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THE SAFFRON EFFECTS ON THE DYNAMICS OF EXPERIMENTAL EPILEPSY

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Abstract. The scientific work is devoted to the influence of saffron extract on the dynamics of the formation of experimental epilepsy. The dynamics of amygdala-like epileptogenesis created by penicillin sodium salt has been studied, with the registration of electrical activity in the structures of the visual system.

The exsperiments was carried out on rabbits. The electrical activity of the structures of the visual system was registered by electroencephalography. Recorded electrical activity of the brain in the central and subcortical structures of the visual analyzer (visual cortex, colliculus superior, lateral geniculata body) normally, as well as against the background of the development of epilepsy. As a result of the research, it was found that the introduction of penicillin solution into the amygdala of animals led to the development of prolonged convulsive activity. To determine the effect of saffron extract on the dynamics of amygdala epileptogenesis, a comparative analysis of the dynamics of epilepsy in control and saffron-treated animals was performed based on several parameters. The results obtained give reason to speak about the presence of the effect of the clarifying effect of saffron on the dynamics of epileptogenesis.

Keywords: *Epilepsy, amiqdala, EEG, visual cortex, retina, lateral geniculate body, superior colliculus*.

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1. Introduction

Despite the successes achieved in studying the problem of epilepsy, interest in it does not weaken, but, on the contrary, increases. Based on the data obtained as a result of statistical studies, currently, about 50-65 million people worldwide suffer from this disease (Singh *et al*., 2016). The study of epileptogenesis in new aspects is directly related to the creation and use of various medical technologies and new achievements in fundamental sciences. Despite the accumulation of a sufficient amount of scientific data, to date, the etiology of this disease has not yet been fully determined and is one of the problems requiring study by neurophysiologists.

There are various taxonomies of epilepsy in the literature, but the most interesting is its taxonomy, created in connection with localization in the brain. So, the most common is its temporal form, in which the pathological focus develops in the temporal structures

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belonging to the limbic system of the brain (hippocampus, amygdala). These structures are involved in the regulation of various behavioral and cognitive processes; in pathological conditions, especially when convulsive activity occurs, the regulation of the mechanisms of functioning of this system is disrupted. Temporal lobe epilepsy is associated with specific memory problems: verbal memory deficiency in left temporal lobe epilepsy and visual memory deficiency in right temporal lobe epilepsy.

Epilepsy is accompanied by a continuing deterioration of cognitive functions. It is believed that this is due to the accumulation of minor neurodegenerative effects of toxic neurochemical agents, metabolic disorders that deplete the compensatory ability of brain functions during epileptic seizures that have been occurring for decades. Impaired long-term memory negatively affects learning, ability to function and social status and is therefore important for people with epilepsy (Sloane *et al*., 2020)

It is known that correlations of cognitive functions of the brain are rhythmic processes in various frequency ranges. During epileptogenesis, this rhythmic activity of the brain is disrupted. Thus, the study of disorders of rhythmic activity in the brain is of great interest and it can be used in the development of approaches to the treatment of temporal lobe epilepsy.

According to the literature, patients with amygdala epilepsy have dysfunctions of the structures of the visual analyzer. Therefore, the study of the neurophysiological mechanisms of epilepsy is very relevant and important, which allows us not only to understand the pathogenesis of this disease but also makes an important contribution to the study of the fundamental mechanisms of the brain (Gaetano *et al*., 2021). As technologies used to diagnose epilepsy improve, brain abnormalities are increasingly being detected even in people who have not yet had epilepsy in early adulthood. It takes a lot of time and patience to answer the basic questions of epilepsy research, such as understanding how brain damage causes epilepsy or developing new treatments. The scientific results obtained in the laboratory are now increasingly being applied to patients with neurological disorders. The study of electrical or magnetic brain waves during clinical experimental epileptogenesis (neurophysiology), localization of brain function, and the possibility of its interaction between neuropsychological studies and neurodegenerative processes to understand how seizures are disrupted. Despite the accumulation of sufficient scientific data, to date, the etiology of this disease has not yet been fully determined and is among the problems requiring study by neurophysiologists.

Currently, the most convenient method for understanding the mechanisms of epileptogenesis and studying the functioning of the brain as a whole and epileptic processes is the use of electroencephalogram (EEG) analysis. The EEG allows you to evaluate brain activity in various parts of the brain and allows you to obtain certain information about epileptic activity.

How to determine the dynamics of epilepsy? How to prevent it, determine the methods of treatment and how easy and fast to do it? To investigate these questions, scientists refer to many different animal models of epilepsy. That is, they study laboratory animals with accidental or created seizures to understand the main manifestation of epilepsy in humans and the causes of this manifestation. During epileptic seizures, opinions are expressed that there are interactions between many areas of the brain, as well as between the visual structures of these areas (https://www.simplypsychology.org/amygdala.html).

In the treatment of epilepsy, as well as several neurodegenerative diseases, preference is given to the use of natural antioxidants. One of these plants is saffron. In experiments on rats, the antiepileptic effects of crocin, an ingredient in saffron, have been studied by several scientists. The results demonstrated that the stages of seizure and cumulative afterglow duration were significantly depressed by crocin (20 and 50 mg/kg) during hippocampal rapid kindling acquisition (Kai *et al.*, 2022; Sucher *et al.*, 2015; Tamaddonfard *et al.*, 2022).

In this aspect, the study of the effect of saffron on the dynamics of epileptic seizures in rabbits was the main goal of our research.

2. Objects and research methodogy

In experimental explores, the following objects were used adult Chinchilla rabbits weighing 2.5-3 kg. To rabbits kept in vivarium conditions, we disinfected the wound, clearing the skull of hair, skin and flesh and then placed nichrome electrodes by the coordinates of the stereotactic atlas into the brain structures we studied. Considering the size of the brain structures, the diameter of the electrodes used was 0.5 mm for cortical structures and 0.1-0.15 mm for structures under the cerebral cortex. EEG recording and analysis were performed using the Neuron Spectrum 5 program.

An experimental model of epilepsy was created by injecting penicillin sodium salt from a cannula implanted in the basolateral amygdala (BLA). To do this, 300 units of the sodium salt of penicillin were dissolved in 10 µl of distilled water. One unit of penicillin corresponds to the specific activity of 0.6 micrograms of sodium penicillin. Thus, 1 mg of penicillin sodium is 1,667 units of penicillin. Some reference books use an approximate translation of 1000 units per mg (https://www.sciencedirect.com/science/article/abs/pii/B9780323244855004435). Experimental animals took saffron solution dissolved in water for 3 months.

3. Results and discussion

Of the more than 10 nuclei that make up the amygdala, the basolateral nucleus (BLA) plays the most important role in the initiation and spread of a seizure. It is known that correlations of cognitive functions of the brain are rhythmic processes in various frequency ranges. During epileptogenesis, this rhythmic activity of the brain is disrupted. Thus, the study of disorders of rhythmic activity in the brain is of great interest and can be used in the development of approaches to the treatment of temporal lobe epilepsy (Aliyev *et al.*, 2018)

The experimental studies were carried out in several stages. First, background activity in the studied structures was recorded in animals. It is known from the results obtained that a high degree of correlation between the activity of the studied structures in healthy animals indicates their close functional relationships, which is confirmed by the available data on the presence of anatomical connections between them. Activity in all analyzed structures was recorded in the delta, teta, alpha and beta ranges, which is probably due to their strong connections with each other (Figure 1).

At a later stage of research, penicillin is injected into the amygdala from a cannula implanted in a BLA. The EEG was recorded from nichrome electrodes placed in the animal's brain, placed in a soundproof and light-proof chamber. As a result of the research, it was found that the introduction of penicillin solution into the amygdala of animals led to the development of prolonged convulsive activity. In control animals, single epileptiform secretions appear after 1 minute and in experimental animals -after 5 minutes on the EEG of all studied structures. Epileptiform activity affects all brain structures (Figure 2).

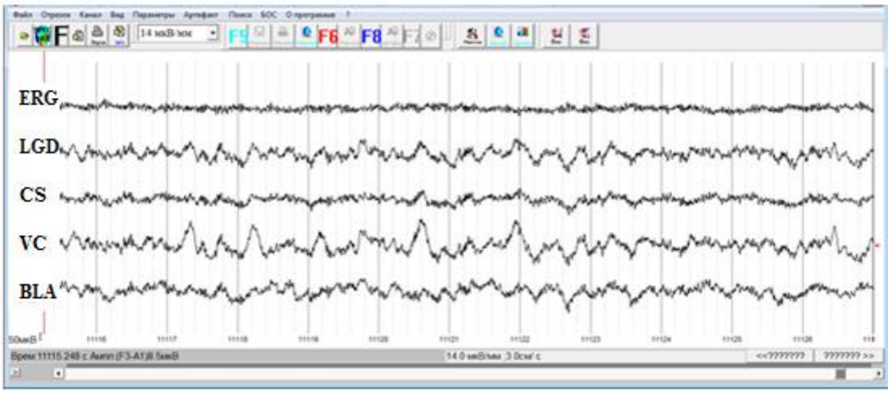
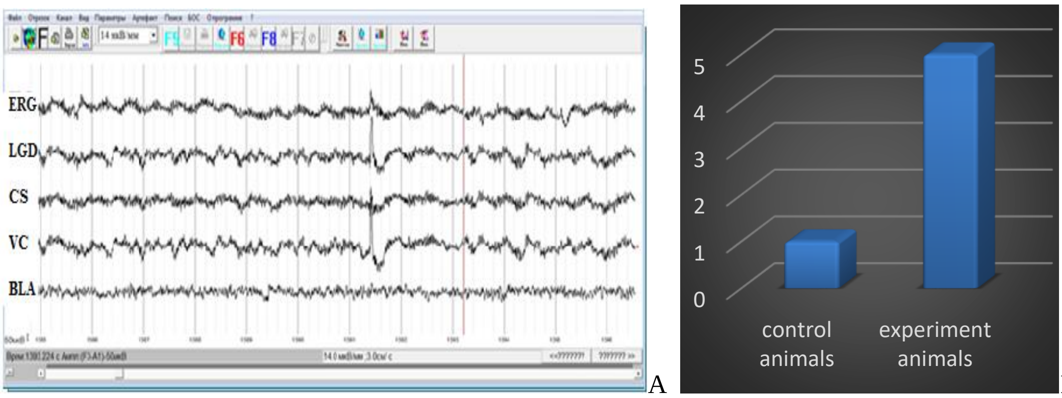


Figure 1. Background activity in visual analyzer structures and amygdala

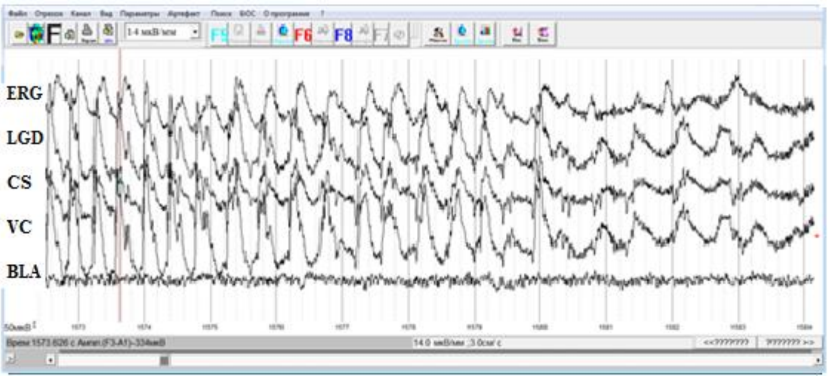


A B

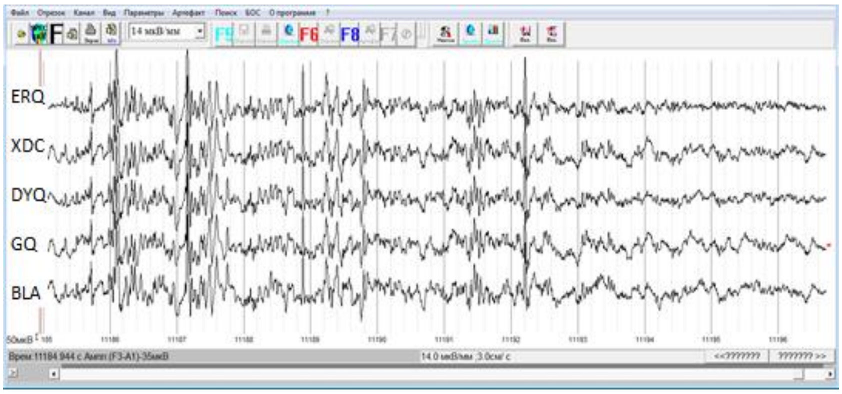
Figure 2. Formation of the first peaks after penicillin injection (min)

During experimental epileptogenesis, changes in the activity of brain structures begin to synchronize. The activity that begins in the amygdala begins to spread to the visual structures and retina. Penicillin caused the appearance of generalized peaks in all structures, accompanied by massive myoclonic tremors. There were myoclonic seizures, which sometimes quickly developed into an epileptic seizure (Figure 3 A, B).

Synchronous waves begin to appear in control animals after 10 minutes after the introduction of penicillin and in subjects - after 20 minutes (Figure 4, A).

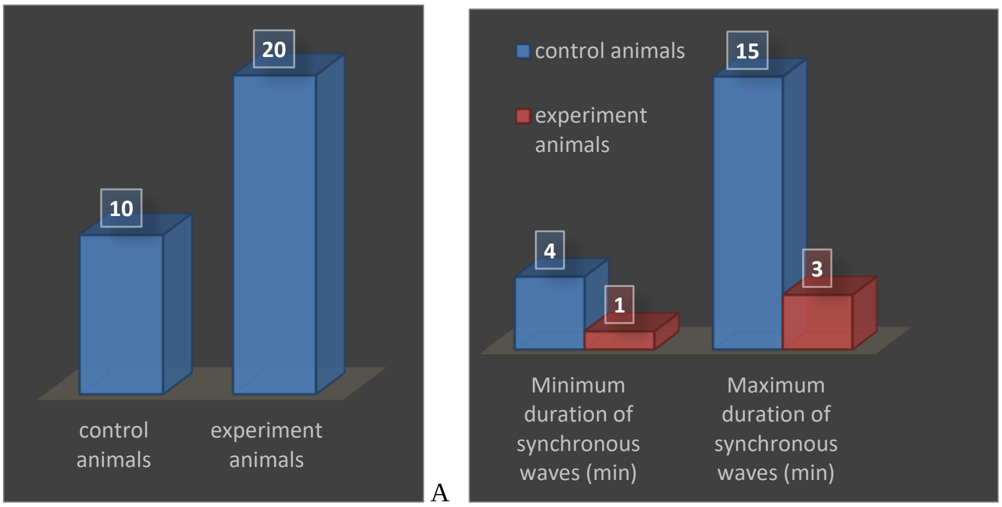


A



B

Figure 3. Epileptic activity-synchronous waves (A, B)



B

Figure 4. Formation and duration of synchronous waves after penicillin injection (min) (A, B)

If in control animals the activity on the EEG lasted 3-4 hours, then in experimental animals this period lasted 2-2.5 hours. Within an hour, convulsions reach their peak, after which a certain dynamics of epileptiform waves is formed. So, over time, the attacks begin to alternate (Figure 5).

At this time, we also recorded evoked potentials (EP) from the structures under study and an electroretinogram (ERG) through the retinas. During this time, reactions to light are formed in both the retina and the amygdala. This fact confirms that the efferent pathway continues from the retina to the amygdala. Also, the potentials generated in the structures of the visual analyzer under study, the configuration of the responses we received corresponded to these structures.

In control animals, the number of alternating epileptic seizures begins to decrease and activity ceases 2.5 hours after injection of the sodium salt of penicillin into the amygdala and in experimental animals - after 1 hour.

During epileptogenesis, spontaneous reactions are generated in the amygdala that spread to the retina. These responses evoked in the amygdala resembled EP, although no external stimulus was applied (Figure 6).

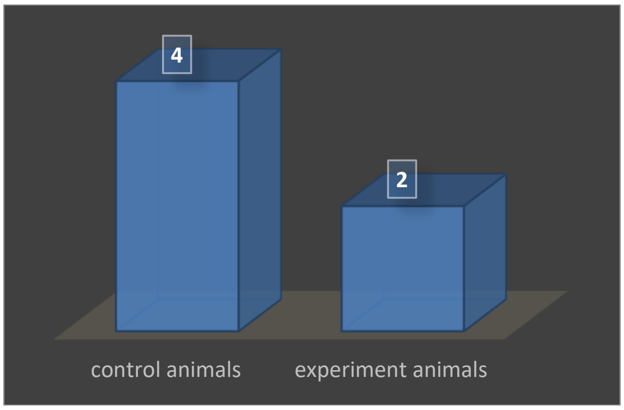


Figure 5. Epilepsy duration (hours)

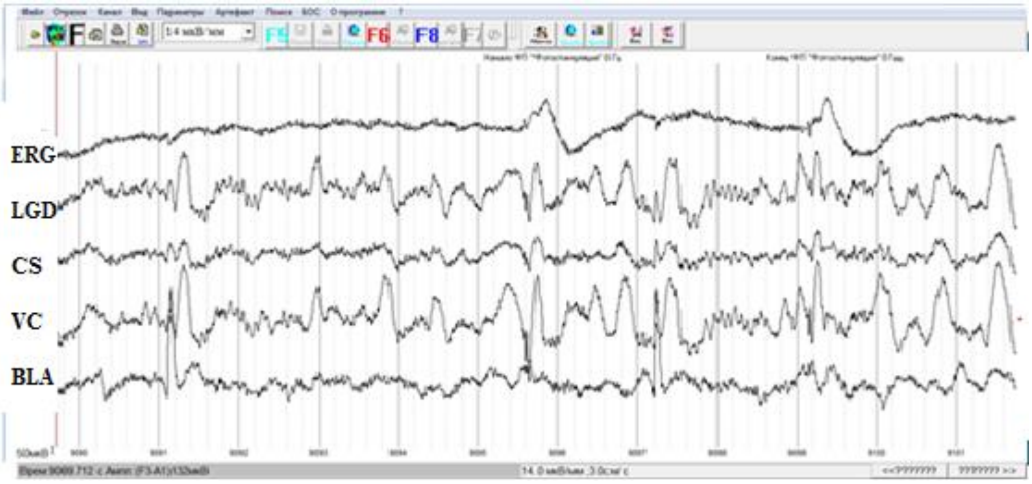


Figure 6. Spontaneous activity in the amygdala

Registration of intracerebral EEG from several brain structures makes it possible to study the temporal sequence of involvement of the studied structures in the pathological process. EEG analysis showed that epileptic activity first occurs in the amygdala, then in the visual cortex, superior colliculus and external abduction of the geniculate body and also affects retinal activity. Most likely, the manifestations of such a sequence of activity distribution between structures are associated with the presence of unilateral and bilateral morphofunctional connections between these structures.

The experimental material obtained suggests that saffron has a moderating effect on the dynamics of epilepsy. The decrease in the duration of epilepsy in experimental animals compared to control animals, as well as the fact that the initial peaks and synchronous waves appear later than in control animals and quickly disappear, give reason to talk about this idea.

4. Conclusion

The duration of experimental epilepsy caused by the injection of penicillin sodium salt (300 units + 10 μl) into the amygdala in experimental animals was 2 times shorter than in control animals. In control animals, the first peaks and synchronous impulses occurred earlier and their duration was longer in control animals. Registration of clonic convulsions of the body and peripheral muscles, that is, epileptic seizures, is observed a long time after the first activity in the brain (30-40 min.).

Thus, the results obtained provide evidence of a direct connection between the basolateral amygdala and the primary area of the visual cortex (field 17). This is evidenced by the appearance of epileptic discharges (ictal and interictal). First, epileptic spikes appeared in the visual cortex, then similar spikes (ictal and interictal) were observed in the retina.

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