INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 4, April 2026 | ISSN: 2456-4184 | IJNRD.ORG

A Review on Epilepsy and its Management

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ABSTARCT

According to the World Health Organization's (WHO) most recent data, epilepsy was responsible for 30,307 deaths in India in 2020, or 0.36 percent of all deaths. India has the 47th highest age-adjusted death rate in the world, with 2.44 deaths per 100,000. The World Health Organization's Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders 2022–2031 (WHOiGAP) was approved by the 75th World Health Assembly in May 2022 under decision WHA 75 (Sharma et al., 2020) following consultation with Member States and other significant stakeholders, including individuals with neurological disorders (Leonardi et al., 2024). As of current today, 50 million people have been diagnosed with epilepsy. (Egesa et al., 2022; Meyer et al., 2010). With almost 13 million epileptics impacted by the Disability-Adjusted Life Years (DALYs) index in 2016, the GBD analysis indicates that children and young people with epilepsy incur the biggest burden of any neuropathy (Fiest et al., 2017). 0.5% of the world's illness burden is attributed to the Disability-Adjusted Life Years (DALYs) index, which calculates the loss of health based on the total number of years of life lost owing to premature death and years lived with disability. In India, the world's most populous nation with a population of approximately 1.4 billion, between 10 and 12 million people have epilepsy (Tana et al., 2024).

Key words: Anti-epileptic drugs, pathophysiology, seizures, epidemiology, hypersynchrony.

INTRODUCTION

Epilepsy is a dangerous neurological illness characterized by a transient occurrence of abnormal, excessive, and/or coordinated neuronal activity in the brain along with a number of neurobiological, cognitive, and psychosocial signs and symptoms. (Trinka et al., 2015; Viswanatha et al., 2016). The International League Against Epilepsy (ILAE) defines epilepsy as at least two unprovoked (or reflex) seizures occurring more than 24 hours apart, one unprovoked (or reflex) seizure and a probability of additional seizures that is equivalent to the overall recurrence risk (at least 60%) following two unprovoked seizures, occurring over the following ten years, and a diagnosis of epilepsy syndrome. However, for population-based investigations, the ILAE Epidemiology Commission suggests defining epilepsy as two or more unprovoked seizures that happen at least twenty-four hours apart (Berg et al., 2010, Sharma et al., 2020).

Spontaneous seizures are those that happen when there are no known triggers. Patients with antecedent stable (non-progressing) CNS insults (remote symptomatic seizures), progressive CNS abnormalities (brain tumors or degenerative conditions) (progressive symptomatic seizures), or events that occur without known risk factors or etiological factors (idiopathic and cryptogenic seizures) are considered to have unprovoked seizures (De Bruijn et al., 2019, Walter Falco., 2020, Egesa et al., 2022).

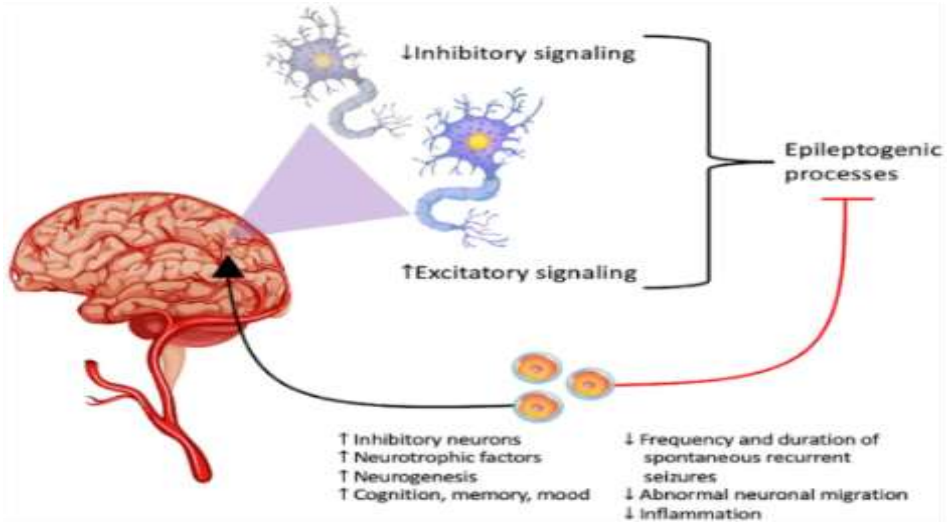


Fig 1; Shows the primary underlying pathophysiology of epilepsy: aberrant excitatory and inhibitory signaling at the neural level. Stem cells may ameliorate this imbalance in signaling pathways, while also promoting brain repair secondary to epileptic episodes (Alayli et al., 2023)

Epilepsy is the second most prevalent cause of mental health problems globally, especially in young individuals. Its disease burden is comparable to that of lung cancer in males and breast cancer in women (Weatherburn et al. (2017). People of

all ages are affected by epilepsy, one of the most prevalent and devastating neurological conditions. Since some people will obtain an incorrect diagnosis of epilepsy while others will receive a true diagnosis, it is critical that seizures be accurately diagnosed. In reality, many patients do not receive the proper treatment, which frequently has serious repercussions, and diagnostic errors are commonplace. While many patients can control their seizures with a single prescription, others need multiple drugs, neuromodulation devices, reconstructive surgery, or diet. Furthermore, one-third of individuals will still experience uncontrollable seizures. (Kanmounye et al., 2022 & Mosüge and Patel., 2020.

A variety of pharmacologic drug families, such as benzodiazepines (Diazepam), barbiturates (Phenobarbitone), gamma amino butyric acid (GABA) analogs, succinimides (ethosuximide), hydrations (Phenytoin), carbamazepine, etc., have historically been used to treat epilepsy.

Vigabatrin, levetiracetam, topiramate, lamotrigine, zonisamide, lacosamide, rufinamide, and stiripentol are only a few of the several novel pharmacological families that have lately been identified and are believed to be rather safe. Drugs that have been used and known for a long period, such as phenytoin and carbamazepine, are considered classics (Chue et al., 2023). These medications have comparable effects, but they differ in terms of how cost-effective they are and how many unfavorable side effects they produce, such as ataxia, mental slowness, dizziness, mental confusion, disrupted sleep, anorexia, somnolence, and anger. (Falco-Walter 2020 & Doan Duy Linh et al., 2022).

EPIDEMIOLOGY

The first worldwide report on epilepsy, A Public Health Imperative, was published in 2019 by WHO and important partners. It highlighted the facts on the prevalence of epilepsy and the public health response needed at the national, regional, and international levels (Beghi., 2020).

The Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031 was endorsed by the 75th World Health Assembly. According to Odintsova et al., 2023 & Leonardi et al., 2024, it acknowledges that there are common preventative, pharmacological, and psychosocial strategies for epilepsy and other neurological disorders that can serve as beneficial foundations for strengthening and accelerating services and support for these ailments.

The World Health Organization has released a technical brief on epilepsy that provides policymakers and healthcare planners with steps to take to lower the frequency of epilepsy in nations by identifying and ranking the best solutions across a variety of socioeconomic dimensions. The World Health Organization (WHO), the International League Against Epilepsy (ILAE), and the International Bureau for Epilepsy (IBE) spearheaded the Global Campaign Against Epilepsy in order to increase awareness of the disorder, enhance governmental and private measures to improve care, and minimize its impacts. The World Health Organization has published a technical brief on epilepsy that lists and ranks the best solutions across a range of socioeconomic variables to assist legislators and healthcare planners in taking action to reduce the condition's prevalence in countries. (Leonardi et al., 2024; Behr et al., 2016).

PHASES OF SEIZURES

1. The Aura Phase: This phase takes place right before a seizure starts. more than five to twenty minutes, with an average duration of sixty minutes. If you experience severe fear, nausea, headache, vertigo, numbness, or "pins and needles,"
2. The Ictal Phase. This phase causes drastic electrical changes in the brain. Here are a few common signs of this stage: bewilderment, flashing lights, loss of consciousness (blacking out), difficulties speaking, loss of muscle control, and repeated movements (lips, arms).
3. The Postictal Stage: During this final stage, the brain tries to stop the misfiring nerve cells while the body begins to relax. The physical repercussions of the seizure also started to show. The postictal phase may last for seconds, minutes, hours, or even days. Confusion and sleepiness are the most common symptoms. (Peng and May, 2020; Sobayo et al., 2013; Kähn et al., 2024).

CLASSIFICATION OF EPILEPSY

The classification of epilepsy types is more thorough than that of seizures; it includes information regarding the general clinical picture, imaging, genetics, laboratory testing, prognoses, and comorbidities in addition to considering the possibility of having multiple seizure types. The etiology and symptoms often provide additional information that is essential for guiding the patient's treatment. (Scheffer et al., 2017).

There are several types of epilepsy: (1) Focal (2) All-around applicable (3) In conjunction Focal and Generalized (4) Not known. To place the patient in one of these groups, all of the patient's seizure types are categorized and then mapped to one of these four groups. Certain epilepsy syndromes, like Lennox-Gastaut syndrome and Dravet syndrome, frequently cause both focal and generalized seizures. For this reason, a new classification called "Combined Generalized and Focal Epilepsy" was developed (Scheffer et al., 2018)

1) FOCAL SEIZURE

Cerebral hemisphere's networks are the source of focal seizures, which can occur with or without cognitive impairment.

• Brain structural abnormalities are typically linked to focal seizures.

Focal seizures are caused by a neural network that is either more widely dispersed but still located within the hemisphere or discretely contained within one hemisphere of the brain. In 2020, Ratcliffe et al.

• Focal seizures (sometimes known as "simple focal seizures" and "complex focal seizures") with or without dyscognitive characteristics.

Generalized seizures, also known as focal seizures with secondary generalization, can develop from focal seizures. Interictal EEG: Usually normal or may exhibit sharp waves or short discharges known as epileptiform spikes (Lai et al., 2023).

(a) Attacks by focal motors

These start in the precentral motor cortex and are brought on by clonic movements in particular muscle groups, such the hand or face. If they continue for hours, they are called partial epilepsia continuants. The discharge propagating along the precentral gyrus may cause a march of clonic movements throughout the body (Jacksonian seizure). Following the seizure, Todd's paresis—a transient weakening of the affected body parts—may happen (Ivarola & colleagues, 2023).

(b) Attacks by focal sensory perception

Either localized or spreading paresthesias result from them, which begin in the postcentral sensory cortex**.**

(c) Epilespy of temporal lobe

Memories and hallucinations from any of the five senses may fall under this category. Gustatory and olfactory hallucinations are typically unpleasant. Whereas jamais vu is a sudden feeling of unfamiliarity when the patient is in their own environment, déjà vu is a strong sense of familiarity with the current situation. When a patient has automatism, they may continue with their daily activities while still conscious but "dreamy." The patient is unable to remember these events after the attack. (Ratcliffe et al., 2020; Fisher, 2017; Kehn et al., 2024; Fisher et al., 2022).

2) GENERALIZED SEIZURE

The most common sort of seizures (60%) are convulsive ones. " - One-third of cases begin with generalized seizures that impact both hemispheres of the brain. At first, two-thirds are focal seizures, which only impact one side of the brain. Generalized seizures may later emerge from these events. Generalized seizures may be categorized into six primary types: absence, myoclonic, clonic, tonic-clonic, tonic, and atonic seizures. They typically happen abruptly and are all marked by unconsciousness. In tonic-clonic seizures, the back arches for 10 to 30 seconds (the tonic half), and the limbs contract and then expand. The tightening of the chest muscles may cause a yell followed by a clonic phase or coordinated limb shaking (Tittensor 2018).

(a) Tonic-clonic (grand mal) seizures

The patient may have mild symptoms like myoclonic twitches and anxiety before to the seizure. The seizure may start suddenly and be preceded by an odd sensation (aura). The muscles tense violently during the tonic phase. After being struck senseless, the patient collapses to the ground. Cleaning your teeth might cause cyanosis. The clonic phase, marked by intense convulsive jerks, begins after approximately a minute. Both tongue biting and fecal or urine incontinence are possible. After that, the patient starts to feel sleepy or nods out for a few hours. The Babinski sign is positive and the reflexes are depressed. When the patient awakens, postictal disorientation may occur. (Steriade and others, 2022).

(b) Absence attacks (petit mal)

These begin in childhood and are characterized by three spike-and-wave discharges per second on the EEG. Congenital neurological instability is the cause. There are brief periods of unconsciousness, occasionally accompanied by frequent eyelid blinking. To an observer, the child can appear perplexed or daydreaming. Recovery occurs immediately, and there are no side effects. Children may experience these events hundreds of times a day. When evaluating a child who may have petit mal seizures, inquire about school performance and other indicators because these seizures may impede scholastic development (Haoudy et al., 2022).

(c) Myoclonic seizures and epilepsy

This kind of idiopathic epilepsy first appears in early childhood. There are other types of generalized seizures, including myoclonus, which is typified by sudden, jerky limb movements (Fisher et al., 2022).

(d) Clonic seizures

The arm, neck, and face muscles twitch in a rhythmic manner during these unusual convulsions. They could last between three and five minutes (French et al., 2022).

(e) Tonic seizure

Tonic seizures are characterized by facial and truncal muscle spasms, flexion or extension of the upper and lower extremities, and decreased consciousness (French et al., 2022).

(f) Atonic seizure

The outcome of an atonic seizure is a sudden reduction in muscle strength (Steriade et al., 2022; Hirsch et al., 2022).

Problem	Clinical manifestation	Postictal state
Focal seizures without impairment of consciousness or awareness • With observable motor and autonomic symptoms • Jacksonian	Tonic and then clonic movements that start unilaterally in the hand, foot, or face and spread to other body parts on the same side. Turning of the head and eyes to one side or tonic and clonic movements of an arm or leg without the Jacksonian spread.	Normal consciousness
Other motor	A ‘funny feeling’ in the epigastrium, nausea, pallor, flushing, light-headache.	Normal consciousness
With automatic symptoms	Numbness, tingling simple visual auditory or olfactory hallucination such as flashing lights buzzing or odors.	Normal consciousness
-Without subjective sensory or psychic phenomena	Anxiety or fear; feelings of familiarity or unreality; dreamy States; fair or Rage flashback experiences; more complex hallucinations.	Normal consciousness

Focal seizures with impairment of consciousness	The seizure may or may not start with the autonomic or psychic symptoms outlined above. consciousness is impaired, and the person appear confused. Automatisms include automatic motor behaviors such as chewing smacking the lips, walking about, the unbuttoning clothes; also, more complicated and skilled behaviors such as driving a car.	The patient may remember initial autonomic or psychic symptoms but in amnesia for the rest of the seizure temporary confusion and headache may occur.
Focal seizures that become generalized	Partial seizure that becomes generalized resemble tonic clonic seizure unfortunately the patient may not recall the focal onset, and observes may overlook it	As in a tonic clonic seizure described two attributes indicate a partial seizure that has become generalized (1) the recollection of aura and (2) a unilateral neurologic deficit during the postictal period.

Table 1: Report of Classification and Terminology of the International League Against Epilepsy. Berg AT, Berkovic SF, Brodie MJ et al. (Whitney, 2022)

Problem	Clinical manifestation	Postictal (post seizure)
Generalized seizure Tonic clonic (grand mal)	The body goes into tonic extensor stiffness and the person abruptly loses consciousness, sometimes while screaming. The victim stops breathing and turns cyanotic. After respiration returns, there is a clonic period of rhythmic muscle contraction that is frequently loud, accompanied by excessive salivation, tongue biting, and the possibility of urine incontinence.	confusion, drowsiness, exhaustion, headaches, muscle aches, and occasionally the transient persistence of bilateral neurological impairments including Babinski responses and hyperactive reflexes. For the seizure, the subject has amnesia and does not remember any aura.
Absence	Two variants are identified: a sudden, transient lapse in consciousness accompanied by brief blinking, staring, or hand and lip motions without falling. Usually, absences last longer than 10 seconds.	No aura recalled. in petit mal absences a prompt return to normal in atypical absence some postictal confusion.
Myoclonic	Sudden brief rapid jerks involving the trunk or limbs associated with a variety of disorders.	Variable
Myoclonic atomic (drop attack)	Sudden loss of consciousness with a variety of disorder. Sudden loss of consciousness with falling but no movement. injury may occur	Either a prompt return to normal or a brief period of confusion
Pseudo seizures May mimic seizure but are due to a conversion reaction (a phycological disorder)	The movement frequently deviates from a neuroanatomic pattern and may have personally symbolic meaning. Accidents are rare.	Variable

Table 2: Report of Classification and Terminology of the International League Against Epilepsy. Berg AT, Berkovic SF, Brodie MJ et al. (Whitney, 2022)

6 Pathophysiology

The electrical activity of the brain is typically not coordinated. Numerous elements both inside the neuron and in the cellular environment regulate the neuron's activity. Ion channel type, number, and distribution, receptor changes, and gene expression variations are internal determinants; ion concentrations, synaptic plasticity, and glial cell regulation of transmitter breakdown are external impacts (Boleti et al., 2024, Kirmse and Zhang 2022).

(a) GABA Synthesis, Release and Metabolism

GABA, a neurotransmitter inhibitor, is produced by glutamic acid decarboxylase (GAD), and most GABA is encoded by the GAD1 gene. A mutation in the GAD1 gene causes an imbalance between activating and inhibitory neurotransmitters. The primary inhibitory neurotransmitter in the central nervous system is GABA.

When the carboxyl group is deprotonated and the amino group is protonated, the molecule transforms into a zwitterion. Because GABA may bind to several receptors with different conformations, its structural flexibility is essential to its biological activity. Pharmaceutical companies have created a

number of GABA analogs with stiffer structures to better regulate their binding to their receptors (Righes Marafiga et al., 2021).

GABA, which regulates neuronal activity, is present in the majority of intermediate neurons that form synapses on cell bodies and proximal axons. At the GABAergic axon terminals, ketoglutarate is transaminated into glutamic acid to create GABA, which is then transformed back into GABA by glutamic acid decarboxylase (GAD). After being released into the synapse, the drug operates via activating GABA-A and GABA-B receptors. GABA-A receptors are ligand-gated ion channels that increase the entry of chloride ions into the cell to provide a quick inhibitory response. G protein-linked ion channels called GABA-B receptors enhance the extracellular transit of potassium. By lowering calcium influx, GABA-B receptors exert a gradual inhibitory effect (McKay et al., 2019).

GABA-B receptors are G protein-linked ion channels that enhance the extracellular transit of potassium. By lowering calcium influx, GABAB receptors have a gradual inhibitory effect. Both activating and inhibitory axon terminals include GABAB receptors. When a stimulus is activated, the release of neurotransmitters is reduced. After GABA is released from the presynaptic axon terminals, the GABA transaminase catabolizes it to succinic semialdehyde. The enzyme succinic acid semialdehyde dehydrogenase converts succinic semialdehyde into succinic acid, which subsequently enters the Krebs cycle. Disruptions in GABA transmission have been associated with several types of epilepsy (Gallagher, 2023; Absalom et al., 2022).

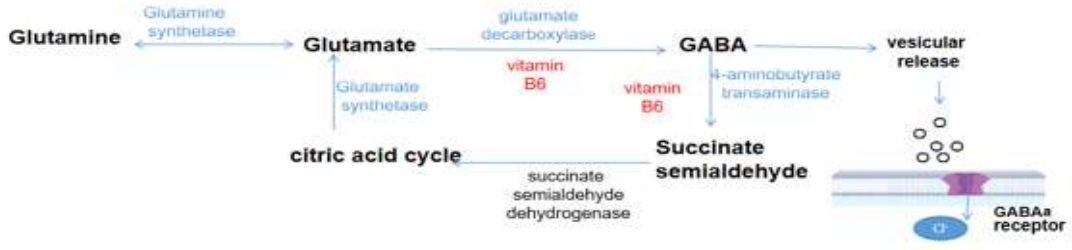


Fig 2: The image depicts a diagram of the synaptic cleft, which is the gap between two neurons where chemical signals are transmitted. The diagram shows the process of neurotransmission, specifically the release and uptake of the neurotransmitter GABA (gamma-aminobutyric acid) (Katzung & Trevor, 2015).

GABA acts through a number of receptors, including GABA-A, GABA-B, and GABA-C receptors, after leaving the presynaptic terminal. When engaged, GABA-A receptors, which are pentameric ligand-gated ion channels made up of five different subunits, permit a hyperpolarizing Cl− current. Twenty distinct GABA-A receptor subunits have been found thus far: five α (α1 to α6), four β (β1 to β4), three γ (γ1 to γ3), one δ, three ρ (ρ1 to ρ3), and one of the ε, θ, and π subunits. These 20 subunits are crucial for pharmacology, kinetics, trafficking, and localization since they can create a wide variety of combinations. (Castellano et al., 2020; Sieghart & Savic, 2018).

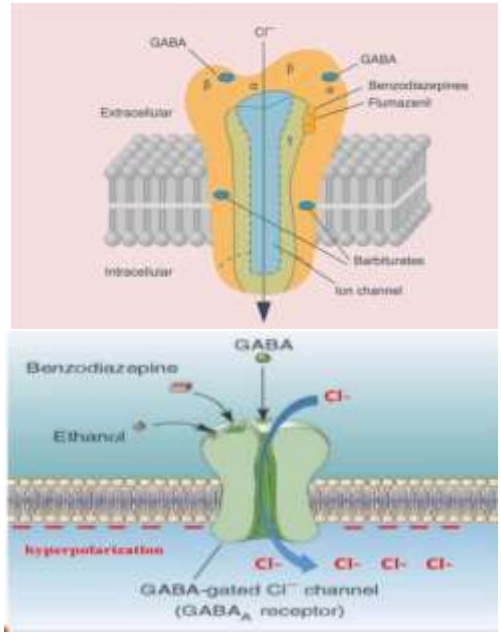


Fig 3: The image depicts the GABA-A receptor, a ligand-gated ion channel responsible for inhibitory neurotransmission in the brain. The receptor is composed of multiple subunits that form a chloride channel. When GABA binds to the receptor, it triggers the opening of the chloride channel, allowing chloride ions to flow into the neuron and hyperpolarize the membrane potential (Sharma et al., 2020).

GABA-B receptors, which are G protein-coupled ion channels, allow GABA to also activate the G protein-coupled inward rectifier potassium channel (GIRK), which results in a potassium channel efflux from the cell. Walterlain (2023) states that GABA or other neurotransmitters including glutamate, norepinephrine, 5-hydroxytryptamine, and dopamine are released less frequently when presynaptic GABA-B receptors function as autoreceptors. GABA-B receptors regulate neuronal excitability in these ways. GABAC receptors are among the several ligand-gated ionotropic channels found in the retina. When GABA binds to GABA-C receptors, which are distinguished by the presence of a ρ subunit, they cause a Cl− current. Unlike GABAA receptors, GABAC receptors are not responsive to the convulsant bicuculline.(REFERENCE)

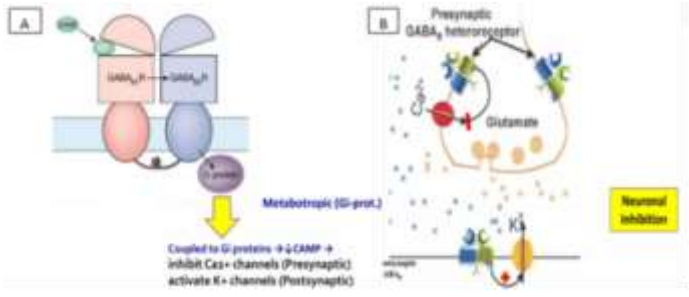


Fig 4: The image depicts the GABA-B receptor, a metabotropic receptor that plays a crucial role in inhibitory neurotransmission in the brain. The receptor is

composed of two subunits, GABA-B1R and GABA-B2R, which are coupled to Gi proteins (De Bruijn et al., 2019, Kirmse & Zhang, 2022)

(c) The Effect of Development and Disease States on GABAA Receptor Responses

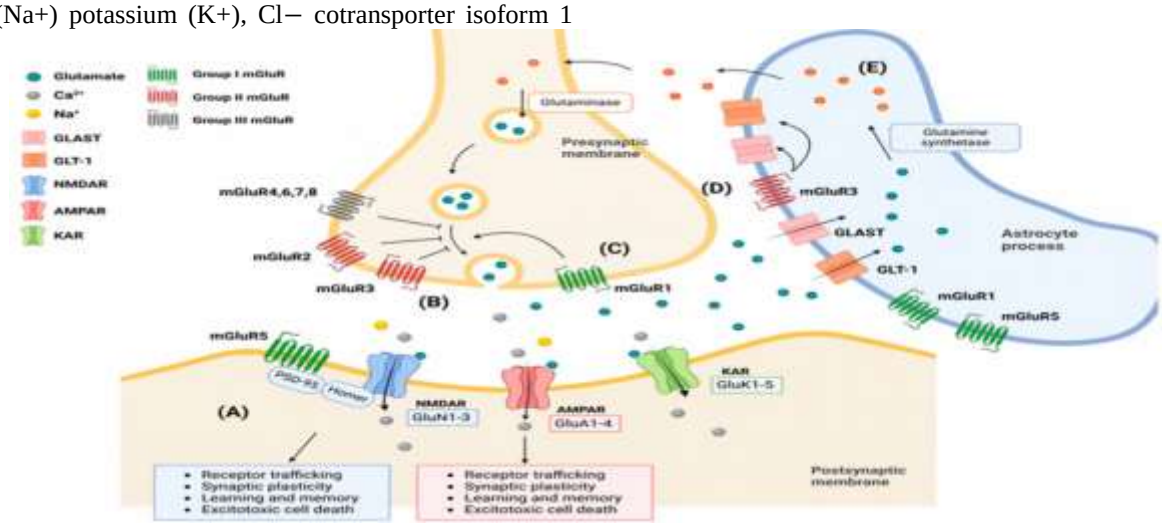
When GABA binds to GABAA receptors in the mature brain, the concentration gradient of GABA from high external levels to low intracellular Cl− levels causes a hyperpolarizing influx of Cl−. GABAA receptor stimulation in the immature brain, in contrast to the adult brain, is primarily depolarizing and may have a pro-convulsive impact because of an outward flux of chloride from high intracellular to lower extracellular Cl− levels. The action of two cotransporters maintains the intracellular Cl− level, which determines whether GABAA-mediated neurotransmission is depolarizing or hyperpolarizing. Cl− is transported into the cell by the sodium (Na+) potassium (K+), Cl− cotransporter isoform 1 (NKCC1) and extruded out of the cell by the K+, Cl− cotransporter isoform 2 (KCC2). It has been suggested that the switch from depolarizing to hyperpolarizing GABA occurs before or soon after birth, while the precise point in brain development is unknown (R. Sharma et al., 2020, Kim & Yoon, 2023).

(1) Glutamate

The most prevalent amino acid in the brain, glutamate, is one of the primary neurotransmitters that stimulate the central nervous system (CNS). By encouraging quick signal transmission in glial cells, especially astrocytes, glutamate plays a crucial role in neuronal excitability and is engaged in cognitive processes including learning and memory (Albrecht and Zielińska 2017). The enzyme glutaminase produces glutamate, the anion of glutamic acid. Presynaptic neurons and nearby glial cells produce this during the glutamate-glutamine cycle in the central nervous system. Glutamate-mediated cellular processes involve cell surface receptors (Danbolt et al. 2016). N-methyl-D-aspartate receptors (NMDAR), kainate receptors (KAR), metabotropic glutamate receptors (mGluR), and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors are the four different types of glutamate receptors that have been found. Three transmembrane domains are present in each of the four ionotropic glutamate receptor proteins. When triggered, ionotropic receptors open membrane channels to allow ions to pass through. Each of the four distinct proteins that make up the ionotropic glutamate receptor family has three transmembrane regions. Ionotropic receptors are ligand-gated ion channels with an iron-conducting pore and a ligand binding site for neurotransmitter molecules. A conformational change takes place when the ligand attaches itself to the receptor protein. When the receptor's channel opens, it becomes active (Sibarov and Antonov, 2018).

AMPAR and KAR are permeable to potassium and sodium, but NMDAR is permeable to calcium. Once the channel is opened, a number of factors regulate the ion flow, including the driving force on permeable ions. These receptors regulate the effects of neurotransmitter. Ionotropic glutamate receptors depolarize neurons when engaged, demonstrating a stimulatory function, whereas glutamate acts on a portion of metabotropic receptors. They might, however, also have an inhibitory effect (Bramham & Zhang, 2020).

G-protein receptors, or mGluRs, function by way of second messengers.



The intracellular domain of the mGluR monomeric proteins binds to G-proteins, while the extracellular domain has a neurotransmitter binding site. Neurotransmitters that bind to mGluR activate G-proteins that separate from the receptor and interact with effector proteins, including intracellular messengers that open or close ion channels and enzymes that control ion channels. The primary mediators of glutamatergic transmission are ionotropic glutamate receptors, whereas mGluR typically serve as modulators (Goel et al., 2020). The channel opening caused by neurotransmitter binding occurs in ionotropic receptors faster than in metabotropic receptors.

Thus, ligand-gated ion channels facilitate rapid synaptic transmission. Glutamate accumulation has been demonstrated to result from overstimulation of ionotropic and metabotropic receptors. Free radicals are produced when the glutamate receptor is overstimulated. These radicals cause oxidative stress, which in turn causes an imbalance in mitochondrial function. Disruption of mitochondrial activity contributes to the onset and progression of epilepsy because it sets off the cascades of apoptosis, the basic process of cellular death. The role of this family in cell death during epilepsy has been the subject of numerous research (Huang et al., 2024). The results demonstrate that both apoptotic and necrotic neuronal cell death pathways contribute to epilepsy, in addition to excitotoxic mechanisms.

Fig 5: Mechanism and types of ionotropic and metabotropic glutamate receptors with associated proteins (Huang et al., 2024) .

(A) Four subunits from a central ion channel pore make up ionotropic glutamate receptors. These consist of KAR (GluK1–5 subunits), AMPAR (GluA1–4 subunits), and NMDAR (GluN1–3 subunits). In addition to controlling Ca2+ permeability, these channels are involved in learning, memory, synaptic plasticity, receptor trafficking, and even cell death.

(B) G-protein-coupled metabotropic glutamate receptors regulate neuronal excitability and synaptic transmission. They are separated into three categories: mGluR1 and 5 are in Group I; mGluR2 and 3 are in Group II; and mGluR4, 6, 7, and 8 are in Group III.

(C) Group I metabotropic receptors improve neuronal excitatory activity. While postsynaptic mGluR5 controls the activity of postsynaptic NMDARs via PSD-95 and Homer protein, resulting in NMDAR phosphorylation and NMDAR current potentiation, presynaptic mGluR1 promotes vesicular release of glutamate.

(D) Excitatory activity is mostly inhibited by Group II and Group III metabotropic receptors. Presynaptic glutamate release is suppressed by mGluR2, 3, mGluR4, 6, 7, and 8. Additionally, mGluR3 is present on astrocytes, where it increases synaptic glutamate reuptake and decreases neuronal hyperexcitability by modulating the glutamate transporter proteins GLAST and GLT-1.

(E)Astrocytes surrounding synapses absorb glutamate from the synaptic cleft, where it is transformed into glutamine by the enzyme glutamine synthetase. In order to preserve neuronal connection, the resultant glutamine is then turned back into glutamate at presynaptic terminals, where it remains in vesicles (Figure generated with Bio Render.com, viewed on February 23, 2023).
The direct binding ligand that triggers AMPAR is glutamate. AMPARs are engaged in fast excitatory neurotransmission in the brain and are expressed in the postsynaptic neuronal membrane. Four subunit kinds, GluA1 to GluA4 (sometimes called GluR-A to GluR-D), are arranged in various configurations inside their tetrameric structure. The primary location for controlling calcium permeability is the GluA2 subunit.

Posttranscriptional changes affect how the GluA2 subunit regulates calcium permeability (Eiro and colleagues, 2023). If the AMPARs have the unaltered GluA2 subunit or the GluA2-lacking structure, they are calcium (Ca2+) permeable. The majority of AMPARs in the brain are Ca2+-impermeable because they contain the mutant GluA2 subunit. There is growing evidence that Ca2+-permeable AMPARs have a role in learning, memory, synaptic plasticity, excitotoxic cell death, and receptor trafficking (Lovinger et al., 2022). Synaptic homeostatic plasticity results from dynamic changes to AMPARs during their synthesis, membrane trafficking, and destruction, all of which are controlled by intricate regulatory proteins. More calcium-impermeable GluA2-containing AMPARs were found in their brains, which may indicate a long-term change in neuroplasticity for neuroprotection in reaction to neurotoxicity caused by epilepsy. (Rogawski 2013; Hanada 2020, Phillips et al., 2020)

(ii) N-Methyl-D-Aspartate Receptors (NMDARs)

Glutamate release depolarizes postsynaptic neurons and causes an inward cation current by activating glutamate receptors. There are two types of excitatory postsynaptic currents. While NMDARs mediate a slower current that lasts anywhere from tens to hundreds of milliseconds, AMPAR activation mediates a fast current that rises quickly before decreasing. Furthermore, the tetrameric structure of NMDARs is composed of various combinations of GluN1, GluN2, and GluN3 subunits, each of which has many isoforms (Thapa & Jewett, 2020). All functional NMDARs require the GluN1 subunit, which has binding sites for glycine and D-serine. Glycine-binding (B) sites for receptor forward trafficking to the cell surface are present in both the GluN1 and GluN3A subunits. NMDAR surface expression is significantly decreased by a mutation in the GluN3A subunit's glycine-binding region.

These results imply that glycine-binding sites are essential for NMDAR modulation. In addition to providing glutamate binding sites, the GluN2 subunits regulate NMDAR production and function (Haiti, 2020). A few different kinds of NMDAR modulators are briefly described. These include allosteric sites that differ from natural agonist binding sites, glycine site antagonists, sodium and calcium blockers, and competitive antagonists that function at the agonist binding site. Because the magnesium ion (Mg2+) blocks the channel at the resting membrane potential, glutamatergic ligand binding is insufficient to activate the NMDAR channel. The removal of Mg2+ causes the membrane to depolarize, allowing potassium (K+) ions to exit the cell and sodium (Na+) and calcium (Ca2+) ions to enter in a voltage-dependent manner. Low extracellular magnesium is associated with brain discharges that resemble seizures due to the unblocking of NMDARs. It is thought that calcium influx through NMDARs, which can activate the binding proteins, has a major impact on synaptic plasticity, a biological mechanism for learning and memory (Sivakumar et al., 2022; S. Chen et al., 2022).

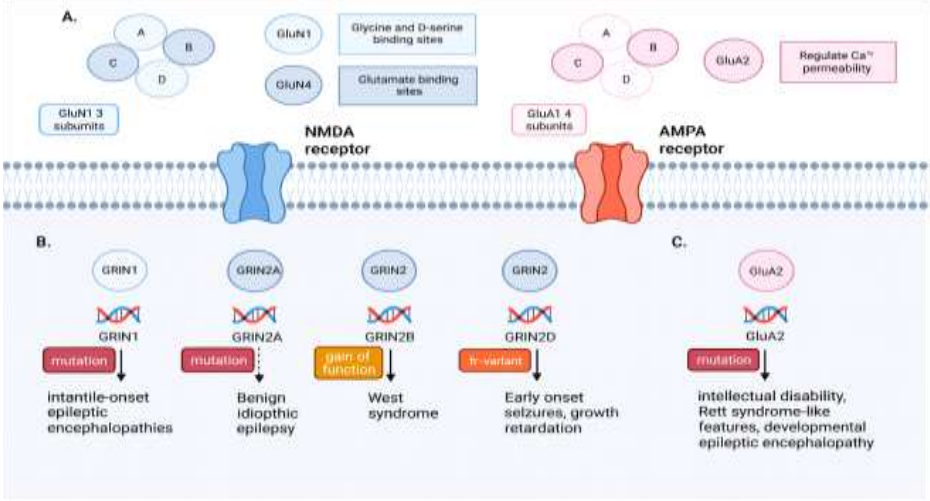


Fig 6: The image illustrates the structure and function of NMDA and AMPA receptors, which are crucial for neurotransmission in the brain. The top section of the image shows the composition of these receptors: NMDA receptors consist of GluN1-3 subunits and AMPA receptors comprising GluA1-4 subunits (Figure created with BioRender.com, accessed on 23 February 2023; Jewett & Thapa, 2020)

(a) Kainate Receptors

Ionotropic glutamate receptors include kainate receptors (KARs) in addition to AMPA and NMDARs. KARs participate in postsynaptic excitatory neurotransmission and are activated by the agonist kainate. Functional KARs are produced by various Glu K1-Glu K5 assemblages forming tetrameric structures. Alternation splicing of Glu K1, Glu K2, and Glu K3 can result in variations such as GluK1a, GluK1b, GluK1c, and GluK2a-2c. KARs are expressed intracerebrally in the amygdala, hippocampus, and entorhinal cortex. Together with the biophysical characteristics of 21 different types of heteromeric receptors, their interaction with their auxiliary subunits when activated results in a distinct electrophysiological response with a delayed decay current and low amplitude. Both canonical ionotropic and non-canonical metabotropic signals are mediated by KARs. Like metabotropic glutamate receptors, which also regulate transmitter release and neuronal excitability, KARs initiate a non-canonical signaling cascade. A non-canonical activity of KARs is thought to be involved in some of the methods by which presynaptic KARs regulate neurotransmitter releases. The activation of second messenger signaling pathways is one potential non-canonical mechanism of action for KARs. According to (Lerma and Valbuena 2016), abnormal KAR recruitment at recurrent mossy fiber synapses causes epileptogenic neuronal activity in temporal lobe epilepsy. Additionally, temporal lobe epilepsy (TLE), a common form of partial epilepsy marked by the loss of neurons in the CA1 and CA3 regions of the hippocampus, can be experimentally modeled with kainic acid (KA).

Intra-hippocampal KA injections cause identical preconditions for TLE, such as encephalitis, epilepsy, or prior brain traumas; intra-amygdaloid KA injections generate psychomotor seizures and neuropathological abnormalities. KA1 subunit expression is high in CA3 pyramidal cells, but KA2 subunit expression is high in CA1 and CA3 pyramidal cells (Mulle and Crépel 2015). Because of this, KA1 and KA2 receptors have a strong affinity for glutamate and are widely expressed in the hippocampal CA3 region. As a result, in this activation model, the hippocampus often becomes the epileptogenic zone, making it vulnerable to the excitotoxic damage that KA causes.

As mentioned before, KARs work in the central nervous system by modifying neuronal excitability and controlling synaptic network activity through complex expression patterns. The movement of KARs from the endoplasmic reticulum (ER) to the cell surface or their retention in the ER is one important regulating mechanism. Some KAR-interacting proteins are involved in surface trafficking (Nair et al., 2021).

For example, NETO (neuropilin and tolloid-like) proteins may be involved in the trafficking of KARs. Other protein modifications, such as SUMO (small ubiquitin-related modifier) and PKC (protein kinase C)-mediated phosphorylation, have been reported to have an impact on surface expression and endocytosis. Furthermore, research employing calcium imaging and molecular modeling have demonstrated that the entire activation of GluK2/GluK5 heteromeric KAR channels needs the occupancy of both GluK2 and GluK5 ligand binding domains.

Notably, by preventing glutamate receptor trafficking, neurotransmitter release, and slowing down following hyperpolarization, KARs' non-canonical signaling, which stimulates phospholipase C and PKC through a metabotropic G-protein dependent pathway, may regulate neuronal excitability. Further investigation into the roles of the canonical and non-canonical KAR pathways in the generation of seizure activity is worthwhile. The synthesis, assembly, and cell surface trafficking of KARs play a major role in determining neuronal excitability in the central nervous system. Since KAR malfunction is linked to ischemia, chronic pain, epilepsy, and mental disorders like schizophrenia, it is essential to comprehend how KAR-interacting proteins

function in surface expression and trafficking in order to develop innovative treatment strategies for these conditions (Mulle and Crépel, 2021).

(b) Metabotropic Receptor

Metabolotropic receptors (mGluRs) are G-protein-coupled non-ionotropic receptors that can affect presynaptic glutamate release or postsynaptic ionotropic receptors. The primary functional subtypes of Group I mGluRs are postsynaptic mGluR1 and mGluR5, which are also present in astrocytes. Excitatory signaling is enhanced by Group I mGluRs, particularly mGluR1 and mGluR5. Presynaptic mGluR1 enhances the vesicular release of glutamate, whereas postsynaptic mGluR5 regulates the activation of postsynaptic ionotropic receptors. By activating mGluR1, a specific agonist can prolong and sustain interictal discharge. Long-term depression (LTD) and long-term potentiation (LTP), two long-lasting synaptic plasticities, can be initiated by activating mGluR1 at multiple glutamatergic synapses through the depolarization of hippocampal CA1 pyramidal cells and intracellular calcium increases (Eng et al., 2016). It has been demonstrated that brain slices from patients with pharmaco-resistant TLE have increased hippocampal mGlu5. The hyperexcitability of the hippocampus is more likely to be caused by the elevation of mGluR5 in surviving neurons than to be the primary cause of epileptic seizures in pharmaco-resistant TLE patients because this phenomenon has been observed in both individuals with and without hippocampal sclerosis.

Moreover, protein–protein interaction is an essential coupling mechanism for the operation and regulation of metabotropic receptors. When mGlu5 binds to NMDARs via scaffolding proteins, namely Homer protein and postsynaptic density protein 95 (PSD-95), NMDARs get phosphorylated (Celli et al, 2019). This leads to the potentiation of NMDAR currents. Group II metabotropic receptors, including mGluR2/3, are mostly located in the presynaptic terminal and have the capacity to prevent presynaptic glutamate release. mGluR2/3 expression was markedly and progressively down-regulated in both CA1 and CA3 in a pilocarpine-induced SE paradigm. Astrocytes contain mGluR3, which inhibits hyperexcitability by positively regulating GLAST and GLT-1, the glutamate transporter proteins for synaptic glutamate reuptake (Su et al., 2022).

Astrocytic mGluR3 and mGluR5 expression is interestingly elevated in TLE, indicating that seizure-induced overexpression of two opposing mGluR subtypes in reactive astrocytes may mediate glial function modulation and glial–neuronal communication alterations during epileptogenesis (Eng et al., 2016). Group III metabotropic glutamate receptors include the inhibitory presynaptic receptors mGluR4, 6, 7, and 8. While mGluR1 can make a person more prone to seizures, mGluR4 is increased in TLE to balance the excitatory activity and seizure-associated vulnerability of hippocampus neurons. In conclusion, metabotropic glutamate receptors are important for hippocampal excitability, neuronal degeneration, and epileptogenesis. Additionally, they change the glutamate receptor's expression and position (Huang et al., 2024; Celli et al., 2019).

(3.) The voltage-Gated calcium channels

Calcium channels can be classified as low voltage-activated (LVA) or high voltage-activated (HVA) based on whether they open at more positive (e.g., -40 mV) or more negative (e.g., -60 mV) membrane potentials. The structure of high voltage-activated channels can be used to further categorize them. These are voltage-gated calcium channels.

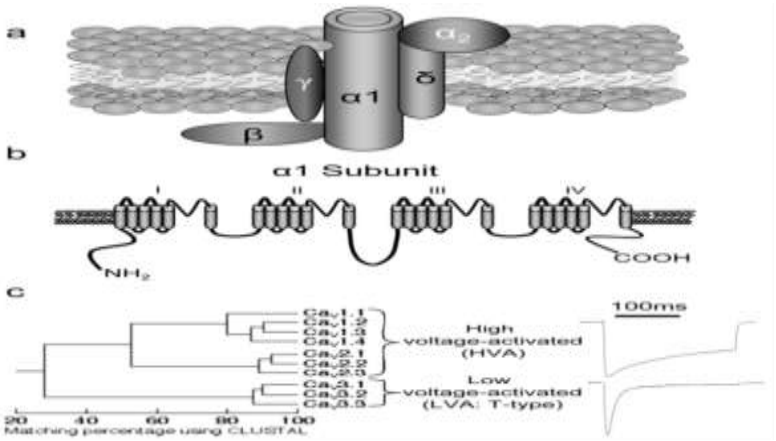


Fig 7: The image depicts the structure and function of voltage-gated calcium channels, which play a crucial role in various physiological processes, including neuronal signaling. In epilepsy, these channels are often implicated due to their involvement in regulating neuronal excitability. (Sibarov & Antonov, 2018)

The right panel shows representative calcium current traces obtained from reticular thalamic neurons in response to membrane potential depolarization. The upper trace shows a slow inactivating high voltage-activated current, whereas the lower trace shows a fast-inactivating low voltage-activated current. Low voltage-activated channels, also known as "T-type," are further classified according to the composition of their α1 subunits (CaV3.1-CaV3.3) because of their comparatively "tiny" or "transient" currents. The L-type calcium channels are mostly observed post-synapsically and are categorized as slowly inactivating. They promote extended calcium ion influx in postsynaptic neurons, which further intensifies neuronal depolarization. L-type calcium channel antagonists have antiepileptogenic properties, however they can make absence epilepsy worse. (Park et al., 2015) A number of ancillary proteins (β, α2δ, and γ subunits) are connected to the various types of HVA channels and change the biophysical properties and expression of the channels, even though the molecular machinery needed to conduct calcium ions is present in each calcium channel α1 subunit (calcium-selective pore, voltage sensing, and gating mechanisms). In 2018, Carpenter and Schorge found Four β subunit genes (β1-β4), eight γ subunit genes (γ1-γ8), and four α2δ subunit genes (α2δ1-α2δ4) have been identified in vertebrates. There is currently no conclusive biochemical evidence that accessory subunits are required for the proper operation of T-type calcium channels. Nine of the 10 calcium α1 subunits (all save Cav1.1) are expressed in the central and

peripheral nervous systems, and some of these have been connected to the pathophysiology of epilepsy. Despite having antiepileptogenic qualities, L-type calcium channel antagonists can exacerbate absence epilepsy. Park and associates (2015) Although each calcium channel α1 subunit contains the molecular machinery required to conduct calcium ions (calcium-selective pore, voltage sensing, and gating mechanisms), several ancillary proteins (β, α2δ, and γ subunits) are linked to the different types of HVA channels and alter the biophysical characteristics and expression of the channels. Carpenter and Schorge discovered in 2018 Vertebrates have been shown to have four β subunit genes (β1-β4), eight γ subunit genes (γ1-γ8), and four α2δ subunit genes (α2δ1-α2δ4). As of right now, there is no solid scientific proof that accessory subunits are necessary for T-type calcium channels to function properly. The central and peripheral nervous systems express nine of the ten calcium α1 subunits (all except Cav1.1), and some of these have been linked to the pathophysiology of epilepsy.

4. The voltage-gated sodium channels

Excessive synchronized neuronal activity is a hallmark of epilepsy, a condition of neuronal excitability. Electroencephalogram recordings from patients with partial epileptic disorders show two types of abnormal activity: interictal events, which are short asymptomatic episodes that recur periodically in between seizures, and ictal discharges, which are longer-lasting abnormalities in neuronal activity associated with behavioral manifestations. (Musto and others, 2020) Both ictal and interictal discharges are characterized by prolonged firing of Na+-dependent action potentials riding on a sluggish depolarized potential, mostly generated by synaptic ligand-gated cation currents. (Large, 2020) The a-subunits NaV1.1, NaV1.2, NaV1.3, and NaV1.6 are most frequently expressed in the central nervous system. The b-subunits consist of one transmembrane domain, one N-terminal domain, and one C-terminal domain. The b-subunits can increase neuronal excitability and sodium channel density by regulating VGSC expression. Voltage-dependent sodium channels are the main source of both normal action potentials and seizures. Epileptic seizures are associated with mild sustained depolarization below the inactivation threshold for sodium channels that produce action potentials. (Arribas-Blázquez and others, 2021) (Menezes and others, 2020) The electrocorticographic correlate of synchronous, high-frequency neuronal firing enabled by depolarization is called an ictal epileptic field potential. Antagonists of voltage-dependent sodium channels decrease the maximum amplitude of sodium current and prolong the duration of the channel's inactivation. (Menezes and others, 2020) They reduce sodium channel availability during high-frequency epileptic discharges in this way.

6. The voltage-dependent potassium channel

Potassium channels, the most diverse class of ion channels, control a variety of physiological functions. The potassium channel subunits are encoded by 78 human genes, however their alternative splicing and heteromerization result in the biggest functional protein complexes. Based on their structure and mode of activation, potassium channels can be classified into four main subfamilies: voltage-gated channels (Kv), calcium-activated K+ channels (KCa), two-pore K+ channels (K2P), and inwardly rectifying K+ channels (Kir). Twelve subfamilies of voltage-gated potassium channels, Kv1–Kv12, which vary in homology and tetramer-forming ability, are now encoded by 40 human genes. In 2016, Pérez-Verdaguer et al.

The voltage-dependent potassium channel mechanism that inhibits neuronal excitability is mostly dependent on the KCNQ2/3 potassium channels. It has been shown that mutations in either KCNQ2 or KCNQ3 produce the benign family newborn convulsions known as BFNC epilepsy, and that even a small decrease in KCNQ2/KCNQ3 function can be epileptogenic. There is no excitability control when the voltage-dependent potassium channel malfunctions. However, KCNQ2 and KCNQ3 heteromerization, which has anti-epileptogenic effects, significantly increases the M current. (Ozawa and others, 2015) Since M-currents are the only currents that stay steady at the beginning of an action potential and have the ability to attenuate epileptic discharges, their modulation has a significant effect on neuronal excitability. (Barrese and others, 2010). M channels do not take part in the repolarization of individual action potentials, but they do lessen recurrent discharges and neural excitability. (Y. Huang and others, 2023) Retigabine stabilizes the neuronal KCNQ (Kv7) channels in an open conformation by binding to the activation gate area and interacting with a particular amino acid segment. In particular, the substantial hyperpolarizing shift in voltage-dependent activation has been explained by the theory that retigabine binds to a hydrophobic pocket created upon channel opening between the cytoplasmic portions of S5 and S6 segments of Kv7.2 involving Trp236 and the channel's gate. (Abidi and others, 2015) The unique amino acid pocket that retigabine binds to in brain cells is absent from cardiac muscle cells. KCNQ2/KCNQ3 potassium channels are activated by retigabine, which causes their voltage dependency to change to more negative values. In 2019, Manville and Abbott Retigabine stops epileptic episodes and sodium depolarizing currents via opening the Kv7 channels. Pharmacological treatments for neuropathic pain, bipolar depression, stroke, migraine, dementia, and epilepsy target the Kv7.2/Kv7.3 channels. Manville and Abbott (2018) It is known that when a neuron depolarizes close to the action potential threshold, the non-inactivating K+ M-current is gradually triggered, hyperpolarizing the cell and reducing neuronal excitability. Activating several Gq/G11-coupled receptors primarily slows the M-current, which is regulated by intracellular calcium and the convergent routes of multiple second messengers. (Hoshi, 2020). Since the M-current is the only persistent current that reverses depolarization close to the action potential threshold, it appears to be important in regulating neuronal excitability. Thus, it is believed that the M-current effectively inhibits the firing of recurrent action potentials. Peripheral and central nervous system cells exhibit increased neuronal excitability when muscarinic receptor agonists block M-current. In addition to KCNQ2/KCNQ3, pharmacological and molecular evidence suggests that other potassium channels, including as KATP, Kv1.1, and GIRK2, control neuronal excitability and may be involved in the pathophysiology of seizures. (Smets and others, 2015) Neuronal excitability and action potential firing patterns are regulated by Kv 1 channels in particular.

While mutations in Kcna1 and Kcna2 are linked to epilepsy and ataxia in humans, animals lacking the Kv1.1 or Kv1.2 genes were more likely to have seizures. Central nervous system disorders have been connected to a different potassium channel subtype. (Li et al., 2023; Hill et al., 2022). Since abnormalities in intrinsic membrane excitability may be the cause of both epilepsy and fatal cardiac arrhythmias, ion channels that are co-expressed in the brain and the heart, such as potassium channels, make sense as risk factors for sudden unexplained death in epilepsy (SUDEP). Voltage-gated potassium channels and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels share structural similarities. It has been discovered that patients with temporal lobe

epilepsy have different levels of HCN1 subunit expression in the hippocampus. On the other hand, non-convulsive seizures are caused by the silence of the gene that codes for the HCN2 subunit, which is abundant in the thalamus. According to these findings, HCN may be a target for antiepileptic treatment and may be involved in both limbic and absence epilepsy (Crunelli et al., 2023).

Changes in membrane lipids, free radicals, second messengers, and protein kinases

Large increases in arachidonic acid concentrations, diacylglycerol-mediated activation of protein kinase C, calcium-mediated alterations in calmodulin kinase 11, and potentially the production of free radicals that may be crucial to the mechanism of neuronal damage are among the significant alterations in membrane phospholipids brought on by epilepsy. (Łukawski & Czuczwar, 2023) excitatory neurotransmitter glutamate stimulates cyclic GMP concentrations, which lead to significant increases in seizures, and nitric oxide mediates this activity. The oxidative damage to neurotransmitters caused by glutamate may involve nitric oxide.(Ambrogini et al., 2019) Activation of the calcium-independent form of calmodulin kinase I1 could mediate the prolonged toxic effects of evanescent increases in free calcium concentrations and play a role in delayed neuronal death. (Barker-Haliski & Steve White, 2015) However, it is yet unclear how exactly these elements contribute to neuronal damage during epilepsy. (Puttachary et al., 2015)

Causes of epilepsy

It is not possible to spread epilepsy. About 50% of cases worldwide still have an unidentified origin, even though epilepsy can result from a variety of underlying illness mechanisms. The following categories comprise the causes of epilepsy: immunological, metabolic, infectious, genetic, structural, and unknown. (Vera-González, 2022, Beghi et al., 2019) Examples include:

1. **Common structural aetiologies**

Epilepsy and seizures can be caused by any structural injury to the cortex. The location of the lesion, not the kind of lesion, will determine the seizure semiology. Even though neuroimaging can give an indication of the nature of a structural lesion, histopathological investigation—either from resected brain tissue (as part of epilepsy surgery for drug-resistant focal epilepsy) or at post-mortem—is required for a conclusive diagnosis. (Xie et al., 2023, Blumcke et al., 2017) Every brain tissue removed during epilepsy surgery should undergo a thorough histological evaluation in accordance with the guidelines set forth by the ILAE Commission on Diagnostic Methods for the neuropathological work of such tissue. The six main disease categories into which structural lesions that are commonly removed for the treatment of focal epilepsy fall are hippocampal sclerosis, brain tumors, cortical development abnormalities, vascular malformations, glial scarring (including stroke and traumatic brain injury), and brain inflammation (Blümcke et al., 2016).

2. **Genetic causes of epilepsy**

The advances in next-generation sequencing (NGS) have led to the discovery of several genes that contribute to the aetiology of epilepsy. Depending on whether they impact ≥1% or less than 1% of the population, genetic variants that contribute to the aetiology of epilepsy can be categorized as common or rare. The frequency of a genetic risk factor in the population has an inverse relationship with how much of an impact it has on the development of disease. The first genetic aetiologies identified in family monogenic disorders were pathogenic variants in the protein coding sequence that resulted in amino acid substitutions (e.g., a missense variant) or protein truncation (e.g., nonsense, frameshift, deletion, or splicing variants). (Helbig, 2015)

A causative role for the variant is supported by evidence that the pathogenic variant affects the encoded protein's function, which can have a direct effect on brain activity or development. Although autosomal recessive or X-linked inheritance is less common, many genes associated to monogenic epilepsies follow autosomal dominant inheritance. Many genes linked to epilepsy have monogenic causative pathogenic mutations, which are usually rare or unique (i.e., rare or absent in healthy populations). Correlating genotype and phenotype in monogenic epilepsies can be challenging. Even in situations when the genotype-phenotype correlation is well documented, as the association between SCN1A mutations and Dravet syndrome, it is still challenging to understand the interaction. For instance, several other genes have been implicated in causing Dravet syndrome. (Zaganas et al., 2021) Conversely, there are a broad range of epilepsies associated with SCN1A mutations, including mild disorders such as genetic epilepsy with febrile seizures plus, and developmental and epileptic encephalopathies (DEEs) which are more severe than Dravet syndrome. (Smets et al., 2015, Ramantani & Holthausen, 2017)

3. **Infectious causes of seizures and epilepsy**

Even if they do not directly impact the brain, severe systemic infections can increase the risk of seizures by causing pyrexia, cytokine release, metabolic dysfunction, and autoimmune. Cerebral infections will be our main topic here. Among the most frequent causes of seizures and epilepsy globally, cerebral infections brought on by bacteria, viruses, fungi, and parasites are especially widespread in underdeveloped nations (Bonello et al., 2015).

Acute seizures are common in all types of viral encephalitis and the risk of epilepsy depends on the type of virus and the occurrence of early seizures.

Herpes simplex virus (HSV) type (I) is the most frequently found cause of sporadic viral encephalitis; other significant causes include varicella zoster, CMV, enteroviruses, and HSV.

Type (ii) Arthropod-borne viruses, such as Nipah virus, West Nile virus, and Japanese B encephalitis, frequently cause endemic encephalitis and exhibit distinct regional distributions. Haemophilus influenzae,

Streptococcus pneumoniae, and Meningococcus are the common causes of bacterial meningitis, which affects around a million people worldwide each year. (Vezzani et al., 2016) In developing nations, bacterial meningitis is far more prevalent and carries a significant risk of neurological aftereffects. Up to 15% of patients in underdeveloped nations have convulsions and epilepsy, which are frequently brought on by tuberculous meningitis, which is frequently linked to HIV. This contrasts with about 3% of people with HIV who have new-onset seizures, mostly related to toxic or metabolic causes (Ahlers et al., 2019) .

4. **Metabolic causes of epilepsy**

There are two types of metabolic factors for seizures and epilepsy: acquired and genetic (inborn). Type I diabetes mellitus, autoimmune cerebral folate insufficiency, dietary deficiencies, exogenous medications and toxins, and organ failure (liver, kidney, or pancreas) are examples of acquired metabolic causes of seizures. (Carpio et al., 2019) Unless they result in irreversible brain damage, as can happen, for instance, with hypoglycemia or hyperammonemia, many of these induce acute seizures (sometimes with an acute encephalopathy) rather than epilepsy. One possible genetic

explanation for epilepsy is inborn metabolic abnormalities (Jaume & Plecko, 2015) . However, the resulting metabolic abnormality—rather than the faulty protein—causes epilepsy. Seizures can generally be caused by a breakdown in brain metabolism, cerebrovascular disease, a lack of certain vitamins or co-factors, the buildup of toxins, the accumulation of aberrant storage material, the disruption of neurotransmitter systems, or related abnormalities of cortical development. (Ramantani & Holthausen, 2017, Balestrini et al., 2021)

5. **Immune causes of epilepsy**

The two components of the immune system are adaptive immunity, which is a pathogen-specific immune response, and innate immunity, which is a non-specific immunological response. (Vezzani, Lang, et al., 2016) development and maintenance of epilepsy in a wide range of diseases, including hippocampus sclerosis and familial cerebral dysfunction, may be significantly influenced by innate immunity through the release of specific cytokines, such as interleukin-1β, tumor necrosis factor-α, and transforming growth factor-β. As a result, targeting these cytokines may have anti-epileptogenic effects. Systemic lupus erythematosus, sarcoidosis, celiac disease, Behcet's, and Hashimoto's encephalopathy are among the autoimmune illnesses that have long been linked to seizures. Many of these connections, which range from vasculitis to metabolic derangement, have unclear explanations (Chen et al., 2022). associated seizures have also been described in paraneoplastic syndromes. There are, however, an increasing number of autoantibodies specifically associated with seizures. These antibodies either cause disease by directly affecting the target proteins and/or by fixing complement and mediating an inflammatory reaction. These auto antibody mediated syndromes result in seizures but rarely result in epilepsy, as the seizures usually resolve once the antibodies have been successfully treated. The exceptions are GABA(A)R and LGI1 antibodies which can result in chronic epilepsy (Spatola & Dalmau, 2017,Shen et al., 2020).

6. **Common neurodegenerative causes of epilepsy**

People with neurological diseases frequently have epilepsy. It is not always evident, though, if this link is merely secondary to neuronal death causing network disruption, the outcome of the underlying neurodegenerative pathophysiological process, or coincidental .(Cano et al., 2021) to epidemiological research, there is a higher chance of epilepsy in people with Parkinson's and Alzheimer's diseases. However, the ILAE categorization of epilepsy prefers to describe the condition under various etiological categories rather than naming neurodegeneration as a distinct etiological category. (Negi et al., 2023) The mechanisms underlying epilepsy associated with Alzheimer's disease may relate to both cell loss and increases in network excitability; this hyperexcitability can lead to compensatory increases in inhibition that impact upon cognition. Certain types of Alzheimer's disease, such as a specific familial variant caused by a mutation in presenilin 2, are more likely to cause epilepsy. (Neri et al., 2022,Casillas-Espinosa et al., 2020, Neri et al., 2022).

7. **Role of Oxidative Stress in epilepsy**

An imbalance between the production and elimination of reactive nitrogen species (RNS), or ROS, is known as oxidative stress, and it can play a role in the development of conditions like epilepsy. (Bonello et al., 2015) Because of the early electron leakage from the electron transport chain, aerobically active organs are especially vulnerable to the production of ROS and free radicals. Superoxide anions ($O_2^{\bullet-}$) are one byproduct of electron transport to O_2. (Raimondi et al., 2020) Superoxide dismutase (SOD) counteracts this by converting $O_2^{\bullet-}$ to H_2O_2, which is then transformed into water and oxygen by glutathione peroxidase (GPX) and catalase (CAT). ROS generation typically accounts for 1–5% of a cell's oxygen consumption, although it can be accelerated by changes in mitochondrial homeostasis, such as those that occur during Ca^{2+} overload. (Jomova et al., 2024) In the end, oxidative stress damages cells by oxidizing proteins, lipids, and DNA. The iron-sulfur clusters in complexes I and III of the electron transport chain are particularly susceptible to oxidative degradation.

The brain is particularly susceptible to oxidative stress because of its high metabolic needs, which cause it to actively engage in aerobic metabolism. (Pearson-Smith & Patel, 2017) Furthermore, because iron is essential for neurological function, it is abundant in the brain; nevertheless, its presence also makes the brain more vulnerable to oxidative stress. It has been noted that seizures cause the creation of ROS and RNS, which leads to oxidative stress and eventual cellular damage. Inhibiting ROS production has been indicated to prevent the neuronal damage that accompanies epileptic seizures. Epileptic seizures induce oxidative stress, which can cause further neuronal damage and lead to the development of subsequent seizures in a chain reaction. Acute seizures result in excess ROS formation through increased mitochondrial dysfunction and increased NOX activity. (Borowicz-Reutt & Czuczwar, 2020) Additionally, glutamate receptor activation and excitotoxicity, which are two mechanisms of brain injury in epilepsy, contribute to oxidative stress. The persistent neuronal firing that accompanies epilepsy can lead to the formation of free radicals, which can leak from the electron transport chain and react with oxygen to cause oxidative stress. (Parsons et al., 2022) with this, persistent epileptic seizures have been found to result in nucleic acid, lipid, and protein oxidation, leading to cellular damage. (Kaproń et al., 2020, Madireddy & Madireddy, 2023)

Prevention

- An estimated 25% of epilepsy cases are potentially preventable.
- The best strategy to prevent post-traumatic epilepsy is to prevent head traumas, such as those caused by falls, auto accidents, and sports injuries.
- New cases of epilepsy brought on by birth trauma can be decreased with proper prenatal care. (Li et al., 2022)
- The risk of febrile seizures can be decreased by using medications and other techniques to lower a sick child's body temperature.
- Reducing cardiovascular risk factors, such as avoiding or controlling high blood pressure, diabetes, and obesity, as well as abstaining from tobacco and excessive alcohol consumption, is the main goal of preventing epilepsy linked to stroke.
- Central nervous system infections are common causes of epilepsy in tropical areas, where many low- and middle-income countries are concentrated. Elimination of parasites in these environments and education on how to avoid infections can be effective ways to reduce epilepsy worldwide, for example those cases due to neurocysticercosis. (Klein & Tyrlikova, 2020)

Treatment

It is possible to manage seizures. When antiseizure medications are used appropriately, up to 70% of persons with epilepsy can stop having seizures. After two years without seizures, stopping antiseizure medication may be considered, considering pertinent clinical, social, and

individual considerations. The two most reliable indicators of seizure recurrence are an abnormal electroencephalography (EEG) pattern and a confirmed seizure etiology. (Sills & Rogawski, 2020).

- Approximately 75% of individuals with epilepsy may not obtain the necessary therapy in low-income nations. We refer to this as the "treatment gap."
- Antiseizure medications are not widely available in many low- and middle-income nations. According to a recent study, less than 50% of generic antiseizure medications are typically available in the public sector of low- and middle-income nations. This could make it more difficult to get treatment.
- It is possible to diagnose and treat most people with epilepsy at the primary health-care level without the use of sophisticated equipment.
- According to WHO pilot studies, the treatment gap for epilepsy can be efficiently closed by teaching basic healthcare practitioners how to detect and treat the condition. (Yassin et al., 2020)
- Patients who don't respond well to medication therapies may benefit from surgery. (Liu et al., 2023)

Table 3: Anti-epileptic Drugs' Therapeutic Use and Proposed Mechanisms of Action

	Drug	Mechanism of action	Characteristics	Possible side effects	References
First generation	Phenytoin	Block sodium channels	Partial seizure, complex partial seizure, GTC seizures, trigeminal neuralgia, status epilepticus, and arrhythmia	Gingival hypertrophy, hepatitis, ataxia, nystagmus, vertigo, diplopia, arrhythmias, and skin necrosis	(Kobayashi et al., 2020)
	Phenobarbital	Enhances GABA action, reduces voltage-dependent Ca++ currents	Partial seizures, GTC seizures	Drowsiness, impotence, depression, poor memory, lethargy respiratory depression, vitamin D, and folic acid deficiency	(Rahim et al., 2021)
	Primidone	Decrease sustained repetitive firing: inhibit voltage-dependent Na+ currents	Partial and generalized seizure, essential tremor, and psychomotor seizure	Sedation, ataxia, vertigo nystagmus, nausea, decreased libido, and skin rashes	(Victor & Tsirka, 2020)
	Ethosuximide	Reducing T-type Ca++ currents, Blocking synchronized thalamic firing	Absence seizures	Gastrointestinal intolerance, (nausea, vomiting, diarrhea) tiredness, sedation, lethargy, insomnia, and headache	(Odawara et al., 2018)
	Carbamazepine	Shows anticonvulsive action when solubilized with chemically modified cyclodextrins	Intravenous administration is efficient against seizures • Poorly water soluble, mainly target sodium channels	Confusion, agitation, aggression	(Ali, 2020)
	Valproic acid	Increases central nervous system GABA levels by increased synthesis and reduced catabolism, block T-type Ca++ current, enhances Na+ channel inactivation	All types of epilepsy, migraine prophylaxis, and bipolar mania	Gastrointestinal irritation, hair loss, tremors, ankle swelling, weight gain, drowsiness, and aplastic	(Jette et al., 2017)
Second generation (new)	Felbamate	Targets calcium channels and GABA	US Food and Drug Administration (FDA) approved, good efficacy against seizures • Specific for epilepsy treatment	Agitation, behavioral changes	(Marshall et al., 2021)
	Gabapentin	Enhances GABA release, inhibit entry of Ca2+ into presynaptic neurone that reduce glutamate release	Refractory partial seizures, GTC, myoclonus, anxiety, neuropathic pain, and migraine prophylaxis	Mild sedation, tiredness, dizziness, and unsteadiness	(Grubb, 2022)

	Lamotrigine	Reduces glutamate release Inhibits voltage-activated Ca2+ currents, Na+ channel blockade	Partial seizures, GTC seizures, absence, myoclonus (JME), Lennox-Gastaut, neuropathic pain, trigeminal neuralgia, and bipolar	Dizziness, light-headedness, drowsiness, nausea, blurred vision, weight loss, and weakness	(He et al., 2022)
	Topiramate	Inhibit Na+ and Ca2+ channel, enhance GABA activity, block glutamate and carbonic anhydrase activity	Partial seizures, GTC seizures, myoclonus, absence, migraine headache, and essential tremor, with phentermine, for weight loss	Cognitive impairment, poor memory, ataxia, sedation, diplopia, nystagmus, loss of appetite, weight loss, and kidney stones	(Reuter et al., 2022)
	Tiagabine	Neuronal and glial GABA-uptake inhibitor	Add-on therapy for partial seizures	Sedation, nervousness, asthenia, amnesia, and abdominal pain.	(Hariri et al., 2020)
	Levetirecetam	SV2A modulation	Partial seizures, myoclonus (JME), and absence of epilepsy, mainly as add-on drug	Sleepiness, dizziness, weakness, sedation, thrombocytopenia, and psychiatric events, such as agitation and psychosis	(Direk et al., 2023)
	Oxcarbazepine	Inhibit Na+ and Ca++ channel	Partial seizures, GTC seizures, neuropathic pain, and bipolar mania	Fatigue, headache, dizziness and ataxia, hyponatremia, nausea and gastrointestinal disturbance	(Beydoun et al., 2020)
	Zonisamide	Blocks Na+ channels, blocks T-type Ca++ channels, enhance GABA action, and inhibit carbonic anhydrase	Add-on drug in refractory partial seizures, GTC seizures, myoclonus (JME), absence, infantile spasms, kidney stones, Lennox-Gastaut, and bipolar mania	Somnolence, dizziness, headache, irritability, anorexia, metabolic acidosis, and renal calculi paraesthesia	(McCluskey et al., 2021) (Baya et al., 2024)
Newest	Pregabalin	Binds to α2δ subunit of voltage-gated calcium channels	Focal-onset epilepsy, painful neuropathies, generalized anxiety disorder, and fibromyalgia	Dizziness/incoordination, somnolence, abnormal thinking, weight gain, and peripheral edema	Łukawski & Czuczwar, 2023)
	Rufinamide	Enhance slow inactivation of sodium channels	Refractory partial seizures and Lennox-Gastaut syndrome	Somnolence, headache, dizziness, fatigue, diplopia, and gastrointestinal disturbances	(Falco-Walter, 2020)
	Lacosamide	Increases fraction of sodium channels for depolarization	Hypothesized to produce a neuroprotective effect	Nausea, Diplopia, CNS affected	(Tittensor, 2018)
	Vigabatrin	Inhibit GABA aminotransferase that degrades GABA	Partial seizures and infantile spasms approved only for adjuvant medication	Visual field constriction, behavioral change insomnia, psychosis limited its use as a reserve drug	(Beghi et al., 2019)
	Clobazam	GABA potentiation	Adjunctive for Lennox-Gastaut syndrome	Ethargy, somnolence, aggression, insomnia, ataxia, and fatigue	(Ambrogini et al., 2019)
	Retigabine (Ezogabine)	Activated voltage-gated potassium channels (KCNQ [Kv7]), causes hyperpolarization	Add-on treatment for treatment resistant focal epilepsy	Dizziness, fatigue, confusion, vertigo, and tremor discontinued form the market due to safety issues such as skin and	(Patel & Moshé, 2020)

		and stabilize resting membrane potential		retina discolorations	
	Perampanel	Noncompetitive α-amino-3-hydroxy5-methyl-4-isoxazolepropionic acid glutamate re	Add-on therapy for drug-resistant focal epilepsy and GTC seizure	Dizziness, somnolence, headache, irritability, fatigue, ataxia, nausea, vertigo, and back pain	(Beydoun et al., 2020)
	Eslicarbazepine Acetate	Blockade of voltage dependent sodium channels	Partial seizures	Dizziness, headache, diplopia, somnolence, nausea, emesis, and poor coordination	(Lavu et al., 2022)
	Stripentol	Enhancing GABAA receptor, inhibition of lactate dehydrogenase	Add-on therapy of seizures in children with Dravet syndrome status epilepticus	Anorexia, weight loss, drowsiness, ataxia, lethargy, nausea, vomit, and tremor	(Jette et al., 2017)
	Brivaracetam	SV2A modulation	Refractory partial onset seizures	Asthenia, somnolence, and behavioral symptoms	(Ademuwagun et al., 2021)

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