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Mini Review

Comparative Characterisation of Brain Amino Acid Pool Changes During Complete and Partial Ischemia in Mongrel white Rats

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Abstract

The relevance of the topic is due to the leading positions of cerebrovascular pathology in the structure of morbidity and mortality both in the world and in the Republic of Belarus. Thus, according to statistical data, the incidence of cerebrovascular pathology in the Republic of Belarus in 2020 was 3154 per 100,000 people, and mortality - 753.9 per 100,000 people. Cerebrovascular diseases of ischaemic genesis tend to grow, rejuvenate, and are associated with a severe clinical course, high rates of disability and mortality.

Amino acids (AA) play an important role in the metabolism and functioning of the brain. This is not only due to the exclusive role of amino acids as sources of synthesis of a large number of biologically important compounds (proteins, mediators, lipids, bioactive amines). The revealed nonspecific and specific changes in the AA pool (AA markers of CI) can be used to detect both the fact of CI and to assess its severity. Their experimental study in brain structures is important for the development of neuroprotective therapy, the effectiveness of which can be assessed by changes in the content of AA markers.

Keywords: brain; amino acid; ischemia; rats

Introduction

The relevance of the topic is due to the leading positions of cerebrovascular pathology in the structure of morbidity and mortality both in the world and in the Republic of Belarus. Thus, according to statistical data, the incidence of cerebrovascular pathology in the Republic of Belarus in 2020 was 3154 per 100,000 people, and mortality - 753.9 per 100,000 people. Cerebrovascular diseases of ischaemic genesis tend to grow, rejuvenate, and are associated with a severe clinical course, high rates of disability and mortality [4-5]. Amino acids (AA) play an important role in the metabolism and functioning of the brain. This is not only due to the exclusive role of amino acids as sources of synthesis of a large number of biologically important compounds (proteins, mediators, lipids, bioactive amines). Amino acids and their derivatives participate in synaptic transmission as neurotransmitters and neuromodulators (glutamate, aspartate, glycine, GABA, taurine), and some AAs are involved in the formation of mediators of the nervous system: methionine - acetylcholine, DOPA, dopamine; tyrosine - catecholamines; serine and cysteine - taurine; tryptophan - serotonin; histidine - histamine; L-arginine - NO; glutamic acid – glutamate [1-13].

Role Of Omega-3 Polyunsaturated Fatty Acids in The Brain

A possible target of AFC in brain neurons is omega-3 polyunsaturated fatty acids (omega-3 PUFAs), which, being components of cell membranes, ensure their functioning, the operation of transmembrane ion channels, and participate in the regulation and realisation of the main functions of neurons - impulse transmission and receptors. It is known that brain neurons are electrically active cells, rich in ion channels, and therefore can be sensitive to the deficiency of omega-3 PUFAs [1].

Omega-3 PUFAs influence many biological processes of the body by exerting the following effects:

1) improve endothelial function, which leads to a decrease in peripheral vascular resistance due to improved endothelium-dependent and independent vasodilation, increased blood levels of nitric oxide and decreased levels of endothelin-1;
2) reduce susceptibility to thrombosis as a result of decreased platelet aggregation reactivity, suppression of monocyte adhesion to endothelium, decreased expression of adhesion molecules VCAM-1, TLAM-1, ICAM-1;
3) reduce the activity of chronic non-specific inflammation, which is manifested by a decrease in the blood content of tumour necrosis factor, interleukins-1 and -6, increase in the formation of anti-inflammatory eicosanoids;

4) contribute to an increase in ATP formation, decrease in oxygen consumption and calcium content, improve mitochondrial function;
5) increase the activity of calcium-magnesium ATPase, contribute to the inhibition of fast voltage-dependent sodium channels and L-type calcium channels.

Omega-3 PUFAs are competitors for arachidonic acid in binding the enzyme 5-lipoxygenase because omega-3 PUFAs replace arachidonic acid in membrane phospholipids, reducing eicosanoid production [8]. In addition to an anti-inflammatory effect based on interruption of the arachidonic acid cascade, omega -3 PUFAs exert anti-inflammatory effects through reducing the activity of nuclear factor kappa-B (NF-κB), a potent stimulator of pro-inflammatory cytokine production, including interleukin-6 and tumour necrosis factor alpha. In general, enrichment of cell membranes with omega-3 PUFAs impairs dimerisation and participation of toll-like receptor-4, which may contribute to anti-inflammatory effects by suppressing NF-κB activation. Thus, omega-3 PUFAs inhibit lipogenesis and increase the production of resolvins and protectins, small lipid molecules that suppress the inflammatory process [4].

In addition, the effects of omega-3 PUFAs include the ability to increase the secretion of adiponectin, an anti-inflammatory adipokine. Omega-3 PUFAs act as a modulator of the G-protein-coupled receptor and are also capable of and influence direct regulation of gene expression through nuclear receptors and transcription factors, which in turn are modulated by intracellular lipid-binding proteins that transport these fatty acids to the nuclei. This effect leads to increased synthesis of anti-inflammatory proteins associated with antioxidants [5].

Omega-3 PUFAs participate as coenzymes in the oxidative decarboxylation of pyruvic acid and alpha-keto acids, and are a necessary component in the recycling of major endogenous antioxidants such as vitamin E (alpha-tocopherol), vitamin C, glutathione, ubiquinone (coenzyme Q10) [2]. In addition, they have their own antioxidant and lipotropic activity due to activation of coenzyme A formation, transport of acetate and fatty acids from cytosol to mitochondrial matrix, acceleration of fatty acid oxidation, stabilisation of cell membranes. Omega-3 PUFA is a precursor of neuroprotectin, which in turn suppresses apoptosis and pro-inflammatory gene expression, promotes neurogenesis both in vitro and in vitro, and is involved in neuroprotection.

Methods of Studying the Brain Amino Acid Pool

Amino acids pool was studied in prepared homogenates of the studied brain structures of experimental animals isolated 1 hour after modelling ischemia [7]. For this purpose, a fragment of parietal cortex and hippocampus was taken after brain extraction and subsequently frozen in liquid nitrogen. Sample preparation for the study included homogenisation in a 10-fold volume of 0.2M perchloric acid, centrifugation for 15 min at 13000 g at 4°C followed by supernatant collection. Amino acids were analysed by reversed-phase chromatography with pre-column derivatisation with o-phthalic aldehyde and 3-mercaptopropionic acid in Na-borate buffer on an Agilent 1100 chromatograph [11]. To prevent systematic measurement error, brain samples from the compared control and experimental groups of animals were studied under identical conditions [3].

Statistical Processing. Quantitative continuous data were obtained as a result of the research. Since small samples were used in the experiment, which had non-normal distribution, the analysis was carried out by methods of nonparametric statistics using the licensed computer program Statistica 10.0 for Windows (StatSoft, Inc., USA). Data are presented as Me (LQ; UQ), where Me is the median, LQ is the value of the lower quartile, and UQ is the value of the upper quartile. Differences between groups were considered reliable at $p<0.05$ (Kruskell-Wallis test with Bonferoni correction). Parametric analysis of variance with a posteriori comparison of selected contrasts was used to determine the pool indices of amino acids and biogenic amines if the conditions of applicability (normality of samples and homogeneity of dispersions) were met; if the conditions of applicability were not met, non-parametric analysis of variance was used, followed by multiple contrasts test after Fisher transformation [10].

The studies of amino acid (AA) pool changes in the parietal lobe and hippocampus of the brain of rats with ischaemia of different severity (partial (PCI), subtotal (SCI), staged subtotal (SSCI) with different periods between ligations of both common carotid arteries, CCA (1 subgroup, pg - 7 days, 2 pg - 3 days, 3 pg - 1 day), total (TCI) revealed homotypic changes (increase in L-arginine content, as well as decrease in methionine in all models of CI, except for TCI) [6]. The presence of these changes may be a sign of the presence of cerebral ischaemia. Along with this, distinctive changes were noted, which can be interpreted as specific manifestations of CI of a certain degree of severity. In particular, only in PCI there was an increase in the content of glutamate, GABA and aspartate. The peculiarity of changes in PCI was an increase in the content of taurine and lysine and a decrease in the content of cysteate. Administration of omega-3 PUFAs at a dose of 5 g/kg body weight for a week to rats with PCI had no effect on the level of L-arginine, methionine, taurine and lysine, the changes of which occurred in PCI ($p>0.05$). The study of the amino acid pool in rats with SSIHM with intervals between ligations of CCA 1 day and 3 days did not reveal any specific changes and they were similar to those observed in SCI, except for an increase in the content of asparagine and alanine [9]. In SSIGM with an interval between ligations of both CCA of 7 days, the distinctive manifestations were an increase in the content of valine, leucine and tryptophan. In the most severe type of CI - TCI, an increase in the content of methionine, threonine and tryptophan was observed. Changes in the pool of amino acids in the parietal lobe and hippocampus were similar, except for the severity of some changes (in SSCI with an interval between ligations of both CCA of 7 days, there was a more significant decrease in the content of cysteate in cortex, and in PCI - in the level of methionine).

Thus, the study of the amino acid pool in the brain structures of rats with cerebral ischaemia of different severity revealed the presence of both homotypic changes (increased L-arginine content, decreased methionine content, except for TCI), indicating the presence of ischaemic damage in the brain [10]. Specific changes for CI of different severity have also been revealed, which can act as markers of ischaemic damage severity. Thus, for the most severe models of CI - TCI - an increase in methionine content is characteristic, and for milder models (TCI and SSCI with an interval between CCA ligations of 7 days) - a decrease in the content of amino acids with branched carbohydrate chain (valine and leucine) and an increase in tryptophan content [12]. The peculiarity of the changes in the AA pool at SCI was an increase in the content of taurine and lysine and a decrease in the content of cysteate. The revealed nonspecific and specific changes in the AA pool (AA markers of CI) can be used to detect both the fact of IHM and to assess its severity. Their experimental study in brain structures is important for the development of neuroprotective therapy, the effectiveness of which can be assessed by changes in the content of AA markers.

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