Behavioural Brain Research 306 (2016) 178–196

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Maternal inflammation linearly exacerbates offspring age-related changes of spatial learning and memory, and neurobiology until senectitude

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HIGHLIGHTS

- Using LPS-exposure to mimic maternal systemic inflammation during pregnancy.
- Examining influence on spatial learning and memory in the offspring from the midlife onwards.
- Maternal inflammation worsen impaired spatial performance in midlife-elderly offspring.
- Maternal inflammation worsen changed neurobiological indicators in midlife-elderly offspring.
- Changed neurobiological indicators significantly correlated with impaired spatial performance.

ARTICLE INFO

Article history:
Received 23 January 2016
Received in revised form 1 March 2016
Accepted 5 March 2016
Available online 16 March 2016

Keywords:
Aging
Histone acetylation
Lipopolysaccharide
Memory
Mice

ABSTRACT

Maternal inflammation during pregnancy can elevate the risk of neurodegenerative disorders in offspring. However, how it affects age-related impairments of spatial learning and memory and changes in the neurobiological indictors in the offspring in later adulthood is still elusive. In this study, the CD-1 mice with maternal gestational inflammation due to receiving lipopolysaccharide (LPS, i.p. 50 or 25 μg/kg) were divided into 3-, 12-, 18-, and 22-month-old groups. The spatial learning and memory were evaluated using a six-radial arm water maze and the levels of presynaptic proteins (synaptotagmin-1 and syntaxin-1) and histone acetylation (H3K9ac and H4K8ac) in the dorsal hippocampus were detected using the immunohistochemical method. The results indicated that there were significant age-related impairments of spatial learning and memory, decreased levels of H4K8ac, H3K9ac, and syntaxin-1, and increased levels of synaptotagmin-1 in the offspring mice from 12 months old to 22 months old compared to the same-age controls. Maternal LPS treatment significantly exacerbated the offspring impairments of spatial learning and memory, the reduction of H3K9ac, H4K8ac, and syntaxin-1, and the increment of synaptotagmin-1 from 12 months old to 22 months old compared to the same-age control groups. The changes in the neurobiological indicators significantly correlated with the impairments of spatial learning and memory. Furthermore, this correlation, besides the age and LPS-treatment effects, also showed a dose-dependent effect. Our results suggest that maternal inflammation during pregnancy could exacerbate age-related impairments of spatial learning and memory, and neurobiochemical indicators in the offspring CD-1 mice from midlife to senectitude.

1. Introduction

Brain aging inevitably leads to a decline in cognitive function, including problem solving, memories [1], and especially the hippocampus-dependent memories (e.g., spatial memory) [2,3],

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http://dx.doi.org/10.1016/j.bbr.2016.03.011
0166-4328/

which may seriously affect quality of life. Although many pathogenesis hypotheses have been repeatedly proposed, no single theory can fully explain the mechanisms of age-associated memory impairment (AAMI). Thus, it is crucial to explore the neurobiological mechanisms underlying AAMI.

Mounting evidence indicates that brain dysfunction is a consequence of a multifactorial process involving the interaction of genes and environment [4,5]. The hypothesis of the fetal origins of adult diseases, including dementia [5], emphasizes that critical windows of brain development are susceptible to stress and can result in permanent effects [6]. In humans, maternal inflammations from infections of viruses or bacteria are common forms of stress for embryo development. Epidemiological studies have found that increased incidence of maternal infections–both viral and bacterial–is associated with later psychotic disorders in the offspring [7]. Our previous study also found that maternal exposure to lipopolysaccharide (LPS) could accelerate the AAMI in middle-aged (400-day-old) CD-1 mice [8]. However, the mechanism that mediates the effects of an adverse environment on the embryonic brain is still elusive. Moreover, although interest is growing in this field, so far it has not been reported that maternal inflammation from LPS administration during embryo development will affect the AAMI in these mice offspring from midlife to senectitude.

LPS administration during pregnancy can cause a well-documented and widely accepted mouse model of maternal gestational infection [9]. This treatment incites the activation of inflammatory cells and results in a higher expression of some special pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α [10]. These cytokines may affect the function of the normal brain and program an unsuccessful brain aging via certain signaling pathways [11–13]. This may eventually lead to an age-related deterioration of synaptic function in corresponding brain regions, such as the changes in synaptic plasticity, neurogenesis, and neuromodulation [14,15]. Existing evidence demonstrates that synaptic plasticity is directly related to the AAMI [16,17]. A number of reports have revealed that abnormal synaptic function is likely involved in the impairment of synaptic connections between axonal buttons and dendritic spines by affecting the size and number of dendritic spines on neurons [18,19]. Moreover, the changes in synaptic-protein levels play a key role in synaptic plasticity and exert an influence on the AAMI [20].

Synaptotagmin-1 (Syt-1) and syntaxin-1 (Stx-1) are important pre-synaptic active-zone proteins in the neurotransmitter release [21,22]. Syt-1 acts a major Ca^{2+} sensor for fast synchronous neurotransmitter release [21] and Stx-1 is a key element of the SNARE complex that mediates vesicle fusion [22]. Our published studies have indicated that increased Syt-1 and decreased Stx-1 levels in the dorsal hippocampus were associated with the degree of AAMI in old SAMP8 mice [23–25]. Moreover, our studies also found that the hindering effects of acarbose and 1-deoxynojirimycin (both of which are inhibitors of intestinal α-glycosidases) on the AAMI were linked to recovered levels of Syt-1 and Stx-1 [24,25]. Although there is a lot of research on maternal inflammation induced by LPS administration during pregnancy, studies are rare on relationships between the exacerbated AAMI and the age-related changes of neurobiological indicators in the offspring during later adulthood.

Epigenetic modulation has been regarded as a potential novel mechanism in the changes in synaptic plasticity [26]. Accumulating evidence confirms that epigenetics can mediate the influence of experience on critical mechanisms of plasticity through altering the expression of synaptic proteins [26,27], and ultimately incite AAMI during senescence. Today, epigenetics are considered to be the modifications—without changing the DNA sequence—that result in heritable changes in gene expression levels [28], mainly including DNA methylation and histone modifications (acetylation, methylation, phosphorylation) [29]. Of the several types of epigenetic modifications, histone acetylation has been extensively studied and is most robustly relevant to promoting memory formation [29]. Recently, researchers have confirmed that histone (H) acetylation modification (HAM) plays a vital role in synaptic plasticity and memory formation in different model systems [30,31]. HAM influences gene expression by controlling the chromatin modification, particularly in the N-terminal regions of H3 and H4. For example, one study shows that enhanced acetylation on H4 lysine 8 (H4K8ac) strengthens the effect of exercise, and converts a subthreshold learning event into long-term memory [32]. Our recent studies have indicated that H4K8ac expression in the dorsal hippocampus of aged SAMP8 mice was reduced, and acarbose and 1-deoxynojirimycin could improve the ability of spatial learning and memory (SLM) perhaps through increasing H4K8ac [24,33]. In a model of iron-induced memory impairment, H3K9ac significantly reduces in the dorsal hippocampus of rats with neonatal iron overload, but excludes changes in H3K14ac, H4K5ac, and H4K12ac [34]. However, another study found that in the mouse and rat hippocampus the level of H4K12ac, but not H3K9ac, was in line with age-related cognitive decline [35]. This may be attributable to different times of evaluation after exposure to stimulations [35]. Growing evidence demonstrates that acetylation of other H3 and H4 residues is also involved in memory formation, such as H3K14 and H4K5/8/12/16 [36]. Despite the knowledge that environmental factors can influence the epigenome throughout life [37], data are scarce regarding the long-term effect of maternal exposure to adverse factors during pregnancy on adult HAM in the offspring, especially until senectitude.

Therefore, we assumed that maternal inflammatory insult can linearly exacerbate the offspring AAMI from midlife to later adulthood via deteriorating age-related alterations in the HAM and the synaptic proteins. In this study, we mainly explored whether maternal exposure to LPS linearly worsens: i) the age-related decline of SLM assessed with a six-radial arm water maze (RAWM) in the offspring CD-1 mice from middle age to the twilight years; ii) the age-related changes in the hippocampal levels of Syt-1, Stx-1, H3K9ac, and H4K8ac quantified using immunohistochemical staining. The correlations between SLM and measured neurobiological indicators were also analyzed.

2. Materials and methods

2.1. Animals

The CD-1 mice (7–8 weeks old, 40 males and 80 females) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd., whose foundation colonies were all introduced from Charles River Laboratories, Inc. The colony was maintained at 22–25 °C with a humidity of 55 ± 5% on a 12-h light/dark cycle (lights on at 7:00 a.m.). Food and water was freely obtained.

2.2. General procedures

After 2 weeks acclimation to the colony room, the males and females (1:2) were paired into breeders. The presence of a vaginal plug was designated as gestational day (gd) 0. The pregnant mice were consecutively handled for 3 days to minimize stress before the injections. During gds 15–17, they received an intraperitoneal injection of LPS (50 or 25 μg/kg, serotype 0127:B8, L3129; Sigma) or normal saline (control group, CON). On postnatal day 21, the offspring were separated from their mothers and housed in cages with 4–5 mice of the same sex. At 3 months old, the offspring mice (8 males and 8 females) were randomly selected from the CON, the H-LPS (LPS 50 μg/kg), and the L-LPS (LPS 25 μg/kg) groups, respectively, to complete the tests described in Sections 2.3–2.5.