Ab Initio Modeling of Calcium Channel Voltage-Sensing Domain

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Voltage-gated calcium channels are involved in several diseases and, consequently, constitute a target for many drugs. Since they are membrane proteins, 3D structures are difficult to obtain through crystallization; hence, up to now, their mechanism is not completely clear yet and further studies are necessary to better understand their functions and modulation.

In particular we focused on $Ca_v1.1$ alpha1 subunit to investigate the voltage-sensing domain and the implications of mutations for voltage sensitivity [1]. Since no crystal structures are available on the Protein Data Bank and the sequence identity between calcium and other ion channels is too low to use homology modeling, we generated models through ab initio modeling. We applied the Rosetta method [2] to generate 3D structures of native and several mutated channels, and then compared our results with experimental data.

As known from sodium and potassium channels [3], positive-charged residues in transmembrane segment S4 of alpha1 subunit have a central role in channel opening; in detail we investigated the S3-S4 loop and D1196 involvement in voltage sensitivity. We demonstrate how structural models can be helpful in the interpretation of complex assay data.

References

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