THE ROLE OF DOCOSAHEXAENOIC ACID IN PHASE SEPARATION FROM LIPID RAFTS: IMPLICATIONS FOR CELLULAR SIGNALING

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Abstract

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It has become increasingly evident that dietary intake of the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA, 22:6) has profound benefits on normal health and chronic disease states. However, the molecular mechanism by which DHA exerts its effects remains elusive. One hypothesis is that DHA-containing phospholipids influence the organization of the mammalian plasma membrane by phase separating from the cellular signaling platforms known as lipid rafts. Here the role of a DHA-containing phosphatidylethanolamine (PE) in phase separation from the lipid raft molecules sphingomyelin (SM) and cholesterol (CHOL) is investigated in model membranes and cellular systems. Phase separation between a DHA-containing PE in comparison to an oleic acid (OA, 18:1)-containing PE with SM and CHOL molecules is examined in model membranes using analysis of pressure-area isotherms, differential scanning calorimetry (DSC), nuclear magnetic resonance (^{2}H and ^{31}P NMR) spectroscopy, atomic force microscopy (AFM), and detergent extractions studies. Data from these studies suggest greater phase separation with the DHA-PE compared to the OA-PE in the presence of equimolar SM/CHOL. The molecular rationale for phase separation is attributed to a decreased solubility of CHOL for the DHA-PE vs. the OA-PE, as determined by X-ray

diffraction measurements. Further evidence for DHA-induced phase separation is found using the biochemical detergent extraction method in neonatal cardiomyocytes. Findings from these studies demonstrate a greater affinity of OA for detergent resistant rafts compared to DHA. It is concluded that DHA may exert its effect, in part, on human health by influencing cellular signaling events that are lipid raft mediated.

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