

Public Abstract

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Title:SECRETORY PHOSPHOLIPASE A2-IIA IN ALZHEIMERS DISEASE AND INFLAMMATORY RESPONSES IN ASTROCYTES

Alzheimer's disease (AD) is a progressive, fatal neurodegenerative disease and is the most common form of dementia. AD pathology includes neurofibrillary tangles, amyloid plaques, chronic inflammation, and oxidative stress. Secretory phospholipase A2-IIA (sPLA2-IIA) is an inflammatory protein known to have a role in the pathogenesis of multiple inflammatory diseases and is implicated in several neurodegenerative diseases. In AD, astrocytes become reactive and have increased expression of inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$ , and undergo increased oxidative stress. NADPH oxidase is one of the major enzymatic sources of reactive oxygen species in the central nervous system; activation of this enzyme may contribute to increased oxidative stress in cells of AD brains, including astrocytes. The expression and localization of sPLA2-IIA in human AD brains has not been studied in detail. In these studies, we show that sPLA2-IIA mRNA is up-regulated in AD brains (compared to non-demented elderly brains) and sPLA2-IIA immunoreactivity is increased in AD astrocytes. To further elucidate involvement of oxidative pathways in induction of sPLA2-IIA mRNA and protein by pro-inflammatory cytokines, we performed in vitro studies with immortalized astrocytes (DITNC). These studies demonstrated the involvement of PI-3 kinase and ERK1/2, but not p38 MAPK, in the cytokine-induced sPLA2-IIA expression in astrocytes. Furthermore, inhibition of sPLA2-IIA mRNA expression by apocynin, a known NADPH oxidase inhibitor, and botanical antioxidants including resveratrol and epigallocatechin gallate, suggests the involvement of oxidative pathways, possibly the NADPH oxidase pathway. These results, taken together, identify sPLA2-IIA as an inflammatory factor for Alzheimer's disease, and support the involvement of NADPH oxidase in the cytokine induction of sPLA2-IIA in astrocytes and the possibility of using botanical antioxidants to ameliorate the inflammatory response in these cells.