Implications for Anesthesia and Beyond

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Abstract

Gamma-aminobutyric acid (GABA), a nonpeptide amino acid transmitter, is a major component of modern neuropharmacology and one of the most crucial target sites for general anesthetics and therapeutic drugs. GABA type A receptors ($GABA_A$Rs) are the most abundant inhibitory neurotransmitter receptors in the central nervous system. They are part of the rapid-acting, ligand-gated ion channel (LGIC) receptor category, a pentameric Cys-loop superfamily member that mediates inhibitory neurotransmission in the mature brain. $GABA_A$Rs mainly consist of two α subunits, two β subunits, and one additional subunit from either γ or δ arranged around a central chloride (Cl^-) selective channel. Multiple $GABA_A$R subunit subtypes and splice variants have been identified. Each variant of $GABA_A$R exhibits distinct biophysical and pharmacologic properties. Several compounds allosterically modulate the $GABA_A$R positively or negatively. The widely used positive $GABA_A$R modulators include benzodiazepines (anxiolytic and anticonvulsant), general anesthetics (volatile agents like isoflurane, and intravenous agents like barbiturates, etomidate, and propofol), long-chain alcohols, some anticonvulsants, and neuroactive steroids. The binding sites for each drug are distinctly different. The anesthetic drugs enhance receptor-mediated synaptic transmission and thus interrupt the thalamocortical transmission, which controls the sleep–wake patterns. Abnormality in the $GABA_A$R function has been implicated in several neurological conditions, such as sleep disorders, seizures, depression, cognitive function, neurological recovery after injury, and neuroplasticity. Understanding the $GABA_A$R lays the foundation for the development of highly specific drugs in the treatment of neurological disorders and general anesthesia.

Keywords
- GABA
- $GABA_A$ receptor
- isoforms
- general anesthesia
- modulation
- neurological disorders

Introduction

Gamma-aminobutyric acid (GABA), a nonpeptide amino acid, is the primary inhibitory neurotransmitter in the brain and a major inhibitory transmitter in the spinal cord, acting through the GABA receptor. The various levels of amnesia and loss of consciousness produced by many current general anesthetics such as benzodiazepines, barbiturates, propofol, etomidate, and volatile anesthetics are also mediated via their effects at the GABA receptor, notably the type A GABA receptor ($GABA_A$R). The advances in modern molecular pharmacology and neuroscience have enabled investigators to understand the role of $GABA_A$R in physiological and pathological conditions. Modulation of $GABA_A$R is also one of the major components of modern neuropharmacology for several disorders. Understanding $GABA_A$R has received a great deal of attention in the search for highly specific drug targets in the central nervous system (CNS). This narrative review gives a brief overview of the biochemistry

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of $GABA_A$R, including structure, function, and modulation by drugs and disease.

The GABAergic System

The GABAergic system of the brain consists of GABA-releasing cells and receptors that bind GABA. The GABA-releasing cells are incredibly diverse. They control the activity of local networks (interneurons) and form the output of some areas of the brain and nuclei (e.g., striatal medium spiny neurons and cerebellar Purkinje cells). GABA neurons are involved in the transmission of afferent pain signals and descending pain-modulating pathways. The GABA receptors are virtually located on every neuron in the brain and represent a diverse array of receptor types. GABA signaling also plays a vital role in controlling neuronal differentiation during development.[1] In the spinal cord, GABA neurons have ubiquitous distribution with maximal concentration in the dorsal gray matter, followed by the ventral gray and white matter.[2]

GABA Receptors

Three types of GABA receptors are described: type A ($GABA_A$R), type B ($GABA_B$R), and type C ($GABA_C$R). $GABA_A$Rs are fast-acting, ligand-gated, chloride ion channel (LGIC) receptors that mediate inhibition in the brain.[3,4] $GABA_B$Rs are relatively slow, class C of G-protein-coupled receptors.[5] $GABA_C$ R, also named GABA-A-rho, is now classified as a subtype of $GABA_A$R. GABA is more selective and nearly 10 times more potent at $GABA_C$ than $GABA_A$ receptors due to the higher number of agonist-binding sites in the $GABA_C$ complex. The structural and pharmacological action of these three receptors is illustrated in ►**Table 1**.

$GABA_A$R is the most abundant fast inhibitory neurotransmitter receptor in the CNS. It is a member of the pentameric Cys-loop superfamily. The other receptors of this family are the nicotinic acetylcholine, glycine, 5-HT3, and zinc-activated receptors. The intercellular communication mediated by GABA receptor activation differs from the "point-to-point" communication that underlies the synaptic transmission or the gap junction-mediated electrical coupling. It is more akin to the paracrine transmission associated with the actions of neuromodulators such as serotonin, histamine, dopamine, acetylcholine, and peptides in the brain.[6]

Structure and DIstribution of GABAA Receptor

$GABA_A$R mainly consists of two α subunits, two β subunits, and one additional subunit from either a γ or δ, arranged as a pentameric ring around a central chloride selective channel (►**Fig. 1A**). When the receptor is activated, this ring serves as a channel through which chloride ions pass (►**Fig. 1B**). The receptor has extracellular, transmembrane, and cytosolic domains. Each subunit comprises of a long N-terminal extracellular hydrophilic domain, four transmembrane-α-helices (TM1–TM4), three inter-helix loops, and a short C-terminal extracellular domain[7–9] (►**Fig. 1C**).

The $GABA_A$ pentamer receptor includes various isoforms, and the possible arrangement of these isoforms is illustrated in ►**Fig. 2A**. The common $GABA_A$R isoforms in the brain are αβγ and αβδ receptors. About 19 $GABA_A$R subunit subtypes and splice variants have been identified: α (1–6), β (1 to 3), γ (1 to 3), δ, ε, π, θ and ρ (1–3)[7] (►**Fig. 2B**). Each of the receptor subtypes exhibits distinct pharmacological and electrophysiological properties. These physiological and pharmacological properties of a receptor are determined by subunit composition, their arrangement, and developmental expression pattern.[10] The properties of the subunits of α are mentioned in ►**Table 2**. Recently, Laverty et al developed a high-resolution cryo-electron microscopy structure of the full-length human α1β3γ2L isoform of the synaptic $GABA_A$R.[11] The cryo-EM structure demonstrates the organization of heterooligomeric $GABA_A$R receptors and provides a reference framework for the future of molecular principles of GABAergic signaling and pharmacology. The stoichiometry and subunit arrangement of αβγ receptors are well established, but the αβδ receptors need further research.

The distribution and function of the receptor subtypes are varied. The α1β2γ2 $GABA_A$R subtype is distributed in the thalamus. The α5βγ2 $GABA_A$R subunits are distributed in the hippocampus and neocortical pyramidal cells. The δ subunits coassemble with α6 subunits in the cerebellum and with α4 subunits in the hippocampus, striatum, thalamus, and cortex. The vital role of maintaining an inhibitory tone is contributed by the β3 subunit. Both $GABA_A$R $GABA_B$Rs have been located in the spinal cord. $GABA_A$Rs are uniformly distributed in the gray matter (on dorsal and ventral interneurons), while $GABA_B$Rs are spread in the dorsal horn (laminae I-III), both having a presynaptic location on primary afferent fibers and mediate synaptic inhibition.[2,12,13] These GABA neurons enable excitatory proprioceptive signal integration, which permits the spinal cord to amalgamate sensory information and create smooth movements.[14,15] Direct $GABA_A$R or $GABA_B$R-mediated inhibition of opioid-containing neurons facilitates pain transmission by reducing the release of these endogenous analgesics. GABAergic neurons located in the gray matter, anterior horn, and the substantia gelatinosa of Rolando explain the muscle relaxant effect of benzodiazepines.

GABAergic Inhibition

The $GABA_A$Rs are most prevalent, localized mainly in the synapses.[16] However, $GABA_A$Rs do not exclusively locate to synapses. A small portion of the receptor subtypes, like α5βγ $GABA_A$R and others containing the δ subunit like the αβδ receptors, has been found in the extrasynaptic regions (►**Fig. 3**).

Three kinetically distinct forms of $GABA_A$R-mediated inhibition are exhibited:

(i) Rapid phasic inhibition at synaptic $GABA_A$Rs—The α 1β2γ2 $GABA_A$R mediates phasic inhibition in response to transient high concentrations of synaptic GABA release[17] (►**Fig. 4A**)

(ii) Persistent tonic inhibition at extrasynaptic receptors—Mediated by α 4β2δ $GABA_A$Rs. When activated by low-concentration extrasynaptic GABA, they produce tonic inhibitory currents[17] (►**Fig. 4B**).

(iii) A prolonged albeit phasic "spillover" inhibitory postsynaptic current. GABA spilling from the synaptic cleft can activate presynaptic terminals

Table 1 Types of GABA receptors

Pharmacology	$GABA_A$ receptor	$GABA_B$ receptor	$GABA_C$/rho receptor
Type	Fast, short-acting ionotropic (cys- loop ligand-gated chloride ion channel) transmembrane receptor	Slow, metabotropic (G protein-coupled), seven transmembrane receptor	Slow, sustained Ionotropic (ligand-gated chloride ion channel) transmembrane receptor
Structure	Heteropentamer (2α, 2β and 1 γ/δ subunits) with Cl^- in the center.	Heterodimer (R1, R2)	Homo/heteropentamer (3 ρ subunits: ρ1, ρ2, ρ3) with Cl^- in the center.
Mechanism of action	Postsynaptic inhibition by (+) of Cl^- influx	Inhibits adenyl cyclase. (- cAMP). Presynaptic inhibition by (-) of voltage gated Ca^{+2} channels and postsynaptic inhibition by (+) of K^+ channels	Postsynaptic inhibition by (+) of Cl^- influx
Distribution	CNS: Widespread The postsynaptic membrane of CNS High concentration in the limbic system and the retina Others: liver, endocrine pancreas, placenta	CNS: Widespread The presynaptic and postsynaptic membrane of CNS. High concentration in thalamic pathways and cerebral cortex Others: PNS	Brain: Widespread postsynaptic Spinal cord, retina, superior colliculus, and pituitary gland Others: PNS, GIT, sperm cells
Molecular weight	300 kDa	80 kDa	Similar to $GABA_A$
Site of action:	1^{st} site: brain: IPSP	1^{st} site: spin cord: (slow IPSP polysynaptic and monosynaptic reflex)	Similar to $GABA_A$
Endogenous agonist	GABA	GABA	GABA
Agonists	Muscimol	Baclofen	Muscimol, CACA, CAMP
Modulators	Neuroactive steroids, barbiturates, benzodiazepine (anxiolytic, anticonvulsant) Long chain alcohol Muscle relaxants (thiocolchicoside) Propofol, isoflurane Etomidate	–	Neuroactive steroids, Zn^{+2}
Antagonists	Flumazenil, bicuculline, picrotoxinin (Cl^-channel blocker)	THIP	TPMPA, picrotoxinin
Insensitive to	Baclofen	Bicuculline	$GABA_A$/ $GABA_B$ agonist, saclofen or bicuculline
Pharmacological effects	Sedation, amnesia, hypnosis, anticonvulsant, muscle relaxation	Epileptogenesis, central muscle, relaxation	Analgesia, visual image processing

Abbreviations: CACA, cis-4-aminoacrotonic acid; CAMP, cis-2-amino-methylcyclopropane-carboxylic acid); Cl, chloride ion; CNS, central nervous system; $GABA_AR$, gamma-aminobutyric acid type A receptor; K^+, potassium ion; GIT, gastrointestinal system; IPSP, inhibitory postsynaptic potential current; PNS, peripheral nervous system; THIP, 4,5,6,7-tetrahydroisoxazolo[5,4-c] pyridine-3-ol; TPMPA, 1,2,5,6- tetrahydropyridine-4-yl methyl-phosphonic acid; Zn^+, zinc.

receptors or neighboring synapses on the same or adjacent neurons to produce inhibitory postsynaptic currents (IPSCs) (►**Fig. 4C**).

Any disturbance in the phasic or tonic inhibition is associated with many neurological and psychiatric diseases. Thus, modulating these signals has led to the basis of drug therapy as well as anesthesia.

Role of Extrasynaptic $GABA_A$ Receptors

Tonic inhibition produced by extrasynaptic inhibition is vital in regulating states of consciousness. The extrasynaptic $GABA_ARs$ are essential targets for anesthetics, sleep-promoting drugs, neurosteroids, and alcohol. Disorders such as schizophrenia, epilepsy, and Parkinson's disease are found to involve disruptions in network dynamics associated with alterations in the tonic $GABA_AR$-mediated conductance. The extrasynaptic $GABA_ARs$ are potential therapeutic targets for the treatment of these diseases to enhance cognition and aid post-stroke functional recovery.

Desensitization of $GABA_A$ Receptor

A variety of kinases and phosphatases are involved in the regulation of $GABA_AR$. Phosphorylation plays a crucial role in the allosteric modulation of $GABA_ARs$ and governs its trafficking, expression, and interaction partner.[18] The initial binding

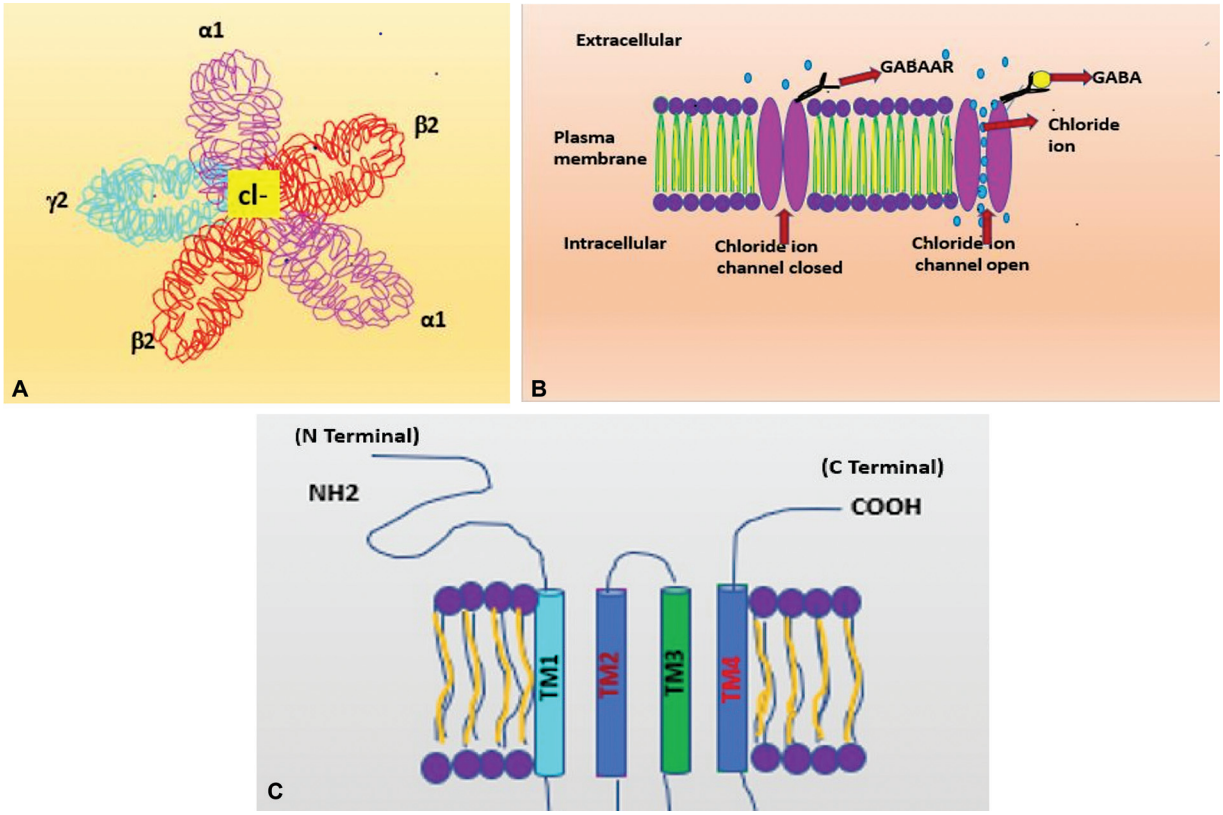


Fig. 1 Gamma-aminobutyric acid type A receptor ($GABA_AR$) structure: Top view, side view, and composition. (**A**) Schematic representation of the top view of heteropentamer $GABA_AR$ isoform consisting of β2, α1, β2, α1, γ2 subunits arranged counter-clockwise as a ring around a central chloride ion. (**B**) Schematic representation of the opening of chloride ion channel facilitated by the binding of GABA to $GABA_AR$. (C) Schematic representation of the side view of $GABA_AR$ displaying extracellular, transmembrane, and cytosolic domains. Extracellular domain contains a large hydrophilic N-terminal and a small C-terminus. Transmembrane domain comprises four hydrophobic helices (TM: TM1-TM4). TM1 and TM2 helices are connected by a short intracellular loop. TM2 and TM3 helices are connected by a short extracellular loop. TM3 and TM4 helices are connected by a long intracellular phosphorylated loop.

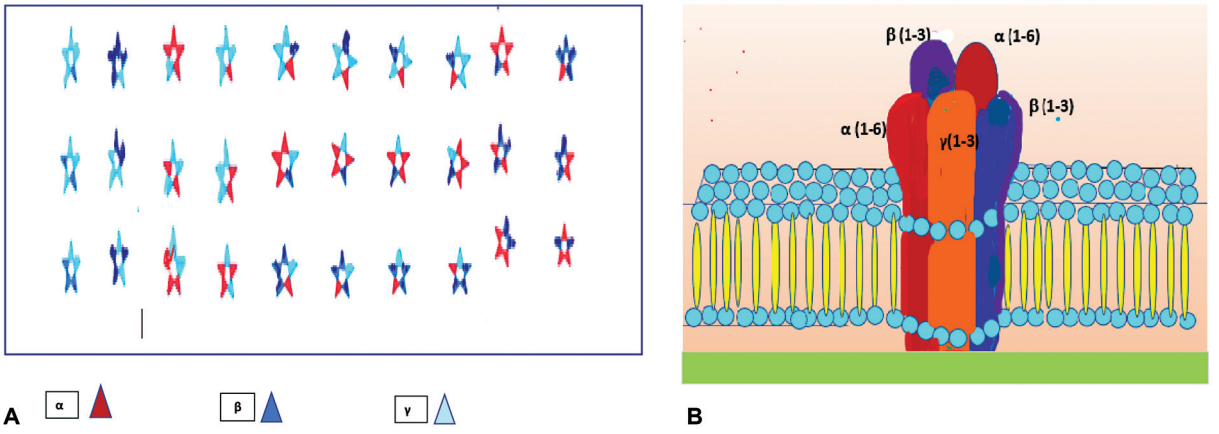


Fig. 2 (A) Possible arrangements of isoforms of gamma-aminobutyric acid type A receptor ($GABA_AR$). Schematic representation of possible arrangements of isoforms of α, β, and γ subunits arrangement in $GABA_AR$ pentamer. (B) Splice variants of $GABA_AR$. This part depicts the side view of $GABA_AR$ comprising splice variants of α (1–6), β (1 to 3), γ (1–3) or δ, ε, π, θ and ρ (1to3) subunits.

of an agonist to $GABA_AR$ causes activation of the LGIC (which facilitates the selective flow of permeant ions across the plasma membrane) and affects cell excitability. But sustained binding of the agonist renders LGICs to enter a shut state, which is refractory to activation, called the desensitized state.[19] The exact roles of desensitization in vivo are still controversial. Still, they may include the prolongation of synaptic currents, decrement of responses during high-frequency neurotransmitter release, and modulation of extrasynaptic receptors subjected to tonic activation by low ambient concentrations of neurotransmitters.[20–23]

Table 2 Pharmacological actions of isoforms of α subunits of $GABA_AR$

α subunit	Effect
α 1	Amnesia/sedative + muscle relaxant effects
α 2	Anxiolytic+ anticonvulsant effects
α 3	Anxiolytic+ anticonvulsant effects
α 4, α 6	Augment benzodiazepine action
α 5	Augment cognitive effects

Abbreviation: $GABA_AR$, gamma-aminobutyric acid type A receptor.

Pharmacological Modulation of $GABA_A$ Receptors

Several compounds allosterically modulate the $GABA_AR$ positively or negatively in the presence of GABA. The widely used positive $GABA_AR$ modulators include benzodiazepines (anxiolytic and anticonvulsant), general anesthetics (volatile agents like isoflurane, and intravenous agents like barbiturates, etomidate, and propofol), long-chain alcohols, some anticonvulsants, and some neuroactive steroids.[7] The notable negative $GABA_AR$ modulator includes proconvulsant flumazenil.

Mechanism of Modulation

GABA binding to the $GABA_AR$ increases the opening of the chloride ion channel. Many potent general anesthetics allosterically enhance the activation of $GABA_AR$s by decreasing the kind of the receptor.[24,25] This enhanced $GABA_AR$ function comes about by at least four actions: enhanced affinity at the GABA binding site, enhanced channel opening, conductance, and modulation. At high concentrations, they cause direct activation of $GABA_AR$. General anesthetics also inhibit GABA uptake into neurons and glia, thus increasing GABA concentrations at postsynaptic $GABA_AR$s.[26] (►**Fig. 5**)

Differences in the $GABA_AR$ Enhancement by General Anesthetics

Although all anesthetics have principal effects on the $GABA_AR$, the binding sites are distinctly different. The details of the binding sites of various drugs on the subunits

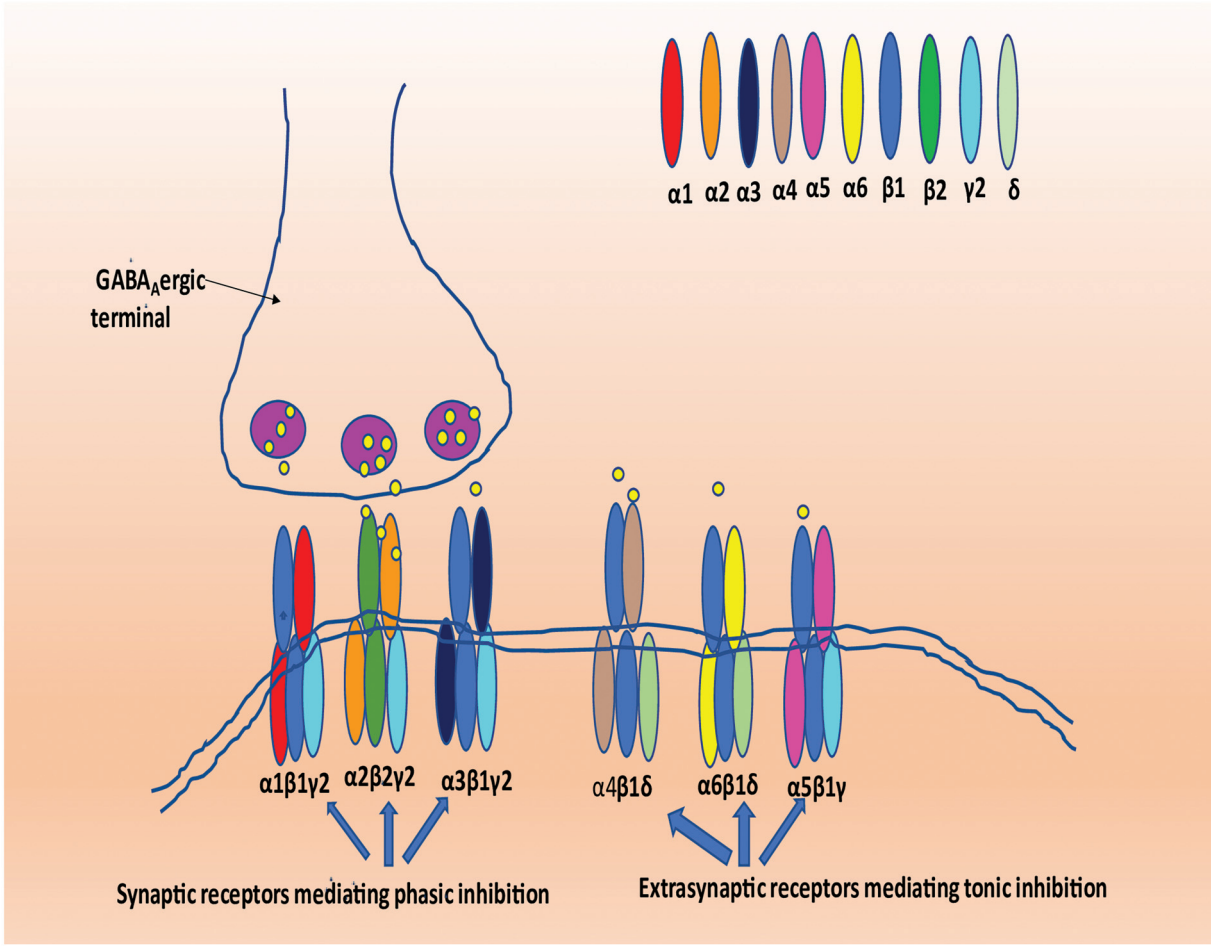


Fig. 3 Schematic representation of action of synaptic and extrasynaptic gamma-aminobutyric acid type A receptors ($GABA_AR$). Synaptic $GABA_AR$: $\alpha_{1/2/3}\beta_{1/2}\gamma$ receptors mediate rapid phasic inhibition in response to transient high concentrations of synaptic GABA release. Extrasynaptic $GABA_AR$: α4/5/6βδ receptors produce persistent tonic inhibitory currents when activated by low-concentration extrasynaptic GABA. They are crucial targets for anesthetics, barbiturates, benzodiazepines, propofol, etomidate, sleep-promoting drugs, neurosteroids, and alcohol, schizophrenia, epilepsy disorders.

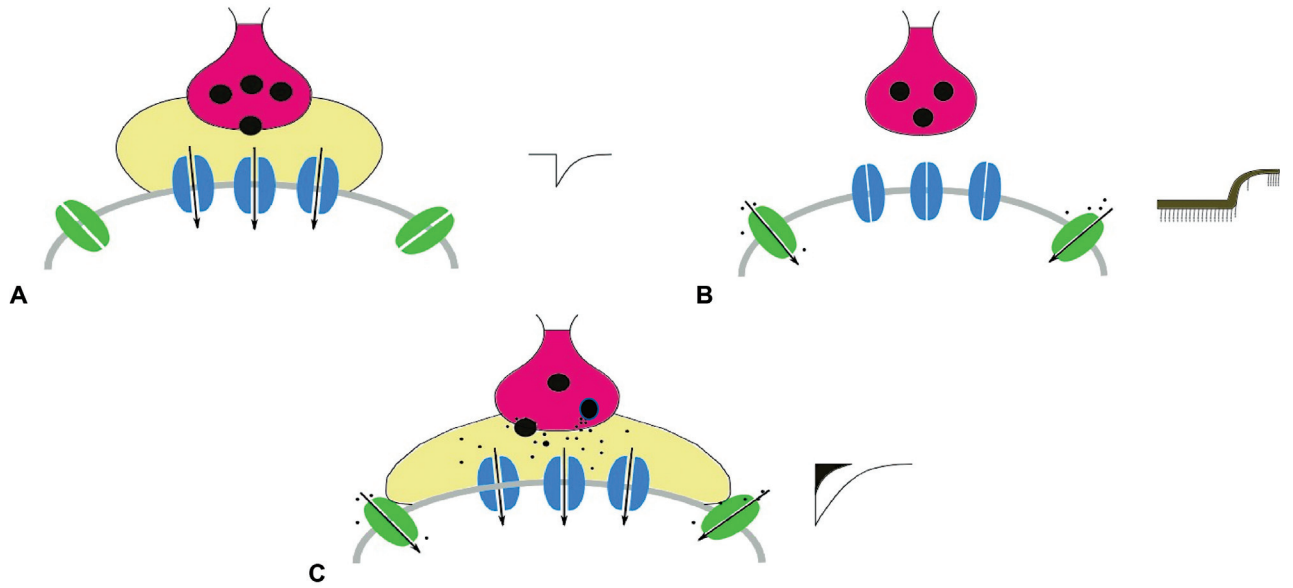


Fig. 4 Phasic, tonic, and spillover inhibition of thalamic neurons mediated by gamma-aminobutyric acid type A receptors (GABA$_A$R). (A) Phasic inhibition at extrasynaptic GABA $_A$R illustrates rapid phasic inhibition at synapse: it allows the fast and precise presynaptic activity transmission into a postsynaptic signal. (B) Tonic Inhibition at extrasynaptic GABA $_A$R illustrates persistent tonic inhibition at extrasynaptic receptors: it occurs due to activation of extrasynaptic GABA $_A$R sensing the low GABA levels in extracellular space. Sites of action include hippocampal neurons, thalamic relay neurons, and neocortical neurons, crucial in consciousness regulation. (C) Spillover inhibition at extrasynaptic GABA $_A$R. Schematic representation of prolonged "spillover" inhibition: GABA spilling from the synaptic cleft can activate either presynaptic terminals receptors or neighboring synapses on the same or adjacent neurons generating inhibitory postsynaptic currents (IPSC).

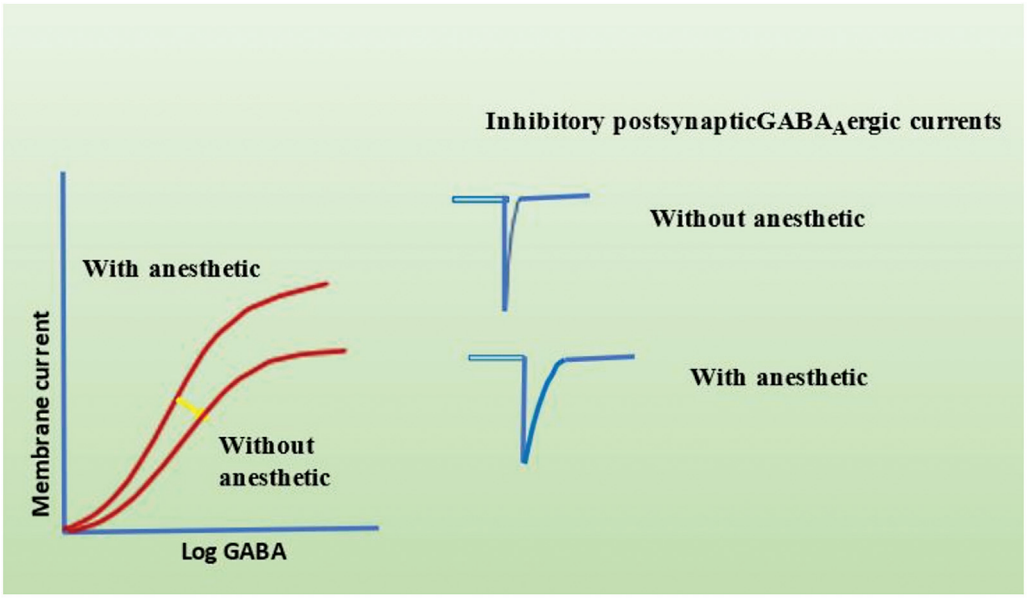


Fig. 5 Effects of anesthetic drugs on gamma-aminobutyric acid GABA binding site and post-inhibitory GABA$_A$ergic currents. This part illustrates the effects of anesthetic drugs on GABA binding site and postinhibitory GABA$_A$ergic currents. X axis is time and Y axis is current. The figures are not to scale.

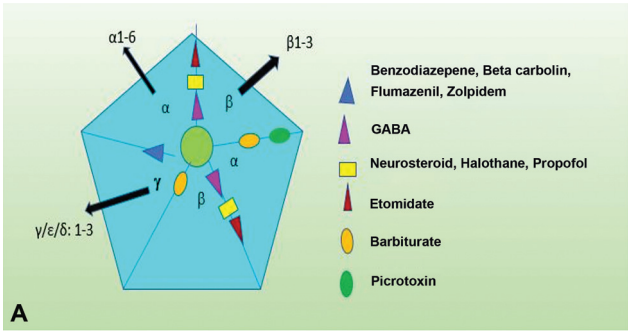
of GABA$_A$R are mentioned in ►**Table 3** and ►**Fig. 6A**. There is good evidence that the intravenous anesthetics act near the extracellular end of the membrane-spanning domain (M) of various subunits. Amino acid residues located in the nonchannel lining face of the M1, M3, and M4 α-helices have been proposed as the binding sites for a range of compounds, including neurosteroids and general anesthetics.[27] The differences in their effects are explained by the differences in affinity for the high agonist efficacy of GABA αβγ receptors and intermediate action at the αβδ receptors.[28]

The general anesthetics act by selectively binding to the transmembrane intersubunit pockets of αβγ receptors. The α 1β2γ2 GABA$_A$R has five subunit interfaces that harbor sites for drug binding and functional modulation of GABA$_A$R, and each compound uses a different set of subunit interfaces: (i)

Table 3 Pharmacological effects of anesthetic agents mediated by $GABA_AR$ subtypes

Anesthetic agent	$GABA_AR$ subtype	Pharmacological effects
Etomidate	β2	Hypnosis, sedation
	β3	Hypnosis, anesthesia, immobility
Propofol	α1β3γ2	Sedation
	α6β3γ2	Sedation
Benzodiazepine	α1βγ2	Antiepileptic effects, sedation, anterograde amnesia
	α2βγ2	Anxiolysis, myorelaxation, analgesia
	α3βγ2	Myorelaxation, analgesia
	α5βγ2	Impaired cognition, myorelaxation

Abbreviation: $GABA_AR$, gamma-aminobutyric acid type A receptor.



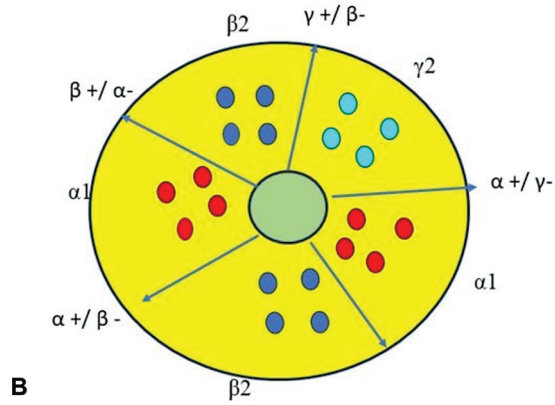


Fig. 6 Drug binding sites on gamma-aminobutyric acid type A receptors ($GABA_AR$) subunit and on their interfaces. (A) Binding sites of the drugs on the subunits of $GABA_AR$. Schematic illustration of binding sites of various drugs on the subunits of $GABA_AR$. (B) Subunit interfaces of α1β2γ2$GABA_AR$. It represents 5 subunit interfaces of α1β2γ2$GABA_AR$. Etomidate binds selectively at interface 1 (γ β +/ α– β) and γ +/ β interface. Propofol acts predominantly at interface 1 (γ β +/ α– β), interface 2 (αβ +/α- γ) and γ +/ β interface, while pentobarbital acts predominantly at interface 2 (αβ +/α- γ), α +/β- interface and α +/ γ interfaces of $GABA_AR$.

Table 4 Influence of isoforms of α subunits on anesthetic effects of drugs

Drug	Isoform	Effect
Benzodiazepines	Combination of γ and β subunits with α1/ 2 isoforms Combination of γ and β subunits with α 4/6 isoforms α1 isoform α2 isoform	Sensitivity Insensitivity Sedation Anxiolysis at the limbic system
Propofol	α6 isoform α1 isoform	Higher gating Lower gating
Pentobarbital	α6 isoform α1-5 isoforms	Highest agonist efficacy Lower agonist efficacy

γβ +/α-β (interface 1), (ii) αβ +/ α-γ (interface 2), (iii) α +/β-, (iv) α +/γ, and (v) γ +/β. Etomidate acts predominantly at interface 1 and γ +/β subunit interfaces, propofol acts predominantly at interface 1, interface 2, γ +/β, and pentobarbital acts predominantly at interface 2 and additionally at α +/β-, and/or α +/γ subunit interfaces. The asymmetry in anesthetic potentiation of the α 1β2γ2 $GABA_AR$ contributes to the differences in their effects[29] (►**Fig. 6B**).

Influence of Isoform on Anesthetic Drug Effects

The subunit composition of the $GABA_AR$ plays a key role in determining the sensitivity to agonists, antagonists and modulators. The effect of the drug varies with the isoforms.[30–35] The influence of the isoforms on anesthetic drug effects is shown in ►**Table 4**.

Functional Effects of Anesthetics on $GABA_AR$ in the Thalamocortical Pathway

The thalamus has a pivotal role in controlling conscious state transitions and has been recognized as an essential locus for anesthetic-induced sedation and hypnosis. There is impairment of thalamocortical (GABAergic neurons projecting from the thalamic reticular nucleus (TRN) toward the ventral basalis [VB]) and corticocortical projections during the general-anesthetic-induced unconscious state. Glutamatergic cells from the ventro-postero-medial nucleus (VPM) and cortex loop with the GABAergic TRN neurons. The excitatory glutamatergic pathway offers a tonic depolarization of the VPM neurons in the wakeful, activated state. It prevents them from entering synchronized, oscillatory states, which close the "gate" of the information procession.[36] The anesthetic drugs enhance the $GABA_AR$–mediated synaptic transmission and inhibit these glutamatergic pathways, thus interrupting the thalamocortical transmission. The extent of this inhibition determines the level of consciousness. The neural reactivity of the primary sensory cortices to external stimuli is preserved at the sedation level of anesthesia.

Functional Effects of Anesthetics on Extrasynaptic αβδ $GABA_AR$

The possibility of extrasynaptic $GABA_AR$ site of action of general anesthetics is suggested by enhanced tonic inhibition at hippocampal neurons, thalamic relay neurons, and neocortical neurons by anesthetics like propofol and isoflurane.[37] Thus, both αβδ and αβγ receptors are targets for several general anesthetics. General anesthetics such as barbiturates, benzodiazepines, propofol, and etomidate have been shown to induce changes in GABA-dependent receptor activation mediated by αβγ and αβδ receptors. The application of general anesthetics increases the mean channel open time by inducing long-lived open states in the $GABA_A$Rs. General anesthetics at high concentrations also directly activate αβδ receptors.

The allosteric modulation of $GABA_A$Rs by the general anesthetics disrupts the normal physiologic circuits, which require precise timing of GABA-ergic input. The $GABA_A$Rs are involved in mediating some of the standard components of general anesthesia: hypnosis, depression of spinal reflexes, and amnesia.[38] However, the contribution of $GABA_A$Rs in mediating immobility and analgesia is less clear. Different classes of anesthetics can have differing effects on these pathways.

Functional Effect on Synaptic Phasic Inhibition

Spill Over Inhibition

Etomidate,[39] propofol,[40] the barbiturate, pentobarbital,[41] and the neurosteroids tetrahydro deoxycorticosterone (THDOC) and alfaxalone,[42] all prolong neuronal IPSCs decay by phasic inhibition associated with αβγ receptors. The drug effects are studied for desensitization (current reduction during agonist application) and deactivation (current return to baseline after terminating agonist application). Propofol decreases the extent of desensitization of α1β3γ2 and α6β3γ2 receptors, while THDOC and etomidate do not alter desensitization of α1β2/3γ2 receptors. General anesthetics prolong the deactivation of α1β2/3γ2 and α6β3γ2 receptors. Hence, desensitization may contribute to the differences in the apparent maximal intrinsic efficacy at αβγ receptors.

Functional Effect on Spillover Inhibition

The GABA spills over from the synapse to activate extrasynaptic or perisynaptic $GABA_A$Rs at relatively high frequencies of presynaptic stimulation, producing IPSCs. Pentobarbital, propofol, the steroidal anesthetic alfaxalone, and etomidate are known to act as positive allosteric modulators of both synaptic $GABA_A$Rs and extrasynaptic δ-$GABA_A$Rs, and they are predicted to enhance "spillover" inhibition. In contrast, benzodiazepines, such as diazepam or midazolam, do not affect δ-$GABA_A$Rs and, therefore, are predicted to have only a modest influence on "spillover" inhibition.[43] (►**Table 5**)

Effects of General Anesthetics on $GABA_A$ Receptor

Barbiturates: The direct effect of pentobarbital on the α1β3γ2 $GABA_A$Rs appears biphasic, with maximal currents due to direct agonism and inhibition at higher concentrations via a distinct inhibitory site. The anticonvulsant effect is mediated at the γ+/β−-interfaces on α1β3γ2 $GABA_AR$. The γ+/β−interface can mediate allosteric channel gating shifts in opposing directions, perhaps depending on the specific orientation of hypnotic and convulsant barbiturates within the site (►**Fig. 6 B**).

Etomidate: Etomidate is a potent stereoselective imidazole ester anesthetic. The $GABA_AR$ site of effect for etomidate for multiple effects at synapses containing $GABA_A$Rs differs from the site for the enhancing effect of etomidate on the modulation of GABA-induced chloride currents. The former site lies within the outer third of the transmembrane domain of the $GABA_AR$ and is located between subunits. The latter exists within the transmembrane helical bundle of the subunit. Evidence suggests that etomidate binds selectively in the two β+ /α−interfaces of α1β2/3γ $GABA_A$Rs in the transmembrane domain (►**Fig. 6B**). R-(+)-etomidate positively modulates and directly activates α1β2γ2 receptors about 20-fold more potently than S(−) etomidate.[27]

Etomidate has a more substantial effect on the β3 subunit at $GABA_A$ slow synapses than on $GABA_A$ fast receptors. Thus, etomidate effects lower-frequency electroencephalogram rhythms (i.e., δ and θ oscillations) more than higher-frequency activity (i.e., γ oscillations). The amnesic effects of etomidate are mediated through α5–containing receptors forming "tonic" $GABA_A$Rs, but this does not produce the sedative or immobilizing effects. The loss of recall, sedation, loss of consciousness, and surgical immobility effects of etomidate may be mediated by actions on other ion channels and signaling pathways. Etomidate analogs have been developed with selective $GABA_A$ effect and avoidance of prolonged adrenocortical suppression.

Propofol: The alkylphenol propofol (2,6, di-isopropyl phenol) has both GABA-potentiating effects and direct effects on $GABA_AR$. The property of direct activation of the GABA receptor by propofol depends on the β subunit, while

Table 5 The effects of anesthetic drugs on phasic, tonic, and spillover inhibition

Type of inhibition	Effect	By agent
Phasic inhibition	Augmented	Benzodiazepine, neuroactive steroid, etomidate, propofol, pentobarbital
Tonic inhibition	Augmented	Neuroactive steroid, etomidate, propofol, pentobarbital
	No effect	Benzodiazepine
Spillover inhibition	Modest augmented	Benzodiazepine
	Augmented	Neuroactive steroid, etomidate, propofol, pentobarbital

the modulatory effects were considered to involve α and β subunits. The α, β, and γ subunits contribute to the sensitivity of $GABA_AR$ to propofol[44](►**Fig. 6 B**). Propofol was shown to be less efficacious at β1-containing receptors than at those containing β2 or β3 subunits.[45]

Benzodiazepines: The drugs of the benzodiazepine family, including the newer drugs like remimazolam, bind to the interface between α and γ subunits, while barbiturates bind to the β and γ interface subunit of $GABA_AR$ (►**Fig. 6A**). So, there is the additive effect between benzodiazepine and barbiturate and no competitive effect. Benzodiazepines are GABA facilitatory and increase the frequency of chloride ion channel opening, while barbiturates are GABA mimetic and increase the duration of chloride ion opening.

Volatile Anesthetics: Isoflurane, desflurane, and sevoflurane enhance the amplitude and prolong the duration of GABA-mediated synaptic inhibition at low concentrations. At supraclinical concentrations, they can cause "direct activation" by opening the receptor's anion channel even in the absence of GABA.

Ketamine: The primary target site for ketamine is the N-methyl-D-aspartate (NMDA) receptor, but it also inhibits GABAergic-enhanced conductance arising from α6-containing $GABA_A$ Rs.[46] Ketamine has a high affinity for NMDA receptors on the inhibitory GABAergic interneurons. Thus, ketamine may also share the exact hypnotic mechanism as that of the GABAergic anesthetics.

Modulation of $GABA_AR$ by Nonanesthetic Drugs

Several nonanesthetic drugs that modulate $GABA_A$ positively and negatively are used in the treatment of neurological conditions such as seizures, pain, cognitive dysfunction, and sleep disorders. The drug gabapentin is used to treat partial-onset seizures, sleep disorders, and alcohol withdrawal. Its mechanism of action is still unclear; it possibly acts by enhancement of GABA synthesis. Vigabatrin increases the ambient GABA levels by an irreversible block of GABA transaminase and is used to manage refractory complex partial seizures and infantile spasms but has the drawback of visual field loss. Pregabalin enhances the activity of glutamic acid decarboxylase, leading to increased GABA synthesis and higher ambient GABA levels. Pregabalin is used in the management of partial seizures (with or without secondary generalization), neuropathic pain (diabetes, postherpetic neuralgia), and anxiety disorder. Ganaxolone and alphaxalone are the positive allosteric modulators of most $GABA_ARs$ with greater potency at δ-$GABA_ARs$, leading to selective enhancement of the tonic conductance. Ganaxolone is used for catamenial epilepsy management, while alphaxalone is used for anesthetic and long-term sedation in the intensive care unit.

GABA Antagonists

These drugs bind to GABA and inhibit its action, exhibiting convulsant and stimulant effects. They are used to treat the overdose of sedative drugs. They act at the GABA receptor site and are classified as competitive, noncompetitive antagonists and negative allosteric modulators. The details of these drugs are summarized in ►**Table 6**.

Role of $GABA_AR$ in Neurological Conditions

Abnormality in the GABAR function has been implicated in several neurological conditions.

Sleep Disorders

$GABA_ARs$ play a pivotal role in the control of sleep rhythms. The alterations in the dynamics of the thalamo-striatal-cortical network and the alterations in extrasynaptic $GABA_AR$ function play a vital role in sleep. The alterations in ambient GABA levels may contribute to the sleep disturbances commonly associated with several neurological disorders, including depression.

Sleep abnormalities are the frequent nonmotor and early symptoms of Parkinson's disease.[47] The caudate-putamen of the striatum that is linked to Parkinson's disease also expresses high levels of extrasynaptic α4βδ subunit-containing $GABA_ARs$. In Parkinson's disease, the loss of dopaminergic drive enhances the GABA concentrations in the striatum, and this change may underlie the sleep disruptions associated with Parkinson's disease.[48]

Table 6 GABA antagonists

Type of GABA antagonist	Mechanism	Drugs
Competitive/orthosteric antagonists	Bind to the active/ orthosteric receptor site of the GABAR complex (but do not activate it) Compete with GABA and block its binding to GABAR	$GABA_A$ antagonists: bicuculline, gabazine, suramin
		$GABA_B$ antagonist: THIP
		$GABA_C$ antagonist: TPMPA
Negative allosteric modulators	Bind to an allosteric site on the GABAR complex in a negative manner. reduce the efficiency of the leading active site by reducing Cl^- conductance	$GABA_A$ antagonists: flumazenil, samazenil, zinc
Noncompetitive channel Blockers	Bind to the central pore of the GABA receptor and inhibit Cl^- ion conductance	$GABA_A$ antagonists: picrotoxinin, fipronil
Inverse benzodiazepine agonists	Inhibit GABA binding. Can induce seizures	β-carbolines

Abbreviations: Cl^-chloride ion; $GABA_AR$, gamma-aminobutyric acid type A receptor; THIP, tetrahydroisoxazolopyridinol; TPMPA, 1,2,5,6-Tterahydropyridin-4-yl methylphosphonic acid.

Drugs that potentiate $GABA_AR$ currents, such as benzodiazepines and zolpidem, are the mainstay in the treatment of insomnia.

The problems of producing tolerance, addiction, and withdrawal prompt the search for more refined drug interventions; δ-selective $GABA_ARs$ such as gaboxadol have failed phase III clinical trials as an alternative to benzodiazepines for sleep promotion due to side effects such as hallucinations and disorientation. More potent δ-$GABA_AR$ selective agonists are under development.

Epilepsy

Disturbances in synaptic and extrasynaptic $GABA_AR$ function have been implicated in many forms of epilepsy.[49] Maintaining appropriate levels of tonic inhibition is vital for controlling neuronal network behavior. δ-$GABA_ARs$ are often targeted in the treatment of specific forms of epilepsy, and drugs altering ambient GABA levels in the brain are used as antiepileptics. The mechanism of modulation of GABA by the antiepileptics is tabulated (►**Table 7**).

All epilepsies do not respond to enhancing tonic inhibition. The defining feature of absence seizures is slow-wave discharges within the thalamocortical network, and this correlates with increased levels of tonic inhibition due to dysfunction of the GABA transporter (GAT-1) and the resulting elevated ambient GABA levels within the thalamus.[50] This type of seizure is triggered by enhanced δ-$GABA_AR$ with drugs like tiagabine and vigabatrin.

Memory and Cognition

Neuronal plasticity is regarded as the mechanism underlying learning and memory. Long-term potentiation at glutamatergic synapses plays a role in neuronal plasticity, and GABAergic inhibition obstructs this plasticity.[51] Drugs that modulate tonic inhibition mediated by δ-$GABA_ARs$ have potential as novel treatments for Alzheimer's disease or other neurological and psychiatric disorders characterized by deficits in learning, memory, or cognition.[52]

Anesthetic-Induced Neurocognitive Changes

Anesthetics are known to produce a prolonged effect on cognition, which is maintained long after the agent is eliminated. Animal studies revealed a persistent increase of the CA1 neuron tonic current mediated by α5-$GABA_ARs$ and an associated decrease in the magnitude of long-term potentiation. The inflammation triggered by surgical trauma, by the anesthetic per se, or both may increase circulating concentrations of IL-1b, which has been shown to increase cell surface expression of a5-$GABA_ARs$ and, consequently, to increase the CA1 tonic current. The anesthetics may act synergistically with IL-1b to enhance the CA1 tonic current mediated by $GABA_ARs$.[53]

Neuroprotection and Recovery of Function after Brain Injury

The adult brain comprises a remarkable structural and functional plasticity, but some barriers may impede its plasticity once a developmental window is closed. Enhanced tonic inhibition has a role in acute neuroprotective quality. The mechanisms involving an enhanced tonic inhibition of $GABA_ARs$ may impede functional plasticity during recovery from cerebral insult.[54] Recovery of function following acute cerebral injury may be controlled by the availability of GABA.[55]

The pathogenesis of several chronic neurological and psychiatric disorders involving neuroplasticity is also attributed to the defects of GABAergic neurotransmission. The mechanism of anesthetic-induced plasticity is not yet entirely known.

Neurosteroids

Neurosteroids are brain-synthesized metabolites of ovarian and adrenal cortical steroid hormones. The glial cells synthesize endogenous neurosteroids like THDOC. δ-$GABA_ARs$ are a preferred site of action for neurosteroids,[56] and at physiological concentrations, they selectively enhance tonic currents mediated by αβδ receptors.[57] The neurosteroid sensitivity of the extrasynaptic $GABA_ARs$ may explain their

Table 7 GABA receptor modulation by antiepileptics

Drug	GABA receptor modulation
Benzodiazepines: clobazam, clonazepam	Enhance the frequency of chloride channel opening and increase the binding of GABA to the GABA receptor
Benzodiazepines: topiramate and felbamate	Cause GABA modulation
Barbiturates	Prolong the open time of the chloride channel burst opening. Effective in GTCS
Valproate	Enhances sodium channel inactivation and reduction in both T-type Ca^{2+}channel currents and release of gamma-hydroxybutyric acid. Effective in partial onset and absence seizures
Tiagabine	Inhibit GABA reuptake into neurons and glia through presynaptic membrane. Enhance GABA catabolism resulting in higher synaptic GABA concentration. Effective in complex-partial seizures
Vigabatrin	unique permanent suicide inhibitor of GABA transaminase enzyme required for GABA catalysis Enhance GABA catabolism, resulting in higher synaptic GABA concentration.

Abbreviations: GABA, gamma-aminobutyric acid type A; GTCS, generalized tonic–clonic seizures.

importance in stress-, ovarian cycle, and pregnancy-related mood disorders. Stress hormones heavily regulate $GABA_A$Rs, and changes in extrasynaptic $GABA_A$R expression are often associated with stress-related disorders.

Future Research Areas

The cryoelectron microscopy of the receptor structure offers critical, novel insights into structure-based drug design that may facilitate the development of better molecules to treat neurological diseases and safer general anesthetics. Neurosteroids binding sites are distinct from etomidate, propofol, and barbiturates binding sites. Neurosteroids enhance $GABA_A$R activation by etomidate and barbiturate and synergize with etomidate in anesthetizing animals.[58] The synergism of neurosteroids and anesthetics has the potential for clinical research. Understanding the actions of the anesthetic drugs on the receptors may enable the development of selective anesthetic drugs devoid of adverse effects, such as etomidate, with no adrenocortical effects.[59,60]

Conclusion

$GABA_A$, the most prominent fast inhibitory neurotransmitter in the CNS, has various subunits and split variants exhibiting different structures and pharmacology. Various drugs, though bind to the same GABA receptor, produce different effects due to the structural heterogeneity of the receptors, the presence of multiple allosteric binding sites, and a broad range of ligands that can bind to them. Abnormalities of $GABA_A$R have been associated with neurological disorders like epilepsy, neurocognitive disorders, and insomnia. Significant progress in understanding the mechanisms of general anesthetic action at the molecular, cellular, and neural systems levels is essential.

Conflicts of Interest
None declared.

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