In-Silico Electrophysiology of Inner-Ear TMC1 Models

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Mechanical stimuli from sound and head movements are converted into electrical signals in the inner ear during a process known as mechanotransduction. The molecular identity of the cation channel involved in inner-ear mechanotransduction has been unclear for years, although four transmembrane proteins (PCDH15, TMIE, TMHS, and TMC1/2) have been shown to be part of the mechanotransduction complex. Recent studies suggest that TMC1/2 proteins are the pore-forming subunits of the mechanotransduction complex and that they assemble as dimers, yet the structure of any TMC protein and the molecular mechanisms of ion conduction and activation remain to be elucidated. Bioinformatics analyses suggest that TMC1/2 are related to the dimeric TMEM16/OSCA family of membrane proteins, including lipid scramblases as well as cation and anion channels for which high-resolution structures are available. Here we present molecular dynamics simulations of TMC1 models based on various TMEM16 and OSCA structures. Unlike most ion channels, these templates, and consequently all our TMC1 models, do not show a central ion conduction pore. Instead, the ion conduction pores and lipid scrambling regions lie in the side facing the lipids and are hydrated. Simulations of open TMC1 models carried out at different biasing voltages predict ion conduction at the rates measured for the native hair-cell transduction channel. Interestingly, the ion conductive groove remains partially exposed to the lipid bilayer and the simulations also predict cationic transduction currents with a minor anionic component. Models in which transmembrane helix 4 occludes the extracellular entrance of the pore are non-conductive. Together, our results suggest gating mechanisms involving protein conformational changes as well as tension-induced, membrane-mediated widening of the pore. Overall, our models provide an atomistic view of inner-ear sensory perception with implications for regulatory mechanisms of tonotopic variations of conductance.