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REVIEW

Past and Present Definitions of Epileptogenesis and Its Biomarkers

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Abstract Descriptions of epileptic seizures and epilepsy date back to antiquity, and research into fundamental mechanisms of epilepsy in animal models, as well as patients, has been carried out for over a century. Studies of epileptogenesis, however, as distinct from ictogenesis, have been pursued for only a few decades, and antiepileptogenesis, the prevention of epilepsy or its progression, and the reversal of the epileptogenic process or cure, are relatively recent interests of the basic research community. The goal to develop antiepileptogenic interventions would be greatly facilitated by the identification of reliable biomarkers of epileptogenesis that could be used to create cost-effective, high-throughput screening models for potential antiepileptogenic compounds, as well as enrich patient populations and serve as surrogate endpoints for clinical trials. Without such biomarkers, the cost for clinical validation of antiepileptogenic interventions would be prohibitive. Epileptogenic mechanisms, antiepileptogenic interventions, and biomarkers are likely to be specific for the many different causes of epilepsy, which include genetic influences, cell loss and synaptic plasticity, malformations of cortical development, and autoimmune disorders, to name but a few. A high priority is currently being placed on investigations to elucidate fundamental mechanisms of epileptogenesis and identify biomarkers for specific models of human epilepsy, such as mesial temporal lobe epilepsy with hippocampal sclerosis, traumatic brain injury, and a variety of pediatric diseases, including tuberous sclerosis and West syndrome.

Keywords Animal model · antiepileptogenesis · disease-modification · epilepsy · genetics

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Introduction

Epilepsy was well known to the ancients. Different types of epileptic seizures were clearly described in Mesopotamian writings over 3000 years ago [1] and in Indian vadas from approximately the same period of time [2, 3]. Although Hippocrates and Galen recognized that epileptic seizures were generated in the brain as a result of various natural etiologies, a multitude of presumed supernatural causes of epilepsy predominated well into the nineteenth century until natural philosophers and physicians began to undertake studies of brain function.

Animal research on localization of brain function became possible with the advent of electrical stimulation [4], and it must have been obvious to physicians that the result mimicked epileptic seizures. Hughlings Jackson [5] received credit, at least in the English-speaking world, for describing the relationship between the clinical characteristics of specific focal seizures in patients with epilepsy, and the location of structural lesions in the brain identified postmortem. Indeed, an important contribution of Jackson was the recognition of focal ictal events as epileptic seizures originating in localized areas of cerebral cortex, at a time when epilepsy was generally considered to be characterized by grand mal ictal events believed to be generated in the medulla oblongata. Ferrier then reproduced these focal ictal behavioral events by stimulating

neocortex in the monkey [6]. This work led directly to the surgical treatment of epilepsy [7–9].

Evolution of the Concept of Epileptogenesis

The history of research into epileptogenesis, as opposed to ictogenesis, is not long. Both basic and clinical twentieth century neuroscientists were initially interested in the neuronal mechanisms responsible for the generation of epileptic seizures (ictogenesis) rather than the processes that caused the brain to develop an enduring epileptogenic potential in the first place. Although Penfield and Jasper opined that there must be a ripening of the scar to explain the latent phase between traumatic injuries and the appearance of chronic epileptic seizures [10], and some animal models of chronic epilepsy were created, particularly using cortical freezing [11], cortical undercutting [12], and local application of metals [13, 14], virtually all early electrophysiological studies into fundamental neuronal mechanisms were carried out during acute animal experiments, where epileptic seizures were induced in a normal brain using electrical stimulation or topical convulsants such as strychnine [15] and penicillin [16, 17]. Much was learned about why these insults induced epileptiform activity; however, such studies provided no insights into how a brain naturally develops an enduring predisposition to generate spontaneous epileptic seizures.

It would seem that interest in epileptogenesis developed not out of curiosity about mechanisms responsible for ripening of the scar, but because of observations about secondary epileptogenesis, the ability of an epileptogenic region to make a distant region epileptogenic. Specifically, a "mirror focus" was shown to develop contralateral and homotopic to an experimental primary epileptogenic focus [18]. This curious phenomenon suggested that the brain learned to become epileptic and that elucidation of the plastic changes resulting in secondary epileptogenesis might provide insights into fundamental neuronal mechanisms of learning and memory. Subsequently, Goddard [19], a physiological psychologist using brain stimulation to study mechanisms of learning, noticed that after repeated stimulation some of his rats developed epileptic seizures. Although others had also noticed this phenomenon, they discarded these rats as obstacles to their experimental protocols, while Goddard recognized that this was equivalent to the mirror focus, providing a mechanism to bring secondary epileptogenesis under laboratory control. This then was, perhaps, the true beginning of serious neurobiological investigations into epileptogenesis per se, and kindling sustained neuroscientists interested in epilepsy for several decades [20, 21].

The kindling model of epileptogenesis, however, failed to mimic the development of human epilepsy on two counts. First, mechanisms whereby a lesion of some type initially induces epileptiform electrical activity are bypassed by the artificial electrical stimulation and therefore they cannot be studied; kindling is a model of secondary epileptogenesis, not of epileptogenesis per se. Second, kindled rats have seizures when stimulated but do not have spontaneous seizures. Although it *is* possible to kindle animals for prolonged periods of time to produce spontaneous seizures, this is very difficult to do and is rarely practiced [22].

The paradigm shift was the creation of truly chronic epilepsy animal models in which the epilepsy developed over time following status epilepticus induced by chemical agents such as picrotoxin or bicuculline [23], pilocarpine [24], kainic acid [25, 26], or electrical stimulation [27]. In contrast to the early chronic models caused by local application of metals, which produced such severe scarring that they broke micropipettes and prevented the type of electrophysiological research that could be done with acute models, status epilepticus produced lesions very similar to hippocampal sclerosis, which is much more amenable to continuous or sequential electrophysiological investigations during epileptogenesis. Most of our current assumptions of fundamental neuronal mechanisms of epileptogenesis, therefore, come from epileptogenic changes that occur in the sclerotic hippocampus, created in animals and reported in patients with mesial temporal lobe epilepsy [28]. Epileptogenesis in hippocampus, however, may not be the same as epileptogenesis elsewhere. A variety of other chronic animal models of human epilepsy, such as fluid-percussion injuries mimicking closed head traumatic brain injury (TBI) in humans, post-stroke epilepsy using medial cerebral arterial ligation or cortical photothrombosis, and models of a variety of pediatric epilepsies such as tuberous sclerosis and infantile spasms, have recently been developed [29, 30]. Even with the caveats that the major focus in the development of some of the models was to reproduce the clinical phenotype rather than underlying pathology (e.g., some infantile spasm models), these advances in modeling have provided us tools to determine the extent to which our understanding of epileptogenesis based on studies of hippocampal sclerosis can be extrapolated to other structural and metabolic epilepsies, and to elucidate mechanisms that may be unique to each of the great varieties of epileptic seizures types, as well as epilepsy syndromes and diseases, encountered in our patients, some of which are likely to be age-dependent [31–34].

Studies of human epileptogenesis are difficult to perform because they require observation of patients from the time of a clear epileptogenic event. This can be possible when specific insults occur, such as TBI, leading to post-traumatic epilepsy (PTE), but most epilepsies arise owing to causes that have no clear time of onset. There is no precise period of occurrence for malformations of cortical development, indolent neoplasms, or hippocampal sclerosis, and these lesions are usually not identified until patients begin having epileptic seizures.

The reasons why most genetic epilepsies manifest at specific periods of brain maturation, and whether there is a unique epileptogenic process involved, are also unknown. Therefore, in order to study the process of epileptogenesis in patients, there needs to be a reliable way to determine who is going to develop epilepsy well before epileptic seizures manifest. This objective would be greatly facilitated with the use of biomarkers that identify the existence of an epileptogenic process. Such biomarkers of epileptogenesis are now the subject of considerable research interest.

Concepts and Definitions

Epileptogenesis

Epileptogenesis is the development and extension of tissue capable of generating spontaneous seizures, resulting in a) development of an epileptic condition and/or b) progression of the epilepsy after it is established [35].

Ictogenesis

Ictogenesis is a propensity to generate epileptic seizures, including initiation and evolution of the epileptic seizures [35].

Disease or Syndrome Modification

Disease or syndrome modification has two components: antiepileptogenesis and comorbidity modification [35].

Antiepileptogenesis

Antiepileptogenesis is a process that counteracts the effects of epileptogenesis, including prevention, seizure modification, and cure.

- Prevention: Complete prevention aborts the development of epilepsy. Partial prevention can delay the development of epilepsy or reduce its severity. For example, seizures occur but they may be fewer in frequency, shorter, or of milder seizure type (seizure modification). Antiepileptogenesis can also prevent or reduce the progression of epilepsy after it has already been established.
- Cure: The complete and permanent reversal of epilepsy, such that no seizures occur after treatment withdrawal [35].

Comorbidity Modification

Treatment alleviates or reverses the symptomatic development or progression of epilepsy-related comorbidities, such as anxiety, depression, somato-motor impairment, or cognitive decline [35].

Antiepileptogenic Treatment

Antiepileptogenic treatment can be given prior to or after epilepsy onset. When an antiepileptogenic treatment is given *prior* to epilepsy onset it prevents or delays the development of epilepsy. If seizures occur, they may be fewer in frequency, shorter, or of milder severity. When such a treatment is given *after* the diagnosis of epilepsy, it can alleviate seizure severity, prevent, or reduce the progression of epilepsy, or change the seizures from drug-resistant to drug-sensitive. Both antiepileptogenic and comorbidity-modifying treatments can also alleviate or reverse the associated pathology [35].

Biomarker for Epileptogenesis

A biomarker for epileptogenesis is an objectively measurable characteristic of a biological process that reliably identifies the development, presence, severity, progression, or localization of an epileptogenic abnormality [36–38]. An epileptogenic abnormality refers to the pathophysiological substrate(s) responsible for the initiation and/or maintenance of epilepsy.

Evolution of the Concept of Biomarkers for Epileptogenesis

There are currently no biomarkers that can be used to reliably measure aspects of epileptogenesis in the same way that blood sugar, for instance, is used as a biomarker of diabetes.

Epileptogenesis biomarkers would have a variety of applications for diagnosis, as well as for discovery and validation of antiepileptogenic interventions. For the purposes of this discussion, biomarkers of epileptogenesis would greatly reduce the cost of clinical trials to validate antiepileptogenic drugs by enriching patient populations, and by acting as surrogate endpoints to document remission, prevention, or cure without the need to wait for seizures to occur. Identification of reliable biomarkers of epileptogenesis could also be used to devise more cost-effective, rapid-throughput approaches to screening potential antiepileptogenic compounds.

Considerable research on basic mechanisms of epileptogenesis in animal models in recent years has provided a list of potential targets for development of biomarkers (Table 1), and a few potential biomarkers are currently under investigation (Table 2). Should the

identification of reliable biomarkers of epileptogenesis result in the discovery and validation of effective antiepileptogenic treatments, biomarkers of epileptogenesis would then be useful to identify patients in whom such treatments would be necessary. Furthermore, the elucidation of biomarkers of epileptogenesis would likely provide insights into underlying fundamental neuronal mechanisms of epileptogenesis that could serve as targets for the development of new antiepileptogenic compounds and devices.

Table 2 Potential Biomarkers

- Hippocampal structural and functional changes on MRI/PET
- Interictal spike features, including fMRI
- Pathological high-frequency oscillations
- Excitability—TMS
- AMT–PET imaging
- Gene expression profiles
- microRNAs

MRI = magnetic resonance imaging; PET = positron emission tomography; fMRI = functional MRI; TMS = transcranial magnetic stimulation; AMT = alpha-methyl tyrosine

Examples of Different Types of Epileptogenesis

Genetic Influences

Genetics contributes to epileptogenesis in multiple ways that overlap with the examples of epileptogenesis in the following sections. Some epilepsies are genetic, either single-gene disorders or those with complex inheritance. Examples of monogenic epilepsy syndromes are shown in Table 3. The most common genetic epilepsy syndromes with complex inheritance are childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy, formally referred to as idiopathic generalized epilepsies, as well as benign epilepsy with centrotemporal spikes and other related genetic focal epilepsies. Epilepsies can also be caused by genetic diseases, such as tuberous sclerosis, where the epileptic seizures are not a direct result of the aberrant genetic expression, but of an intermediate abnormality caused by the genetic disturbance, such as a tuber. In these conditions, epilepsy is not necessarily an invariant feature of the disease. Finally, genetic influences contribute to the propensity of a normal brain to respond to insults with epileptic seizures, and to develop epilepsy as a result of acquired disturbances. These susceptibility genes are likely different in different individuals, and for different epileptic seizure types and epilepsy syndromes. Advances in genetic engineering have made it possible to introduce epileptic genetic mutations in animals to create experimental models of human epilepsy, providing opportunities to investigate the processes underlying epileptogenesis in these conditions. Currently, the armamentarium of genetic animal models expands from "naturally-occurring genetic models", such as GAERS or WAG/Rij rats, to mice with mutations in single or multiple ligand or voltage- gated ion channels to complex syndromes with epilepsy as one of the phenotypic features, including tuberous sclerosis and autism [47–49].

Table 1 Target mechanisms

- Cell loss (e.g., hippocampal atrophy)
- Neurogenesis
- Axonal sprouting, axonal and myelin injury
- Synaptic reorganization
- Angiogenesis
- Dendritic damage, plasticity (e.g., basal dendrites), and spine alterations
- Gliosis and altered glial function
- Blood–brain barrier damage
- Reorganization of extracellular matrix
- Altered intrinsic properties of neurons (e.g., gene expression profiles, ion channel functions)
- Innate and adaptive immunity

Cell Loss and Circuitry Reorganization

The most common structural abnormality in human epilepsy is hippocampal sclerosis [50], the major cause of mesial temporal lobe epilepsy. Hippocampal sclerosis is no longer believed to be a single disease, but most likely it consists of several subtypes, and the causes of this condition are unknown. Animal models exist that have permitted detailed investigations into mechanisms by which epileptogenesis arises from age-dependent cell loss and synaptic reorganization in the hippocampus, and also in other injured brain areas. PTE is of increasing interest, in part because of the increased incidence of this condition now that civilians, as well as military personnel, are more likely than in the past to survive severe TBI. Other causes of human epilepsy that may utilize similar mechanisms include stroke and infectious processes, where hemoglobin and toxins (e.g., with parasitic infestations), may also play a role. Neoplastic lesions cause cell loss and neuronal reorganization, but some may also produce excitatory substances. Although these are extremely diverse clinical conditions, several experimental animal models are currently being used to mimic epileptogenesis due to hippocampal sclerosis, stroke, TBI, tumors, or encephalitis, and to study neuronal mechanisms underlying epileptogenesis and accompanying comorbidites in a syndrome-specific manner in these clinically relevant conditions, as reviewed in other articles in this special issue.

Table 3 Selected examples of genes associated with monogenic epilepsy syndromes, compiled from [39–46]

	Syndrome	Gene
Autosomal dominant familial epilepsies inherited mutations	**Neonatal/infantile epilepsies**	
	Benign familial neonatal seizures	*KCNQ2*
		KCNQ3
	Benign familial neonatal-infantile seizures	*SCN2A*
	Benign familial infantile seizures	*PRRT2*
	Generalized epilepsies	
	Genetic epilepsy with febrile seizures Plus	*SCN1A*
		SCN1B
		GABRG2
	Idiopathic/genetic generalized epilepsy	*GABRA1*
		CLCN2
		EFHC1
		SLC2A1 (*GLUT1*)
	Focal epilepsies	
	Familial partial epilepsy with variable foci	*DEPDC5*
	Familial lateral temporal lobe epilepsy	*LGI1*
	Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4*
		CHRNA2
		CHRNB2
		KCNT1
Epileptic encephalopathies *de novo* mutations	**Epileptic encephalopathies**	
	Dravet syndrome	*SCN1A*
	Epilepsy—aphasia spectrum	*GRIN2A*
	Atypical Rett syndrome, CDKL5 encephalopathy	*CDKL5*
	Othahara syndrome	*STXBP1*
	Myoclonic-astatic epilepsy, atypical Dravet syndrome	*CHD2*
	Othahara syndrome, unclassified epileptic encephalopathy	*SCN2A*
	Unclassified epileptic encephalopathy, absences, ID	*SYNGAP1*
	Malignant migrating partial seizures of infancy	*KCNT1*
	West syndrome, lissenencephaly	*ARX*

ID = intellectual disability

Malformations of Cortical Development

Severe malformations of cortical development are recognized as important causes of epilepsy. A classification scheme of malformations of cortical development is shown in Table 4. With the advent of high-resolution magnetic resonance imaging, however, much more subtle localized forms of focal cortical dysplasia are now identified as a common cause of focal epilepsies [52] that in the past were considered to be "cryptogenic". The classification of focal cortical dysplasias is shown in Table 5. Identification of these lesions in patients with pharmacoresistant epilepsy is particularly important because many are amenable to surgical treatment, with excellent

Table 4 Classification scheme of malformations of cortical development

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
- A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size
  1. Microcephaly with normal to thin cortex
  2. Microlissencephaly (extreme microcephaly with thick cortex)
  3. Microcephaly with extensive polymicrogyria
  4. Macrocephalies
- B. Abnormal proliferation (abnormal cell types)
  1. Nonneoplastic
     a. Cortical hamartomas of tuberous sclerosis
     b. Cortical dysplasia with balloon cells
     c. Hemimegalencephaly
  2. Neoplastic (associated with disordered cortex)
     a. Dysembryoplastic neuroepithelial tumor
     b. Ganglioglioma
     c. Gangliocytoma

II. Malformations due to abnormal neuronal migration
- A. Lissencephaly/subcortical band heterotopia spectrum
- B. Cobblestone complex/congenital muscular dystrophy syndromes
- C. Heterotopia
  1. Subependymal (periventricular)
  2. Subcortical (other than band heterotopia)
  3. Marginal glioneuronal

III. Malformations due to abnormal cortical organization (including later neuronal migration)
- A. Polymicrogyria and schizencephaly
  1. Bilateral polymicrogyria syndromes
  2. Schizencephaly (polymicrogyria with clefts)
  3. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes
- B. Cortical dysplasia without balloon cells
- C. Microdysgenesis

IV. Malformations of cortical development, not otherwise classified
- A. Malformations secondary to inborn errors of metabolism
  1. Mitochondrial and pyruvate metabolic disorders
  2. Peroxisomal disorders
- B. Other unclassified malformations
  1. Sublobar dysplasia
  2. Others

Reproduced from [51], with permission.

Table 5 The three-tiered international league against epilepsy (ILAE) classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD types I and II) from those associated with another principal lesion (FCD type III)

FCD type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD type Ic)	
FCD type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD type IIa)		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD type IIb)	
FCD type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD type IIIa)	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD type IIIb)	Cortical lamination abnormalities adjacent to vascular malformation (FCD type IIIc)	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD type IIId)

FCD type III (not otherwise specified): if clinically/radiologically suspected principal lesion is not available for microscopic inspection.
Please note that the rare association between FCD types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD type III variant.
Reproduced from [52], with permission.

results. Several acquired and genetic approaches have been used to create cortical malformation in animals ranging from generation of cortical gross abnormalities, such as microgyri by cortical freezing, to engineering of selective neuronal subtypes to undergo abnormal migration in the cerebral cortex [53, 54]. However, none of these adequately mimic the complete spectrum of a clinical condition, and it remains to be explored how well the mechanisms of epileptogenesis in animal models mimic the human condition.

Autoimmune Disorders

Inflammation and other immune-mediated processes are clearly important in epileptogenesis [55]. Clinically, injury to the brain activates innate immunity, and breakdown of the blood–brain barrier permits adaptive immunity and peripheral immune responses, as well as specific antibody production, to affect the brain. Rasmussen's encephalitis has been recognized for some time as an inflammatory disorder, but a number of autoimmune epileptic conditions have been described recently. These were previously referred to as limbic encephalitis, which may or may not be paraneoplastic, but are now known to be due to specific autoantibodies to the n-methyl-D-aspartate receptor, γ-aminobutyric acid receptor, α-amino-3-dehydroxy-5-methyl-4-isoxazole proprionic acid receptor, and molecules associated with the voltage-gate potassium channel complex, all located on the surface of neurons [56]. Similar mechanisms may also contribute to epileptogenesis in many of the acquired, and perhaps some genetic, epilepsies. So far, only a few attempts have been made to generate animal models based on inflammatory or immune response. In many acquired models (e.g., after status epilepticus (SE), stroke, TBI), a robust inflammatory response occurs in parallel with other pathologies, and it has been difficult to extract the specific contribution of inflammation to epileptogenesis. Induction of encephalitis, for example, with measles virus or Theiler's virus has been shown to result in seizures and/or increased seizure susceptibility. However, further characterization of these models is needed to assess their clinical validity [57, 58]. Another approach would be to introduce mice with antibodies generated, for example, against K^+ channels, LGI1 or n-methyl-D-aspartate receptors, as discussed by Lerche et al. [49].

Antiepileptogenesis

Epileptogenic processes are naturally accompanied by homeostatic protective mechanisms that work to suppress the development of epilepsy, as well as to prevent, contain, and terminate epileptic seizures. Indeed, it is appropriate to ask why patients have epileptic seizures, but it is equally appropriate to ask why those with similar insults never develop epilepsy, why those with epilepsy do not have continuous epileptic seizures, and why focal seizures do not necessarily propagate. Research in utilizing animal models to investigate mechanisms of epileptogenesis must clearly distinguish pathophysiologic changes that occur in response to an epileptogenic insult that are epileptogenic from those that are protective and antiepileptogenic. Elucidation of the natural homeostatic protective mechanisms will provide insights into the development of novel antiepileptogenic interventions. Understanding fundamental neuronal mechanisms of epileptogenesis and homeostatic protective processes is essential in order to develop antiepileptogenic interventions that would not only prevent epilepsy before it manifests, but cure epilepsy after it has been established, without compromising the mechanisms that help the brain to recover itself.

Appreciating the large number of potential molecular and cellular mechanisms that can contribute to different types of

Table 6 Various treatments have shown disease-modifying effects in proof-of-concept studies in models of epileptogenesis caused by acquired or genetic etiologies

Drug	Mechanism	Model	Disease-modifying effect		Reference
			Antiepileptogenesis	Comorbidity modification	
Models of acquired epileptogenesis—SE models					
Atipamezole	α_2-adrenergic antagonist	Electrical stimulation-induced SE in rats	Yes	n.d.	[59]
Celecoxib	COX-2 inhibition	Li-pilocarpine-induced SE in rats	Yes	n.d.	[60]
FK506 (Tacrolimus)	Inhibition of T-cell response by binding to immunophilin	Electrical stimulation-induced SE in rats	No	n.d.	[61]
α_4 integrin-specific mAb	α_4 integrin	Pilocarpine-induced SE in mice	Yes	Yes	[62]
Erythropoietin	Erythropoietin receptor	Li-pilocarpine-induced SE in rats	Yes	n.d.	[63]
SC58236	COX-2 inhibition	Electrical stimulation-induced SE in rats	No	n.d.	[64]
FGF-2 and BDNF gene therapy	FGF receptors, TrkB	Pilocarpine-induced SE in rats	Yes	n.d.	[65]
Rapamycin	mTOR inhibition	KA-induced SE in rats	Yes	n.d.	[66]
		Pilocarpine-induced SE in rats	Yes	n.d.	[67]
		Pilocarpine-induced SE in mice	No	n.d.	[68]
		Electrical stimulation-induced SE in rats	Yes	n.d.	[69]
		Electrical stimulation-induced SE in rats	No	n.d.	[70]
		Pilocarpine-induced SE in mice	No	n.d.	[71]
Bumetadine	NKCC1 inhibitor	Li-pilocarpine-induced SE in rats	No	No	[72]
Parecoxib	COX-2 inhibition	Pilocarpine-induced SE in rats	Yes	No	[73]
SR141716A	CB1 receptor antagonist	KA-induced SE in rats	No	n.d.	[74]
NRSE-sequence decoy oligodeoxynucleotides	Neuron-restricted silencing factor	KA-induced SE in rats	Yes	n.d.	[75]
Aspirin	COX-2 inhibition	Li-pilocarpine SE in rats	Yes	n.d.	[76]
Fingolimod (FTY720)	anti-inflammatory	Li-pilocarpine-induced SE in rats	Yes	n.d.	[77]
Pentylenetetrazol	$GABA_A$ receptor antagonist	i.h. KA in rats	Yes	n.d.	[78]
		Li-pilocarpine in rats	No	n.d.	
Adenosine	Reduced DNA methylation	KA-induced SE in rats	Yes (progression of epilepsy ⇩)	n.d.	[79]
Anakinra and VX-765 duotherapy	IL-1 receptor antagonist, inhibition of IL-1β cleavage	Electrical stimulation-induced SE in rats	No	n.d.	[80]
Melatonin	Antioxidant	KA-induced SE in rats	Yes	Yes	[81]
1NMPP1	TrkB kinase inhibition	i.a. KA in *TrkBF*^{616A} mice	Yes	Yes	[82]
WP1066	JAK/STAT inhibition	Pilocarpine-induced SE in rats	Yes	n.d.	[83]
Models of acquired epileptogenesis—TBI models					
SR141716A	CB1 receptor antagonist	Lateral FPI-induced TBI in rats	Seizure susceptibility ⇩	n.d.	[84]
Minozac®	Reduction of pro-inflammatory cytokine production by activated glia	Closed skull TBI in CD-1 mice	Seizure susceptibility ⇩	Yes	[85]
Ketogenic diet	Multiple	Lateral FPI-induced TBI in rats	No	n.d.	[86]
Hypothermia	Multiple	Parasagittal FPI-induced TBI in rats	Seizure susceptibility ⇩	n.d.	[87]
Ceftriaxone	Stimulation of glutamate transporter	Lateral FPI-induced TBI in rats	Yes	n.d.	[88]
Rapamycin	mTOR inhibition	Controlled cortical impact in CD1 mice	Yes	n.d.	[89]
Models of acquired epileptogenesis—other models					
SR141716A	CB1 receptor antagonist	Hyperthermia in P16-18 rats	Seizure susceptibility ⇩		[90]

Table 6 (continued)

Drug	Mechanism	Model	Disease-modifying effect		Reference
			Antiepileptogenesis	Comorbidity modification	
Models of cortical malformations					
Rapamycin	mTOR inhibition	*Tsc1*^{GFAP} CKO mice	Yes	Yes	[91]
		Pten CKO mice	Yes	Yes	[92]
		Pten CKO mice	Yes	n.d.	[93]
Genetic epilepsies					
Levetiracetam	Binding to synaptic vesicle protein SV2A	Spontaneously epileptic rats	Yes	n.d.	[94]
		WAG/Rij rats with spontaneous absence seizures	Yes	Worsening of depressive behavior	[95]
		WAG/Rij rats with spontaneous absence seizures	Yes	n.d.	[96]
		GAERS rats	Yes (not permanent)	n.d.	[97]
Ethosuximide	T-type calcium-channel blocker	WAG/Rij rats with spontaneous absence seizures	Yes	n.d.	[98]
		WAG/Rij rats with spontaneous absence seizures	Yes	Yes	[99]
		WAG/Rij rats with spontaneous absence seizures	Yes	n.d.	[95]
		WAG/Rij rats with spontaneous absence seizures	Yes	Yes	[96]
		GAERS rats	Yes	Yes	[100]
Zonisamide	Na^+-channel blocker	WAG/Rij rats with spontaneous absence seizures	Yes	No	[96]
Vigabatrin	GABA transaminase inhibitor	WAG/Rij rats with spontaneous absence seizures	Yes	Yes	[101]
Carbamazepine	Na^+-channel blocker	WAG/Rij rats with spontaneous absence seizures	No	No	[96]
Rapamycin	mTOR inhibition	WAG/Rij rats with spontaneous absence seizures	Yes	Worsening of depressive behavior	[102]

SE = status epilepticus; TBI = traumatic brain injury; mAB = monoclonal antibody; FGF = fibroblast growth factor ; BDNF = brain-derived neurotrophic factor; COX-2 = cyclo-oxygenase 2; CB1 = cannabinoid receptor 1; TrkB = tropomyosin-related kinase B; mTOR = mammalian target of rapamycin (serine-threonine protein kinase); NKCC1 = sodium-potassium-chloride co-transporter; $GABA_A$ = gamma-aminobutyric acid A receptor; IL = interleukin; JAK/STAT = Janus kinase/signal transducer and activator of transcription; KA = ainic acid; i.h. = intra-hippocampal; i.a. = intra-amygdala; FPI = fluid-percussion injury; Tsc = tuberous sclerosis complex; CKO = conditional knock-out; Pten = phosphatase and tensin homolog; n.d. = no data.

epileptogenesis in various epilepsy syndromes, it is amazing that, so far, we were able to identify 21 different treatment approaches that have produced antiepileptogenic effects in proof-of-concept experimental studies. That is, they have delayed the development of epilepsy, resulted in a milder epilepsy phenotype, or even reversed the epilepsy phenotype (Table 6). Moreover, favorable results have been obtained in several models, including models of hippocampal sclerosis and PTE, as well as in several genetic epilepsies. However, owing to the labor intensity related to these studies it would currently be impossible to utilize any of these study designs to screen the tens of thousands of compounds that might have antiepileptogenic potential. This supports the need to develop validated high-throughput, cost-effective models, for example using zebrafish, *Drosophila*, or slice cultures [103]. Currently, clinical trials of potential antiepileptogenic drugs would be prohibitively expensive because seizures occur only in a relatively small percentage of patients, even after the most severe TBI, and may take more than 10 years to develop. Cost-effective discovery and validation of antiepileptogenic agents requires biomarkers of epileptogenesis for rapid-throughput screening, to enrich populations for clinical trials, and to document that an intervention has resulted in prevention or cure without the need to wait until seizures occur. Use of biomarkers to facilitate therapy development is actively discussed in other diseases such as glioma and Alzheimer's disease [104, 105]. Antiepileptogenesis is another significant challenge for neurology, requiring vigorous research in epileptogenesis and biomarkers to realize the development of therapies that will prevent and cure epilepsy.

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