Available online at www.sciencedirect.com
SCIENCE DIRECT®
IJBCB
The International Journal of Biochemistry & Cell Biology 37 (2005) 289–305
www.elsevier.com/locate/biocel

Review

The role of inflammation in Alzheimer's disease

Ehab E. Tuppo[a,*], Hugo R. Arias[b,1]

[a] *Center for Aging, University of Medicine and Dentistry of New Jersey-School of Osteopathic Medicine, Stratford, NJ 08084, USA*
[b] *Department of Pharmaceutical Sciences, College of Pharmacy, Western University of Health Sciences, Pomona, CA 91766, USA*

Accepted 9 July 2004

Abstract

Considerable evidence gained over the past decade has supported the conclusion that neuroinflammation is associated with Alzheimer's disease (AD) pathology. Inflammatory components related to AD neuroinflammation include brain cells such as microglia and astrocytes, the classic and alternate pathways of the complement system, the pentraxin acute-phase proteins, neuronal-type nicotinic acetylcholine receptors (AChRs), peroxisomal proliferators-activated receptors (PPARs), as well as cytokines and chemokines. Both the microglia and astrocytes have been shown to generate beta-amyloid protein (Aβ), one of the main pathologic features of AD. Aβ itself has been shown to act as a pro-inflammatory agent causing the activation of many of the inflammatory components. Further substantiation for the role of neuroinflammation in AD has come from studies that demonstrate patients who took non-steroidal anti-inflammatory drugs had a lower risk of AD than those who did not. These same results have led to increased interest in pursuing anti-inflammatory therapy for AD but with poor results. On the other hand, increasing amount of data suggest that AChRs and PPARs are involved in AD-induced neuroinflammation and in this regard, future therapy may focus on their specific targeting in the AD brain.

Keywords: Alzheimer's disease; Neuroinflammation; Glial cells; Beta-amyloid protein; Senile plaques; Chemokines; Complement system; Cytokines; Interleukin; Tumor necrosis factor; Cyclooxygenase; NSAIDS; Steroids; Pentraxins; Nicotinic acetylcholine receptors

Abbreviations: αBTx, α-bungarotoxin; Aβ, beta-amyloid protein; ACh, acetylcholine; AChBP, acetylcholine-binding protein; AChR, nicotinic acetylcholine receptor; AD, Alzheimer's disease; AICD, amyloid precursor protein intracellular domain; AP, amyloid P; APP, amyloid precursor protein; C/EBP, CCAAT/enhancer-binding protein; CNS, central nervous system; NO, nitric oxide; NOS, nitric oxide synthase; ACT, α1-antichymotrypsin; COX, cyclooxygenase; CRP, C-reactive protein; IDE, insulin-degrading enzyme; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; MAC, membrane attack protein; M-CSF, macrophage colony-stimulating factor; MHC II, major histocompatibility complex type II; MIP, macrophage-inflammatory protein; mRNA, messenger ribonucleic acid; NFTs, neurofibrillary tangles; NSAIDs, nonsteroidal anti-inflammatory drugs; PPARs, peroxisomal proliferators-activated receptors; SPs, senile plaques; TNFα, tumor necrosis factor alpha; TNFβ, tumor necrosis factor beta; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration

* Corresponding author. Tel.: +1 856 566 6843; fax: +1 856 566 6781.
E-mail addresses: tuppoee@umdnj.edu (E.E. Tuppo), harias@westernu.edu (H.R. Arias)
[1] Tel.: +1 909 469 5424; fax: +1 909 469 5600.

1357-2725/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2004.07.009

Contents

1. Introduction

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disorder that is the most common form of dementia affecting people 65 years and older. The pathologic features of AD are the presence of senile plaques (SPs) and neurofibrillary tangles (NFTs) in the brain. SPs are extracellular beta-amyloid protein (Aβ) deposits derived from amyloid precursor protein (APP) while NFTs are intraneuronal structures composed of tau protein. Clinically AD is characterized by impairment in memory, visuospatial skills, complex cognition, language, emotion and personality. Although the exact cause of AD remains elusive, mounting evidence continues to support the involvement of inflammation in the development of AD (Akiyama et al., 2000a).

Traditionally thought of as an immunologically privileged organ, today the CNS is known to have an endogenous immune system that is coordinated by immunocompetent cells such as the microglia. The inflammation associated with the CNS, neuroinflammation, differs from that found in the periphery. The brain lacks pain fibers, making it difficult to recognize the occurrence of inflammation and the classic signs of inflammation such as rubor (redness), tumor (swelling), calor (heat), and dolor (pain) are typically not seen in the CNS. Also, the CNS differs from other organs in that it contains a blood–brain barrier, a system of tight junctions at the capillaries within the CNS that obstructs the entry of inflammatory cells, pathogens, and some macromolecules into the subarachnoid space. Although not complete, this barrier acts to protect the sensitive, fragile, and post-mitotic neurons from the damages typically associated with inflammation.

2. Cellular components of inflammation

The major players involved in the inflammatory process in AD are thought to be the microglia and the astrocytes and possibly to a less extent the neurons, all of which are cellular components of the brain who have many critical roles in the homeostasis and function of the brain (Akiyama et al., 2000a,b).

2.1. Microglia

The microglia are cells that support and protect the neurons and their functions in the CNS and act as immunocompetent defense cells that orchestrate the endogenous immune response of the CNS. The mi-