

Abnormalities in the Pool of Amino Acids in the Parietal Lobe of the Brain in Rats in Modeling Partial Cerebral Ischemia

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Abstract:

When modeling partial cerebral ischemia (PCI) by unilateral ligation of the common carotid artery (CCA), 1 hour later, there were no morphological changes at the microscopic and ultrastructural levels. At the same time, no pronounced changes in the parameters of respiration of the mitochondrial fraction and changes in the parameters of the prooxidant-antioxidant balance of brain homogenates, compared with the control, were observed, which reflects the relative safety of the enzymatic complexes of the electron transport chain in this model of ischemia. However, the results of behavioral tests indicated the development of a minor neurological deficit, and the existing decrease in the content of ATP synthase is the rationale for a possible cause of its development. The change in the pool of amino acids in the parietal lobe shows a significant decrease in the level of methionine as a reflection of the higher activity of oxidative processes in this area of the brain.

Keywords: ischemia; rat; experimental; parietal lobe

Introduction

When modeling partial cerebral ischemia (PCI) by unilateral ligation of the common carotid artery (CCA) [1], 1 hour later, there were no morphological changes at the microscopic and ultrastructural levels [8]. At the same time, no pronounced changes in the parameters of respiration of the mitochondrial fraction and changes in the parameters of the prooxidant-antioxidant balance of brain homogenates, compared with the control, were observed, which reflects the relative safety of the enzymatic complexes of the electron transport chain in this model of ischemia [1-12]. However, the results of behavioral tests indicated the development of a minor neurological deficit [5], and the existing decrease in the content of ATP synthase is the rationale for a possible cause of its development [1,2,3,4].

Materials and research methods

The experiments were carried out on 16 male outbred white rats weighing 260 ± 20 g in compliance with the requirements of the Directive of the European Parliament and of the Council No. 2010/63/EU of September 22, 2010 on the protection of animals used for scientific purposes.

IHM modeling was carried out under conditions of intravenous thiopental anesthesia (40-50 mg/kg).

Partial cerebral ischemia (PCI) was modeled by ligation of one common carotid artery on the right. The control group consisted of sham-operated rats of similar sex and weight.

The material was taken 1 hour after the operation. After removing the brain, a fragment of the hippocampus was taken, followed by freezing in liquid nitrogen. Sample preparation for the study included homogenization in a 10-fold volume of 0.2 M perchloric acid, centrifugation for 15 min. at 13000 g at 4°C, followed by collection of the supernatant. Amino acids were analyzed by reversed-phase chromatography with pre-column derivatization with o-phthalaldehyde and 3-mercaptopropionic acid in Na-borate buffer on an Agilent 1100 chromatograph.

Results

When studying the content of amino acids (AA) in the homogenates of the parietal lobe in rats with a one-hour PCI, an increase in the median values of the content of AA with neurotransmitter properties was revealed, namely, an increase in glutamate by 20%.

An increase in glutamate levels while maintaining glutamine and GABA levels may be associated with an increase in glutaminase activity and/or

transamination/reductive amination in neurons. At the same time, changes in the levels of AA with the properties of excitatory neurotransmitters (aspartate and glutamate) had a multidirectional character: a tendency to an increase in the level of glutamate and to a decrease in aspartate. The decrease in aspartate, in contrast to glutamate, can be explained by its increased utilization as a glycogenic AA in oxidation reactions with the formation of energy.

As for the inhibitory mediators (GABA, glycine, taurine), one can note a trend towards an increase in their content in the parietal lobe (PL): glycine - by 13% ($p > 0.05$), taurine - by 13% ($p > 0.05$), GABA - by 14% ($p > 0.05$).

At the same time, the median level of GABA differed from its value in the control group in approximately the same way as that of glutamate, but the differences in their values were not statistically significant ($p > 0.05$).

Changes in the level of glycogenic AA (aspartate, asparagine, threonine, serine, glutamine, glutamate, glycine, alanine, valine, methionine, histidine, arginine) and ketogenic AA (leucine, lysine) for the brain, from the point of view of biochemical research, are mostly non-specific, since the processes of gluconeogenesis and ketogenesis do not occur in the brain. However, it should be noted that aspartate, glutamate and glycine play the role of neurotransmitters; methionine is a precursor to a number of compounds with antioxidant properties; arginine is a substrate for NO synthase, and lysine is a precursor of the endogenous NMDA receptor antagonist α -amino adipate.

With PCI, there was an increase in the median value of L-arginine in parietal lobe (PL) by 38% ($p < 0.05$). An increase in the content of L-arginine in PL indicates a decrease in the utilization of the substrate for NO synthase, which may be the cause of the existing slight neurological deficit due to the lack of NO, one of the mediators of the central nervous system that mediates the regulation of many processes, including higher nervous activity. Also, in PL, a decrease in the median value of the methionine content by 24% ($p < 0.05$) was noted, which may reflect its participation in the formation of the most important component of antioxidant protection - glutathione. At the same time, the level of taurine in the PL is unchanged, and the level of cysteine sulfinic acid is increased by 52% ($p < 0.05$). The level of cysteate and cystathionine was not changed as a reflection of the low activity of oxidative processes in this type of cerebral ischemia.

In rats with PCI, there was a decrease in the median values of the content of branched hydrocarbon chain amino acids (BCAA), as AA, included in the energy processes of PL: valine - by 30% ($p < 0.05$), isoleucine - by 33% ($p < 0.05$) and leucine - by 30% ($p < 0.05$), which may be due to their utilization in transamination reactions. Along with changes in ABCC in the parietal lobe, there was a trend towards a decrease in the levels of aromatic AAs (tyrosine, tryptophan, phenylalanine), which may reflect their utilization in catecholamine and serotonin synthesis reactions or a decrease in transport to the brain. At the same time, in TD there was a trend towards a decrease in the ratio of ARUC to aromatic AAs from 1.43 to 1.06 PL ($p > 0.05$).

There was a decrease in the median values of all essential AA in PL: methionine by 24 ($p < 0.05$), valine - by 30% ($p < 0.05$), isoleucine - by 33% ($p < 0.05$), leucine - by 30% ($p < 0.05$), and there was also a tendency to decrease lysine by 55% ($p > 0.05$) and threonine - by 32% ($p > 0.05$), which indicates the possible inclusion of PL in metabolic processes, primarily as alternative energy substrates, as a result of inhibition of glucose utilization processes. At the same time, in the PL, the indicator of the "Replaceable/Indispensable" AA ratio in the PCI group increased from 10.0 to 17.6 ($p > 0.05$), which may be a consequence of impaired utilization of nonessential AA in protein synthesis reactions along with increased utilization of irreplaceable AA.

Discussion

One-hour PCI is characterized by the following changes in the AA pool: an increase in glutamate and GABA without changes in the ratios of

excitatory and inhibitory amino acid transmitters, a decrease in the level of essential AAs with an increase in the "Essential/Essential" AA ratio, as a reflection of increased utilization of essential AAs. There were no changes in sulfur-containing AAs, except for a decrease in the content of methionine in the parietal lobe, which indicates minor violations of the prooxidant-oxidant balance in this model of IHM. There was a decrease in the content of amino acids with a branched hydrocarbon chain and a trend towards a decrease in the level of aromatic AAs (tyrosine, tryptophan, phenylalanine) with a decrease in their ratio as a reflection of a more pronounced utilization of BCAAs, compared with aromatic AAs.

Conclusion

Thus, the change in the pool of amino acids in the parietal lobe shows a significant decrease in the level of methionine as a reflection of the higher activity of oxidative processes in this area of the brain.

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