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Mechanisms underlying lipid-sensing by the nicotinic acetylcholine receptor in both normal and diseased states

The neuromuscular nicotinic acetylcholine receptor (nAChR) is the prototypic member of the pentameric ligand-gated ion channel (pLGIC) superfamily, a superfamily of neurotransmitter receptors that plays a central role in information processing in the brain. It is well documented that nAChR function is exquisitely sensitive to its lipid environment. Lipids influence function by both conformational selection and kinetic mechanisms – they stabilize different proportions of activatable versus non-activatable conformations, and influence the rates of transitions between the different states. In the absence of activing cholesterol and anionic lipids, the nAChR adopts a conformation where agonist binding is uncoupled from channel gating. Lipids likely influence the "coupling" of binding and gating *via* the lipid-exposed transmembrane α-helix, M4. M4 in the neuromuscular nAChR is also the site of both point and truncation mutations that alter expression and/or function leading to congenital myasthenic syndromes. In this seminar, I will focus on the mechanisms by which the peripheral M4 transmembrane α-helix modulates pLGIC function. The M4 C terminus extends beyond the bilayer to interact with key structures that link the agonist binding to the transmembrane gate – referred to here as the coupling interface. We hypothesized that interactions between M4 and the coupling interface are essential to pLGIC function. We show here that such interactions are essential to function in some pLGICs and do participate in lipid-sensing. In the neuromuscular nAChR, however, such interactions between M4 and the coupling interface are less important. Instead, M4 influences function *via* a cluster of polar residues located in the core of the transmembrane domain near the center of the lipid bilayer. Altered M4 structure leads to changes in the energetic coupling between these polar residues, with the changes coupling ultimately propagating to both the gating helix, M2, and the aforementioned coupling interface. Here, we map out the conformational pathway that leads from the lipid-exposed surface of M4 to the channel gate, and thus illustrate how M4 "allosterically" modulates channel function.

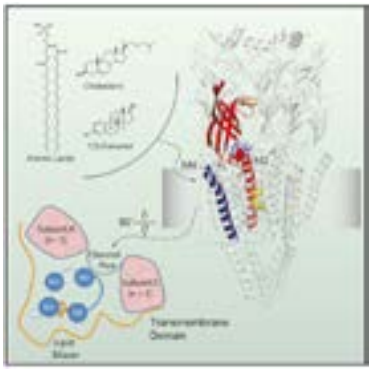

Figure1: *Some allosteric modulators, including lipids, act via the lipid-exposed M4 α-helix of the nAChR. We elucidate the allosteric pathway by which this peripheral structure influences channel gating.*

Biography

John Baenziger is a professor of Biochemistry at the University of Ottawa in Ottawa, Canada. His research is focused on understanding the mechanisms by which lipids influence nicotinic acetylcholine receptor structure and function in both normal and diseased states, with increasing focus on how lipid-nAChR interactions participate in congenital myasthenic syndromes. Dr. Baenziger has served on the editorial board of the Journal of Biological Chemistry. He is the President of the Biophysical Society of Canada and is Treasurer-elect of the International Union of Pure and Applied Biophysics.

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