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Review article

Prospects of epileptogenesis prevention

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ABSTRACT

Epilepsy is a common neurologic disease, affecting about 1–2% of the population. In around 30% of patients with epilepsy, their seizures are not satisfactorily controlled and drug-resistant epilepsy constitutes a real therapeutic challenge. Consequently, there are efforts aimed at the inhibition of epileptogenesis, a process of converting a normal into an epileptic brain. Data on this problem have been mainly obtained in post-status epilepticus rodent models in which spontaneous seizure activity and behavioral disturbances develop over time. Among antiepileptic drugs, diazepam at high dose of 20 mg/kg given during status epilepticus, significantly inhibited the development of spontaneous seizures and also, a strong neuroprotective effect was evident. Also gabapentin and valproate (over a period of 40 days) proved effective in the inhibition of spontaneous seizure activity and reduction of behavioral deficit. However, there are also data that valproate (over 28 days) significantly improved the behavioral performance without affecting the occurrence of spontaneous seizures. A number of antiepileptic drugs, carbamazepine, lamotrigine, levetiracetam, phenobarbital, and topiramate were completely ineffective. Among non-antiepileptic drugs, some promise show rapamycin, losartan and combinations of anti-inflammatory drugs, targeting different inflammatory pathways. Inhibition of epileptogenesis may become a valuable therapeutic approach provided that there are reliable markers of this process. Actually, such markers begin to emerge.

Contents

Abbreviations: AED(s), antiepileptic drug(s); AMPA, α-amino-3-hydroxy-5-isoxazole-4-propionate; CBZ, carbamazepine; GABA, γ-aminobutyric acid; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; NS1209, 8-methyl-5-(4-(*N*,*N*-dimethylsulfamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2-h]-iso-quinoline-2,3-dione-3-*O*-(4-hydroxybutyric acid2yl)oxime; PGB, pregabalin; SE, status epilepticus; TPM, topiramate; VPA, valproate.

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Introduction

Epilepsy is a chronic neurological disease and affects around 1–2% of the population [1–5]. It is defined as the syndrome of chronic pathological symptoms which disturb the function of the central nervous system and may be expressed in the form of seizures. In the group of patients, in whom the cause of seizures could not be explicitly determined, genetic factors probably play an important role [1]. Moreover, it has been shown that genetic predisposition is present in 40% of patients diagnosed with "idiopathic" epilepsy. There are also suggestions on the causative role of the immune system [2]. The mechanism of epileptic seizures, in the case of Rasmussen's encephalitis (chronic focal encephalitis), is directly connected with the functioning of immune system disorders [2]. Among patients who have been diagnosed with epilepsy, there is an increased risk of cognitive disorders [6]. Those disorders have multifactorial basis such as acquired or innate brain damage and the side effects of treatment. The risk of their occurrence can be increased by the early beginning of seizures, their great frequency, damage to the hippocampal formation, long-term epilepsy, polytherapy, fast and significant increase in doses and, finally, exceeding of recommended doses [6–9].

Drug-resistant epilepsy, which is diagnosed in ca 30% of patients, is an actual and therapeutic problem [10]. In 2003, the International League Against Epilepsy defined drug-resistant epilepsy as "chronic epilepsy without seizure remission despite right diagnosis, correct choice of medicines at their highest tolerable doses and sticking to doctor's orders concerning drug intake" [10].

One of the most drug-resistant epilepsies is, among others, temporal lobe epilepsy. Hippocampus plays a dominant role in pathogenesis of this type of epilepsy [11]. Temporal lobe epilepsy and hippocampal sclerosis are more often connected with organic brain damage, which causes the appearance of morphological changes in nerve tissue in the brain [10]. Importantly, this type of epilepsy exhibits a higher mortality rate [10].

Epileptogenesis, as a process of converting the properly functioning brain into the epileptic brain, can result from a variety of factors including genetic causes, infections of central nervous system, traumatic brain injuries or status epilepticus (SE) [12]. The causes of epileptic seizures are abnormal and excessive bioelectric discharges in the brain which can appear in almost every group of neurons [13]. Such discharges are caused by unbalanced neuronal excitability [14]. When it takes over the neighboring cells it can lead to an abrupt disturbance of the whole brain activity. Then, it causes generalized seizures accompanied by loss of consciousness, as it is observed in tonic–clonic or absence seizures [15]. When the impulse is not transferred to other groups of cells but stays in a particular structure, the "focal", partial seizures appear [1]. This area in the brain is called an epileptic focus. It constitutes a spatial neuronal network in the brain. The secondary epileptic focus may develop among healthy nerve cells, which are characterized by extensive links with primary focus [16]. Classification of focal epileptic seizures discriminates between partial seizures with simple symptomatology (without impairment of consciousness) with origin in neocortex and partial seizures with complex symptomatology (with impairment of consciousness) originating in old cortical structures in the temporal lobe (or in orbitofrontal cortex). The newer classification assumes Focal Aware Conscious Seizures and Focal Impaired Consciousness Seizures, respectively [17]. The occurrence of SE makes epileptogenesis highly probable. A suggestion has been made that patients experiencing this serious neurologic condition could have been expected to undergo preventive treatment with antiepileptic drugs (AEDs) sharing neuroprotective activities, provided that there was a clear-cut relationship between neuroprotection and inhibition of epileptogenesis [18]. If this is really a case, then the preventive use of at least some AEDs with significant neuroprotective potential could be of value in order to inhibit epileptogenesis.

Do AEDs possess neuroprotective effects?

Research carried out on animal models of seizures and neurodegeneration has provided a deep insight into mechanisms governing neuronal death or survival. While examining AEDs, attention is paid to their antiepileptic effects as well to their actions modifying the course of disease and their neuroprotective effectiveness. In the case of SE, an early modification of damaging factors, such as intensity and duration of the initial seizure is important and aimed at reducing the consequences of seizure activity [3].

Some AEDs can exert neuroprotective effects in the areas of diffused damages of the brain caused by experimental SE. Specifically, neuroprotection has been afforded by benzodiazepine derivatives (e.g. diazepam), phenobarbital, lamotrigine (LTG), gabapentin (GBP), tiagabine, topiramate (TPM), valproate (VPA), and vigabatrin [16,17]. Among AEDs possessing low or no neuroprotective potential, there are phenytoin and carbamazepine (CBZ) [19]. Later, it has turned out that levetiracetam (LEV) is deprived of neuroprotective effect, following SE induced by electric stimulation of the amygdala in rats [20].

The available evidence on the possible association between SE (or initial precipitating injury) and epileptogenesis may be summarized as follows: SE is responsible for seizure-related brain damage [21] and later on, for recurrent spontaneous seizure activity [22]. Spontaneous seizure activity is a real proof for the occurring process of epileptogenesis initiated apparently by SE. A very important question thus emerges whether seizure-related diffused brain damage reflected by neurodegeneration is tightly associated with epileptogenesis. If so, then the inhibition of neurodegeneration after SE or initial precipitating injury should be a sufficient preventive strategy for stopping epileptogenesis and subsequent spontaneous seizures, resulting from the abnormal activity of epileptic brain. If neurodegeneration triggered by SE or initial precipitating injury is actually required for epileptogenesis to occur, then, as already mentioned, all AEDs exhibiting neuroprotective properties should be considered as good candidates for the prevention of epileptogenesis. Before seeking for a possible correlation between neurodegeneration and epileptogenesis, a short description of the mechanisms of action of currently used AEDs follows.

Basic mechanism of action of AEDs

It is known that γ-aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters in the brain. GABA collaborates with three types of receptors – $GABA_A$, $GABA_B$ and $GABA_C$ [23]. Stimulation of the first receptor type results in a hyperpolarization of mature neurons, which is due to the opening