AMYLOID-β PEPTIDE INDUCES TEMPORAL MEMBRANE BIPHASIC CHANGES IN ASTROCYTES THROUGH CYTOSOLIC PHOSPHOLIPASE A_2

Jacob Hicks

Dr. James Lee, Thesis Supervisor

ABSTRACT

Oligomeric amyloid-β peptide (Aβ) is known to induce cytotoxic effects and damage cell functions in Alzheimer's disease. However, mechanisms underlying the effects of Aβ on cell membranes have yet to be fully elucidated. In this study, Aβ 1-42 ($Aβ_{42}$) was shown to cause a temporal biphasic change in membranes of astrocytic DITNC cells using fluorescence microscopy of Laurdan. $Aβ_{42}$ made astrocyte cell membranes become more molecularly-disordered after 30 minutes to 1 hour, transitioning to more molecularly-ordered after 3 hours. However, $Aβ_{42}$ caused artificial vesicle membranes made of rat whole brain lipid extract to become more disordered only. The trend for more molecularly-ordered membranes in astrocytes was abrogated by either an NADPH oxidase inhibitor, apocynin, or an inhibitor of cytosolic phospholipase A_2 ($cPLA_2$), but not by an inhibitor of calcium-independent PLA_2 ($iPLA_2$). Apocynin also suppressed the increased production of superoxide anions ($O_2^{\cdot -}$) and phosphorylation of $cPLA_2$ induced by $Aβ_{42}$. In addition, hydrolyzed products of $cPLA_2$, arachidonic acid (AA), but not lysophosphatidylcholine (LPC) caused astrocyte membranes to become more molecularly-ordered. These results suggest (1) a direct interaction of $Aβ_{42}$ with cell membranes making them more molecularly-disordered, and (2) $Aβ_{42}$ indirectly makes membranes become more molecularly-ordered by triggering the signaling pathway involving NADPH oxidase and $cPLA_2$.