The Importance of a Lipid Bilayer Environment for Membrane Proteins

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Introduction
Structures of the M2 protein from Influenza A virus have been characterized by x-ray crystallography in a detergent environment [1], by aligned sample solid state NMR in liquid crystalline phase lipid bilayers [2,3] and by solution NMR in detergent micelles [4]. The native environment for membrane proteins is a cellular membrane composed of lipids and proteins and while the lipid phase is liquid crystalline the samples for SA-NMR are far from a perfect mimetic of the cellular membrane. Even so, these structures give us an opportunity to compare the influence of various typical environments used by all of the front line technologies in sample preparation for protein structural characterization [5].

Experimental
The ssNMR structures were characterized using all of the high field ssNMR instrumentation at the NHMFL.

Results and Discussion
The solution NMR structure is of a somewhat longer construct (18-60) than the other structural characterizations (22-46). All of the structures lead to a tetrameric bundle of helices for the transmembrane domain as shown in Fig. 1. However, the molecular packing interactions between the helices in these structures are all very different. The two structures in the lower half of the figure have an anti-viral drug bound while the two at the top do not. Clearly the crossing point for the helices in the x-ray and ssNMR structure are very different. In Figure 2A it becomes very clear that detergent molecules have penetrated into the helical bundle forcing the lower half of the structure apart. In addition the two tetramers are packed tightly together in the crystallographic unit cell developing a strong molecular interactions that appear to dominate the intratetramer interactions. In the solution NMR structure the helical tilt with respect to the bilayer normal is so small that the drug does not bind on the pore axis, but rather binds to the exterior of the tetramer in close proximity to the natural lipid binding position of this highly lipid soluble drug.

Conclusions
Detergents are used for almost all solution NMR and x-ray crystallographic membrane protein structure characterizations. It is becoming clear that these detergents do not model the membrane environment well enough to support the native structure that appears to be similar to that determined by ssNMR.

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References