Uncoupling binding from gating in the nicotinic acetylcholine receptor: a possible role for lipids modulating synaptic function

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Allosteric modulators influence protein function by binding preferentially to, and thus preferentially stabilizing different conformational states. For ligand-gated ion channels, such as the nicotinic acetylcholine receptor (nAChR), allosteric effects are usually interpreted in terms of model involving three pre-existing conformations; resting (but activatable), open (active), or desensitized (non-activatable). Many allosteric modulators influence the pool of activatable nAChRs by shifting the conformational equilibrium between resting and desensitized nAChRs. The nAChR, however, can also adopt a lipid-dependent non-activatable conformation that does not undergo allosteric transitions upon ligand-binding, but is neither resting nor desensitized. Given that agonist binding and channel gating are uncoupled; we refer to this novel conformation as the “uncoupled” state. Neither the global secondary structure nor the thermal denaturation of the nAChR is greatly affected by uncoupling, although previously buried peptide hydrogens become exposed to aqueous solvent. We propose that uncoupling results from a weakening of the physical interactions at the interface between the agonist binding and transmembrane pore domains. The highly lipid-exposed M4 transmembrane α-helix extends beyond the hydrophobic bilayer to interact with the Cys-loop at this coupling interface. Given the importance of the Cys-loop in translating agonist-binding into channel gating, we suggest that M4/Cys-loop interactions are essential for allosteric transitions. M4 may act as a lipid sensor translating altered membrane properties into altered M4/Cys-loop interactions and thus ultimately altered nAChR function. This novel uncoupled conformation may play a role in the allosteric modulation of all ligand-gated ion channels. For example, neurosteroid-induced potentiation of ligand-gated ion channels is thought to be mediated by the C-terminus of the M4 transmembrane α-helix. The structural basis of uncoupling is discussed in light of recently solved structures of bacterial pentameric ligand-gated ion channels. Preliminary data suggest that aromatic residues may influence the strengths of transmembrane helix-helix interactions thus defining the lipid sensitivity of pentameric ligand-gated ion channels.