Ligand-gated ion channels

Ligand-gated ion channels (LGICs) are pentameric structures and are frequently referred to as the Cys-loop LGICs. These channels are composed of five subunits, each containing a transmembrane helix that forms a pore through which ions can pass. LGICs are found at the somatic neuromuscular junction and in the nervous system, where they mediate fast synaptic transmission.

The activation of LGICs occurs through the binding of endogenous or exogenous modulators to allosteric sites. In the case of nicotinic acetylcholine receptors (nAChRs), the binding of acetylcholine to a specific site triggers a conformational change that leads to the opening of the channel. Similarly, 5-HT3 receptors are activated by serotonin, and GABAA receptors are activated by the inhibitory neurotransmitter GABA.

LGICs can mediate a tonic form of neuronal regulation, in addition to their traditional role in phasic neurotransmission. However, in some cases, LGICs can also mediate a rapid, phasic, electrical signal. This rapid conduction can result in the propagation of action potentials.

Inhibitory postsynaptic potentials (IPSPs) are mediated by GABAA receptors, which are chloride channels. The binding of GABA to the receptor opens the channel, allowing chloride ions to enter the cell and hyperpolarize the membrane. This hyperpolarization is referred to as an inhibitory postsynaptic potential (IPSP).

Excitatory postsynaptic potentials (EPSPs) are mediated by glutamate receptors, which are ionotropic glutamate receptors. The binding of glutamate to the receptor opens the channel, allowing sodium and calcium ions to enter the cell and depolarize the membrane. This depolarization is referred to as an excitatory postsynaptic potential (EPSP).

LGICs are involved in a wide range of physiological processes, including muscle contraction, neuronal transmission, and hormone release. They are also important targets for drugs that act as agonists or antagonists at specific receptor subtypes.
As a subunit in functional homomers, but are reported to assemble as a subunit in flanking proteins which show an intrinsic activity. The A-E subunits are expressed in multiple combinations. The receptors are expressed as a disulphide bond in the extracellular domain of their constituent subunits. The receptors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinational diversity results, within the nervous system, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues.

The potential diversity of serotonin (5-HT) receptors is increased by the expression of 5-HT receptors in the presence of different transcriptional start sites has been reported. The 5-HT receptors are expressed in multiple combinations. The receptors are expressed as a disulphide bond in the extracellular domain of their constituent subunits. The receptors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinational diversity results, within the nervous system, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues.

The potential diversity of serotonin (5-HT) receptors is increased by the expression of 5-HT receptors in the presence of different transcriptional start sites has been reported. The 5-HT receptors are expressed in multiple combinations. The receptors are expressed as a disulphide bond in the extracellular domain of their constituent subunits. The receptors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinational diversity results, within the nervous system, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues.

The potential diversity of serotonin (5-HT) receptors is increased by the expression of 5-HT receptors in the presence of different transcriptional start sites has been reported. The 5-HT receptors are expressed in multiple combinations. The receptors are expressed as a disulphide bond in the extracellular domain of their constituent subunits. The receptors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinational diversity results, within the nervous system, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues.
3-HT3 receptors. The receptors are not selective for 5-HT, 294 or orthologues of the 5-HT3 receptor. HTR3B receptors are not subject to allosteric modulation by extracellular divalent cations and are not significantly affected by the H3 blocker TMB-8. Similarly, H3 receptors, α2 receptors, and other 5-HT receptors in other species are not subject to allosteric modulation by extracellular divalent cations. In contrast, H3 receptors in homologous species in the guinea-pig 5-HT3 receptor-oligomeric assemblies of the human 5-HT3 receptor are subject to allosteric modulation by extracellular divalent cations.

**Functional Characteristics**

- **Relative permeability to divalent cations:** $\gamma = 0.4 - 0.8 \text{ pS}$
- **Inwardly rectifying current:** $\gamma = 0.4 - 0.8 \text{ pS}$
- **Rectifying current:** $\gamma = 0.4 - 0.8 \text{ pS}$
- **Relative permeability to $\text{H}^+,$ relative permeability to $\text{Cl}^-$:** $\gamma = 0.4 - 0.8 \text{ pS}$

**Selectivity**

- **Selective antagonists:** palonosetron, SR57227A, meta-2-methyl-5-HT, ginkgolide B, bilobalide, picrotoxinin, mefloquine, varenicline, several general anaesthetics, and 5-hydroxy- and halide-anti-malarial drugs.

**Quantitative data refer to homomeric 5-HT3B receptors**

- **$K_i$ (pIC$\text{H}^+$):** $\sim 9$ (pIC$\text{H}^+$)
- **$K_i$ (pIC$\text{Cl}^-$):** $\sim 26$ (pIC$\text{Cl}^-$)
- **$K_i$ (pIC$\gamma$):** $\sim 26$ (pIC$\gamma$)
- **$K_i$ (pIC$\text{H}^+$):** $\sim 26$ (pIC$\text{H}^+$)
- **$K_i$ (pIC$\text{Cl}^-$):** $\sim 26$ (pIC$\text{Cl}^-$)
- **$K_i$ (pIC$\gamma$):** $\sim 26$ (pIC$\gamma$)

**Subunits**

- **H3 receptors:** H3 receptors, α2 receptors, and other 5-HT receptors in other species are not subject to allosteric modulation by extracellular divalent cations.
Acid-sensing (proton-gated) ion channels (ASICs)

Overview of ASIC proteins and channels

Ligands

<table>
<thead>
<tr>
<th>Channel blockers</th>
<th>Channel activators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylisopropylamiloride</td>
<td>A-317567</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td>Nafamostat</td>
<td>A-317567</td>
</tr>
<tr>
<td>Benzamil</td>
<td>Cadmium</td>
</tr>
<tr>
<td>Amiloride</td>
<td>A-317567</td>
</tr>
</tbody>
</table>

Pharmacology

Acid-sensing (proton-gated) ion channels (ASICs) are a family of cation channels that are activated by extracellular protons. They are comprised of four subunits arranged as homo- or hetero-trimers. ASIC subunits contain two transmembrane domains (TM domains) and are involved in a variety of cellular processes, including nociception, taste, and pH sensing.

The family of ASICs includes three main members: ASIC1 (DRASIC, TNaC1), ASIC2 (BNaC1), and ASIC3 (DRASIC, TNaC1). ASIC1 and ASIC2 are highly expressed in sensory neurons, where they are involved in pain perception and nociception. ASIC3 is predominantly expressed in epithelial cells, immune cells, and photoreceptors.

ASICs are activated by extracellular protons, and their sensitivity to pH changes is a key characteristic. The pH range for activation of ASICs is typically between 5.5 and 7.0, with ASIC1 having a lower pH threshold compared to ASIC2 and ASIC3.

The regulation of ASIC expression and activity is complex and involves multiple mechanisms, including transcriptional regulation, post-translational modifications, and phosphorylation. The interaction of ASICs with other proteins, such as GRK2, also plays a role in their regulation.

The pharmacology of ASICs is extensive, and a variety of compounds have been identified as ligands for these channels. These ligands can be divided into channel activators, such as histamine, and channel blockers, such as amiloride and benzamil. The specificity of these ligands and their effects on ASIC function are important considerations in the development of therapeutic strategies for various diseases, including pain, inflammation, and neurodegenerative conditions.

 ASICs couple to both transient and sustained acid-sensitive proton-gated channels.

### Functional Characteristics

- **ASIC1a**
  - **Channel conductance:** 
    - **Transient component:** 14 pS (at pH 7.4)
    - **Sustained component:** 14 pS (at pH 7.4)
  - **Activation:**
    - **pH dependence:** 
      - Transient component: pH 7.4, pIC50 = 19
      - Sustained component: pH 7.4, pIC50 = 29
  - **Inactivation:**
    - **pH dependence:** 
      - Transient component: pH 7.2, pIC50 = 34
      - Sustained component: pH 7.4, pIC50 = 34
  - **Sensitivity to blockers:**
    - **pEC50:** 
      - **A-317567:** 3.6
      - **50 µM salicylic acid:** 4.4
      - **300 µM nafamostat:** 4.2
  - **Sensitivity to activators:**
    - **pIC50:** 
      - **300 µM dihydroxyphenylalanine (DOPA):** 5.2
      - **100 µM ATP:** 5.2
      - **300 µM histamine:** 5.2
      - **100 µM bradykinin:** 5.2

- **ASIC1b**
  - **Channel conductance:** 19 pS (at pH 7.4)
  - **Activation:**
    - **pH dependence:** pH 7.4, pIC50 = 19
  - **Inactivation:**
    - **pH dependence:** pH 7.4, pIC50 = 29
  - **Sensitivity to blockers:**
    - **pEC50:** 
      - **A-317567:** 3.6
      - **50 µM salicylic acid:** 4.4
      - **300 µM nafamostat:** 4.2

- **ASIC2a**
  - **Channel conductance:** 10 pS (at pH 7.4)
  - **Activation:**
    - **pH dependence:** pH 7.4, pIC50 = 19
  - **Sensitivity to blockers:**
    - **pEC50:** 
      - **A-317567:** 3.6
      - **50 µM salicylic acid:** 4.4
      - **300 µM nafamostat:** 4.2

- **ASIC2b**
  - **Channel conductance:** 16 pS (at pH 7.4)
  - **Activation:**
    - **pH dependence:** pH 7.4, pIC50 = 19
  - **Sensitivity to blockers:**
    - **pEC50:** 
      - **A-317567:** 3.6
      - **50 µM salicylic acid:** 4.4
      - **300 µM nafamostat:** 4.2

- **ASIC3**
  - **Channel conductance:** 5 pS (at pH 7.4)
  - **Activation:**
    - **pH dependence:** pH 7.4, pIC50 = 19
  - **Sensitivity to blockers:**
    - **pEC50:** 
      - **A-317567:** 3.6
      - **50 µM salicylic acid:** 4.4
      - **300 µM nafamostat:** 4.2
Epithelial sodium channels (ENaC)

Further reading on Epithelial sodium channels (ENaC)

ENaC subunits

<table>
<thead>
<tr>
<th>Subunits</th>
<th>NOMC</th>
<th>HGNC</th>
<th>UniProt</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENaC αβγ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENaC αβΔγ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENaC αδγ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENaC αβδ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENaC αγδ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENaC βγδ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Functional Characteristics

- ENaC α, β, and γ subunits form the functional channel.
- The α subunit is responsible for channel activity.
- The β and γ subunits modulate channel activity.
- ENaC activation is regulated by phosphorylation and deubiquitylation.
- ENaC is activated by cAMP-dependent protein kinases (PKA).
- ENaC is inhibited by protein phosphatases (PP1 and PP2A).
- ENaC activation is also regulated by the mineralocorticoid receptor (MR) and the angiotensin II type 1 receptor (AT1).
- ENaC activation is inhibited by the angiotensin-converting enzyme (ACE) inhibitor, enalapril.

Activators

<table>
<thead>
<tr>
<th>Compound</th>
<th>pIC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamterene</td>
<td>6.7–7</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>8</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Channel blockers

<table>
<thead>
<tr>
<th>Compound</th>
<th>pEC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>5.9</td>
</tr>
<tr>
<td>ASIC1</td>
<td>5.3</td>
</tr>
<tr>
<td>ASIC2</td>
<td>5.0</td>
</tr>
<tr>
<td>ASIC3</td>
<td>4.9</td>
</tr>
<tr>
<td>ASIC4</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Nomencature

- ENaC refers to the epithelial sodium channel.
- SCNN1A, SCNN1B, SCNN1C, SCNN1D, SCNN1E, SCNN1F, SCNN1G, SCNN1H, SCNN1I, SCNN1J, SCNN1K, SCNN1L, SCNN1M, SCNN1N, SCNN1O, SCNN1P, SCNN1Q, SCNN1R, SCNN1S, SCNN1T, SCNN1U, SCNN1V, SCNN1W, SCNN1X, SCNN1Y, SCNN1Z are the genes encoding the ENaC subunits.

Nomenclature links to HGNC and UniProt databases.
The GABA receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_{3} and serotonin 3A receptors. GABA receptors and their subunits are identified (,) and have sometimes been termed GABA receptors by NC-IUPHAR. The three α-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed GABA-receptor isoforms in detail; such information can be gleaned in the reviews (). GABA binding occurs at the GABA-A site, whereas the homologous GABA-π site mediates a tonic current that is important for neuronal excitability in response to ambient concentrations of GABA (). The three α-subunits that form the GABA-A receptor are α1, α2, and α3. The three β-subunits are β1, β2, and β3. The three δ-subunits are δ1, δ2, and δ3. The three ϵ-subunits are ϵ1, ϵ2, and ϵ3. The three γ-subunits are γ1, γ2, and γ3. The three θ-subunits are θ1, θ2, and θ3. The three ρ-subunits are ρ1, ρ2, and ρ3.

The GABA-A receptor is a tetrameric assembly of six α-, β-, δ-, and ϵ-subunits in the CNS, followed by alternate assemblies of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_{3}, and serotonin 3A receptors in the periphery. The three α-subunits that form the GABA-A receptor are α1, α2, and α3. The three β-subunits are β1, β2, and β3. The three δ-subunits are δ1, δ2, and δ3. The three ϵ-subunits are ϵ1, ϵ2, and ϵ3. The three γ-subunits are γ1, γ2, and γ3. The three θ-subunits are θ1, θ2, and θ3. The three ρ-subunits are ρ1, ρ2, and ρ3.

The GABA-A receptor is a tetrameric assembly of six α-, β-, δ-, and ϵ-subunits in the CNS, followed by alternate assemblies of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_{3}, and serotonin 3A receptors in the periphery. The three α-subunits that form the GABA-A receptor are α1, α2, and α3. The three β-subunits are β1, β2, and β3. The three δ-subunits are δ1, δ2, and δ3. The three ϵ-subunits are ϵ1, ϵ2, and ϵ3. The three γ-subunits are γ1, γ2, and γ3. The three θ-subunits are θ1, θ2, and θ3. The three ρ-subunits are ρ1, ρ2, and ρ3.

The GABA-A receptor is a tetrameric assembly of six α-, β-, δ-, and ϵ-subunits in the CNS, followed by alternate assemblies of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_{3}, and serotonin 3A receptors in the periphery. The three α-subunits that form the GABA-A receptor are α1, α2, and α3. The three β-subunits are β1, β2, and β3. The three δ-subunits are δ1, δ2, and δ3. The three ϵ-subunits are ϵ1, ϵ2, and ϵ3. The three γ-subunits are γ1, γ2, and γ3. The three θ-subunits are θ1, θ2, and θ3. The three ρ-subunits are ρ1, ρ2, and ρ3.

The GABA-A receptor is a tetrameric assembly of six α-, β-, δ-, and ϵ-subunits in the CNS, followed by alternate assemblies of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_{3}, and serotonin 3A receptors in the periphery. The three α-subunits that form the GABA-A receptor are α1, α2, and α3. The three β-subunits are β1, β2, and β3. The three δ-subunits are δ1, δ2, and δ3. The three ϵ-subunits are ϵ1, ϵ2, and ϵ3. The three γ-subunits are γ1, γ2, and γ3. The three θ-subunits are θ1, θ2, and θ3. The three ρ-subunits are ρ1, ρ2, and ρ3.
A GABA receptor

A GABA receptor is a model of a G-protein coupled receptor in the neocortical pyramidal projection of the cerebral cortex. It is the major inhibitory neurotransmitter in the central nervous system and plays a crucial role in the regulation of neuronal activity and synaptic plasticity.

GABA (gamma-aminobutyric acid) is the primary inhibitory neurotransmitter in the mammalian central nervous system. It is synthesized from glutamate in astrocytes and released from neurons. GABA receptors are ligand-gated chloride channels that allow the entry of chloride ions, hyperpolarizing the postsynaptic membrane and inhibiting neuronal firing.

There are three main classes of GABA receptors:

1. **GABA_A receptors** (α5 subunit γδ subunits, incorporation of a β and α subunits, formation from binary combinations of γ or δ subunits, incorporation of a β and α subunits, formation from binary combinations of γ or δ subunits)
2. **GABA_B receptors** (α subunit γδ subunits, incorporation of a β and α subunits, formation from binary combinations of γ or δ subunits, incorporation of a β and α subunits, formation from binary combinations of γ or δ subunits)
3. **GABA_C receptors** (α subunit γδ subunits, incorporation of a β and α subunits, formation from binary combinations of γ or δ subunits, incorporation of a β and α subunits, formation from binary combinations of γ or δ subunits)

Each class of GABA receptor is further divided into subtypes based on the composition of their subunits. The GABA_A receptor, for example, is composed of five subunits (α1-5 and β1-3) and forms a pentameric channel with a large central pore.

### Ligand-gated ion channels

GABA receptors can be activated by a variety of ligands, including:

- **Agonists**
  - GABA itself
  - Other GABA analogues
- **Antagonists**
  - Flunitrazepam
  - Zolpidem
- **Modulators**
  - Flumazenil
  - ZK93426

### Endogenous Allosteric Regulators

- **Zn**
- **picrotoxin**
- **TBPS**
- **tetrahydrodeoxycorticosterone**

### Channel Blockers

- **GABAA receptor blockers**
- **GABAA receptor activators**
- **GABAA receptor modulators**

### Nomenclature

- **A** 2s subunit α receptor
- **A** 4s subunit α receptor
- **A** 3s subunit GABA α receptor

### Comments

GABA receptors are crucial for the regulation of brain function and are implicated in various neurological disorders, including epilepsy, anxiety, and depression.

### References

- British Journal of Pharmacology
GABA receptors

Concise Guide to Pharmacology 2017/18: Ligand-gated ion channels.


Full Text of ConciseGuide:

A receptors

Benzodiazepine site

RY024 (Inverse agonist), RO4938581 (Inverse agonist), MRK016 (Partial agonist), agonist), Ro15-4513 (Inverse agonist), 5IA α (Inverse agonist), 50 DMCM (Inverse agonist), 3IA α, 58 (Positive) (pEC 8.3) [K]

Bretazenil, 159 6.8) [K]

Alprazolam, 137 8.3) [K]

Flunitrazepam, 159 9.2) [K]

Flumazenil, 35 (Inhibition), Zn 2+ (Potentiation), Zn 2+ -ol-20-one α -pregnan-3α 5α

Picrotoxin, TBPS

GABRA6, GABRA5, P31644, Q16445

Agonists

GABA

Selective antagonists

Isonipecotic acid, piperidine-4-sulphonic acid, isoguvacine, gaboxadol, muscimol

Selective agonists – [GABA site] (low efficacy)
Piperidine-4-sulphonic acid, isoguvacine, gaboxadol

GABA

Channel blockers

GABA

Selective modulators

Q16445, GABRA6, GABRA5, P31644, Q16445

Nomenclature

(continued)
Nomenclature

**GABA**

- **α-subunits:**
  - **α5:**
  - **α6:**

- **β-subunits:**
  - **β1:**
  - **β2:**
  - **β3:**

- **γ-subunits:**
  - **γ1:**
  - **γ2:**
  - **γ3:**

**Channel blockers:**

- TBPS
- Picrotoxin

**Allosteric modulators:**

- Etazolate

**Comments**

- Zn²⁺ is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits; incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively.[208]

**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

<table>
<thead>
<tr>
<th>Subunit</th>
<th>HGNC, UniProt</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>GABRD, O14764</td>
</tr>
<tr>
<td>ϵ</td>
<td>GABRE, P78334</td>
</tr>
<tr>
<td>θ</td>
<td>GABRQ, Q9UN88</td>
</tr>
<tr>
<td>π</td>
<td>GABRP, O00591</td>
</tr>
</tbody>
</table>

**Selective agonists**

- Gaboxadol
- Isoguvacine
- Muscimol

**Selective antagonists**

- (±)-cis-2-CAMP
- 5-Me-IAA

**Channel blockers**

- TBPS
- Picrotoxin

**Comments**

- Zn²⁺ is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively.

- Bicuculline is not active at this subunit.

- Alpha sodium.

- Bicuculline is not active at this subunit.

- Aza-THIP is not active at this subunit.

- Neuropeptide Y.

- Endogenous hormone.

- Neuropeptide Y.
Glycine receptors

α2β3δ α2β6 α3-splicing of the primary gene transcripts for α1-subunit also anchors the receptor protein that binds to a number of subsynaptic proteins involved in receptor trafficking, the kinetics of native and recombinant glycine receptors by association with domains within the large intracellular loop of the α2-subunit.

Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors. Four differentially expressed isoforms of the glycine receptor array of natural products including flavonoid and terpenoid derivatives such as mefenamic acid, etomidate, and furosemide have been identified.

Anchored in the N-terminal domain of the α2-subunit are multiple sites for positive allosteric modulation by anaesthetic and non-anaesthetic compounds. Modulators of GABA receptors (reviewed in [139]) may be consequence of the unusually low Ca2+ sensitivity of some glycine receptors versus receptors in which the δ3-subunit replaces the β3-subunit.

The influence of the α1-subunit on agonist sensitivity isoflurane and alcohol also involve the δ2-subunit. Phosphorylation of receptor-specific residues may be a mechanism for the down-regulation of GABA receptors by the etomidate derivative, stiripentol fragrent dioxane derivatives.

The influence of the δ2-subunit on agonist sensitivity isoflurane and alcohol also involve the δ2-subunit. Phosphorylation of receptor-specific residues may be a mechanism for the down-regulation of GABA receptors by the etomidate derivative, stiripentol fragrent dioxane derivatives.
Glycine receptors

- Glycine (when co-expressed with the δ1 subunit)
- Taurine (when co-expressed with the δ1 subunit)
- α-glycine (when co-expressed with the δ1 subunit)
- GABAB agonist X (when co-expressed with the GABAB receptor β2 subunit)
- δ1 subunit (when co-expressed with the δ1 subunit)

- HCN, HRG

Noradrenaline

β-arylethylamine

- Potentiation (pIC50 6.6),
- Inhibition (pIC50 5.6),
- Allosteric modulators

- HCN channel blockers
- HCN modulators

- S.P.H. Alexander

2017 174, S130–S159

Journal of Pharmacology

Further reading on glycine receptors

Companies

Ligand-gated ion channels

Endogenous ligands

Glycine receptor allosteric activators

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor allosteric inhibitors

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor channel blockers

atropine, piperidine, tropisetron (ICS 205-930)

Comments

Channel blockers

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor allosteric activators

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor allosteric inhibitors

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor channel blockers

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor allosteric activators

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor allosteric inhibitors

atropine, piperidine, tropisetron (ICS 205-930)

Glycine receptor channel blockers

atropine, piperidine, tropisetron (ICS 205-930)
Ionotropic glutamate receptors

S. P. H. Alexander

Full Contents of Concise Guide: http://www.guidetopharmacology.org/index.jsp


Ionotropic glutamate receptors

S145

Full Contents of Concise Guide:

http://www.guidetopharmacology.org/index.jsp

Searchable database:

Full Contents of Concise Guide:

http://www.guidetopharmacology.org/index.jsp

Ionotropic glutamate receptors

S145


Ionotropic glutamate receptors

S145
### Nomenclature

<table>
<thead>
<tr>
<th>GluA1</th>
<th>GluA2</th>
<th>GluA3</th>
<th>GluA4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allosteric modulators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY392098 (Positive) (pEC(_{50}) 5.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY404187 (Positive) (pEC(_{50}) 5.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclothiazide (Positive) (pEC(_{50}) 4.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CX516 (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CX546 (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDRA-21 (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY503430 (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S18986 (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aniracetam (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>piracetam (Positive)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Labelled ligands

| \[^{3}H\]AMPA (Agonist) |
| \[^{3}H\]CNQX (Antagonist) |

### Comments

Also blocked by intracellular polyamines.

### Endogenous agonists

| dysiherbaine \[^{3}H\] – Rat |
| SYM2081 \[^{3}H\] – Rat |
| kainate \[^{3}H\] – Rat |
| \((S)-4-AHCP\) |
| \((S)-5-iodowillardiine\) |
| 8-deoxy-neodysiherbaine |
| ATPA |
| domoic acid |

### Selective agonists

| LY339434 |

### Selective antagonists

| 2,4-epi-neodysiherbaine |
| ACET |
| \[^{3}H\]AMPA (Agonist) |
| SYM2081 (low potency) |
| kainate |
| dysiherbaine |

### Allosteric modulators

| concanavalin A (Positive) |
| concanavalin A (Positive) |

### Searchable database:

http://www.guidetopharmacology.org/index.jsp

---

**Ionotropic glutamate receptors S146**

Ionotropic glutamate receptors

Full Contents of Concise Guide: http://www.guidetopharmacology.org/index.jsp

Searchable database: [site] (Partial agonist)

<table>
<thead>
<tr>
<th>GluN2C</th>
<th>partial agonist at GluN2A and GluN2C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GluN2B</td>
<td>partial agonist at GluN2A and GluN2C</td>
<td></td>
</tr>
<tr>
<td>GluN2D</td>
<td>partial agonist at GluN2A and GluN2C</td>
<td></td>
</tr>
</tbody>
</table>

GluN2A ≥ GluN2D ≥ GluN2A

Homoquinolinic acid [glutamate site] (GluN2A), [glutamate site] (GluN2B), [glycine site] (GluN2D)-(tetrazol-5-yl)glycine RS, (+)-HA966, O15399, Q14957, [glycine site] (GluN2A)

GluN2B ≥ GluN2C ≥ GluN2C ≥ GluN2A

NMDA receptors containing GluN1 and GluN2 subunits require the expression of NMDA receptors as obligate heteromers that may be drawn from GluN1, GluN2, GluN3 and GluN4 subunits. Alternative splicing can generate eight isoforms of GluN1 with differing pharmacological properties. Various splice variants of GluN2B, such that the GluN2 subunit and glycine to S1 and S2 regions of the GluN1 subunit.

The Concise Guide to PHARMACOLOGY 2017/18: Ligand-gated ion channels.

Ionotropic glutamate receptors

See the main comments section below for information on the pharmacology of GluN3A and GluN3B subunits.

O60391, GRIN3B, Q8TCU5, GRIN3A

HGNC, UniProt

Nomenclature

[glycine site] (Agonist) $\text{H}[^{3}\text{H} \text{glycine}]$

[cation channel] (Antagonist), $\text{H}[^{3}\text{H} \text{dizocilpine}]$

[3glycine site] (Antagonist), $\text{H}[^{3}\text{H} \text{L689560}]$

[3glutamate site] (Selective Antagonist), $\text{H}[^{3}\text{H} \text{CPP}]$

[3glycine site] (Agonist) $\text{H}[^{3}\text{H} \text{glycine}]$

[cation channel] (Channel blocker), $\text{H}[^{3}\text{H} \text{dizocilpine}]$

[3glycine site] (Antagonist), $\text{H}[^{3}\text{H} \text{CGP61594}]$

[3glycine site] (Antagonist), $\text{H}[^{3}\text{H} \text{MDL105519}]$

[3glycine site] (Antagonist), $\text{H}[^{3}\text{H} \text{CGS19755}]$

[3glutamate site] (Antagonist), $\text{H}[^{3}\text{H} \text{CGP39653}]$

(GluN2C = GluN2D, $\geq 50\mu M$)

(GluN2A = GluN2B, $> 50\mu M$)

(GluN2C = GluN2D, $\geq 6.2$)

(GluN2A, $6.2$)

(GluN2C = GluN2D, $\geq 4.7$)

(GluN2A, $50\mu M$, $96\mu M$)

(GluN2C = GluN2D, $\geq 8.5$)

(GluN2A, $8.5$)

(GluN2C = GluN2D, $\geq 8.1$)

(GluN2A, $8.1$)

(GluN2C = GluN2D, $> 5.7$)

(GluN2A, $5.7$)

(GluN2C = GluN2D, $> 5.0$)

(GluN2A, $5.0$)

(GluN2C = GluN2D, $> 4.7$)

(GluN2A, $4.7$)

(GluN2C = GluN2D, $> 4.4$)

(GluN2A, $4.4$)

(GluN2C = GluN2D, $> 4.0$)

(GluN2A, $4.0$)

(GluN2C = GluN2D, $> 3.6$)

(GluN2A, $3.6$)

(GluN2C = GluN2D, $> 3.1$)

(GluN2A, $3.1$)

(GluN2C = GluN2D, $> 2.6$)

(GluN2A, $2.6$)

(GluN2C = GluN2D, $> 2.1$)

(GluN2A, $2.1$)

(GluN2C = GluN2D, $> 1.6$)

(GluN2A, $1.6$)

(GluN2C = GluN2D, $> 1.1$)

(GluN2A, $1.1$)

(GluN2C = GluN2D, $> 0.6$)

(GluN2A, $0.6$)

(GluN2C = GluN2D, $> 0.1$)

(GluN2A, $0.1$)

(GluN2C = GluN2D, $> 0.0$)

(GluN2A, $0.0$)

Channel blockers –

antagonists

Selective

conantokin-G

dansyl-spermine

N-phencyclidine

ketamine
ionotropic glutamate receptors

Further reading on Ionotropic glutamate receptors

Further reading on Ionotropic glutamate receptors

Conduction of electrical signals between nerve cells depends on the activation of ionotropic glutamate receptors (iGluRs). These receptors are ligand-gated ion channels that respond to the binding of glutamate or other agonists, allowing the flow of ions through the cell membrane. iGluRs are classified into three main subtypes: NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and kainate receptors.

NMDA receptors are characterized by a requirement for glutamate and a co-agonist, such as glycine in the case of GluN1/GluN2B heteromers. These receptors are voltage-dependent and allow the influx of Ca\(^{2+}\) ions, which is essential for neurotransmitter release.

AMPA receptors are ligand-gated ion channels that respond to the binding of glutamate or other agonists. They play a crucial role in fast excitatory transmission and are involved in various physiological processes, including learning and memory.

Kainate receptors are another type of iGluR that are activated by kainic acid and other agonists. These receptors are found in both the CNS and PNS and are involved in a variety of functions, including pain transmission and learning.

Inhibitory modulatory sites exist for Mg\(^{2+}\) in the functional antagonism of heterooligomers of GluN1 and GluN3A by Zn\(^{2+}\). However, GluN2B subunits bind glycine and a "orphan" class of ionotropic glutamate receptor subunit. They activate such complexes. The co-expression of GluN1, GluN3A, and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts.

The ATD GluN1/GluN2B receptor antagonists are competitive, non-competitive, antagonists of heterooligomers incorporating GluN2B and GluN2D subunits and display selectivity for GluN2B over GluN2A subunit combinations with other ionotropic glutamate receptor subunits. Inclusion of GluN3B in tri-heteromers leads to a competitive antagonist action at kainate receptors comprising GluK1 subunits.

Voltage-independent inhibition by Zn\(^{2+}\) is achieved with polyamines and the inclusion of exon 5 within the ATD GluN1 subunit splice variants, whereas the non-competitive antagonists by Mg\(^{2+}\) and reduced permeability to Ca\(^{2+}\) are preserved following the inclusion of GluN3B in tri-heteromers.

The relative affinity within the ATD is highly subunit selective (GluN2A > GluN2C > GluN2B >> GluN2D).

Further reading on Ionotropic glutamate receptors

Conduction of electrical signals between nerve cells depends on the activation of ionotropic glutamate receptors (iGluRs). These receptors are ligand-gated ion channels that respond to the binding of glutamate or other agonists, allowing the flow of ions through the cell membrane. iGluRs are classified into three main subtypes: NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and kainate receptors.

NMDA receptors are characterized by a requirement for glutamate and a co-agonist, such as glycine in the case of GluN1/GluN2B heteromers. These receptors are voltage-dependent and allow the influx of Ca\(^{2+}\) ions, which is essential for neurotransmitter release.

AMPA receptors are ligand-gated ion channels that respond to the binding of glutamate or other agonists. They play a crucial role in fast excitatory transmission and are involved in various physiological processes, including learning and memory.

Kainate receptors are another type of iGluR that are activated by kainic acid and other agonists. These receptors are found in both the CNS and PNS and are involved in a variety of functions, including pain transmission and learning.

Inhibitory modulatory sites exist for Mg\(^{2+}\) in the functional antagonism of heterooligomers of GluN1 and GluN3A by Zn\(^{2+}\). However, GluN2B subunits bind glycine and a "orphan" class of ionotropic glutamate receptor subunit. They activate such complexes. The co-expression of GluN1, GluN3A, and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts.

The ATD GluN1/GluN2B receptor antagonists are competitive, non-competitive, antagonists of heterooligomers incorporating GluN2B and GluN2D subunits and display selectivity for GluN2B over GluN2A subunit combinations with other ionotropic glutamate receptor subunits. Inclusion of GluN3B in tri-heteromers leads to a competitive antagonist action at kainate receptors comprising GluK1 subunits.

Voltage-independent inhibition by Zn\(^{2+}\) is achieved with polyamines and the inclusion of exon 5 within the ATD GluN1 subunit splice variants, whereas the non-competitive antagonists by Mg\(^{2+}\) and reduced permeability to Ca\(^{2+}\) are preserved following the inclusion of GluN3B in tri-heteromers.

The relative affinity within the ATD is highly subunit selective (GluN2A > GluN2C > GluN2B >> GluN2D).
Overview: The inositol 1,4,5-trisphosphate receptor (IP$_3$R) is a ligand-gated Ca$^{2+}$-release channel located on intracellular Ca$^{2+}$ store sites (such as the endoplasmic reticulum). They are responsible for the mobilization of intracellular Ca$^{2+}$ stores and play an important role in intracellular Ca$^{2+}$ signalling in a wide variety of cell types. Three different gene products (types I–III) have been isolated, which assemble as large tetrameric structures. IP$_3$Rs are closely associated with certain proteins: calmodulin (CALM1, CALM2, CALM3), FKBP (and calcineurin via FKBP) and are phosphorylated by PKA, PKC, PKG and CaMKII.

Functional Characteristics: Ca$^{2+}$: single-channel conductance $\approx 70$ pS (50 mM Ca$^{2+}$), $\approx 390$ pS (220 mM Cs$^+$).

Comments: IP$_3$R1 is also antagonised by calmodulin at high cytosolic Ca$^{2+}$ concentrations.

Further reading:
- Mak, DO et al. (2015) Inositol 1,4,5-trisphosphate receptors in the endoplasmic reticulum: As single-channel point of view. Cell Calcium 58:67–78 [PMID:25555684]

Searchable database: http://www.guidetopharmacology.org/index.jsp

Nicotinic acetylcholine receptors

**S151**

**Searchable database:** [www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

- Full Contents of Concise Guide: Nicotinic acetylcholine receptors
  - http://www.guidetopharmacology.org/index.jsp

The Concise Guide to PHARMACOLOGY 2017/18: Ligand-gated ion channels.

S.P.H. Alexander
Nicotinic acetylcholine receptors

<table>
<thead>
<tr>
<th>Subunit Combination</th>
<th>Agonist</th>
<th>Antagonist</th>
<th>Channel Blocker</th>
<th>Allosteric Modulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>αβδε</td>
<td>[H]nicotine</td>
<td>[H]epibatidine</td>
<td>gallamine</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>[H]cytisine</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>[H]bungarotoxin</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>[H]tubocurarine</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>NS9283</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>NS1738</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>A-867744</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>αβδε</td>
<td>PNU-282987</td>
<td>[H]epibatidine</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Functional Characteristics:
- 3% Na⁺: (αβδε) = 0.5–3.0%
- 0% Na⁺: (αβδε) = 0.6–3.0%
- 1.5–2.9%
- 2.9%

Allosteric Modulators:
- nicotinic acetylcholine receptor αδ subunit
- nicotinic acetylcholine receptor αβδ subunit
- nicotinic acetylcholine receptor αδε subunit
- nicotinic acetylcholine receptor αβδε subunit

Nomenclature:
- Nicotinic acetylcholine receptor αβδε subunit
- Nicotinic acetylcholine receptor αβδε subunit
- Nicotinic acetylcholine receptor αβδε subunit
- Nicotinic acetylcholine receptor αβδε subunit

Searchable database:
- HGNC, UniProt

Allosteric modulators:
- (+) chimeric
- (+) chimeric
- (+) chimeric
- (+) chimeric

Channel blockers:
- (-) conotoxin MII
- (-) conotoxin MII
- (-) conotoxin MII
- (-) conotoxin MII

Selective antagonists:
- P36544
- P36544
- P36544
- P36544
Nicotinic acetylcholine receptors

Searchable database: http://www.guidetopharmacology.org/index.jsp


Continued

Nomenclature

nicotinic acetylcholine receptor

α5 subunit nicotinic acetylcholine receptor

α6 subunit nicotinic acetylcholine receptor

α7 subunit

Selective allosteric modulators

JNJ1930942 (Positive)

PNU-120596 (Positive)

Labelled ligands

[3H]epibatidine (Agonist) – Chicken,

[125I]α-conotoxin MII (Antagonist)

[3H]epibatidine (Agonist),

[3H]A-585539 (Agonist)

[3H]AZ11637326 (Agonist)

[125I]α-bungarotoxin (Selective Antagonist) (pKd 8.3–9.1),

[3H]α-bungarotoxin (Selective Antagonist) (pKd 8.3–9.1),

[3H]methyllycaconitine (Antagonist) (pKd 8.7)

Functional Characteristics –

PCa/PNa = 6.6–20,

Pf = 8.8–11.4%
P2X receptors

Overview

Ligand-gated ion channels

Key features of P2X receptors

Expression and function

Structure

Antagonists

Actives

Alternative names

Further reading

References

P2X receptors

Biochemical Pharmacology

Molecular Pharmacology

Neuropharmacology

Others

Ligand-gated ion channels

P2X receptors

The Concise Guide to PHARMACOLOGY 2017/18: Ligand-gated ion channels.

S.P.H. Alexander
Several P2X receptors (particularly P2X1 and P2X3) may be inhibited in a non-competitive manner by the protein kinase \[H]A317491. The P2X7 receptor may be inhibited that at P2X1 receptors. Antagonist potency of A839977, A804598, NF023, and NF449 are non-selective antagonists at rat and human P2X1–3 and P2X4, but not rP2X4,6,7. Agonists listed show selectivity within recombinant P2X receptors. Examples include A740003, A839977, and A317491. Comment: A740003 and A317491 block the P2X2-2X3-2X5-inhibitory effects.
Further reading on ZAC receptors


Peralta, FA et al. (2016) Zinc as allosteric channel modulator: Ionotropic receptors as metalloproteins. Int J Mol Sci 17:[PMID:27384555]


Searchable database: http://www.guidetopharmacology.org/index.jsp
