Chapter 8

# Antiepileptic Drug Targets: An Update on Ion Channels

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Additional information is available at the end of the chapter

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**Abstract**

Different mechanisms of action have been proposed to explain the effects of antiepileptic drugs (AEDs) including modulation of voltage-dependent sodium calcium and potassium channels, enhancement of γ-aminobutyric acid (GABA)-mediated neuronal inhibition, and reduction in glutamate-mediated excitatory transmission. Recent advances in understanding the physiology of ion channels and genetics basis of epilepsies have given insight into various molecular targets for AEDs. Conventional AEDs predominantly target voltage- and ligand-gated ion channels including the $\alpha$ subunits of voltage-gated $Na^+$ channels, T-type, and $\alpha_2$-δ subunits of the voltage-gated $Ca^{2+}$ channels, A- or M-type voltage-gated $K^+$ channels, the γ-aminobutyric acid (GABA) receptor channel complex, and ionotropic glutamatergic receptors. Molecular cloning of ion channel subunit proteins and studies in epilepsy models suggest additional targets including hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel subunits, responsible for hyperpolarization-activated current ($I_h$), voltage-gated chloride channels, and acid-sensing ion channels. This chapter gives an update on voltage- and ligand-gated ion channels, discussing their structures, functions, and relevance as potential targets for AEDs.

**Keywords:** epilepsy, antiepileptics, voltage-gated ion channels, ligand-gated ion channels

## 1. Introduction

Epilepsy is one of the most common neurological disorders characterized by recurrent and repeated seizures that vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Between 1 and 3% of the World's population suffers from epilepsy [1],

making it the most prevalence neurological disorder. This debilitating neurological disorder may either be symptomatic of various disorders (e.g., malformative, vascular, infectious, traumatic, metabolic, or tumoral conditions) or idiopathic, which is unrelated to any underlying cause other than a possible hereditary predisposition [2].

The etiology of epilepsy is not fully understood; however, an abnormality of potassium conductance, a defect in the voltage-sensitive ion channels, or deficiency in the membrane ATPase likened to ion transport has been implicated in neuronal membrane instability and seizures [3]. Selective neurotransmitters such as glutamate, aspartate, acetylcholine, noradrenaline, histamine, corticotrophin-releasing factor, purines, peptides, cytokines, and steroid hormones enhance the excitability and propagation of neuronal activity, whereas γ-aminobutyric acid (GABA) and dopamine inhibit neuronal activity and propagation [3]. A relative deficiency of inhibitory neurotransmitters such as GABA or an increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity.

The control of abnormal neuronal activity with antiepileptic drugs (AEDs) is accomplished by elevating the threshold of neurons to electrical or chemical stimuli or by limiting the propagation of seizures discharged from its origin. The AEDs may attenuate or prevent seizures through effects on pathologically altered neurons of seizure foci or alternatively by reducing the spread of excitation from seizure foci to additional brain regions. Raising the threshold involves stabilization of neuronal membranes, whereas limiting the propagation involves reduction of nerve conduction and depression of synaptic transmission. Different mechanisms of action have been proposed to explain the clinical effects of AEDs including the modulation of voltage-dependent sodium channels, modulation of voltage-dependent calcium channels, enhancement of GABA-mediated neuronal inhibition, and reduction in glutamate-mediated excitatory transmission.

Ion channels play an important role in the pathophysiology of all forms of epilepsy, making them obvious targets for AEDs. Aberrant excitability associated with an epileptic discharge is mediated by voltage-gated and/or ligand-gated ion channels, which may be the result of defects in the function of these channels. Modern cellular neurophysiological and biochemical approaches have made it possible to identify these likely molecular targets of AEDs. This chapter gives an update on voltage- and ligand-gated ion channels, discussing their structures, functions, and relevance as potential targets for AEDs.

## 2. Voltage gated ion channels

This ion channels superfamily, which include the voltage-gated sodium, calcium, and potassium channels, represents the critical sites of action for AEDs. They comprise of 143 genes and encompass the S4 family in which the pore-forming subunits are built on six transmembrane segments (S1–S6), and the fourth segment (S4) contains a voltage-sensing element (**Figure 1**). The voltage-gated ion channels are primarily gated by changes in membrane potential, which cause movement of gating charges across the membrane and drive conformational changes that open and close the pore [4]. The detailed mechanism of voltage-dependent gating is not

well understood, but the positively charged S4 segments are thought to undergo outward and rotational movement through the protein structure during the gating process, as proposed in the sliding helix and helical screw models of gating [4].

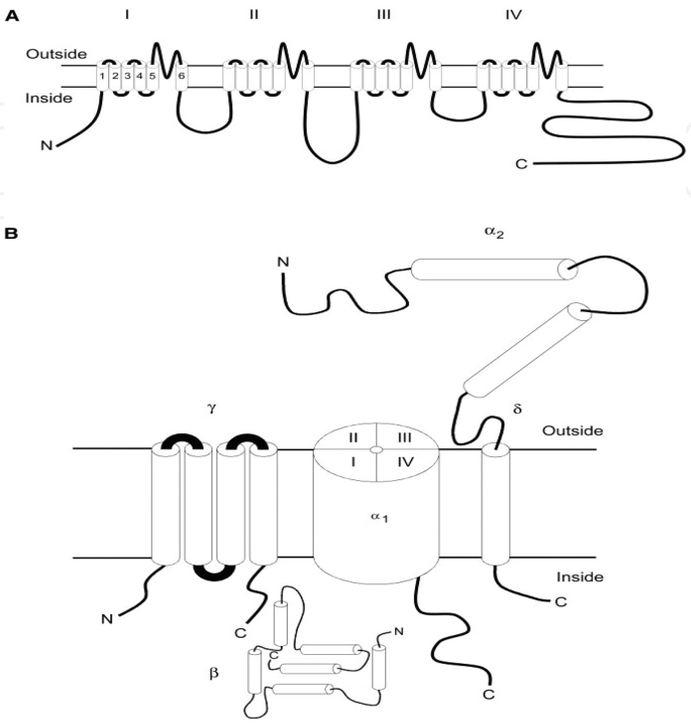


**Figure 1.** (A) The $\alpha$ subunit of voltage-gated ion channels consisting of four homologous repeats (I–IV), each with six transmembrane domains (1–6). The fourth transmembrane voltage sensor domain (4) has positively charged segments. (B) An assembled calcium channel with auxiliary (β, $\alpha$-2δ and γ) subunits. The four homologous repeats (I–IV) a1 subunit form the channel pore. The sodium channels are similar, but only has auxiliary β subunits [5].

In voltage-gated $Na^+$ and $Ca^{2+}$ channels, four domains referred to as I–IV or D1–D4 are expressed around a central pore that conducts the ionic current, while in voltage-gated $K^+$ channels, the channel is a tetramer of four individual subunits, each containing a single S1–S6 domain, which is also present in calcium-activated $K^+$ channels, cyclic-nucleotide-gated and the hyperpolarization-activated cyclic nucleotide modulated cation channels [4]. Voltage-gated ion channels also control excitability in the peripheral autonomic nervous system, the cardiovascular system and the digestive system as well as control all secretory functions including the release of hormones [6]. The voltage-gated $Na^+$, $Ca^{2+}$, and $K^+$ channels expressed in the heart are often distinct from, but closely homologous to, those expressed in the brain.

### 2.1. Voltage gated sodium channels (VGSCs)

The VGSCs are responsible for action potential initiation and propagation in excitable cells, including nerve, muscle and neuroendocrine cell types [7]. They are also expressed at low levels in nonexcitable cells where their physiological role is unclear [8]. VGSCs are heteromers composed of $\alpha$ and β subunits [9]. Four β subunits (β1–β4) have been described, and each $\alpha$ subunit is associated with one or more β subunits [10].

Nine mammalian VGSCs $\alpha$ subunits, designated $Na_v1.1$ to $Na_v1.9$, have been functionally characterized [11]. Four of these including $Na_v1.1$ (*SCN1A*), $Na_v1.2$ (*SCN2A*), $Na_v1.3$ (*SCN3A*) and $Na_v1.6$ (*SCN8A*) are predominantly expressed in the central nervous system and two—$Na_v1.7$ (*SCN9A*) and $Na_v1.8$ (*SCN10A*)—are expressed in the peripheral nervous system and dorsal root ganglia [11]. $Na_v1.4$ (*SCN4A*) and $Na_v1.5$ (*SCN5A*) are expressed in skeletal muscle and cardiac muscle, respectively, but the later is also found in some limbic neurons in the rat brain, including the peri-form cortex. $Na_v1.3$ is significantly expressed in the brain only early in development. $Na_v1.9$ (*SCN11A*) is expressed widely in the brain and spinal cord. There are four auxiliary (β) subunits ($Na_v\beta1$–$Na_v\beta4$; genes *SCN1B–SCN4B*) that can be found in association with the $\alpha$-units expressed in the brain and have an intramembrane segment and an immunoglobulin-like extracellular element [11]. Fast, transient $Na^+$ currents that generate action potentials in the mammalian brain are mediated by $Na_v1.1$, $Na_v1.2$, and $Na_v1.6$ isoforms.

VGSCs are key mediators of intrinsic neuronal and muscle excitability making the abnormal VGSCs activity central to the pathophysiology of epileptic seizures. Mutations of neuronal voltage-gated $Na^+$ channel genes are the most common known cause of familial epilepsy including generalized epilepsy with febrile seizures plus (GEFS+) type 1 and 2, severe myoclonic epilepsy of infancy, intractable childhood epilepsy with generalized tonic-clonic seizures, simple febrile seizures (FS), benign familial neonatal-infantile seizures, and benign familial infantile seizures [12].

VGSCs mediate the persistent, resurgent, or late $Na^+$ currents that may play a significant role in epilepsy and in the action of AEDs [13]. Many of the most widely used antiepileptic drugs including phenytoin, carbamazepine, and lamotrigine are inhibitors of VGSC function. AEDs produce a voltage- and use-dependent block of the channels by binding predominantly to the inactivated state of the channels, thus suppressing high-frequency, repetitive action potential firing [14]. The downstream effect may reduce action potential-dependent synaptic neurotransmitter release during the high-frequency firing that occurs with epileptic discharges [15]. Some $Na^+$ channel blocking AEDs may preferentially inhibit glutamate release as a result of selective interactions with $Na^+$ channels that are located on presynaptic glutamatergic terminals [16]. Voltage-dependent $Na^+$ channel block may also reduce the propagation of action potentials from the soma into the dendrites and the dendritic amplification of synaptic potentials [17].

Several marketed AEDs including felbamate, topiramate, and zonisamide interact with other ion channel targets [18]. The combination of actions may contribute to the unique clinical efficacies of each of these drugs, suggesting that it may be possible to optimize the activity of drugs that target $Na^+$ channels with minimal adverse effects [4].

### 2.2. Voltage gated calcium channels (VGCCs)

The VGCCs are mediators of calcium entry into neurons in response to membrane depolarization [19], which results to a number of essential neuronal responses, such as the activation of calcium-dependent enzymes gene expression, the release of neurotransmitters from presynaptic sites, and the regulation of neuronal excitability [20].

VGCCs are classified into two major categories: the low voltage-activated (LVA) calcium channels (i.e., T-type channels) and the high voltage-activated (HVA) channels [18]. Some of the HVA channel subtypes can be activated at relatively negative voltages under certain circumstances. The LVA channels are activated by small depolarization near typical neuronal resting membrane potentials and are key contributors to neuronal excitability [4]. The HVA channels, which require larger membrane depolarization to open, are further subdivided into L-, N-, R-, P-, and Q-types [4]. The L-type channels are found on cell bodies where they participate, among other functions, in the activation of calcium-dependent enzymes and in calcium-dependent gene transcription events [21]. P- and Q-type channels, like N-type channels, are concentrated at presynaptic nerve terminals where they are linked to the release of neurotransmitters [22]. In the context of neurotransmitter release, N-type channels tend to support inhibitory neurotransmission, whereas the P/Q-type channels have more frequently been linked to the release of excitatory neurotransmitters but can also support inhibitory release [23]. R-type channels are distributed in proximal dendrites and presynaptic nerve termini [24]. Their precise physiological function remains enigmatic; however, there is evidence that these channels may mediate neurotransmitter release at select synapses [25].

HVA calcium channels are heteromultimers that are formed through association of $\alpha_1$, $\beta$, $\alpha_2$-$\delta$, and $\gamma$ subunits. Conversely, the LVA channels may contain only the $\alpha 1$ subunit. The $\alpha 1$ subunit is the pore-forming subunit of both LVA and HVA calcium channels that are sufficient to form a voltage-gated calcium-selective pore by itself and it is the sole determinant of the calcium channel subtype [18]. The $\alpha 1$ subunit is associated with auxiliary subunits including the intracellular $\beta$ subunits ($\beta 1$–$\beta 4$), the largely intramembranal $\gamma$ subunits ($\gamma 1$–$\gamma 8$), and the intramembranal/extracellular $\alpha 2$-$\delta$ subunits (types 1–4) that are unrelated to the sodium channel auxiliary subunits [18].

Ten functional calcium channel $\alpha 1$ subunits are known in vertebrates, which fall into three major classes ($Ca_v1$, $Ca_v2$, and $Ca_v3$) according to their physiological functions and regulations [26]. The $Ca_v1$ subfamily ($Ca_v1.1$ to $Ca_v1.4$) conducts L-type calcium currents [27], while the $Ca_v2$ subfamily ($Ca_v2.1$ to $Ca_v2.3$) conducts N-, P/Q- and R-type calcium currents that initiate fast synaptic transmission at synapses in the central and peripheral nervous systems [28]. Among the $Ca_v2$ family, alternate splice isoforms of $Ca_v2.1$ encode P- and Q-type channels, $Ca_v2.2$ represents N-type channels, and $Ca_v2.3$ corresponds to R-type channels [28]. The $Ca_v3$ family represents three different types of T-type channels (i.e., $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$) with distinct kinetic properties.

A variety of mutations involving voltage-gated $Ca^{2+}$ channels have been identified in mice that exhibit absence-like seizures [29]. Three recessive mutations in *Cacna1a* ($Ca_v2.1$) that produce absence-like syndromes in *tottering*, *leaner* and *rocker* mice impair channel function, reducing P/Q-type $Ca^{2+}$ currents. L-type channels have not been associated with epilepsy syndromes in mice or humans and are not considered to be targets for AEDs.

AEDs have been reported to inhibit $Ca^{2+}$ currents with the T-type $Ca^{2+}$ channels being the primary target for seizure protection. The T-type $Ca^{2+}$ channels are believed to be the targets of antiabsence agents such as ethosuximide that weakly block native and recombinant T-type $Ca^{2+}$ channel currents [30]. The anticonvulsant action of the barbiturate phenobarbital

may be due, in part, to inhibition of $Ca^{2+}$ current as well as an action on $GABA_A$ receptors [31]. Lamotrigine that is widely believed to act primarily on voltage-gated $Na^+$ channels also inhibits high voltage-activated N- and P/Q-type $Ca^{2+}$ channels and inhibits R-type minimally [32].

The molecular targets for gabapentin and pregabalin are $\alpha$2-δ proteins, particularly the $\alpha$2-δ-1 and $\alpha$2-δ-2 proteins [33, 34]. The exact mechanism by which binding to these proteins protects against seizures is not fully understood. Studies have shown inhibitory effects on voltage-gated $Ca^{2+}$ currents that can selectively block either P/Q- or N-type $Ca^{2+}$ channels [35]. Other studies have shown inhibition of the release of neurotransmitters [36]. Gabapentin and pregabalin inhibit neurotransmitter release in many systems mainly by interaction of $\alpha$2-δ with synaptic proteins that are involved in the release or trafficking of synaptic vesicles rather than inhibition of calcium influx [4]. The variability in the effects on $Ca^{2+}$ current may relate to differences in expression of the $\alpha$2-δ subunit in different cell types or in response to different conditions.

### 2.3. Voltage gated potassium channels ($K_V$)

Voltage-gated potassium channels are the most diverse group of ion channels that play a key role in setting the resting membrane potential and serve to limit excitability in neural cells. They are activated by depolarization and the outward movement of potassium ions through these channels repolarizes the membrane to end action potentials and hyperpolarizes the membrane potential immediately following action potentials [6].

A typical $K^+$ channel is a tetramer of $\alpha$ subunits that can assemble into homo- and hetero-tetramers, leading to a wide diversity of different channel complexes including the six transmembrane helix voltage-gated ($K_v$) channels, the two transmembrane-helix inward-rectifier ($K_{ir}$) channels, the $Ca^{2+}$-activated $K^+$ channels ($K_{Ca}$), and the tandem-pore domain ($K_{2P}$) channels [37]. The $K_v$ and $K_{Ca}$ families are of particular relevance in epilepsy.

The $K_v$ channels are involved in diverse physiological processes ranging from repolarization of neuronal or cardiac action potentials, overregulating calcium signaling and cell volume to driving cellular proliferation and migration. The $K_v$ family has more than 40 members that are classified into 12 distinct subfamilies based on their amino acid sequence homology ($K_v$1 to $K_v$12) [37]. They conduct voltage-gated $K^+$ currents that have diverse functions in neurons, including the $K_v$1 (delayed rectifier and A-current), $K_v$2 (delayed rectifier), $K_v$3 (high-voltage-activated, fast kinetics), $K_v$4 (somatodendritic A-current), and $K_v$7 (M-current) [37]. A-currents and M-currents play important roles in regulating the excitability of neurons in brain regions relevant to epilepsy such as the neocortex and the hippocampus [38].

Several $K^+$ channel genes have been associated with different forms of epilepsy including *KCNA1* (encodes $K_v$1.1), auxiliary β2 subunit *KCNAB2* (encodes $K_v$1), *KCNQ2* (encodes $K_v$7.2), *KCNQ3* (encodes $K_v$7.3), *KCNMA1* gene that encodes the $\alpha$subunit of $K_{Ca}$1.1, *KCNJ3* (encodes $K_{ir}$3.1), *KCNJ6* (encodes $K_{ir}$3.2), *KCNJ10* (encodes $K_{ir}$4.1), *KCNJ11* ($K_{ir}$6.2), *KCNK9* (TASK3) [6].

$K_v$ channels are valid molecular targets for both convulsant and anticonvulsant agents. Classical pharmacological antagonists of $K_v$ channels include 4-aminopyridine (4-AP) commonly used to induce seizures in rodent models and brain slices [39], which is a blocker of

$K_v1$, $K_v3$, and $K_v4$ channels. Several classes of compounds identified as $K^+$ channel openers could potentially have anticonvulsant activity. $K_{ATP}$ ($K_{ir}6.x$) channel openers, such as cromakalim and diazoxide, were reported to inhibit epileptic discharges in brain slices [40].

Actions of several established AEDs on various $K^+$ currents have been reported. Ethosuximide reduces sustained $K^+$ currents in thalamic neurons by blocking $Ca^{2+}$-activated $K^+$ current [41]. Pregabalin opens ATP-sensitive $K^+$ channels [42], while lamotrigine reduces the amplitude of A-type $K^+$ currents in cultured hippocampal neurons and levetiracetam inhibits delayed rectifier in isolated hippocampal neurons [4]. These inhibitory actions enhance excitability and unlikely contribute to anticonvulsant activity.

A broad range of $K^+$ channels offers many unexploited molecular targets, particularly the channels generating the A-type and M-type currents. Other members of the voltage-gated ion channel superfamily, including inwardly rectifying, $Ca^{2+}$-activated $K^+$ channels, are also potential targets that have not been validated.

### 2.4. Voltage-gated chloride channels (ClCs)

CICs are expressed in the hippocampus where they mediate chloride currents in pyramidal cells of the hippocampus. They are involved in regulating chloride homeostasis [43], excitability [44], and acidification of synaptic vesicles [45]. One of the CICs expressed in neurons is ClC-2, which is a widely expressed chloride channel of the CLC family of chloride channels and transporters. ClC-2 is activated by hyperpolarization, cell swelling, a rise in intracellular chloride concentration, or mild extracellular acidification [46, 47].

Genes encoding nine voltage-gated chlorides channels ($ClCs^-$) with diverse functions in plasma membranes and intracellular organelles have been identified by molecular studies. One of these channels, ClC-2, a homodimeric channel found in neurons and glia (encoded by the *CLCN2* gene), has been implicated in epilepsy [48]. Over the past years, several mutations in the gene encoding for ClC-2 have been described [49], but whether mutations in ClC-2 cause epilepsy or not has been controversial. However, functional studies in transfected cells suggest that the mutations cause a loss of function [50]. Although ClC-2 knockout mice do not have epilepsy [51], ClC-2 mutations cosegregated in three families with various idiopathic generalized epilepsy syndromes, including juvenile myoclonic epilepsy (JME), juvenile absence epilepsy, childhood absence epilepsy (CAE), and epilepsy with grand mal seizures on awakening (EGMA) [52]. Epilepsy-associated ClC-2 mutations may lead to impairment of $GABA_A$-mediated inhibition or may even become excitatory [4]. Strategies that attempt to influence $Cl^-$ gradients by altering the activity of the transporters that determine $Cl^-$ gradients (NKCC1 and KCC2) are an attractive area of research, given the widespread expression of ClC-2 in many tissues.

### 2.5. Hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels activation mechanism, their modulation *in vivo*, their cellular and subcellular distribution and their interaction with agonists or antagonists remain unclear [53]. HCN channels, members of the superfamily of

voltage-gated cation channels that open upon hyperpolarization and close at positive potential [54], represent the molecular $\alpha$subunits of native "funny" channels found in the heart (where they are referred to as "pacemaker" channels) and the brain. Although the first complete functional description of the funny current was made in the cardiac sino-atrial node (SAN), an equivalent current (termed $I_h$ for hyperpolarization-activated current) was also reported and its properties were investigated in a large variety of neuronal cells, where they contribute to a set of functions such as working memory, motor learning, generation of rhythmic activity, control of the membrane resting potential, regulation of cell excitability, dendritic integration, and synaptic transmission [55].

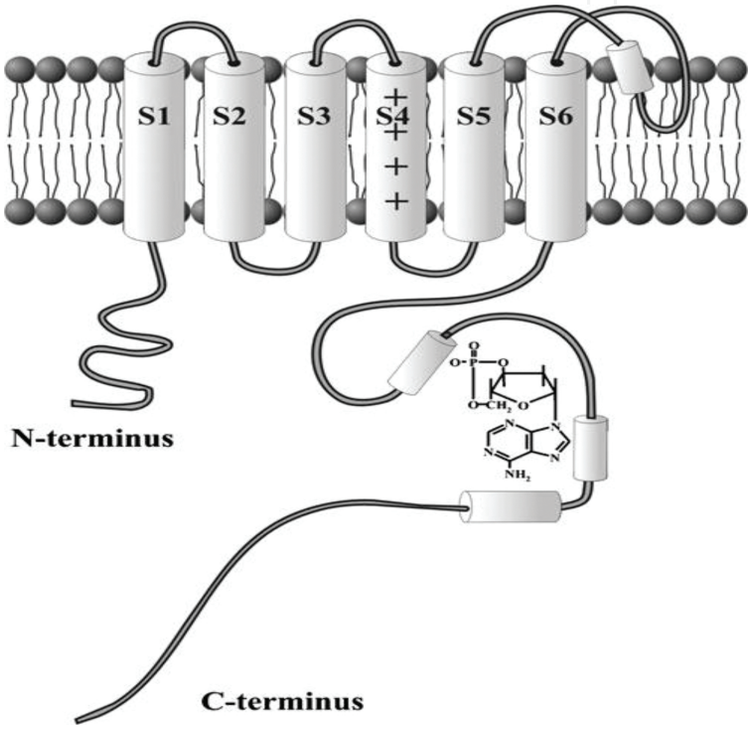


**Figure 2.** HCN channel topology consisting of six transmembrane domains (S1–S6). S4, the putative voltage sensor characterized by the presence of 11 basic amino acids (two lysines, seven arginines, and two histidines) within its domain, is present in all the four HCN subunits. Here, the domains involved in cyclic nucleotide binding (CNBD) in the C-terminus and the cAMP molecule are also shown [57].

HCN channels form macromolecular complexes that consist of the principal ion-conducting channel core and auxiliary subunits that are either permanently assembled with the channel core or can bind and unbind in a regulated fashion [38]. HCN channels (h-channels) are a family of six transmembrane domains (**Figure 2**), single pore-loop, hyperpolarization-activated, nonselective cation channels, which are key regulators of neuronal excitation and inhibition, and have a rich diversity of subunit composition, distribution, modulation, and function. Genes coding for four distinct channel isoforms have been cloned (HCN1–4), and HCN channel transcripts and proteins are widely and variably distributed throughout the mammalian central nervous system [56]. Each of the four identified subunits (HCN1–4) has six transmembrane segments. HCN2 is generally considered to be widely distributed in the

nervous system, and HCN3 is generally poorly expressed except for the olfactory bulb, hypothalamus and retinal cones pedicles [53]. HCN1 has been detected specifically in the neocortex, hippocampus, cerebellar cortex, and brainstem [56], whereas HCN4 channels are highly expressed in particular in thalamic nuclei, basal ganglia, and olfactory bulb [56].

At the cellular level, several basic functions including control of the membrane resting potential and dendritic integration have been attributed to these channels. It was therefore hypothesized that the dysfunction and/or inadequate expression of HCN channels may be a disease-causing factor. Dysregulation of HCN channel expression and aberrant HCN channel function have been implicated in various types of idiopathic and acquired epilepsies. HCN2 deficiencies are pathological hallmarks of absence epilepsy [58]. Deletion of HCN1 is associated with increased seizure severity and risk of seizure-related death in different limbic seizure induction models [59]. Genetic studies suggest that the suppression of HCN channels in neurons is involved in generation of neuronal hyperexcitability, which have been reported in temporal lobe epilepsy, the most common and severe form of epilepsy in adults [60].

The reciprocal interactions between neuronal activity and h-channels indicate that these ion channels could be promising novel targets for antiepileptic therapies. $I_h$ is an attractive potential AED target for different types of epilepsy. However, the complexity and diversity of the mechanisms connecting impaired HCN channel activity with epilepsy make it very challenging to develop a generally applicable rationale for the design of anticonvulsant drugs based on HCN channels. Drugs targeting HCN1 might be relevant for limbic seizures, whereas those affecting HCN2 may be more relevant to absence epilepsy. ZD-7288, a blocker of HCN channels, inhibits spontaneous epileptiform bursting in the hippocampal slice, confirming the potential of $I_h$ inhibition as an anticonvulsant approach [61]. Lamotrigine and gabapentin upregulate the activity of HCN channels [62, 63]. It may be speculated that the action of both drugs is directed primarily at HCN1, which is the main HCN subtype in the cortex and hippocampus. In rat hippocampal pyramidal neurons, lamotrigine has also been reported to decrease dendritic excitability by increasing $I_h$ [64].

## 3. Ligand-gated ion channels

Ligand-gated ion channels in the mammalian brain include the Cys-loop receptors comprising the $GABA_A$, glycine, nicotinic cholinergic and 5-$HT_3$ receptors (**Figure 3**), and the ionotropic glutamate receptors comprising the (±)-*α*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors besides the adenosine triphosphate (ATP)-gated P2X channels and the transient receptor potential (TRP) channels. $GABA_A$ receptors are permeable to $Cl^-$ and $HCO_3^-$, while the ionotropic glutamate receptors are cation permeable, with significant variation in the extent of $Ca^{2+}$ permeability. The majority of known convulsant compounds act via the ligand-gated ion channels to diminish GABA-mediated transmission either by direct action on $GABA_A$ receptors or by other effects on GABAergic function.

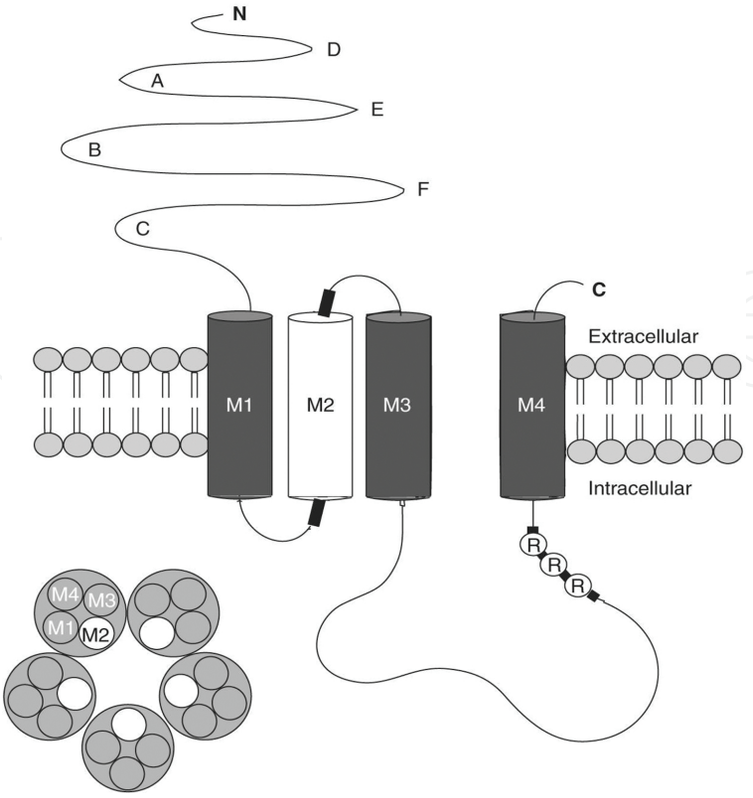


**Figure 3.** A typical Cys-loop receptor subunit. A cross section of the transmembrane region at the lower left shows five subunits that form a central ion-conducting pore. Six loops form the ligand binding site (A–F) and the region that influences ion conductivity (R-R-R) [65].

### 3.1. $GABA_A$ receptors

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the vertebrate central nervous system (CNS) that activates $GABA_A$, $GABA_B$, and $GABA_C$ receptors. $GABA_A$ receptors are pentameric structures composed of different combinations of subunits arranged around a central $Cl^-$-selective pore [66]. Studies have indentified 19 subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, ρ1–3) encoded by 19 distinct genes that form ligand-gated ion channel complexes [67]. The inclusion of a ρ subunit (ρ1–ρ3) distinguishes the bicuculline-insensitive $GABA_C$ receptor family [68]. The subunit composition determines the biophysical properties, pharmacological characteristics [most notably the sensitivity to benzodiazepines (BZ)], and subcellular localization of the $GABA_A$ receptors [67]. Their modulatory domains include binding sites for benzodiazepines (BZ site), GABA, barbiturates, nonbarbiturate anesthetics and ethanol, neurosteroids, picrotoxin, penicillin, and zinc.

Genetic studies in humans reveal a range of idiopathic generalized epilepsy syndromes linked to mutations in the $GABA_A$ receptor [69]. A mutation in the $GABA_A$ receptor α1 subunit is associated with autosomal dominant juvenile myoclonic epilepsy [70]. Mutations involving the γ2 subunit in two cases are associated with GEFS+ and in two cases associated with childhood absence epilepsy with febrile convulsions [69]. Studies revealed spontaneous

seizures in β3 knockout mice [71], supporting that seizures that are prominent feature of the Angelman syndrome are due specifically to defects in $GABA_A$ receptors.

$GABA_A$ receptors are acknowledged targets of many available anticonvulsants including drugs enhancing $GABA_A$ receptor action through a direct interaction with the receptor (benzodiazepines, barbiturates, propofol, stiripentol, topiramate, carbamazepine, phenytoin, felbamate) or indirectly by increasing the available GABA (tiagabine, vigabatrine, gabapentin, valproate) [68]. Furthermore, anticonvulsants can reduce the depolarizing effects of $GABA_A$ receptors by inhibiting carbonic anhydrase (topiramate, zonisamide, acetazolamide) [68]. Studies in genetically modified mice have helped establish the role played by subunit composition in the antiepileptic and other pharmacological actions of drugs acting on the $GABA_A$ receptor [72].

Majority of drugs that act on $GABA_A$ receptors do so at modulatory sites distinct from the GABA recognition site. The anticonvulsant actions of benzodiazepines result in large part from their ability to enhance GABA-induced increase in the conductance of chloride ions [73]. A therapeutically relevant concentration of benzodiazepines acts at subsets of $GABA_A$ receptor channel complex and increases the frequency, but not duration of opening of GABA-activated chloride channels [74]. The mechanisms underlying the actions of barbiturates on $GABA_A$ receptors appear to be distinct from those of either GABA or the benzodiazepines. Barbiturates potentiate GABA-induced chloride currents by prolonging periods during which bursts of channel opening occur rather than by increasing the frequency of these bursts [74].

Substantial effort has been devoted to obtaining $GABA_A$ receptor positive allosteric modulators with reduced activity on $GABA_A$ receptors containing $\alpha 1$ subunits, to avoid the sedation mediated by these receptors. Nonbenzodiazepines that bind to the benzodiazepine site have been developed; some are partial agonists with reduced efficacy. These subtype-selective agents could potentially be superior to benzodiazepines for chronic epilepsy therapy, but have not been demonstrated that they are less sedative or more importantly less susceptible to tolerance [4].

### 3.2. Ionotropic glutamate receptors

The ionotropic glutamate receptors consist of three receptor superfamilies of ligand-gated cation channels including AMPA, kainate, and NMDA that mediate most of the fast excitatory transmission in the CNS and are thus involved in all brain functions. They are tetrameric structures with four subunits for the AMPA receptors, five subunits for the kainite receptors and seven subunits for the NMDA receptors [75].

Little evidence for spontaneous mutations involving glutamate receptors has been demonstrated in epilepsy syndromes in human or mouse. Juvenile absence epilepsy has been associated with a nine-repeat allele of a tetranucleotide repeat polymorphism in a noncoding region of the GluR5 receptor gene (*GRIK1*) [76]. Studies have shown that alterations in GluR2 editing that cause AMPA receptors to be $Ca^{2+}$ permeable lead to seizures.

Substantial effort has been devoted toward the development of ionotropic glutamate receptor antagonists for epilepsy therapy because of the role of glutamate in the pathophysiology of

seizures and the empirical evidence that these antagonists are protective in various animal seizure models [77]. Competitive and noncompetitive NMDA receptor antagonists demonstrated the ability to block seizures in rodent epilepsy and possess protective activity in some rodent models [78, 79]. Competitive NMDA antagonists appeared the most promising in models of generalized seizures.

AMPA receptor antagonists, which are anticonvulsant in a broad range of rodent animal models, have been identified and may have greater potential clinical utility than do the NMDA antagonists [15]. AMPA receptor antagonists have the potential to stop seizures more effectively and may confer neuroprotection by blocking glutamate-induced excitotoxicity, which could diminish the brain damage and neurological morbidity typically associated with status epilepticus.

Three marketed AEDs have been shown to interact with glutamate receptors. Phenobarbital decreases the depolarizing or excitotoxic action of AMPA and kainate at concentrations similar to those at which it potentiates GABA [80]. Topiramate has been reported to block kainate-induced currents in cultured hippocampal neurons [81] by acting specifically on GluR5 kainate receptors and with lower potency on AMPA receptors [82]. Felbamate has several different pharmacological actions including specific inhibitory effect on NMDA receptors that have been proposed as contributing to its clinical efficacy [83].

### 3.3. Acid-sensing ion channels (ASICs)

Acid-sensing ion channels (ASICs) are superfamily of ligand-gated cation channels that are widely distributed in the mammalian brain, the spinal cord and the peripheral sensory organs. ASICs belong to the degenerin/epithelial $Na^+$ channels that are activated by external protons. Increase in extracellular proton concentrations, which is associated with physiological conditions such as synaptic signaling and pathological conditions such as tissue inflammation, ischemic stroke, traumatic brain injury, and epileptic seizure, activates this unique family of membrane ion channels. The ASICs rapidly respond to a reduction in extracellular pH with an inward cation current that is quickly inactivated despite the continuous presence of protons in the medium. Abundant experimental evidence shows that ASICs play important roles in physiological/pathological conditions, such as sensory transduction, learning/memory, retinal function, seizure, and ischemia [84].

Seven different ASICs subunits of ASICs (1a, 1b1, 1b2, 2a, 2b, 3, and 4) encoded by four genes have been identified [85, 86]. The 1a, 2a, 2b, and 4 subunits are expressed in the CNS neurons, while all other ASICs subunits with the exception of ASIC4 are expressed in peripheral sensory neurons. ASIC genes are also expressed in non-neuronal tissue such as vascular smooth muscle cells [87] and bone [88].

ASICs are involved in nociception in sensory neurons when injury or inflammation causes acidification. Protons released during high-frequency stimulation of excitatory synapses in the brain activate ASICs to cause postsynaptic depolarization [4], resulting in a reduction in the $Mg^{2+}$ block of NMDA receptors, which promotes epileptic activity. The inhibition of ASICs might therefore reduce excitatory synaptic neurotransmission resulting to anticonvulsant

actions [4]. Acidification that occurs during intense seizure activity could activate ASICs and contribute to seizure-induced brain damage because of $Ca^{2+}$ permeability in many ASICs [89]. ASIC antagonists might minimize these adverse consequences of seizures. There are no selective ASIC antagonists available to test the role of ASICs as anticonvulsant targets; however, the potassium-sparing diuretic amiloride does act as an ASIC antagonist and appears to have anticonvulsant properties [90].

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