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BRAIN DAMAGE LED TO A DECREASE OF NITRIC OXIDE CONTENT IN THE HIPPOCAMPUS OF RATS: INVESTIGATION BY EPR SPECTROSCOPY

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Abstract

Direct measurements of the content of nitric oxide (NO) by the method of spectroscopy of electron paramagnetic resonance were performed. It was found that NO production in hippocampus tissues decreased to 46% after 5 h of ischemic stroke as compared to the control group and remained at the same level after 72 h. Following the hemorrhagic stroke, the level of NO production in the hippocampus decreased to 32% after 5 h of hemorrhagic stroke of the control level. After 72 hours of hemorrhagic stroke NO production was higher than after 5 h and amounted to 48% of the level of intact animals.

Keywords: nitric oxide, ischemic brain stroke, hemorrhagic brain stroke, hippocampus, electron paramagnetic resonance

Introduction

Tissue functioning depends on a number of factors, such as sufficient amount of oxygen delivered through the bloodstream to maintain the oxidative processes. Long-term oxygen deficiency leads to brain hypoxia, which, under certain conditions, triggers tissue ischemia: inadequate oxygen supply to tissues disrupts the normal process of biological oxidation. The above-mentioned is an important component of the pathogenesis in many diseases. Notably, the failure of cerebral blood flow decreases the oxygen supply to the brain and leads to brain ischemia, thereby causing completed ischemic stroke followed by a damage of the brain tissue and its functions [1].

Nitric oxide (NO) is an important signaling molecule for the cardiovascular and nervous systems [2–4]. NO typically acts physiologically by binding to iron (Fe^{2+}) of heme or by S-nitros(yl)ation of proteins [2, 5]. It has been shown that NO can play both protective and destructive roles in the occurrence and development of ischemic and hemorrhagic strokes – different forms of NO-synthases are involved in these processes [3, 4, 6].

Taking into account that NO participates in the development of various pathological conditions of the body, theoretical and practical studying of the mechanisms and methods of stroke correction is highly relevant. Based on the literature data and the results of our previous studies in this area, we performed a comparative research on the NO production using the method of electron paramagnetic resonance (EPR) spectroscopy in the hippocampus of rats after modeling both ischemic and hemorrhagic strokes.

Materials and Methods

Ischemic and hemorrhagic strokes were modeled on white outbred rats kept under standard vivarium conditions (12/12-light/dark cycle, air temperature of 22 °C, and stable supply and exhaust ventilation) with free access to water and food (ad libitum) and a diet in accordance with the standards for keeping laboratory animals. In the hemorrhagic stroke modeling experiments, the heads of the anesthetized animals ($n = 34$) were secured to a stereotaxic apparatus and 40 mL of the autologous blood was injected into the hippocampal CA1 region [7]. For the ischemic stroke modeling, the animals ($n = 27$) were subjected to a 5-min hypoxia (conditional rise to a height of 4500 m above sea level) [8]. The hippocampus sampling was carried out 5, 24, and 72 h following the hemorrhagic and ischemic stroke modeling. The tissue samples from control animals ($n = 14$) were extracted in a similar way. The weight of the samples was 100 mg. All extracted tissue samples were immediately frozen in liquid nitrogen. The spin trap complex with NO in this state was well preserved, and the signal from the complex did not change for at least a month. The rats of all experimental series were anesthetized by intraperitoneal injection of a mixture of ketamine-chloralose-acepromazine (55.6, 5.5, and 1.1 mg/kg, respectively) on the day of the experiment.

The method of EPR spectroscopy with the technique of spin traps, which allows the detection of NO in low concentrations, was used for quantitative determination of NO in the tissues of the hippocampus [3, 5]. The complex of Fe^{2+} with diethyldithiocarbamate was used as a spin trap. This complex of spin traps with NO ($(DETC)_2$–Fe^{2+}–NO) was characterized by easily recognizable EPR spectrum at $g = 2.038$ and triplet hyperfine structure. The components of spin traps for NO (DETC–Na, $FeSO_4$, and sodium citrate) were injected 30 min before the extraction of the tissues. The detailed procedure and methods of the experiment were described earlier [9]. $(DETC)_2$–Fe^{2+}–NO spectra were recorded with a ER 200 SRC Bruker spectrometer operating at the X-band frequency. The amplitude of the EPR spectra was always normalized to the weight of the sample and to the amplitude of the EPR signal of the reference sample [3].

The experimental results were statistically processed and represented as mean ± SEM. Comparative analysis of the two groups was performed with the help of the unpaired Student's *t*-test and non-parametric Mann–Whitney test. The SigmaStat32 statistics software was used. The obtained values were considered statistically significant at $p < 0.05$.

Results

The results obtained during the experiments were represented as the spectra of hippocampus tissues of the intact rats and the rats used in the stroke modeling. The EPR spectra of the hippocampus in rats of the control group (1) and 5 h after the ischemic stroke (2) are shown in Fig. 1. The typical triplet signal bound to $(DETC)_2$–Fe^{2+}–NO at g=2.038 was observed on all spectra [3, 5]. The signal of the $(DETC)_2$–Cu complex was present in the same area. The relative change in the number of the NO-containing complexes was evaluated based on the integrated signal intensity of the spin trap, $(DETC)_2$–Fe^{2+}–NO. The $(DETC)_2$–Fe^{2+}–NO signal intensity after the stroke modeling decreased.

The signal intensity of $(DETC)_2$–Fe^{2+}–NO in the hippocampus spectra decreased from 100% in the control group to 46% in rats 5 h after the ischemic stroke modeling (Fig. 2). At the same time, the intensity of NO production after the hemorrhagic stroke modeling decreased to 32% as compared to the control group (Fig. 3). The level of NO production in the hippocampus did not change in 72 h after the ischemic stroke modeling and amounted to 45% of the level of intact animals. In the case of hemorrhagic stroke, the level of NO production in the hippocampus was higher than after 5 h and amounted to 48% of the level of intact animals. Therefore, the level of NO production stayed almost the same 72 h after the ischemic and hemorrhagic stroke (Fig. 2, 3).

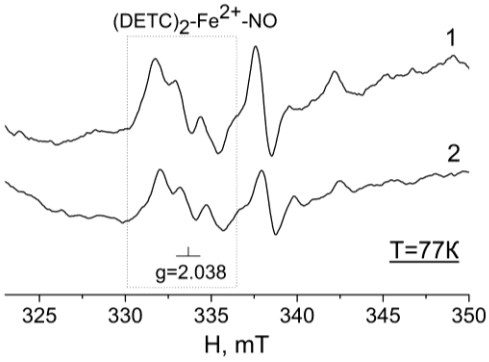

Fig. 1. EPR spectra of hippocampus in healthy rat (1) and rat 5 h after the ischemic stroke (2). Temperature is 77 K. Solid line is the EPR signal; dotted line is the received signal from $(DETC)_2$–Fe^{2+}–NO. The rats were injected with (DETC)–Fe^{2+} – citrate. g = 2.038

Discussion

The role of NO in ischemia development has attracted the attention of researchers for a long time. Nowadays, brain ischemia and subsequent stroke are associated with cerebral blood flow disorders and disrupted blood supply regulation in the brain tissues by the NO system. Some researchers believe that an increase in the NO content can be observed during the development of stroke. There are evidences of an increased enzyme activity of NO-synthases (NOS) under hypoxia [10]. Thus, it was shown by measuring the NOS activity that the activity of the neuronal NOS increased in 10 min after the beginning of brain ischemia and reached the maximum value after 3 h [11], and the expression of iNOS started between 24 and 48 h after the ischemia [12]. However, the results obtained in a number of studies with the models of cerebral ischemia showed

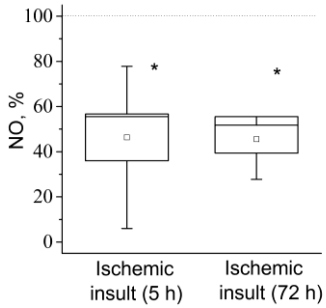

Fig. 2. Changes of the NO content in the hippocampus of rats after 5 (Ischemic insult, 5 h) and 72 (Ischemic insult, 72 h) h of the ischemic stroke relative to healthy rats (dashed line – 100%). Two-Way ANOVA and independent *t*-test. The Y-axis is the average integral intensity of the signal (⌶ – min-max, ☐ – mean, ▭ – SEM and median

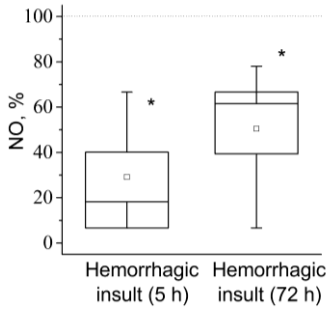

Fig. 3. Changes of the NO content in the hippocampus of rats after 5 (Hemorrhagic insult, 5 h) and 72 (Hemorrhagic insult, 72 h) h of the hemorrhagic stroke relative to healthy rats (dashed line – 100%). Two-Way ANOVA and independent *t*-test. The Y-axis is the average integral intensity of the signal. (⌶ – min-max, ☐ – mean, ▭ – SEM and median

a decrease in the level of NO in the ischemic part of the left hemisphere of rats after the modeling of ischemic stroke [3]. In the EPR measurements of the dynamics of NO production after the spinal cord contusion, a general decrease (in the spinal cord, liver, heart, blood, and tissues of rats) of NO production in the acute period was revealed [13]. On the contrary, with the point of view that NO plays a neurotoxic role in the development of ischemia, it was shown that the use of NO-synthase inhibitors, L-NNA and L-NAME, did not reduce the value (volume) of infarction in the model of focal brain ischemia in rats [14], but intensified focal ischemic stroke [15].

Through the main contribution of NO produced by nNOS and iNOS, the dynamics of NO maintenance in the brain tissues during the occurrence and in the course of brain ischemia remains unclear [2]. It is impossible to determine the exact role of NO in changes of the functional activity of cells under hypoxia. Probably, the action of NO is not limited only by cytotoxicity or by the protective effect, but it is determined by the ratio of the stress factors and the factors of cell survival, which directs NO in a particular way.

Hypoxia can affect NO production and its concentration in tissues and NOS expression by several mechanisms. At the early stages, the limitation of NO production causes the deficiency of oxygen as a NOS substrate. The hypoxia slows down the NOS-

dependent synthesis of NO from L-arginine. It is known that deep hypoxia (0.1 to 0.2% O_2) reduces the production of NO in the cell culture as a result of inhibition of all three isoforms of NOS by 60–80% [16, 17]. Under heavy hypoxia, this compensatory mechanism does not work, and NO deficiency is developed [18]. Less seriously hypoxia (4.8% O_2) causes only moderate inhibition of NO synthesis, and this effect of hypoxia can be compensated by increasing the Ca^{2+} influx into cells and activating Ca^{2+}/calmodulin-dependent eNOS and nNOS.

According to the results of our measurements, the decrease in NO production in the hippocampus in 5 h after hemorrhagic stroke was more pronounced than in the model of ischemic stroke. Possibly, in the case of hemorrhagic stroke simulation, when the autologous blood was injected directly into the hippocampus area, it led to a stronger effect on the system of NO production in the hippocampus than in the modeling of ischemic stroke, in which the effect of hypoxia was common. The general hypoxia of the brain probably caused more shifts in new areas of the brain because of their greater sensitivity to hypoxia, whereas the hippocampus, as an older phylogenetic structure, less suffers from hypoxia. On the third day of hemorrhagic stroke, NO production was somewhat restored, whereas in the model of ischemic stroke it did not change.

Obviously, the changes in the NO system during stroke depend on the expression of the hypoxic state. Moderate hypoxia leads to activation of the NO cycle, which is the basis of compensatory-adaptive changes in response to hypoxia. This view was confirmed by our previous studies of NO production after spinal cord injury. The decrease of NO production in the acute period changed by increasing up to three times on average during two weeks after the injury. This activation of the NO system, possibly, indicated the development of compensatory rearrangements in the conditions of brain tissue hypoxia, since the use of NO-synthase blocker in spinal cord injury deteriorated the condition of the neuromotor apparatus [13].

In this work, it was demonstrated that the method of direct measurement by EPR spectroscopy enables to obtain data of the dynamics of NO production in the nervous tissue during the development of brain ischemia. In our opinion, this approach is more promising than the methods focused on determining the role of NO in ischemia by the activity of NO-synthases, which do not take into account the reductase pathway of NO formation, as well as the use of NO from other depo, primarily from blood vessels [19]. The analysis of published data and the results of our experiments show that heterogeneous shifts occur during NO production, both in time and in different types and/or severity of brain hypoxia. Therefore, in order to manipulate the NO system for stroke treatment, several strategies should be applied for NO production regulation: the use of donors or NOS blockers should be carried out based on the time of the change in the NO level in the brain induced by ischemia.

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Ишемия мозга приводит к снижению содержания оксида азота в гиппокампе крыс: исследование методом ЭПР спектроскопии

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Аннотация

На основе прямых измерений содержания оксида азота (NO) методом спектроскопии электронного парамагнитного резонанса показано, что после ишемического инсульта синтез NO в тканях гиппокампа уменьшился до 46% через 5 ч по сравнению с контрольной группой и остался на этом же уровне через 72 ч. После геморрагического инсульта синтез NO в гиппокампе снизился до 32% через 5 ч от уровня контроля, а через 72 ч данный показатель был выше показателя, наблюдаемого через 5 ч, и составил 48% от уровня NO интактных животных, то есть оказался практически аналогичен результату измерений синтеза NO при ишемическом инсульте.

Ключевые слова: оксид азота, ишемический инсульт, геморрагический инсульт, гиппокамп, электронный парамагнитный резонанс

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