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Change in orientation of the Ca2+ sensor protein hippocalcin in its membrane-bound state as a mechanism for the development of primary dystonia

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A detailed study of the collective behavior of the lipid bilayer in the presence of peripheral proteins is essential for understanding the molecular signaling processes that occur on membranes. The N75K mutation of the neuronal Ca2+ sensor protein hippocalcin, which is partially embedded in the inner layer of the plasmatic membrane, leads to the development of a severe disease, primary autosomal dystonia. However, how exactly the mutation changes the functioning of the protein remains unclear. In this work, we tested the hypothesis that the orientation of wild-type (WT) hippocalcin and its N75K mutant relative to the normal bilayer surface in a steady state of lipid parameters does differ, which may lead to steric hindrance of protein interaction with its membrane targets.

For simulations, a lipid bilayer model was created. It consists of POPC/DPPC/POPI25/DMPI25 lipids and cholesterol in ratios corresponding to a realistic mammalian plasma membrane. The wild-type hippocalcin model was obtained from the rcsb.org database under code 5G4P. Modeling of unstructured N-terminus and C-terminus and modification of N-terminus with myristoyl were performed using the CHARMM-GUI service. The following parameters were obtained to describe the lipid bilayer collective behaviour: order parameters and area per lipid. Analysis of the WT and N75K location data in the bound position shows a significant difference in their tilt angles, close to 45 degrees with a high spread of values for the N75K mutant. The high dispersion in the case of N75K is explained by low kinetic barriers to other equilibrium positions, which reduces the mutant's ability to self-stabilize through electrostatic interactions after introducing momentum into the system. Such differences in the dynamics of WT and N75K hippocalcin indicate the possibility of steric hindrance in protein-protein interactions with membrane targets and lower stability of the bound state.

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