Ligand gated channels and voltage gated channels
similarities and differences

Nicotinic acetylcholine receptors (nAChR)

Properties
- ligand gated ion channel
  when receptors bind to ACh $\Rightarrow$ channel open
- specific to Na$^+$ and K$^+$
- 5 subunits with similar structure
- 4 transmembrane (TM) regions (M1-M4)
- M2 segment from each subunit form the pore.

Nicotinic acetylcholine receptors
5 subunits ($\alpha_2\beta\gamma\delta$)

![Diagram of nAChR structure](image)

FIGURE 5. A nACh receptor model based on electron microscopy and X-ray
diffraction experiments. The order of the subunits is based on experiments sup-
gesting that ACh-binding sites are at the junctions of the $\alpha$ and $\beta$ subunits. Other experiments suggest that the positions of the $\beta$ and $\gamma$ subunits are
reversed.
Characteristic amino acid residues along the M2 segment of nAChR subunits

Reversing ionic conductivity of nAChR

Galzi et al. demonstrated that the ion selectivity of nAChR (α7) can be converted from cationic to anionic by mutagenesis. Nature 359, 500-505 (1993)

Comparison between α7 nAChR and α1 GlyR subunit

Site directed mutagenesis

insertion of proline or alanine in loop M1-2, E237A, V251T,

Specific amino acid residues in and near the M2 TM domain are particularly important.
Ligand-gated ion channel receptor superfamily
conserved features

- Large N-terminal ligand binding domain
- Hydrophobic membrane spanning domains (M1-M4)
- Charged pore-lining domains (M2)
- Large intracellular loop between M3 and M4

Closely related families

<table>
<thead>
<tr>
<th>Receptor</th>
<th>ion specificity</th>
<th>Stoichiometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle-type nAChR</td>
<td>cations</td>
<td>pentamer</td>
</tr>
<tr>
<td>Neuronal nAChR</td>
<td>cations</td>
<td>pentamer</td>
</tr>
<tr>
<td>Serotonin 5-HT3R</td>
<td>cations</td>
<td>?</td>
</tr>
<tr>
<td>GABA_A,R</td>
<td>Cl^-</td>
<td>pentamer</td>
</tr>
<tr>
<td>Glycine R</td>
<td>Cl^-</td>
<td>pentamer</td>
</tr>
</tbody>
</table>

Distantly related families

- Ionotropic glutamate receptors
  - Kainate receptors
  - AMPA receptors
  - NMDA receptors

Diversity of ligand gated ion channel receptor subunits

Subunit structure

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subunit</th>
<th>Binding site</th>
<th>Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal nAChR</td>
<td>α</td>
<td>Ach</td>
<td>α1- α9</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td></td>
<td>β1- β4</td>
</tr>
<tr>
<td>GABA_A,R</td>
<td>α</td>
<td>benzodiazepine, GABA</td>
<td>α1- α7</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>GABA</td>
<td>β1- β3</td>
</tr>
<tr>
<td></td>
<td>γ</td>
<td>for ion channel function</td>
<td>benzodiazepine binding</td>
</tr>
<tr>
<td>Glycine R</td>
<td>α</td>
<td>glycine</td>
<td>α1- α3</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

also additional subunits (ε and ρ) have been cloned.
Ionotropic glutamate receptors (iGluR)

Glutamate
Most common excitatory neurotransmitter in the CNS involves in neuronal plasticity, and learning and memory related to neuronal toxicity

TIPS (1996) 17:348-355