Brain, Behavior, and Immunity 63 (2017) 160–175

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Special Issue on Perinatal Inflammation

Early-life stress lastingly alters the neuroinflammatory response to amyloid pathology in an Alzheimer's disease mouse model

Lianne Hoeijmakers [a], Silvie R. Ruigrok [a], Anna Amelianchik [a], Daniela Ivan [a], Anne-Marie van Dam [b], Paul J. Lucassen [a,#], Aniko Korosi [a,*,#]

[a] Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, Science Park 904, Amsterdam, The Netherlands
[b] Department of Anatomy & Neurosciences, Amsterdam Neuroscience, VU University Medical Center, De Boelelaan 1108, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 15 September 2016
Received in revised form 12 December 2016
Accepted 23 December 2016
Available online 25 December 2016

Keywords:
Early life
Stress
Neuroimmune
Microglia
Alzheimer's disease
Inflammation
Amyloid
Hippocampus

ABSTRACT

Exposure to stress during the sensitive period of early-life increases the risk to develop cognitive impairments and psychopathology later in life. In addition, early-life stress (ES) exposure, next to genetic causes, has been proposed to modulate the development and progression of Alzheimer's disease (AD), however evidence for this hypothesis is currently lacking. We here tested whether ES modulates progression of AD-related neuropathology and assessed the possible contribution of neuroinflammatory factors in this.

We subjected wild-type (WT) and transgenic APP/PS1 mice, as a model for amyloid neuropathology, to chronic ES from postnatal day (P)2 to P9. We next studied how ES exposure affected; 1) amyloid β (Aβ) pathology at an early (4 month old) and at a more advanced pathological (10 month old) stage, 2) neuroinflammatory mediators immediately after ES exposure as well as in adult WT mice, and 3) the neuroinflammatory response in relation to Aβ neuropathology.

ES exposure resulted in a reduction of cell-associated amyloid in 4 month old APP/PS1 mice, but in an exacerbation of Aβ plaque load at 10 months of age, demonstrating that ES affects Aβ load in the hippocampus in an age-dependent manner. Interestingly, ES modulated various neuroinflammatory mediators in the hippocampus of WT mice as well as in response to Aβ neuropathology. In WT mice, immediately following ES exposure (P9), Iba1-immunopositive microglia exhibited reduced complexity and hippocampal interleukin (IL)-1β expression was increased. In contrast, microglial Iba1 and CD68 were increased and hippocampal IL-6 expression was decreased at 4 months, while these changes resolved by 10 months of age. Finally, Aβ neuropathology triggered a neuroinflammatory response in APP/PS1 mice that was altered after ES exposure. APP/PS1 mice exhibited increased CD68 expression at 4 months, which was further enhanced by ES, whereas the microglial response to Aβ neuropathology, as measured by Iba1 and CD11b, was less prominent after ES at 10 months of age. Finally, the hippocampus appears to be more vulnerable for these ES-induced effects, since ES did not affect Aβ neuropathology and neuroinflammation in the entorhinal cortex of adult ES exposed mice.

Overall, our results demonstrate that ES exposure has both immediate and lasting effects on the neuroinflammatory response. In the context of AD, such alterations in neuroinflammation might contribute to aggravated neuropathology in ES exposed mice, hence altering disease progression. This indicates that, at least in a genetic context, ES could aggravate AD pathology.

1. Introduction

Alzheimer's disease (AD) is a highly prevalent, age-related neurological disorder characterized by a progressive deterioration of cognitive functions and the accumulation of specific neuropathological hallmarks, like amyloid β (Aβ)-containing plaques and neurofibrillary tangles in various brain regions (Querfurth and LaFerla, 2010). Next to specific genetic factors, like APP or PS1, AD etiology

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; CA, cornu ammonis; Ctrl, control; DG, dentate gyrus; EC, entorhinal cortex; ES, early-life stress; IL, interleukin; LPS, lipopolysaccharide; ML, molecular layer; P, postnatal day; SML, stratum lacunosum-moleculare; SR, stratum radiatum; WT, wild-type.

* Corresponding author.
E-mail address: a.korosi@uva.nl (A. Korosi).
Shared senior author.

http://dx.doi.org/10.1016/j.bbi.2016.12.023
0889-1591/

and progression is influenced by environmental factors (Mayeux and Stern, 2012; Reitz and Mayeux, 2014). Of interest in this respect is that high levels of (perceived) stress have been previously associated with a stronger cognitive decline and increased AD incidence (Johansson et al., 2013; Kaplan et al., 2001; Katz et al., 2016; Lupien et al., 1999; Wilson et al., 2003).

These epidemiological studies are consistent with preclinical work showing that adult stress (hormone) exposure could aggravate amyloid pathology in several Aβ-based mouse models for AD (Baglietto-Vargas et al., 2015; Dong et al., 2008; Green et al., 2006; Han et al., 2016; Jeong, 2006; Rothman et al., 2012), accompanied by increased cognitive impairments and reductions in synaptic plasticity (Grigoryan et al., 2014; Huang et al., 2015). In addition, clinical and preclinical studies have shown that exposure to early-life stress (ES), such as childhood abuse or parental neglect, is strongly associated with cognitive impairments throughout life (Chugani et al., 2001; Li et al., 2015; Mueller et al., 2010; Philip et al., 2015; Rice et al., 2008; Vallee et al., 1999). In fact, ES seems to affect many health outcomes across the life span (Price et al., 2013; Ravona-Springer et al., 2012; Tyrka et al., 2010; Wolkowitz et al., 2010) and can increase the vulnerability to develop age-related disorders, such as AD (Kaplan et al., 2001; Lahiri and Maloney, 2012, 2010; Mishra and Gazzaley, 2014; Price et al., 2013; Schury and Kolassa, 2012). While a few studies have shown that perinatal stress could modulate AD related neuropathology in mouse models (Lesuis et al., 2016; Sierksma et al., 2013), little is known about possible biological substrates.

One possible mechanism through which ES might affect AD-related neuropathology could be changes in the neuroinflammatory response that are mediated among others by microglia in the brain. In the developing and adult brain, microglia and inflammatory factors are in fact essential for the formation and maintenance of the neuronal network (Bilbo and Schwarz, 2012; Harry, 2013; Reemst et al., 2016; Schwarz and Bilbo, 2012). Large-scale genetic studies have further identified immune-related pathways as risk factors for AD (reviewed in Malik et al., 2015), highlighting the relevance of the inflammatory system in the context of AD. Indeed, both the involvement of inflammatory factors and microglial cells in AD neuropathology is well established, and progression of Aβ pathology occurs in close association with inflammatory changes, that are among others mediated by microglia in the brain (Cunningham, 2013; Heneka et al., 2015; Mhatre et al., 2015; Spangenberg and Green, 2017).

Microglial activation in the presence of Aβ neuropathology can have beneficial effects (Wang et al., 2015, 2016), and mediate e.g. internalization and clearance of Aβ peptides (Fu et al., 2012; Lee et al., 2010; Liu et al., 2010; Majumdar et al., 2007). Nonetheless, the lasting microglial response to Aβ pathology is rather complex, and both beneficial and detrimental consequences have been reported for progression of the neuropathology (Guillot-Sestier et al., 2015; Heppner et al., 2015; Mhatre et al., 2015).

Interestingly, several recent clinical studies have reported an elevation of pro-inflammatory factors after childhood adversities (Baumeister et al., 2015; Bücker et al., 2015; Coelho et al., 2014; Machado et al., 2015; Redlich et al., 2015; Tyrka et al., 2015). These findings are supported by preclinical studies showing that exposure to prenatal stress (Diz-Chaves et al., 2012; Gómez-González and Escobar, 2009) or to daily postnatal maternal separation in rodents (Delpech et al., 2016; Roque et al., 2014), alters cytokine expression and maturation of microglia in the rodent brain. Moreover, the pro-inflammatory response to lipopolysaccharide (LPS) in adulthood is exacerbated after prenatal exposure to stress (Diz-Chaves et al., 2012; Szczesny et al., 2014), suggesting a long-term sensitization, or 'priming', of microglia after exposure to stress early in life (Hoeijmakers et al., 2015, 2016).

We here address whether perinatal stress-related, persistent alterations in the neuroinflammatory response may contribute to a more vulnerable profile that can subsequently lead to an aberrant response to accumulating Aβ peptides, and ultimately modify the extent of Aβ neuropathology. To test this, we exposed mice to chronic ES from postnatal day (P)2 to P9 (Naninck et al., 2015; Rice et al., 2008), and investigated if ES: 1) modulates amyloid pathology in the hippocampus and the entorhinal cortex (EC) at an early (4 months) and an advanced (10 months) pathological stage in APP/PS1 transgenic mice; 2) affects neuroinflammatory mediators (i.e. microglia and cytokine expression) directly after exposure to chronic ES at P9, and in adult wild-type (WT) offspring of 4 and 10 months of age; and 3) affects the neuroinflammatory response to Aβ accumulation in APP/PS1 mice of the same ages.

2. Materials and methods

2.1. Mice and breeding

Bigenic APPswe/PS1dE9 hemizygous males on a C56Bl/6J background were used to model AD related amyloid pathology. These APP/PS1 mice express chimeric mouse/human mutated APP K595N/M596L (Swedish mutation) and PS1, carrying an exon 9 deletion, driven by the mouse prion promoter. For more details, see B6C3-Tg (APPswe,PSEN1dE9)85Dbo/Mmjax strain of the Jackson Laboratory. Survival of the APP/PS1 mice was monitored, as various APP overexpressor lines including the APP/PS1 line, were reported to die prematurely (Hsiao et al., 1995; Moechars et al., 1999). Indeed, APP/PS1 overexpression decreased mouse survival by 8.0% at 4 months of age, and by 37.1% at 10 months. This survival was not affected by ES (*Ctrl:* $N = 62$, *ES:* $N = 46$, *Log-rank test:* $\chi^2(1) = 0.060$, $p = 0.807$).

To standardize the perinatal environment, all experimental mice were bred in house. For breeding, 8–10 week old virgin female C57Bl/6J mice were purchased from Harlan Laboratories B.V. (Venray, The Netherlands) and habituated for one week to the breeding room. Two females were housed together with one male (C57Bl/6J for a P9 cohort, APP/PS1 for a P120 cohort) and after one week, breeding males were removed, and females housed in pairs for another week. Afterwards, pregnant females were single-housed in a cage with filtertop, standard bedding material and nesting material consisting of one square piece of cotton nesting material (5 × 5 cm; Technilab-BMI, Someren, The Netherlands), in a ventilated, airflow-controlled cabinet to ensure a stable, quiet environment. Birth of pups was monitored every 24 h in the morning between 8.00 and 9.00 AM. Litters born before 9.00 AM were assigned to P0 on the previous day.

Standard housing conditions included cage enrichment, ad libitum water and standard chow, a temperature range of 20–22 °C, and a 40–60 % humidity. Animals were kept on a standard 12/12 h light/dark schedule (lights on at 8 AM). After weaning at P21, all mice were housed with same-sex littermates, 2–4 mice/cage, under standard housing conditions. All experimental procedures were conducted according to the Dutch national law and European Union directives on animal experiments, and were approved by the animal welfare committee of the University of Amsterdam.

2.2. Early-life stress paradigm

The early-life stress (ES) paradigm consisted of limiting the nesting and bedding material from P2 to P9 as described previously (Naninck et al., 2015; Rice et al., 2008). On the morning of P2, dams were randomly assigned to the ES or control (Ctrl) condition. Litters were culled to six pups to ensure litters of 5 to 6 pups,