Conformational Heterogeneity of the M2 Proton Channel: A model for channel activation

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Introduction

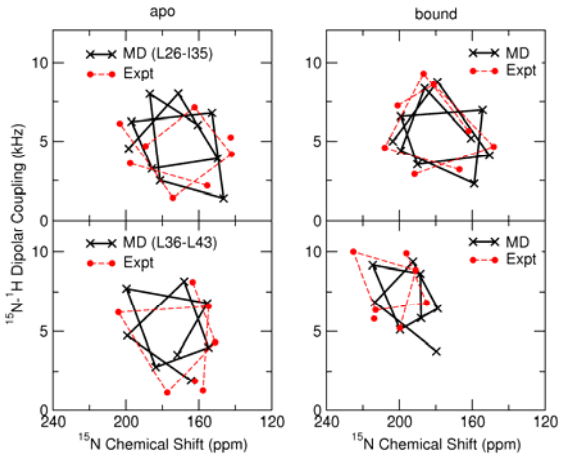
The M2 protein is a proton selective ion channel activated by low pH, and its channel activity is essential for the life cycle of the Influenza A virus. Recent structures determined by X-ray crystallography and solution NMR suggested models for open and closed states of the M2 proton channel. However, these models are based on limited data, and other important functional states need to be characterized. Indeed, solid-state NMR data demonstrate that the M2 protein possesses significant conformational heterogeneity [1]. Here, we report MD simulations of the M2 transmembrane domain in the absence and presence of the anti-viral drug, amantadine.

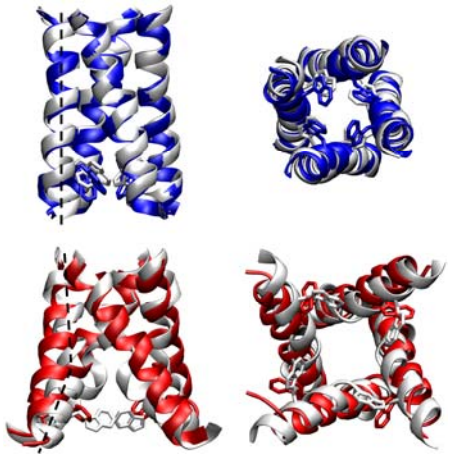
Molecular Dynamics Simulations

The apo and amantadine-bound M2 transmembrane domain have been modeled based on the structures solved by solid-state NMR in the absence and presence of amantadine, respectively. They were simulated in the fully hydrated DMPC bilayer, and each simulation was repeated with a different seed number. The simulations started with energy minimization to remove bad contacts. The simulation systems were then heated up to 310 K for 50 ps under constant volume condition, and thereafter the simulations were continued at constant temperature and pressure.

Results and Discussion

The ensembles of MD conformations for both apo and bound forms reproduce the PISEMA data well (Figure on right hand side). The helices kink around Gly34, where a water molecule penetrates deeply into the backbone. The bound form exhibits a single peak around 10° in the distribution of helix kinking angle, but the apo form exhibits two peaks, around 0° and 40°. Conformations with the larger kinking angles have a wider opening around the primary gate formed by His37 and Trp41, reproducing some of the key observations on the low-pH activated state by ^{19}F NMR [2]. We propose that this population is stabilized by low pH and leads to proton conductance. The figure on left hand side shows the model structures of closed and open states of M2 transmembrane domain of the channel compared with the recent solution NMR (blue) and X-ray (red) structures.





Conclusions

Here we present a novel mechanism for M2 proton channel conductance mechanism using MD simulations, which are consistent with the solid-state NMR experimental observations.

References

[1] Li, C., *et al.*, Biochim Biophys Acta. **1768**:3162-3170 (2007).
[2] Witter, R., *et al.*, J. Am. Chem. Soc. **130**: 918-924 (2007)