PHOL 466: CELL SIGNALING
Neurotransmitter-Gated Ion Channel Receptors
February 14 and February 16, 2017
J.M. CREGG & G.R. DUBYAK

READINGS:

Review Readings for the Feb. 14 Session:

1) Collingridge GL, Olsen RW, Peters J, and Spedding, M. 2009. A nomenclature for ligand-gated ion channels. *Neuropharmacolo*gy 56:2-5.
2) Lester, H.A., Dibas, M.I., Dahan, D.S., Leite, J.F., and Dougherty, D.A. 2004. Cys-loop receptors: new twists and turns. *Trends Neurosci.* 27: 329-336.
3) Wollmuth, L.P. and Sobolevsky, A.I. 2004. Structure and gating of the glutamate receptor ion channel. *Trends Neurosci.* 27: 321-328.
4) Browne LE, Jiang LH, North RA. 2010. New structure enlivens interest in P2X receptors. Trends Pharmacol Sci. 31(5):229-37.
5) Jacob TC, Moss SJ, Jurd R. 2008. GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat Rev Neurosci*. 9: 331-43.

Original Research Papers for the Feb 16 Session:

1) Miller PS, Aricescu AR. 2014. Crystal structure of a human $GABA_A$ receptor. *Nature* 512: 270-275.
2) Du J, Lü W, Wu S, Cheng Y, Gouaux E. 2015. Glycine receptor mechanism elucidated by electron cryo-microscopy. *Nature* 526: 224-229.

Objectives and Questions for the Feb 14 Discussion: This discussion section will review the basic structure and function of receptors belonging to the superfamilies of ligand-gated ion channels for neurotransmitters. You should be prepared to discuss in depth the following 12 questions:

1. What are the similarities and differences that characterize “excitatory” and “inhibitory” neurotransmitter-gated ion channel receptors? **(GROUP 1)**

2. Explain the concepts of “gating”, “conductance”, and “selectivity” as applied to the function of neurotransmitter-gated ion channel receptors. **(GROUP 1)**

3. Explain the structural changes that couple agonist binding to channel activation for a “Cys-loop receptor” such as the nicotinic acetylcholine receptor. **(GROUP 1)**

4. Explain the structural changes that couple agonist binding to channel activation for a trimeric P2X receptor? **(GROUP 1)**

5. Explain how co-operativity may contribute to the coupling between agonist binding and channel activation for multimeric neurotransmitter-gated ion channel receptors. **(GROUP 1)**

6. Explain the structural determinants of ion selectivity for a typical neurotransmitter-gated ion channel receptor. **(GROUP 1)**

7. How is the method called “cysteine-scanning mutagenesis” used to characterize ion conducting properties of neurotransmitter-gated ion channel receptors? **(GROUP 2)**

8. Explain the concept of “densitization” or “inactivation” as it applies to neurotransmitter-gated ion channel receptors. **(GROUP 2)**

9. Besides “desensitization” or “inactivation”, what other mechanisms can contribute to the termination of signal transduction by neurotransmitter-gated ion channel receptors? Provide some specific examples. **(GROUP 2)**

10. Using GABAA receptors as an example, explain the mechanisms by which neurotransmitter-gated ion channels are appropriately trafficked to synaptic junctions and maintained at optimal levels within such specialized microenvironments of the plasma membrane? **(GROUP 2)**

11. Describe the differences between inhibitory ligands that act as “antagonists” versus “blockers” for neurotransmitter-gated ion channel receptors? **(GROUP 2)**

12. Although glycine acts as a direct agonistic ligand for “inhibitory” glycine-gated ion channels, it also acts as co-agonist for certain “excitatory” glutamate-gated ion channels. Explain this. **(GROUP 2)**