



Review

Untangling the pathomechanisms of temporal lobe epilepsy—The promise of epileptic biomarkers and novel therapeutic approaches



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ABSTRACT

Epilepsy is one of the most common neurological diseases and it is characterized by the reoccurrence of seizures with variable severity and frequency. The burden of epilepsy, however, is more than having seizures, as the disease is frequently associated with comorbid cognitive and behavioral disorders. Diagnosis as well as treatment suffers both from the inadequate understanding of the underlying epileptogenic molecular, cellular and network mechanisms and the related lack of reliable biomarkers for the development, progression, or even the presence and severity of the epileptic condition. Here we summarize the recent advances in both clinical and experimental approach regarding epilepsy, which may create the premise for identification of clinically useful, reliable biomarkers. Identification of the basic pathomechanisms of epileptogenesis and epilepsy would potentially create new therapeutic approaches that could not only treat but also prevent and cure epilepsy. Current knowledge regarding the electrophysiological alterations as well as the underlying cellular and molecular mechanisms regarding temporal lobe epilepsy is also critically scrutinized.

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Abbreviations: ADK, adenosine kinase inhibitors; AED, antiepileptic drugs; AMT-PET, α -methyltryptophan positron emission tomography; AMPA, α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BBB, blood-brain barrier; CB1-R, type 1 cannabinoid receptor; CCK, cholecystokinin; FDG-PET, fludeoxyglucose positron emission tomography; GABA, gamma-aminobutyric acid; EPSP, excitatory postsynaptic potential; HFO, high-frequency oscillation; I_{NaP} , persistent sodium current; MRI, magnetic resonance imaging; MR spectroscopy, magnetic resonance spectroscopy; NMDA, N-methyl-D-aspartate; NMDARs, N-methyl-D-aspartate receptors; nNOS, neuronal nitric oxide synthase isoform; NO, nitric oxide; NPY, neuropeptide Y; NR1, NR2, NMDA receptor GluN1, GluN2 subunits; O-LM cells, oriens – lacunosum moleculare cells; PET, positron emission tomography; PV, parvalbumin; RNAi, RNA interference; TLE, temporal lobe epilepsy.

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1. Introduction

Epilepsy is a common neurological disorder that affects about 0.5–1.5% of the people of all ages (Hesdorffer et al., 2013; Hirtz et al., 2007). The disease is actually a spectrum of disorders that are characterized by the unpredictable occurrence of seizures with a variable range of severities, widely differing seizure types and causes, and varying impacts on individuals and their families (Berg et al., 2010). About 30–40% of people with epilepsy in the industrialized world have seizures that cannot be completely controlled by medication, and more than 80% of people with epilepsy live in the developing world, where may not receive treatment at all (Berg, 2004) (Table 1).

The seizures and coexisting health conditions create many challenges for people living with epilepsy and their relatives, including the inability for independent living, less access to high-quality health care and to various community services as well as dealing with stigma and common public misunderstandings (Coelho, 2006; Dua et al., 2006).

It is increasingly recognized that epilepsy is a relevant socio-economic burden not only at the individual and family level but also involving health services, and societal level. Several studies had investigated the economic burden of epilepsy in different geographical regions (Hong et al., 2009; Thomas et al., 2001; Wilner et al., 2012), the estimated costs related to epilepsy being as high as €15.5 billion/year in Europe only (Pugliatti et al., 2007). The cost impending on the side effects of antiepileptic treatments probably

increases further more the economic impact of a pharmacotherapy (de Kinderen et al., 2014).

Currently there is no cure nor prophylaxis available and all therapeutic choices are only symptomatic, with the goal to eliminate seizures without interfering with normal function (Glauser et al., 2013; Jacobs et al., 2009). This sparked a renewed focus on the understanding of the pathophysiology of epileptogenesis in order to reverse the epileptogenic process or cure the disorder (Pitkanen and Immonen, 2014).

2. Classification of epilepsy and epileptic seizures

Recent advances in diagnostic methods, including neuroimaging and genetics coupled with a better understanding of the pathophysiological background of epilepsies shifts the emphasis from seizure phenomenology to the etiological factors creating an unprecedented evolution of clinical classification schemes that now, based on the underlying cause, differentiates epilepsies with genetic, structural/metabolic, and unknown origin (Berg et al., 2010; Engel, 2006). In the case of genetic epilepsies, the disease is the direct result of a known or presumed genetic defect and seizures are the core symptom of the disorder while in structural/metabolic type of epilepsy there is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy. The recognized structural lesions may include acquired disorders such as stroke (Brodie et al., 2009; Gibson et al., 2014), trauma (Pitkanen and Immonen, 2014), and infection (Bern et al., 1999; Mewara et al., 2013); however, the term does not imply that there cannot also be a genetic origin, e.g. malformations of cortical development (Palmini et al., 2013). In order to be able to classify an epilepsy as structural/metabolic, gross anatomical and/or pathological abnormalities must be identified, i.e. any anatomical or pathological abnormality that can be identified during normal clinical investigation (including physical examination, microscopy, histology and/or neurochemistry). Although much progress has been made in the identification of causes and pathomechanisms involved in epilepsy about 40% of epilepsies still have an unknown origin (Shorvon, 2011).

Indifferently of the underlying cause the hallmark events of epilepsy, the seizures are classified according to their mode of onset and progression as well as their clinical characteristics into generalized, focal and unknown type of seizures. According to the current classification scheme of the International League Against Epilepsy any seizure that does not correspond clearly to these existing categories is considered unclassified until further information allows their accurate diagnosis (Berg et al., 2010).

3. Diagnosing epilepsy: current methods

3.1. EEG and video-EEG

Electroencephalography (EEG) is probably the most specific method to define epileptogenic cortex but its sensitivity and specificity will depend on several factors such as age and recording procedures. EEG is able to reveal characteristic interictal findings in several epileptic syndromes including spikes, sharp waves, spike-wave complexes, slow spike-wave complexes, 3-Hz spike-wave complexes, polyspikes, etc.; however, rarely,

Table 1
Epilepsy terminology.

Epilepsy: is a disorder of the brain characterized by a predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.
Epileptic seizure: a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Epileptogenesis: the development and extension of tissue capable of generating spontaneous seizures, including the development and progression of the condition.
Antiepileptogenesis: a process that counteracts the effects of epileptogenesis, including:
Prevention: treatment given prior to epilepsy occurrence that completely prevents the development of epilepsy (or partial prevention that delays the development of epilepsy).
Cure: complete and permanent reversal of epilepsy such that no seizures occur even after treatment withdrawal.
Seizure modification (antiictal treatment given after epilepsy occurrence): seizures occur but they may be fewer in frequency, shorter or of milder seizure type; can also prevent or reduce the progression of epilepsy.
Electroclinical syndrome: is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder (the focus of treatment trials as well as of genetic, neuropsychological, and neuroimaging investigations usually are electroclinical syndromes).
Obsolete/discouraged terms:
Idiopathic: replaced with genetic epilepsies (as there is a minimum threshold for presuming a form of epilepsy is to have a genetic basis); also the cause is no longer equated with prognosis, and the implication that “idiopathic” confers the quality of “benign” is intentionally discarded.
Symptomatic: the term is a truism; all epilepsy is symptomatic of something; replaced by structural/metabolic.
Cryptogenic, initially defined as “presumed symptomatic”: replaced by “unknown”, as it is considered that a clinical hunch should not be the basis of a scientific classification.

Source: Berg et al. (2010) and Fisher et al. (2005).

epileptiform discharges are recorded in healthy individuals as well. Although surface EEG recordings are less sensitive than invasive studies, they provide the best overview and are probably the most efficient and cost-effective way to define the approximate localization of the epileptogenic zone. Invasive recordings are used in patients in whom the epileptogenic zone either cannot be located with noninvasive diagnostic methods or is adjacent to eloquent cortex (Noachtar and Remi, 2009). High-frequency oscillations have been proposed as a clinically useful biomarker of seizure generating sites and it may even be used to establish an underlying neural mechanism for delayed-onset, sustained ictal high-frequency oscillations, and provide a practical, efficient method for using them to identify the small ictal core regions (Weiss et al., 2013). It must be noted, however, that most currently commercially available electroencephalographs have a built-in low-pass filter 35–70 Hz and analog-to-digital sampling typically occurs at 256–512 Hz, therefore they are not suitable for recording high-frequency oscillations (Niedermeyer and da Silva, 2005). Also, the problems related to the analysis of a large amount of EEG data must be solved in order to be able to move forward from proof-of-principle studies (Pitkanen and Lukasiuk, 2011).

In order to diagnose epilepsy the current gold standard is video-EEG, i.e. continuous EEG recorded for a more or less prolonged period with simultaneous video recording of the clinical manifestations. Having a correlation of the recorded behavior (video) and the EEG activity, the diagnosis of seizures or nonepileptic attacks can be made definitely in nearly all cases (Benbadis et al., 2004, 2009; Donat, 1994). The method was originally used only in specialized centers as part of the evaluation for epilepsy surgery. However, it is now widely available and often utilized as a cost-effective method (Chemmanur et al., 2009) for other indications including: clarifying the nature of paroxysmal events, quantifying the frequency of seizures, and identifying the epilepsy syndrome (Guerrini et al., 2013; Nordli, 2006). Video-EEG also reduces significantly the diagnostic delay in psychogenic nonepileptic seizures (LaFrance et al., 2013; Reuber et al., 2002). Ictal recordings can be obtained in patients with refractory seizures during relatively brief studies (i.e. recordings lasting less than 24 h) in many circumstances and the information obtained through the analysis of the ictal events can be very helpful in clarifying the true nature of the epilepsies (Nordli, 2006). The method is especially useful in patients with drug-resistant epilepsy (Villanueva et al., 2011), in children (Riquet et al., 2011; Sieglar et al., 2013) and can even be used in ambulatory settings.

3.2. Putative biomarkers in epilepsy

Indifferently of the underlying cause, during the development of epilepsy, the reorganization of the neuronal network, changes in the number and function of individual neurons and the consecutive modification of the electrical properties of both the cells and the network leads to the synchronized firing of a large number of neurons and reoccurring seizures (Ben-Ari, 2001; Shukla and Prasad, 2012). A major breakthrough regarding the pathophysiology of epilepsy would be the identification of valid epileptic marker. During the past years significant advances were made in our understanding not only at the clinical but also at the molecular and cellular level. However, the heterogeneity of epileptic syndromes creates an almost insurmountable challenge for the search for valid biomarkers and at least at this point the identification of a single marker that is specific and sensitive for a given epileptogenic pathology remains an unmet need (Pitkanen and Lukasiuk, 2011). Therefore, multiple biomarker platforms (e.g., imaging, proteomics, electrophysiology) should probably be used in combination and/or in a defined temporal sequence (Pitkanen and Lukasiuk, 2011). In recent years nesfatin-1 levels were shown to change in the plasma

and saliva of epileptic patients during the course of the disease; currently it is considered as a promising marker to diagnose patients who suffered a recent epileptic seizure (Aydin et al., 2009, 2011).

Currently there are several studies of well known epileptogenic etiologies (e.g. traumatic brain injury) that are aimed to identify molecular markers in blood and cerebrospinal fluid that predict may outcome, by using proteomics and metabolomics (Dash et al., 2010; Pelinka et al., 2004). Electrophysiological activity changes during epileptogenesis are a hallmark of the disease; however there are only a handful of potential biomarkers, probably the most promising ones being the high-frequency oscillations, interictal spikes and Up-spikes. Establishing these abnormal events as biomarkers of epilepsy will largely depend on a better understanding of the mechanisms underlying their generation, which will not only help distinguish pathological from physiological events, but will also determine what roles these pathological events play in epileptogenesis and epileptogenicity (Staba and Bragin, 2011). Nevertheless interictal high-frequency oscillations seem to be preferentially localized to the brain region generating spontaneous seizures, and are a potential biomarker of epileptogenic brain that has the potential to significantly advance epilepsy surgery by improving outcomes through improved localization and potentially eliminating the reliance on chronic intracranial EEG monitoring (Worrell and Gotman, 2011).

Changes in the anatomy or activity of neural networks can be shown with FDG-PET and basic and clinical investigations are suggesting that PET with α -methyl tryptophan could be a useful biomarker for epileptogenicity (Chugani, 2011). Volumetric and functional MRI can identify areas of cell loss and perhaps changes that precede neuronal death and synaptic reorganization in animal models (Nehlig, 2011) and in clinical studies as well (Gomes and Shinnar, 2011) although the latter's findings may only be applied to the developing brain (Galanopoulou and Moshe, 2011; Kubova et al., 2012).

Neurobiological investigations including transcranial magnetic stimulation measurements of cortical inhibition and excitability, magnetic resonance spectroscopy of GABA and glutamate brain concentration, and positron emission tomography studies of various neurotransmission systems are so far seldom used in patients with epilepsy (Lothe et al., 2008; Theodore et al., 2007).

Measures of gene expression profiles and their protein products could provide opportunities for development of biomarkers of epileptogenesis (Pitkanen and Lukasiuk, 2011). Epileptogenesis- and epileptogenicity-related alterations in gene expression profiles in the brain might be imaged by selective PET tracers; however, it is conceivable that such changes might also be identified in peripheral blood, for instance in white blood cells, providing a diagnostic fingerprint that could serve as a noninvasive biomarker of epileptogenesis and/or epileptogenicity (Engel, 2011) (Table 2).

4. Cognitive and psychiatric comorbidities in epilepsy

Accounting only for seizures we grossly underestimate the true impact of epilepsy. In recent years it has been recognized more and more that the burden of epilepsy is more than having seizures as the disease is frequently associated with comorbid cognitive (Elger et al., 2004) and behavioral problems (Helmstaedter et al., 2014; Swinkels et al., 2005). Up to 80% of patients with chronic epilepsies may suffer from cognitive impairment and there are studies which report up to half of the patients to have behavioral problems (Helmstaedter et al., 2011). Depression is the most frequent psychiatric comorbidity (Ettinger et al., 2004) but problems in memory, psychomotor speed, and executive functions are prevalent as well (Helmstaedter and Witt, 2012). Also, the introduction of several antiepileptic drugs (AEDs) in the decades between 1990 and 2010,

Table 2
Potential biomarkers of epilepsy.

Potential target mechanisms for biomarkers of epilepsy	Method of investigation with potential human diagnostic use	Selected references
<i>Altered excitability and synchrony</i>	EEG, corticography	Avoli (2014), Bragin et al. (2002), Nariai et al. (2011), Worrell and Gotman (2011), Wu et al. (2008) and Wu et al. (2010) Wu et al. (2006)
	Interictal magnetoencephalography/magnetic source imaging	
	Paired pulse transcranial magnetic stimulation	Badawy et al. (2006), Kamida et al. (2007), Saisanen et al. (2010) and Schmidt et al. (2010) Chugani (2011) and Fedi et al. (2001)
	Uptake of α -methyltryptophan (AMT) with PET	
<i>Altered neuronal function (e.g., gene expression profiles, protein products)</i>	Plasma and saliva determination of peptides, such as nesfatin-1 or ghrelin Gene expression	Aydin et al. (2009, 2011), Pitkanen and Lukasiuk (2011) and Portelli et al. (2012) Badawy et al. (2009a, 2009b), Elliott et al. (2003), Ferraro (2014) and Gallentine and Mikati (2012)
<i>Cell loss (e.g., hippocampal atrophy)</i>	Fluorodeoxyglucose PET, MRI, magnetoencephalography/magnetic source imaging, functional MRI	Chandra et al. (2006) and Ogren et al. (2009)
<i>Axonal growth (sprouting)</i>	Possibly volumetric and functional MRI	Polli et al. (2014)
<i>Synaptic reorganization</i>	Possibly volumetric and functional MRI	Gomes and Shinnar (2011) and Nehlig (2011)
<i>Inflammatory changes</i>	Biochemical measurements of inflammatory mediators in blood and serum PET ligands to detect activated microglia	Aronica et al. (2011) and Vezzani et al. (2013) Banati (2002), Butler et al. (2013) and Kumar et al. (2008) Dube et al. (2010) and Tomkins et al. (2008)
<i>Altered glial function and gliosis</i>	Quantification of BBB permeability changes MR spectroscopy PET ligands to detect activated microglia	Banati (2002), Butler et al. (2013), Hammen et al. (2008), Kumar et al. (2008) and Mizuno et al. (2000)

with quite strong chemical profiles that enabled better seizure control to be achieved in some previously treatment-intractable cases, revealed a spectrum of side effects, which included psychiatric disorders, including depression (Ring et al., 1993). Whatever the cause may be representative population-based studies in England have indicated that the associations of psychiatric and neurodevelopmental conditions are overrepresented in epilepsy, and the association is stronger than in non-neurologic chronic diseases (Rai et al., 2012).

A long-held view that comorbidities of epilepsy are only consequences of the disorder has undergone substantial transformation during the past decade, as emerging clinical evidence and experimental evidence suggest the involvement of specific neurobiological mechanisms in the evolution of neurobehavioral deficits in patients with epilepsy (Helmstaedter et al., 2014). The impact of these common pathogenic mechanisms may not be restricted to high comorbidity only, but can play a pivotal role on the worse course and response to pharmacologic and surgical treatment of seizure disorders of patients with a lifetime history of depression (Kanner et al., 2012). Several studies in large groups of untreated, newly diagnosed and new-onset epilepsies demonstrated that, dependent on the type of epilepsy, cognitive impairments are present in nearly half of the patients at the time of first diagnosis (Taylor et al., 2010; Witt and Helmstaedter, 2012). Furthermore, there is evidence that academic and behavioral problems in children antedate the first recognized seizure. If cognitive impairment precedes seizures (Austin et al., 2001; Jones et al., 2007) than it must result from a common underlying brain pathology rather than be due to the epilepsy. Such assumptions cannot be made as easily with other psychiatric conditions as these can be considered as diseases or as symptoms alternatively. However, epidemiological studies suggest that psychiatric comorbidity can precede epilepsy and that most likely a common underlying central nervous system disorder links premorbid psychiatric comorbidity and new-onset epilepsy (Ettinger et al., 2010). Psychiatric disorders and cognitive impairment in patients with epilepsy thus may be considered to reflect the degree of brain dysfunction and to be predictive for the

epilepsy outcome. In light of these findings, several studies tried to use comorbidities as biomarkers for epilepsy outcome but with inconsistent findings (Lackmayer et al., 2013; Talos et al., 2012).

In light of this progress, the study of the neurobehavioral comorbidities has become acute, as the latter are frequently more detrimental to patients' quality of life compared with seizures. This calls for an increase in efforts to effectively predict, manage, and ideally cure these comorbidities (Helmstaedter et al., 2014).

Interestingly we have extensive knowledge regarding chronic epilepsy but we lack the knowledge about the exact factors that lead to epilepsy and also to cognitive impairment or behavioral and psychiatric disorders in epileptic patients. As such clinical research should focus more on new-onset epilepsy and put particular emphasis on longitudinal studies in large cohorts of patients and groups at risk, while translational research should primarily focus on the development of valid preclinical systems which would allow investigating the fundamental mechanism of epilepsy comorbidities (Helmstaedter et al., 2014).

Not surprisingly the large array of methods that can be used to explore the structural and functional changes of relevant cerebral networks as well as the neurobiological abnormalities associated with epilepsy coincide with the methods deployed for the diagnosis of cognitive impairment and psychiatric disorders. For instance in major depressive disorders they demonstrate converging evidence of altered cortical excitability (Maeda et al., 2000) and inhibition (Lefaucheur et al., 2008), reduced GABA concentration (Sanacora et al., 1999) and GABA_A-benzodiazepine receptor density (Klumpers et al., 2010) and also hippocampal atrophy (Cole et al., 2011). In contrast with the number and quality of the functional studies in psychiatric conditions without epilepsy we lack even basic data regarding epilepsy with psychiatric comorbidities.

5. Therapeutic perspectives in epilepsy

Although there is a plethora of structurally and functionally diverse antiepileptic drugs (Howard et al., 2011), currently there is no cure nor prophylaxis available for epilepsy. To further

complicate the problem, clinically relevant differences exist among antiepileptics with presumably similar way of action (Howard et al., 2011). Therefore the choice of drugs sometimes remains partly empirical (Perucca, 2005).

Most of the classical AEDs exert their actions by inhibition of the voltage-gated sodium or calcium channels or by potentiation of the GABA-mediated synaptic transmission.

Some already approved AEDs mostly work through distinct mechanisms of action, e.g. modulation of the synaptic vesicle glycoprotein 2A (e.g. levetiracetam), allosteric inhibition of the AMPA-R (e.g. perampanel), or by activation of the voltage-gated potassium channels KCNQ2/Q3 (e.g. retigabine). Based on these identified mechanisms of action, systematic research is carried out to discover drugs that maintain the favorable properties of the original compound but improve on its deficiencies. Plenty of structure–activity relationship data was collected and several new drugs are already in different stages of clinical trials. For a comprehensive review, see Mittapalli and Roberts (2014).

Some drugs with novel mechanisms of action are also at various stages of the clinical development, e.g. inhibitors of interleukin converting enzyme, modulators of neuronal gap junctions, or galanin receptor agonists (Bialer et al., 2013).

It must be noted however that all currently available therapeutic choices are only symptomatic, with the goal to eliminate (or at least reduce the number and/or severity of) seizures (Glauser et al., 2013; Jacobs et al., 2009). The molecular and cellular data regarding epileptogenesis suggests a wide spectrum of potential treatment targets. However, the lack of a validated biomarker prevents the development of a truly antiepileptic therapeutic measure (Pitkanen and Immonen, 2014).

A significant portion of patients with epilepsy are refractory to antiepileptic drugs. The exact mechanisms behind drug-resistance are far from being understood completely (Kovacs and Heinemann, 2014). For some of these patients (e.g. patients with temporal lobe epilepsy, TLE) surgical treatment has been shown to be beneficial. However, surgery can only be applied for selected patients and fails to provide a seizure-free outcome in 20–30% of TLE patients (Harroud et al., 2012). Animal models of secondary epileptogenesis demonstrated that early resection or disconnection of the primary focus led to remission of the secondary focus, while if it was delayed, persistent interictal discharges and seizures were seen from the secondary focus (Badawy et al., 2009a, 2009b; Morrell, 1989). The ineffectiveness of surgery may be explained by inadequate presurgical evaluation or delay in applying the surgical treatment. Indeed, a recent randomized controlled trial demonstrates that early surgery for patients with mesial temporal lobe epilepsy may be superior to medical therapy (Engel et al., 2012). In recent years progress, including fundamental advances in imaging and neurophysiology, greatly improved presurgical evaluation and planning for epilepsy surgery, thus guiding to a more appropriate surgical referral (Jette and Wiebe, 2013).

Ketogenic diet is a high-fat, low-carbohydrate diet that restricts glucose and forces metabolism of ketones. Ketogenic diet therapy reduces seizures, being as effective as drugs, especially in some pediatric and medically refractory epilepsy (Freeman et al., 2007; Neal et al., 2008). In recent years studies showed that purines play a key role in the anticonvulsant effects of the ketogenic diet (Kawamura et al., 2010; Masino et al., 2011). Additional research pointed to adenosine acting mainly on A₁R and this discovery led to new insights into metabolic therapy as well as to new targets for drug development (Masino et al., 2012). Indeed, adenosine kinase inhibitors (ADK), adenosine uptake inhibitors and adenosine releasing implants seem to have beneficial effects on seizures (Kovacs et al., 2014).

In recent years, RNA interference (RNAi) has been developed both into an experimental tool and a promising novel therapeutic

method. In contrast to conventional antiepileptic treatments the method tries to exploit the endogenous regulatory mechanism of gene expression and may prevent or reverse pathogenetic mechanisms involved in seizure development (Boison, 2010). Although brilliant in principle the method (and generally all types of gene therapies) still has several issues, it may only be applied (if ever) to focal epilepsies (Simonato, 2013) and even then, due to the multifactorial condition the identification of proper molecular targets seems elusive yet (Boison, 2010). Probably the most promising advances were made regarding the adenosine system, either ADK downregulation by RNAi or by implantation of adenosine releasing cells (Kovacs et al., 2014).

In the last decade more and more evidence has emerged, both from experimental and clinical studies, that inflammation is an intrinsic feature of the hyperexcitability observed in pharmacoresistant epilepsies of different etiologies (Vezzani et al., 2011). Drugs that entered clinical trials as therapy for autoimmune and inflammatory pathologies may also have a therapeutic potential in epilepsies associated with proinflammatory processes. An antiepileptic strategy targeting inflammation should be considered, with the intent to provide disease-modifying drugs that interfere with etiopathogenetic mechanisms (Vezzani et al., 2013).

Neuropeptides are a class of neuromodulators that effect excitation in neural tissues. Most neuropeptides seem to have direct endogenous neuroprotective effect and basically all of them modulate the effect of classical excitatory and inhibitory neurotransmitters (Dobolyi et al., 2014). Furthermore more than 20 neuropeptides show aberrant expression and/or release in both animal models of epilepsy and patients. As such these neuropeptides as well as their receptors emerged as exciting targets to develop new antiepileptic drugs (Clynen et al., 2014). However, oral application of the neuropeptides is not efficient due to low bioavailability. Therefore, there is a need to develop non-peptide agonists and antagonists of the neuropeptide receptors (Dobolyi et al., 2014). A positive allosteric modulator of galanin receptor type 2 was recently discovered (Lu et al., 2010) which demonstrates an alternative approach to traditional discovery of orthosteric non-peptidic agonists (Mittapalli and Roberts, 2014). An other interesting approach would be the enhance of the local release of neuroprotective peptides with the help of gene transfer by viral tools (McCown, 2010). This approach is probably in the most advanced stage for NPY (Richichi et al., 2004).

6. Temporal lobe epilepsy

6.1. The role of the hippocampus

One area of particular interest is the hippocampus. This beautifully laminated, readily identifiable structure at both the gross and histological level is one of the most thoroughly studied areas of the central nervous system. The reasons for this are multiple. First the cellular organization that creates a highly laminar structure is well suited for both neuroanatomical and electrophysiological studies. Secondly, the hippocampus is involved in learning and memory and displays a variety of synchronous oscillations under physiological or pathophysiological conditions, such as theta and gamma rhythms, ripples, and epileptic seizures. The latter are caused by the enormous synchronous and rhythmic firing of hippocampal neurons. Therefore the hippocampus may be involved in temporal lobe epilepsy (Tellez-Zenteno and Hernandez-Ronquillo, 2012), which is one of the most frequent forms of epilepsy, and the cognitive impairment associated with the disorder.

High-frequency oscillations (HFOs) in the 80–200 Hz range, also called ripples, can be recorded from normal or epileptic hippocampal structures, and are considered to reflect mainly inhibitory field

potentials. HFOs in the higher frequency range (200–600 Hz, also called fast ripples) reflect abnormal bursts of population spikes, and are considered always pathologic (Engel et al., 2009). It is hypothesized that local decreases in inhibitory influences, can cause widely spaced clusters of neurons which generate pathologic HFOs, to increase in size, coalesce, and synchronize (Bragin et al., 2000, 2003).

6.2. Cell loss and reorganization of the epileptic hippocampus

Probably the earliest description of epilepsy induced cell loss pattern in the human hippocampus can be attributed to Sommer, who described principal cell loss in the subiculum as well as in the CA1 area (Sommer, 1880). This is associated with neuronal network changes in virtually all limbic system structures, such as the amygdala, entorhinal cortex, habenula (Ben-Ari, 1987). The most frequently described epilepsy induced change is the hippocampal sclerosis, which is characterized by massive pyramidal cell loss in the CA1 and CA3c regions accompanied by the loss of several types of interneurons, as well as gliosis (Margerison and Corsellis, 1966).

Besides cell loss, axonal sprouting is an other important morphological change, which was described quite early, first at the level of granule cells (Franck et al., 1995; Sutula et al., 1989, 1992); later aberrant axon collaterals of CA1 pyramidal cells were characterized (Lehmann et al., 2000). Furthermore a wide range of evidence shows axonal sprouting of the GABAergic interneurons (Babb, 1999; de Lanerolle et al., 1989; Wittner et al., 2002).

The changes of interneurons are generally more subtle, although there is a wide range of calretinin, parvalbumin and somatostatin containing interneurons that are more sensitive to epilepsy and are destroyed (de Lanerolle et al., 1988; Maglóczy and Freund, 1993; Maglóczy et al., 2000). Due to the diversity of GABA neurons in the hippocampus and cerebral cortex, resulting functional deficits are unlikely to be compensated fully by remaining GABA neurons of other subtypes.

The surviving interneuron types may show subtle morphological changes. The soma of the calbindin containing interneurons in the dentate gyrus and the sclerotic CA1 region increases (Wittner et al., 2002) and the dendrites become spiny (Maglóczy et al., 2000). The number of the parvalbumin expressing perisomatic inhibitory interneurons decreases in the sclerotic dentate gyrus, however their axons do not disappear (Wittner et al., 2001). This is probably due to the intense epileptic stimulation, which either reduces the expression of the parvalbumin at the level of the soma or changes the conformation of parvalbumin and therefore reduces the immunopositivity (Scotti et al., 1997). Consequently, this is not a real reduction of the number of the parvalbumin expressing perisomatic inhibitory interneurons, but merely our lack of possibilities to identify them with immunocytochemistry. It must be noted however that in the sclerotic CA1 region the axons will disappear as their target cells, the pyramidal neurons, die (Wittner et al., 2005).

Reorganization of the hippocampus during epileptogenesis is influenced by several factors. Besides their physiological role in synaptic transmission and long-term potentiation, N-methyl-D-aspartate receptors (NMDARs) play a key role in excitotoxic neuronal damage and epileptogenesis. NMDARs are heterotrimeric complexes, most often composed of two GluN1 (NR1) and two GluN2 (NR2) subunits. The latter can be of four subtypes (A, B, C, D).

NMDARs are mainly localized at the postsynaptic densities, but NMDARs containing the NR2B subunit have also been identified extrasynaptically or presynaptically (Woodhall et al., 2001). Synaptic and extrasynaptic NMDA receptors seem to have opposing effects in the neurodegeneration associated with glutamate induced excitotoxicity. Synaptic NMDAR activation is involved in neuroprotection, but the stimulation of the NR2B subunit

containing extrasynaptic NMDARs triggers cell destruction pathways (Vizi et al., 2013).

Glutamate release is tonically facilitated by presynaptic NMDA receptors. Using whole-cell voltage clamp in slices of the rat entorhinal cortex, it was demonstrated that in juvenile rats the presynaptic receptors are predominantly of the NR1–NR2B subtype (Yang et al., 2006). NR2B receptor blockade was less effective in adult than in young rats, suggesting a decline in autoreceptor function with development. However, in slices from adult rats exhibiting spontaneous recurrent seizures induced with a lithium-pilocarpine protocol, increased effect of presynaptic NR2B receptors was observed. This result suggests that properties of cortical networks in epilepsy may bear resemblance to those during early development, a stage of heightened susceptibility to epileptogenesis (Yang et al., 2006).

In organotypic hippocampal slice cultures chronically treated with NR2B selective antagonists the number and duration of seizures induced by bicuculline was dramatically reduced (Wang and Bausch, 2004). Moreover, less sprouting of granule cell mossy fiber axons and more surviving granule cell layer neurons were observed.

In a rat model of electrically induced status epilepticus evolving to spontaneous seizures, redistribution of the NR2B subunit was observed, with an increased localization in extrasynaptic and presynaptic compartments, and a concomitant decrease at postsynaptic sites (Frasca et al., 2011). Moreover, ectopic expression of NR2B and NR1 was described on astrocytes. Extrasynaptic NMDARs are predominantly activated by glutamate released by astrocytes, or spilled over from the synaptic cleft during episodes of high-frequency synaptic activity. Presynaptic NR2B-containing receptors, which facilitate glutamate release, may promote excitotoxicity and reinforce seizures by an increased glutamatergic neurotransmission. Pharmacological blockade of NR2B-containing NMDARs during epileptogenesis significantly attenuated neuronal loss in CA1 and CA3 area of the hippocampus (Frasca et al., 2011).

These results suggest that pharmacological targeting of nonsynaptic NR2B-containing NMDARs should be considered to block excitotoxicity and to prevent epileptogenesis.

An other recently described mechanism involved in the synaptic reorganization during epileptogenesis is the cannabinoid system. Strong acute seizures cause significant changes in the type 1 cannabinoid receptor (CB1-R) expression, but these changes are undetectable in case of milder seizures in which hardly any cell loss is observed. However, it must be noted that human TLE patients most frequently have significant cell loss and sclerosis. CB1 knock out animals have an extremely high mortality rate during the first seizure, which suggests that CB1 receptors may have a protective role and prevent reaching a “no-return” state. In this context the initial decrease in CB1-R observed during acute seizures (Karlocai et al., 2011) may lead to glutamate excitotoxicity, recurrent seizures as well as cell loss (Ludanyi et al., 2008). The decrease in the acute phase is followed by increased density of CB1-R during the chronic phase, which may serve as a protective mechanism (Guggenhuber et al., 2010; Karlocai et al., 2011).

6.3. Spatio-temporal dynamics of inhibitory interneuron activity

The relatively uniform principal cells are supported by a rich diversity of GABAergic interneurons whose classification is still a matter of debate (DeFelipe et al., 2013; Klausberger and Somogyi, 2008; Petilla Interneuron Nomenclature et al., 2008). The inhibitory innervation governs the threshold of activation, pattern of action potential firing and modification of synaptic strength (Buhl et al., 1994). These interneurons not only provide general inhibition but also temporally regulate pyramidal cell activity, therefore have pivotal role in any synchronous network activity. There is a division

of labor among inhibitory interneurons. Distinct interneuron types subdivide the surface of pyramidal cells and act in discrete time windows. They also interact with excitatory inputs in a domain-specific manner.

In the area CA1 of the hippocampus more than 21 inhibitory interneuron types were identified (Klausberger and Somogyi, 2008). The most thoroughly studied cell types are the basket cells, which provide inhibition to the cell bodies and proximal dendrites of pyramidal cells. They are strategically positioned to influence the output of principal cells, to regulate spike timing, oscillation rate and synchronization of their targets. Axo-axonic cells (Somogyi et al., 1983) innervate exclusively the axon initial segment, therefore they can modulate the action potential initiation. The GABAergic axon terminals of the bistratified cells (Buhl et al., 1994) are co-aligned with the glutamatergic Schaffer collateral input to the dendrites of pyramidal cells, therefore they can provide pathway-specific inhibition. Similarly, the oriens – lacunosum moleculare (O-LM) cells (McBain et al., 1994) provide pathway-specific inhibition, but for a different dendritic region, the apical dendritic tuft, which is innervated mainly by glutamatergic inputs from the entorhinal cortex and the thalamus.

Selective increase in somatic inhibition combined with the loss of dendritic inhibition has been reported in the hippocampus of epileptic rats (Cossart et al., 2001). A later study suggests that loss of O-LM cells are mainly responsible for the deficit of dendritic inhibition, but meantime death of axo-axonic cells was also observed, which indicates that perisomatic inhibition and the mechanisms of action potential generation are also affected (Dinocourt et al., 2003). Although perisomatic inhibition provided by basket cells seems to remain unchanged, preferential loss of GABAergic innervation from cholecystokinin (CCK)-containing hippocampal basket cells was reported in the pilocarpine model of epilepsy (Wyeth et al., 2010). Decreased inhibition of pyramidal cells by CCK-containing neurons was associated with increased contribution from parvalbumin (PV)-containing interneurons. Loss of CCK-containing GABAergic synapses to granule cells was described also in the dentate gyrus (Sun et al., 2014).

Finer analysis of spatio-temporal dynamics of interneuron activity and comparison of data obtained with or without anesthesia demonstrates that the widely used distinction between perisomatic and dendritic inhibition is a very coarse classification. Since adjacent GABAergic synapses can have completely opposite temporal dynamics *in vivo*, these terms no longer make sense without specifying the GABA-releasing cell type (Somogyi et al., 2014). Genetic labeling with fluorescent proteins of defined subsets of interneurons would allow their identification and targeting during electrophysiological recordings or imaging experiments. Several transgenic mouse lines were developed to identify certain cell types, e.g. somatostatin-containing GABAergic interneurons (Ma et al., 2006; Oliva et al., 2000), parvalbumin-positive neurons (Meyer et al., 2002), parvalbumin or glutamic acid decarboxylase expressing neurons (Chattopadhyaya et al., 2004), several interneuron subsets (Taniguchi et al., 2011). After these promising pioneering works, major progress can be expected when more selective molecular markers will become available for distinct cell types.

6.4. Transition from interictal to ictal activity

Besides morphological identification of affected cell types it is important to know the casual relation between events observed during epileptogenesis, and the sequence of events during transition from interictal to ictal activity. Extracellular recording with chronically implanted drivable tetrodes and advanced data analysis make possible to identify putative interneuron and pyramidal cell activity. In the CA3 area of hippocampus of freely moving

pilocarpine-treated rats exhibiting chronic recurrent spontaneous seizures, Grasse et al. (2013) have identified a specific sequence of neuronal behaviors prior to the onset of rhythmic ictal spiking. In this model of epilepsy interneurons display synchronous behavior minutes before local field potential ictal spiking. They become more correlated with each other and progressive synchrony with local field oscillations at theta, gamma, and finally ictal spiking frequencies occur. Interneurons increase their firing rate seconds before the onset of ictal spiking, and only after these synchronous activities occurred, and ictal spiking has begun, do pyramidal cells begin to show increases in firing rate and coherence with ictal spikes. These results support the view that synchronous interneuron activity is a hallmark of the transition from interictal to ictal states in CA3 (Grasse et al., 2013).

This method did not allow to subclassify the interneurons and to distinguish dendritic from somatic inhibition, because neither individual electrophysiological characteristics, nor combinations of them, could produce distinct clusters in feature space needed to identify distinct classes of interneurons.

6.5. *In vitro* epilepsy models and *in vivo* firing patterns

To clarify the network mechanism of neuronal synchronization, dual (or multiple) intracellular recording combined with cell labeling and morphological identification of neurons can be performed from slice preparations. Various *in vitro* experimental models were developed to induce seizure-like activity, for example: stimulating neurons electrically, altering the ionic composition of the extracellular environment (low Ca^{2+} or low Mg^{2+} or high K^{+}), blocking potassium channels or GABA_A receptors.

The role of identified inhibitory interneurons was studied by eliciting seizure-like afterdischarges in isolated hippocampal CA1 slices using tetanic stimulation (Fujiwara-Tsukamoto et al., 2004). Based on morphological and electrophysiological classification of the recorded interneurons it was shown that interneurons located in the strata lacunosum-moleculare and radiatum were hardly active during the afterdischarge, and lesions restricted to these layers did not influence significantly the synchronization of the network.

Interneurons in the strata oriens and pyramidale, exhibited prominent firings that were precisely synchronous with oscillatory responses in the pyramidal cells, and it was proposed that a positive feedback circuit formed by pyramidal cells and interneurons in s. oriens/pyramidale was responsible for neuronal synchronization. Although many interneurons were classified as basket, chandelier and bistratified cells, no functional distinction could be made among them, therefore fine analysis of the inhibitory network was not possible.

In hippocampal theta oscillations basket and axo-axonic (chandelier) cells discharge in counterphase with pyramidal cells, whereas the bistratified and O-LM cells discharge synchronously with the pyramidal cells (Klausberger et al., 2003, 2004). During ripple oscillations, basket and bistratified cells strongly increase their firing rate and discharge phase-coupled to the oscillatory cycles, but axo-axonic and O-LM cells are suppressed (Klausberger et al., 2003, 2004).

The fact that in the *in vitro* tetanic stimulation model (Fujiwara-Tsukamoto et al., 2004) all interneurons fired synchronously with pyramidal cells raises the question whether this alteration of interneuron behavior is representative for the modeled pathological condition or the very strong stimulation together with the *in vitro* conditions create a preparation which phenomenologically can reproduce the seizure-like events, but the underlying mechanisms are different from those observed *in vivo*.

Besides the PV-expressing basket, axo-axonic, and bistratified cells, a new cell type coexpressing neuronal nitric oxide (NO)

synthase isoform (nNOS) and neuropeptide Y (NPY) was identified in the CA1 pyramidal cell layer, which seems to be quantitatively the most abundant type of GABAergic interneuron in this region (Fuentealba et al., 2008). These cells were named Ivy cells because they have very fine and dense axons in the stratum radiatum and stratum oriens. They have low firing frequency, and provide synaptic and extrasynaptic GABAergic input, as well as NPY and NO to pyramidal cell dendrites. Novel microdrives for glass electrode placement and mini-preamplifiers makes possible to record from unequivocally identified neurons in naturally behaving animals. Ivy cells fire on average with similar rates during slow-wave-sleep, body-movement, quiet wakefulness, and different network oscillations (Lapray et al., 2012). This firing pattern, together with the slowly rising and decaying postsynaptic potentials (Fuentealba et al., 2008), is appropriate to control homeostasis in the network.

Nitric oxide released by Ivy cells may act as a second messenger, neuromodulator and neurotransmitter, and may have an essential role in epilepsy and epileptogenesis, but current data from the literature (Banach et al., 2011) regarding the involvement of NO in seizure phenomena is controversial. Several experimental models of seizures, NOS inhibitors and NO donors were used to assess pro- or anticonvulsant activity of NO, but the exact role of NO still remains unclear.

A major decrease in the temporal precision of EPSP–spike coupling in dentate gyrus granule cells was observed in hippocampal slices obtained from pilocarpine-treated rats that experienced spontaneous seizures (Epsztein et al., 2010). The jitter was mediated by the selective voltage dependent amplification of EPSP_{Kainate}, but not EPSP_{AMPA}, by persistent sodium current (I_{NaP}) leading to long-lasting plateaus associated with poor spike timing precision. I_{NaP} blockers were sufficient to restore a high spike timing precision in dentate gyrus granule cells from epileptic rats. Reduced spike timing reliability may cause learning deficits and cognitive impairments. If similar lability of spike timing exists in other hippocampal regions too, it could facilitate the entrainment of principal cells by strong synchronous inhibitory interneuron activity observed by Grasse et al. (2013).

Using hippocampal slices in the temporal lobe epilepsy model induced by pilocarpine, many CA1 neurons exhibiting bursting behavior were observed (Chen et al., 2011). Bursting neurons may entrain other neurons into synchronized population bursts, and thus may serve as the initiators and pacemakers of epileptic discharges. Inward currents augment depolarization near threshold and enhance neuronal firing. An increase in I_{NaP} in conjunction with an increase in I_{CaT} contributed strongly to the preponderance of intrinsic bursting behavior in CA1 pyramidal cells (Chen et al., 2011). Enhancement of the persistent sodium current was observed already one week after pilocarpine induction of status epilepticus, remained stable for about one month and then declined slowly over time. Even if the enhanced I_{NaP} fades about 1 month following status epilepticus, it might orchestrate hyperexcitable network firing and contribute to the formation of a long-lasting epileptic condition.

I_{NaP} can be activated by veratridine which binds to the neurotoxin receptor site 2 of voltage-gated sodium channels and inhibits channel inactivation and shifts the channel activation threshold toward a more negative membrane potential. In veratridine treated acute rat hippocampal slices the membrane potential and the intracellular sodium ($[Na^+]_i$) and calcium concentrations ($[Ca^{2+}]_i$) were measured under the same experimental conditions (Fekete et al., 2009). The marked increase of $[Na^+]_i$ was accompanied by sustained membrane depolarization, bursts of action potentials and a biphasic $[Ca^{2+}]_i$ increase. Because Ca^{2+} is an important intracellular regulator, the increased $[Ca^{2+}]_i$ can turn on several other processes. The $[Na^+]_i$ increase was more than 30 mM, which could be sufficient for reversing the operation of the $Na^+–Ca^{2+}$ exchanger (Fekete

et al., 2009). The influx of Ca^{2+} through the voltage-gated Ca^{2+} channels and the net effect of mitochondrial Ca^{2+} uptake and release, events with different time course, also contributed to the complex interaction between persistent Na^+ current and $[Ca^{2+}]_i$ regulation in CA1 pyramidal cells. Because the amount of sodium ions transferred across the membrane during an action potential is very small compared with the total intracellular pool, the extent to which sustained high-frequency firing can activate all of the above mentioned mechanisms has to be determined.

In a study using two genetic epilepsy animal models (spontaneously epileptic rats and tremor rats) increased immunoreactivity was found for the voltage-gated sodium channel subtypes $Nav1.1$, $Nav1.2$, $Nav1.3$, $Nav1.6$ and for calmodulin in the hippocampus. In contrast, the expression of the same proteins was downregulated in the temporal lobe cortex (Xu et al., 2013). Partially different results were obtained in other genetic epilepsy animal models (e.g. WAG/Rij absence epileptic rats – (Klein et al., 2004)), pointing out that future investigations are necessary to obtain a deeper understanding of hereditary epilepsies. Nevertheless, animal models of hereditary epilepsy can be valuable tools in screening new antiepileptic drugs, and for the development of gene therapy methods.

6.6. Ionic plasticity at GABAergic synapses

In most *in vitro* models the seizure-like afterdischarge occurs all over the hippocampal areas in synchrony and requires both glutamatergic and GABAergic transmissions among pyramidal cells and interneurons. Using tetanic stimulation in the presence of ionotropic glutamate receptor antagonists, short-lasting oscillatory activity was observed near the stimulation site ($<250\ \mu m$). This “prototypic afterdischarge,” was abolished by GABA_A receptor antagonists or gap junction blockers (Fujiwara-Tsukamoto et al., 2010). In this model, in mature hippocampus GABA had depolarizing and excitatory effect on interneurons as well as on the pyramidal cells close to the stimulation site. In this case the afterdischarge seems to be driven by an interneuron network and the pyramidal cells can be considered as followers. In the presence of glutamatergic transmission the seizure-like activity can propagate to different hippocampal areas through axonal projections from the pyramidal cells.

To study the complex balance between excitation and inhibition in neural circuits, the classical pharmacological manipulation and single-cell or paired intracellular recordings should be combined with recently developed network imaging methods. There is accumulating evidence that hyper-active network activity driven, short-term changes in the reversal potential for the GABA_A receptors can occur (Raimondo et al., 2012). It is demonstrated by combined high-speed two-photon imaging (Lillis et al., 2008) with electrophysiological recordings that ictal activity in GABAergic interneurons cause sufficient neuronal chloride accumulation that subsequent GABAergic activity will be depolarizing (Lillis et al., 2012). An activity-dependent shift in GABA reversal potential during the preictal phase is shown also in a low Mg^{2+} *in vitro* hippocampal preparation from juvenile rats (Lasztocki et al., 2009).

These studies also show that synchronous GABAergic interneuron activity precedes seizure-like events (Lasztocki et al., 2009; Lillis et al., 2012).

6.7. Entrainment of quiet neurons and the “dark matter” problem

Based on whole brain energy consumption and total energy cost of sustained level of spiking activity of single cells (action potential conduction plus synaptic mechanisms), theoretical calculations indicate an average firing frequency of 0.16 spikes/s/neuron

(Lennie, 2003). Comparing anatomically determined cell densities with extracellular electrophysiological data, Shoham et al. (2006) estimate that at least 90% of neurons are silent or fire at a very low frequency. Moreover, the ratio of pyramidal cells to interneurons detected by tetrode recordings in the hippocampus CA1 pyramidal layer is in general around 1:6 (Henze et al., 2000), what is five times larger than estimated by anatomical methods (1:33) (Aika et al., 1994). This can be explained by the assumption that interneurons are active in any environment and have much higher firing rates than pyramidal cells (Freund and Buzsáki, 1996). As interneurons are critical elements shaping the input–output relations of any brain area, they are taken into account in almost any model of oscillatory events and synchronization. However, the large number of principal cells, which are undetected because they fire only occasionally under physiological conditions, must be taken into account when we want to study the transition from normal oscillatory behavior of neural networks to seizure-like events. If entrainment is dynamically changing the interacting neuronal population maybe that not only quantitative but qualitative changes should be expected in the network's mode of operation.

To answer the question of silent neurons and their possible entrainment during epileptogenesis, simultaneous intracellular recordings should be obtained from a large number of neurons. There are promising results which suggest that it will be possible in the not too distant future to merge the advantages of extracellular microelectrode arrays and intracellular microelectrodes by using nano- and micro-electrophysiological technologies (Spira and Hai, 2013).

7. Conclusions

A breakthrough regarding the early detection, prevention, modification of the progression and/or cure for epilepsy can only come from a greater understanding of pathogenesis of epilepsy. Experimental models are able to provide additional insight into mechanism of normal and pathological network functioning as well as describing the potential involvement of various molecular pathways and processes. However, it still remains unclear which mechanisms are required or necessary for epileptogenesis in the human brain. Also experimental models may pose many limitations when comparing the results with human epileptic models including different etiologies, representativeness and difficulty of evaluation of behavioral alteration in animal models. As such, data coming from these models must be interpreted with caution. However only by understanding the fundamental processes of epileptogenesis and translating this information to the clinical diagnosis may help identifying biomarkers for epilepsy and can contribute to the development of new antiepileptogenic or disease-modifying therapies.

Conflict of Interest statement

The authors declare that there are no conflicts of interest.

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