THE ROLE OF ERYTHROCYTES IN CEREBRAL ISCHEMIA

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RELEVANCE

Cerebral ischemia occurs as a result of insufficient cerebral blood flow in regard to cerebral metabolic functions. The main cause of death of neurons in the age aspect and with ischemia is apoptosis, a genetically programmed cellular event that follows ischemia and leads to biochemical and morphological changes in the cells of the cerebral cortex. Enhanced attention to the mechanisms of a human brain neurons aging and the features of this process in ischemia of brain caused by the high mortality rate in the world due to stroke or apoplexy [3].

In spite of numerous concepts about neuronal damage due to ischemia or stroke, the problem of etiology and pathogenesis of neuron death still not solved completely. Treatment, which is not based on pathogenetic mechanisms, without knowledge about etiological principles is only symptomatic one [6]. To the one of a key pathogen for insult development, independent from ischemic or hemorrhagic forms, today are disturbance in the system of neural, endothelium dependent and myogenic mechanisms of regulation of trophic ensuring in the human brain structures. But 60% of death rate, 30% of disability and only 10% successful returning to active life and work of such patients, casts doubt in correct using of treatment based on these theories and shows a high relevance of this study [1, 2].

AIM

To study the dynamic of aging mechanisms of microcirculation in the paraventricular zone of III ventricle of human brain in condition of ischemia in the area of precentral gyrus.

MATERIAL AND METHODS

The characteristics of changes in the system of "neuron-neuroglia" in age aspect and ischemia in the part of human brain locating far from damaged zone were described. Clinical material was taken with the permission of the ethical committee of the FEFU, in accordance with the legislation of the Russian Federation on the rules for the collection of cadaveric material. Brain biopsies of 69 patients who died from ischemia were studied using immune histochemistry methods to detect apoptotic cells, as well as on the expression of CD68 CD163 marker cells. Analysis of the results and illustrative material was obtained with the help of a microscope by Schlimpus with the software for morphometry.

RESULTS

We found, that age changes of neurons in paraventricular zone of hypothalamus lead not only to lipofuscin accumulation, but also, in condition of chronic ischemia, deposition of transferrin in cytoplasm of neurons that closely related with inca-

pability of cells to internalize and utilize oxygen. This conclude that there is disturbance in the system of oxygen ejection by hemoglobin to neurons, adaptive accumulation of iron for compensation of oxygen dependent energetic processes in the neuron and intoxication of brain tissue by hemoglobin metabolites, follows to apoptosis of neuroglia and neurons. This inducts the process of disbalance in the system of "neuron-neuroglia", which is a trigger factor for development of ischemic stroke.

DISCUSSION

The mechanisms of pathogenesis of a brain ischemia and stroke can be attributed to cascade of reaction caused by oxygen deficiency of neuronal energetic request, also related from the central mechanisms of erythropoiesis regulation. Considering a toxic of hemoglobin metabolites, the damage a systems of eritrogenin and erythropoietin, we presume that this process is not local but generalized. which requires appropriate medical measures, inducting compensatory-adaptive mechanisms on a higher level [4, 6]. The obtained data that in the zones remote from the ischemia region, the changes of the hemato-encephalic barrier are identified, hemosiderin accumulates in the neurons. These data do not confirm the results of other researchers obtained in the models of experimental animals that brain ischemia is a local problem of circulatory disturbance in the zone death and apoptosis of neurons. Brain ischemia is a generalized problem associated with abnormalities in erythrocytes, distortion of oxygen transfer to tissues and destruction of red blood cells before returning to the spleen.

Our data are consistent with the results of studies by Yao Z, Wang L, Wu X, with coauthors (2017), who found that defects in the biochemical composition of erythrocyte membranes are observed in patients with brain ischemia [5].

The role of phosphatidylserine (PS)-mediated procoagulant activity (PCA) in stroke remains unclear. To ascertain this role, early dynamic evolution of PS exposure on blood cells and released microparticles (MPs) and the corresponding PCA were evaluated in patients with acute ischemic stroke (AIS). Thrombin generation promoted by platelets and MPs at 12 h was significantly higher in patients with cardioembolism than in patients without.

The thrombophilic susceptibility of AIS patients can be partly ascribed to PS exposure on blood cells and the release of MPs. Therefore, we consider it promising to study the state of erythrocytes and platelets in patients who have suffered a stroke both in terms of predicting the course of the disease, and in terms of preventing repeated strokes. Also, these data can be used to study the biochemistry of red blood cells in order to use them as targets for effective therapeutic measures and drug delivery.

REFERENCES

1. **Choi MH, Park GH, Lee JS, Lee SE, Lee SJ, Kim JH, Hong JM.** Erythrocyte Fraction Within Retrieved Thrombi Contributes to Thrombolytic Response in Acute Ischemic Stroke.//Stroke. 2018 Mar;49(3):652–659
2. **Desal HA, Lee SK, Kim BS, Raoul S, Tymianski M, TerBrugge KG.** Multiple de novo vascular malformations in relation to diffuse venous occlusive disease: a case report.//Neuroradiology. 2005 Jan;47(1):38–42
3. **Ivanov KP.** Brain hypoxia and the role of active forms of oxygen and of energy deficit in the neuron degeneration.//Usp Fiziol Nauk. 2012 Jan-Mar;43(1):95–110.
4. **Kizmazoglu C, Aydin HE, Sevin IE, Kalemci O, Yüceer N, Atasoy MA.**Neuroprotective Effect of Resveratrol on Acute Brain Ischemia Reperfusion Injury by Measuring Annexin V, p53, Bcl-2 Levels in Rats.//J Korean Neurosurg Soc. 2015 Dec;58(6): 508–12.
5. **Yao Z, Wang L, Wu X, Zhao L, Chi C, Guo L, Tong D, Yang X, Dong Z, Deng R, Novakovic VA, Thatte HS, Bi Y, Tian Y, Shi J, Zhou J, Kou J, Hu S.** Enhanced Procoagulant Activity on Blood Cells after Acute Ischemic Stroke.//Transl Stroke Res. 2017 Feb;8(1):83–91.
6. **Yokota C, Kaji T, Kuge Y, Inoue H, Tamaki N, Minematsu K.** Temporal and topographic profiles of cyclooxygenase-2 expression during 24 h of focal brain ishemia in rats.//Neurosci Lett. 2004 Mar 11;357(3):219–22.