IL-6 AND NEUROINFLAMMATION: A CAUSE AND A CONSEQUENCE OF ALZHEIMER'S DISEASE

Aina Mogas Barcons

Degree in Biology 2014 - 2015

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting more than 35 million people worldwide. The main risk factor is age, but genetics also play an important role, as well as having suffered a severe head trauma or severe infection in the past.

Neuroinflammation in AD is considered a consequence of neuronal degeneration by some, but also an enhancer and driving force by others. Since IL-6 is produced by microglia and astrocytes and it influences their activation, its role is crucial in the development of the disease.

This paper aims to enumerate the inflammatory properties of IL-6 in the brain and to link these properties with the development of Alzheimer's disease. As stated above, it is not clear whether neuroinflammation is a cause or a consequence of Alzheimer's disease, in order to give a little light to it, there will be a study about the factors that make microglia and astrocytes release IL-6 and what does it provoke.

ALZHEIMER'S DISEASE

AD brains show two characteristic lesions: accumulation of **β-amyloid peptides** and intracellular **neurofibrillary tangles**. Both are found in other neurodegenerative diseases and also in healthy brains, suggesting that other factors may contribute to stablish the disease. Mild cognitive impairment (MCI) is a term that includes patients who perform worst in cognitive tasks, but whom are able to live independently. The incidence of AD among MCI patients goes from 10% to 15% every year. Although amnestic MCI and mild AD patients have little cognitive differences, atrophy levels differ (Fig. 1). However, the fact that triggers the change from MCI to AD is not known.

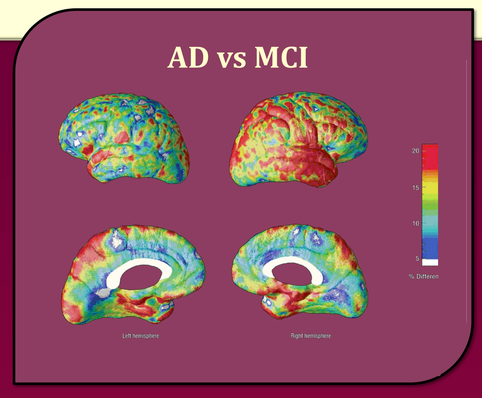


Figure 1: Percentage of difference between mild AD and amnestic MSI brains. **Source:** Arch Neurol. 2007 October; 64(10): 1489 – 1495.

IL-6

AD is accompanied by a rise in IL-6 levels, however it cannot be used as a biomarker because it is also increased with mere age. Both astrocytes and microglia can produce this cytokine and, at the same time, IL-6 induces their proliferation and activation and enhances the production and release of inflammatory mediators: prostaglandins, cytokines, chemokines and acute phase proteins, like APP. Moreover, IL-6 upregulates the cdk5/p35 complex which is involved in the hyperphosphorilation of Tau protein.

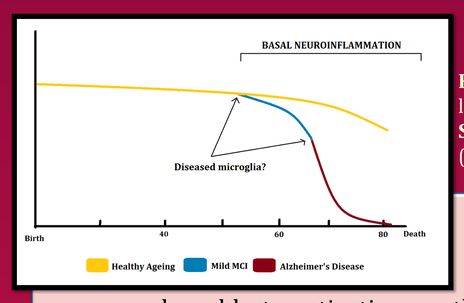
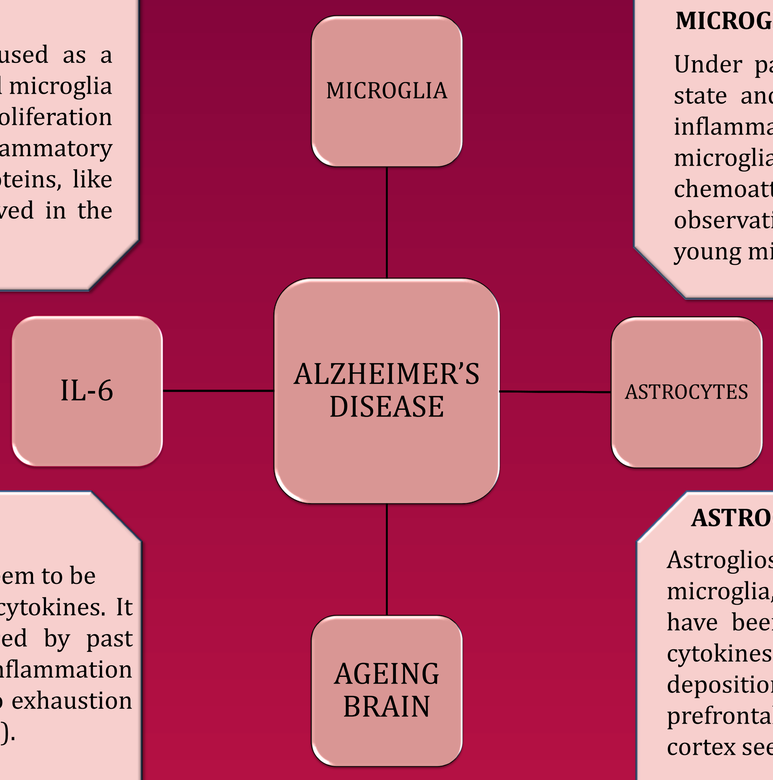


Figure 2: Progression of cognition during a lifetime. **Source**: National Institute on Ageing (Adaptation)



MICROGLIA

Under pathological conditions, microglia shifts from its resting to its activated state and migrate to the affected area where it upregulates genes related to inflammation and oxidative stress and acquires phagocytic properties. Besides, microglia cluster around senile plaques and produce MCP-1 which is an astrocytic chemoattractant. As far as its phagocytic capacities are concerned, is the observation that microglia from aged mice internalize less Aβ than microglia from young mice.

THE AGEING BRAIN

With age, microglia and astrocytes seem to be more vulnerable to activation, so they release more proinflammatory cytokines. It has been postulated that this state of activation might be enhanced by past activations provoked by head trauma or infection. The state of basal inflammation that appears with age causes chronic stress to microglia, contributing to exhaustion and senescence. These atrophic cells are named diseased microglia (Fig 2).

ASTROCYTES

Astrogliosis in AD can be initiated by the signaling from damaged neurons or microglia, or extracellular deposition of Aβ. Both activated and atrophic astrocytes have been found in AD brains. Activated astrocytes produce pro-inflammatory cytokines and oxygen reactive species while atrophic astrocytes allow Aβ deposition. Atrophic changes are significant first in the entorhinal cortex, then in prefrontal cortex and later in the hippocampus. Entorhinal cortex and prefrontal cortex seem to be more vulnerable to AD than the hippocampus.

CONCLUSIONS

IL-6 is an inflammatory cytokine which can be produced by microglia and astrocytes in response to pathological insult, for example, as a response to Aβ. High levels of IL-6 display prominent astrogliosis and microgliosis.

When activated, neuroglia produce more inflammatory cytokines. Moreover, IL-6 induces the production of APP in microglia, which is an Aβ precursor and also activates de cdk5/p35 complex which is involved in the hyperphosphorilation of the Tau protein. Activated microglia and astrocytes show phagocytic properties and are able to remove senile plaques.

Age is seen as a state of basal inflammation enhanced by the production of proinflammatory cytokines by microglia and astrocytes which seem to be more vulnerable to activation in an advanced age. Probably, this vulnerability is increased by having suffered activations due to infection or head trauma in the past, which are known risk factors in the development of AD.

This state of basal inflammation appears to cause chronic stress to microglia, and leads it to an atrophic state. Atrophic astrocytes and microglia lack of phagocytic properties and are also found in AD brains allowing the deposition of plaques (Fig 3).

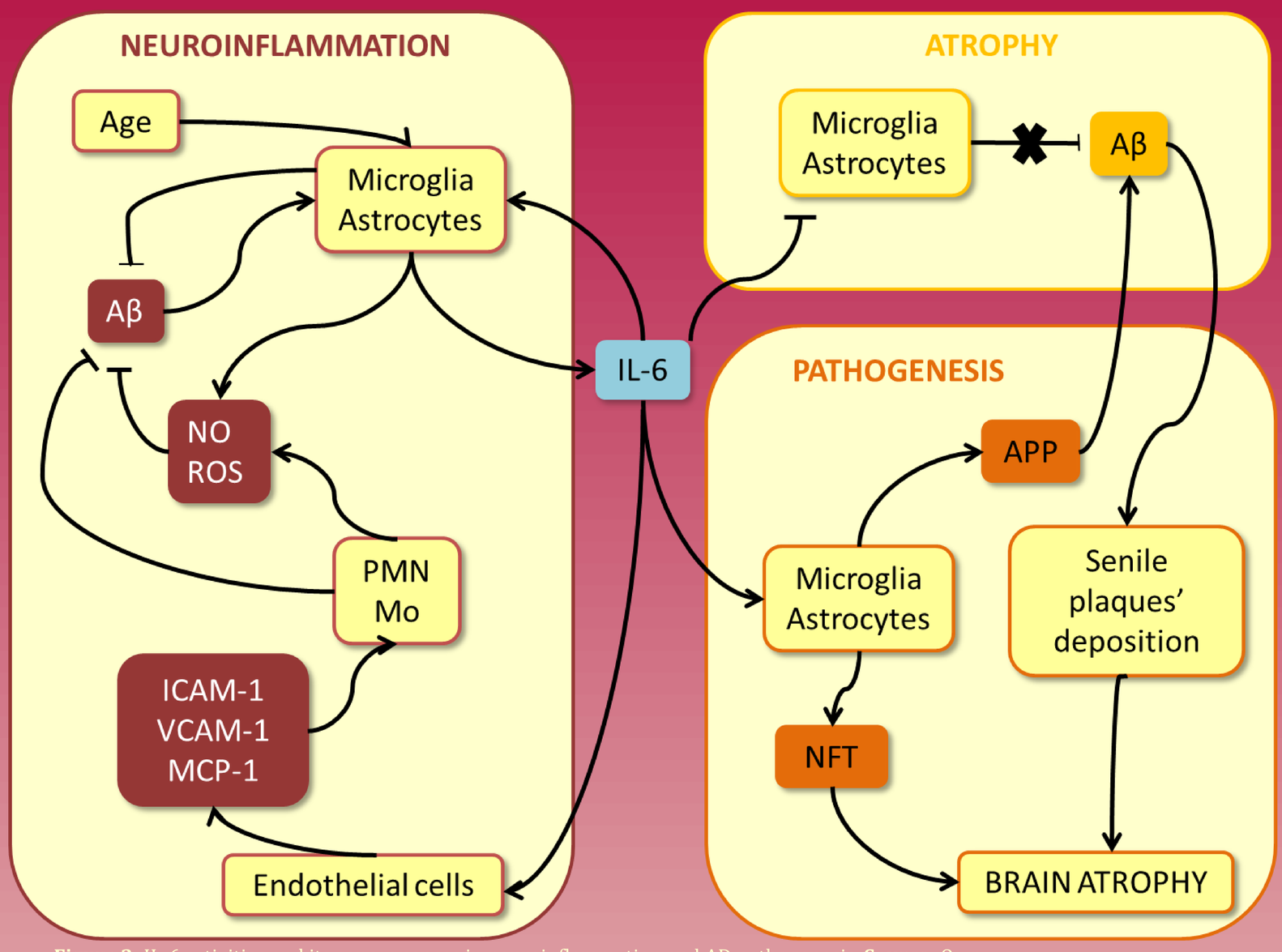


Figure 3: IL-6 activities and its consequences in neuroinflammation and AD pathogenesis. **Source:** Own.

Fig 1. Liana, G; Apostolova, MD; Calen, A; Steiner, BS; Gohar, G; Akopyan, BS; Rebecca, A; Dutton, BS; Kiralee, M; Hayashi, BS; Toga, A; Cummings, J; Thompson, PM. **Three-Dimensional Gray Matter Atrophy Mapping in Mild Cognitive Impairment and Mild Alzheimer Disease.** Arch Neurol. 2007 Oct; 64(10); 1489-1495. // Fig 2. **National Institute on Ageing** (NIH) [on line]. <www.nia.nih.gov> Consulted: 03/04/2015.