B-AMYLOID RESULTS IN ELEVATED ROS AND CYTOKINES LEVELS IN SENESCENT HUMAN ASTROCYTES

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Introduction: Ap accumulates in the brain with age and its elevated concentrations cause neuroinflammation leading to dementia through production of neurotoxic molecules such as reactive oxygen species (ROS), nitric oxide, pro-inflammatory chemokines and cytokines. Neurons are the main source of Ap and individual astrocytes may not produce high levels of AP; however, during long development period of neurodegenerative diseases, astrocytes may still contribute to overall AP production due to their abundance in the brain. Astrocytes turn to senescence in response to oxidative stress and exhaustive replication expressing p16, p21, p53, 53BP1, G1 cell cycle arrest and telomere shortening and accumulate in aged brain producing high levels of cytokines and chemokines in the brain of patients suffering from neurodegenerative diseases. However, the effect of Ap production on pro-inflammatory proteins in the brain is still unclear. The aim of this study therefore was to investigate the mechanisms of cytotoxic actions of β-amyloid peptide in senescent astrocytes.

Materials and methods: Human astrocytes were aged by multiple passaging of cells *in vitro* then senescent and young astrocytes were treated with β-amyloid oligomers. Astrocyte senescence was confirmed by SA-P-galactosidase staining method. The effect of β-amyloid on normal and senescent astrocytes was assessed by monitoring ROS levels, IL-6 and ERK1/2 activity and analyzed in MesoScale Discovery (MSD). N-acetyl-L-cysteine (NAC) was used as oxidative stress inhibitor.

Results: Human astrocytes reached a replicative senescence after 15-20 population doublings. β-amyloid was shown to induce increased ROS production in both, young and senescent astrocytes compared to untreated cells, however with significantly higher ROS levels in young 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 with young astrocytes after β-amyloid treatment. Incubation of cells with selective inhibitor of p38 MAPK (10 μM /24 hours) suppressed AP1-42 induced activation of p38 MAPK but didn't affect JNK activity.

Conclusion: Our findings from this study suggest that senescent astrocytes are more susceptible to cytotoxic actions induced by β-amyloid rather than young astrocytes.