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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).

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).

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,