HAMP-membrane interactions correlate with the signaling mechanism and subcellular localization of HAMP-containing receptors

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HAMP domains convert extracellular sensory input into intracellular signaling response in more than 5000 membrane-embedded bacterial receptors. These domains are almost invariably found adjacent to the inner leaflet of the cell membrane. We therefore examined the interaction of peptides corresponding to either AS1 or AS2 of four different, well-characterized HAMP domains with several membrane model systems. HAMP domains were selected from an *Archaeoglobus fulgidus* protein (Af1503), the *Escherichia coli* osmosensor EnvZ*Ec*, the *E. coli* nitrate/nitrite sensor NarX*Ec*, and the aspartate chemoreceptor of *E. coli* (Tar*Ec*). Far-UV CD and NMR spectroscopy were used to monitor the induction of secondary structure upon association with neutral or acidic large unilamellar vesicles (LUVs) and bicelles. We observed significant increases in a-helicity within AS1 from NarX*Ec* and Tar*Ec* but not in AS1 from the other proteins. To characterize these interactions further, we determined the solution structure of AS1 from Tar*Ec* associated with acidic bicelles. AS1 formed an amphipathic a-helix, whereas the N-terminal control cable, the region between TM2 and AS1, was unstructured. We observed that the conserved prolyl residue found in AS1 of many membrane-adjacent HAMP domains defined the boundary between the unstructured and helical regions. These results strongly support the helix-interaction model for HAMP signaling and suggest roles for AS1-membrane interactions during transmembrane communication and subcellular localization of HAMP-containing receptors.