Neuroscience and Biobehavioral Reviews 77 (2017) 148–164

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

Psychosocial stress on neuroinflammation and cognitive dysfunctions in Alzheimer's disease: the emerging role for microglia?

Sami Piirainen[a], Andrew Youssef[a], Cai Song[b,c], Allan V. Kalueff[b,d,e,f], Gary E. Landreth[g], Tarja Malm[h], Li Tian[a,i,j,*]

[a] Neuroscience Center, HiLIFE, University of Helsinki, Viikinkaari 4, FIN-00014, Helsinki, Finland
[b] Research Institute of Marine Drugs and Nutrition, Key Laboratory of Aquatic Product Processing and Safety, College of Food Science and Technology, Guangdong Ocean University, Zhanjiang 524088, China
[c] Department of Psychology and Neuroscience, Dalhousie University, 1355 Oxford St, Life Sciences Centre, Halifax, Nova Scotia B3H4R2, Canada
[d] Institute of Translational Biomedicine, St Petersburg State University, St Petersburg 199034, Russia
[e] Ural Federal University, Ekaterinburg 620002, Russia
[f] ZENEREI Research Center, Slidell, LA 70458, USA
[g] Department of Neurosciences, Alzheimer Research Laboratory, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA
[h] A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finland, Neulaniementie 2, 70150, Kuopio, Finland
[i] Zhejiang University-University of Edinburgh Joint Institute, 718 East Haizhou Rd., Haining, Zhejiang 314400, China
[j] Psychiatry Research Centre, Beijing Huilongguan Hospital, Peking University, Beijing 100096, China

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form 20 January 2017
Accepted 31 January 2017
Available online 6 February 2017

Keywords:
Late-onset Alzheimer's disease
Psychosocial stress
Microglia
Amyloid clearance
Dementia

ABSTRACT

Chronic psychosocial stress is increasingly recognized as a risk factor for late-onset Alzheimer's disease (LOAD) and associated cognitive deficits. Chronic stress also primes microglia and induces inflammatory responses in the adult brain, thereby compromising synapse-supportive roles of microglia and deteriorating cognitive functions during aging. Substantial evidence demonstrates that failure of microglia to clear abnormally accumulating amyloid-beta (Aβ) peptide contributes to neuroinflammation and neurodegeneration in AD. Moreover, genome-wide association studies have linked variants in several immune genes, such as *TREM2* and *CD33*, the expression of which in the brain is restricted to microglia, with cognitive dysfunctions in LOAD. Thus, inflammation-promoting chronic stress may create a vicious cycle of aggravated microglial dysfunction accompanied by increased Aβ accumulation, collectively exacerbating neurodegeneration. Surprisingly, however, little is known about whether and how chronic stress contributes to microglia-mediated neuroinflammation that may underlie cognitive impairments in AD. This review aims to summarize the currently available clinical and preclinical data and outline potential molecular mechanisms linking stress, microglia and neurodegeneration, to foster future research in this field.

Contents

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's Disease; AMPA, 2-amino-3-(5-methyl-3-hydroxyl-1,2-oxazol-4-yl) propanoic acid; APOE, apolipoprotein E; APP, amyloid precursor Protein; ATP, adenosine triphosphates; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CaMK, calcium/calmodulin-dependent protein kinase; CD, cluster of differentiation; CNS, central nervous system; CR, complement receptor; CX3CR1, CX3C chemokine receptor 1; DISC1, disrupted in schizophrenia 1; GC, glucocorticoid; GWAS, genome-wide association study; HPA, hypothalamic-pituitary-adrenal axis; IDO, indoleamine-2,3-dioxygenase; IL, Interleukin; IL-1RA, IL-1 receptor antagonist; LOAD, late-onset Alzheimer's Disease; LPS, lipopolysaccharide; LTP, long-term potentiation; MCI, mild cognitive impairment; NE, norepinephrine; NMDAR, N-methyl-D-aspartate receptor; NSAIDs, non-steroidal anti-inflammatory drugs; PPARγ, peroxisome proliferator activated receptor-gamma; PTSD, posttraumatic stress disorder; TNF-α, tumor necrosis factor-α; TREM2, triggering receptor expressed on myeloid cells 2.

* Corresponding author.
E-mail address: li.tian@helsinki.fi (L. Tian).

http://dx.doi.org/10.1016/j.neubiorev.2017.01.046
0149-7634/

1. Introduction

Human cognition is a complex process that involves memory, attention, executive functions, perception, language and psychomotor functions. The ability to form and retrieve memories is one of the most fundamental aspects of human cognition, while attention and memory are most prominently affected by age (Glisky, 2007). Alzheimer's disease (AD) is a severely debilitating chronic neurodegenerative disorder, accounting for 50–60% of all forms of dementia. AD is clinically characterized by progressive impairment of episodic memory and cognitive deficits, including impaired judgment, decision-making and orientation (Blennow et al., 2006). AD pathology is characterized by extracellular amyloid-beta (Aβ) plaques (Mirra et al., 1991) and intracellular neurofibrillary tangles comprised of hyper-phosphorylated tau protein (Braak and Braak, 1991), along with neuronal and synaptic degeneration (Spires-Jones and Hyman, 2014). Neurodegeneration is estimated to begin 20–30 years before the onset of clinical symptoms (Davies et al., 1988), during which Aβ plaques and tau tangles accumulate with accompanied slow neurodegeneration and mild cognitive impairment (MCI) (Petersen, 2004).

The role of chronic neuroinflammation in MCI and AD dementia has gained attention recently, implicating an early involvement of inflammation in the disease onset and progression (Querfurth and LaFerla, 2010). Neuroinflammation may indeed contribute to AD since genes of immune receptors, such as TREM2 (Guerreiro et al., 2013), CD33 (Bettens et al., 2013; Bradshaw et al., 2013) and CR1 (Karch and Goate, 2015; Lambert et al., 2013), are associated with AD. Microglia represent resident macrophages in the brain and are a key player in mediating neuroinflammatory response and clearance of cellular debris, thereby contributing to AD pathology and neurodegeneration (Heppner et al., 2015; Kettenmann et al., 2011). Furthermore, studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) have a marked effect on preventing the onset and progression of AD (McGeer et al., 2016).

Various physiological and cellular stressors, including aging and hypoxia, can "prime" microglia and exacerbate neuroinflammation in AD, as reviewed elsewhere (Head et al., 2016; Heikkinen et al., 2014; Leszek et al., 2016; Song et al., 2016). We instead focus on the psychosocial stress in AD here. As with the ever-changing and fast-paced lifestyle of modern society, it is common for many to suffer from chronic psychosocial stress during certain periods of their lives. Psychological stress, as well as its pathological comorbidities such as depression, is increasingly recognized as a risk factor for the development of AD (Alkadhi, 2012; Norton et al., 2014), as people prone to stress or depression are more likely to develop AD (Gracia-Garcia et al., 2015; Green et al., 2003; Sacuiu et al., 2016; Wilson et al., 2005). Paralleling clinical data, in a rat model of AD, chronic stress also decreases basal levels of memory-related signaling molecules in the hippocampus and exacerbated cognitive impairment (Alkadhi and Tran, 2015; Srivareerat et al., 2009).

However, our understanding of how psychosocial stress exacerbates AD-related neuroinflammation remains limited. Here, we first discuss the impacts of psychosocial stress on microglial phenotypical transformation and on cognitive impairments in AD, respectively. We also summarize findings on microglia-mediated neuroinflammation in compromising Aβ clearance and exacerbating synaptic dysfunction in AD. We further suggest potential molecular mechanisms by which psychosocial stress may exacerbate cognitive impairments in AD. We postulate that psychological stress impacts both Aβ clearance and synaptic regulation mediated by microglia, thus contributing to AD-related pathological progression. However, the exact nature of the impact of psychological stress on microglia and neuro-glia crosstalk in AD remains to be investigated further.

2. Microglial phenotype and immune gene expression in conditions of psychosocial stress

Microglial cells are the first line of defense against invading pathogens in the central nervous system (CNS). They constantly surveil the brain parenchyma, sensing even slight alterations in the concentrations of extracellular ions and molecules. Microglia express a unique sensome of transcripts encoding proteins for sensing endogenous ligands and microbes, with genes for endogenous ligand-recognition downregulated whereas those involved in microbe recognition and host defense upregulated, alongside aging (Hickman et al., 2013). Although conventional microscopic images show that these cells are highly ramified in the healthy brain, live multiphoton imaging reveals microglial processes as extremely motile, constantly extending and retracting to survey the surrounding approximately 80 um^3 of environment (Nimmerjahn et al., 2005). Upon activation by pathogen or injury, microglia adopt an amoeboid morphology, bearing enlarged soma along with shortened and thickened processes, and capable of migrating toward the site of the damage (Nimmerjahn et al., 2005). Meanwhile, a "dystrophic" morphology, readily distinguished from both so-called "resting" and "activated" microglia by their fragmented cytoplasmic components, has also been described for microglia in the aged brain (Kettenmann et al., 2011).

Both acute and chronic stressors prime microglia, by inducing either hyper-ramification, characterized by an elongation of microglial processes along with a larger soma size (Hellwig et al., 2016; Hinwood et al., 2012; Hinwood et al., 2013), or de-