What are ligand-gated channels?
The membrane of a cell is like a dam. With a ‘lipid bilayer’ it segregates molecules known as ions by preventing them from flowing freely inside and outside of the cell. Ions affected by this separation are integral to biological functions, including sodium, calcium, chloride, and potassium. However, to carry out these functions, simply separating the amount of these ions inside and outside of cells won’t do. The cell needs to be able to influence which side of the cell membrane they must be, and when.

Cells solve this issue with ‘ion channels’ which are embedded within the cell membrane. Working very similarly to floodgates within a dam, they open and close, allowing ions to pour through the membrane and alter concentrations on either side. These channels don’t simply allow any ion to fall through, they are specific to what can pass, dictated by the type of ion channel, in which there are many. A channel that opens in the presence of a particular chemical messenger, or ligand, is known as a ligand-gated ion channel.

Ligands bind to a site on the ligand-gated ion channels, also known as LGICs, which causes it to change shape, and open a pore that allows ions to flow straight into or out of the cell. This process is effective and doesn’t require any energy from the cell, as ‘passive diffusion’ comes into action when the channel opens. Referring back to the dam, this mechanism is easy to visualise. When specific ions pool up, becoming concentrated on one side of the membrane and sparse on the other, just like water in a dam, they will pour through when the channel opens, due to the concentration gradient.

Why are they important?
LGICs are vital to many important functions throughout the body, such as regulating pain, moods, sleep, and addictions.

LGICs however deserve a special mention due to the role they play in the nervous system. Unlike other ion channels, they have the ability to open and close in the fraction of a millisecond, allowing them to change ion concentration gradients rapidly, and propagate action potentials instantaneously, or even prevent them from occurring. This property is excellent for nerve cells, as action potentials are how nerves communicate, and subsequently how the brain sends messages throughout the body. Additionally, the inverse of this, when the opening of these channels prevents action potentials, the nerves won’t communicate messages. This is exactly how the sensation of pain can be stopped; by preventing nerves from communicating pain.
How do Ligand-Gated Ion Channels carry out this role?

LGICs have a special site on them known as the binding site. Here, ligands can attach to the ion channel. Once attached, the channel changes shape, and will let specific ions into, or out of, the cell. The channel then shuts once the ligand detaches. One more time, if we compare this to the dam, we can think of the ligand as a key to the floodgates. When the key is used on the lock, the floodgate opens, just as the ion channel does when the ligand attaches. This mechanism can be seen in the image below.

There are numerous different families of LGICS which have their own functional nuances, and allow different ions through the channel. For example, the ‘ionotropic glutamate receptors’ are a family that only allows positively charged ions (cations) through, whilst the ‘GABA_A receptors’ family allows only negatively charged ions (anions) through.

Lidocaine and Diazepam

Most medications work by targeting ion channels. Two important medications which target LGICs are Lidocaine and Diazepam. Diazepam, once known as valium, is primarily used for treating anxiety, muscle spasms, and as a sedative, due to its calming effects. It does so by targeting the family of LGICS on neurons called GABA_A receptors. The binding of diazepam to GABA_A doesn’t actually directly cause the channel to open. Rather it binds to an ‘allosteric site’ which causes the receptor site to change shape and become more accessible for the ligand, GABA, to bind to. GABA causes the channel to open, allowing negatively charged chloride ions to cross the membrane, and subsequently makes it significantly more difficult for action potentials to occur. This prevents neurons from sending signals to, and receiving signals from the brain. It’s the reduction of these signals that explains the calming effects of diazepam.

Lidocaine, a drug that is used as an anaesthesia to manage pain, targets the family of LGICs known as NMDA receptors. Lidocaine inhibits the receptor and prevents positive calcium ions to pass through the channel, however the exact method in which this occurs isn’t clear yet. The duration in which the cell remains open is greatly reduced by lidocaine, again stalling the propagation of action potentials, and the neurons ability to send messages. Stopping these signals can stop messages of pain being sent to the brain, and thereby producing therapeutic effects. The targeting of NMDA receptors with Lidocaine is an effective way to manage and treat pain related issues.

Diazepam and lidocaine are only the tip of the iceberg when it comes to drugs targeting LGICs to produce powerful effects. More examples include memantine for Alzheimer’s disease and agomelatine for depression. It’s always worth remembering “the dose makes the poison” and that if any of these drugs are taken in incorrect doses they can produce harmful, rather than therapeutic, effects.
References


