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Sex Dimorphism of Memory Response to Long-term Effect Lipopolysaccharide Administration in Wistar Rats

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Abstract

Lipopolysaccharide (LPS) is bacterial endotoxin and a pathogenic factor that contributes to multiple organ failure, including brain injury. The mechanisms undergoing in cognitive alterations are unknown. In this study, we evaluated the effects of LPS administration on the memory in male and female adolescent rats. Twenty rats were distributed into two groups: control group which received an intraperitoneal (IP) injection of saline on postnatal day (PND) 60 (five females and five males) and LPS-treated group which received an IP injection of LPS on PND60 (five females and five males), After two, three and ten months, rats were tested in the Y Maze and the object recognition test (ORT), to assess the working and spatial memory. Compared to controls, rats in the LPS groups scored significantly lower on memory-related measures. Gender differences in response were mainly observed in the LPS group. Exposure to the combination of stressors led to a characteristic decrease in working memory measures in both genders. These results suggest that LPS administration caused damage in adolescent male rat brains, also a strong role of gender in the response of adolescent subjects to LPS.LPS administration affect working and spatial memory. Sexual dimorphisms are present in memory response to LPS. More in-depth studies on animal and cellular models (cell culture) seem be necessary to determine the neurobiological mechanisms involved in these responses.

Keywords: Memory response, LPS administration, sex dimorphism, Wistar rats

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1. Introduction

Cognitive functions represent all the brain processes by which humans, or animals, acquire information, process it, manipulate it, communicate it, and use it to act [1]. They include perception, attention, memory, executive functions, oral language, written language, calculation, representation in space and time, gesture, reasoning, emotions, the ability to know, to interact with others [2]. Cognitive disorder is any substantial, lasting or permanent alteration of one or more cognitive functions resulting from brain dysfunction, whatever the etiology [2, 3]. Memory problems constitute one of the modalities of these cognitive dysfunctions.

Memory is a higher cognitive function, allowing us to capture, encode, retain, and restore the information we perceive, which ensures rapid adaptation to the environment. In reality, there are several types of memory, which are classified according to the cognitive mechanisms involved (mainly consciousness) into explicit and implicit memories, and according to the retention period, into sensory memory, short- and long-term memories, and working memory. Working memory is a temporary storage system, with limited capacities, allowing complex cognitive processing to be carried out on stored elements (mental calculation, adaptation to change, goal selection, etc.), it is a sensitive system to distraction, and escapes the effect of age, its anatomical support is the prefrontal cortex. Neonatal intracerebral exposure to LPS 1 mg/kg causes a reduction in the survival of granule neurons and astrocytes in the dorsal hippocampus in C57/BL6 mice; this reduction did not cause learning deficits and memory assessed in adulthood using the “trace fear conditioning (TFC) paradigm” [4]. Another study carried out in Sprague–Dawley rats, using the same dose and the same mode of injection of LPS, demonstrated that the latter causes chronic inflammation at the level of Ammon's Horn 1 (CA1) of the dorsal hippocampus. linked to learning and memory deficits, these deficits were assessed using the passive avoidance test [5, 6] , which clearly demonstrates the involvement of the CA1 region (and CA3 too) of the dorsal hippocampus in learning and memory processes [7].

By using Morris pool, a study have shown that a chronic administration of LPS (0.25µl/h for 28 days) at the level of the fourth ventricle of the Wistar rat is responsible for deficits in spatial working memory [8]. Therefore, in this study, we evaluate the memory responses of

Lipopolysaccharide Administration in Male and Female Wistar Rats during long time, and further analyzed individual differences.

2. Materials and Methods

2.1. Chemicals

LPS (Escherichia coli LPS; lyophilized powder purified), obtained from Sigma Aldrich, was dissolved in sterile nonpyrogenic normal saline (PBS). DL-α-LA was mixed with sterile normal saline in a dark bottle and NaOH was added until the solid was dissolved. Sterile deionized water was used throughout the study.

2.2. Animals

The experiments carried out in this work were carried out on male Wistar strain laboratory rats, born and raised in the animal facility of the Department of Biology, Faculty of Sciences, Ibn Tofail University, Kenitra (Morocco). The age and weight of the rats at the start of the handling were 14 days and 15 ± 5g, respectively. They had free access to water and food, subject to a photoperiod of 12/12 (12 light/12 dark) and an ambient temperature of 22°C. They were regularly monitored by an increase in body weight during their breeding. The cages were regularly cleaned.

The animals were divided into 2 groups:

- Group 1: control group consisting of 10 rats injected with PBS (Phosphate-Buffered Saline) (a single injection).
- Group 2: made up of 10 rats treated with LPS 250 µg/Kg (a single injection).

2.3. Memory tests

2.3.1. Y Maze

It is a test to assess working memory. This test is made up of three identical aisles (branches) arranged along the medians of an equilateral triangle. These paths have a length of 13 cm, a width of 4.5 cm and a height of 5.5 cm. This test is also called a "spontaneous alternation" test, because in the absence of a reinforcer (food for example), the rat, once placed in one of the three aisles, spontaneously seeks to explore the other aisles which they are unknown. In our procedure, the rat is placed in one of the three aisles, its head directed towards the point of intersection of the 3 aisles, then it is left for 5 minutes to freely explore. It is considered to have entered an alley if all 4 of its legs are inside. We count the order of visits, from which we extract the total number of visits as an index of general activity, and the number of alternations, which makes it possible to deduce the percentage of alternation, according to the formula: [Number of alternation / (number of visits-2)]*100 [9] (Figure 1). This percentage correlates inversely with the memory capacities of working memory.

2.3.2. Object recognition Test (ORT)

Object recognition is commonly used in rodents to assess the recognition memory (object-position association). The test evaluates the capacity of rat to discriminating between different objects, allowing to quantify the behavioral reactions of rodents following the introduction of a new object in a familiar environment. The test principle is based on the natural tendency of rats to explore new objects or the new object location in an open environment. The device consists of an open field, made up of square horizontal floor translucent and white vertical walls. Three objects were used, two similar and the third is different. (Figure 2).

The ORT takes place over 3 days (Figure 3). In the first day, called habituation (T0), the animal explores freely the open field without objects during a 10-minute. In day 2, called training (T1), the animal explores the open field with two identical objects placed along the diagonal. After 24 h of T1, the test (T2) takes place in 5min, the animal explores the open field with one familiar object (previously explored) and another new object, placed along the diagonal. Discrimination index: corresponds to the proportion of time that the animal spends explore the new object. It therefore varies between -100% (if the animal only explores the familiar object) and 100% (if it only explores the new object). Discrimination index = (Exploration time of the new object - exploration time of the familiar object)/ Total time spent exploring the new and familiar object.

3. Results and Discussions

3.1. Working memory

In 2 months(adolescence), the results obtained show significant difference in alternation percentage in rats injected with LPS compared to control rats ($p<0.05$). Statistical analyzes show no significant interaction of LPS vs sex ($p=0.74$) (Figure 4). In 3 months, the results show no significant difference in alternance percentage in LPS-injected male and female rats compared to control rats (Figure 4). The comparison between gender shows a significant interaction between the response of males and females with respect to LPS. The statistical results show no significant interaction of LPS vs sex ($p>0.05$). In 10 months, the results reveal significant difference in alternation percentage in male and female rats injected with LPS compared to control rats at this age ($p<0.01$). The comparison between gender shows a significant difference in performance of male rats compared to females. Statistical analyses show no significant in LPS vs sex interaction ($p<0.05$).

3.2. Recognition memory

In 2 months, the discrimination index shows that females injected with LPS contact less the novel object compared to LPS-injected males. Statistical analysis shows a significant interaction of LPS vs sex ($p<0.01$). In 3 months, the discrimination index shows that females contact the new object less compared to males with a non-significant difference. The comparison between male and female rats injected with LPS and control male and female rats fall under the absence of significant difference (Figure 5), of significant interaction of LPS vs sex ($p=0.05$). In 10 months, the discrimination index shows that LPS females contact the new less object compared to males, with a significant difference.

The comparison between male and female rats injected with LPS and male and female control rats, females do not detect any significant LPS vs sex interaction ($p>0.05$).

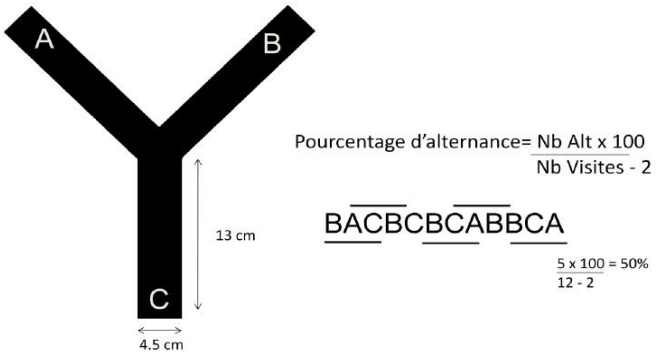

Figure 1: Experimental design for the Y-maze test, with the adapted formula for calculating the alternation percentage and an example of alternation counting (Alternation= visit to the 3 different aisles A, B and C)

Figure 2: Picture of the open field device

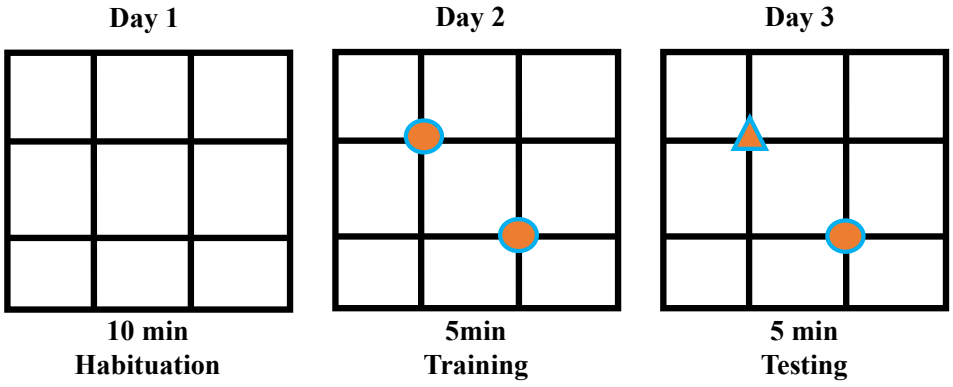

Figure 3: Experimental setup for ORT

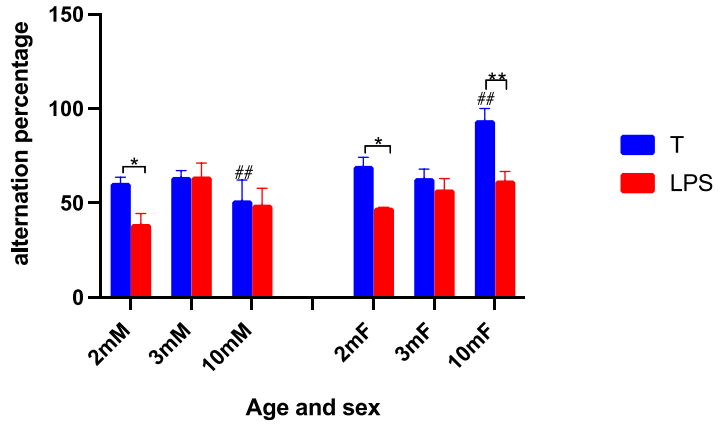

Figure 4: Effect of postnatal LPS injection on alternation percentage in Wistar Rats according to age and sex (n=20, ANOVA, *p<0.05 treatment effect, $p<0.05. m: month; M: male; F: female

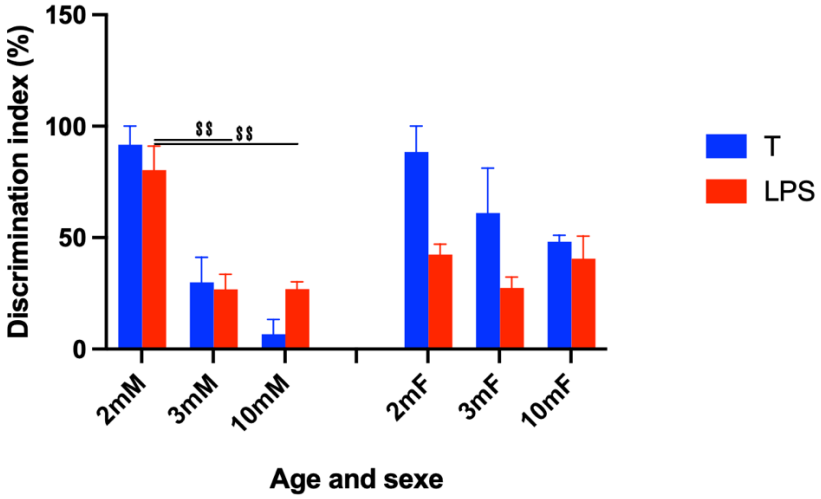

Figure 5: Effect of postnatal LPS injection on discrimination index in Wistar Rats according to age and sex (n=20, ANOVA, *p<0.05 treatment effect, $p<0.05 sex effect and £p<0.05 sex vs treatment interaction). m: month; M: male; F: female

The test used during this work to evaluate this type of memory is the Y maze; the percentage of entries in the arms of this test correlate inversely with the capacity of this type of memory. The study demonstrates that LPS causes a non-significant deterioration of working memory in the Y-maze test. As assessed by the contextual fear condition test in adult rats infected with LPS, this effect was related to age of rats [10]. In a model of vascular dementia, a treatment improved the performance of rats during open field and Morris pool tests [11], the latter test is known to the evaluation of the different modalities of spatial memory (reference, working, and long-term) [9], this test made it possible to demonstrate an improvement in spatial learning (spatial memory) in mice models of Alzheimer's disease[6], and transgenic rats for the amyloid precursor treated with Minocycline [12].

The ORT is an effective method for studying memory in mice. Before starting the experiment, a number of variables must be taken into consideration, such as exploration time can influence absolute discrimination [8, 13, 14]. Mouse strains may have lower discrimination values at shorter retention intervals, such as 1 or 4 h, which could obscure results when looking for memory disorders. Therefore, the retention interval should be carefully considered and a temporal analysis is probably necessary to determine the most appropriate interval. Finally, the choice of objects is a very important factor in the test [15]. These objects should be pre-tested to avoid any induced object preferences.

Lipopolysaccharide (LPS), component of the cell wall of Gram bacteria negative, has been used to induce infection in several animal studies because it triggers a well-characterized immune response through activation of the TLR4 receptor. In the immature rat brain, LPS induces a rapid and robust increase in expression of cytokines and chemokines, including IL-1β, IL6, TNF α, CXCL1 (GROKC), CXCL2, CXCL10, CCL2, and CCL7…, [16] and

a strong increase in circulating corticosterone levels at the time of exposure [17].

Treating pregnant rats or newborn babies with doses high LPS is able to damage the white matter, reduce the development of oligodendrocytes, hypo-myelinate neurons [5, 11, 18], and increase the sensation of pain in old age adult [19]. Prenatal exposure to LPS causes a decrease sensitivity to stress and a blunted immune response to immune challenges later during the neonatal period [20]. The proposed mechanism to explain these effects suggests that exposure to LPS during early life delays the development of the immune response in the neonatal period, but it also affects immune function in senescence by decreasing production monocytes in aged rats [21]. Similar studies consider the prenatal period determines immune function later in life. Based on these data, it can be predicted that early exposure to LPS causes blunted immune responses later in life, and can establish relative immunosuppression in rats throughout life. Thus, rats exposed to immune challenge may be more vulnerable to dysfunction or death neuronal.

Several studies have shown the existence of sexual dimorphism in the development and functioning of the brain. The differences manifest themselves in ways surprising in animal models of normal and pathological cases [22–24]. Early LPS administration can change the performance of animals in tests of spatial and working memory. For evaluate the postnatal impact of LPS on long-term memory, we observed the animal behavior at Y-Maze and OF with object at ages 2, 3 and 10 months. Our results show no significant difference between rats injected with LPS and control male and female rats in the test of Y-maze. On the other hand, at the MWM test level, our results show that females and males witnesses have acquisition memory or episodic memory. For rats injected with LPS, the results show that the deterioration affects females more than males at the level of episodic acquisition memory.

Other studies have found that memory is made up of units different, linked together. With age, each unit is affected independently of the other [25], Explicit memory includes episodic memory, which involves conscious recall of events and experiences, and semantic memory, which involves the conscious recall of facts and information [26]. The studies have shown that episodic memory is affected by aging more than semantic memory. Research carried out on humans at ages 35 to 80 has shown a sudden decrease in episodic memory performance in older adults [27]. These changes are probably due to an age-related dysfunction of the hippocampus and cortex. Since memory explicit is largely encoded in the hippocampus, as well as other regions of the brain, including the neocortex [28]. Thus, the neuroinflammation would induce a decline in cognitive function which may be explained by the association between markers of inflammation and several conditions pathological conditions, such as Alzheimer's, Parkinson's disease and cognitive impairment mild [29].

The relationship between non-pathological neuroinflammation and cognitive impairment has been established in several species, including rodents [30]. Peripheral inflammation induces an increase in the expression of pro-inflammatory cytokines in the brain parenchyma and potentiates cognitive decline [31]. This is done either by direct signaling of inflammatory molecules or indirectly. Studies have revealed that peripheral inflammation is a powerful regulator of neurocognition [32].

Working memory results obtained in the Y-maze test revealed no differences between LPS-injected male and female rats and controls. On the other hand, regarding recognition memory, the results show a very significant difference in female rats injected with LPS and the control. On the other hand, the results for males show no significant difference. These changes in behavior may be due to overexpression of cytokines responsible for changes in neurotransmitter levels. Our results also show sexual dimorphism in the level of decline in cognitive behaviors. It was revealed that female control rats experienced acquisition memory impairment more than male control rats. The same observation was found by a study which compared the performance of male and female rats and in association with the rats' monthly cycle and the cortisol level [33].

Sexual dimorphism, in our results, exists at the performance level of rats in the three tests (Y maze and OP with object). Studies show that men have greater age-related cognitive decline compared to women. [34]. By using tests, Maylor et al examined sex differences and age differences by sex on various cognitive tasks in a very large sample of healthy individuals [35]. Sexual dimorphism in the central nervous system, in adulthood, is due to the organizational effects of gonadal steroid hormones at fetal age, such as androgens and estrogens, both of which are present in very high concentrations elevated in male fetuses due to testicular steroidogenesis. The brain differences between the sexes can also arise from various factors, including the expression of genes carried on the sex chromosomes and abnormalities in the mother's treatment of male and female offspring. Taken together, these factors can explain the differences in neurogenics, myelination, synaptic pruning, dendritic branching, axonal growth, apoptosis and other neuronal parameters [36].

Large studies show that men showed greater age-related decline than women. In summary, some studies report that women perform better in immediate learning [37], verbal memory, and episodic memory [38], while others found no sex differences in verbal memory [39]. Other work has shown that older men have better visual memory, better working memory and better episodic memory compared to women [37]. In summary, sex differences in healthy older adults' memory capacity, where described, appear to be significantly dependent on the specific task [40]. Our results show that after postnatal exposure to LPS, females become more vulnerable to cognitive decline than males.

4. Limitations

Our study has several limitations. First, the small number of rats in each group could have skewed our results and reduced the power of the results. The use of the post hoc test in our analysis helped to explain this drawback. The LPS-epigenetic changes relationship was not evaluated in this study. The administration of LPS can cause epigenetic modifications whose evaluation becomes necessary for a better understanding of the changes observed subsequently. Another limitation concerns the administered dose of LPS and the postnatal day of injection which constitutes a criticism of this study and which can have neurobehavioral and biochemical effects and requires a more developed study.

5. Conclusions

The results of our study show that LPS administration elicits sex-dependent responses in memory measures. Sexual dimorphisms are present in response to LPS-related stress. More in-depth studies on animal and cellular models (cell culture) are essential to understand the neurobiological mechanisms involved in the effects of LPS on both sexes.

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Compliance with ethical standards

All experimental procedures were performed according to the NIH Guidelines for the Care and Use of Laboratory Animals and under observation and authorization of the doctoral studies center at Ibn Tofail University Kenitra, Morocco.

Conflict of interests

All the Authors declare that have no conflict of interest.

Author contributions

A. N., M. C., L.C S.M.C and conducted experiments and assisted with manuscript preparation. A. N., A. M. and A. E. contributed to the experimental design, data analysis, conceived the study, conducted, and oversaw experiments. M.C., M.L. performed all statistical analyses, and oversaw manuscript preparation. All authors have read and approved the final manuscript published version.

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