Transmembrane Helix Uniformity Examined by Spectral Mapping of Torsion Angles

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Introduction

Here, we describe the biophysical foundations for the remarkable uniformity of many transmembrane helices that result from the molecular interactions within lipid bilayers. In fact, the characteristic uniformity of transmembrane helices leads to unique spectroscopic opportunities allowing for ϕ,ψ torsion angles to be mapped directly onto solid state NMR PISEMA spectra. Results from spectral simulations, the solid state NMR derived structure of the Influenza A M2 proton channel transmembrane domain, and high resolution crystal structures of 27 integral membrane proteins demonstrate that transmembrane helices tend to be more uniform than previously thought.

Results and Discussion

As demonstrated in Fig. 1 *A* the root mean square (rms) variation of φ,ψ torsion angles for residues in transmembrane helices of 27 membrane proteins decreases as the structural resolution improves and approaches 5° for the 1.5 Å resolution structures. A Ramachandran-δ plot (Fig. 1 *B*) illustrates that for a series of four Bacteriorhodopsin structures, the rms variation decreases as the resolution improves. Utilizing hydrogen bond geometry constraints a preferred α-helical region (*shaded green*) of φ,ψ space can be defined (Fig. 1 *C*) and mapped into the corresponding spectral space (Fig. 1 *D*). These simulations (for residues of the transmembrane peptide of the Influenza A M2 proton channel) provide the first direct examination of a range of torsion angle space mapped into spectral space.

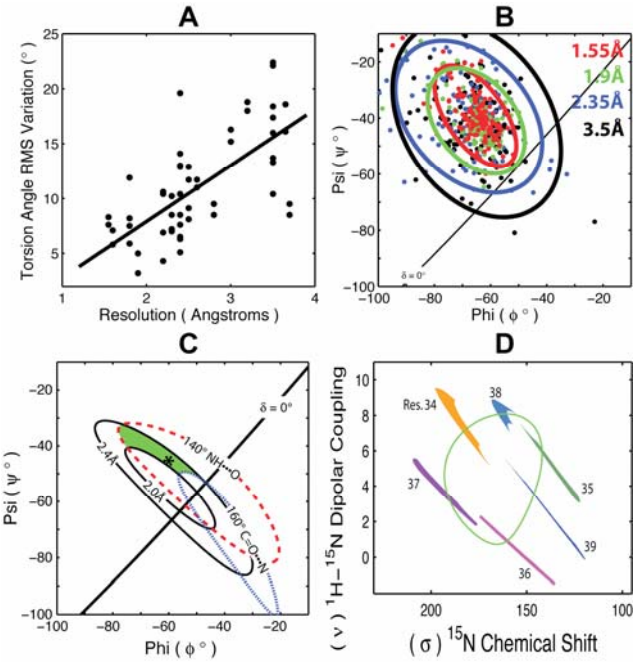

Fig. 1 – Torsion angle rms variations within 27 X-ray crystal structures (*A*,*B*) and hydrogen bond geometry restrictions (C) mapped to PISEMA spectra (resulting in torsion angle maps (*D*)), in combination with PISA wheel analyses (*D, green line*), all illustrate that transmembrane helices can be highly uniform structures.

Throughout the literature, results of structural studies of membrane proteins by solid state NMR are uniformly consistent with an average peptide plane tilt angle (relative to the helix axis) of 8° and a maximum variation in backbone φ,ψ torsion angles of just ±6°. Interestingly, the torsion angles originally suggested by Pauling in 1951 (1), based upon calculations *in vacuo*, provide a tilt angle of 8° (ϕ = -60° and ψ = -45°) consistent with the NMR data from many membrane proteins and peptides. We have seen repeatedly through solid state NMR data, spectral simulations, transmembrane helix energetics (2,3) and analyses of membrane protein crystal structures that transmembrane helices are typically highly uniform structures. It is now clear that transmembrane α-helices, as a result of their amino acid composition, the lack of water in the bilayer interstices and the low dielectric of the environment, have a tendency to be far more uniform in structure than their counterparts in water soluble proteins.

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References

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