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A preclinical perspective on the enhanced vulnerability to Alzheimer's disease after early-life stress

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A B S T R A C T

Stress experienced early in life (ES), in the form of childhood maltreatment, maternal neglect or trauma, enhances the risk for cognitive decline in later life. Several epidemiological studies have now shown that environmental and adult life style factors influence AD incidence or age-of-onset and early-life environmental conditions have attracted attention in this respect. There is now emerging interest in understanding whether ES impacts the risk to develop age-related neurodegenerative disorders, and their severity, such as in Alzheimer's disease (AD), which is characterized by cognitive decline and extensive (hippocampal) neuropathology. While this might be relevant for the identification of individuals at risk and preventive strategies, this topic and its possible underlying mechanisms have been poorly studied to date. In this review, we discuss the role of ES in modulating AD risk and progression, primarily from a preclinical perspective. We focus on the possible involvement of stress-related, neuro-inflammatory and metabolic factors in mediating ES-induced effects on later neuropathology and the associated impairments in neuroplasticity. The available studies suggest that the age of onset and progression of AD-related neuropathology and cognitive decline can be affected by ES, and may aggravate the progression of AD neuropathology. These relevant changes in AD pathology after ES exposure in animal models call for future clinical studies to elucidate whether stress exposure during the early-life period in humans modulates later vulnerability for AD.

1. Introduction

Alzheimer's disease is the most prevalent neurodegenerative disease among elderly and a major burden to society (Prince et al., 2013; Wimo et al., 2013). AD patients are characterized by progressive cognitive decline, that starts with mild cognitive impairments (MCI) and develops over time in full blown dementia. The brains of AD patients are characterized by the abundant presence of amyloid plaques, that are located extracellularly and contain various β-amyloid (Aβ) peptides, and by neurofibrillary tangles that are made up of hyper-phosphorylated tau inside of neurons (Querfurth and LaFerla, 2010; Scheltens et al., 2016). Neurodegeneration in the hippocampus, as the results of these neuropathological changes, is one of the key features of AD and in concert to the hippocampus other brain regions involved in the medial temporal lobe memory circuit are affected too (Weiner et al., 2015).

A small percentage of the demented population suffers from familial AD, in which the disease results from genetic mutations and/or specific gene variants. For the majority of patients with sporadic, late-onset AD, however, no genetic or heritable causes have been identified. These patients have been reported to show a high degree of heterogeneity in the progress of clinical symptoms, hippocampal plasticity and neuropathological characteristics (Komarova and Thalhauser, 2011; Mufson et al., 2015; Weiner et al., 2015). It is suggested that the etiology of sporadic AD relates to an interaction of specific genetic risk variants with various environmental and lifestyle factors, potentially leading to a dysregulated epigenome (Andrieu et al., 2015; Gatz et al., 2006; Haaksma et al., 2017; Maloney and Lahiri, 2016).

One of these environmental factors is stress. The frequency of lifetime distress has repeatedly been associated with accelerated cognitive decline, enhanced incidence of MCI and increased risk for late-onset AD (Aggarwal et al., 2014; Johansson et al., 2014; Sindi et al., 2016; Wilson et al., 2006, 2003; 2007). Particularly stress occurring during the sensitive period of early-life may additionally aggravate the later vulnerability to AD (Lahiri and Maloney, 2012, 2010). Individuals with a history of early-life stress (ES) have been shown to age less “successful” (Kok et al., 2017) and have an increased probability to develop diseases in old age (Dong et al., 2004; Ferraro et al., 2016; Schafer and Ferraro, 2012). Interestingly, the occurrence of parental death between the age

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of 0 and 18 years has been associated with a higher risk for AD (Norton et al., 2011; Ravona-Springer et al., 2012). Also, childhood neglect and traumatic events have been associated with an augmented risk to develop early MCI with age (Wang et al., 2016a) and childhood stress have been associated with dementia and AD in Australian aboriginals (Radford et al., 2017). On the other hand, early-life adversity was not associated with aging-related cognitive decline in Caucasians, and may even be protective against cognitive decline in an aging African American population (Barnes et al., 2012). Importantly, these retrospective studies may contain bias as the variation in the later-life questionnaires on (self-reported) childhood maltreatment in elderly can be a potential confounder in these study designs (Ayalon, 2015; Jivraj et al., 2017). Whereas prospective longitudinal studies in humans would be an important addition, they are difficult from a logistic point of view, given the long interval between the early-life period and the age at which clinical AD symptoms appear.

Animal studies, however, provide a great opportunity to gain further insight into the ES-mediated modulation of aging-related cognitive decline and AD development. Notably, various specific AD characteristics are modeled in mice, i.e. by transgenic (over) expression of mutant genetic variants that underlie familial AD (Box 1). These transgenic models develop transgene driven AD-related neuropathological features such as amyloid plaques, and portray at least some of the associated cognitive deficits. This provides a useful approach to study whether and how risk factors, like ES, can modulate later neuropathological hallmarks, cognitive decline and related impairments in neuroplasticity.

Here, we discuss whether stress in early-life acts as a vulnerability factor for AD. We summarize the available pre-clinical literature and focus on the biological substrates that might mediate such vulnerability. Finally, we highlight the outstanding questions that can help bring the field forward.

2. Early-life experiences affect AD neuropathological hallmarks and cognition

In recent years, the vulnerability to develop AD after ES was investigated with the use of different ES rodent models (Box 2). These studies demonstrate that both positive and adverse early-life experiences can modulate disease severity and AD pathology (Cañete et al., 2015; Hoeijmakers et al., 2017; Hui et al., 2017; Lesuis et al., 2016, 2017; Martisova et al., 2012, 2013; Sierksma et al., 2012, 2013; Solas et al., 2010, 2013).

Interestingly, ES triggered Aβ formation in non-transgenic rats; MS from P2 to P21 induced an elevated ratio of the amyloid precursor protein (APP)-derived fragments C99 and C83, and an increased expression of Aβ40 and Aβ42 peptides in the hippocampus of adult (Martisova et al., 2012, 2013; Solas et al., 2010, 2013) and aged rats (Solas et al., 2010). While it is interesting to learn that ES enhances amyloidogenic processing in the brain of wild type rodents, these rats do not develop the pathological oligomeric or fibril forms of Aβ. ES experiments performed in transgenic AD models that do express these pathological Aβ species help to uncover if ES advances or accelerates these specific features of AD pathology with age.

Perinatal stress was shown to affect the later development of amyloid neuropathology in transgenic AD models in an age- and thus intrinsically pathological stage-dependent manner. In fact, both prenatal maternal-restraint stress (PS) from embryonic day (E)1 to E7 as well as chronic ES from postnatal day (P)2-P9 reduced Aβ in the hippocampus of 4-month-old APPswe/PS1dE9 mice, a relatively early pathological stage. Specifically, Aβ plaque load in the hippocampus of female, but not male, APPswe/PS1dE9 mice was decreased after PS, while no effects were found on intracellular Aβ immunoreactivity, nor on hippocampal soluble Aβ40 and Aβ42 peptide levels (Sierksma et al., 2012, 2013). Chronic ES from P2 to P9 also reduced intraneuronal Aβ levels in the dentate gyrus of male APPswe/PS1dE9 mice (Hoeijmakers et al., 2017). On the other hand, 4-month-old bigenic (BiAT) mice, which express both amyloid and tau mutant genes, exposed to the same chronic ES design showed an elevation of Aβ peptide levels (Lesuis et al., 2016). Interestingly, at a later pathological stage in 9- and 10-month-old APPswe/PS1dE9 mice, hippocampal plaque load was aggravated after exposure to chronic ES from P2-P9 or after 3 weeks of MS (Hoeijmakers et al., 2017; Hui et al., 2017), while cortical plaque load was affected by MS at this age as well (Hui et al., 2017). This shows that although in some models Aβ is initially reduced in young adulthood, the pathology is exacerbated by ES exposure at later ages.

In contrast to the modulation of Aβ peptides, tau pathology received very little attention in ES studies so far. Interestingly, tau protein in the hippocampus undergoes specific isoform switches and phosphorylation

Box 1

Modeling AD-related neuropathology in mice.

AD is characterized by the accumulation of Aβ and tau neuropathology, that is comprised of β-amyloid peptides and hyperphosphorylated tau (Buerger et al., 2006; Hardy, 2002). Aβ peptides are generated from the amyloid precursor protein (APP) that is cleaved by β- and γ-secretases. They accumulate firstly in cells, but ultimately end-up in fibrillar amyloid plaques in the extracellular space. The neuropathological progression of Aβ involves the presence of different Aβ species (i.e. soluble/insoluble Aβ peptides, Aβ oligomers, intraneuronal/cell-associated Aβ or Aβ plaques). Next to this, tau pathology develops by an increased phosphorylation of the protein tau. Tau hyperphosphorylation destabilizes neuronal microtubules, ultimately leading to the formation of neurofibrillary tangles. Similar to the rate-determining factors for amyloidogenic processing, expression of total tau protein and (the activity of) kinases mediate tau phosphorylation and pathological progression.

Aβ and tau pathology can be modeled in mice by transgenic (over)expression of human genetic mutations that drive the neuropathology in familial AD. Many different transgenic lines have been developed over the last decade, overexpressing (a combination of) genes carrying familial AD mutations (Götz et al., 2004). As examples, the Tg2576 and APPswe transgenic lines both overexpress the Swedish familial APP mutations KM670/671NL (Borchelt et al., 1997; Hsiao et al., 1996). The inclusion of mutated presenilin 1 (PSEN1 or PS1), one of the proteins of the γ-secretase complex, accelerates Aβ onset and progression in the APPswe/PS1dE9 and APPswe/PS1M146L models. The APPswe/PS1dE9 model for instance develops the first Aβ plaques around 4 months of age and cognitive deficits occur between 4 and 6 months (Edwards et al., 2014; Jankowsky et al., 2004).

Similar to Aβ models, the microtubule associated protein tau (MAPT) gene is overexpressed to generate tau neuropathological characteristics in mice. The JNPL3 transgenic model overexpresses MAPTP301L to drive an age-related increase in hyperphosphorylated tau with the first tangles around 6 months of age (Lewis et al., 2000). Lastly, several models express APP as well as MAPT variants. An example is the so-called bigenic (BiAT) mice expressing APP.V717I and MAPTP301L, and 3xTgAD mice that harbor three mutant genes (APPswe, PS1M146L and MAPTP301L variants). These 3xTgAD mice firstly display cognitive impairments at 3 months, Aβ plaque pathology by 6 and tau pathology by 10 months of age (Oddo et al., 2003).