Hyperactive connexin hemichannels and genetic diseases: the role of calcium

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Gap junction channels directly connect the cytoplasm of adjacent cells in virtually every tissue in vertebrates. They are formed by the extracelllar head to head docking of two hemichannels (or connexon). Hemichannels are hexamers of proteins in the connexin family and can work as regular membrane channels when unpaired: under physiological conditions hemichannels are mostly closed, but they can open in response to a variety of stimuli allowing the release of autocrine and paracrine molecules.

The interplay between calcium and hemichannels is very rich. Calcium permeates through them and also modulates their gating. In particular, a physiological concentration of calcium in the extracellular medium is required to keep hemichannels in the closed state. Connexin mutations that perturb this gating mechanism, i.e. that produce hyperactive hemichannels, lead to a variety of hereditary human diseases.

Despite being very well characterized by electrophysiological studies, a complete understanding of the molecular mechanism of the calcium mediated gating process is still lacking, due to the difficulties in obtaining high quality structural data for gap junction channels or hemichannels.

Computer simulations can bridge the gap between the known structural and electrophysiological properties of connexin hemichannels. By using a computational model based on multiscale molecular dynamics simulations, we propose a possible pathway for the transition of a connexin hemichannel towards the open state and show that the presence of calcium in the extracellular vestibulum is sufficient to impair such transition. We also analyze the effect of mutations in the putative binding site of calcium of the connexin hemichannel and provide a possible explanation of why such mutations lead to hyperactive hemichannels.