ROLE OF ASTROCYTE AGING IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is the most abundant severe and irreversible neurodegenerative disease in the world that affects people over 65 years old. The major hallmarks of AD pathology are the senile β-amyloid plaques, hyperphosphorylated neurofibrillary tangles, accompanied by severe neuroinflammation, synaptic disruption, neuronal degeneration and apoptosis, eventually triggering cerebral atrophy, memory loss and cognitive decline. The deposition and increase of β-amyloid levels in the brain induce the cascade of signals triggering production of neurotoxic molecules such as reactive oxygen species, nitric oxide, and pro-inflammatory cytokines and chemokines that cause neuroinflammation and neurodegeneration eventually resulting into dementia. Aging is the key risk factor for many inflammatory diseases including AD. However, the correlation of aging and AD is poorly investigated. Especially, the cytotoxic effects of β-amyloid in aging glial cells have been poorly explored. Human astrocytes are the most abundant CNS cells that undergo senescence with age and in response to stress. Therefore, it is hypothesized that sensitivity to β-amyloid may significantly change during in vitro senescence of astrocytes. The aim of this study is to investigate the mechanisms of cytotoxic actions of β-amyloid peptide in senescent astrocytes.

Materials and methods: Human astrocytes were senesced through repeated passaging in vitro and then senescent and normal astrocytes were treated with β-amyloid oligomers. The senescence of astrocytes was assessed by β-galactosidase expression. The effect of β-amyloid on normal and senescent astrocytes was assessed by monitoring ROS levels, IL-6 and ERK1/2 activity. N-acetyl-L-cysteine (NAC) was used as oxidative stress inhibitor.

Results: Though human astrocytes reached senescence after 15-20 population doublings. β-amyloid was shown to induce increased ROS production both in normal and senescent astrocytes compared to untreated cells, but with significantly higher ROS levels in normal astrocytes compared to senescent cells. NAC was shown to inhibit oxidative stress in all treatment groups. Furthermore, senescent astrocytes showed five-fold higher IL-6 levels in comparison to normal astrocytes after β-amyloid treatment. The similar trend was observed in ERK1/2 activity.

Conclusion: From the obtained results, it can be concluded that, senescent astrocytes are more susceptible to cytotoxic actions induced by β-amyloid rather than normal astrocytes.