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Rotational Mechanism for Transmembrane Signaling by the Atrial Natriuretic Peptide Receptor. H. Ogawa, Y. Qiu, C.M. Ogata*, K.S. Misono, Dept. of Biochemistry & Molecular Biology, Univ. of Nevada, Reno, NV 89557, *Advanced Photon Source, Argonne National Laboratory, IL 60439, USA.

Atrial natriuretic peptide (ANP) plays a major role in blood pressure and volume regulation. ANP activities are mediated by a specific receptor coupled to guanylyl cyclase (GCase). The receptor occurs as a dimer of a single transmembrane polypeptide containing an extracellular hormone-binding domain and an intracellular domain consisting of an ATP-dependent regulatory domain and a GCase catalytic domain. The mechanism of signaling by the ANP receptor is not unknown. Here we report the crystal structure of the dimerized hormone-binding domain of the receptor complexed with ANP. Structural comparison with the unbound receptor reveals that hormone binding causes the receptor monomers to undergo an intermolecular twist with little intra-molecular conformational change. This motion produces a Ferris wheel-like translocation of the two juxtamembrane domains in the dimer with essentially no change in the interdomain distance. This movement alters the relative orientation of the two domains by a change equivalent to counter-clockwise rotation of each by 24 degrees. These results suggest that transmembrane signaling by the ANP receptor is mediated via a hormone-induced rotation mechanism.