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Novel Frontiers in Epilepsy Treatments: Preventing Epileptogenesis by Targeting Inflammation

Raimondo D'Ambrosio, Ph.D.^{1,2}, Clifford L. Eastman, Ph.D.¹, Cinzia Fattore, M.D.³, and Emilio Perucca, M.D., Ph.D.³

¹Department of Neurological Surgery, University of Washington, Seattle, Washington, USA

²Regional Epilepsy Center, University of Washington, Seattle, Washington, USA

³Department of Internal Medicine and Therapeutics, University of Pavia and National Institute of Neurology IRCCS C Mondino Foundation, Pavia, Italy

Abstract

Currently available epilepsy drugs only affect the symptoms (seizures), and there is a need for innovative treatments that target the underlying disease. Increasing evidence points to inflammation as a potentially important mechanism in epileptogenesis. In the last decade, a new generation of etiologically realistic syndrome-specific experimental models have been developed which are expected to capture the epileptogenic mechanisms operating in the corresponding patient populations, and to exhibit similar treatment-responsiveness. Recently, an intervention known have broad-ranging anti-inflammatory effects (selective brain cooling) has been found to prevent the development of spontaneously occurring seizures in an etiologically realistic rat model of post-traumatic epilepsy. Several drugs used clinically for other indications also have the potential for inhibiting inflammation, and should be investigated for anti-epileptogenic activity in these models. If results of such studies are positive, these compounds could enter rapidly Phase III trials in patients at high risk of developing epilepsy.

Keywords

epilepsy; epileptogenesis; disease-modification; inflammation; hypothermia; traumatic brain injury; experimental models; clinical trials; drug treatment

There is presently no cure for epilepsy, no way to prevent it in those at risk, and over one third of people with epilepsy remain resistant to available treatments. Currently used drugs offer only symptomatic relief, and the more than 15 new anti-seizure drugs introduced in the last two decades have had only a very modest impact on the proportion of patients who achieve complete freedom from seizures [1].

Progress in tackling pharmacoresistance may require a shift away from the search for drugs which inhibit the symptoms (seizures) in favor of a focus on identifying treatments targeting the underlying disease [2]. Specifically, there is an unmet need for interventions targeting the epileptogenic processes that render tissue capable of generating paroxysmal epileptiform activity. Such interventions could prevent or restrict the development of chronic spontaneous recurrent seizures that are the hallmark of epilepsy.

While identification of anti-epileptogenic agents is a hot topic in epilepsy research, previous clinical trials for the prevention of post-traumatic epilepsy have failed, and there are formidable hurdles to their success [3-7]. First of all, the mechanisms underlying human epileptogenesis are not fully known, and clinically relevant targets for therapy development remain hypothetical [8,9]. Second, some of the models commonly used to test for anti-epileptogenic effects may not adequately reflect events occurring in the clinical situation. In particular, commonly used paradigms such as the kindling model and the post-status epilepticus models, which are relatively simple to implement, involve as initial triggering events electrical stimulation or chemoconvulsant exposure, which may not be representative of the most common epileptogenic insults in humans [9-12]. Additionally, the design used in some of these studies may not have been adequate to demonstrate a true antiepileptogenic effect, i.e. prevention of spontaneous seizures after treatment termination and without modification of the initiating insult. For example, in studies testing antiepileptogenic effects during the kindling acquisition phase, drugs are usually given before each electrical stimulus, so that the acute anticonvulsant effect of each drug administration alone could be sufficient to delay kindling and produce therefore a false positive result [10]. Similarly, it is often difficult to determine whether treatments applied during or shortly after status epilepticus modify the severity of the initiating injury or its outcome [12]. Lastly, clinical trials in anti-epileptogenesis are more complex to design and require larger populations and longer duration of follow-up than trials of anti-seizure treatments [3,7,9]. Factors that can crucially affect the outcome of a clinical trial include not only the choice of the best drug candidate, but also the optimization of critical variables such as eligibility criteria, therapeutic windows, doses and duration of treatment.

To better compensate for our poor understanding of the mechanisms of human epileptogenesis, and permit optimization of future clinical trials for the prevention of acquired epilepsy, a new generation of models have been developed based on brain injuries that closely mimic insults that are epileptogenic in man. Such etiologically realistic syndrome-specific models are expected to capture the yet to be identified epileptogenic mechanisms operating in the corresponding patient populations, and to exhibit similar treatment-responsiveness. This approach has resulted in the development and investigation of animal models in which epilepsy is caused by experimentally-induced contusive brain injury [13-15] febrile seizures [16, 17], glioma [18], hypoxia-ischemia [19], perinatal hypoxia [20], stroke [21,22] and viral encephalopathy [23]. All these models prominently feature the development of focal seizures, which represent a seizure type often resistant to treatment in humans [1]. The same models are suitable for testing subchronic treatments that are likely needed for anti-epileptogenesis, and could potentially translate well to the corresponding human condition. On the other hand, these models are also labor intensive, and reliable seizure counting generally requires expert interpretation of electrocorticographic recordings.

As an example of the challenges and opportunities offered by the approaches discussed above, this article will discuss briefly mechanisms of epileptogenesis and promising interventions in traumatic brain injury (TBI), a condition that could be realistically targeted to assess epilepsy preventive treatments in humans. Key issues for the design of clinical trials of anti-epileptogenic agents will also be addressed.

Prevention of post-traumatic epilepsy by mild cooling: further evidence for a role of inflammation in epileptogenesis?

TBI is one of the leading causes of acquired focal epilepsy [24-27]. Among the models of acquired epilepsy, the rostral parasagittal fluid percussion injury (rpFPI) in the rat has been particularly well characterized and adapted for the assessment of anti-seizure and anti-epileptogenic interventions [28, 29]. Fluid percussion injury mimics closely contusive closed head injury in humans, and reproduces most of its pathophysiological sequelae, including both destructive and regenerative inflammatory processes [30] and the development of post-traumatic epilepsy [13,14,28,29,31]. Before progressing to multifocal epilepsy months after injury [14], rpFPI-induced post-traumatic epilepsy appears initially in the form of a frontal neocortical epilepsy, which is also a common form of human post-traumatic epilepsy [32,33]. rpFPI-induced neocortical spontaneous focal seizures resemble corresponding human frontal neocortical focal seizures from both the electrical and behavioral standpoints [34-39]. Similar to human epilepsy, rpFPI-induced focal seizures show a wide variability in frequency (from one seizure per week to 35 seizures per hour) and duration (from one second to 30 minutes). rpFPI-induced epilepsy is a very severe form of post-traumatic epilepsy, which progresses dramatically in seizure frequency and duration over the months post-injury, and cannot be controlled by carbamazepine, valproic acid and carisbamate [28,29]. Using this model, a recent study demonstrated for the first time that chronic spontaneous recurrent seizures can be prevented almost completely by mild focal cooling of an incipient epileptic focus [31]. Cooling the perilesional neocortex by just 2°C for 5 weeks, beginning 3 days after the insult, resulted in 99% prevention of ictal activity compared to untreated control animals (Figure 1). The preventive effect of cooling was observed for seizures of all types and durations, was temperature-dependent over the 0.5°C-2°C cooling range, and persisted for the entire duration of follow-up (10 weeks) after cooling was terminated. Importantly, prolonged mild focal brain cooling is clinically feasible in the target population of head injury patients at risk for post-traumatic epilepsy. In fact, prolonged mild systemic hypothermia has been found to be relatively safe in humans and to improve functional recovery in patients with severe head injury [40-43], and mild selective brain cooling is also being investigated clinically to minimize some of the risks associated with systemic hypothermia [44,45].

While the mechanistic links between TBI and post-traumatic epilepsy remain to be elucidated, inflammation is a likely contributor. Many epileptogenic insults induce inflammation, inflammation is evident in resected epileptic brain tissue [46] and strong evidence exists for a role for inflammation in ictogenesis and epileptogenesis [47-49]. Head injury is immediately associated with brain deformation and mechanical disruption of cell membranes and blood vessels, that result in inflammatory changes. In particular, the exposure of brain parenchyma to blood and the release of danger-associated molecular signals from damaged cells initiate inflammatory cascades [50-53]. Inflammatory signaling, in turn, dynamically orchestrates both the destructive processes (apoptosis, phagocytosis, etc.) and the regenerative events (neurogenesis, angiogenesis, etc.) required for restoration of function in the damaged brain [54-58]. Overall, the brain's complex response to injury

results in substantial secondary injury, as well as some functional recovery, and contributes to the capability of damaged brain tissue to generate seizures.

Thus, a plausible mechanism by which hypothermia prevents epilepsy after fluid percussion injury is inhibition of inflammatory pathways. Neuronal activity is not silenced by 2°C of cooling [31,59]. However, mild to moderate hypothermia inhibits many of the inflammatory processes thought to contribute to secondary damage after brain injury [60-65]. The hypothesis that cooling inhibits epileptogenesis by modulating injury-induced inflammation is further supported by growing literature demonstrating close relationships among inflammation, epileptogenesis and ictogenesis in a variety of animal models and probably also in some forms of human epilepsy [66,67]. There is also data indicating that glial activation and associated inflammatory mechanisms may adversely affect neurological outcome after TBI [68-70], and recent imaging data have confirmed that TBI patients exhibit signs of widespread and prolonged microglial activation [71,72].

Based on the evidence discussed above, neuroinflammatory pathways represent novel and promising targets for the development of clinically effective agents with anti-epileptogenic as well as anti-seizure activity. In fact, there are many drugs that could target inflammation and are already approved for other indications (Table 1). Many of these have already been shown to be neuroprotective and to improve outcomes after experimental or human CNS insults, and, thus, could be rapidly entered into clinical trials of epilepsy prevention provided robust evidence of anti-epileptogenesis is obtained in appropriate preclinical models. These compounds range from drugs thought to narrowly target specific enzymes or receptors (e.g. celecoxib and anakinra) to those known to have wider ranging effects. It should be stressed that, as shown in Table 1, evidence of neuroprotection in non-epilepsy models, such as models of cerebral ischemia, does not necessarily imply an antiepileptogenic action. It has been argued that multifunctional drugs or combination therapies may be most appropriate for treatment of complex or multigenic disorders [73,74]. TBI is a complex injury, and the testing of multifunctional therapies has been specifically advocated in this condition [75,76]. Because the only intervention which to date has been found to prevent chronic spontaneous recurrent seizures after experimental head injury (mild focal cooling) is known to have diverse actions on many of the biochemical and inflammatory cascades unleashed by brain injury, compounds with highly pleiotropic anti-inflammatory effects are of particular interest for clinical trials.

Examples of pleiotropic anti-inflammatory drugs that are candidates for anti-epileptogenic interventions in TBI include minocycline and progesterone. Both compounds have long been approved for human use and have been reported to improve outcomes in preliminary clinical trials in TBI or stroke [77-79]. These drugs readily cross the blood-brain barrier and are known to have wide-ranging effects on processes mediating secondary cellular damage after brain injury. Minocycline, in particular, has been shown to decrease the expression of TNF- α and IL-1 β , to reduce microglial and T-lymphocyte activation, metalloproteinase activity and blood-brain barrier permeability [80,81], and to display neuroprotective effects and improve functional recovery in animal models of TBI, intracerebral hemorrhage, and ischemic stroke [82-83]. Moreover, minocycline has been reported to have anti-ictogenic activity in the 6-Hz seizure model [84], to reduce hippocampal damage after chemically-

induced status epilepticus [85] and to attenuate brain injury-induced increases in seizure susceptibility [86-87]. A recent case report in an astrocytoma patient with drug-resistant seizures is also consistent with the possibility of minocycline having clinically significant anti-seizure effects [88], and a phase I/II trial (NCT01058395) aimed at assessing its safety in patients with moderate to severe TBI is currently in progress. Like minocycline, progesterone displays a wide range of anti-inflammatory and neuroprotective effects [89-94] and, in particular, has been found to suppress the synthesis of TNF- α , IL-1 β and IL-6 and to increase BDNF expression [95,96]. Likewise, progesterone has been reported to have beneficial effects in a variety of brain injury models, and to decrease lesion volume and reduce apoptosis and blood-brain barrier leakage after brain injury [96,97]. Improved functional outcomes after progesterone treatment in patients with head injury have been reported in two phase II clinical trials [98,99].

From animal models to the clinic: Challenges in the clinical testing of anti-epileptogenic agents

Elements required for a successful clinical trial include an effective treatment, a suitable study population, and an adequate study design and treatment protocol. No intervention has yet been found to be effective in preventing epileptogenesis in the clinical setting [4-6,9]. Whether the negative results of clinical trials conducted to date reflect the testing of ineffective treatments, or the use of suboptimal trial designs or treatment protocols is unclear. It is a fact, however, that no trial has yet investigated interventions which exhibit well defined anti-epileptogenic effects in animal models closely resembling the relevant human condition. However, as discussed above, efforts are now being increasingly directed to the development of models for conditions in which trials of anti-epileptogenesis could be realistically applied, and agents with promising anti-epileptogenic profiles in these models are starting to emerge.

The study population is a paramount concern in trial design [3,7,9]. The ideal population for testing a potential anti-epileptogenic intervention is represented by patients with common, etiologically homogeneous conditions for which promising animal models exist, and which are associated with a high risk of developing epilepsy over a relatively short period. The suggestion has been made that patients with severe TBI or stroke may be the most promising targets for future trials of potential anti-epileptogenic agents [7,9]. A major challenge in the design of such trials, however, relates to the incidence of easily diagnosed epilepsy following TBI or stroke. In the 5 years after severe head injury, unprovoked focal seizures were found to occur in 30% of military TBI victims [100] and 10% of civilian TBI populations [101]. For stroke, the risk of seizures appears to be 3-5% [102]. Thus, any future trial of an anti-epileptogenic intervention in an unselected population of TBI or stroke patients will include a majority of patients who will not develop easily identifiable seizures, and a very large sample size will be required to demonstrate the efficacy of any preventive treatment. A potentially more efficient approach would be to select patients who carry additional risk factors for developing epilepsy. In the case of stroke, etiology, location, severity, early seizures in the first week after the insult and certain comorbidities have all been found to affect the risk of late epilepsy [103]. For TBI, risk factors for late epilepsy

may include depressed skull fracture, dural penetration, subdural or intra-cerebral hematoma, post-traumatic amnesia >24h, and early seizures in the week after the event [101,103,104]. Incorporating such variables into eligibility criteria can significantly improve the efficiency of a trial and reduce the sample size required to ensure adequate statistical power. However, adopting more stringent eligibility criteria can make recruitment more difficult, and patients with additional risk factors for epilepsy may also be subject to higher mortalities rates, potentially precluding a sufficient duration of follow-up. Moreover, even TBI and stroke patients with additional risk factors still have a less than 50% probability of developing epilepsy over a follow-up period of two to three years.

A major breakthrough that could enhance the feasibility and efficiency of human anti-epileptogenesis trials would be a substantial improvement of non-invasive epilepsy diagnosis methods for prospective clinical trials. Both animal and human neocortical epileptic foci often generate short (<10s) non-spreading focal seizures, which are more difficult to detect than longer spreading ones originating from the same sites [105,106]. In fact, behaviorally subtle seizures that are common for acquired epileptic foci are also easily overlooked [107-109]. Thus, better monitoring techniques, capable of detecting currently under-diagnosed and under-reported focal seizures, or at least the presence of an epileptic focus, would facilitate demonstration of treatment effects in post-traumatic epilepsy prevention trials. Examples of promising technologies for improved detection of epileptic foci are magnetoencephalography [110] and dense-array-EEG [111]. Another major breakthrough would be the discovery of reliable biomarkers that allow early identification of subjects with the highest risk of developing epilepsy. Biomarkers could find application not only in identifying patients at risk but also in determining the mechanisms of epileptogenesis prevailing in individual subjects, in predicting clinical response to specific interventions and in selecting candidates for specific therapies. Although no clinically validated predictor of epileptogenesis has been identified yet, massive discovery efforts for such biomarkers are currently ongoing in Europe and the U.S. Candidate markers that show promise in this respect include a variety of molecules detectable in serum, including markers of neuronal injury, blood brain barrier damage and inflammation [112-114], genomic profiles including epigenetic markers [115], multimodal brain imaging, including MRI and PET [116], and remote sensing technologies such as actigraphy and ambulatory 3-point EEG [114,117]. Neurophysiological measures that could translate into valuable biomarkers include pre- and interictal spikes and high-frequency oscillations (ripples and fast ripples) recorded from scalp EEG [117]. Given the complexities of the epilepsies and the multiplicity of epileptogenic mechanisms, it is likely that the most important breakthroughs will not come from the discovery of a single biomarker, but by a combination of biomarkers or combined measures made possible by powerful bioinformatics analyses. Appropriately validated biomarkers could also be used to monitor response to interventions and to provide an early estimate of the potential effectiveness of investigational agents. It should be noted that potential applications of biomarkers are not restricted to acquired epilepsies. For example, recent reports have suggested that it may be possible to pre-emptively modify the course of genetic epilepsies [118-122]. Early treatment with ethosuximide, for instance, has been found to prevent the development of seizures in rat models of genetic absence epilepsy, and the frequency of seizures in treated animals remained significantly less than that in untreated

controls for at least 3 months after cessation of treatment [118, 119]. However, until a clinically validated biomarker exists to estimate a child's risk of developing absence epilepsy prior to onset of clinical manifestations, such pre-emptive treatments will not be possible.

Expert commentary: Which new epilepsy treatments should we expect for the future?

The introduction of over 15 second-generation anti-seizure drugs since the early 90s has improved considerably the management of epilepsy, mainly by providing physicians with unprecedented opportunities to tailor drug choice to the individual patient [123]. Many of the second generations drugs offer advantages in terms of an improved tolerability profile and a reduced risk of drug-drug interactions. However, these drugs had a very modest impact on the number of patients whose seizures cannot be fully controlled by available treatments. In fact, about one third of people with epilepsy remains pharmacoresistant, similarly to the situation that existed in the 70s [1,2]. This implies that the need for newer drugs with improved efficacy, or greatly improved tolerability, is as acute today as it was many decades ago [124]. Unfortunately, however, the number of anti-seizure drugs in clinical development has been declining over the years [125]. This is due to a combination of factors such as increasing development costs, industry's disillusion about the possibility of identifying more efficacious agents with the available discovery tools, and the difficulties involved in differentiating a new anti-seizure drug in an already crowded epilepsy market [124]. Industry is also aware that in many countries of the world, national health systems, insurance schemes and individuals are increasingly reluctant to pay for highly priced drugs which provide only small incremental value in terms of efficacy or tolerability compared with older and inexpensive medicines, many of which are now available as generics [126].

Because of the challenges outlined above, a major switch in the paradigms used to discover and to develop new drugs for epilepsy is required. To justify investment, a credible strategy should be put together that will enable identification of truly innovative agents which will reduce significantly the burden of pharmacoresistant epilepsy. Ideally, such a strategy should involve coordinated efforts at various levels. First of all, governments and funding agencies should realize the high cost associated with epilepsy, both in monetary terms and in terms of human suffering, and support high quality research into the pathophysiological mechanisms underlying the disease and its manifestations. It is only through a better understanding of pathophysiological mechanisms that we can identify new targets for innovative treatments. An example of this approach, discussed above in this article, is provided by the identification of the potentially major role of inflammation in epileptogenesis and ictogenesis, which provides a rationale for testing the value of anti-inflammatory treatments [48,49]. Second, we need to develop models of seizures and epilepsy that mimick more closely the clinical disease. This aspect has also been discussed extensively in this article, focusing on models of post-traumatic epilepsy as an example. Third, we need to broaden the search for novel treatments by focusing not only on better symptomatic drugs, but also on agents that could prevent the development of epilepsy, or modify favourably its course, or target common co-morbidities. Again, the findings

discussed above in relation to the possibility of inhibiting epileptogenesis after brain trauma is a good example of this approach. Lastly, we need to improve the efficiency of drug development in the clinical setting. As already discussed, major progress in this area is expected to come from the discovery of biomarkers (or combination of biomarkers) which can identify individuals most likely to benefit from the treatment(s) being investigated. Biomarkers could also be used to monitor the response to treatment, and ultimately could be used as surrogate marker for the effect being targeted. In parallel, ample evidence exists that the clinical trial designs currently used to demonstrate the efficacy of drugs for epilepsy are difficult to implement, can be inefficient and may raise significant ethical concerns [127]. Ways to address these concerns are currently being debated in the epilepsy community [128].

The approaches discussed above will require a concerted action from all stakeholders, and will require time. However, some innovative pharmacological targets already identified by existing research, such as inflammation [46-49] or the mTOR pathway [122], could be addressed by testing drugs with a proven safety record that are already available for other indications. For a rational choice of the best candidate(s) drugs, and the best treatment modalities, further preclinical work is desirable. Because of the complexities of the systems involved, it cannot be excluded that the most effective approach could require use not of a single agent, but a combination of agents [75].

Five-year view

The assumption that human epileptogenesis can be modeled by seizures or epilepsies induced by insults not reproducing clinically occurring etiologies is fading. The number of etiologically realistic models of chronic recurrent spontaneous seizures will continue to grow in order to match the spectrum of human epilepsies. Because no single model can be expected to predict the efficacy of antiepileptogenic interventions in the diverse human population, diverse models will be introduced to identify novel antiepileptogenic agents and to inform the design of clinical trials to test them. At the same time, knowledge on the mechanisms underlying epileptogenesis will continue to increase, which will lead to the discovery of compounds with innovative mechanisms to be tested in the relevant models and, hopefully, in the clinic. Clinical trials of anti-epileptogenesis in high-risk patients are already being initiated, and more will be designed and implemented in the near future based on dose and therapeutic window optimization data obtained with preclinical models that match the patient population to be treated. At least preliminary clinical results are expected to be available in the next 5 years.

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Key-issues

- • The mechanisms of human acquired epileptogenesis are still hypothetical, but inflammation is thought to have a role.
- • Etiologically realistic models of epileptogenesis after brain insult are being introduced in the hope to capture mechanisms relevant to corresponding human epilepsies.
- • Recent findings demonstrate that posttraumatic epilepsy in a rat model of head injury can be prevented by selective mild brain cooling, an effect potentially linked to broad-spectrum inhibition of inflammatory processes.
- • There are many approved safe anti-inflammatory drugs available that target different aspects of inflammation and are candidates for testing as antiepileptogenic agents.

Figure 1. Mild focal cooling prevents the development of posttraumatic epileptic seizures in blinded randomized studies

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A) Graded focal neocortical cooling in freely moving rats after rostral parasagittal fluid percussion injury is achieved with headsets that dissipate heat with varying efficiency. The rank order for cooling of the perilesional neocortex (A>B>C>D) is the same as that for heat dissipation of the headset. Body temperature is unaffected by focal brain cooling. B) Dose-response of the effect of mild focal cooling. Four weeks after injury, log-transformed time spent seizing varied as a linear function of the steady state temperature (or inversely with the magnitude of cooling) measured in the perilesional neocortices of rats implanted with the indicated headsets. C) Mild focal cooling decreased inflammation in the injured neocortex. After three weeks of treatment with either control headset A (FPI) or headset D (FPI +cooling), the gene expression levels of the inflammatory cytokines IL-1 α and IL-1 β in the neocortices of cooled rats were reduced compared to headset A controls, and comparable to expression levels in sham-injured animals. D) Temporary cooling prevents posttraumatic epileptic seizures. Injured animals were randomized to cooling or mock-cooling headsets, which were implanted 3 days after injury, and ECoG recordings were obtained at the indicated post-injury intervals. After 5 weeks of treatment cooling was terminated by swapping metal cooling elements in cooling headsets for insulating elements identical to those used in mock-cooling headsets. Seizure activity was virtually abolished in treated rats, but not in controls, both during cooling and after termination of treatment. E-H) Thermal images of a mock-cooling control headset (E,F) and a cooling headset (G,H). Brain heat is better dissipated by the cooling headset with a steel rod (G,H) than the control headset with an acrylic rod (E,F). E) Side view. Note the progressive cooling of the acrylic rod and headset with the distance from the brain. F) Top view. Note the cold top surface of the acrylic rod. G) Side view. Note the ring of hot acrylic surrounding the base of the metal rod (arrow). H) Top view. Note the ring of hot acrylic surrounding the steel rod, and the overall higher temperature of the whole headset compared to F. Throughout: 1= nose bar; 2= ear cone; 3= ECoG pedestal; 4=acrylic or steel rod. In panels A-C Statistical significance is color coded: black filled symbols indicate a statistically significant difference from the matched rectal temperature (gray symbols).

Table 1

Clinically approved treatments with anti-inflammatory effects that are promising for preclinical or clinical testing in epilepsy prophylaxis. All treatments listed have regulatory approval for other indications in either the US and/or EU, and have shown neuroprotective in some animal model. In view of the large number of studies and models of neuroprotection, comprehensive review articles are cited whenever available. For all cited studies, treatments were administered after an experimental brain insult (to exclude the possibility of interference with the action of the insult) and epilepsy prevention was determined after cessation of treatment.

Treatment	Primary target	Evidence of neuroprotection after CNS injury (animals or humans)	Evidence of anti-epileptogenesis (prevention of epilepsy in animal models, documented by assessment after cessation of treatment)	
			Prevention	Model
NSAIDs				
Aspirin	COX1/2 [129]	ND	yes ^{BR} [130]	pSEcc [130]
Celecoxib	COX2 [129]	Yes ^A [131, 132]	ND	
Indomethacin	COX1/2 [129]	Yes ^A [133, 134]	ND	
Nimesulide	COX2 [129]	Yes ^A [135, 136]; No ^A [134]	ND	
Parecoxib	COX2 [129]	Yes ^A [137]	no ^R [137]	pSEcc [137]
Statins				
Atorvastatin	HMG-CoA-r [138, 139]	Yes ^A [140]	ND	
Lovastatin	HMG-CoA-r [138, 139]	Yes ^A [141]	ND	
Pravastatin	HMG-CoA-r [138, 139]	No ^A [141]	ND	
Rosuvastatin	HMG-CoA-r [138, 139]	Yes ^A [142]	ND	
Simvastatin	HMG-CoA-r [138, 139]	Yes ^A [141-144]	ND	
Miscellaneous				
Anakinra	IL-1R [145]	Yes ^A [146]	ND	
Erythropoietin	EpoR [147]	Yes ^A [148, 149]; ^H [150] [143]	ND	
Minocycline	Various [81, 151]	Yes ^A [83, 84 152]; ^H [77]	Possibly* [88]	pSEcc [88] [80]
Montelukast	CysLT ₁ [153]	Yes ^A [154]	ND	
Progesterone	Various [155]	Yes ^A [91, 92]; ^H [78, 79]	ND	
Rapamycin	mTOR [156, 157]	Yes ^A [158, 159]	Yes ^B [160]; ^{BR} [161], No [162]	PTEN k.o. [160], WAG/Rij [161], pSEe [162]
Thalidomide	Various [163]	Yes ^A [164, 165]	ND	
Brain cooling	Various [61, 62, 63]	Yes ^A [64, 65]; ^H [40]	yes ^{BR} [31]	FPI ^{BR} [31]

Notes and Abbreviations: CNS=central nervous system; Cox=cyclooxygenase; CysLT₁=cysteinyl leukotriene receptor 1; EpoR=erythropoietin receptor; FPI=fluid percussion injury; HMC-CoA-r inh.=3-lydroxy-3-metliylglutaryl coenzyme A reductase; IL-1R= interleukin-1 receptor; mTOR= mammalian target of rapamycin; ND=no data; NSAIDs = non-steroidal anti-inflammatory drugs; PTEN k.o.=Phosphatase and tensin homolog gene knock out mouse (a cortical dysplasia model); pSEcc =post-status epilepticus (status induced by chemoconvulsants); pSEe=post-status epilepticus (status induced by electrical stimulation);

*
=prevents injury-induced increase in evoked seizure susceptibility;

H
=human;

A
=animal;

B
=blinded study;

R
=randomized study.