**Ligand Gated Ion Channel Annotated Bibliography**

Peer Reviewed Journal Sources

Burgos, C. F., Yévenes, G. E., & Aguayo, L. G. (2016). Structure and Pharmacologic Modulation of Inhibitory Glycine Receptors. *Molecular Pharmacology*, *90*(3), 318–325. <https://doi.org/10.1124/mol.116.105726>

A cys-loop receptor, glycine receptors traffic mainly chloride ions and lead to cellular hyperpolarization, leading to a decrease in excitability. The structure of the channel subsists of five subunits of either 5 alpha subunits or a combination of 5 alpha and beta subunits, with 5 glycine binding sites present on the homopentamer of the alpha subunits. The opening of the pore involves the binding of the agonists and a general “twisting” in the confirmation of the protein, thought the size and complexity of the complex makes exact changes difficult to project. A potential modulator of the GlyR receptor is the Zn+ ion, which acts as a biphasic and concentration dependent manner and has been shown to increase potentiation of glycinergic currents in the presence of alcohol. Other modulators include general anesthetics.

Olsen, K. M., & Sheng, M. (2012). NMDA receptors and BAX are essential for Aβ impairment of LTP. *Scientific Reports*, *2*. <https://doi.org/10.1038/srep00225>

NMDA receptor over-activation can lead to calcium cytotoxicity. Accumulation of amyloid-β is a defining feature of Alzheimer’s disease, which is marked by dementia and loss of memory. These Aβ plaque buildups appear to have agonist activity with the NMDA receptors, which lead to an overall loss of ability to maintain potentiation in the hippocampal circuit. Hippocampal slices treated with Aβ have a decreased ability to maintain potentiation compared to untreated slices, and NMDA channel blockers have varying effects on reversing this trend depending on their mechanism and binding site. In slices from a BAX knockout mouse line, this ability to maintain potentiation is less affected than the wild type, implying that BAX’s role in the mitochondrial apoptotic pathway being knocked out somehow prevents part of the loss of function. This would indicate the possibility that in Alzheimer’s cases, excess intracellular calcium enters from over-activated NMDA receptors channels, activates the mitochondrial apoptosis pathway, and leads to cell death and the behavioral symptoms of Alzheimer’s.

Padilla, K., Gonzalez-Mendoza, D., Berumen, L. C., Escobar, J. E., Miledi, R., & García-Alcocer, G. (2016). Differential gene expression patterns and colocalization of ATP-gated P2X6/P2X4 ion channels during rat small intestine ontogeny. *Gene Expression Patterns*, *21*(2), 81–88. <https://doi.org/10.1016/j.gep.2016.08.002>

P2X is expressed by neuronal and non-neuronal systems. Modulated by extracellular ATP, the channels are formed from a 7 subunit complex. These channels are notably expressed in the gastrointestinal tract to transport monovalent cations and calcium, as well as serving a regulatory role in the absorption of magnesium. Within the small intestine, developmental changes necessitate changes in diet and thus a change in nutrient absorption. Two of the subunits that make up these complexes, P2X6 and P2X4, are shown to be differentially expressed in terms of location with the age of mice, ranging from P0 through adulthood. This would indicate that the channels will vary in function in the different areas of the bowels and that the bowels themselves will change during development.

Palmai, Z., Houenoussi, K., Cohen-Kaminsky, S., & Tchertanov, L. (2018). How does binding of agonist ligands control intrinsic molecular dynamics in human NMDA receptors? *PLoS ONE*, *13*(8). <https://doi.org/10.1371/journal.pone.0201234>

The human NMDA glutamatergic receptor is a heterotetramer with a cation channel presented between the subunits. A specific domain of each subunit, the M3 area, forms the pore of the channel and serves a bottle neck for the flow of ions. Presenting a ligand specific binding site (though not necessarily glutamate specific) on each of the four subunits, the channel changes conformation in a rotating twisting motion to open internal channel. Given the size of the protein complex, there are numerous spaces for non-competitive modulators to bind.

Sigel, E., & Steinmann, M. E. (2012). Structure, Function, and Modulation of GABAA Receptors. *The Journal of Biological Chemistry*, *287*(48), 40224–40231. <https://doi.org/10.1074/jbc.R112.386664>

GABA-A receptors are a cys loop ligand gated ion channel that serves mainly as an inhibitory modulator of cellular activity. The pentameric complex is highly variable with regard to subunit composition, with up to 19 isoforms being identified and as many as 8 isoforms being expressed on a single neuron. They are mainly conductors of chloride ions, though they are slightly permeable to bicarbonate ions. Given the amount of variability, within subunit composition, general statements about the channel are difficult to make, though some subunits and their interactions with modulators such as benzodiazepines have been well characterized experimentally.

Sihra, T. S., Flores, G., & Rodríguez-Moreno, A. (2014). Kainate Receptors: Multiple Roles in Neuronal Plasticity. *The Neuroscientist*, *20*(1), 29–43. <https://doi.org/10.1177/1073858413478196>

Kainate receptors are heteromeric tetramers that respond to activation by glutamate. At the hippocampal synapse, they have been shown to mediate GABA and glutamate release presynaptically while mediating excitability responses. KARs have been implicated to play a role in short term potentiation with a positive feedback mechanism that would lead to the release of more transmitter at the MF-CA3 synapse and initiate metabotrophic activity. Experiments with knockout mice have indicated that specific subunits are involved in mediating paired pulse facilitation, but these results have been disputed with experiments in the presence of channel blockers yielding different results. There is solid evidence that frequency dependent facilitation and long term potentiation are both mediated by GluK2/GluK3 subunits at the MF-CA3 synapse.

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. *Journal of Neuroscience*, *27*(48), 13151–13160. <https://doi.org/10.1523/JNEUROSCI.3772-07.2007>

Dopamine is a low efficiency agonist to the human serotonin receptor. The human 5-HT3A receptor was cultured in human embryonic kidney cells and subjected to whole cell patch electrophysiology with controlled exposure to both serotonin and dopamine. The data indicate that the kinetics of channel activation and sensitization are significantly different between the two agonists. This is attributed to the rates at which they cause the channels to open and the rates at which they dissociate from the receptor when the receptor is in a given confirmation.

Sung, K.-W., Engel, S. R., Allan, A. M., & Lovinger, D. M. (2000). 5-HT3 receptor function and potentiation by alcohols in frontal cortex neurons from transgenic mice overexpressing the receptor. *Neuropharmacology*, *39*(12), 2346–2351. <https://doi.org/10.1016/S0028-3908(00)00064-2>

A transgenic mouse line was designed to over express the 5-HT3 receptor. Using whole cell patch clamp, cultured frontal cortex neurons were exposed to serotonin and selected modulators and the effect on the channel currents were observed. The effects of alcohol on these overexpressed channels were also observed, noting that alcohol appears to potentiate receptor function. The findings also indicate that there is a difference in transgenically expressed serotonin receptors may be more sensitive to alcohol.

Tian, Y., Hou, X., Wen, L., Guo, W., Song, Y., Sun, H., … Zhu, D. (2010). A biomimetic zinc activated ion channel. *Chemical Communications*, *46*(10), 1682–1684. <https://doi.org/10.1039/B918006K>

A novel zinc activated ion channel was characterized by etching into a PET membrane. By defining zinc binding as the “activated” or “on” state and zinc not being bound as the “deactivated” or “off” state, ion flow was measured in both conformations to assess the open or closed state of the channel. Calcium and magnesium ions were shown to have little effect on the activation of the channel, highlighting its selectivity in binding. The successful creation and regulation of artificial ion channels highlights a huge potential in future research involving regulation of synaptic activity.

Vyklicky, V., Korinek, M., Smejkalova, T., Balik, A., Krausova, B., Kaniakova, M., … Vyklicky, L. (2014). Structure, Function, and Pharmacology of NMDA Receptor Channels, *63*, 13.

A major focus of NMDA receptor research has focused on clinically relevant antagonists that will prevent cytotoxicity without interfering with functions necessary for regular synaptic transmission and plasticity. Glycine is necessary for channel activation, but it is found in high enough endogenous amounts that most of its binding sites are occupied. Due to the complexity of the molecule, a wide variety of modulators have been shown to alter activation, but most of the compounds developed have failed clinical trials in the last 20 years. Software modeled interactions with endogenous steroid 3α5βS indicates potential viability of the steroid as a voltage independent blocker of the channel.

Website Sources

Pitt Medical Neuroscience Module 5: Glutamate Receptors  
<http://pittmedneuro.com/glutamate.html>

Glutamate receptors can be classified as either metabotropic or ionotropic. The ionotropic receptors are heavily involved in long term potentiation, with AMPA receptors allowing a sodium influx that allows for the activation of the NMDA receptors. With the displacement of the inlaid magnesium ion, the NMDA channels allow an influx of cations, including calcium ions that can set off a cascade of effects within the cell that includes allowing the addition of more AMPA receptors to the cell membrane at the synapse and many potential metabolic effects.

LibreTexts Online Biology: Cell Signaling Chapter  
<https://bio.libretexts.org/TextMaps/Biochemistry/Book%3A_Biochemistry_Free_and_Easy_(Ahern_and_Rajagopal)/08%3A_Signaling/8.2%3A_Ligand-gated_Ion_Channel_Receptors>  
  
A highlight of a free online textbook, this snippet on ligand gated ion channels shows an easy to understand general mechanism for the ion channels. The rest of the chapter also focuses on the larger aspects of cell signaling, including other kinds of receptors and the intracellular pathways associated with them.   
  
Quizlet Study Tools and Games  
<https://quizlet.com/16352528/ligand-gated-ion-channels-flash-cards/>

This website offers a few interactive ways to study the different features of ion channels, using a few different flash games and tests. It allows you to familiarize yourself with the basic principles of the channels.

Ligand Gated Ion Channels | Nervous system physiology | NCLEX-RN | Khan Academy

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

A short and simple breakdown on membrane protein properties and how ligand gated ion channels contribute to action potentials and cellular activity.

University of Hawaii, Maui College Pharmacology Lecture  
<https://www.youtube.com/watch?v=XwDZE9C8M5o>

In a more in depth look than the previous video sources, Dr. Steven Farmer lectures on the process of neurotransmission, neurotransmitters, and pre- and post-synaptic activity during the process of cell signaling.

## NCBI and Molecular Cell Biology. 4th edition. MCAT/GRE Prep <https://www.ncbi.nlm.nih.gov/books/NBK21476/>

Through an agreement with the publisher of the textbook, a quiz and study guide for standardized tests has been set up with free searchable access to the textbook available. A section of prepared material on ligand gated ion channels is available as a study guide.

Protopedia Ion Channel Modeling   
<http://proteopedia.org/wiki/index.php/Ion_channels>

This website offers 3D models of a variety of ligand gated ion channels with short descriptions of subunit composition, modulators, binding sites, and channel properties. They also have models for many other types of ion channels and facilitators.

#### IUPHAR/BPS Guide to Pharmacology

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=697>

This database offers a list of known pharmaceutical targets and a list of drugs that target the ligand gated ion channels that are or previously have been approved for human clinical trials by a regulatory agency. It includes a description of the mechanism of action and drug interactions with each.

Two Minute Neuroscience: Neuroscientifically Challenged <https://www.youtube.com/watch?v=E6SuVmeqs2o>

In a series of short videos, a wide array of neuroscience topics are covered. In the ones selected, the roles of ligand gated ion channels at the neuromuscular junction, glutamate signaling, and drug interactions with the selected ion channels.

The Brain from Top to Bottom <http://thebrain.mcgill.ca/flash/i/i_01/i_01_m/i_01_m_ana/i_01_m_ana.html>

This website is an interactive guide to neuroscience in the human body. The selected link and the ones available on the page from there offer a direct, step by step lesson in the neuroanatomy, physiology, pharmacology, and some examples of electrophysiology with neurotransmitters and their receptors. It also offers levels of complexity for readers who are new to the topic, intermediate, or advanced in the field so that the material is easier to follow based on your background knowledge.