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Consequences of Systemic Immune Activation on the Central Nervous System after Immunological Tolerance in the Neonatal Period: A Pre-Clinical Study

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Abstract

Objective: Evaluate the consequences of systemic immune activation on the central nervous system after immunological tolerance in the neonatal period.

Methods: Pre-clinical study of the experimental type. 156 male and female C57BL / 6 mice were used. The animals were mated, and the offspring used for this study. The collected data were inserted into a database, developed electronically, using the IBM SPSS Statistics 24.0 software. The statistical analysis of the parametric data was performed using the ANOVA test with post-hoc Tukey, and the statistical analysis of the non-parametric data was performed using the Kruskal-Wallis tests.

Results: It was observed that the animals that received LPS in the neonatal phase did not present memory deficits and low levels of IL-1b. In the group that received LPS in the neonatal and adult phase, there was an increase in the MDA equivalents and protein carbonylation in an equivalent way to the group of untreated animals.

Conclusion: The study showed how important it is to understand tolerance and to plan therapeutic strategies for many diseases based on CNS inflammation, as well as the use of a technique that has been improved for years as early immunization therapyas in the case of neonatal immune activation.

Keywords: Immune Tolerance; Central Nervous System; Immune System; Neonatal; Memory; Animals

Abbreviations: CNS: Central Nervous System; BBB: Blood-Brain Barrier; RRP: Recognition Receptors; ROS: Reactive Oxygen Species; UFSC: Federal University of Santa Catarina; PBS: Phosphate-Buffered Saline; DNPH: Dissolved with Dinitrophenylhydrazine

Introduction

Immune activation is characterized by an inflammatory process caused by infectious pathogens, such as bacteria (gram-positive or gram-negative), as well as through endotoxins (or inflammatory mediators) such as LPS [1]. Increased expression of systemic proinflammatory mediators, due to immune activation, can increase the permeability of the blood-brain barrier (BBB)

and lead to microglial and astrocytic activation in the central nervous system (CNS) [2]. The activation of microglia initiates a process of neuroinflammation sustained mainly by the release of pro-inflammatory cytokines in brain tissue [3]. This process can cause changes in specific areas of the CNS such as cortex and hippocampus associated with changes in cognitive functions such as memory and learning [4]. Pre-clinical studies have shown that exposure to LPS is associated with long-term results, such as changes in memory, learning and neuronal loss in the hippocampus, an important area in cognitive processing [5,6]. In this context, infections caused by gram-negative bacteria are highly prevalent throughout life [7,8]. LPS is an endotoxin derived from the cell wall of gram-negative bacteria after being phagocyted and degraded by defense cells [9,10]. It is considered highly toxic for inducing the release of cytokines and for increasing the production of reactive oxygen species (ROS). LPS is a ligand for the toll-like 4 (TRL-4) receptors. This receptor is part of the set of pattern recognition receptors (RRP) and is specialized in recognizing molecular patterns associated with pathogens (PAMPs). Activation of TLR-4 forms an intracellular heterodimer - the inflammasome. Therefore, there is activation of the signaling pathway responsible for the release of interleukin (IL)-1b and the beginning of an inflammatory process [11].

Studies have shown that endotoxin tolerance is an important phenomenon, as the body is exposed to small amounts of microbial products, inducing a decreased inflammatory response and subsequently to a second challenge where the response is characterized by the decreased release of pro-inflammatory cytokines 9. Tolerance to LPS represents a selective reprogramming whose main objective is to limit immune activation and consequently to decrease the inflammatory process generated by a pathogenic stimulus [12,13]. It is believed that this first exposure may protect the body against a later challenge to LPS. In this sense, the tolerance mechanism is accompanied by a reduction in the levels of some pro-inflammatory cytokines such as IL-1b [13].

Childhood is known to be a critical period, where the innate immune system is still developing. However, it has greater plastic capacity, because external stimuli such as pathogens, may be able to program immune responses until adulthood [14,15]. Pre-clinical studies have shown that a sublethal dose in this period is effective in promoting a long-term immune tolerance mechanism and protecting the CNS against possible inflammation after immune activation in adulthood caused by exposure to lethal doses of LPS [16,17]. In this sense, the investigation of the tolerance mechanism, because of exposure to LPS in low doses in the neonatal period, becomes relevant because it aims to understand whether this first immune activation may predispose to the development of late changes after a second exposure to endotoxemics as an adult [16]. Thus, the role of the immune system may be the key to understanding the acute and late changes caused by exposure to endotoxins in a system still in formation. Therefore, future treatment strategies can focus on the balance between immune actions at specific periods in an individual's life. To understand this relationship, the following research question was formulated: What are the consequences of systemic immune activation on the central nervous system after immunological tolerance in the neonatal period: a preclinical study?

Materials and Methods

Animals

Male and female C57BL / 6 mice from the Federal University of Santa Catarina (UFSC) were used. The animals were mated (one male for each female) and the offspring used for this study. The animals were kept in polypropylene boxes, a 12-hour light and dark cycle (6 am to 6 pm) and free food and water. The environment was maintained at a temperature of 23 + 1ºC. The animals were placed in the Experimental Vivarium of the Experimental Neuroscience Laboratory (LANEX) located on the Pedra Branca campus, in Block I2. The number of animals per group was calculated at n = 8. The formula used for the calculation was the equation n / group = 2 [(Zα / 2 + Zβ) X d / Δ] 2, for comparison of two averages, considering the test power of 80%, the level of significance 5%, the standard deviation of 12.5% and the value of the difference to be detected equal to 18%. Eight animals were used in each experimental group, thus ensuring that the conclusions of the experiments were valid, within an acceptable risk of not observing differences where they exist, nor observing differences where they do not exist. For data safety and reliability, 10 animals per group were used in this study. Mortality was assessed throughout the experiment. The literature reports that this experimental model may have a 60% mortality in the first days after endotoxemic exposure. Thus, 156 animals were used. All procedures were approved by the Unisul Animal Care and Experimentation Committee (protocol number 19.018.4.01.IV).

Exposure to Endotoxin

Exposure to endotoxin is based on a first dose at two days of life, characterized as being sublethal because it is a low dose. The animals received a single subcutaneous injection of LPS at a concentration of 0.2 mg / kg with a volume of 5 ml / kg of body weight (Escherichia coli 0111: B4, L-2630; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) dissolved in PBS. The dose (0.2 mg / kg) of LPS was based on previous studies, in which LPS preconditioning has been shown to abolish exacerbated inflammation and protect against cognitive impairment in animal models [16,18,19]. As adults (60 days), the animals received the second dose of LPS, characterized by being a lethal exposure because it is a high dose. The animals received a single subcutaneous injection of LPS at a concentration of 0.5 mg / kg with a volume of 5 ml / kg of body weight (Escherichia coli 0111: B4, L-2630; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) dissolved in PBS [16,20]. The animals in the control group received an injection of PBS with the same regimen. The administration of LPS and / or PBS took place between 8:00 and 9:00 am.

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Locomotory Activity

Habituation to an open field was carried out in a 40 × 60 cm open-field surrounded by 50-cm high walls made of brown plywood with a frontal glass wall. The floor of the open field was divided into 9 equal rectangles by black lines. The animals (n = 12 per group) were gently placed on the left rear quadrant and left to explore the arena for 5 min (training session). Immediately afterward, the animals were taken back to their home cages. Two observers that were blind to rats' treatment status counted crossings of the black lines and rearing performed by the animals. The quantitative analyses of the moves of rats through the open field are useful for measuring the behavior [21].

Inhibitory Avoidance

The evasive memory assessment consisted of two stages: training and testing, performed at an interval of 24 hours to assess aversive long-term memory. The evaluation was carried out by the same researchers using specific equipment for such evaluation: passive dodge box. In the training session, the animals were placed on the platform and the time the animal took to descend with the four legs of the platform was timed. This period is called latency. Immediately after descending from the platform (with four legs), the animal received a shock of 0.2 mA for 2 seconds. In the test session, the animal was again placed on the platform and the time it took to descend (latency) was measured, but without shock. After aversive stimulation, a low latency in tests is associated with a reduction in cognitive or memory capacity [22].

Determination of the Cytokine Content

The concentration of cytokines IL-1β was determined by ELISA (R&D Systems, Minneapolis, MN). All samples were assayed in duplicate. Briefly, the capture antibody (13 ml, contains 0.1% sodium azide) was diluted in phosphate-buffered saline (PBS), added to each well and left overnight at 4°C. The plate was washed four times with PBS and 0.05% Tween 20 (Sigma, St. Louis, MO, USA). The plate was blocked with 1% bovine serum albumin and incubated for 1 h at room temperature before washing four times with PBS and 0.05% Tween 20. The samples and standards were added, and the plate was incubated overnight at 4°C. After washing the plate, detection antibody (concentration provided by the manufacturer) diluted in PBS was added. The plate was incubated for 2 h at room temperature. After washing the plate, streptavidin (DuoSet R&D Systems, Minneapolis, MN, USA) was added and the plate was incubated for 30 min. At last, color reagent o-phenylenediamine (Sigma, St. Louis, MO, USA) was added to each well and the reaction was allowed to develop in the dark for 15 min. The reaction was stopped with the addition of 1 M sulfuric acid to each well. The reaction was stopped with the addition of 1 M sulfuric acid to each well. The absorbance was read on a plate reader at 492-nm wavelength (Emax, Molecular Devices, Minneapolis, MN, Mol Neurobiol USA). The total protein was measured using bovine serum albumin as a standard [23].

Oxidative Stress

Oxidative damage to tissue proteins was determined by measuring carbonyl groups as previously described. Briefly, the obtained samples were precipitated in addition of 20% trichloroacetic acid and the proteins dissolved with dinitrophenylhydrazine (DNPH). Carbonyl group contents were measured by absorbance at 370 nm by spectrophotometer [24,25].

Statistical Analyses

Data from the habituation to an open field and biochemical analyses are reported as means ± S.E.M and were analysed by the ANOVA Tukey post hoc. $p < 0.05$ was considered statistically significant.

Results

Figure 1 showed the results of habituation (Figure 1A) and aversive memory (Figure 1B). It was observed that animals of PBS+PBS and LPS+PBS groups did not present memory deficities. However, the animals of PBS+LPS showed a habituation and aversive memory impairment. This result was reverted in the group of animais that received two doses of LPS in diferentes concentrations and periods of life. The results of IL-1β were demonstrated in Figure 2. It was observed that there was an increase of IL-1β levels in all structures evaluated in the PBS+LPS group. These results were reverted in the LPS+LPS group in the same structures demonstrating a pre-conditioning with low doses of LPS in the neonatal can be effective agains the effecs of hight doses of LPS in adulthood. Figure 3 demonstrated the effects of pre-conditioning with LPS on the oxidative damage through the analysis of MDA equivalets (Figure 3A) and protein carbonilation (Figure 3B). There was observed that in the LPS+LPS group na increase of the MDA equivalets and protein carbonilation in all structures evaluated when compared to the PBS+PBS animals' group. In the LPS+LPS group there was a decrese of these levels in prefrontal cortex, cerebelum, hippocampus and striatum when compaed to the PBS+LPS group.

Discussion

Results from previous studies have demonstrated that bacterial lipopolysaccharides (LPS) applications can induce sepsis/endotoxemia in animals. Thus, LPS has been used by many researchers to produce experimental endotoxemia in animals [26]. In our study, it was demonstrated that exposure to low doses of LPS in the neonatal period conditions the individual to protective high doses in adulthood. This demonstration was evidenced in Figure 2 showing increased levels of Interleukin1 Beta (IL-1β) at all levels and in all structures in the PBS+LPS group that received a dose of LPS in adulthood; in contrast the LPS+PBS and LPS+LPS groups, which yielded low levels of IL-1β, a pro-inflammatory cytokine activated by viruses and bacteria, which characterizes immune activation through LPS. Thus, the effects of endotoxin tolerance as a potential neuroinflammation reducer were studied [19,27,28].

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This adaptation response to endotoxins is an important answer to the issue that has driven this investigation, which aimed to identify the consequences of systemic immune activation on the central nervous system after immune tolerance in the neonatal period. In this aspect of immunological conditioning, the positive side of inflammation was observed [29].

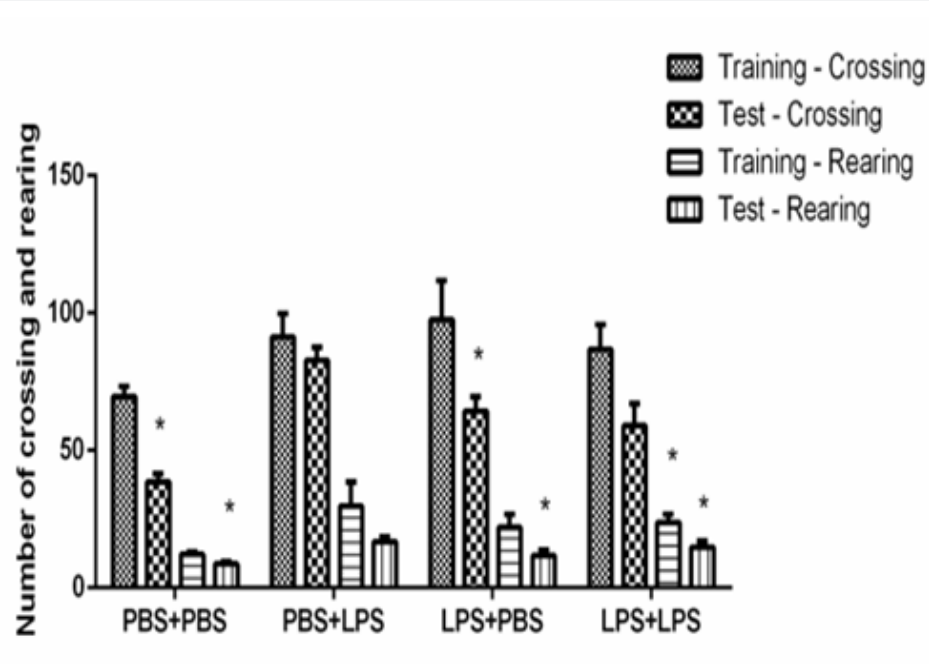

Figure 1A: Showed the results of habituation (Figure 1A) and aversive memory (Figure 1B). There were observed that animals of PBS+PBS and LPS+PBS groups did not presented memory deficities. However, the animals of PBS+LPS showed a habituation and aversive memory impairment.

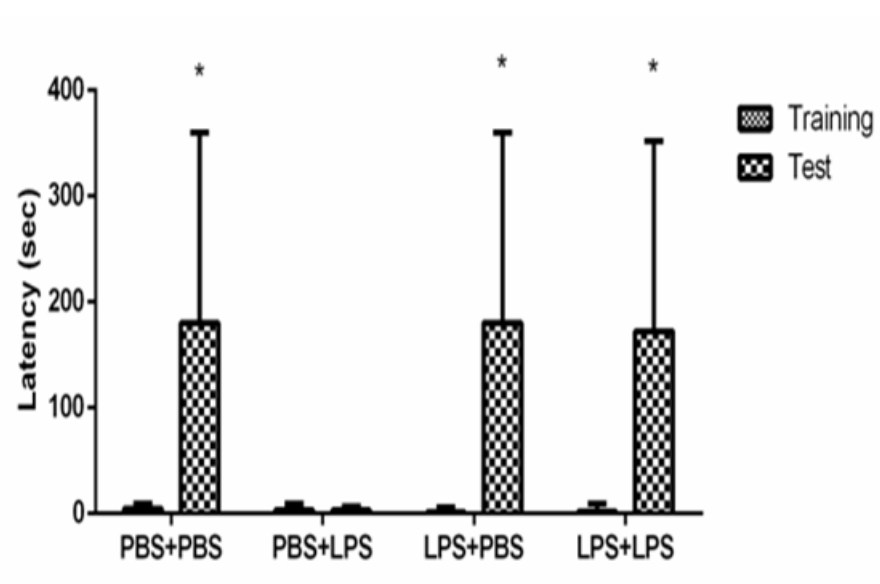

Figure 1B: Showed the results of habituation (Figure 1A) and aversive memory (Figure 1B). There were observed that animals of PBS+PBS and LPS+PBS groups did not presented memory deficities. However, the animals of PBS+LPS showed a habituation and aversive memory impairment.

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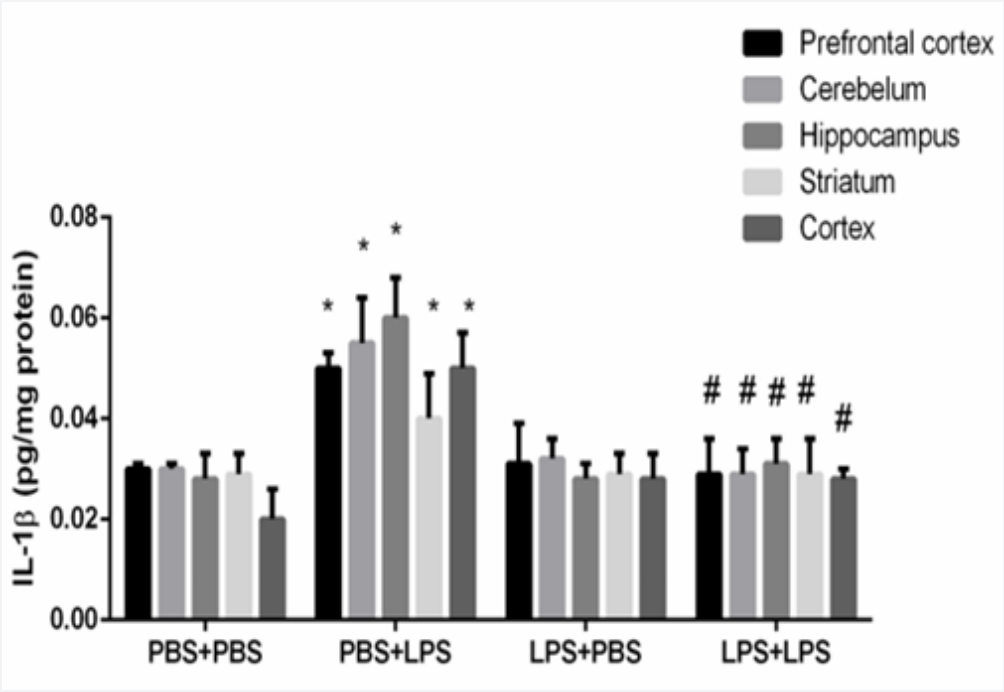

Figure 2: The results of IL-1β were demonstrated in Figure 2. It was observed that there was an increase of IL-1β levels in all structures evaluated in the PBS+LPS group.

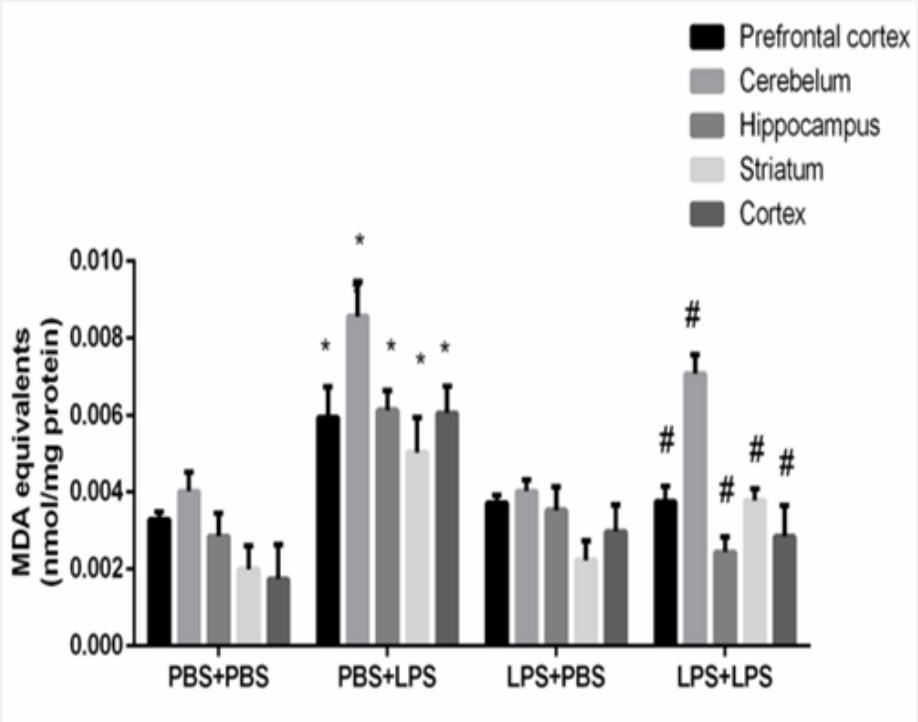

Figure 3A: Demonstrated the effects of pre-conditioning with LPS on the oxidative damage through the analysis of MDA equivalets (Figure 3A) and protein carbonilation (Figure 3B).

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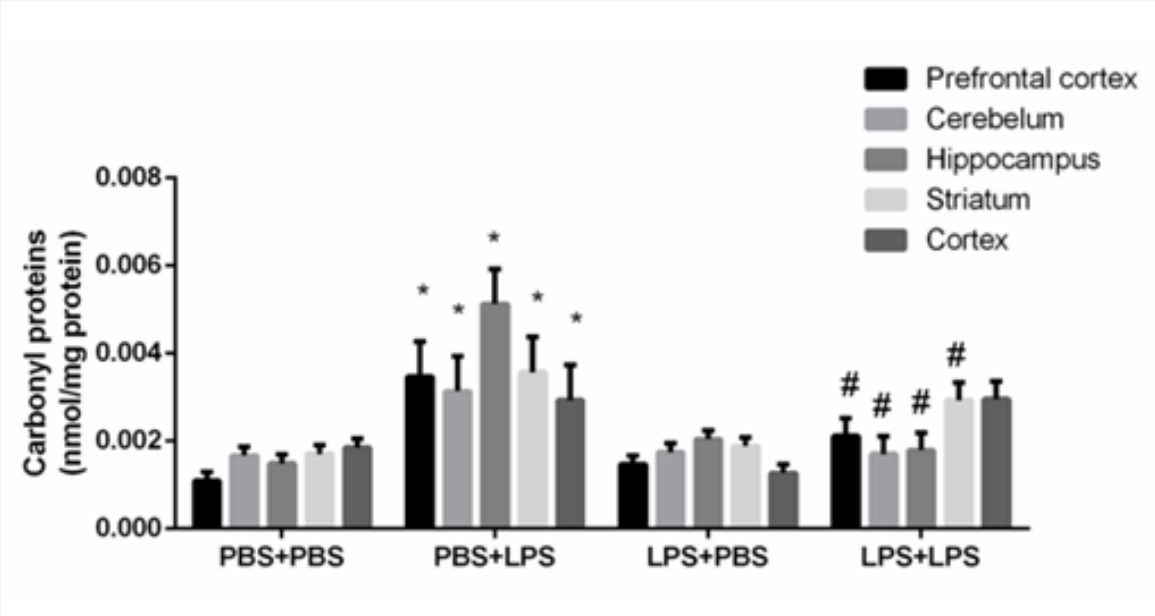

Figure 3B: Demonstrated the effects of pre-conditioning with LPS on the oxidative damage through the analysis of MDA equivalets (Figure 3A) and protein carbonilation (Figure 3B).

Regarding memory and learning tests, it was shown that there are extensive communications between the central nervous system and the immune system and that pro-inflammatory cytokines can influence the brain and the structures that mediate cognition [30]. In this sense, the results shown in Figure 1A and Figure 1B, respectively, have shown that the control group, untreated PBS+PBS, and the group that received one dose of LPS in the neonatal phase (LPS+PBS-treated animals) did not show memory deficits, corroborating the claim of endotoxemic tolerance benefits which can be activated by the exposure to sub-lethal doses of a powerful inflammation trigger, mediated by macrophages, such as LPS, used in this study, that was consistent with literature reports 16. In contrast, regarding the results of the habituation and aversive memory tests in PBS+LPS animals, which received only one dose of LPS in the adult phase, showed habituation and aversive memory deficiency. It has been suggested that inflammations in the region corresponding to memory in the hippocampus are responsible for dysfunctions, such as those related to spatial orientation and the individual's conditions, corroborating with the deficiencies reported in the present study [31]. In this connection, the level of deficiency in PBS+LPS animals was reduced when compared to the group that received doses of LPS at different stages of life (neonatal and adult), suggesting that neuroinflammation does not affect already consolidated memory [32].

Finally, another test performed corresponded to the measurement of oxidative damage levels used for the measurement of protein oxidation. The parameters used were the measurement of malondialdehyde (MDA) levels, which indicate indices of lipid peroxidation and protein carbonylation, shown in previous studies [33,34]. as being one of the most toxic substances that cause important oxidative changes and is considered a major mark of disorders related to oxidative stress. In this study, it was noticed that there was an increase in these factors in animals in the LPS + LPS group in all structures, indicating that LPS adversely caused oxidative stress in untreated PBS+PBS rats. In the LPS+LPS group, there was a decrease in these levels in the prefrontal cortex, cerebellum, hippocampus and striatum when compared to the group of PBS+LPS animals, which received a dose in adulthood, suggesting, according to previous observations, that the induction of LPS in the neonatal phase plays an important role in activating the immune system that reduces the neural damage caused by toxins [35,36].Therefore, knowing that humans are often exposed to these endotoxins, as is the case of the well investigated sepsis, it is suggested that further studies related to neonatal activation be performed, in order to better understand how to increase the inhibitory response of these inflammatory cytosines. Funding This study was financed in part by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Conflicts of Interest Disclosure

The authors declare no competing interests relevant to the content of this study.

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Authors' Contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve, the version to be published.

Availability of Data and Responsibility for the Results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

References

1. Cardoso FL, Jasmin Herz, Adelaide Fernandes, Rocha J, Bruno Sepodes, et al. (2015) Systemic inflammation in early neonatal mice induces transient and lasting neurodegenerative effects. J Neuroinflammation 12(82): 1-18.
2. Hagberg H, Carina Mallard, Donna M Ferriero, Susan JV, Steven JV, et al. (2015) The role of inflammation in perinatal brain injury. Nat Rev Neurol 11(4): 192-208.
3. Sankowski R, Mader S, Valdés-Ferrer SL (2015) Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. Front Cell Neurosci 9(28): 1-20.
4. Subhramanyam CS, Wang C, Qidong H, Dheen, ST (2019) Microglia-mediated neuroinflammation in neurodegenerative diseases. Semin Cell Dev Biol 94: 112-120.
5. Anderson ST, Commins S, Moynagh PH, Coogan AN (2015) Lipopolysaccharide-induced sepsis induces long-lasting affective changes in the mouse. Brain Behav Immun 43: 98-109.
6. Lin L, Xuan Chen, Quiping Zhou, Peixian H, Shuqi J, et al. (2019) Synaptic structure and alterations in the hippocampus in neonatal rats exposed to lipopolysaccharide. Neuroscience Letters 709: 1-10.
7. Claypoole LD, Zimmerberg B, Williamson LL (2017) Neonatal lipopolysaccharide treatment alters hippocampal neuroinflammation, microglia morphology and anxiety-like behavior in rats selectively bred for an infantile trait. Brain Behav immun 59: 135-146.
8. Koulenti D, Andrew S, Aaron Ellingboe, Mohd Hafiz Abdul-Aziz, Patrick H, et al. (2019) Infections by multidrug-resistant Gram-negative Bacteria: what's new in our arsenal and what's in the pipeline? Int J Antimicrob Agents. 53(3): 211-224.
9. Li P, Li M, He K, Zhong K, Gong J, et al. (2014) The effects of Twist-2 on liver endotoxin tolerance induced by a low dose of lipopolysaccharide. Inflammation 37(1): 55-64.
10. Vojtechova I, Tomas Petrasek, Maleninska K, Brozka H, Tejkalova H, et al. (2018) Neonatal immune activation by lipopolysaccharide causes inadequate emotional responses to novel situations but no changes in anxiety or cognitive behavior in Wistar rats. Behav Brain Res 349: 42-53.
11. Xiong L, Miller VM, Hunter LW, Li Y, Jayachandran M (2011) Leukocyte- and platelet-derived microvesicle interactions following in vitro and in vivo activation of toll-like receptor 4 by lipopolysaccharide. PloS one 6(9): 1-7.
12. Ariga SK, Bernardes Abatepaulo F, Edielle Sant AM, Irineu Tadeu V, Fabiano Pinheiro da S, et al. (2014) Endotoxin tolerance drives neutrophil to infectioussite. Shock 42(2): 168-173.
13. Liu D, Cao S, Zhou Y, Xiong Y (2019) Recent advances in endotoxin tolerance. J Cell Biochem 120(1):56-70.
14. Amani M, Hanieh S, Mohannad-Hossein D, Maryam A, Amir B, et al. (2013) Neonatal NMDA receptor blockade alters anxiety- and depression-related behaviors in a sex-dependent manner in mice. Neuropharmacology 73: 87-97.
15. Yu JC, Hesam Khodadadi, Aneeq Malik, Brea Davidson, Jatinder Bhatia, et al. (2018) Innate Immunity of Neonates and Infants. Front Immunol 9: 1-12.
16. Seeley JJ, Ghosh S (2017) Molecular mechanisms of innate memory and tolerance to LPS. J Leukoc Biol 101(1): 107-119.
17. Monguió-tortajada M, Franquesa M1, Sarrias MR, Borràs FE (2018) Low doses of LPS exacerbate the inflammatory response and trigger death on TLR3-primed human monocytes. Cell Death & Disease 9(5):1-14.
18. Turner RC, Zachary J Naser, Brandon P Lucke-Wold, Aric F Logsdon, Reyna L Vangilder, et al. (2017) Single low-dose lipopolysaccharide preconditioning: neuroprotective against axonal injury and modulates glial cells. Neuroimmunol Neuroinflamm 4: 6-15.
19. Zhang Z, Muhuo JI, Yanlin L, Jianjun Y, Jun G (2018) Endotoxin tolerance induced by lipopolysaccharide preconditioning protects against surgery-induced cognitive impairment in aging mice. molecular medicine reports 17(3): 3845-3852.
20. Gnauck A, Lentle RG, Kruger MC (2015) The Characteristics and Function of Bacterial Lipopolysaccharides and Their Endotoxic Potential in Humans. International Reviews of Immunology 35(3): 189-218.
21. Osmon KJ, Vyas M, Woodley E, Thompson P, Walia JS (2018) Battery of Behavioral Tests Assessing General Locomotion, Muscular Strength, and Coordination in Mice. J Vis Exp 131: 1-6.
22. Jahn-Eimermacher A, Lasarzik I, Raber J (2011) Statistical analysis of latency outcomes in behavioral experiments. Behavi brain res 221(1): 271-275.
23. Jang JS, Yeon-Hee Lee, Hemant K Kandahar, Suman K Shrestha, Jae Sung Lee et al. (2018) Changes in the tumor necrosis factor-level after an ultrasound-guided femoral nerve block in elderly patients with a hip fracture. Rev Bras Anestesiol 68(6): 558-563.
24. Levine R L, Garland D, Oliver CN, Amici A, Climent I, et al. (1990) Determination of carbonyl content in oxidatively modified proteins. Methods in enzymology 186: 464-478.
25. Weber D, Davies MJ, Grune T (2015) Determination of protein carbonyls in plasma, cell extracts, tissue homogenates, isolated proteins: Focus on sample preparation and derivatization conditions. Redox Biology 5: 367-380.
26. Ilçe F, Gök G, Pandir D (2019) Acute effects of lipopolysaccharide (LPS) in kidney of rats and preventive role of vitamin E and sodium selenite. Human & Experimental Toxicology 38(5): 547-560.
27. Li XL, Jin Lv, Na-Na Xi, Tan Wang, Xiao-Feng S, et al. (2010) Neonatal endotoxin exposure suppresses experimental autoimmune encephalomyelitis through regulating the immune cells responsivity in the central nervous system of adult rats. Biochem Biophys Res Commun 398(2): 302-308.
28. Morris MC, Gilliam EA, Li L (2015) Innate immune programing by endotoxin and its pathological consequences. Front Immunol 5: 680.
29. Disabato DJ, Quan N, Godbout JP (2016) Neuroinflammation: the devil is in the details. J Neurochem 139(2): 136-153.

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DOI: 10.19080/AJPN.2023.13.555915

30. Huang Z, Hao Wang, Xiu-Rong R, Liang T, Jing Xu, et al. (2010) Effects of immune activation on the retrieval of spatial memory. Neurosci Bull 26(5): 355-364.

31. Andy SN, Pandy V, Alias Z, Kadir H (2018) Deoxyelephantopin ameliorates lipopolysaccharides (LPS)-induced memory impairments in rats: evidence for its anti-neuroinflammatory properties. Life Sci 206: 45-60.

32. Czerniawski J, Guzowski JF (2014) Acute neuroinflammation impairs context discrimination memory and disrupts pattern separation processes in hippocampus. J Neurosci 34(37): 12470-12480.

33. Doğanyiğit Z1, Küp FÖ, Silici S, Deniz K, Yakan B, et al. (2013) Protective effects of propolis on female rats' histopathological, biochemical andgenotoxic changes during LPS induced endotoxemia. Phytomedicine 20(7): 632-639.

34. Fedorova M, Bollineni RC, Hoffmann R (2014) Protein carbonylation as a major hallmark of oxidative damage: update of analytical strategies. Mass Spectrometry Reviews 33(2): 79-97.

35. Khan MS, Tahir Ali, Min Woo Kim, Myeung Hoon Jo, Min Gi Jo, et al. (2016) Anthocyanins protect against LPS-induced oxidative stress-mediated neuroinflammation and neurodegeneration in the adult mouse cortex. Neurochem Int 100: 1-10.

36. Berkiks I, H Benmhammed, A Mesfioui, A Ouichou, A El Hasnaoui, et al. (2018) Postnatal melatonin treatment protects against affective disorders induced by early-life immune stimulation by reducing the microglia cell activation and oxidative stress, International Int J Neurosci. 128(6): 495-504.

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