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REVIEW

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Pharmacological perspectives and mechanisms involved in epileptogenesis

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Abstract

Background: Epileptogenesis can be defined as the process by which a previously healthy brain develops a tendency toward recurrent electrical activity, occurring in three phases: first as an initial trigger (such as stroke, infections, and traumatic brain injury); followed by the latency period and the onset of spontaneous and recurrent seizures which characterizes epilepsy.

Main body: The mechanisms that may be involved in epileptogenesis are inflammation, neurogenesis, migration of neurons to different regions of the brain, neural reorganization, and neuroplasticity.In recent years, experimental studies have enabled the discovery of several mechanisms involved in the process of epileptogenesis, mainly neuroinflammation, that involves the activation of glial cells and an increase in specific inflammatory mediators. The lack of an experimental animal model protocol for epileptogenic compounds contributes to the difficulty in understanding disease development and the creation of new drugs.

Conclusion: To solve these difficulties, a new approach is needed in the development of new AEDs that focus on the process of epileptogenesis and the consolidation of animal models for studies of antiepileptogenic compounds, aiming to reach the clinical phases of the study. Some examples of these compounds are rapamycin, which inhibits mTOR signaling, and losartan, that potentiates the antiepileptogenic effect of some AEDs. Based on this, this review discusses the main mechanisms involved in epileptogenesis, as well as its pharmacological approach.

Keywords: Status epilepticus, Epileptogenesis, Antiepileptic drug

1 Background

Epilepsy is one of the most common neurological diseases in the world, affecting around 50 million people, being that 70% of people living with epilepsy could live without seizures if they were accurately diagnosed and treated. Almost 80% of the cases occur in low- and middle-income countries, and in these places, most of the affected people are poorly treated [1].

The pathophysiology of epilepsy is not completely understood. After brain injuries such as stroke, infections, status epilepticus, and traumatic brain injury, a person's chances of developing epilepsy vary with the type, severity, and structures affected in the injury [2].

Most individuals with acquired lesions of the nervous system, like traumatism or stroke, will develop epilepsy after some time. In these cases, studies suggest that the lesion induces a reorganization of the brain circuits, becoming a generating focus of epileptic discharges [3].

Regarding classification, the International League Against Epilepsy (ILEA) in 2017 classified epileptic seizures as focal, generalized, or unknown seizures. Following this classification, focal seizures were divided

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into awake and impaired consciousness; motor and non-motor onset, and focal to bilateral tonic–clonic onset. Generalized seizures were subdivided into motor tonic–clonic or other motor and non-motor, not being characterized as to the level of consciousness, since it is not always impaired [4].

The clinical diagnosis of the disease according to [5] is often based on one or more unprovoked seizures occurring within a week of injury, indicating that epileptogenesis is occurring, that is, the process in which a brain in its normal physiological state becomes epileptic, and it occurs in three distinct phases [6]: first, as an initial trigger, followed by the latency period and onset of spontaneous and recurrent seizures which characterizes epilepsy. It is important to remark that this process is different from ictogenesis, which leads to epileptic seizures, through several fast chemical or electrical events [7].

According to [8], in the brief insult such as stroke or head trauma, both cellular and molecular changes occur in the places where the injury occurred. The latent period begins with (tumors or encephalitis) or shortly after the brief insult and continues until chronic unprovoked seizures occur, which can last for months or year. In addition, cerebral seizures are not apparent during this period, and this window can profoundly contribute to the eventual presentation of the disease. In the third moment, after the manifestation of recurrent seizures, these molecular and cellular changes that arise after the injury often continue to exacerbate the severity of the disease.

The initial trigger can come from a variety of origins, such as cerebrovascular damage, traumatic brain damage, chemical neurotoxicity, infections, or prolonged seizures. These alterations may lead to changes in an epileptic brain, such as damage to the blood–brain barrier, neurogenesis, neurodegeneration, dendritic plasticity, axonal damage, recruitment of inflammatory cells to brain tissue, reorganization of the extracellular matrix and molecular architecture of individual neuronal cells [6]. According to [6], these changes may arise through aberrant neural connectivity, or a disruption of neurotransmitter balance leading to hyperexcitability, or from the combination of both conditions.

Despite advances in science regarding epilepsy, concerning treatment and diagnosis, much remains to be discussed, as to the mechanisms of epileptogenesis and as to the pharmacological treatment used.

According to [9], pharmacological treatment remains the main approach to achieve long-term seizure control and [10] adds that tailoring treatment options to individual characteristics is critical to maximizing drug efficacy and tolerability. Therefore, this review highlights the main mechanisms involved in epileptogenesis, including inflammation, neurogenesis, neural reorganization, aberrant sprouting and neural plasticity, as well as pharmacological approaches, aiming to suggest new possibilities for the cure of epilepsy.

2 Mechanisms involved in epileptogenesis

2.1 Inflammation

The process of inflammation involves a cascade of inflammatory mediators from tissues and cells present in the bloodstream, and in some situations can have several pathological consequences leading to cellular impairment or loss in tissues [11]. Studies show that inflammation plays an important role during the epileptogenic process, causing a reduction in seizure threshold, neurodegeneration, neurogenesis, synaptic plasticity, and dysregulation of blood–brain barrier (BBB) permeability [12].

Inflammation in the brain, also known as neuroinflammation, is common after traumatic brain injuries (TBI), infections in the central nervous system (CNS), cerebral vascular accident (CVA), and status epilepticus (SE) in humans and animals, having a dual function after injury, manifested through the action of different cell types by generating an immune/inflammatory response in specific CNS cells and BBB component cells [13].

According to [13], one of these common manifestations is the rapid activation of microglia, releasing several inflammatory molecules, including HMGB1, adenosine triphosphate (ATP), S100β (damage-associated molecular patterns); various cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor—α (TNF-α), interleukin-6 (IL-6); various chemokines and related effector pathways cyclooxygenase-2 (COX-2) / prostaglandin-2 (PGE2), and; complement factors, as pictured below (Fig. 1).

In addition to the release of these inflammatory molecules, after the activation of microglia, the production of inflammatory mediators and reactive oxygen species (ROS) will occur, contributing to tissue injury and neurotoxicity from mechanisms associated with cognitive impairments, such as oxidative stress and synapse remodeling. The increase of this oxidative stress in inflammation associated with mitochondrial dysfunction may affect cognitive function through hippocampal neurogenesis [14].

Similarly, a study shows that the induction of a seizure may cause a rapid activation of glial cells in the surrounding parenchyma, which accounts for the production and release of inflammatory molecules. These experimental models using models of SE suggest that the inflammatory response exhibits a distinct profile soon after induction, characterized by early activation of both astrocytes and microglia followed by BBB damage and neuronal activation [5].

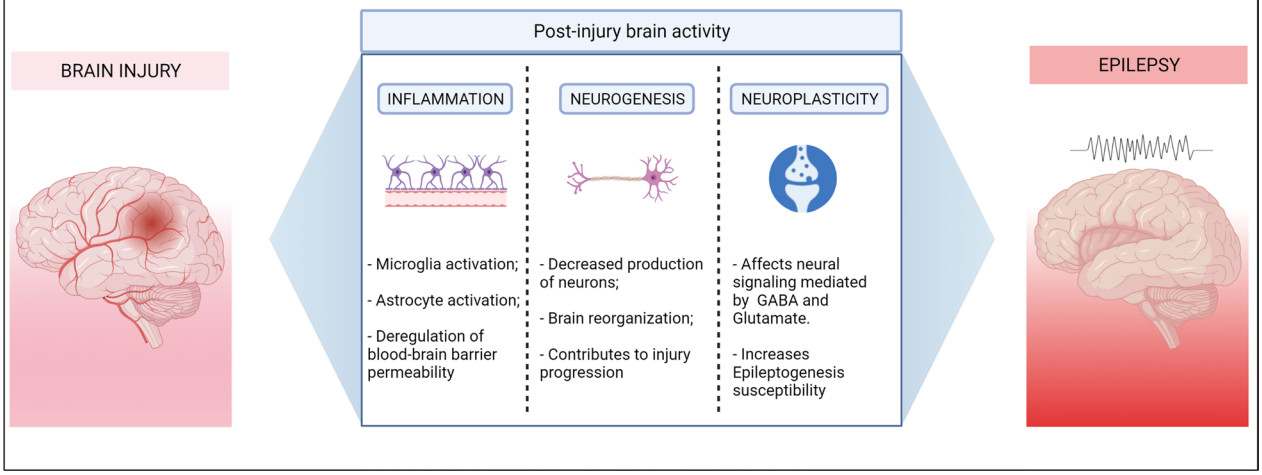

Fig. 1 Post-injury brain activity

For example, astrocytes promote tissue repair in the CNS by releasing insulin-like growth factors but are also involved in perpetuating inflammation by an overproduction of cytokines such as IL-6, as well as modulating BBB and neuronal function, producing excitability and seizures [5]. Furthermore, the mechanisms by which pro-inflammatory molecules can establish chronic neuronal network hyperexcitability involve rapid, non-transcriptional effects on glutamate and gamma-aminobutyric acid (GABA) receptors and transcriptional activation of genes involved in synaptic plasticity [15].

More and more studies evidence that inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and TNF-α, are related to the molecular mechanisms underlying learning, as well as memory consolidation, that is, studies suggest that the release of TNF-α and IL-1β induces synaptic pruning, leading to impaired neuroplasticity and various changes in the brain that may negatively impact cognition; IL-1 may affect neurogenesis and long-term potentiation (LTP); IL-6 may affect synaptic plasticity and neurogenesis; TNF-α may also affect LTP and synaptic scaling [14].

However, there is a need to better understand the difference between pathological responses, repair, and recovery, and to assess in detail the potential similarities between brain injuries, to produce drugs with broad therapeutic potential. As the term "inflammation" is very broad and may have some beneficial pathways after injury, a targeted intervention could succeed when global suppression has failed [13].

According to [16], studies suggest that the fundamental components of epileptogenesis after brain injury are inflammation and BBB breakdown: The positive regulation of inflammatory mediators leads to central and peripheral inflammation which disrupts BBB, thus facilitating the infiltration of leukocytes, generating neuronal hyperexcitability and further increasing the inflammatory mediators, leading to the emergence of morphological synaptic changes in the hippocampus and, as a consequence, the development of epilepsy.

2.2 Neurogenesis, neural reorganization, and aberrant sprouting

A series of epileptogenic changes occur in the hippocampus after an initial lesion, such as SE. These changes lead to hyperexcitability in the dentate gyrus (DG), as well as in the subfield CA1, which eventually evolves to a chronic epileptic state, typified by spontaneous recurrent motor seizures. After SE, DG neurogenesis is characterized by dramatic decreases in the production of new neurons and aberrant migration of newborn neurons to the dentate hilum and the molecular layer [17].

These changes can also lead to brain reorganization, which enlists neural networks previously not involved, or less involved, in a particular task, to compensate for directly injured or disconnected areas [18]. The usual reorganizations found in patients and animal models of SE epilepsy are cell loss, particularly of GABA interneurons, reactive synaptogenesis, and axonal budding of glutamatergic neurons [13]. Studies on molecular and organizational changes that occur after trauma reported that in animal models of neocortical trauma, hippocampal trauma, and human epileptogenic temporal lobes, neuronal circuits reorganize in response to injury and

may become hyperexcitable. In the neocortical isolation (cortical recessionalization) model of post-traumatic epilepsy (PTE), pyramidal neurons from axotomized layer V sprouted new collateral axons over several weeks. This reactive emergence is associated with recurrent excitatory connectivity and in vitro epileptiform activity, which propagates throughout the cortical circuitry. Epileptiform activity and seizures in vivo were also developed after a latency in this model of PTE [19].

According to [20], little is known about the underlying pathological mechanisms in patients affected by post-ischemic epileptogenesis, resulting in the development of chronic seizures. However, the author highlights the hypothesis that persistent neuroinflammation and glial scar formation cause aberrant neuronal firing. According to [21], the glial scar works as a physical and chemical barrier against the regeneration of neurons and works as a dense isolation, creating an inhibitory environment that consequently limits optimal neural function and leads to deficits in the human body. However, the glial scar in neurological damage is responsible for the activation of resident astrocytes that surround the lesion nucleus, isolating intact neurons.

Studies indicate that morphological and functional changes also arise in the remaining neural tissue when no seizure is expressed in the latent period. Researchers believe that this period may provide a therapeutic window to modify the disease progression [22]. Studies have also suggested that aberrant sprouting of mossy fibers is a major cause of temporal lobe epilepsy (TLE). Although there is no consensus on this question, there is evidence to believe that it contributes to the frequency and intensity of spontaneous recurrent seizures (SRS) in TLE [7].

Although the manifestation of TLE in humans after SE can take months, years, or even decades, it is noticeable that multiple epileptogenic and neurogenic alterations contribute to the progression of SE-induced injuries into chronic epilepsy typified by SRS, impairments in learning, memory, and mood [7].

A study suggests that the alteration of adult neurogenesis is influenced by several factors, such as the severity of the initial epileptogenic insult, the age of the brain, and the stage of epileptogenesis. In addition, neurogenesis is expected to play a crucial role in epileptogenesis through various aspects such as proliferation, survival, migration and integration after brain injury; however, functional implications of neurogenesis have not yet been fully elucidated [23].

2.3 Neural plasticity

One of the multiple attributes of the CNS is its ability to restructure itself in response to physiological and pathological stimuli, through a process known as neuroplasticity, which is determined by cellular and molecular mechanisms that modify the structure, density, and functionality of synaptic connections. For example, after neuronal damage, various neuroplastic changes predispose the brain to develop spontaneous recurrent seizures, in the process of epileptogenesis [24].

According to [25], there are two widely recognized categories of activity-dependent plasticity, known as synaptic and non-synaptic. According to studies, synaptic plasticity, also called Hebbian plasticity, is related to the strength of synapses between neurons, while non-synaptic plasticity is involved in modifying neuronal excitability in the dendrites, axon, and soma of a single neuron.

Furthermore, synaptic plasticity is essential for normal brain functioning, such as in our ability to learn and to modify our behavior. However, long-term changes in synaptic efficacy are involved in network-dependent activities and can produce either facilitation or depression, depending on the parameters of repetition and stimulus. Long-term potentiation (LTP) of glutamatergic synapses, in neurons of the hippocampus, produce the strengthening of synaptic efficacy and can be induced by high-frequency stimulation or by coincidence, between the pre-and postsynaptic mechanism [26].

The long-term plasticity of glutamatergic and GABAergic transmission occurs in a combined manner, precisely adjusting the inhibitory–excitatory (I/E) balance [26]. The primary excitatory neurotransmitter in the mammalian CNS, known as glutamate (Glu), plays a critical role in the excitation/inhibition balance in the brain [27]. Its effects depend on the activation of several types of specific plasma membrane receptors (GluR), three of which are of the ionotropic type (iGluR), that are nominated by selective agonists and act as ligand-dependent sodium/calcium channels N-methyl D-Aspartate (NMDA); alpha-amino-3-hydroxy-5 methylI-isoxazolepropionate (AMPA); kainate and eight are of the metabotropic type metabotropic glutamate receptor (mGluR), which are G-protein dependent [24].

Diversely, the GABAergic neurotransmitter interacts with two types of receptors: an ionotropic, or gamma-aminobutyric acid ionotropic receptor family A (GABA-A), acting as a ligand-controlled chloride channel, and a metabotropic, or gamma-aminobutyric acid ionotropic receptor family B (GABA-B), which is G-protein dependent. Neuroplastic changes can affect neuron signalings mediated by these neurotransmitters, such as their transport, synthesis, or degradation, and consequently, decreased neuronal inhibition and enhanced excitation, resulting in a brain more susceptible to seizures and epileptogenesis [24].

3 Promising antiepileptogenic compounds

Most antiepileptic drugs (AEDs) act on ion channels, by a mechanism related to the development of epileptic seizures, a process known as ictogenesis [28], while antiepileptogenics most likely act on other components: neurotransmitters, apoptosis, neurotrophic factors, and the nitric oxide chain [29]. Due to the mechanisms of the AEDs, researchers discuss whether such drugs should be called antiepileptics since they do not suppress the development of the disease and its progression. Perhaps a more appropriate name for existing AEDs is anti-ictogenics since they act on ictogenesis, and compounds that are antiepileptogenic should be called antiepileptic [28].

The development of new AEDs focusing on the process of epileptogenesis is crucial, for treating not only the symptoms of epileptic seizures but also protecting against the reorganization of the neurobiological circuitry that contributes to the development of such seizures, hence preventing the epileptic condition [30].

A compound that has a function in epileptogenesis should seek to preserve homeostatic effects, while also avoiding the eventual brain damage caused by this process [31]. A strategy that results in less severe forms of the disease, such as reducing seizure frequency, duration, or severity of seizures, or even promoting a better patient response to AEDs, is not considered antiepileptogenic, but rather a disease-modifying strategy, since the epileptic picture is already established [29].

Another challenge is consolidating animal models for the study of antiepileptogenic compounds that can reach clinical study phases [32]. Experimental models for antiepileptogenic approaches must be well delineated, considering the clinical applications. Thus, the treatments should be administered after the insult to the brain tissue, during the latent period, allowing the antiepileptic activity of the compound to be differentiated from an antiepileptogenic activity [33].

Hence, to implement a clinical trial of a new compound with antiepileptogenic potential, one must keep in mind several issues: the need for a better establishment of animal models, developing new models dealing with genetic and acquired epilepsies; development and validation of biomarkers in animal and clinical studies; studies of new potential therapeutic targets, and studies on the reuse of already approved drugs that can be used to suppress epileptogenesis [34]. Epileptogenic biomarkers are an interesting approach because they would allow, for both experimental and clinical studies, the selection of individuals with a high probability of developing the disease after an insult [34]. However, they have to be sensitive, non-invasive, specific, and affordable [31].

Identifying genetic mutations that lead to a high probability of developing epilepsy could provide an opportunity to interfere genetically in the disease [35]; an increasing number of epilepsies with genetic causes are evidencing that certain genes are involved in the development of epileptogenesis [34]. Several techniques that can help identify patients with a high risk of developing epilepsy are in use in the clinic nowadays: magnetic resonance imaging, to identify where the neuronal abnormalities might be occurring, positron emission tomography (PET) scanning, to examine neuronal function and receptors, and electroencephalogram (EEG), to observe abnormal brain activity [36].

To investigate antiepileptogenic compounds plenty of animal models can be of use, such as the kindling model and models using chemical convulsants to induce SE followed by chronic seizures, which are well-established models. Models of acquired epilepsy due to (TBI), stroke, or febrile and genetic epilepsies should also be used since these are common conditions in the clinic [37]. In vitro preparations for epileptogenesis studies can also be considered in the search for new drugs, but with the necessary validation using in vivo models [38].

Reusing already approved drugs for other conditions or even the already available AEDs for studying antiepileptogenic activity offers advantages, such as saving time and resources, and an approved drug's risk profile is already understood (Table 1). Immunomodulatory drugs for other diseases may have an antiepileptogenic potential and thus can be reused for epilepsy prevention, for example, fingolimod [33].

In a study by [39], early long-term treatment with fingolimod (1 mg/kg/day), initiated before the onset of absence seizures, was shown to have antiepileptogenic and antidepressant effects in WAG/Rij rats, but transient, as 5 months after stopping treatment, both absence seizures and depressive behavior returned to control levels, in addition, a temporary reduction in the activity of the mammalian target of rapamycin (mTOR) signaling pathway was observed.

Losartan, together with some AEDs, such as valproic acid, has been shown to potentiate the antiepileptogenic effect [40, 41]. Most clinical and preclinical studies used treatment with only one AED, which may have led to a suppression of only a part of the many processes involved in epileptogenesis [42]. But due to the multifactorial characteristic of this process, perhaps approaches using more than one AED in combination would potentiate the antiepileptogenic effect [43, 44].

Taking into consideration that neurodegeneration is one of the mechanisms of the epileptogenesis process, there have been many questions about whether AEDs with neuroprotective characteristics could halt or delay epileptogenesis [30, 45]. There are several drugs with neuroprotective potential. But neuroprotection alone

Table 1 Antiepileptic drugs tested against the epileptogenesis

Antiepileptic drug	Dosage	Animal	Model	Effect	Reference
Valproic Acid (VPA)	A bolus dose of 400 mg/kg, followed by three times daily administration of 200 mg/kg for 4 weeks, ip	Female Sprague–Dawley rats	A self-sustaining SE was induced by prolonged electrical stimulation of the basal amygdala via a depth electrode	Effective against hippocampal neurodegeneration, but did not protect against epileptic seizures	[64]
Carbamazepine	40 mg / kg, 3x / day, ip	Male Wistar rats	Pilocarpine-induced model	Administered during the latent phase did not prevent epileptogenesis, even though it decreased the number of seizures and hippocampal damage	[49]
CCR2 receptor antagonist	20 mg/kg/day, v.o	Wistar rats	Pilocarpine-induced model	Neuroprotective characteristics, but was not able to alter epileptogenesis	[50]
Daidzina	1, 5 or 10 mg/kg, ip	Male mice (albino, BALB/c)	Pentylenetetrazole -induced model	Potential effect on preventing epileptogenesis, in a dose-dependent manner	[55]
Eslicarbazepine	150 mg/kg or 300 mg/kg, ip., once daily for 6 weeks	Male Wistar rats	Pilocarpine-induced model	Antiepileptogenic effects on animal models of chronic epilepsy, by blocking T-type calcium channels, primarily Cav 3.2, which plays a role in epileptogenesis	[57]
Fingolimod	1 mg/kg/day, ip	Male WAG/Rij rats	Pentylenetetrazole-induced model	Antiepileptogenic effects of fingolimod. However, the antiepileptogenic effects were transitory	[39]
Gabapentin	100 mg/kg/day 3x / day, ip	Male and female FVB mice	Focal neocortical SE induced by application of a pledget with 4AP and GABAzine	Prevented gliosis, increased excitatory synaptic density in the affected neocortex, prevented morphological abnormalities post-FSE	[51]
	200 mg / kg, 2x/day ip.; 100 mg / kg, 2x/day then 50 mg /kg/dose IP for 5 days, ip	Male Sprague–Dawley rats	kainate-induced SE	Neuroprotective effect and inhibited epileptic seizures	[52]
Levetiracetam	80 mg / kg / day, v.o	Male WAG/Rij rats and Wistar rats	Genetic absence epilepsy model	Protected against seizure development, in rats	[39]
Losartan	10, 20 or 50 mg/kg, i.p	Male Swiss mice	Model of maximal electroshock	Potentiated antiepileptogenic effect	[41]
Topiramate	10, 30, or 60 mg/kg, ip	Male Sprague–Dawley rats	Pilocarpine-induced model	Neuroprotective effect on hippocampal formation, but this effect was not sufficient to suppress the appearance of recurrent seizures in animals	[46]

does not promote an antiepileptogenic effect, by inhibiting the cascade of events that makes a brain epileptic [29].

Topiramate, for example, tested at various doses (10–60 mg/kg) after the pilocarpine-induced SE model, showed a neuroprotective effect on hippocampal formation, but this effect was not sufficient to suppress the appearance of recurrent seizures in animals [46].

Levetiracetam in rats with pilocarpine-induced SE showed a neuroprotective effect, but also did not suppress seizures (reviewed in [44]). Other studies have indicated levetiracetam as the most promising AED tested with encephalic brain trauma models [21], tested in genetic models of epilepsy [47], acting through the SV2A protein [48].

Carbamazepine in a pilocarpine-induced model of epilepsy (120 mg/kg, i.p.) in rats, administered during the latent phase, did not prevent epileptogenesis, even though it decreased the number of seizures and hippocampal damage [49]. A chemokine (C–C motif) receptor 2 (CCR2) receptor antagonist (20 mg/kg, v.o.) presented neuroprotective characteristics after the pilocarpine-induced epilepsy model in rats but was not able to alter epileptogenesis [50].

Gabapentin and pregabalin showed antiepileptogenic effects in several models [51], mainly by decreasing exaggerated excitatory activity. In a kainate-induced SE model, gabapentin demonstrated a neuroprotective effect and inhibited epileptic [52]. Diazepam manifested an inhibitory effect on epileptogenesis and was neuroprotective, but this required a very high dose (20 mg/kg) in rats for the SE model (reviewed in [44]).

New therapeutic approaches that target neurodegeneration pathways (such as neuroinflammation, tau protein, beta-amyloid, and mTOR) have been demonstrated with antiepileptogenic potentials in animal models of acquired epilepsy [53, 54]. One AED with antiepileptogenic potential that takes these targets into account is rapamycin, an inhibitor of mTOR signaling, tested in post-electric and chemical insult antiepileptogenic animal models, and genetic models (reviewed in [45, 53]. In these models, neurodegeneration of the hilar region of the hippocampal formation and abnormal neuronal sprouting were significantly decreased, as well as the permeability of the BBB [45].

Anti-inflammatory treatments in animal models are also promising as antiepileptogenic therapies, but many of these remain untested in human epilepsy. Neuroinflammation is a promising target for halting epileptogenesis, like most types of epilepsy have some degree of immune dysregulation and cytokine activation [35]. In epilepsies acquired after insults, inflammation is involved in disease development, and anti-inflammatory drugs may be potential treatments [35]. Daidzin (1, 5, and 10 mg/kg), a natural isoflavonoid, known for its anti-inflammatory and neuroprotective potential, was tested in a pentylenetetrazole (PTZ; 35 mg/kg, i.p)-induced chronic epilepsy model in mice, demonstrating a potential effect in preventing epileptogenesis, in a dose-dependent manner [55]. Natural products like this may be a great alternative for antiepileptogenic treatments due to their multiple targets of action [56].

Several other AEDs have already been examined for an antiepileptogenic effect. Eslicarbazepine demonstrated antiepileptogenic effects in animal models of chronic epilepsy, by blocking T-type calcium channels, primarily Cav 3.2, which plays a role in epileptogenesis. Treatment with this AED for six weeks in mice in the pilocarpine-induced status epilepticus model not only decreased the number of epileptic seizures but also reduced neuronal damage and reorganization of the neuronal circuitry, with less sprouting of aberrant fibers in the dentate gyrus, as well as having neuroprotective features in the hippocampal formation [57].

Studies examining the effects of GABAergic drugs, including valproic acid (VPA), have shown that they possess antiepileptogenic properties [58]. Such activities seem to last longer than the period of exposure to these drugs, suggesting that they were not simply masking the expression of seizures [59]. VPA has played a role in several pathways involved in epileptogenesis, in addition to regulating glutamatergic and GABAergic pathways. It modulates the expression of ion channels encoding genes, for example, by decreasing the expression of the SCN3A gene that encodes an isoform of the voltage-dependent sodium channel highly expressed in epilepsy cases [60].

Studies also demonstrated the role of signaling from the endocannabinoid system in epileptogenesis and epilepsy development. Approaches using chronic or single-dose administration of cannabinoid receptor 1 (CB1) receptor agonists, or inhibition of endocannabinoid catabolism have demonstrated a potential to prevent epileptogenesis in animal model kindling-induced brain insults (reviewed in [61]).

According to [6], recent evidence indicates that neurosteroids may also play a role in modulating epileptogenesis and [62] states that, in addition to neurosteroids, new pharmacological agents modulate several receptors such as mTOR, COX-2, JAK-STAT (Janus kinase-signal transducer and activators of transcription) signaling pathway and epigenetic modulators are used to attenuate epileptogenesis.

Epilepsy is a multifactorial disease; for this reason, it is necessary to develop more specific drugs for the processes of epileptogenesis, which should be drugs with

various pharmacological targets or specific for each type of epilepsy [28]. The search for more and more detailed studies of epileptogenesis would help to validate a specific animal model, new biomarkers, and effective therapies [63].

4 Conclusions

In recent years, experimental studies have enabled the discovery of several mechanisms involved in the process of epileptogenesis, mainly neuroinflammation, that involves the activation of glial cells and an increase in specific inflammatory mediators. However, the process seems confusing and is not well described in the literature. The lack of an experimental animal model protocol for epileptogenic compounds contributes to the difficulty in understanding disease development and the creation of new drugs.

It is known that several factors can be involved in epileptogenesis, and the risk for developing epilepsy varies according to the type, severity, and brain structures affected by the insult.

Different pharmacological approaches have been developed and tested, aiming at blocking seizures effectively, as well as preventing the development of epilepsy after brain injury, for example, in studies with gabapentin and pregabalin, decreased exaggerated excitatory activity was observed; losartan presented a potentiation of the antiepileptogenic effect; rapamycin inhibited mTOR signaling; eslicarbazepine blocked T-type calcium channels; daidzin, a natural isoflavonoid, demonstrated a potential effect in the prevention of epileptogenesis, in a dose-dependent manner; among others. However, AEDs only prevent seizures, not the progression of epileptogenesis. The reason why no drug prevents or slows down the progression of epileptogenesis is that there is no comprehensive understanding of the cellular and molecular phenomena related to its process.

Current drugs act on the process of ictogenesis, not on the process of epileptogenesis, and their mechanisms are not the same. Therefore, the development of new treatments is crucial, for example, biomarkers that have shown to be important and promising in the study of the process of epileptogenesis. Hence, we can conclude that more studies about the process are necessary so that new drugs will be developed and enable a better result in the prophylaxis and treatment of epilepsy.

Abbreviations

AEDs: Antiepileptic drugs; ILEA: International League Against Epilepsy; BBB: Blood–brain barrier; TBI: Traumatic brain injuries; CNS: Central nervous system; CVA: Cerebral vascular accident; SE: Status epilepticus; ATP: Adenosine triphosphate; IL-1β: Interleukin-1β; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; COX-2: Cyclooxygenase-2; PGE2: Prostaglandin-2; ROS: Reactive oxygen species; GABA: Gamma-aminobutyric acid; IL-1: Interleukin-1; LTP: Long-term potentiation; DG: Dentate gyrus; PTE: Post-traumatic epilepsy; TLE: Temporal lobe epilepsy; SRS: Spontaneous recurrent seizures; I/E: Inhibitory-excitatory; Glu: Glutamate; GluR: Glutamate receptor; iGluR: Ionotropic glutamate receptor; NMDA: N-methyl D-Aspartate; AMPA: Alpha-amino-3-hydroxy-5 methyll-isoxazolepropionate; mGluR: Metabotropic glutamate receptor; GABA-A: Gamma-aminobutyric acid ionotropic receptor family A; GABA-B: Gamma-aminobutyric acid ionotropic receptor family B; EEG: Electroencephalogram; PET: Positron emission tomography; mTOR: Mammalian target of rapamycin; CCR2: Chemokine (C–C motif) receptor 2; PTZ: Pentylenetetrazole; VPA: Valproic acid; CB1: Cannabinoid receptor 1; JAK-SAT: Janus kinase-signal transducer and activators of transcription.

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