Chapter 2

The Use of Anti-inflammatory Drugs in Epilepsy

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Abstract

Epilepsy is a brain disorder associated with neuroinflammation. Furthermore, it is known that important elements of the inflammatory process increase the susceptibility to epileptic activity. Therefore, the search of pharmacological strategies focused on decreasing both neuroinflammation and neuronal excitability associated with epilepsy is important. This chapter is a review of several drugs that may be used for this purpose.

Key words Anti-inflammatory drugs, Neuroinflammation, Seizures, Epilepsy

1 Introduction

Inflammation is the result of a series of events that arise in response to the presence of different types of agents that are noxious to the organism. It is considered as a defense mechanism that occurs to eliminate and later to repair the damage caused by any harmful agent. However, changes associated with the inflammatory process may cause tissue damage and, in the long term, lead to cell death [1]. In the central nervous system (CNS), inflammatory response, or *neuroinflammation*, is regulated by the interaction of cellular elements of the immune and nervous systems. Neuroinflammation involves the activation of astrocytes, microglia, lymphocytes, and mast cells [2]. The activation of these cells causes the release of inflammatory mediators, including cytokines, histamine, and serotonin, among others [3].

Neuroinflammation may result from central (neuroinfections, stroke, seizures, and *status epilepticus* (SE), among others) or peripheral (infections or autoimmune diseases) events. Neuroinflammation causes the activation of cells from the immune system, damage to the blood-brain barrier (BBB), neuronal death, and the beginning of a chronic state that facilitates the development of epilepsy (*epileptogenesis*) [4, 5]. Therefore, at the level of

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the CNS, it is relevant to identify cellular therapeutic targets to block the process of neuroinflammation and its consequences.

It is known that during the neuroinflammatory process microglia (brain phagocytic cells) produce different mediators such as reactive oxygen species (ROS) and increase the expression of the inducible nitric oxide synthase (iNOS), glutaminase, cytokines such as interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), cathepsin B, matrix metalloproteinases (MMP), and glutamate [6–8]. In this regard, the release of these mediators from microglia contributes to the generation of seizures by increasing neuronal excitability [9].

On the other hand, astrocytes are cells that regulate the electrochemical gradient in the CNS [10] and recognize albumin through transforming growth factor beta receptors (TGF-βRs). At this level, extravasated albumin resulting from BBB damage and/or seizures [11] produces the activation of TGF-βR and decreases the expression of the inwardly rectifying potassium channels (Kir 4.1) with a consequent reduction of astrocytes potassium (K^+) buffering capacity, subsequent neuronal hyperexcitability, and an increase of epileptiform activity [12]. Another situation that results in the decline of the buffer function of astrocytes is produced by the decoupling of gap junctions between these cells and the endothelial cells of the BBB due to the increase of IL-1β and TNF-α [13].

In the CNS, it is considered that mast cells are part of the BBB since they are in intimate contact with this structure and are rarely located in the cerebral parenchyma [14, 15]. Mast cells can migrate from the BBB to the brain parenchyma and release their components by degranulation as a consequence of different factors, such as hyperthermia, changes in pH, exposure to high levels of substance P, interleukins, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) [16–18]. The release of factors contained in mast cells, such as MMP (e. g., MMP-2, MMP-9) [19], vascular endothelial growth factor (VEGF) [20], TNF-α [21], IL-1β, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [22], may contribute to the damage of the BBB. It is possible that the epileptic activity increases the expression of ICAM-1, IL-1β, TNF-α, and IL-6 [23] as a result of mast cell activation. This idea is supported by the decrease in neuronal damage secondary to status epilepticus in animals pretreated with sodium cromoglycate, which stabilizes mast cells and thus prevents the release of their content [24].

Cyclooxygenase, which is located inside the cells, catalyzes the conversion of arachidonic acid into different mediators of inflammation that belong to the family of the prostaglandins and thromboxanes. There are two isoforms of this enzyme: the cyclooxygenase-1 (COX-1), which is expressed constitutively in most tissues, and COX-2, which is found in small amounts and it is inducible by damage such as inflammation and seizures [25]. In the brain, there is an upregulation in the expression of COX-1 and

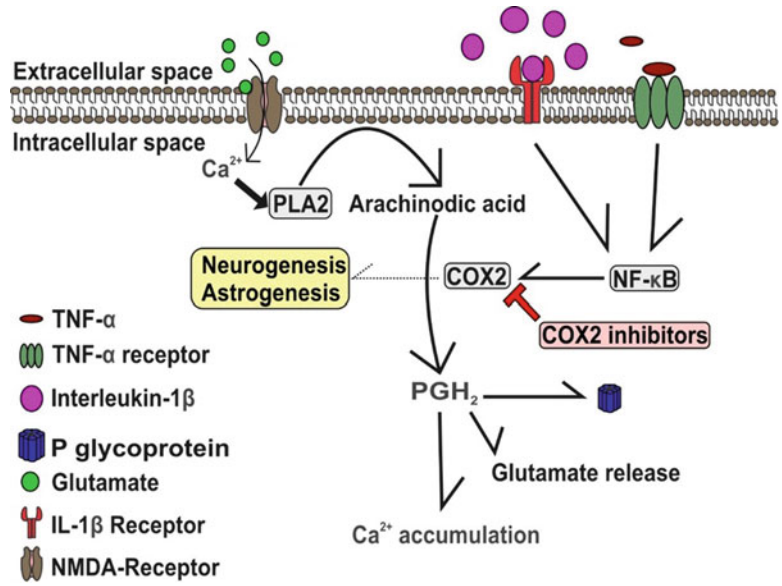

Fig. 1 COX-2 and its inhibitors in the epileptic brain. Glutamate and pro-inflammatory cytokines stimulate the expression of COX-2 in the CNS. This enzyme synthetizes PGH2, a prostaglandin that gives rise to many others; each of them results in a particular effect, such as the increase in the expression of P-glycoprotein, intracellular accumulation of Ca^{2+}, and a rise in the glutamate release, which contribute to the pathophysiology of epilepsy. *CNS* central nervous system, *Ca2+* calcium ion, *PLA2* phospholipase A2, *COX-2* cyclooxygenase-2, *TNF-α* tumor necrosis factor-α, *NMDA N*-methyl-d-aspartate, *NF-kB* nuclear factor kB, *PGH2* prostaglandin H2. The *dotted line* indicates an effect without a specific mechanism. The *red truncated arrow* indicates inhibition

COX-2 as a result of epileptic activity [26–28]. In experimental models, the use of anti-inflammatory drugs that are COX inhibitors diminishes neuroinflammation, an effect associated with a decrease in the frequency of seizures [29, 30] (Fig. 1).

In the cells, oxidative stress occurs when there is an imbalance due to an increase in free radicals and/or a decrease in antioxidants, which may cause tissue damage. As a result of epileptic activity, there is a release of calcium that favors the activation of phospholipase A_2, which in turn increases the release of arachidonic acid at the level of membrane lipids. Arachidonic acid promotes the production of ROS by different routes, thus increasing the inflammatory response [31]. The main biomolecules damaged by oxidative stress produced during epileptic seizures are membrane proteins, lipids, DNA, and RNA in susceptible regions of the CNS, such as the hippocampus and the cerebral cortex [32–35]. In different seizure models, the use of antioxidants showed a decrease in oxidative stress and neuroinflammation [36, 37].

Different neuroinflammatory processes increase neuronal excitability, which in turn produce an increase in seizures, situation that favors neuroinflammation generating a harmful vicious circle for the organism. This recurring sequence of events may contribute to the development of epilepsy [38]. This is the reason for which the search for pharmacological strategies focused on the pharmacological blockade of pro-inflammatory pathways in the CNS, which may be considered antiepileptic, is relevant [39]. Different pharmacological therapies with anti-inflammatory effects and potential antiepileptic use are discussed below.

2 Anti-inflammatory Drugs

2.1 COX Inhibitors

There is some evidence indicating that the selective inhibition of COX-2 may constitute an appropriate pharmacological strategy to prevent neuronal damage and neuroinflammation resulting from epileptic activity. Celecoxib, a selective COX-2 inhibitor, prevents microglia activation and inhibits aberrant neurogenesis as well as astrogliosis through the inhibition of the MAPK/ERK signaling pathway. These effects of celecoxib are associated with a decrease in the production of prostaglandin E [40], a decrease in neuronal excitability, an upregulation of the expression of $GABA_A$ receptors, and anti-epileptogenic effects [29]. On the other hand, it is known that the high expression of P-glycoprotein in the BBB is a mechanism that mediates drug resistance in epilepsy [41]. Experimental evidence suggests that celecoxib prevents the overexpression of P-glycoprotein induced by glutamate overexposure in endothelial cells of the BBB [42]. These studies suggest that celecoxib may represent a therapeutic strategy to prevent drug-resistant epilepsy.

Parecoxib, another selective COX-2 inhibitor, decreases the levels of prostaglandin E2 and neuronal damage in the hippocampus and the piriform cortex when administered during 18 days after lithium-pilocarpine-induced SE model. This treatment also reduces the intensity of spontaneous seizures during the development of epileptogenesis [43].

To the present, the effects resulting from the administration of acetylsalicylic acid, a nonselective COX inhibitor, are controversial. Ma et al. (2012) reported that chronic administration of aspirin after lithium-pilocarpine-induced SE decreases neuronal damage in the hippocampus as well as the frequency and duration of subsequent spontaneous seizures [30]. However, another study found that treatment with acetylsalicylic acid chronically administered before pilocarpine induction of SE increases susceptibility to seizures and does not alter the subsequent neuronal cell death and gliosis in the hippocampus [44]. These data suggest that further studies—in different experimental models using different doses and protocols of management—are needed to determine the possible anti-epileptogenic effect of acetylsalicylic acid.

Furthermore, although the administration of indomethacin, an inhibitor of COX, does not modify the presentation of SE induced by pilocarpine [45], it decreases the expression of IL-1β and TNF-α associated with this event [46]. This suggests that indomethacin may be used to decrease the inflammatory process associated with epileptic activity.

These data suggest that the decreased activity of COX by selective inhibitors may represent a therapeutic strategy to reduce seizure-induced neuroinflammation and avoid drug-resistant epilepsy.

2.2 Glucocorticoids

Seizure activity may induce vasogenic cerebral edema, which is harmful. In addition, the use of anti-inflammatory agents such as dexamethasone, a synthetic glucocorticoid steroid, is considered a therapeutic strategy for treating cerebral edema resulting from seizures [47]. It is described that the continuous administration of dexamethasone reduces the epileptic encephalopathy with continuous spike-and-wave during sleep [48] as well as the epileptic activity associated with neurocysticercosis [49].

Dexamethasone induces a significant reduction of epileptic activity secondary to intracerebral injection of penicillin [50]. However, experimental evidence indicates that dexamethasone increases cerebral edema, an effect associated with a decrease in the volume of the hippocampus and increased mortality of animals subjected to SE [51]. These controversial data can be explained from the fact that anti-inflammatory and antiepileptic effects of dexamethasone depend on the administered dose [52].

2.3 Antioxidants

Due to the increase in oxidative stress during epileptic activity, it is proposed that the use of antioxidant drugs may represent a pharmacological therapy to reduce the process of neuroinflammation associated with epilepsy (Fig. 2). In this regard, it is described that pretreatment with α-tocopherol (i.e., vitamin E) reduces the activation of astrocytes, microglia, neuronal death, and oxidative stress induced by SE in the hippocampus [36]. In addition, treatment with α-tocopherol during the subsequent period to seizure significantly reduces astrocytosis, activation of microglia, and neuronal death, effects associated with a lower oxidative stress [53]. It is suggested that the antioxidant effect of α-tocopherol may increase when it is combined with other antioxidants such as vitamin C (ascorbic acid). Vitamin C by itself reduces hippocampal injury and mortality induced by epileptic activity [54].

The administration of baicalein, another antioxidant suppressor of oxidative stress, reduces epileptiform activity and cognitive impairment in epilepsy like in tremor rat model. These effects are associated to a decrease of oxidative stress and inflammation indicators [37].

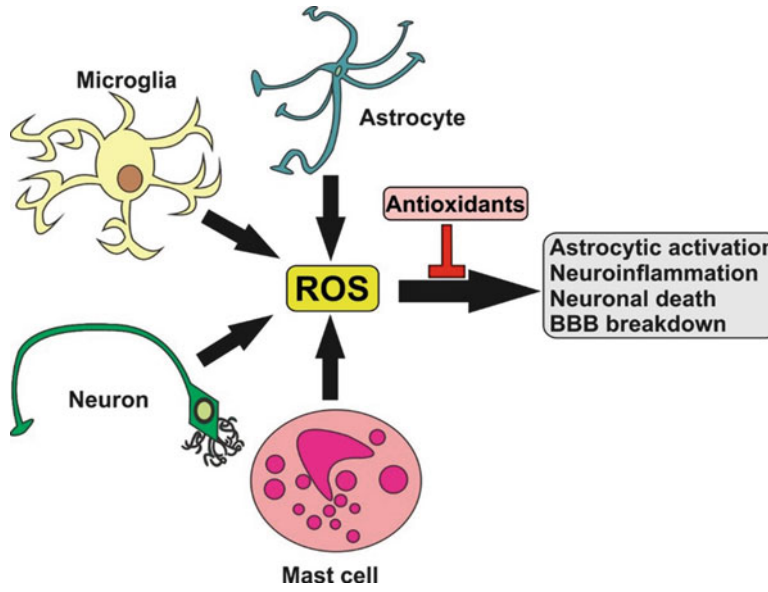

Fig. 2 ROS in epilepsy and the role of antioxidants. Cells in the CNS are able to generate ROS in response to multiple insults (e. g., hypoxia, cell death, and inflammation). ROS may alter cell function through multiple mechanisms. The presence of antioxidants, like vitamin E, controls these effects by binding to ROS and stabilizing these particles. *ROS* reactive oxygen species, *BBB* blood-brain barrier. The *red truncated arrow* indicates inhibition

The evidence described above supports the idea of using antioxidants as adjuvant therapy to prevent the neuroinflammation-associated epileptic activity.

2.4 Antimicrobial Agents

It is known that some antimicrobial agents, such as penicillins, cephalosporins, quinolones, and antimalarials, may induce proconvulsant effects and epileptiform activity in both patients with epilepsy and normal subjects [55]. In addition, many antimicrobials present pharmacokinetic interactions with some antiepileptic drugs [56]. On the other hand, it is described that tetracyclines, such as minocycline, doxycycline, and tetracycline, induce anticonvulsant effects in a dose-dependent manner on the model of partial seizures induced by 6-Hz electrical stimulation. However, at high doses, they cause toxic effects, such as motor and respiratory deficiencies and death [57].

With regard to minocycline, a second-generation tetracycline, it is known that it presents very powerful anti-inflammatory properties which are independent of its antimicrobial activity [58]. At the level of the CNS, these mechanisms of action include the suppression of the activation of microglia and a reduction in the release of pro-inflammatory cytokines [59]. Interestingly, it was found that the repeated administration of minocycline after the induction of SE decreases neuronal damage by preventing microglial

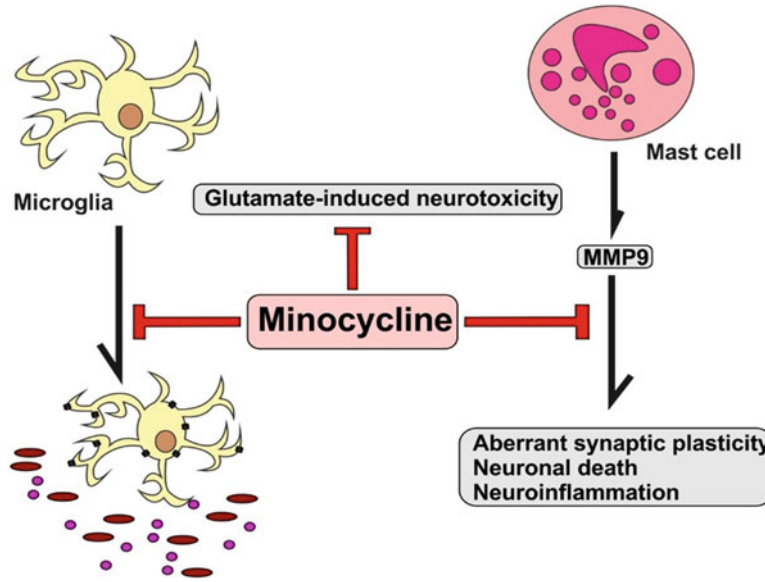

Fig. 3 Mechanisms of minocycline in epilepsy. It has been suggested that minocycline exerts its effects through the inhibition of microglial activation; moreover, it is known that it is able to inhibit MMP-9, an enzyme involved in BBB damage. Finally, it is considered that minocycline decreases glutamate excitotoxicity due to the inhibition of caspases pathway (apoptosis) and the p38 MAPK pathway. *TNF-α* tumor necrosis factor-α, *IL-1β* interleukin-1β, *MMP-9* matrix metalloproteinase-9, *MAPK* mitogen-activated protein kinase. The *red truncated arrow* indicates inhibition

activation and producing IL-1β and TNF-α in the CA1 region of the hippocampus and the adjacent neocortex. These anti-inflammatory and neuroprotective effects of minocycline resulted in the reduction of the frequency, duration, and severity of spontaneous recurrent seizures subsequent to SE [60]. Such evidence suggests the possibility of using minocycline as an anti-epileptogenic treatment for subjects who have presented SE (Fig. 3).

2.5 Anti-inflammatory Drugs with Antiepileptic Effects

Cytokines are a group of peptides and proteins that are released from the immune system in response to infectious diseases. In the CNS, cytokines are produced and released from glia or blood cells that reach the brain parenchyma as a result of BBB damage. Currently, it is known that, in addition to their immunological effects, cytokines are involved in neuronal excitability through changes in receptors coupled to ion channels, among other mechanisms. This situation results in long-term changes in brain function and facilitation of epileptic activity [61]. At present, there are drugs that prevent the production and release of pro-inflammatory cytokines and reduce epileptic activity, which represents a novel strategy for the control of this disease.

Caspases are a group of proteins that belong to the cysteine protease group, which participate mainly in the process of apoptosis. Some caspases are also involved in protein maturation of some interleukins. In particular, caspase 1, also called IL-1β converting enzyme (ICE), is involved in the maturation and secretion of some interleukins [62]. The administration of VX-765, a selective blocker of IL-1β production by inhibition of the ICE, blocks kindling-induced epileptogenesis in rats [63]. Similarly, repeated treatment with VX-765 reduces chronic epileptic activity secondary to SE as well as the expression of acute seizures in mice [9]. The combination of VX-765 with anakinra (a recombinant human IL-1 receptor antagonist) in animals previously subjected to SE by pilocarpine reduces subsequent neuronal loss and IL-1β expression in astrocytes [64]. These data indicate that the specific blocking of the synthesis of interleukins is capable of modifying the epileptic activity and subsequent neuronal damage (Fig. 4).

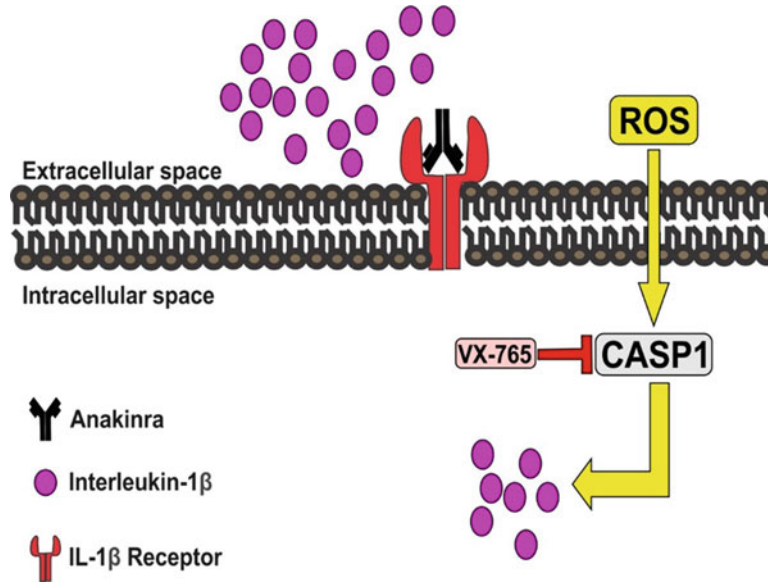

Fig. 4 Role of VX-765 and anakinra in neuroinflammation and epilepsy. ROS are molecules able to induce the expression of IL-1β through the induction of CASP1. VX-765 inhibits CASP1, diminishing IL-1β expression and, in turn, neuroinflammation. Anakinra is a selective inhibitor of IL-1β receptor; this binding allows it to diminish the effects of cytokines in target cells. *ROS* reactive oxygen species, *IL-1β* interleukin-1β, *CASP1* caspase-1 or ICE, interleukin-1β converting enzyme. The *red truncated arrow* indicates inhibition

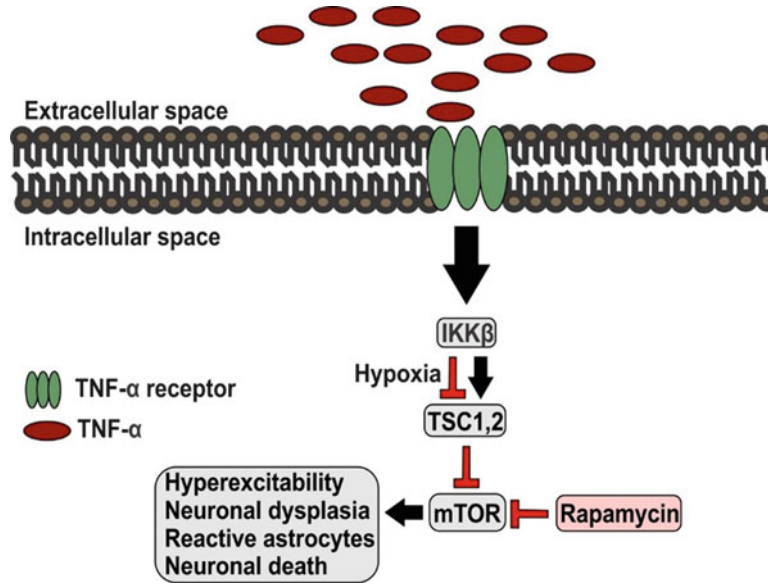

Fig. 5 Role of mTOR inhibitors in epilepsy. The mTOR pathway has an important role in the normal development of the CNS; however, when the TSC is inhibited (by mutations or another intracellular pathway), mTOR is overexpressed leading to deleterious consequences such as hyperexcitability, neuronal dysplasia, reactive astrocytes, and neuronal death. In the epileptic brain, TSC can be inhibited by TNF-α and hypoxia. Under hypoxic conditions, the activation of TNF-α receptor leads to this inhibition, and finally to the overexpression of mTOR. Rapamycin, a selective inhibitor of mTOR, has been used in the treatment of epilepsy in patients with TSC, showing convenient effects. *CNS* central nervous system, *IKKβ* inhibitor of kappa light polypeptide gene enhancer in B-cells, *TSC* tuberous sclerosis complex, *mTOR* mechanistic target of rapamycin, *TNF-α* tumor necrosis factor-α. The *red truncated arrow* indicates inhibition

The mammalian target of rapamycin (mTOR) pathway is an intracellular signaling cascade involved in multiple cellular functions, including the synthesis of proteins, cell growth, and cell proliferation as well as synaptic plasticity. It is also involved in neuronal excitability and epileptogenesis [65, 66]. Rapamycin is an immunosuppressant that specifically inhibits mTOR pathway. In addition, it decreases the expression of IL-1β and TNF-α, very likely through the inhibition of the activation of NF-kB [67] (Fig. 5). In patients, rapamycin has been found to decrease seizures associated with tuberous sclerosis, infantile spasms, seizures secondary to neonatal hypoxia, absence seizures, and temporal lobe epilepsy [68]. Results of experimental models confirm its antiepileptic effects [69]. Currently, inhibitors of the mTOR pathway are being considered as antiepileptic compounds for the control of drug-resistant epilepsy [70].

Within the process of neuroinflammation, mast cells are given little importance despite they play an important role in the process of peripheral inflammation. At the level of CNS, there is a high density of mast cells in the leptomeninges, hypothalamus, hippocampus, thalamus, and dura mater of spinal cord [71]. It is proposed that mast cells are part of the BBB and that their activation is involved in the breakdown of this structure and the subsequent process of neuroinflammation associated with brain disorders [1].

In the CNS, degranulation of mast cells produces the release of factors such as histamine, heparin, and serotonin that can produce BBB rupture and the extravasation of blood elements to the cerebral parenchyma, situation that facilitates neuroinflammation. Therefore, it is considered that the use of drugs such as sodium cromoglycate represents a strategy to stabilize mast cells [72, 73]. The stabilizing effect of cromoglycate is carried out through the blockade of Ca^{2+} channels [74] and by the phosphorylation of a 78 kDa protein located around granules of mast cells that regulates the translation of signals between the membrane and the cytoskeleton [75].

There is experimental evidence that indicates that the administration of cromoglycate prevents the degranulation of mast cells and reduces neuronal damage as well as activation of glial processes of cerebral ischemia [17, 76]. Recently, we reported that pretreatment with sodium cromoglycate resulted in a neuroprotective effect in hippocampus of rats submitted to SE induced by pilocarpine. This effect is associated with a reduced release of histamine in the hippocampus [24], which induces proconvulsant effects [77]. These experimental evidences suggest that systemic administration of cromoglycate may be a good option to avoid or reduce neuronal and BBB damage resulting from the degranulation of mast cells in response to acute events such as SE, which leads to the development of spontaneous seizures (Fig. 6).

3 Conclusion

It is clear that epilepsy is associated with neuroinflammation processes, which in turn induce neuronal damage. For this reason, the use of drugs that facilitate neuroprotection and/or which block transduction cascades associated with neuroinflammation is so relevant. Therefore, the search for combinations of these drugs with traditional antiepileptic drugs may result as a more effective strategy to control epileptic activity and its consequences.

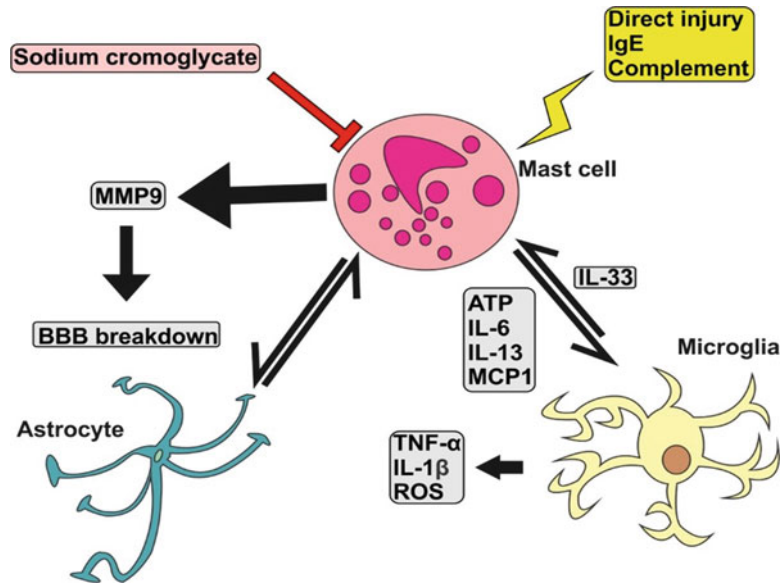

Fig. 6 Role of mast cells and their inhibition in epilepsy. Mast cells have many effects in different cells in the CNS. These target cells produce substances that stimulate mast cells, leading to a neuroinflammation cycle. The activation of microglia and astrocytes, and the BBB-breakdown are consequences of mast cell activation, which lead to negative effects in the epileptic brain. The pretreatment with sodium cromoglycate, a mast cell stabilizer, has proven beneficial effects in the litium-pilocarpine model of temporal lobe epilepsy, suggesting the possible therapeutic effect of this inhibition in epilepsy. *IgE* immunoglobulin E, *MMP9* matrix metalloproteinase-9, *BBB* blood-brain barrier, *IL-6* interleukin 6, *IL-13* interleukin-13, *IL-33* interleukin-33, *MCP1* monocyte chemo-attractant protein 1, *TNF-α* tumor necrosis factor-α, *IL-1β* interleukin-1β, *ROS* reactive oxygen species. The *red truncated arrow* indicates inhibition

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