ, Sözmen E, Pöğün Ş (1997). Sex differences İn nitrite/nitrate levels and antioxidant defence in rat brain. Neuroreport,
8: 881-884

Watts J, Segieth J, Pearce B, Whitton PS (2004). Regulatory role of nitric oxide over extracellular taurine in the hippocampus of freely moving rats. Neurosci. Lett., 357: 179–182.

Yamada K, Noda Y (1995). Role of nitric oxide in learning and memory in monoamine metabolism in the rat brain. Br. J. Pharmacol., 115: 852-858.

Zhu Y, Carvey PM, Ling Z (2007). Altered glutathione homeostasis in animals prenatally exposed to lipopolysaccharide, Neurochem. Int., 50: 671–680.