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Mini Review

Studying the State of the Endothelium Under Conditions of Using Pathway Modulators L-Arginine-no and Against the Background of the Introduction of Omega-3 Polyunsaturated Fatty Acids

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Abstract

The effects of L-NAME and L-arginine have been shown in experiments using biochemical methods and functional tests, however, no quantitative morphological study of the effects of combined administration of L-NAME and L-arginine in conditions of subtotal cerebral ischemia has been conducted. Thus, with subtotal cerebral ischemia in rats, platelet aggregation is activated and stable metabolites [NOx] in the blood are increased, which may be caused by ischemic brain damage. There was no effect of L-NAME administration on platelet aggregation in rats with subtotal cerebral ischemia. There was no effect of L-NAME administration on platelet aggregation in rats with subtotal cerebral ischemia. The administration of Omega-3 fatty acids had a corrective effect in the group of rats with SCI, SCI + L-arginine + Omega-3, and less insignificant in the group of SCI + L-NAME + L-arginine + Omega-3, which is reflected by a decrease in platelet aggregation and [NOx] in this study group. When L-NAME and Omega-3 fatty acids were administered to rats with SCI, the corrective effect of Omega-3 was not observed.

Keywords: l-arginine, omega-3 polyunsaturated fatty acids, cerebral ischemia

Introduction

The effect of ischemic brain damage on the development of endothelial dysfunction is currently insufficiently investigated. An important role in the pathogenesis of ischemic brain damage is played by a violation of primary hemostasis. In the literature, there is a small number of works on a comprehensive study of endothelial function in ischemic conditions, as well as on the evaluation of the interaction of the endothelium and the hemostasis system in cerebral ischemia, and determined the aims and objectives of the work performed [2]. Ischemic damage to brain tissue activates the release of tissue thromboplastin into the blood, which triggers a cascade of secondary hemostasis, which leads to hypercoagulation. In the ischemic area, there is a decrease in prostacyclin synthesis in the vascular endothelium and an increase in the production of thromboxane A2, which leads to the activation of thrombogenic properties of the vascular wall [5].

Based on the fact that more often ischemic lesions occur in people suffering from atherosclerosis and hypertension, it is important to study the effect of endothelial dysfunction on the nature of brain damage during its ischemia, as well as the development of corrective measures. To do this, it is important to assess the nature of morphofunctional changes, which will be further used as a comparison group when studying these changes under the influence of endothelial dysfunction [2].

One of the promising amino acids-neuroprotectors is L-arginine. This amino acid has antihypoxic, analgesic, anti-inflammatory, anti-atherogenic and antiplatelet properties. Most of the effects caused by L-arginine are related to its ability to increase the formation of NO, acting as a source for its formation [3]. It has been shown that the use of L-arginine reduces the size of infarction, reduces vascular tone and causes a hypotensive effect, prevents and corrects ischemic and reperfusion injuries to the brain and other organs [4].

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The important role of ω-3 polyunsaturated fatty acids (Omega-3 PUFAs) is to ensure the functioning of cell membranes, transmembrane ion channels and the regulation of physiological processes through the synthesis of lipid mediators, which, lining up in the phospholipid layer of cell membranes, affect their fluidity. Omega-3 PUFAs are involved in the implementation of the main functions of neurons, such as the transmission of impulses and the work of receptors [7].

Omega-3 PUFAs exercise control over the work of the immune and reproductive systems, being precursors of the biosynthesis of prostaglandins, leukotrienes and thromboxanes and other cytokines [8].

Methods of studying the state of the endothelium

The state of the endothelium was studied by the number of circulating endothelial cells, indicators of stable metabolites of nitric oxide, aggregation properties of platelets [2].

The level of stable NO metabolites – [NO_x] was determined by the concentration of nitrites and nitrates in blood plasma using cadmium and Griess reagent [6].

Platelet aggregation was studied using the platelet aggregation analyzer AP 2110. Blood for the study was taken from the common carotid artery with a needle by gravity into polystyrene tubes. A 3.8% sodium citrate solution added to the blood in a ratio of 1:9 was used as an anticoagulant. To obtain platelet-rich plasma, the blood was centrifuged for 10 min at 1000 rpm. To obtain platelet-free plasma, the blood was centrifuged for 20 minutes at 3000 rpm. This plasma was used to calibrate the optical density scale of the device [1]. ADP at a concentration of $1{,}5x10^{-6}$M was used as an aggregation inducer. Incubation was used to study platelet aggregation. The degree of reversible aggregation was determined – the maximum level of light transmission of blood plasma after the introduction of an aggregation inductor, aggregation time – the time corresponding to the maximum degree of aggregation, aggregation rate – the change in plasma light transmission after the introduction of an aggregation inductor, measured over a 30 second interval from the reference point [3].

The degree of morphological damage to the endothelium of blood vessels was studied by the number of circulating endothelial cells (CEC) in 1 ml of blood plasma by microscopy according to Sinzinger H. 1988 in a modification of 100 µl [1].

Endothelial state

Study of changes in stable nitric oxide metabolites

In the study of stable metabolites of [NO_x] in rats with CCI, an increase in [NO_x] was found to be 3 times higher than in the control group, $p<0.001$ (Table 1), which may be associated with activation of neuronal NO synthase [6].

Groups	Control	SCI	SCI+ Omega-3	SCI+L-NAME+ Omega-3	SCI+L-NAME+L-arginine+Omega-3
[NO_x], µmol/l	30,2 (28,5; 35,9)	88,4* (81,5; 108,3)	34,4# (21,4; 45,9)	46,2 *# (35,3; 59,8)	44,1# (35,6; 62,8)

Notes
* – p<0,05 – relative to the values in the "control" group
# – p<0,05 – relative to the values in the "SCI" group
SCI – subtotal cerebral ischemia
L-NAME – N□-nitro-L-arginine
Omega-3 – Omega-3 PUFAs

Table 1: The content of stable metabolites NO [NO_x] in the blood of rats of the control group, with SCI, SCI+ Omega-3 PUFAs, SCI+L-NAME+ Omega-3 PUFAs and SCI+L-NAME+L-arginine+Omega-3, Me (LQ; UQ)

In the SCI+Omega-3 PUFAs group, there was a decrease in the [NO_x] by 48.7%, p=0,003, relative to the SCI group. The administration of L-NAME and Omega-3 PUFAs to rats with SCI did not lead to a statistically significant difference in the [NO_x] in this group of rats relative to the group «SCI + L-NAME».

Study of changes in platelet aggregation properties.

After ligation of both carotid arteries within an hour, the rats showed an increase in the degree of platelet aggregation by 67.6%, p=0,009, and the rate of platelet aggregation in the first 30 seconds by 123.5%, p=0,009 (Table 2). When Omega-3 PUFAs were administered to rats with SCI, there was a decrease in the degree of platelet aggregation by 66.4%, p<0,001, aggregation rate in 30 seconds by 41,5%, p<0,001 and an increase in aggregation time by 5,3%, p=0,02, compared with the values of the group of rats with SCI. However, the introduction of Omega-3 PUFAs to the group of rats "SCI + L-NAME" did not lead to a decrease in the studied parameters [7].

Indicator	Control	SCI	SCI+ Omega-3	SCI+L-NAME+ Omega-3	SCI+L-NAME+L-arginine+Omega-3
Degree of aggregation, %	39,8 (38,2; 53,4)	66,7* (60; 69,5)	44, 3# (41,2; 48,6)	62,4* (57,8; 75,4)	53, 4#,+ (45,4; 67,2)
Aggregation time, seconds	380,0 (360,2; 411,0)	359,4 (293,2; 422,1)	375,0# (364,5; 397,0)	353,1 (306,9; 378,2)	370,0#,+ (342,5; 402,0)
Aggregation rate (in 30 seconds), %	20,4 (13,0; 31,4)	45,6* (35,6; 49,2)	26,6# (20,1; 36,2)	55,1* (49,7; 64,7)	36,2#,+ (24,1; 44,2)

Notes
* – p<0,05 – relative to the values in the "control" group, # – p<0,05 – relative to the values in the "SCI" group
SCI – subtotal cerebral ischemia, L-NAME – N□-nitro-L-arginine, Omega-3 – Omega-3 PUFAs

Table 2: Platelet aggregation of control group rats, with SCI, SCI+ Omega-3 PUFAs, SCI+L-NAME+ Omega-3 PUFAs and SCI+L-NAME+L-arginine+Omega-3, Me (LQ; UQ)

Thus, with subtotal cerebral ischemia in rats, platelet aggregation is activated and stable metabolites [NO_x] in the blood are increased, which may be caused by ischemic brain damage. There was no effect of L-NAME administration on platelet aggregation in rats with subtotal cerebral ischemia.

There was no effect of L-NAME administration on platelet aggregation in rats with subtotal cerebral ischemia. The administration of Omega-3 fatty acids had a corrective effect in the group of rats with SCI, SCI + L-arginine + Omega-3, and less insignificant in the group of SCI + L-NAME + L-arginine + Omega-3, which is reflected by a decrease in platelet aggregation and [NO_x] in this study group. When L-NAME and Omega-3 fatty acids were administered to rats with SCI, the corrective effect of Omega-3 was not observed.

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