# Neuroprotective agents and modulation of temporal lobe epilepsy

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## TABLE OF CONTENTS

## 1. ABSTRACT

Temporal Lobe Epilepsy (TLE) is a chronic condition characterized by epileptic seizures originating mainly in temporal lobe areas. Epileptogenesis is a process in which a central nervous system injury can lead surviving neuronal populations to generate abnormal, synchronous and recurrent epileptiform discharges producing focal or generalized seizures. Hipocampal sclerosis, a massive cell death in the hippocampal formation and in the other regions of temporal lobe, is considered as hallmark of TLE. Despite the numerous antiepileptic drugs (AEDs) commercially available, about 30-40% of patients remain with seizures refractory to pharmacological treatment. In addition, there is no drug with significant efficacy to modify the epileptogenesis process. In this review we present some data regarding the neuroprotective effect of some adenosinergic agents, erythropoietin and carisbamate regarding the disease- and epileptogenesis-modifying effect.

## 2. INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (1). The term "epileptogenesis" refers to an injury-initiated change that causes surviving neuronal populations to generate abnormal, synchronous and recurring epileptiform discharges that produce focal or generalized behavioral seizures (2). However, Sloviter and Bumanglag (2) suggested that the window to act on the epileptogenesis process encompasses only the first week after *status epilepticus* (SE), and that the first days of the latent period correspond to a period during which a maturation of the epileptic circuitry occurs. Temporal Lobe Epilepsy (TLE) is a term used to define a chronic condition characterized by epileptic seizures originating preferentially, but not exclusively, in temporal lobe areas.

Neuropathological studies indicate that TLE is frequently associated with hippocampal sclerosis (HS) that is routinely detected by imaging studies during the presurgical evaluation of patients with this disorder (3). The histological pattern of HS includes loss of pyramidal cells in the prosubiculum, CA1, CA3 and hilus of dentate gyrus from the hippocampal formation (3). In addition, phenomena of synaptic rearrangement (sprouting of mossy fibers) and dispersion of

granule cells of the dentate gyrus are frequently observed in the HS from patients with TLE (4). Changes can also be found in other regions of the mesial temporal lobe, the entorhinal cortex and white matter (5). Patients who develop TLE demonstrate a progression in both the number of seizures and in the neurological symptoms related to the seizures, such as cognitive and behavioral disorders (6,7). The high prevalence and refractoriness to pharmacological treatment make this disease a subject of great interest for researchers in basic and clinical areas (8).

## 2.1. Molecular changes in epilepsy

Despite technological advances applied to neurosciences, little is known about the cellular and molecular phenomena related to epileptogenesis, the process by which a previously asymptomatic brain becomes capable of generating spontaneous seizures.

Several changes have been associated with epileptogenesis in hippocampus from patients with TLE or animal models of TLE. Hyper-excitability occurs in response to abnormal expression of GABAergic neurons in CA1 which can cause abnormal synchrony leading to seizure appearance (9). Reports of high expression of GluR1 in mossy cells of the hilus and in pyramidal neurons in CA3 have been associated with excitation of granule cells in hippocampus of patients with TLE (10).

Studies have reported that astrogliosis can also contribute to hyper-excitability and cell death resulting from seizures. Astrocytes contribute to the inflammatory response in the central nervous system (CNS). Glial cells can produce a variety of immunological molecules, such as class II major histocompatibility complex antigens, cytokines and chemokines. High levels of pro-inflammatory cytokines have been reported in brain areas involved with generation and propagation of seizures. Studies have shown that IL-1β is up-regulated after 3h and 15 days in animals subjected to pilocarpine (11,12). This up-regulation is also observed in the sclerotic hippocampus of patients with TLE and can contribute to seizure onset through glutamate release (13,14). The genes regulated by IL-1β are also up-regulated in the sclerotic hippocampus from TLE patients (15). IL-1β is pro-ictogenic and the exposure to IL-1β or TNF-α exacerbates the excitotoxic neuronal damage produced by NMDA and AMPA receptors suggesting the role of cytokines in cell death. IL-1β increases the calcium influx mediated by NMDA receptors thereby promoting excitotoxicity (16).

Despite the knowledge of a large number of mechanisms involved in hyper-excitability, seizure onset and cell damage resulting from seizures, the literature still lacks specific experimental models to study antiepileptogenesis. These models should allow the identification of brain areas involved with seizure triggering and what factors are responsible for this change.

To date, there is no report about any antiepileptic drug (AED) effective in treating seizures in patients with TLE which has been efficacious in preventing epileptogenesis (17). In this way, some strategies of neuroprotection with disease-modifying properties have been encouraged. Summarized below there is a brief review of studies on adenosinergic agents, erythropoietin and carisbamate regarding their neuroprotective and epilepsy-modifying action.

## 3. ADENOSINE: A BRIEF REVIEW

Adenosine is an endogenous nucleoside with modulatory action in different physiological processes in the CNS and in peripheral organs with potent neuroprotective action (18-21).

The regulation of the levels of intracellular and extracellular adenosine in the CNS occurs by the balance between the mechanisms of synthesis, release, uptake and degradation (21,22). In physiological conditions, the basal concentration of adenosine is relatively low in intracellular levels (10-50 nM) (23) and extracellular (30-300 nM) (21,24). However, its extracellular levels increase dramatically in conditions of metabolic stress such as ischemia, seizures or trauma (25).

The actions of adenosine in the CNS are mediated via P1 purinergic receptors, a family of G-protein coupled receptors. To date, four subtypes have been cloned and characterized: A1, A2A, A2B and A3 which differ by the type and the G-protein signal transduction triggering (21,24,25). Generally, the A1 and A3 receptors interact with inhibitory G proteins (Gi) promoting the inhibition of adenylate cyclase and thus decreasing the levels of cAMP. A2A and A2B receptors are coupled to stimulatory G protein (Gs) and activate adenylate cyclase, increasing cAMP (24).

Adenosine exhibits high affinity for receptors A1, A2A, A3 and low affinity for A2B receptor. The A1 and A2A receptors are most abundant in the CNS, where they are involved in most physiological activities. A2B and A3 receptors have lower expression in the CNS and may be relevant in some pathologic processes (26).

The A1 receptors are widely distributed in the CNS with pre- and post-synaptic location. They are highly expressed in the neocortex, hippocampus, cerebellum and spinal cord and display a low density in the striatum, amygdala, olfactory bulb, thalamus, substantia nigra and nucleus of the solitary tract (26). Although these receptors are most abundant in neurons, they are also present in astrocytes, microglia and oligodendrocytes (23).

The A2A receptors exhibit a more narrow distribution in the CNS compared to A1 receptors. They are predominantly expressed in the dorsal striatum, particularly in striato-pallidal GABAergic neurons and cortico-striatal glutamatergic terminals (23,25). However, these receptors are also found in other brain regions, including the neocortex, nucleus of the the solitary tract, hippocampus and thalamus, albeit with lower levels of expression (26). As A1, A2A receptors are present in neurons, astrocytes, oligodendrocytes and microglia (23). They are also found in cerebral blood vessels (25). A2A receptors are present in the hippocampus, particularly in glutamatergic nerve terminals, favoring the release of glutamate (23). In presynaptic terminals A2A receptors may be co-localized with A1 receptors; thus, the activation of A2A reduces the inhibitory effects mediated by A1 (23, 27). Moreover, the presence of A2A receptors in the postsynaptic membrane of hippocampal neurons would promote depolarization of these cells (28).

Activation of A1 receptors is the most important inhibitory role played by adenosine in the CNS (25, 26). In contrast, A2A receptors are responsible for the excitatory actions of adenosine in the CNS and are involved in locomotion, anxiety, aggression, motivation and reinforcement in drug abuse and psychotic behaviors (29–31). Furthermore A2A receptors are involved in the control of cerebral blood flow (32).

## 3.1. Adenosine and epilepsy

In the CNS adenosine acts as a neuromodulator, predominantly inhibiting neuronal activity via A1 receptors (21,24). Thus, adenosine has emerged as an important endogenous anticonvulsant agent (33). Microdialysis studies have reported that adenosine levels rise in the extracellular space of the hippocampus during the ictal phases in both experimental models and in patients with complex partial seizures and this increase has been proposed as an intrinsic mechanism for controlling seizures (33,34). Thus, any manipulation able to increase extracellular adenosine level offers significant potential for both preventing and blocking epileptic seizures (35).

In fact, the evidence suggests that the inhibitory effect of adenosine on seizure activity is mediated mainly by the activation of A1 receptors (18-20). These receptors have a high density in the hippocampus and are located in pre- and postsynaptic neuronal locations. Activation of presynaptic A1 receptors modulates excitatory synaptic transmission by decreasing glutamate release through inhibition of voltage-dependent calcium channels. In parallel, activation of postsynaptic A1 receptors depresses neuronal excitability by increasing membrane conductance to potassium ions hyperpolarizing the cell (21,35). These effects are crucial for the maintenance of intracellular calcium homeostasis and thus may protect nerve cells against excitotoxicity (25).

Several reports have shown that the adenosinergic A1 receptor agonist R-N6-phenylisopropyladenosine (R-PIA) and selective or non-selective A2A receptor antagonists are neuroprotective when administrated prior to kainic acid (37) or pilocarpine (18,20,38,39). Accordingly, adenosinergic A1 receptor agonists can attenuate seizures in several experimental models of epilepsy as kindling (40–42), pilocarpine (43,44) or 3-nitropropionic acid (45), but the neuroprotective action was not reported by the authors. In fact, little is known about the action of these agents as modifiers of epileptogenesis.

Several studies have shown decreased density and activity of A1 receptors in epilepsy models (37–39). Since this inhibitory system is deficient it favors glutamate release and occurrence of seizures. Besides the decreased function of A1 receptors, reduction of the extracellular levels of adenosine due to the increase of adenosine kinase (ADK) activity in astrocytes has been reported in models of chronic epilepsy (49). Thus, strategies of activation of A1 receptors and manipulation of ADK in order to increase the extracellular level

of adenosine represent a challenge to control epileptogenesis.

Many authors have shifted their focus of interest to understanding the role of A2A receptor in modulating seizures (50). Contrary to what is observed with the A1 receptors, the density of A2A receptor is increased in the epileptic tissue (51). Furthermore, activation of the A2A receptor can stimulate microglia and astrocytes, causing the release of cytokines, increase of oxidative stress and inflammation (50), contributing to neurotoxicity and neuronal damage (27). Thus, blockade of A2A receptors has been considered a neuroprotective strategy for epilepsy (23,25,50).

According to some authors, the blockade of A2A receptors either using genetic deletion of A2A receptors in the pilocarpine model (52,53) or using non-selective antagonists such as caffeine administered chronically in the bicuculline and pentylenetetrazol models (54), can cause a robust decrease in the severity of seizures. In contrast, the administration of the A2A antagonist, 3,7-dimethyl-1-propylxanthine (DMPX) prior to pilocarpine, increased the number of animals in SE (55). The chronic administration of caffeine prior to lithium-pilocarpine effectively prevented neuronal damage caused by seizures (38). However, the pretreatment with the selective A2A antagonist (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-(4,3-e)-1,2,4-triazolo(1,5-c) pyrimidine) (SCH58261) did not change the pattern of seizure-induced cell death, although it reduced the number of animals presenting SE and the mortality, and increased the latency to SE onset (20).

Numerous studies targeted at understanding the role of A2A receptors in the modulation of epileptogenesis have generated controversial data highlighting the need of studies with new approaches.

Herein, we highlight the important role of adenosine as an endogenous inhibitor of neuronal excitability and neuroprotector, and we provide an overview about the role of each adenosinergic receptor in these process. Knowing the metabolic regulation of adenosine is the major point for understanding the modulation of adenosine on seizures or on epileptogenesis. Several authors detailed these points in reviews, especially Masino *et al*. (35). In summary, studies that show the role of adenosine in the modification of epileptogenesis are

still scarce in the literature although adenosine is emerging as a potent therapeutic target for epilepsy.

## 4. ERYTROPOIETIN

Erythropoietin (EPO), a 34 kDa glycoprotein hormone, is produced primarily in the kidney and regulates the number of erythrocytes within the circulation to provide adequate tissue oxygenation (56-58). Recent studies have shown that EPO is a multifunctional molecule produced and utilized by many tissues. EPO is induced under hypoxia, hypoglycemia, strong neuronal depolarization and excess of oxygen radicals (59–61). The induction of the EPO gene in most tissues is regulated by the hypoxia-inducible factor-1 (HIF-1) (62,63). Both the EPO and EPO receptor (EPOR) can be expressed in various organs, as rodent and human brain, as well as in cultured neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells, and they are related to endogenous neuroprotective effect (64–70).

EPO is present in the CNS and also in the vascular and immune systems. In these systems, EPO offers robust protection against cell death caused by oxidative stress, excitotoxicity and inflammation. In addition, EPO promotes neurogenesis and differentiation in the brain and induces angiogenesis via downstream effectors such as vascular endothelial growth factor (VEGF) (56,57,71–75).

EPOR is expressed constitutively in almost all neurons of the hippocampus, except within the hilus (63). Neuronal EPOR immunolabeling is concentrated within cell bodies and varicosities, except in the CA1 area where EPOR is also found in basal dendrites of pyramidal neurons laying throughout the *stratum radiatum*. The basal expression of EPOR in the hippocampus suggests that it plays a role in neuronal homeostasis (63).

The ability of peripherally administered EPO as well as recombinant human EPO (rhEPO) to cross the blood–brain barrier (BBB), combined with its robust neurotrophic and angiogenic efficacy, has sparked interest in EPO as a potential neuroprotector (61,67,69,70,73,76–78). The administration of exogenous EPO *in vivo* or *in vitro* preparations has shown neurotrophic and neuroprotective actions against central and peripheral neuronal injury associated with trauma, stroke, ischemia, inflammation and epileptic seizures (56,58,61,63,72,73,76,79–82).

## 4.1. EPO and epilepsy

In epilepsy models, EPO has been associated with a variety of functions including reduction of seizure duration, protection against BBB leakage and microglial activation, prevention of aberrant cell genesis and granule cell dispersion, reduction in infiltration of macrophages and in inflammatory cytokines, decreased neuronal damage associated with spontaneous recurrent seizures (SRS) in rats (56,58,61,63,65,70,72–74,78,83–85).

Considering the neuroprotective and anti-inflammatory potential of EPO, some authors tested EPO-derived mimetic peptides regarding its disease modifying or antiepileptogenic ability. When administrated after SE onset, the peptide pyroglutamate helix B surface peptide (pHBSP) promoted hippocampal cell proliferation, neuronal differentiation and cell survival but did not affect the number of rats presenting spontaneous seizures (86). However, pHBSP was able to attenuate mood disorders as well as cognitive deficits associated to epilepsy (86).

In this line, Epotris, another EPO-derived peptide devoid of erytropoietic activity, was administrated to evaluate the histopathological consequences of SE induced by electrical stimulation (69). Epotris attenuated the seizure-associated expansion of the neuronal progenitor cell population and affected the number of basal dendrites in these progenitor cells (69). In addition, Epotris diminished the microglial activation caused by seizures in the thalamus, but did not interfere with hippocampal cell loss. According to the authors, Epotris exerted limited *in vivo* effects on cell consequences caused by prolonged seizures (69). Despite the opposing biological effects, the EPO-derived peptide mimetic design offers intriguing possibilities as therapeutic strategy since it may yield molecules with disease- or epileptogenesis-modifying properties (87).

Several studies have shown enhancement of EPOR in the hippocampus following SE induced by pilocarpine, lithium-pilocarpine or kainic acid (56,60,63,65,78). When administered after SE onset, EPO provides neural protection in the CA1, CA3, and hilus (56,60,63,65,78). According to the authors, the mechanisms underlying this effect can be associated with caspase-3 inhibition, increase in the expression of Bcl-w, elevated expression of Bcl-XL, normal expression of Bim, and up-regulation of Bcl-2, which can neutralize Bid, a pro-apoptotic

Bcl-2 protein, and cause down-regulation of Bax (39,65,84,88,89). In addition, EPO is able to decrease glutamate release, increase GABA release and suppress the influx of calcium via PI3K/Akt and/or ERK1/2 signaling pathway, increasing the expression of p-Akt protein which in turn regulates the expression of caspase-9, hence protecting neurons against excitotoxicity (60,71,61,77,89). Given these data, we consider that treatment with EPO offers exciting opportunities to prevent the onset and progression of neurodegenerative disorders as epilepsy.

## 5. ANTIEPILEPTIC DRUGS

AEDs are the most common treatment of epilepsy (91). However, even with more than 10 new AEDs available for purchase, about 30-40% of patients with TLE remain with refractory seizures even in polytherapy (92). A variety of mechanisms of action has been assigned to new and conventional AEDs, including modulation of ion channels, GABAergic and glutamatergic neurotransmission (metabolism, receptor and secondary messengers) (93). In some cases, more than one mechanism can be attributed to one AED. For example, phenobarbital increases GABA levels, potentiates $GABA_A$ receptors and facilitates chloride ion flux (91). Several authors have focused their interest on studying the modulation of epilepsy by AEDs and some data are shown in Table 1 (93).

As can be seen in Table 1, there is a considerable literature showing that AEDs might have a beneficial effect in the prevention of neuronal death resulting from epileptic seizures (94). Different patterns of neuroprotection can be seen with one AED depending on the epilepsy model tested (Table-1). For example diazepam applied in the pilocarpine model induced neuroprotection in CA1, CA3 and hilus (95). However in the kainic acid model, the neuroprotection induced by diazepam was observed in the amygdala, piriform cortex and endopiriform nucleus (96). In the kindling model diazepam induced a significant neuroprotection in CA1, CA3 and hilus only when administrated 2h after SE (97) (Table-1). Besides neuroprotection, diazepam induced significant SRS changes in a few cases, modifying the duration, frequency and latency of seizures (97–104).

The AED carisbamate (RWJ-333369; (S)-2-O-carbamoyl-1-ochlorophenyl-ethanol), has received special attention due to its ability

**Table 1.** Neuroprotective AEDs and their effect on seizures and epileptogenesis

| AED | Model | Beginning of treatment | Duration of treatment | Doses Mg/kg | Effect on epileptogenesis | Effect on seizures | Neuroprotection | Ref. |
|---|---|---|---|---|---|---|---|---|
| DZP | Pilocarpine | 4, 28, 52 and 76 h after SE | Unique | 2 | ND | ND | CA1, CA3 and hilus | (95) |
| | Kainic acid | 3h after SE | Unique | 25 | ND | ND | amygdala, piriform cortex and endopiriform nucleus | (114) |
| | Amygdala kindling | 2 or 3h after SE | Unique | 20 | Only 42% of rats developed SRS | ↓ frequency | CA1, CA3 and hilus only in 2h after SE | (97) |
| VPA | SSSE | 4h after SE (SE was stopped with diazepam) | 4 weeks | 400-200 (3 × day) | No change | ↓ frequency | hippocampus | (98) |
| CBZ | Pilocarpine | ND | 56 days | 40 (3 × day) | No change | ↓ frequency and duration | hippocampus | (99) |
| | Pilocarpine | 4, 28, 52 and 76 h after SE | Unique | 120 | ND | ND | CA1, CA3 and hilus | (95) |
| PHT | Pilocarpine | 4, 28, 52 and 76 h after SE | Unique | 60 | ND | ND | CA1, CA3 and hilus | (95) |
| FBM | PPS | 10 and 40 min after PPS | Unique | 50, 100 and 200 | ND | ND | CA1, piriform cortex, subiculum and amygdala | (115) |
| LTG | PPS | 1h after PPS | 2 weeks | 12.5. (2 × day) | ND | ND | CA3, hilus and piriform cortex | (116) |
| TPM | Kindling (HPC) | 140 min after stimulation | Unique | 20, 40 and 80 | ND | ND | CA1, hilus and CA3 (contralateral) | (114) |
| | Lithium-Pilocarpine | 10h after SE | 6 days | 10, 30 and 60 (2 × day) | No change | No change | CA1 and CA3 but not hilus, entorhinal and piriform cortex | (117) |
| VGB | Lithium-Pilocarpine | 10 min after Pilocarpine administration | 45 days | 250 | No change | No change | CA3, CA1 and hilus | (118) |
| PGB | Lithium-Pilocarpine | 20 min after pilocarpine | 7 days | 50 | No change | increased latency for SRS | Piriform and entorhinal cortex | (102) |
| TGB | PPS | Immediately after evoked potentials | 4 days | 50 | ND | ND | CA1 and CA3 | (119) |
| LSM | SSSE | 24h after SE (Stopped with diazepam) | 24 days | 10 and 30 (3 × day) | No changes | No change | CA1 and piriform cortex only at the dose of 30 mg/kg | (120) |
| CRS | Lithium-Pilocarpine | 1h after SE | 7 days | 30, 60, 90 and 120 (2 × day) | Suppressed SRS 50% of rats | Delayed the SRS on the other 50% of rats | CA1, CA3, thalamus, amygdala, entorhinal and piriform cortex | (104) |
| | Lithium-Pilocarpine | 1h after SE | 7 days | 90 (2 × day) | Suppressed SRS 50% of rats | | CA1, CA3, thalamus, amygdala, entorhinal and piriform cortex | (103) |

Perforant-path stimulation (PPS); self-sustained *status epilepticus* (SSSE); spontaneous recurrent seizures (SRS); amygdala (AMY); hippocampus (HPC); diazepam (DZP); valproate (VPA); carbamazepine (CBZ); phenobarbital (PHB); phenytoin (PHT); felbamate (FBM); lamotrigine (LTG); topiramate (TPM); vigabatrin (VGB); pregabalin (PGB); tiagabine (TGB); lacosamide (LSM); carisbamate (CRB)

to modify the epileptogenesis besides to induce significant neuroprotection. Indeed, carisbamate is an anticonvulsant with a wide spectrum of activity and a substantial safety margin (105). However, little is known about its mechanism of action. Some authors have reported that carisbamate blocks the voltage-gated sodium channel (106), although other authors demonstrated that carisbamate inhibits excitatory synaptic strength by a presynaptic mechanism without affecting the GABAergic system (107). In a recent study, Shin *et al*. (108) reported that treatments during 2 or 14 days with carisbamate decrease the firing activity in the dorsal raphe nucleus, locus coeruleus and ventral tegmental area, probably due to a reduction in the serotonin (5HT), norepinephrine and dopamine neurotransmission. Nevertheless, in the same study the authors reported increased activation of $5\text{-HT}_{1A}$ receptors in the hippocampus (108).

In post-SE epilepsy models such as kainic acid and lithium-pilocarpine, carisbamate presents an anticonvulsant action by significantly increasing the latency to the occurence of SRS (109,110). In the lithium-pilocarpine model, SRS occurrence was observed only in 50% of carisbamate treated rats (110). Other authors using the lithium-pilocarpine model have shown that the administration of carisbamate (90 and 120 mg/kg, i.p.), at 1 and 9 hours after SE onset, over 6 days, produces a strong neuroprotection in the hippocampus, entorhinal and piriform cortices, thalamus, amygdala, nucleus basalis magnocellularis as well in orbital, infralimbic and prelimbic cortices (103,104,111). In addition a significant preservation of learning and memory, attention, locomotion and coordination capabilities was recorded when animals were subjected to behavioral testing (103,111). In this model, carisbamate prevented mossy fiber sprouting in the dentate gyrus and suppressed SRS in almost 50% of treated rats (104). Interestingly, rats that did not present characteristic SRS displayed spike-and-wave discharges, an electrographic pattern characteristic of absence seizures. In addition, carisbamate exhibited anti-seizure effect in the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) since it abolished spike-and-wave discharges (112). These data show the potential disease-modifying effect of carisbamate

Based on these data, carisbamate has been considered a strong epilepsy-modifying AED with neuroprotective properties whose mechanisms

need to be elucidated. To date, several studies are ongoing to attempt understanding more about the cellular and molecular mechanisms underlying carisbamate action. The proteomic technology using 2-dimensional electrophoresis to determine differential protein expression in brain areas of the epileptic circuit of rats treated with carisbamate have shown changes in glycolytic pathways associated with carisbamate treatment. Besides, differential activation of thalamic nuclei involved with seizure spread, has been observed in carisbamate-treated rats compared to untreated rats. Finally, partial results have shown that carisbamate also alters the level of monoamines (serotonin, dopamine and noradrenaline) and its metabolites in the hippocampus and entorhinal/piriform cortices of rats (data in progress).

In summary, despite numerous AEDs commercially available, about 30-40% of patients with TLE remain with seizures refractory to pharmacological treatment (92). New AEDs have been developed in an attempt to modify SRS occurrence but also to reduce the side effects of classical AEDs (113). Considerable neuroprotection has been observed with the use of AEDs in experimental models of epilepsy, however, little effect on the expression of SRS or epileptogenesis is reported (see Table 1). Interestingly, carisbamate presents neuroprotective effect in post-SE model of epilepsy, exerts a disease-modifying effect, since it increases the latency to SRS onset and presents an epileptogenic-modifying effect, since it may induce spike-and-wave discharges (SWD) instead of limbic seizures in the pilocarpine model. In addition, carisbamate induces a significant behavior and cognitive preservation in the pilocarpine model. Altogether, carisbamate can be considered as very promising tool to study epileptogenic-modifying mechanisms in epilepsy.

## 6. CONCLUSIONS

The development of new strategies able to promote neuroprotection and to modify the epileptogenesis is a topic of high interest. Strategies which allow administrating some molecules in the earlier stage of the epileptogenic process of a post-SE model, and then evaluate the impact on SRS latency or frequency, are promising strategies to find potential therapeutic targets. In this way, adenosinergic agents, EPO and carisbamate are promising molecules, and can bring new knowledge

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**Abbreviations:** 5-HT: 5-hydroxytryptamine; $5\text{-HT}_{1A}$: 5-hydroxytryptamine 1A receptor: ADK: adenosine kinase; AED: antiepileptic drug; Akt: protein kinase B; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMY: amygdala; BBB: blood–brain barrier; CA1: *Cornus ammonis* 1; CA3: *Cornus ammonis* 3; AMPc: 3'-5'-cyclic adenosine monophosphate; CBZ: carbamazepine; CNS: central nervous system; CRS: carisbamate; DMPX: 3,7-dimethyl-1-propylxanthine; DZP: diazepam; EEG: electroencephalography; EPO: erytropoietin; EPOR: erytropoietin receptor; ERK 1: extracellular-signal-regulated kinase 1; ERK 2: extracellular-signal-regulated kinase 2; FBM: felbamate; GABA: gamma-aminobutyric acid; $\text{GABA}_A$: gamma-aminobutyric acid A receptor; GAERS: genetic absence epilepsy rat from Strasbourg; HIF-1: hypoxia-inducible factor-1; HPC: hippocampus; HS: hippocampal

sclerosis; IL-1β: interleukin-1β; LSM: lacosamide; LTG: lamotrigine; NMDA: N-methyl-D-aspartate receptor; PGB: pregabalin; PHB: phenobarbital; pHBSP: pyroglutamate helix B surface peptides; PHT: phenytoin; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PPS: perforant-path stimulation; rhEPO: recombinant human erytropoietin; R-PIA: R-N6-phenylisopropyladenosine; SCH58261: (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-(4,3-e)-1,2,4-triazolo(1,5-c) pyrimidine); SE: *status epilepticus*; SRS: spontaneous recurrent seizures; SSSE: self-sustained *status epilepticus*; SWD: spike-and-wave-discharge; TGB: tiagabine; TLE: temporal lobe epilepsy; TNF-α: tumor necrosis factor-alpha; TPM: topiramate; VGB: vigabatrin; VPA: valproate

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