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Review

Systemic mechanisms of antiepileptic protection

Vladimir Karlov *

Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Russian Federation

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ABSTRACT

Aim: The objectives of this study were as follows: (1) to explore mechanisms that counteract epileptogenesis and provide antiepileptic protection in the life-threatening condition of status epilepticus; and (2) to access functional state of adaptation system and identify the roles of biochemical, humoral, and neurophysiologic factors in the antiepileptic protective system.
Methods: The experimental part of this research included a series of experiments using animal models which studied the influence of apnea (hypoxia and hypercapnia) on seizure activity; in addition, the role of the prefrontal and orbitofrontal cortex in epileptogenesis and antiepileptogenesis was explored. The clinical part consisted of a series of neurophysiological studies, using a method of multistage dipole localization, and clinical models of absence epilepsy and a tumor in the Rolandic region. One more line of clinical investigations was the study of the functional state of the adaptation system. Thirty-one patients with status epilepticus, with ages 14–56, were recruited. Proteins and fractions, electrolytes, acid–base balance, and 17-oxycorticosteroids in the blood plasma and 17-21-dioxy-20-ketosteroids in the urine were examined in relation to clinical data, EEG, and MRI.
Results: As a result of the experiments, it was determined that asphyxia has a two-phase impact on spike activity; an anticonvulsive effect of asphyxia is mediated by hypercapnia, while the orbitofrontal cortex plays the key role in the system of antiepileptic protection through its inhibition of other structures. Further, the mediobasal prefrontal lobe of the dominant hemisphere plays a significant role in antiepileptic protection, and increased levels of blood 17-corticosteroids and catecholamines are protective in the setting of stress from convulsive status epilepticus.
Conclusions: The system of antiepileptic protection includes humoral, biochemical, and neurophysiological mechanisms. We identified the roles of all these factors: hypercapnia, in connection with tonic convulsion, as the humoral factor and inhibitory potential of the prefrontal lobe as the main neurophysiologic factor. In the setting of convulsive status epilepticus, which maximally strains these adaptations, it is essential for endogenous levels of glucocorticoids (17-corticosteroid) and sympathoepinephrine to increase.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

According to the last proposal of ILAE, epilepsy is a disorder of the brain characterized by the enduring predisposition to generate epileptic seizures. The definition of epilepsy requires the occurrence of at least one epileptic seizure. The problem regarding the first unprovoked epileptic seizure is one of the most important problems in epileptology. In spite of the same risk factors, even in similar cases and under similar conditions, the seizure reoccurs in one patient, while it does not in another. Also, during the time when any antiepileptic drugs were not yet available the lethality of the most severe epilepsy condition — status epilepticus — was no more than 50% [1,2]. Therefore, there is a reason to suggest the existence of certain endogenous mechanisms that counteract epileptogenesis. Status epilepticus (SE) is one of the most severe life-threatening conditions in clinical medicine. This problem has been explored by us since 1967 and included a series of experiments and clinical study. There were 220 patients with SE in our study, including 166 patients with convulsive status. As a model for the study of epileptic excitation (spike) and inhibition (postspike slow wave), patients with absence epilepsy (86 patients) and convulsive forms with a pattern of absences on EEG (60 patients) and 14 patients with a tumor located in the Rolandic region were included. In addition to clinical methods, we also used methods of studying homeostasis — proteins and fractions, electrolytes, acid–base balance, adaptation system, as well as hemostasis and EEG. During the last 20 years, we also used neuroimaging (mainly MRI). In the early stages of this work, several series of acute and prolonged animal experiments were conducted, studying the influence of apnea (hypoxia and hypercapnia) on seizure activity. We also explore

* Tel.: +7 916 149 29 42.
E-mail address: v_karlov@barnsly.ru.

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the role of the prefrontal and the orbitofrontal cortex in epileptogenesis and antiepileptogenesis. In this paper, we present, for the first time, the summary data regarding systemic mechanisms of antiepileptic protection of different levels.

2. Experimental part

2.1. Materials and methods

Generalized epileptic seizures, specifically tonic, clonic, and absence, are likely to serve as the best model for the study of this problem. Of the aforementioned seizures, only a tonic seizure does not last more than several minutes. From the biological standpoint, this fact can be explained by the following: a prolonged tonic seizure causes apnea which in turn leads to anoxia and can potentially result in severe consequences up to brain death. It is obvious that a tonic seizure induces the same urgent mechanisms that suppress it. To clarify this problem, we undertook a set of experiments. The subjects of the investigation were animals (rabbits) with strychnine epileptogenic focus in the sensorimotor cortex. Electrical activity was recorded from the cortex, subthalamus, and hippocampus. Animals were subjected to curarization and APV (Artificial pulmonary ventilation). An animal was periodically cut off from the ALV apparatus for 40–60 s. It was obvious that asphyxia evokes two different increasing parallel processes: hypoxia and hypercapnia. We assumed that either one of them was able to influence spike activity. For this reason, we undertook another set of experiments. The animals were prepared by the same method, but they were breathing in a mixture of gas containing 88% oxygen and 12% carbon dioxide, which does not induce hypoxia. The inhalation, however, was acting like asphyxia. The next stage of our investigation was initiated by clinical data: the increased rate of symptomatic convulsive status epilepticus with acute prefrontal destructive lesions in 5 of 12 cases. We hypothesized that the prefrontal cortex has a certain relationship to the mechanism of antiepileptic protection. Experimental investigation was undertaken again. An epileptogenic focus was created in the sensorimotor cortex by the application of penicillin (acute experiment) or aluminum cream (chronic experiment). The clinical picture and EEG were registered. After 'ripening' of the epileptogenic focus, the animals with penicillin were subjected to coagulation of the orbitofrontal cortex. Animals with aluminum focus in one series of experiments were subjected to electrostimulation of the orbitofrontal cortex; in the other series of experiments, coagulation of the orbitofrontal cortex was used.

2.2. Results

The first series of experiments drew the following observations: during the 25–30 s of asphyxia, the amplitude and rate of spikes decreased; as asphyxia stopped, they began to disappear. Following respiration, however, the spike activity not only was restituted, but soon also exceeded its initial level (Fig. 1). Thus, asphyxia has a two-phase impact on spike activity. To explain the mechanism of this phenomenon, we undertook another study series. As a result of the second experimental series, we observed that the spike discharges were always blocked, as well as the seizures (Fig. 2). Based on these experiments, we came to the conclusion that the anticonvulsive effect of asphyxia is mediated by hypercapnia. The results of the third series of experiments are presented in Table 1.

The elimination of the orbitofrontal cortex evoked the acceleration of epileptogenic focus ripening, as well as the increase in seizures and lethality. In contrast, the stimulation of the orbitofrontal cortex resulted in the delay of epileptogenic focus ripening, decrease in its activity, and relief of the seizures. Thus, the investigation determined that the orbitofrontal cortex plays an important and possibly the key role in the endogenous of antiepileptic protection [3]. At the same time, these data raise a principal question as to what exactly the mechanism of this phenomenon is.

3. Clinical part

3.1. Materials and methods

Clinical investigations of the adaptation systems were conducted along 2 lines: neurophysiological and humoral and biochemical. Investigations in neurophysiology were focused on the study of the inhibitory role of slow activity: postspike wave, slow activity as itself, and paroxysmal slow activity (3 Hz). There were 220 patients with SE in our study, including 166 patients with convulsive status. As a model for the study of epileptic excitation (spike) and inhibition (postspike slow wave), patients with absence epilepsy (86 patients) and convulsive forms with a pattern of absences on EEG (60 patients) and 14 patients with tumor located in the Rolandic region were included. Together with Prof. V Gnezditzky (Research Center of Neurology), we conducted a new stage of investigation. An absence seizure was taken as a model of investigation. Earlier, in 1987, by using the method of evoked potentials, we, together with physiologist V. Ovnatanov, were the first group to discover the momentary start of absences from the mediobasal cortex [4], a finding that was supported in 1997 [5]. Later, we also used the method of multistage dipole localization (MDL), which allows the determination of the localization of both spikes and slow waves.

Undoubtedly, certain biochemical factors have antiepileptic protective properties. Our studies of the patients with mesial temporal epilepsy found serious abnormalities in the catecholamine system including the exhaustion of the system and statistically meaningful epinephrine and norepinephrine insufficiency, as well as the signs of denervation hypersensitivity [6,7]. These data encouraged us to proceed to the next step of investigation.

Because the corticosteroid and the sympathoepinephrine systems are the main hormonal links of homeostatic adaptation to stressful

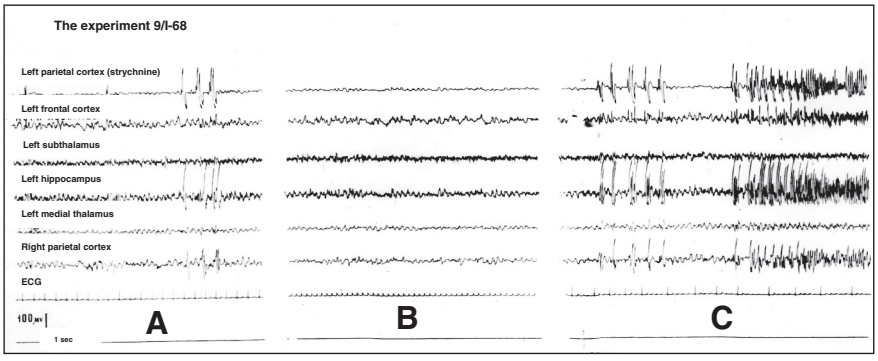

Fig. 1. Impact of asphyxia on epileptiform activity. A) Prior to asphyxia; strychnine spikes in the epileptogenic focus, hippocampus, and the symmetric zone in the cortex of the other hemisphere; B) 30 s after the beginning of asphyxia; the elimination of strychnine spikes; C) 2 min after the end of asphyxia; increase in spikes and their frequency; the beginning of the seizure.

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