*Send Orders for Reprints to reprints@benthamscience.net*

624 *Current Neuropharmacology*, **2020**, *18*, 624-635

**REVIEW ARTICLE**

# How to Find Candidate Drug-targets for Antiepileptogenic Therapy?

Nian Yu[1], Xing-jian Lin[1,*] and Qing Di[1]

[1]*Department of Neurology, The Affiliated Nanjing Brain Hospital of Nanjing Medical University, 210029, Nanjing, China*

**ARTICLE HISTORY**

Received: October 31, 2019
Revised: December 10, 2019
Accepted: January 27, 2020

*DOI:*
*10.2174/1570159X18666200128124338*

**Abstract:** Although over 25 antiepileptic drugs (AEDs) have become currently available for clinical use, the incidence of epilepsy worldwide and the proportions of drug-resistant epilepsy among them are not significantly reduced during the past decades. Traditional screens for AEDs have been mainly focused on their anti-ictogenic roles, and their efficacies primarily depend on suppressing neuronal excitability or enhancing inhibitory neuronal activity, almost without the influence on the epileptogenesis or with inconsistent results from different studies. Epileptogenesis refers to the pathological process of a brain from its normal status to the alterations with the continuous prone of unprovoked spontaneous seizures after brain insults, such as stroke, traumatic brain injury, CNS infectious, and autoimmune disorders, and even some specific inherited conditions. Recently growing experimental and clinical studies have discovered the underlying mechanisms for epileptogenesis, which are multi-aspect and multistep. These findings provide us a number of interesting sites for antiepileptogenic drugs (AEGDs). AEGDs have been evidenced as significantly roles of postponing or completely blocking the development of epilepsy in experimental models. The present review will introduce potential novel candidate drug-targets for AEGDs based on the published studies.

**Keywords:** Epileptogenesis, antiepileptogenesis, anti-epileptogenic drugs, drug targets, immunomodulators, precipitating epileptogenic events.

## 1. SIGNIFICANCE OF ANTIEPILEPTOGENIC THERAPY

Epilepsy, a chronic paroxysmal brain disorder, is one of the most common disabling conditions around the world [1]. Since the first introduction of bromides for seizures in 1850, the modern treatment for epilepsy has passed nearly 170 years [2]. There are over 25 antiepileptic drugs (AEDs) have been currently available for patients [3]. Newer-generation AEDs have become better by getting safer and with fewer side effects [4]. However, the incidence of epilepsy worldwide and the proportions of drug-resistant epilepsy (DRE) among them are not reduced during the past decades [5]. By contrast, the mortality of epilepsy and its social and economic burden in global have been greatly increasing, particularly in the paediatric and geriatric populations [6, 7].

Traditional screens for AEDs have been mainly focused on their anti-ictogenesis roles, and their efficacies primarily depend on suppressing neuronal excitability or enhancing inhibitory neuronal activity [8, 9]. They are primarily symptomatic treatments after the development of chronic epilepsy, without obvious influences on the underlying process of brain abnormalities, causing epilepsy [10, 11]. Several clinical trials have been conducted so as to prevent the epileptic development based on traditional AEDs, but unfortunately they all failed [12, 13]. Moreover, many adverse events, such as cognitive impairment, retarding the recovery of neurological deficits were found in the patients receiving preventive AEDs treatment [14]. The preventive therapy using current AEDs therefore is not recommended after traumatic brain injury (TBI), stroke, brain tumours or brain surgery by the guidelines from various regions and counties [15, 16].

The disappointing results above may be due to current AEDs, which do not really interfere in any substantial way with the epileptogenic process of acquired epilepsies (maybe also including hereditary epilepsy) [17]. The question of how to decrease the incidence of epilepsy in the seizure-free populations but with higher risk for generating epilepsy has long been neglected and not received adequate attention. It is generally believed that blocking epileptogenesis may be not realistic in practice, although it will give better benefits to patients by avoiding the negative lifelong medical therapy and social consequences of epilepsy [18].

Recently growing experimental and clinical studies have discovered the underlying mechanisms for the epileptogenesis, which are multifacial and multistep [19, 20]. These findings provide us a number of interesting sites for antiepileptogenic drugs (AEGDs). AEGDs have been evidenced as roles of postponing or completely blocking the development

*Address correspondence to this author at the Department of Neurology, The Affiliated Nanjing Brain Hospital of Nanjing Medical University, Address: 264 Guangzhou Road, 210029, Nanjing, Jiangsu Province, China; Tel: +86-25-82296396; Fax: +86-25-83719457; E-mails: linxingjian@njmu.edu.cn OR my work-team email: linppmm@126.com

1570-159X/20 $65.00+.00 

of epilepsy in experimental models [21, 22]. The present review will focus on the current understanding of the proposed preventive strategy for epilepsy, so as to address some potential candidate drug-targets for lowering or inhibiting the development of epilepsy.

Moreover, it is also a good way to prevent the development of epilepsy in clinic by identifying and avoiding the risk factors for epileptogenesis after certain precipitating events [23, 24]. Additionally, a ketogenic diet, the high-fat, low-carbohydrate composition, as an alternative metabolic therapy for paediatric DRE, has also proved to be a promising disease-modifying for epilepsy or anti epileptogenic therapy [25]. However both of these are beyond the scope of this review.

## 2. CONCEPTS OF EPILEPTOGENESIS AND ANTIEPILEPTOGENIC DRUGS

Epileptogenesis refers to the pathological process of a brain from its normal situation to the neuron network alterations following initial insults, which can produce continuous prone of unprovoked spontaneous seizures [26, 27]. The precipitating epileptogenic events (PEEs) vary over a wide range including stroke, TBI, neurodegenerative diseases, infectious and autoimmune disorders, prolonged febrile convulsions, as well as some specific genetic conditions [28]. As shown in Fig. **1**, there are usually three different stages for epileptogenesis [29, 30]: **Stage 1** of the triggering phase (with or without seizures) after PEEs; **Stage 2** of the latent phase (a relatively "silent" period without manifestations of "seizures", which offers a therapeutic window for the prevention of epileptogenesis.); and **Stage 3** of the chronic epilepsy phase (this is the definite diagnosis of epilepsy if it has at least 2 unprovoked seizures with an interval of over 24 h in clinic [31]).

The experimental models of epilepsy available, such as chemical-kindling, electric-shocked, prolonged hyperthermia-induced, could well simulate the processes of epileptogenesis [32]. Status epilepticus (SE) had long been focused as a PEE only in animal models for studying epileptogenesis, which had been thought of rarely in patients. Thus, the values of animal models for epileptogenesis had been debated. But presently, more and more new-onset SE occurring in patients has been found with a higher risk for epilepsy [33, 34]. Therefore, the results from the animal models may be persuasive as SE actually exists as a PEE in populations; and current researches on epileptogenesis mostly based on these models of convulsive seizures with clear behavioral symptoms. It is relatively difficult to identify the models of non-convulsive seizures due to more subtle semiology such as altered consciousness and less motor activity. Although it is still controversial, nonconvulsive seizures was defined as characteristic electroencephalographic events in models from several studies [35]. Based on this definition, nonconvulsive seizures have been found as the earliest signs during the latent period of epileptogenesis (**Stage 2**) in pilocarpine (Pilo) [36] or kainic acid (KA) [37] -induced models and electrical stimulation-triggered SE [38]. Thus, the exploration of AEGDs based on mechanisms underlying nonconvulsive seizures during the latent period could even be most effective and promising, such as Y-27632 (one of Rho/Rho-kinase inhibitors) [39] and micro-RNA-211 [40].

The concept of AEGDs is defined as the agents with the ability to partially postponing or completely blocking the development of epilepsy in this review, mainly based on convulsive seizures [41]. These intervention drugs may be used in **Stage 1** (mostly in animal models) or **Stage 2** (both in animal models and several clinical trials) to test its efficacy and safety. The intervention approaches in Stage 2 can be expectedly used in clinic to prevent epileptogenesis in the future.

Generally, the term "antiepileptogenic therapy" refers to the distinct methods of preventing or delaying the development of epilepsy in the susceptible population. In the present review, "antiepileptogenic therapy" was mainly limited to chemical agents for preventing epileptogenesis. Indeed, there are some overlaps among the concepts of "*antiepileptogenic therapy*", "*neuroprotective therapy for epilepsy*" and "*epilepsy-modifying therapy*" [43]. The neuroprotective therapy for epilepsy means the approaches of decreasing the neuronal damage (*i.e.* neuron loss, plastic construction) or improving the neurological deficits (*i.e.* cognitive impairment,

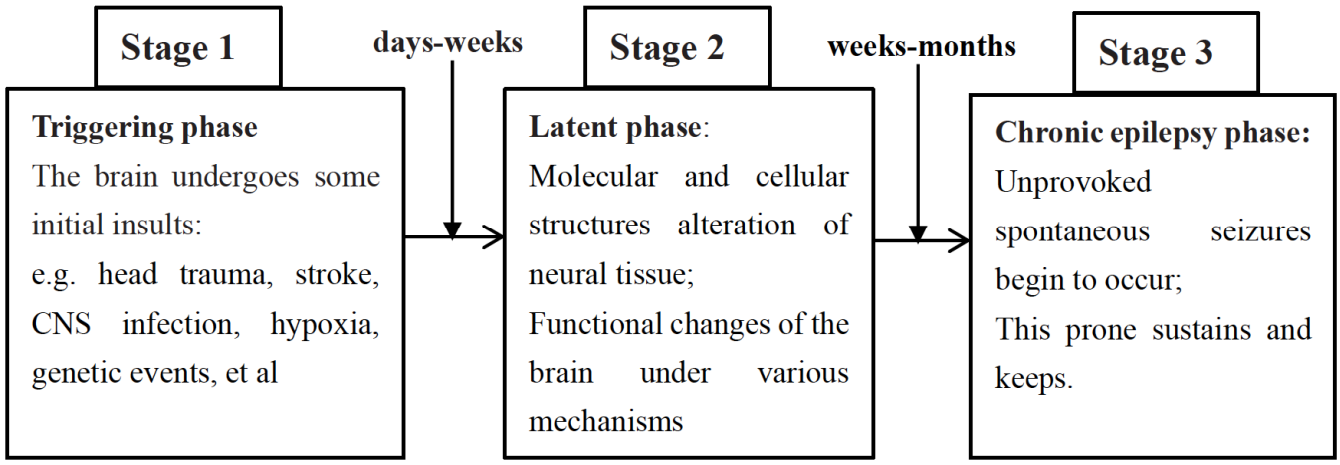


**Fig. (1).** Three continuous stages of epileptogenesis. This picture is based on the data from Ethan M's study [29] and our own data [41, 42].

**Table 1. Brief summary of major signaling pathways underlying the mechanisms of epileptogenesis and related AEGDs targets.**

| Signalling Pathways | Pathophysiology | Example of Antiepileptogenic Treatment |
|---|---|---|
| Neuroinflammatory pathways | Inflammatory brain injuries | Anti-inflammatory and anti OS agents |
| mTOR-ERK1/2 pathways | Linked with the development of cortical malformations | mTOR inhibitor: rapamycin |
| BDNF/TrkB signalling | Cell proliferation and plasticity | BDNF gene duo-therapy |
| TGFβ signalling | Associated with BBB dysfunction | TGF-β signalling blockers: AT1 |
| Adenosine kinase (ADK) hyper-reaction | Decreasing the adenosine levels and lead to astrogliosis | ADK inhibitor 5-iodotubercidin |
| SV2A hyper-reaction | Disrupting action potential-induced γ- GABA | SV2A modulator |

Note: OS= Oxidative stress; TOR=mammalian target of rapamycin; ERK 1/2= extracellular signal-regulated kinase ½; TGFβ =transforming growth factor beta; BBB= Blood-Brain Barrier; BDNF=brain-derived neurotrophic factor; TrkB= tropomyosin related kinase B; FGF-2=fibroblast growth factor 2; ADK=Adenosine kinase; SV2A=synaptic vesicle glycoprotein 2A; γ-GABA=γ-aminiobutyric acid; AT1=angiotensin II type 1 receptor antagonist.

mood disorders) resulting from the initial brain insult events. Epilepsy-modifying therapies aim at reducing seizure frequency, shortening seizure duration, increasing seizure thresholds, or inhibiting the spread and severity of seizures [44]. Different from the antiepileptogenic therapy mainly limited in the experimental models, neuroprotective and disease-modifying therapies have been both used in clinic currently, such as increasing response to AEDs and changing epilepsy from refractory to controllable [45]. The antiepileptogenic roles of an AEGD may depend on its neuroprotective or disease-modifying activity, whereas the latter two may not show a solo role in treating epilepsy [46]. But it may be difficult at times to differentiate the drug effects of "true" antiepileptogenesis, "true" disease-modifying efficacy or "true" neuroprotective effect. Certain neuroprotective and disease-modifying therapies have been used in epilepsy, primarily associated with resolving its pathology, comorbidities, and adverse effect of AEDs [47]. Therefore, antiepileptogenic therapies may belong to one of the epilepsy-modifying approaches.

## 3. MECHANISMS OF EPILEPTOGENESIS

Epileptogenesis is an extraordinarily complex process. Till date, its detailed mechanisms have not been fully clarified. In general, the development of epilepsy may be initially precipitated by various etiologies with distinct PEEs, such as stroke, TBI, CNS infectious and autoimmune disorders, alongside some specific genetic conditions [48]. Epileptogenesis is characterized by distinct histopathologic and biochemical changes, which include astrogliosis and imbalance between excitatory and inhibitory neurotransmitters [49]. However, the studies currently available have suggested some convergences of molecular mechanisms underlying epileptogenesis following different PEEs [50]. The common signal pathways involved in the processes of epileptogenesis are listed in Table **1**.

Although there seems to be the inherent complexity and heterogeneity of known mechanisms of epileptogenesis, there are still some common fundamental pathophysiologic mechanisms shared by various PEEs. For instance, neuroinflammatory pathways and mammalian target of rapamycin (mTOR)-extracellular signal-regulated kinase (ERK) 1/2 pathways can both involved the development of epilepsy after TBI, stroke, infectious, immune disorders and certain genetic diseases [51, 52]. Moreover, genetic factors may play a general role in the likelihood of epileptogenesis [53]. It is important to note that some of these mechanisms may benefit the repair or the recovery process after brain injury, which are not appropriate as targets of AEGDs, *e.g*. reactive astrogliosis in TBI could contribute to the recovery of neurological function and epileptogenesis in the meanwhile [54]. The intervention without any selection on drug targets may do harm to the brain. For example, tumor necrosis factor-α (TNF-α), one of important pro-inflammatory cytokines has proved to predispose epileptogenesis by upregulating microglial glutamate release and causing neurotoxicity [55], whereas anti-TNF-α therapy for epilepsy may increase the suspected risks of infection and cancer development [56]. The more instances like this were not fully discussed in this review. We mainly focused on promising cases currently.

## 4. CANDIDATE DRUG-TARGETS FOR AEGDS BASED ON ESTABLISHED MECHANISMS FOR EPILEPTOGENESIS

Established mechanisms above provided us many promising targets for AEGDs include anti-inflammatory and antioxidative drugs, mTOR inhibitors, TrkB inhibitors, TGFβ antagonists, ADK inhibitors, the SV2A modulator, and epigenetic interventions, as listed in Table **1**. Due to amounts of crosstalk existing among different signal pathways, single drug candidate may have several potential action targets. For instance, both TrkB inhibitors and TGFβ antagonists may generate predominantly anti-inflammatory roles in some animal models [57, 58]; whereas anti-inflammatory drugs can also inhibit the TrkB or TGFβ pathways [59]. So, it is only relatively easy to introduce them separatedly below.

### 4.1. Neuroinflammatory Pathways as AEGDs Targets in Prophylaxis for Epilepsy

Excessive activation of inflammation response in the brain might be one of the most extensively studied pathways underling epileptogenesis, which has been commonly identified in various animal models of epilepsy and in humans [60]. The main inflammatory pathways for epilepsy include the damage-associated molecular pattern of high-mobility group box 1(HMGB1)-Toll-like receptor 4(TLR4)/advanced

glycation end products(RAGE)-nuclear factor-kappa B (NF-κB)-interleukin(IL)-1 beta axis [61], and the arachidonic acid (AA)-cyclooxygenases (COX)-prostaglandin (PGs) cascade [62]. Neuroinflammation can be initiated by numbers of PEEs for epilepsy, such as infectious diseases and non-infectious brain injuries [63]. Pathogen-associated molecular patterns (PAMPs) from infectious agents, like herpes virus, can also activate TLRs and promote similar consequences of neuroinflammation above [64]. Recently, it was found that the conditions of post-herpes virus encephalitis could trigger to produce anti-neuronal antibodies, like N-Methyl-D-aspartate (NMDA) receptor antibody [65], which mediated causing autoimmune epilepsy furtherly [66].

Oxidative stress (OS) can also trigger or be triggered by acute or chronic neuroinflammation for epilepsy, which manifested as an imbalance status of a brain between realising reactive oxygen species and eliminating them under insulting conditions [67]. The downstream of neuroinflammation activation during the period of epileptogenesis may share the common pathways, such as the dysregulation of cytokine balance in the CNS or through the complement pathway, which furtherly cause the neuron loss *via* neurotoxicity or over hyperexcitability [68]. Ischemic processes, one of important PEEs, can block the degradation of hypoxia inducible factor 1-α (HIF-1α), which binds to hypoxia responsive element, resulting in the up-regulation of COX-2 and PGE-2 [69]. Based on the roles of anti-inflammatory, some natural plant products, *e.g.* berberine (a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in such plants as berberis) [70],

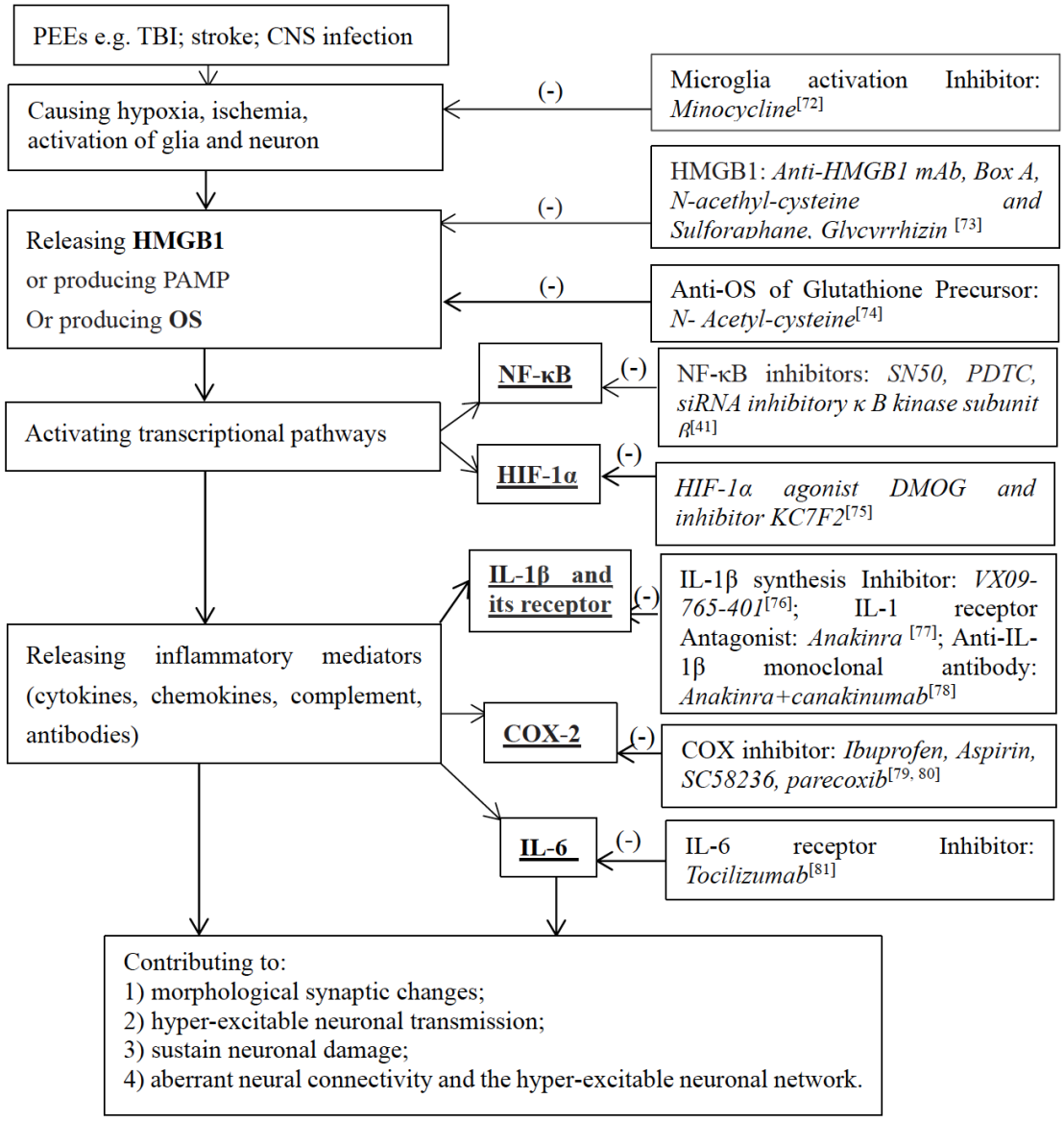


**Fig. (2). The therapeutic targets for prophylaxis of epileptogenesis associated with interconnected inflammatory pathways.** The hyperexcitability, excitotoxicity and neurotoxicity caused by the neuroinflammatory process could predispose to spontaneous recurrent seizures and mediate the epileptogenesis. Multiple targets for AEGDs are presented *via* modulating the inflammatory pathways. "(-)" means the intervened targets. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and curcumin (a principal curcuminoid present in turmeric) [71] also exhibited anti-epileptogenic properties. The complex relationships among the inflammation signal pathways and corresponding molecular targets for anti-epileptogenic therapies through anti-inflammatory were established in Fig. **2**.

Apart from its therapeutic effects, we recently reported that neuroinflammatory pathways could modulate expression of the ATP-binding cassette transporters [41] and the enzymes of cytochrome P450 family [82], both of which can mediate the development of DRE. So, inflammatory mediators could also provide diagnostic, prognostic and predictive biomarkers for epilepsy or DRE, which will be useful tools for patient stratification futurely.

### 4.2. mTOR Signaling Pathway as Candidate Targets for AEGDs

Mammalian target of rapamycin (mTOR) is a key protein kinase regulating cellular division and proliferation [83]. mTOR has two distinct complexes—mTORC1 and mTORC2, encoded by tuberous sclerosis complex 1 (*TSC1*) and *TSC2* genes respectively [84]. mTOR hyper-activation, as a consequence of *TSC1 and TSC2* mutations could lead to dysplastic neurons, abnormal cortical organization and astrogliosis, which are considered as the primary cause for TSC, linked with the development of cortical malformations and epilepsy [85, 86]. Furthermore, giant cell astrocytoma, angiomyolipoma, hemimegalencephaly, and lymphangioleiomyomatosis are all also associated with mTOR hyperactivation [87]. In addition to genetic epilepsy, hyperactivation of mTOR signalling has also been involved in animal models of acquired epilepsy in particular with the controlled cortical involvement, including TBI [88], ischemic stroke [89], and KA [90] or electrical stimulation induced-SE [91]. According to a large randomized clinical trial [92], everolimus, one mTOR inhibitor and also an analogue of rapamycin, has been recently approved by the FDA of the United States and European Union for TSC-associated partial-onset seizures alongside with many other aspects of TSC, such as cortical dysplasia, subependymal giant cell astrocytomas and renal angiomyolipomas; and the efficacy of mTOR inhibitors has also been confirmed in epileptic patients [93]. From another long-term prospective trial [94], vigabatrin also showed a preventative antiepileptic effect in TSC infants with paroxysmal EEG changes before clinical seizures, probably relevant with its mTOR inhibitory effect. Therefore, mTOR is currently a very greater candidate for anti-epileptogenesis. Many other mTOR inhibitors are being explored or in clinical trials.

### 4.3. BDNF/TrkB Signaling

Neurotrophic factors (NTFs), such as brain derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2), are a family of endogenous soluble biomolecules, with critical roles in regulating the growth, survival, and differentiation of both developing and mature neurons [95]. Their actions are at tropomyosin related kinase (Trk) receptors, which include TrkA (bind with NGF), TrkB (selectively bind with BDNF), and TrkC [96]. Early studies have found that frequency seizures or other brain injuries could increase the expression of BDNF and TrkB, which consequently increased neuron network excitability, giving us the clues of the link between the BDNF and epileptogenesis [97]. Another report found that conditional deletion of TrkB independently prevented epileptogenesis in a kindling model [98]. Nowadays, increasing evidences addressed the role of increased BDNF/TrkB signalling on the progressive development of epilepsy by different models [99]. Therefore, several drugs targeting BDNF/TrkB signaling have been used to prevent epileptic generation following PEEs, showing an innovative promising strategy [100].

### 4.4. TGFβ Signal Associated with Blood-brain Barrier Dysfunction for AEGDs

Blood-brain barrier (BBB) dysfunction, usually with increasing permeability and extravasation of serum albumin in perivascular brain tissue, is an important etiological player in epileptogenesis following various brain insults [101]. The PEEs may directly damage the integrity of BBB, or produce indirect injury to BBB mediated by inflammatory mediators, impairment of tight junctions, and OS [102]. Consequently, the secondary events to the above furtherly activated transforming growth factor beta (TGFβ) receptor signalling pathway in astrocytes, which consequently influenced the function of potassium channel, the aquaporin 4 channel and the glutamate transporters [103]. This pathological process demonstrated a key role for astroglia and profoundly involved in the development of epilepsy. Blockers of TGF-β signalling, such as angiotensin II type 1 receptor antagonist (AT1), losartan, could effectively prevent the development of delayed spontaneous seizures in different rat models of vascular injury, which effect persisted weeks after drug withdrawal [104]. These findings could be considered as a key epileptogenic process, indicating the manipulation of the TGF-β-pathway as another potential strategy for anti-epileptogenic therapy.

### 4.5. Modulating Neurotransmitters and their Metabolic Enzymes as AEGDs Targets

Dysfunctional release of neurotransmitters (including synaptic neurotransmitters) and their metabolic enzymes is closely involved in the pathogenesis of epilepsy [105]. In this respect, the following features have been found in the epileptogenic process: loss of c-aminobutyric acidergic (GABAergic) interneurons, increasing glutamatergic neurons, and the molecular reorganization of glutamate and GABA receptor subunits [106]. The pathophysiology of epileptogenesis has been found profoundly relevant with overexpression and activity of both types of glutamate receptors, including ionotropic glutamate receptor (*eg*. NMDA, AMPA) and metabotropic glutamate receptors (mGluRs), as well as their related signal transduction pathways [107]. The following changes have been as marked characteristics during epileptogenesis: altered excitability of neurons and/or neuronal circuits, reactive synaptogenesis and axonal sprouting, activation of microglia, and astrocyte dysfunction. mGluR antagonist (LY367385 + MPEP) [108] and NMDA receptor antagonist (MK-801, dizocilpine) [109] both have been evidenced to successfully block prolonged epileptiform discharges in experimental models.

Among the metabolisms of neurotransmitter systems, the adenosine-metabolizing enzyme adenosine kinase (ADK) is extensively studied by various models of PEEs. Increased expression of ADK could contribute astrogliosis associated with epileptogenesis, therefore providing us another target for therapeutic intervention [110]. Pre-treatment with ADK inhibitor 5-iodotubercidin (5-ITU) significantly reduced the susceptibility and severity of seizures in intrahippocampal KA mouse model of temporal lobe epilepsy (TLE) [111]. 5-ITU also showed neuroprotective roles by suppressed granule cell dispersion in these protected mice [111]. So, the transient use of a small-molecule ADK inhibitor may yield both anti-epileptogenesis and disease-modifying properties. Synaptic vesicle glycoprotein 2A (SV2A) is a membrane protein specifically expressed in synaptic vesicles, regulating action potential-dependent neurotransmitter release in brain [112]. It serves as one of specific binding sites for the current AED-levetiracetam and its analogues [113]. Blocking SV2A's action showed that the dysfunction of SV2A preferentially disrupted action potential-induced γ-GABA, but not glutamate in kindling epileptogenesis, indicating that enhancing SV2A function could decrease epileptogenesis and encourage future research on the novel AEGDs [114]. Levetiracetam has also been identified to act primarily through SV2A, so it is taken into account as possessing promising antiepileptogenic properties in addition to its anti-seizure effect [115]. But it still needs large clinical trials on distinct types of subjects with higher risk for epilepsy.

### 4.6. Epigenetic Chromatin Modifications

Epigenetic signalling has proved to exert predominant regulation of gene expression, widely linked with the pathophysiology of epileptogenesis [116]. The potential epigenetic mechanisms included histone modifications, DNA methylation, microRNA-based transcriptional control, and bromodomain reading activity [117]. This process can explain the synergistic mis-regulation of multiple genes in major epileptogenic pathways-including neuroinflammation and synaptic reorganization [118]. Increased levels of DNA promoter methylation have been found in resected brain specimens from TLE patients [119, 120]. Reddy *et al*. [121] have showed that the histone deacetylase (HDAC) inhibitor *sodium butyrate* in the hippocampus kindling model of TLE markedly attenuated seizure persistence many weeks and resulted in a striking retardation of epileptogenesis. However, this effect was not evident in early studies by selective HDAC inhibition of *trichostatin A* [122] or *suberoylanilide hydroxamic acid* [123]. We speculated the controversial results may contribute to those inhibitors targeting different informs of HDAC. Although it provides some insights from this aspect, targeting the epigenetic HDAC pathway for preventing curing epilepsy still need to be further explored in future.

### 4.7. Others Potential Candidates for AEGDs

There were numerus other experimental studies attempting to find an effective prophylactic treatment for epileptogenesis, as listed in Table **2**. These drug-targets may be distinct from the mentioned above. Occasionally, there were contrary conclusions from the studies using same drugs. For example, an antagonist of transient receptor potential cation channel subfamily M member 8 showed significant protective effects on febrile− and pentylenetetrazol (PTZ)-induced seizures; however, it did not produce similarly protective effects on electroshock-induced seizures model [124]. Another similar example, bumetanide, an inhibitor of the $Na^{(+)}K^{(+)}2Cl^{(-)}$ co-transporter could prevent epileptogenesis in a model of the febrile seizures in neonatal rats [125] as well with a model of genetic epilepsy [126] but this effect was not found in the lithium-Pilo model in adult rats [127] . Both examples illustrated that the groups with different models (or PEEs) and ages may undergo different pathophysiological changes of brain underlying the epileptogenesis. Importantly, models are not naturalistic, and do not have high validity pertaining to the human epilepsy aetiology. Even where they do, success in one model and not another is also valuable as it represents a potential tailored treatment for one group of patients. This is in line with modern principles of drug discovery.

## 5. POTENTIAL AEGDS BASED ON KNOWN DRUGS AVAILABLE FOR NON-EPILEPSY DISORDERS

The drugs clinically approved for non-epilepsy indications, such as glatiramer acetate (an immunomodulator currently used in the treatment of multiple sclerosis)[139], statins (cholesterol-lowering drugs used for the treatment of hypercholesterolemia and related atherosclerotic diseases)[140], isoflurane(an anesthetic agents) [141], and the first-line antidiabetic agents(metformin [142] and rosiglitazone [143]), and cannabinoids (a group of compounds found in the Cannabis sativa plant, licenced for Lennox-Gastaut syndrome and Dravet syndrome)[144] have also offered the roles of preventing the development or progression of epilepsy in different animal models at some extent. Their antiepileptogenic effect may primarily or partially depend on their anti-inflammatory and antioxidative properties. It should be noted that statins are the only drugs with clinical evidence of antiepileptogenic efficacy from large clinical trials [145]. But the enrolled participants in the previous trials are all geriatric populations usually with stroke or cardiovascular disease.

## 6. CHALLENGES AND PERSPECTIVES

Most of potential candidates for AEGDs summarized above all reflect the mechanisms underlying generation of epilepsy to a certain extent. Among them, the targets on neuroinflammatory pathways and mTOR-ERK1/2 pathways may provide a more promising application for prevention of epilepsy. Some known drugs available for widely using in non-epileptic disorders are worth further being evaluated in clinic due to their multiple acting targets and safety.

However, preclinical data may not be completely equal to clinical outcomes. There is a long way of translating knowledges from bench to bedside. Many mysteries and challenges still exist on exploring and employing the AEGDs in future. Sloviter *et al*'s study showed that the latency of injury-induced epileptogenesis may be a much more rapid process than previously thought, inconsistent with a delayed epileptogenic mechanism [146]. As one research suggested that antiepileptogenic therapy may need to start earlier after the

**Table 2. Other potential AEGDs candidates and corresponding PEE models.**

| Drugs | Pharmacological Activity | Models of Preventive | Authors and Published Years |
|---|---|---|---|
| Lycopene | alleviating oxidative stress, elevated SOD activity and suppressed NMDA level | KA-induced seizure mice | Li S, *et al*, 2019 [128] |
| Fingolimod (FTY720) | a sphingosine-1-phosphate analogue | suprahippocampal KA/ Pilo-induced SE mice | Pitsch J, *et al*, 2019 [129] |
| PSD95BP or Tat-NR2B9c) and 1400W | postsynaptic density protein-95 blocking peptide, a highly selective inducible nitric oxide synthase inhibitor | C57BL/6J mouse model of KA-induced epileptogenesis | Tse K, *et al*, 2019 [130] |
| Scoparone (6,7-dimethoxycoumarin) | multiple beneficial activities, including antitumor, anti-inflammatory and anti-coagulant properties | Pilo-induced seizures in mice | Xia J, *et al*, 2018 [131] |
| acetaminophen | transient receptor potential vanilloid-1 antagonists | PTZ induced seizures in mice | Suemaru K, *et al*, 2018 [132]<br>Fu M, *et al*, 2009 [133] |
| sodium cromoglycate | blockage of $Ca^{2+}$release-activated $Ca^{2+}$channels of mast cells for allergic events | Pilo-induced SE in Wistar rats | Valle-Dorado MG, *et al,* 2009 [134] |
| atipamezole | brain-penetrant α2-adrenoceptor antagonist | post-TBI model in SD rats | Nissinen J, *et al*, 2017[135] |
| WP1066 | a selective inhibitor of the JAK/STAT pathway | Pilo-induced in adult SD rats | Grabenstatter HL, *et al*, 2014 [136] |
| Uncaria rhynchophylla and Rhynchophylline | reducing the c-Jun aminoterminal kinase expression of MAPK signal pathways | KA-induced seizures in rats | Hsu HC*, et al*, 2013 [137] |
| pHBSP | nonerythropoietic erythropoietin-derived peptide | Electronic induced- SE model in rats | Seeger N, *et al*, 2011 [138] |

Note: SE=status epilepticus; KA= kainic acid; PTZ=pentylenetetrazol; Pilo=pilocarpine; Sprague-Dawley=SD.

brain insult [147], how do we precisely define and control the time when to start this prophylaxis for epilepsy? Furthermore, which specific subjects at risk for epilepsy following PEEs will get benefit from the earlier therapy? Since the mechanisms underlying the epileptogenisis are multitargeted, multistep, and multi-interactional, will the combined therapy acting on distinct targets get better effects than monotherapy? Last but not the least, how long does the prevention treatment need sustain? It is also necessary to define which specific forms of AEGDs should be administered, at what doses, and for what duration of treatment, in order to promote repair of neuronal damage. We have also acknowledged that rationally based on specific molecular targets validated in animal models-have failed to show significant effects in humans [148]. Therefore, we still need perform proof-of-concept clinical trials with the most promising drugs, which will be essential to make prevention of epilepsy a reality.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

This work was supported by two grants, one from the Nanjing Medical Science and Technology Development Foundation (QRX17179) and the other from National Natural Science Foundation of China (Grant No. 81400981).

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

[1] Singh, A.; Trevick, S. The epidemiology of global epilepsy. *Neurol. Clin.,* **2016**, *34*(4), 837-847. http://dx.doi.org/10.1016/j.ncl.2016.06.015 PMID: 27719996

[2] Rho, J.M.; White, H.S. Brief history of anti-seizure drug development. *Epilepsia Open,* **2018**, *3 (Suppl. 2),* 114-119. http://dx.doi.org/10.1002/epi4.12268 PMID: 30564769

[3] Santulli, L.; Coppola, A.; Balestrini, S.; Striano, S. The challenges of treating epilepsy with 25 antiepileptic drugs. *Pharmacol. Res.,* **2016**, *107*, 211-219. http://dx.doi.org/10.1016/j.phrs.2016.03.016 PMID: 26995307

[4] Chen, Z.; Brodie, M.J.; Liew, D.; Kwan, P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol.,* **2018**, *75*(3), 279-286. http://dx.doi.org/10.1001/jamaneurol.2017.3949 PMID: 29279892

[5] Janmohamed, M.; Brodie, M.J.; Kwan, P. Pharmacoresistance - Epidemiology, mechanisms, and impact on epilepsy treatment. *Neuropharmacology,* **2020**,*168*,107790. http://dx.doi.org/10.1016/j.neuropharm.2019.107790 PMID: 31560910

[6] Beghi, E. Addressing the burden of epilepsy: Many unmet needs. *Pharmacol. Res.,* **2016**, *107*, 79-84. http://dx.doi.org/10.1016/j.phrs.2016.03.003 PMID: 26952026

[7] van den Berg, L.; de Weerd, A.W.; Reuvekamp, H.F.; van der Meere, J.J. The burden of parenting children with frontal lobe epilepsy. *Epilepsy Behav.,* **2019**, *97*, 269-274. http://dx.doi.org/10.1016/j.yebeh.2019.05.034 PMID: 31254848

[8] Sankaraneni, R.; Lachhwani, D. Antiepileptic drugs--a review. *Pediatr. Ann.,* **2015**, *44*(2), e36-e42. http://dx.doi.org/10.3928/00904481-20150203-10 PMID: 25658217

[9] Kobayashi, K; Endoh, F; Ohmori, I; Akiyama, T. Action of antiepileptic drugs on neurons. *Brain Dev.,* **2020**, *42*(1),2-5.

[10] Clossen, B.L.; Reddy, D.S. Novel therapeutic approaches for disease-modification of epileptogenesis for curing epilepsy. *Biochim. Biophys. Acta Mol. Basis Dis.,* **2017**, *1863*(6), 1519-1538. http://dx.doi.org/10.1016/j.bbadis.2017.02.003 PMID: 28179120

[11] Mani, R.; Pollard, J.; Dichter, M.A. Human clinical trails in antiepileptogenesis. *Neurosci. Lett.,* **2011**, *497*(3), 251-256. http://dx.doi.org/10.1016/j.neulet.2011.03.010 PMID: 21439351

[12] Wang, J.Z.; Vyas, M.V.; Saposnik, G.; Burneo, J.G. Incidence and management of seizures after ischemic stroke: Systematic review and meta-analysis. *Neurology,* **2017**, *89*(12), 1220-1228. http://dx.doi.org/10.1212/WNL.0000000000004407 PMID: 28835405

[13] Wilson, C.D.; Burks, J.D.; Rodgers, R.B.; Evans, R.M.; Bakare, A.A.; Safavi-Abbasi, S. Early and late posttraumatic epilepsy in the setting of traumatic brain injury: a meta-analysis and review of antiepileptic management. *World Neurosurg.,* **2018**, *110*, e901-e906. http://dx.doi.org/10.1016/j.wneu.2017.11.116 PMID: 29196247

[14] Spoelhof, B.; Sanchez-Bautista, J.; Zorrilla-Vaca, A.; Kaplan, P.W.; Farrokh, S.; Mirski, M.; Freund, B.; Rivera-Lara, L. Impact of antiepileptic drugs for seizure prophylaxis on short and long-term functional outcomes in patients with acute intracerebral hemorrhage: A meta-analysis and systematic review. *Seizure,* **2019**, *69*, 140-146. http://dx.doi.org/10.1016/j.seizure.2019.04.017 PMID: 31048270

[15] Turnbull, D.; Singatullina, N.; Reilly, C. A systematic appraisal of neurosurgical seizure prophylaxis: Guidance for critical care management. *J. Neurosurg. Anesthesiol.,* **2016**, *28*(3), 233-249. PMID: 26192247

[16] Won, S.Y.; Dubinski, D.; Herrmann, E.; Cuca, C.; Strzelczyk, A.; Seifert, V.; Konczalla, J.; Freiman, T.M. Epileptic seizures in patients following surgical treatment of acute subdural hematoma-incidence, risk factors, patient outcome, and development of new scoring system for prophylactic antiepileptic treatment (GATE-24 score). *World Neurosurg.,* **2017**, *101*, 416-424. http://dx.doi.org/10.1016/j.wneu.2017.02.024 PMID: 28213197

[17] Schmidt, D.; Sillanpää, M. Prevention of epilepsy: issues and innovations. *Curr. Neurol. Neurosci. Rep.,* **2016**, *16*(11), 95. http://dx.doi.org/10.1007/s11910-016-0695-9 PMID: 27628962

[18] Terrone, G.; Pauletti, A.; Pascente, R.; Vezzani, A. Preventing epileptogenesis: A realistic goal? *Pharmacol. Res.,* **2016**, *110*, 96-100. http://dx.doi.org/10.1016/j.phrs.2016.05.009 PMID: 27173399

[19] Becker, A.J. Review: Animal models of acquired epilepsy: insights into mechanisms of human epileptogenesis. *Neuropathol. Appl. Neurobiol.,* **2018**, *44*(1), 112-129. http://dx.doi.org/10.1111/nan.12451 PMID: 29130506

[20] Maguire, J. Epileptogenesis: More than just the latent period. *Epilepsy Curr.,* **2016**, *16*(1), 31-33. http://dx.doi.org/10.5698/1535-7597-16.1.31 PMID: 26900375

[21] Patel, D.C.; Wilcox, K.S.; Metcalf, C.S. Novel targets for developing antiseizure and, potentially, antiepileptogenic drugs. *Epilepsy Curr.,* **2017**, *17*(5), 293-298. http://dx.doi.org/10.5698/1535-7597.17.5.293 PMID: 29225544

[22] Kaminski, R.M.; Rogawski, M.A.; Klitgaard, H. The potential of antiseizure drugs and agents that act on novel molecular targets as antiepileptogenic treatments. *Neurotherapeutics,* **2014**, *11*(2), 385-400. http://dx.doi.org/10.1007/s13311-014-0266-1 PMID: 24671870

[23] Vespa, P.M.; Shrestha, V.; Abend, N.; Agoston, D.; Au, A.; Bell, M.J.; Bleck, T.P.; Blanco, M.B.; Claassen, J.; Diaz-Arrastia, R.; Duncan, D.; Ellingson, B.; Foreman, B.; Gilmore, E.J.; Hirsch, L.; Hunn, M.; Kamnaksh, A.; McArthur, D.; Morokoff, A.; O'Brien, T.; O'Phelan, K.; Robertson, C.L.; Rosenthal, E.; Staba, R.; Toga, A.; Willyerd, F.A.; Zimmermann, L.; Yam, E.; Martinez, S.; Real, C.; Engel, J., Jr. The epilepsy bioinformatics study for antiepileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. *Neurobiol. Dis.,* **2019**, *123*, 110-114. http://dx.doi.org/10.1016/j.nbd.2018.07.025 PMID: 30048805

[24] Tomari, S.; Tanaka, T.; Ihara, M.; Matsuki, T.; Fukuma, K.; Matsubara, S.; Nagatsuka, K.; Toyoda, K. Risk factors for post-stroke seizure recurrence after the first episode. *Seizure,* **2017**, *52*, 22-26. http://dx.doi.org/10.1016/j.seizure.2017.09.007 PMID: 28957721

[25] Chen, F.; He, X.; Luan, G.; Li, T. Role of DNA methylation and adenosine in ketogenic diet for pharmacoresistant epilepsy: focus on epileptogenesis and associated comorbidities. *Front. Neurol.,* **2019**, *10*, 119. http://dx.doi.org/10.3389/fneur.2019.00119 PMID: 30863356

[26] Jehi, L.E.; Vezzani, A. Novel concepts in epileptogenesis and its prevention. *Neurotherapeutics,* **2014**, *11*(2), 229-230. http://dx.doi.org/10.1007/s13311-014-0268-z PMID: 24652605

[27] Pitkänen, A.; Engel, J., . Past and present definitions of epileptogenesis and its biomarkers. *Neurotherapeutics,* **2014**, *11*(2), 231-241. http://dx.doi.org/10.1007/s13311-014-0257-2 PMID: 24492975

[28] Devinsky, O.; Vezzani, A.; O'Brien, T.J.; Jette, N.; Scheffer, I.E.; de Curtis, M.; Perucca, P. Epilepsy. *Nat. Rev. Dis. Primers,* **2018**, *4*, 18024. http://dx.doi.org/10.1038/nrdp.2018.24 PMID: 29722352

[29] Goldberg, E.M.; Coulter, D.A. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. *Nat. Rev. Neurosci.,* **2013**, *14*(5), 337-349. http://dx.doi.org/10.1038/nrn3482 PMID: 23595016

[30] Pitkänen, A.; Lukasiuk, K. Mechanisms of epileptogenesis and potential treatment targets. *Lancet Neurol.,* **2011**, *10*(2), 173-186. http://dx.doi.org/10.1016/S1474-4422(10)70310-0 PMID: 21256455

[31] Fisher, R.S.; Acevedo, C.; Arzimanoglou, A.; Bogacz, A.; Cross, J.H.; Elger, C.E.; Engel, J., Jr; Forsgren, L.; French, J.A.; Glynn, M.; Hesdorffer, D.C.; Lee, B.I.; Mathern, G.W.; Moshé, S.L.; Perucca, E.; Scheffer, I.E.; Tomson, T.; Watanabe, M.; Wiebe, S. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia,* **2014**, *55*(4), 475-482. http://dx.doi.org/10.1111/epi.12550 PMID: 24730690

[32] Pitkänen, A.; Kharatishvili, I.; Karhunen, H.; Lukasiuk, K.; Immonen, R.; Nairismägi, J.; Gröhn, O.; Nissinen, J. Epileptogenesis in experimental models. *Epilepsia,* **2007**, *48*(Suppl 2), 13-20.

[33] Jayalakshmi, S.; Vooturi, S.; Sahu, S.; Yada, PK.; Mohandas, S. Causes and outcomes of new onset status epilepticus and predictors of refractoriness to therapy. *J. Clin. Neurosci.,* **2016**, *26*, 89-94.

[34] Chakraborty, T.; Hocker, S. The clinical spectrum of new-onset status epilepticus. *Crit. Care Med.,* **2019**, *47*(7), 970-974. http://dx.doi.org/10.1097/CCM.0000000000003776 PMID: 30985452

[35] Anjum, S.M.M.; Käufer, C.; Hopfengärtner, R.; Waltl, I.; Bröer, S.; Löscher, W. Automated quantification of EEG spikes and spike clusters as a new read out in Theiler's virus mouse model of encephalitis-induced epilepsy. *Epilepsy Behav.,* **2018**, *88*, 189-204. http://dx.doi.org/10.1016/j.yebeh.2018.09.016 PMID: 30292054

[36] Smith, Z.Z.; Benison, A.M.; Bercum, F.M.; Dudek, F.E.; Barth, D.S. Progression of convulsive and nonconvulsive seizures during epileptogenesis after pilocarpine-induced status epilepticus. *J. Neurophysiol.,* **2018**, *119*(5), 1818-1835. http://dx.doi.org/10.1152/jn.00721.2017 PMID: 29442558

[37] Williams, P.A.; White, A.M.; Clark, S.; Ferraro, D.J.; Swiercz, W.; Staley, K.J.; Dudek, F.E. Development of spontaneous recurrent seizures after kainate-induced status epilepticus. *J. Neurosci.,* **2009**, *29*(7), 2103-2112. http://dx.doi.org/10.1523/JNEUROSCI.0980-08.2009 PMID: 19228963

[38] Bertram, E.H.; Cornett, J.F. The evolution of a rat model of chronic spontaneous limbic seizures. *Brain Res.,* **1994**, *661*(1-2), 157-162. http://dx.doi.org/10.1016/0006-8993(94)91192-4 PMID: 7834366

[39] Çarçak, N.; Yavuz, M.; Eryiğit Karamahmutoğlu, T.; Kurt, A.H.; Urhan Küçük, M.; Onat, F.Y.; Büyükafsar, K. Suppressive effect of Rho-kinase inhibitors Y-27632 and fasudil on spike-and-wave discharges in genetic absence epilepsy rats from Strasbourg (GAERS). *Naunyn Schmiedebergs Arch. Pharmacol.,* **2018**, *391*(11), 1275-1283. http://dx.doi.org/10.1007/s00210-018-1546-9 PMID: 30073384

[40] Bekenstein, U.; Mishra, N.; Milikovsky, D.Z.; Hanin, G.; Zelig, D.; Sheintuch, L.; Berson, A.; Greenberg, D.S.; Friedman, A.; Soreq, H. Dynamic changes in murine forebrain miR-211 expression associate with cholinergic imbalances and epileptiform activity. *Proc. Natl. Acad. Sci. USA,* **2017**, *114*(25), E4996-E5005. http://dx.doi.org/10.1073/pnas.1701201114 PMID: 28584127

[41] Yu, N.; Liu, H.; Zhang, Y.F.; Su, L.Y.; Liu, X.H.; Li, L.C.; Hao, J.B.; Huang, X.J.; Di, Q. Effects of brain IKKβ gene silencing by small interfering RNA on P-glycoprotein expression and brain

damage in the rat kainic acid-induced seizure model. *CNS Neurol. Disord. Drug Targets,* **2014**, *13*(4), 661-672. http://dx.doi.org/10.2174/18715273113129990106 PMID: 24040792

[42] Yu, N.; Zhang, Y.F.; Zhang, K.; Cheng, Y.F.; Ma, H.Y.; Di, Q.; Pregnane, X. Pregnane X receptor not nuclear factor-kappa b up-regulates p-glycoprotein expression in the brain of chronic epileptic rats induced by kainic acid. *Neurochem. Res.,* **2017**, *42*(8), 2167-2177. http://dx.doi.org/10.1007/s11064-017-2224-x PMID: 28303499

[43] Löscher, W. The holy grail of epilepsy prevention: Preclinical approaches to antiepileptogenic treatments. *Neuropharmacology,* **2020,** *167*,107605.

[44] Fernandes, M.J.; Carneiro, J.E.; Amorim, R.P.; Araujo, M.G.; Nehlig, A. Neuroprotective agents and modulation of temporal lobe epilepsy. *Front. Biosci. (Elite Ed.),* **2015**, *7*, 79-93. http://dx.doi.org/10.2741/e719 PMID: 25553365

[45] Chen, M.; Arumugam, T.V.; Leanage, G.; Tieng, Q.M.; Yadav, A.; Ullmann, J.F.; She, D.T.; Truong, V.; Ruitenberg, M.J.; Reutens, D.C. Disease-modifying effect of intravenous immunoglobulin in an experimental model of epilepsy. *Sci. Rep.,* **2017**, *7*, 40528. http://dx.doi.org/10.1038/srep40528 PMID: 28074934

[46] Stables, J.P.; Bertram, E.; Dudek, F.E.; Holmes, G.; Mathern, G.; Pitkanen, A.; White, H.S. Therapy discovery for pharmacoresistant epilepsy and for disease-modifying therapeutics: summary of the NIH/NINDS/AES models II workshop. *Epilepsia,* **2003**, *44*(12), 1472-1478. http://dx.doi.org/10.1111/j.0013-9580.2003.32803.x PMID: 14636315

[47] Kwon, Y.S.; Pineda, E.; Auvin, S.; Shin, D.; Mazarati, A.; Sankar, R. Neuroprotective and antiepileptogenic effects of combination of anti-inflammatory drugs in the immature brain. *J. Neuroinflammation,* **2013**, *10*, 30. http://dx.doi.org/10.1186/1742-2094-10-30 PMID: 23442201

[48] Krumholz, A.; Wiebe, S.; Gronseth, G.S.; Gloss, D.S.; Sanchez, A.M.; Kabir, A.A.; Liferidge, A.T.; Martello, J.P.; Kanner, A.M.; Shinnar, S.; Hopp, J.L.; French, J.A. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the guideline development subcommittee of the american academy of neurology and the american epilepsy society. *Epilepsy Curr.,* **2015**, *15*(3), 144-152. http://dx.doi.org/10.5698/1535-7597-15.3.144 PMID: 26316856

[49] Klein, P.; Dingledine, R.; Aronica, E.; Bernard, C.; Blümcke, I.; Boison, D.; Brodie, M.J.; Brooks-Kayal, A.R.; Engel, J., Jr; Forcelli, P.A.; Hirsch, L.J.; Kaminski, R.M.; Klitgaard, H.; Kobow, K.; Lowenstein, D.H.; Pearl, P.L.; Pitkänen, A.; Puhakka, N.; Rogawski, M.A.; Schmidt, D.; Sillanpää, M.; Sloviter, R.S.; Steinhäuser, C.; Vezzani, A.; Walker, M.C.; Löscher, W. Commonalities in epileptogenic processes from different acute brain insults: Do they translate? *Epilepsia,* **2018**, *59*(1), 37-66. http://dx.doi.org/10.1111/epi.13965 PMID: 29247482

[50] Vezzani, A.; French, J.; Bartfai, T.; Baram, T.Z. The role of inflammation in epilepsy. *Nat. Rev. Neurol.,* **2011**, *7*(1), 31-40. http://dx.doi.org/10.1038/nrneurol.2010.178 PMID: 21135885

[51] Citraro, R.; Leo, A.; Constanti, A.; Russo, E.; De Sarro, G. mTOR pathway inhibition as a new therapeutic strategy in epilepsy and epileptogenesis. *Pharmacol. Res.,* **2016**, *107*, 333-343. http://dx.doi.org/10.1016/j.phrs.2016.03.039 PMID: 27049136

[52] Yu, N.; Liu, H.; Di, Q. Modulation of immunity and the inflammatory response: a new target for treating drug-resistant epilepsy. *Curr. Neuropharmacol.,* **2013**, *11*(1), 114-127. PMID: 23814544

[53] Thomas, R.H.; Berkovic, S.F. The hidden genetics of epilepsy-a clinically important new paradigm. *Nat. Rev. Neurol.,* **2014**, *10*(5), 283-292. http://dx.doi.org/10.1038/nrneurol.2014.62 PMID: 24733163

[54] Pitkänen, A.; Bolkvadze, T.; Immonen, R. Anti-epileptogenesis in rodent post-traumatic epilepsy models. *Neurosci. Lett.,* **2011**, *497*(3), 163-171. http://dx.doi.org/10.1016/j.neulet.2011.02.033 PMID: 21402123

[55] Patel, DC; Wallis, G; Dahle, EJ; McElroy, PB; Thomson, KE; Tesi, RJ; Szymkowski, DE; West, PJ; Smeal, RM; Patel, M; Fujinami, RS; White, HS; Wilcox, KS Hippocampal TNFα signaling contributes to seizure generation in an infection-induced mouse model of limbic epilepsy. *eNeuro,* **2017**, *4*(2), pii: ENEURO.0105-17.

[56] Ali, T.; Kaitha, S.; Mahmood, S.; Ftesi, A.; Stone, J.; Bronze, M.S. Clinical use of anti-TNF therapy and increased risk of infections. *Drug Healthc. Patient Saf.,* **2013**, *5*, 79-99. http://dx.doi.org/10.2147/DHPS.S28801 PMID: 23569399

[57] Zeng, L.H.; Rensing, N.R.; Wong, M. developing antiepileptogenic drugs for acquired epilepsy: targeting the mammalian target of rapamycin (mtor) pathway. *Mol. Cell. Pharmacol.,* **2009**, *1*(3), 124-129. http://dx.doi.org/10.4255/mcpharmacol.09.16 PMID: 20419051

[58] Kim, S.Y.; Buckwalter, M.; Soreq, H.; Vezzani, A.; Kaufer, D. Blood-brain barrier dysfunction-induced inflammatory signaling in brain pathology and epileptogenesis. *Epilepsia,* **2012**, *53*(Suppl. 6), 37-44. http://dx.doi.org/10.1111/j.1528-1167.2012.03701.x PMID: 23134494

[59] Jin, M.; Sheng, W.; Han, L.; He, Q.; Ji, X.; Liu, K. Activation of BDNF-TrkB signaling pathway-regulated brain inflammation in pentylenetetrazole-induced seizures in zebrafish. *Fish Shellfish Immunol.,* **2018**, *83*, 26-36. http://dx.doi.org/10.1016/j.fsi.2018.09.010 PMID: 30195910

[60] Rana, A.; Musto, A.E. The role of inflammation in the development of epilepsy. *J. Neuroinflammation,* **2018**, *15*(1), 144. http://dx.doi.org/10.1186/s12974-018-1192-7 PMID: 29764485

[61] Choi, J.; Choi, S.A.; Kim, S.Y.; Kim, H.; Lim, B.C.; Hwang, H.; Chae, J.H.; Kim, K.J.; Oh, S.; Kim, E.Y.; Shin, J.S. Association analysis of interleukin-1β, interleukin-6, and hmgb1 variants with postictal serum cytokine levels in children with febrile seizure and generalized epilepsy with febrile seizure plus. *J. Clin. Neurol.,* **2019**, *15*(4), 555-563. http://dx.doi.org/10.3988/jcn.2019.15.4.555 PMID: 31591845

[62] Barbalho, P.G.; Carvalho, B.S.; Lopes-Cendes, I.; Maurer-Morelli, C.V. Cyclooxygenase-1 as a potential therapeutic target for seizure suppression: evidences from zebrafish pentylenetetrazole-seizure model. *Front. Neurol.,* **2016**, *7*, 200. http://dx.doi.org/10.3389/fneur.2016.00200 PMID: 27895618

[63] Ravizza, T.; Vezzani, A. Pharmacological targeting of brain inflammation in epilepsy: Therapeutic perspectives from experimental and clinical studies. *Epilepsia Open,* **2018**, *3*(Suppl)(Suppl. 2), 133-142. http://dx.doi.org/10.1002/epi4.12242 PMID: 30564772

[64] Dupuis, N.; Mazarati, A.; Desnous, B.; Chhor, V.; Fleiss, B.; Le Charpentier, T.; Lebon, S.; Csaba, Z.; Gressens, P.; Dournaud, P.; Auvin, S. Pro-epileptogenic effects of viral-like inflammation in both mature and immature brains. *J. Neuroinflammation,* **2016**, *13*(1), 307. http://dx.doi.org/10.1186/s12974-016-0773-6 PMID: 27955671

[65] Linnoila, J.; Pulli, B.; Armangué, T.; Planagumà, J.; Narsimhan, R.; Schob, S.; Zeller, M.W.G.; Dalmau, J.; Chen, J. Mouse model of anti-NMDA receptor post-herpes simplex encephalitis. *Neurol. Neuroimmunol. Neuroinflamm.,* **2018**, *6*(2), e529. http://dx.doi.org/10.1212/NXI.0000000000000529 PMID: 30697582

[66] Geis, C.; Planagumà, J.; Carreño, M.; Graus, F.; Dalmau, J. Autoimmune seizures and epilepsy. *J. Clin. Invest.,* **2019**, *129*(3), 926-940. http://dx.doi.org/10.1172/JCI125178 PMID: 30714986

[67] Ahmed, N.; Aljuhani, N.; Al-Hujaili, H.S.; Al-Hujaili, M.A.; Elkablawy, M.A.; Noah, M.M.; Abo-Haded, H.; El-Agamy, D.S. Agmatine protects against sodium valproate-induced hepatic injury in mice *via* modulation of nuclear factor-κB/inducible nitric oxide synthetase pathway. *J. Biochem. Mol. Toxicol.,* **2018**, *32*(12), e22227. http://dx.doi.org/10.1002/jbt.22227 PMID: 30273971

[68] Arena, A.; Zimmer, T.S.; van Scheppingen, J.; Korotkov, A.; Anink, J.J.; Mühlebner, A.; Jansen, F.E.; van Hecke, W.; Spliet, W.G.; van Rijen, P.C.; Vezzani, A.; Baayen, J.C.; Idema, S.; Iyer, A.M.; Perluigi, M.; Mills, J.D.; van Vliet, E.A.; Aronica, E. Oxidative stress and inflammation in a spectrum of epileptogenic cortical malformations: molecular insights into their interdependence. *Brain Pathol.,* **2019**, *29*(3), 351-365. http://dx.doi.org/10.1111/bpa.12661 PMID: 30303592

[69] Sedaghat, R.; Taab, Y.; Kiasalari, Z.; Afshin-Majd, S.; Baluchnejadmojarad, T.; Roghani, M. Berberine ameliorates intrahippocampal kainate-induced status epilepticus and consequent epileptogenic

process in the rat: Underlying mechanisms. *Biomed. Pharmacother.*, **2017**, *87*, 200-208.
http://dx.doi.org/10.1016/j.biopha.2016.12.109 PMID: 28061403

[70] Jiang, Z.; Guo, M.; Shi, C.; Wang, H.; Yao, L.; Liu, L.; Xie, C.; Pu, S.; LaChaud, G.; Shen, J.; Zhu, M. Protection against cognitive impairment and modification of epileptogenesis with curcumin in a post-status epilepticus model of temporal lobe epilepsy. *Neuroscience,* **2015**, *310*, 362-371.
PMID: 30152292

[71] Deng, X.; Xie, Y.; Chen, Y. Effect of neuroinflammation on ABC transporters: possible contribution to refractory epilepsy. *CNS Neurol. Disord. Drug Targets,* **2018**, *17*(10), 728-735.
PMID: 30152292

[72] Abraham, J.; Fox, P.D.; Condello, C.; Bartolini, A.; Koh, S. Minocycline attenuates microglia activation and blocks the long-term epileptogenic effects of early-life seizures. *Neurobiol. Dis.,* **2012**, *46*(2), 425-430.
http://dx.doi.org/10.1016/j.nbd.2012.02.006 PMID: 22366182

[73] Paudel, Y.N.; Semple, B.D.; Jones, N.C.; Othman, I.; Shaikh, M.F. High mobility group box 1 (HMGB1) as a novel frontier in epileptogenesis: from pathogenesis to therapeutic approaches. *J. Neurochem.,* **2019**, *151*(5), 542-557.
http://dx.doi.org/10.1111/jnc.14663 PMID: 30644560

[74] Pauletti, A.; Terrone, G.; Shekh-Ahmad, T.; Salamone, A.; Ravizza, T.; Rizzi, M.; Pastore, A.; Pascente, R.; Liang, L.P.; Villa, B.R.; Balosso, S.; Abramov, A.Y.; van Vliet, E.A.; Del Giudice, E.; Aronica, E.; Patel, M.; Walker, M.C.; Vezzani, A. Targeting oxidative stress improves disease outcomes in a rat model of acquired epilepsy. *Brain,* **2019**, *142*(7), e39.
http://dx.doi.org/10.1093/brain/awz130 PMID: 31145451

[75] Li, J.; Jiang, G.; Chen, Y.; Chen, L.; Li, Z.; Wang, Z.; Wang, X. Altered expression of hypoxia-Inducible factor-1α participates in the epileptogenesis in animal models. *Synapse,* **2014**, *68*(9), 402-409.
http://dx.doi.org/10.1002/syn.21752 PMID: 24889205

[76] Terrone, G.; Salamone, A.; Vezzani, A. Inflammation and epilepsy: preclinical findings and potential clinical translation. *Curr. Pharm. Des.,* **2017**, *23*(37), 5569-5576.
http://dx.doi.org/10.2174/1381612823666170926113754 PMID: 28950818

[77] Noe, F.M.; Polascheck, N.; Frigerio, F.; Bankstahl, M.; Ravizza, T.; Marchini, S.; Beltrame, L.; Banderó, C.R.; Löscher, W.; Vezzani, A. Pharmacological blockade of IL-1β/IL-1 receptor type 1 axis during epileptogenesis provides neuroprotection in two rat models of temporal lobe epilepsy. *Neurobiol. Dis.,* **2013**, *59*, 183-193.
http://dx.doi.org/10.1016/j.nbd.2013.07.015 PMID: 23938763

[78] Wang, Y.; Wang, Y.; Sun, R.; Wu, X.; Chu, X.; Zhou, S.; Hu, X.; Gao, L.; Kong, Q. The treatment value of IL-1β monoclonal antibody under the targeting location of alpha-methyl-L-tryptophan and superparamagnetic iron oxide nanoparticles in an acute temporal lobe epilepsy model. *J. Transl. Med.,* **2018**, *16*(1), 337.
http://dx.doi.org/10.1186/s12967-018-1712-3 PMID: 30514296

[79] Holtman, L.; van Vliet, E.A.; van Schaik, R.; Queiroz, C.M.; Aronica, E.; Gorter, J.A. Effects of SC58236, a selective COX-2 inhibitor, on epileptogenesis and spontaneous seizures in a rat model for temporal lobe epilepsy. *Epilepsy Res.,* **2009**, *84*(1), 56-66.
http://dx.doi.org/10.1016/j.eplepsyres.2008.12.006 PMID: 19186029

[80] Polascheck, N.; Bankstahl, M.; Löscher, W. The COX-2 inhibitor parecoxib is neuroprotective but not antiepileptogenic in the pilocarpine model of temporal lobe epilepsy. *Exp. Neurol.,* **2010**, *224*(1), 219-233.
http://dx.doi.org/10.1016/j.expneurol.2010.03.014 PMID: 20353773

[81] Jun, J.S.; Lee, S.T.; Kim, R.; Chu, K.; Lee, S.K. Tocilizumab treatment for new onset refractory status epilepticus. *Ann. Neurol.,* **2018**, *84*(6), 940-945.
http://dx.doi.org/10.1002/ana.25374 PMID: 30408233

[82] Ke, X.J.; Cheng, Y.F.; Yu, N.; Di, Q. Effects of carbamazepine on the P-gp and CYP3A expression correlated with PXR or NF-κB activity in the bEnd.3 cells. *Neurosci. Lett.,* **2019**, *690*, 48-55.
http://dx.doi.org/10.1016/j.neulet.2018.10.016 PMID: 30312753

[83] Ben-Sahra, I.; Manning, B.D. mTORC1 signaling and the metabolic control of cell growth. *Curr. Opin. Cell Biol.,* **2017**, *45*, 72-82.
http://dx.doi.org/10.1016/j.ceb.2017.02.012 PMID: 28411448

[84] Yoshida, S; Hong, S; Suzuki, T; Nada, S; Mannan, AM; Wang, J; Okada, M; Guan, KL; Inoki, K Redox regulates mammalian target of rapamycin complex 1 (mTORC1) activity by modulating the TSC1/TSC2-Rheb GTPase pathway. *J Biol Chem,* **201**, *286*(37), 32651-32660.

[85] Tee, A.R.; Sampson, J.R.; Pal, D.K.; Bateman, J.M. The role of mTOR signalling in neurogenesis, insights from tuberous sclerosis complex. *Semin. Cell Dev. Biol.*, **2016**, *52*, 12-20.
http://dx.doi.org/10.1016/j.semcdb.2016.01.040 PMID: 26849906

[86] Wong, M. Mammalian target of rapamycin (mTOR) pathways in neurological diseases. *Biomed. J.,* **2013**, *36*(2), 40-50.
http://dx.doi.org/10.4103/2319-4170.110365 PMID: 23644232

[87] Wong, M. Mammalian target of rapamycin (mTOR) activation in focal cortical dysplasia and related focal cortical malformations. *Exp. Neurol.,* **2013**, *244*, 22-26.
http://dx.doi.org/10.1016/j.expneurol.2011.10.002 PMID: 22015915

[88] Wang, F.; Chen, F.; Wang, G.; Wei, S.; Fang, F.; Kang, D.; Lin, Y. Rapamycin provides anti-epileptogenic effect in a rat model of post-traumatic epilepsy *via* deactivation of mTOR signaling pathway. *Exp. Ther. Med.,* **2018**, *15*(6), 4763-4770.
http://dx.doi.org/10.3892/etm.2018.6004 PMID: 29904395

[89] Yang, X; Hei, C; Liu, P; Li, PA Prevention of post-ischemic seizure by rapamycin is associated with deactivation of mTOR and ERK1/2 pathways in hyperglycemic rats. *Biochem. Biophys. Res. Commun.,* **2019**, *pii*, S0006-291X(19)31826-1.
http://dx.doi.org/10.1016/j.bbrc.2019.09.096

[90] Zeng, L.H.; Rensing, N.R.; Wong, M. The mammalian target of rapamycin signaling pathway mediates epileptogenesis in a model of temporal lobe epilepsy. *J. Neurosci.,* **2009**, *29*(21), 6964-6972.
http://dx.doi.org/10.1523/JNEUROSCI.0066-09.2009 PMID: 19474323

[91] van Vliet, E.A.; Forte, G.; Holtman, L.; den Burger, J.C.; Sinjewel, A.; de Vries, H.E.; Aronica, E.; Gorter, J.A. Inhibition of mammalian target of rapamycin reduces epileptogenesis and blood-brain barrier leakage but not microglia activation. *Epilepsia,* **2012**, *53*(7), 1254-1263.
http://dx.doi.org/10.1111/j.1528-1167.2012.03513.x PMID: 22612226

[92] French, J.A.; Lawson, J.A.; Yapici, Z.; Ikeda, H.; Polster, T.; Nabbout, R.; Curatolo, P.; de Vries, P.J.; Dlugos, D.J.; Berkowitz, N.; Voi, M.; Peyrard, S.; Pelov, D.; Franz, D.N. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet,* **2016**, *388*(10056), 2153-2163.
http://dx.doi.org/10.1016/S0140-6736(16)31419-2 PMID: 27613521

[93] Wong, M. Mammalian target of rapamycin (mTOR) inhibition as a potential antiepileptogenic therapy: From tuberous sclerosis to common acquired epilepsies. *Epilepsia,* **2010**, *51*(1), 27-36.
http://dx.doi.org/10.1111/j.1528-1167.2009.02341.x PMID: 19817806

[94] Jozwiak, S.; Słowińska, M.; Borkowska, J.; Sadowski, K.; Łojszczyk, B.; Domańska-Pakieła, D.; Chmielewski, D.; Kaczorowska-Frontczak, M.; Głowacka, J.; Sijko, K.; Kotulska, K. Preventive antiepileptic treatment in tuberous sclerosis complex: a long-term, prospective trial. *Pediatr. Neurol.,* **2019**, *101*, 18-25.

[95] Santos, D.; Giudetti, G.; Micera, S.; Navarro, X.; Del Valle, J.; Domańska-Pakieła, D.; Chmielewski, D.; Kaczorowska-Frontczak, M.; Głowacka, J.; Sijko, K.; Kotulska, K. Focal release of neurotrophic factors by biodegradable microspheres enhance motor and sensory axonal regeneration *in vitro* and *in vivo*. *Brain Res.,* **2016**, *1636*, 93-106.

[96] Nafissi, N.; Foldvari, M. Neuroprotective therapies in glaucoma: I. Neurotrophic factor delivery. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.,* **2016**, *8*(2), 240-254.
http://dx.doi.org/10.1002/wnan.1361 PMID: 26306832

[97] Binder, D.K.; Croll, S.D.; Gall, C.M.; Scharfman, H.E. BDNF and epilepsy: too much of a good thing? *Trends Neurosci.,* **2001**, *24*(1), 47-53.
http://dx.doi.org/10.1016/S0166-2236(00)01682-9 PMID: 11163887

[98] He, X.P.; Kotloski, R.; Nef, S.; Luikart, B.W.; Parada, L.F.; McNamara, J.O. Conditional deletion of TrkB but not BDNF prevents epileptogenesis in the kindling model. *Neuron,* **2004**, *43*(1), 31-42.
http://dx.doi.org/10.1016/j.neuron.2004.06.019 PMID: 15233915

[99] Heinrich, C.; Lähteinen, S.; Suzuki, F.; Anne-Marie, L.; Huber, S.; Häussler, U.; Haas, C.; Larmet, Y.; Castren, E.; Depaulis, A. Increase in BDNF-mediated TrkB signaling promotes epileptogenesis in a mouse model of mesial temporal lobe epilepsy. *Neurobiol. Dis.,* **2011**, *42*(1), 35-47.
http://dx.doi.org/10.1016/j.nbd.2011.01.001 PMID: 21220014

[100] Lin, T.W.; Harward, S.C.; Huang, Y.Z.; McNamara, J.O. Targeting BDNF/TrkB pathways for preventing or suppressing epilepsy. *Neuropharmacology,* **2019**, *107734*107734 Epub ahead of print.
http://dx.doi.org/10.1016/j.neuropharm.2019.107734 PMID: 31377199

[101] Bar-Klein, G.; Lublinsky, S.; Kamintsky, L.; Noyman, I.; Veksler, R.; Dalipaj, H.; Senatorov, V.V., Jr; Swissa, E.; Rosenbach, D.; Elazary, N.; Milikovsky, D.Z.; Milk, N.; Kassirer, M.; Rosman, Y.; Serlin, Y.; Eisenkraft, A.; Chassidim, Y.; Parmet, Y.; Kaufer, D.; Friedman, A. Imaging blood-brain barrier dysfunction as a biomarker for epileptogenesis. *Brain,* **2017**, *140*(6), 1692-1705.
http://dx.doi.org/10.1093/brain/awx073 PMID: 28444141

[102] Broekaart, D.W.M.; Anink, J.J.; Baayen, J.C.; Idema, S.; de Vries, H.E.; Aronica, E.; Gorter, J.A.; van Vliet, E.A. Activation of the innate immune system is evident throughout epileptogenesis and is associated with blood-brain barrier dysfunction and seizure progression. *Epilepsia,* **2018**, *59*(10), 1931-1944.
http://dx.doi.org/10.1111/epi.14550 PMID: 30194729

[103] Weissberg, I.; Wood, L.; Kamintsky, L.; Vazquez, O.; Milikovsky, D.Z.; Alexander, A.; Oppenheim, H.; Ardizzone, C.; Becker, A.; Frigerio, F.; Vezzani, A.; Buckwalter, M.S.; Huguenard, J.R.; Friedman, A.; Kaufer, D. Albumin induces excitatory synaptogenesis through astrocytic TGF-β/ALK5 signaling in a model of acquired epilepsy following blood-brain barrier dysfunction. *Neurobiol. Dis.,* **2015**, *78*, 115-125.
http://dx.doi.org/10.1016/j.nbd.2015.02.029 PMID: 25836421

[104] Bar-Klein, G.; Cacheaux, L.P.; Kamintsky, L.; Prager, O.; Weissberg, I.; Schoknecht, K.; Cheng, P.; Kim, S.Y.; Wood, L.; Heinemann, U.; Kaufer, D.; Friedman, A. Losartan prevents acquired epilepsy *via* TGF-β signaling suppression. *Ann. Neurol.,* **2014**, *75*(6), 864-875.
http://dx.doi.org/10.1002/ana.24147 PMID: 24659129

[105] González, O.C.; Krishnan, G.P.; Chauvette, S.; Timofeev, I.; Sejnowski, T.; Bazhenov, M. Modeling of age-dependent epileptogenesis by differential homeostatic synaptic scaling. *J. Neurosci.,* **2015**, *35*(39), 13448-13462.
http://dx.doi.org/10.1523/JNEUROSCI.5038-14.2015 PMID: 26424890

[106] Vendramin, P.M.; Meier, L.; Loureiro, S.; Ganzella, M.; Junges, B.; Barbieri, C. L.; Umpierrez, A. A.; Koeller, D.M.; Goodman, S.; Woontner, M.; Gomes de Souza, D.O.; Wajner, M.; Calcagnotto, M.E. Impairment of GABAergic system contributes to epileptogenesis in glutaric acidemia type I. *Epilepsia,* **2017**, *58*(10), 1771-1781.
http://dx.doi.org/10.1111/epi.13862 PMID: 28762469

[107] Zubareva, O.E.; Kovalenko, A.A.; Kalemenev, S.V.; Schwarz, A.P.; Karyakin, V.B.; Zaitsev, A.V. Alterations in mRNA expression of glutamate receptor subunits and excitatory amino acid transporters following pilocarpine-induced seizures in rats. *Neurosci. Lett.,* **2018**, *686*, 94-100.
http://dx.doi.org/10.1016/j.neulet.2018.08.047 PMID: 30189229

[108] Zhao, W.; Chuang, S.C.; Young, S.R.; Bianchi, R.; Wong, R.K. Extracellular glutamate exposure facilitates group I mGluR-mediated epileptogenesis in the hippocampus. *J. Neurosci.,* **2015**, *35*(1), 308-315.
http://dx.doi.org/10.1523/JNEUROSCI.1944-14.2015 PMID: 25568123

[109] McNamara, J.O.; Russell, R.D.; Rigsbee, L.; Bonhaus, D.W. Anticonvulsant and antiepileptogenic actions of MK-801 in the kindling and electroshock models. *Neuropharmacology,* **1988**, *27*(6), 563-568.
http://dx.doi.org/10.1016/0028-3908(88)90176-1 PMID: 2843782

[110] Hong, S.; Li, T.; Luo, Y.; Li, W.; Tang, X.; Ye, Y.; Wu, P.; Hu, Q.; Cheng, L.; Chen, H.; Jiang, L. Dynamic changes of astrocytes and adenosine signaling in rat hippocampus in post-status epilepticus model of epileptogenesis. *Cell. Mol. Neurobiol.,* **2018**, *38*(6), 1227-1234.
http://dx.doi.org/10.1007/s10571-018-0590-9 PMID: 29770956

[111] Sandau, U.S.; Yahya, M.; Bigej, R.; Friedman, J.L.; Saleumvong, B.; Boison, D. Transient use of a systemic adenosine kinase inhibitor attenuates epilepsy development in mice. *Epilepsia,* **2019**, *60*(4), 615-625.
http://dx.doi.org/10.1111/epi.14674 PMID: 30815855

[112] Serajee, F.J.; Huq, A.M. Homozygous mutation in synaptic vesicle glycoprotein 2A gene results in intractable epilepsy, involuntary movements, microcephaly, and developmental and growth retardation. *Pediatr. Neurol.,* **2015**, *52*(6), 642-6.e1.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.02.011 PMID: 26002053

[113] Tokudome, K.; Okumura, T.; Shimizu, S.; Mashimo, T.; Takizawa, A.; Serikawa, T.; Terada, R.; Ishihara, S.; Kunisawa, N.; Sasa, M.; Ohno, Y. Synaptic vesicle glycoprotein 2A (SV2A) regulates kindling epileptogenesis *via* GABAergic neurotransmission. *Sci. Rep.,* **2016**, *6*, 27420.
http://dx.doi.org/10.1038/srep27420 PMID: 27265781

[114] Ohno, Y.; Tokudome, K. Therapeutic role of synaptic vesicle glycoprotein 2A (SV2A) in modulating epileptogenesis. *CNS Neurol. Disord. Drug Targets,* **2017**, *16*(4), 463-471.
http://dx.doi.org/10.2174/1871527316666170404115027 PMID: 28393712

[115] Chaari, A.; Mohamed, A.S.; Abdelhakim, K.; Kauts, V.; Casey, W.F. Levetiracetam versus phenytoin for seizure prophylaxis in brain injured patients: a systematic review and meta-analysis. *Int. J. Clin. Pharm.,* **2017**, *39*(5), 998-1003.
http://dx.doi.org/10.1007/s11096-017-0507-6 PMID: 28780739

[116] Younus, I.; Reddy, D.S. Epigenetic interventions for epileptogenesis: A new frontier for curing epilepsy. *Pharmacol. Ther.,* **2017**, *177*, 108-122.
http://dx.doi.org/10.1016/j.pharmthera.2017.03.002 PMID: 28279785

[117] Lindhout, D. Somatic mosaicism as a basic epileptogenic mechanism? *Brain,* **2008**, *131*(Pt 4), 900-901.
http://dx.doi.org/10.1093/brain/awn056 PMID: 18339639

[118] Kobow, K.; Blümcke, I. The methylation hypothesis: do epigenetic chromatin modifications play a role in epileptogenesis? *Epilepsia,* **2011**, *52*(Suppl. 4), 15-19.
http://dx.doi.org/10.1111/j.1528-1167.2011.03145.x PMID: 21732935

[119] Kobow, K.; Jeske, I.; Hildebrandt, M.; Hauke, J.; Hahnen, E.; Buslei, R.; Buchfelder, M.; Weigel, D.; Stefan, H.; Kasper, B.; Pauli, E.; Blümcke, I. Increased reelin promoter methylation is associated with granule cell dispersion in human temporal lobe epilepsy. *J. Neuropathol. Exp. Neurol.,* **2009**, *68*(4), 356-364.
http://dx.doi.org/10.1097/NEN.0b013e31819ba737 PMID: 19287316

[120] de Nijs, L.; Choe, K.; Steinbusch, H.; Schijns, O.E.M.G.; Dings, J.; van den Hove, D.L.A.; Rutten, B.P.F.; Hoogland, G. DNA methyltransferase isoforms expression in the temporal lobe of epilepsy patients with a history of febrile seizures. *Clin. Epigenetics,* **2019**, *11*(1), 118.
http://dx.doi.org/10.1186/s13148-019-0721-2 PMID: 31426844

[121] Reddy, S.D.; Clossen, B.L.; Reddy, D.S. Epigenetic histone deacetylation inhibition prevents the development and persistence of temporal lobe epilepsy. *J. Pharmacol. Exp. Ther.,* **2018**, *364*(1), 97-109.
http://dx.doi.org/10.1124/jpet.117.244939 PMID: 29101217

[122] Hoffmann, K.; Czapp, M.; Löscher, W. Increase in antiepileptic efficacy during prolonged treatment with valproic acid: role of inhibition of histone deacetylases? *Epilepsy Res.,* **2008**, *81*(2-3), 107-113.
http://dx.doi.org/10.1016/j.eplepsyres.2008.04.019 PMID: 18538545

[123] Rossetti, F.; de Araujo Furtado, M.; Pak, T.; Bailey, K.; Shields, M.; Chanda, S.; Addis, M.; Robertson, B.D.; Moffett, M.; Lumley, L.A.; Yourick, D.L. Combined diazepam and HDAC inhibitor treatment protects against seizures and neuronal damage caused by soman exposure. *Neurotoxicology,* **2012**, *33*(3), 500-511.
PMID: 31038487

[124] Zandi N, Zaniani NR, Moghimi A, Roohbakhsh A. Protective effects of M8-B, a TRPM8 antagonist, on febrile- and pentylenetetrazol-induced seizures. *Acta Neurobiol. Exp. (Warsz.),* **2019**, *79*(1), 86-91. PMID: 31038487

[125] Koyama, R.; Tao, K.; Sasaki, T.; Ichikawa, J.; Miyamoto, D.; Muramatsu, R.; Matsuki, N.; Ikegaya, Y. GABAergic excitation after febrile seizures induces ectopic granule cells and adult epilepsy. *Nat. Med.,* **2012**, *18*(8), 1271-1278. http://dx.doi.org/10.1038/nm.2850 PMID: 22797810

[126] Marguet, S.L.; Le-Schulte, V.T.; Merseburg, A.; Neu, A.; Eichler, R.; Jakovcevski, I.; Ivanov, A.; Hanganu-Opatz, I.L.; Bernard, C.; Morellini, F.; Isbrandt, D. Treatment during a vulnerable developmental period rescues a genetic epilepsy. *Nat. Med.,* **2015**, *21*(12), 1436-1444. http://dx.doi.org/10.1038/nm.3987 PMID: 26594844

[127] Töllner, K.; Brandt, C.; Erker, T.; Löscher, W. Bumetanide is not capable of terminating status epilepticus but enhances phenobarbital efficacy in different rat models. *Eur. J. Pharmacol.,* **2015**, *746*, 78-88. http://dx.doi.org/10.1016/j.ejphar.2014.10.056 PMID: 25445051

[128] Li, S.; Luo, Z.; Lu, B.; Xia, S.; Li, C.; Guan, X.; Zhang, J.; Huang, K.; Xian, F. Protective effects of lycopene on kainic acid-induced seizures. *Epilepsy Res.,* **2019**, *151*, 1-6. http://dx.doi.org/10.1016/j.eplepsyres.2019.01.010 PMID: 30669043

[129] Pitsch, J.; Kuehn, J.C.; Gnatkovsky, V.; Müller, J.A.; van Loo, K.M.J.; de Curtis, M.; Vatter, H.; Schoch, S.; Elger, C.E.; Becker, A.J. Anti-epileptogenic and anti-convulsive effects of fingolimod in experimental temporal lobe epilepsy. *Mol. Neurobiol.,* **2019**, *56*(3), 1825-1840. http://dx.doi.org/10.1007/s12035-018-1181-y PMID: 29934763

[130] Tse, K.; Hammond, D.; Simpson, D.; Beynon, R.J.; Beamer, E.; Tymianski, M.; Salter, M.W.; Sills, G.J.; Thippeswamy, T. The impact of postsynaptic density 95 blocking peptide (Tat-NR2B9c) and an iNOS inhibitor (1400W) on proteomic profile of the hippocampus in C57BL/6J mouse model of kainate-induced epileptogenesis. *J. Neurosci. Res.,* **2019**, *97*(11), 1378-1392. http://dx.doi.org/10.1002/jnr.24441 PMID: 31090233

[131] Xia, J.; Li, C.Y.; Wang, H.; Zhang, Q.M.; Han, Z.M. Therapeutic effects of scoparone on pilocarpine (Pilo)-induced seizures in mice. *Biomed. Pharmacother.,* **2018**, *97*, 1501-1513. http://dx.doi.org/10.1016/j.biopha.2017.09.127 PMID: 29793313

[132] Suemaru, K.; Yoshikawa, M.; Aso, H.; Watanabe, M. TRPV1 mediates the anticonvulsant effects of acetaminophen in mice. *Epilepsy Res.,* **2018**, *145*, 153-159. http://dx.doi.org/10.1016/j.eplepsyres.2018.06.016 PMID: 30007240

[133] Fu, M.; Xie, Z.; Zuo, H. TRPV1: a potential target for antiepileptogenesis. *Med. Hypotheses,* **2009**, *73*(1), 100-102. http://dx.doi.org/10.1016/j.mehy.2009.01.005 PMID: 19328632

[134] Valle-Dorado, M.G.; Santana-Gómez, C.E.; Orozco-Suárez, S.A.; Rocha, L. Sodium cromoglycate reduces short- and long-term consequences of status epilepticus in rats. *Epilepsy Behav.,* **2018**, *87*, 200-206. http://dx.doi.org/10.1016/j.yebeh.2018.06.021 PMID: 30115604

[135] Nissinen, J.; Andrade, P.; Natunen, T.; Hiltunen, M.; Malm, T.; Kanninen, K.; Soares, J.I.; Shatillo, O.; Sallinen, J.; Ndode-Ekane, X.E.; Pitkänen, A. Disease-modifying effect of atipamezole in a model of post-traumatic epilepsy. *Epilepsy Res.,* **2017**, *136*, 18-34. http://dx.doi.org/10.1016/j.eplepsyres.2017.07.005 PMID: 28753497

[136] Grabenstatter, H.L.; Del Angel, Y.C.; Carlsen, J.; Wempe, M.F.; White, A.M.; Cogswell, M.; Russek, S.J.; Brooks-Kayal, A.R. The effect of STAT3 inhibition on status epilepticus and subsequent spontaneous seizures in the pilocarpine model of acquired epilepsy. *Neurobiol. Dis.,* **2014**, *62*, 73-85. http://dx.doi.org/10.1016/j.nbd.2013.09.003 PMID: 24051278

[137] Hsu, H.C.; Tang, N.Y.; Liu, C.H.; Hsieh, C.L. Antiepileptic effect of uncaria rhynchophylla and rhynchophylline involved in the initiation of c-jun n-terminal kinase phosphorylation of mapk signal pathways in acute seizures of kainic acid-treated rats. *Evid. Based Complement. Alternat. Med.,* **2013**, *2013*, 961289. http://dx.doi.org/10.1155/2013/961289 PMID: 24381640

[138] Seeger, N.; Zellinger, C.; Rode, A.; Roloff, F.; Bicker, G.; Russmann, V.; Fischborn, S.; Wendt, H.; Potschka, H. The erythropoietin-derived peptide mimetic pHBSP affects cellular and cognitive consequences in a rat post-status epilepticus model. *Epilepsia,* **2011**, *52*(12), 2333-2343. http://dx.doi.org/10.1111/j.1528-1167.2011.03302.x PMID: 22050420

[139] Lai, M.C.; Lin, K.M.; Yeh, P.S.; Wu, S.N.; Huang, C.W. The novel effect of immunomodulator-glatiramer acetate on epileptogenesis and epileptic seizures. *Cell. Physiol. Biochem.,* **2018**, *50*(1), 150-168. http://dx.doi.org/10.1159/000493965 PMID: 30278465

[140] Citraro, R.; Chimirri, S.; Aiello, R.; Gallelli, L.; Trimboli, F.; Britti, D.; De Sarro, G.; Russo, E. Protective effects of some statins on epileptogenesis and depressive-like behavior in WAG/Rij rats, a genetic animal model of absence epilepsy. *Epilepsia,* **2014**, *55*(8), 1284-1291. http://dx.doi.org/10.1111/epi.12686 PMID: 24962151

[141] Bar-Klein, G.; Klee, R.; Brandt, C.; Bankstahl, M.; Bascuñana, P.; Töllner, K.; Dalipaj, H.; Bankstahl, J.P.; Friedman, A.; Löscher, W. Isoflurane prevents acquired epilepsy in rat models of temporal lobe epilepsy. *Ann. Neurol.,* **2016**, *80*(6), 896-908. http://dx.doi.org/10.1002/ana.24804 PMID: 27761920

[142] H S, N.; Paudel, Y.N.; K L, K. Envisioning the neuroprotective effect of Metformin in experimental epilepsy: A portrait of molecular crosstalk. *Life Sci.,* **2019**, *233*, 116686. http://dx.doi.org/10.1016/j.lfs.2019.116686 PMID: 31348946

[143] Wong, S.B.; Cheng, S.J.; Hung, W.C.; Lee, W.T.; Min, M.Y. Rosiglitazone suppresses *In Vitro* seizures in hippocampal slice by inhibiting presynaptic glutamate release in a model of temporal lobe epilepsy. *PLoS One,* **2015**, *10*(12), e0144806. http://dx.doi.org/10.1371/journal.pone.0144806 PMID: 26659605

[144] Rosenberg, EC; Patra, PH; Whalley, BJ Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection. *Epilepsy Behav,* **2017**, *70*(Pt B), 319-327. http://dx.doi.org/10.1016/j.yebeh.2016.11.006

[145] Pugh, M.J.; Knoefel, J.E.; Mortensen, E.M.; Amuan, M.E.; Berlowitz, D.R.; Van Cott, A.C. New-onset epilepsy risk factors in older veterans. *J. Am. Geriatr. Soc.,* **2009**, *57*(2), 237-242. http://dx.doi.org/10.1111/j.1532-5415.2008.02124.x PMID: 19207140

[146] Bumanglag, A.V.; Sloviter, R.S. No latency to dentate granule cell epileptogenesis in experimental temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia,* **2018**, *59*(11), 2019-2034. http://dx.doi.org/10.1111/epi.14580 PMID: 30338519

[147] Welzel, L.; Twele, F.; Schidlitzki, A.; Töllner, K.; Klein, P.; Löscher, W. Network pharmacology for antiepileptogenesis: Tolerability and neuroprotective effects of novel multitargeted combination treatments in nonepileptic *vs*. post-status epilepticus mice. *Epilepsy Res.,* **2019**, *151*, 48-66. http://dx.doi.org/10.1016/j.eplepsyres.2019.02.010 PMID: 30831337

[148] Dey, A.; Kang, X.; Qiu, J.; Du, Y.; Jiang, J. Anti-inflammatory small molecules to treat seizures and epilepsy: from bench to bedside. *Trends Pharmacol. Sci.,* **2016**, *37*(6), 463-484. http://dx.doi.org/10.1016/j.tips.2016.03.001 PMID: 27062228