**Ligand Gated Ion Channel Annotated Bibliography**

Peer Reviewed Journal Sources

**[1] Lummis, S. C. (2012). 5-HT(3) receptors. *J Biol Chem, 287*(48), 40239-40245. doi:10.1074/jbc.R112.406496**

This minireview by Lummis is the review paper I picked for the presentation. It gives a nice background on how serotonin type 3 receptors were first proposed back in 1950s and later identified. Furthermore, the paper discusses the general structure of 5-HT3 receptors, the localization and function of its five subunits (A-E, while C-E are less understood), and its binding pocket with a Clustal alignment demonstrating the locations of the key elements on each subunit. However, note that this paper was published before a high-resolution structure of 5-HT3 receptors has been generated, thus the receptor model described here was based on well-studied structure of nACh receptors. Finally, this study also includes existing drugs which are used to treat nausea and irritable bowel syndrome by acting as 5-HT3 antagonists. However, current the lack of understanding of the C-E subunits leads to limitation on 5-HT3 related therapeutic development.

**[2] Thompson, A. J., & Lummis, S. C. (2006). 5-HT3 receptors. *Curr Pharm Des, 12*(28), 3615-3630.**

This is another review paper on 5-HT3 receptors written by Thompson and Lummis. Compare with the other review, this paper has more comprehensive information especially about the distribution of 5-HT3 associated with specific functions, as well as a summary of its agonist, antagonist, and modulator of the receptor. Together, these findings lead to a variety of therapeutic application. A collection of literature describing key residues in each of the 6 loops (A-F) can also be found in this paper.

**[3] Solt, K., Ruesch, D., Forman, S. A., Davies, P. A., & Raines, D. E. (2007). Differential effects of serotonin and dopamine on human 5-HT3A receptor kinetics: interpretation within an allosteric kinetic model. *J Neurosci, 27*(48), 13151-13160. doi:10.1523/JNEUROSCI.3772-07.2007**

This is the experimental paper that I chose to present in class. The authors performed electrophysiology studies on human 5-HT3A receptors expressed in HEK293 cells, specifically to characterize the different activation, deactivation, desensitization, and resensitization kinetics in response to high-efficacy agonist serotonin and low-efficacy agonist dopamine using different pulse settings. An allosteric kinetic model for 5-HT3A receptors was developed to illustrate this kinetics.

**[4] Hassaine, G., Deluz, C., Grasso, L., Wyss, R., Tol, M. B., Hovius, R., . . . Nury, H. (2014). X-ray structure of the mouse serotonin 5-HT3 receptor. *Nature, 512*(7514), 276-281. doi:10.1038/nature13552**

This study (published in 2014) is the first to crystallize the mouse homopentameric 5-HT3A receptor. I used several figures showing high-resolution structure of 5-HT3A receptor in this paper for our class presentation. These results could give us a better understanding of the architecture of the homopentameric receptor, the structural base for ion permeability and selectivity, and residues within the neurotransmitter binding site. Given that Cys-loop receptors are the major targets to treat neurological disorders, this discovery opens new possibilities for drug development.

**[5] Sung, K. W., Engel, S. R., Allan, A. M., & Lovinger, D. M. (2000). 5-HT(3) receptor function and potentiation by alcohols in frontal cortex neurons from transgenic mice overexpressing the receptor. Neuropharmacology, 39(12), 2346-2351.**

It has been suggested that 5-HT3 receptor is involved in neural response to alcohol abuse. This is an interesting paper investigating how acute exposure to alcohol affect 5-HT3 receptor-mediated current, by performing whole-cell voltage clamp recording from dissociated frontal cortex neurons from transgenetic mice overexpressing 5-HT3 receptor. They showed that ethanol potentiates the 5-HT3 receptor-mediated current in a concentration dependent manner.

**[6] Vyklicky, V., Korinek, M., Smejkalova, T., Balik, A., Krausova, B., Kaniakova, M., . . . Vyklicky, L. (2014). Structure, function, and pharmacology of NMDA receptor channels. Physiol Res, 63 Suppl 1, S191-203.**

This is the review on NMDA receptor which we’ve picked for the class presentation. NMDA receptor is a glutamate receptor involved in excitatory synaptic transmission. With its crucial roles in neural plasticity and neuronal excitotoxicity, great amount of effort was put into understanding the structure of NMDA receptor and its subunits, the mechanism of its opening and closing, its binding sites, and its unique activation process where co-agonist glycine is required. Several agonists and antagonists for NMDAR have been explored for their pharmacological application. Additionally, NMDAR antagonists which were developed as potential neuroprotective drugs were non-successful due to their psychomimetic side effects. New modeling study identified neurosteroid 3α5βS as a potential blocker of the channel with therapeutic profiles.

**[7] Olsen, K. M., & Sheng, M. (2012). NMDA receptors and BAX are essential for Aβ impairment of LTP. *Sci Rep, 2*, 225. doi:10.1038/srep00225**

NMDA receptor plays an important role in synaptic transmission and neural plasticity. In Alzheimer’s disease, there’s accumulation of Aβ which results in a disruption in the structure and function of the synapse. This paper tested the effect of acute Aβ exposure to NMDAR-mediated long-term potentiation (LTP) and long-term depression (LTD) of the hippocampal neurons. They found that Aβ suppressed LTP, and this inhibition could be prevented with an NMDA non-selective antagonist, D-AP5. The same suppression was not observed in the hippocampal neurons of mice that lack BAX which is involved in apoptosis. This study suggested that Aβ inhibit LTP through apoptotic pathway, this may provide a different angle for therapeutic development for Alzheimer’s disease.

**[8] Sigel, E., & Steinmann, M. E. (2012). Structure, function, and modulation of GABA(A) receptors. *J Biol Chem, 287*(48), 40224-40231. doi:10.1074/jbc.R112.386664**

This minireview by Sigel and Steinmann described the inhibitory ligand-gated anion-selective ion channel: GABAA receptors, which also belong to the Cys-loop receptors family. This review paper summarizes the gene organization of the numerous GABAA receptor subunits, the possible pentameric receptors assembled with these subunits, and the potential channel opening mechanism and modulation. However, a high-resolution structure of the GABAA receptor was yet to be discovery prior to the publication of this review (2012)，which can be complemented by a recent study by Shaotong Zhu et al.[1] demonstrating the cryo-electron microscopy structures of the human α1β2γ2 GABAA receptor. Additionally, function and localization of the GABAA receptors have also been discussed in this paper. Activation of synaptic localized GABAA receptors lead to phasic inhibition; while those localized in the extrasynaptic sites lead to tonic inhibition activated by ambient GABA concentration. Interestingly, the authors criticized those given statements where individual receptor subunit confers a function for the purpose of simplification. Overall, this paper includes comprehensive aspects of GABAA receptors which serves as a helpful guide for understand the fundamentals of this receptor.

*[1] Shaotong Zhu et al. Structure of a human synaptic GABAA receptor, Nature (2018).*

**[9] Burgos, C. F., Yévenes, G. E., & Aguayo, L. G. (2016). Structure and Pharmacologic Modulation of Inhibitory Glycine Receptors. *Mol Pharmacol, 90*(3), 318-325. doi:10.1124/mol.116.105726**

This is a relatively newer review of the glycine receptor (GlyR), which is another inhibitory anion-selective member of the Cys-loop ligand-gated ion channels family. Given its critical role in motor coordination, sensory processing, respiratory rhythms, and pain transmission, GlyR is seen as a target for pharmacotherapy, which makes it paramount to uncover the structure of GlyR. Following several advanced findings in the crystallographic structure of GlyR, this paper is able to discuss the primary and secondary structure of GlyR, and the conformational changes during channel activation by agonist. Based on these structural information, this paper specifically described the molecular sites for the regulation of GlyR by important pharmacologic modulators, including Zn2+, general anesthetics, and ethanol.

**[10] Chatzidaki, A., & Millar, N. S. (2015). Allosteric modulation of nicotinic acetylcholine receptors. Biochem Pharmacol, 97(4), 408-417. doi:10.1016/j.bcp.2015.07.028**

Nicotinic acetylcholine receptor (nAChR) is the most well-studied member of the Cys-loop family of ligand gated channel. Sixteen human nAChR subunits have been identified. Most of them are expressed widely and form heteromeric complexes. This review paper focus on pharmacological diversity of nAChR allosteric modulators, and summarized positive allosteric modulators (which potentiate the effect of agonist-activation), negative allosteric modulators (which inhibit agonist-activation), and silent allosteric modulators (which interact with non-conventional allosteric site but do not initiate any modulation). Similar to other neurotransmitter-gated ion channels, majority of the binding sites located in transmembrane and extra-transmembrane locations.

Website Sources

<https://www.youtube.com/watch?v=Pl7nzXaVqak>

A short and very easy to understand lecture from Khan Academy about ligand-gated ion channel. The video covers the general concept of the ligand-gated channel, the conformational changes from closing to opening, the allosteric binding sites, and the differentiation between ligand-gated, voltage-gated, and stretch-activated channels.

<https://www.youtube.com/watch?v=DIYQCyzuwEg>

A mini-lecture from Caltech reviewing the nicotinic acetylcholine receptors. The video covers nAChR localization and structure. It also includes several models of the conformational changes during activation, as well as some electrophysiology recording of the channel.

<http://www.sumanasinc.com/webcontent/animations/content/ampa_and_nmda.html>

This is a short video explaining long-term potentiation in post-synaptic site mediated by NMDA receptors and AMPA receptors, results in calcium influx and activation of downstream signaling pathways. This video is one of the several animated tutorials by Sumanas, Inc. More neurobiology/biopsychology videos can be found when click “Back” on the bottom right of the website.

<https://www.coursera.org/lecture/medical-neuroscience/ionotropic-neurotransmitters-receptors-part-2-y5wQf>

This is part of an online tutorial courses presented by Dr. Leonard E. White, from Duke University. This lecture focus on electrophysiology recordings from nicotinic acetylcholine receptors and NMDA receptors.

<https://www.genenames.org/cgi-bin/genefamilies/set/161>

This is the ligand-gated ion channel gene family hierarchy tree provided by HGNC, which is the only worldwide authority that assigns standardized nomenclature to human genes. You can also find the gene family for each one of the ion channel, their approved names, symbols, etc.

<http://www.tocris.com/pharmacologicalBrowser.php?ItemId=187839#.VA51wPmwKSq>

This link to a supplier website which categorized a list of agonists, antagonists, modulators, and ligands under each of the major ligand-gated ion channels.

<https://www.nature.com/subjects/ligand-gated-ion-channels>

This is a link to the collection of newest published research about ligand-gated ion channels on the Nature website.

<http://www.rcsb.org/structure/4PE5>

This is the Protein DATA Bank (PDB) where you can find crystal structure, 3D view, annotation, and sequence of different receptors (this one link to GluN1a/GluN2B NMDAR). This website also allows you to view and rotate the 3D structure of the protein, which will give you a better understanding of the architecture of the protein.

<https://www.drugbank.ca/categories/DBCAT002341>

The DrugBank Database include pharmacological data and target information. This is a good resource to look for agonists or antagonists for certain receptors. This database includes both information about the target receptors and the information about the drugs.

<https://www.jove.com/video/51629/one-channel-cell-attached-patch-clamp-recording>

JOVE is also a good website to learn experimental technique. This video described the procedure for one-channel cell-attached patch-clamp recording.