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Amyloid-beta peptide induces time dependent biphasic change of membrane phase properties in DITNC cells

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Amyloid-beta peptide (Aβ) has been widely implicated in the pathogenesis of Alzheimer's disease (AD). In AD patients amyloid plaques accumulate extensively in the brain, a pathological archetype of the disease. To elucidate one pathway that contributes to AD dysfunction, we demonstrate that oligomeric Aβ1-42 alters the membrane phase properties of DITNC cells time-dependently, with the phase change made quantifiable through fluorescence microscopy and GP analysis. Initially, after oligomeric Aβ1-42 treatment the phase properties became more liquid-crystalline, and subsequently, after 2-3 hours the phase became more gel-like. However, in lipid vesicles the change in membrane phase properties wasn't biphasic; the phase became only more liquid-crystalline, indicating the role of cell signaling in the phenomenon. Western blot analysis demonstrated the ability of oligomeric Aβ1-42 to increase levels of phosphorylated cPLA2 on a time scale corresponding to the observed change in membrane phase, implicating cPLA2 as a likely contributor to the liquid-crystalline to gel transition, with its activation and translocation to the membrane likely the cause of the specific time frame associated with the liquid-crystalline to gel transition. Co-treatment of oligomeric Aβ1-42 with MAFP, an inhibitor of iPLA2 and cPLA2 caused the membrane to become only more liquid crystalline, while oligomeric Aβ1-42 + BEL, a specific inhibitor of iPLA2, resulted in the previously observed biphasic transition, eliminating iPLA2 as a contributor to the phenomenon. Additionally, Aβ1-42 + Apocynine, an antioxidant, caused the membrane to become only more liquid crystalline, which more specifically revealed oligomeric Aβ1-42 triggers the activation of cPLA2 through ROS generation, likely through NADPH oxidase, activating the MAPK cascade. Evaluating the effect of oligomeric Aβ1-42 on membrane phase properties provides a different view of a widely implicated pathogen in AD, revealing that it acts both to immediately cause the membrane to become more liquid-crystalline, while triggering cPLA2 to change the membrane phase to gel-like over time.