Case Study 2: Discovering the Conformational Switch that "Gates" the Channel

•Binding of the neurotransmitter must induce a structural change in the receptor that opens the ion channel

•The metaphor is that a "gate" opens

•We have identified a key proline residue that regulates this process.

Cis-trans isomerisation at a proline opens the pore of a neurotransmittergated ion channel. Sarah C. R. Lummis, Darren L. Beene, Lori W. Lee, Henry A. Lester, R. William Broadhurst, and Dennis A. Dougherty, *Nature*, **438**, 248-252 (2005).



A Model of a Cysloop Receptor

One of five subunits is highlighted

The key, binding-site Trp

The gate - the occlusion of the channel that must move to open the channel

A conserved proline ...

Proline 308 is at a Pivotal Location, Associated with Well-Known Structural Landmarks that Have Been Implicated in Gating



Proline Has Unique Structural Properties



•For all other amino acids, the peptide bond is > 99% trans

•For proline, $\sim 5\%$ of amide bonds are cis, and the cis and trans forms can interconvert

•Could this conformational change be the switch?



71 Dmp



Free-Energy Correlation



A Proposed Mechanism





Overall Layout

Binding Site Trp (183)

6 amino acids of β sheet

Cys loop (162-176)

Pro 308

Direct and simple coupling between the agonist binding site and the key gating residue