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Elucidating the action of a regulatory lipid ligand via molecular simulation: Cholesterol swarms and the inwardly rectifying potassium channel

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Cholesterol is a major regulator of ion channels, activating some while inhibiting others. Despite the ubiquity of high cholesterol as a health risk and the critical role of ion channels in healthy cell function, we know little about how this membrane lipid induces changes in ion channel activity.

Interaction of cholesterol with inwardly rectifying potassium (Kir) channels is known to stabilize these membrane proteins in a closed and inactivated state. Cholesterol suppresses activity of Kir2.1 channels not by altering physical properties of the lipid bilayer, but through direct stereo-specific interactions with the protein. Identification of a putative cholesterol recognition region has previously been achieved by a combination of experimental cell biology and computational molecular docking studies. Identifying the cholesterol binding pathway requires that we bridge the static computational perspective offered by molecular docking and the functional evidence offered by cell electrophysiology. To this end, we have employed coarse-grained molecular simulations to probe spontaneous migration of cholesterol from a lipid bilayer to Kir channel binding sites. These simulations access the multi-microsecond timescale and reveal the complex, dynamic way multiple sterol molecules simultaneously associate with the potassium channel in both relatively stable and transient binding loci. Further, we identify multiple discrete binding sites within the previously identified recognition region and characterize their dependence on sterol content of the bilayer. The differential concentration dependence of these discrete sites points to a possible explanation for the pathological role of elevated cholesterol in modulating Kir structure and, consequently, function.