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

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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 (4month old) and at a more advanced pathological (10month 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 4month old APP/PS1 mice, but in an exacerbation of Aβ plaque load at 10months 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 4months, while these changes resolved by 10months 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 4months, 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 10months 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.

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

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