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Deciphering Phenylalanine–membrane Interaction: Molecular Basis of Pku Pathophysiology

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We examine the interaction of Phenylalanine (Phe) with model membranes to simulate pathological conditions associated with phenylketonuria, an inherited metabolic disorder characterized by Phe accumulation in blood and tissues, including the surface of cell membranes in the white matter. To investigate the role of Phe accumulation in myelin sheaths, we apply phospholipid-based model membranes enriched in glycolipids. Sugars exposed from the outer layer of the membrane were indicated to be the mediator of Phe interactions[1]. NMR and calorimetry, showing a very peculiar highly cooperative behavior of sugar rich multilamellar systems, corroborate this view. Molecular dynamics (MD) simulations provide a powerful tool to investigate molecular interactions at membrane interfaces with atomistic resolution. We focus on how Phe interacts with ganglioside GM1 and GalCer in DMPC for three systems: DMPC-GM1, DMPC-GalCer, and DMPC-GalCer-GM1. We conducted multiple replica MD simulations at 300 K 200 ns long using CHARMM36m force field, with two facing bilayers at a separation of 10 Å and 30 Phe molecules. The results indicate that Phe molecules do not penetrate the hydrophobic core of the DMPC bilayers. Instead, they localize near the membrane surface, forming small clusters near the sugar moiety of the GalCer lipid, suggesting a preferential interaction compared to the DMPC surface.