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VIOLATION IN THE AXIS OF THE "MICROBIOTA OF THE DIGESTIVE TRACT-BRAIN" UNDER CONDITIONS OF ISCHEMIA-REPERFUSION OF THE BRAIN (literature review)

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Abstract

The aim of the study is to analyze current views concerning interrelations between the state of intestinal microbiota and the course of ischemic-reperfusion brain injury.

Conclusion. Literary data are indicative of disputable scientific opinions existing nowadays concerning the role of dysbacteriosis (neuroprotective or neurodegenerative) in the course of ischemic brain injuries. Meanwhile, the studies are in common concerning the evidenced role of the intestinal microbiota in disturbances of T-cell homeostasis, ratio changes of their Treg-Th17 subpopulations, and migration of intestinal lymphocytes to the ischemic brain.

Key words: brain ischemia-reperfusion; intestinal microbiota; interrelations.

Current scientific achievements do not have any doubt concerning cause-and-effect relations available between intestinal microbiota dysbacteriosis, T-cell homeostasis, pro-inflammatory response induction and stroke outcome.

Irrespective of the origin of stroke about 50 % of patients suffer from gastrointestinal complications: dysphagia, gastrointestinal bleedings, constipation or stool incontinence, resulting in deterioration of patients' condition, longer periods of recovery, increased

mortality rate and intensification of neurological dysfunction [1, 2]. These symptoms are considerably associated with intestinal dysbacteriosis, which is based on substantial changes of microbial diversity and amount of bacteria in the stool specimens of patients with strokes and transient ischemic attacks [2, 3]. Certain experimental studies enabled to isolate possible mechanisms promoting post-ischemic microbiota imbalance: systemic immunity inhibition [4, 5], production of pro-inflammatory mediators by damaged areas of the brain [6, 7], sympathetic nervous system activation [8, 9], stress-response induction [10], and motor intestinal disorders [1, 2].

Experiments on mice including middle cerebral artery occlusion (MCAO) in 24 hours showed considerable changes in the content of microbiota mucosa on all the taxonomic levels: reduced variability of microbiota species and excessive growth of certain intestinal bacteria, mainly *Bacteroidetes, Firmicutes* and *Actinobacteria* [10]. Decrease of microbiota different species is indicative of a selective exhaustion of specific bacterial strains and/or possible translocation of bacteria in the intestines. The latter was evidenced by the presence of appropriate bacteria in the pulmonary, bronchial-alveolar washing fluid, liver and spleen [9, 11]. Translocation of microorganisms in the intestines is ensured by considerable increase of the vascular, epithelial and paracellular permeability since the 3rd hour after cerebral ischemia initiation [12, 13].

Bacterial pneumonias are dangerous complications of strokes with fatal outcome. The main source of postapopleptic pulmonary infection is translocation of commensal intestinal bacteria after disturbances of the intestinal barriers [14]. More than 70 % of bacteria in patients with stroke and infectious complications include common commensal intestinal bacteria such as *Enterococcus spp., Escherichia coli* and *Morganella morganii* [15].

Intestinal dysfunction and dysbacteriosis after stroke are associated with imbalance of the sympathetic signaling in the submucous intestinal plexus [8]. The location density of cholinergic neurons in the plexus during the postapopleptic period decreased considerably resulting in imbalance between adrenergic and cholinergic signaling, and administration of β-adrenergic blockers restored intestinal permeability state and reduced the content of translocated bacteria in the lungs, bronchial-alveolar washing fluid, liver and spleen [8]. In addition, an increased level of noradrenalin after stroke disturbed microbial composition, formation of mucoproteins and amount of goblet cells in the ceacum [16]. Activation of noradrenergic innervation inhibits ability of invariant NKT-cells in the liver to respond effectively to bacterial infection after experimental ischemic stroke [17].

There many evidences that it is intestinal microbiota that is a key regulator of T-cells

homeostasis [18-21], which play a crucial role in secondary neuroinflammation after brain ischemia [21, 22]. Subpopulations of Th cells can have different influence on stroke outcome: T1, T17 and γδ-T cells promote pro-inflammatory processes and deterioration of ischemia consequences, and Tregs-cells produce a restricting effect concerning neuroinflammatory reaction [21, 22].

Dysbacteriosis is considered to produce a cause-effect on deterioration of stroke outcome, which is confirmed by microbiota grafting from mice with MCAO to primarily abiotic mice of GF line, undergoing MCAO 3 days after transplantation. Mice that received microbiota from the animals with brain ischemia formed considerably bigger areas of infarction and their functional neurological disorders were more intensified in comparison with those animals that were pseudo-operated on and repeatedly colonized with microbiota [23]. Analysis of the expression of polarization markers Th-cells in the brain – cytokines IL-17 and IFN-γ and transcription factor Foxp3 5 days after MCAO modeling showed an increased expression of pro-inflammatory cytokines IFN-γ and IL-17 in microbiota recipients from the animals with brain ischemia, which is indicative of polarization into the side of subpopulations Th1 and Th17 respectively [24] and is associated with deteriorated stroke course [10, 21, 22, 25]. Expression of Foxp3 – a marker of neuroprotective Treg-cells – did not differ considerably from the recipients of microbiota from pseudo-operated animals and those with simulated MCAO [23]. Examination of microbiota effect on polarization of T-cells in the intestines demonstrated an increased expression of pro-inflammatory Th17 (IL-17+) and Th1 (IFN-γ+) cells in the recipients of microbiota from mice with simulated MCAO, but not in pseudo-operated animals, which corresponds to the results obtained in the brain. It should be noted that induction of pro-inflammatory response of Th1 and Th17 was associated with an enlarged area of infarction. These conclusions correspond to the results of research conducted by other authors who determined that polarization of T-cells is induced by certain representatives of Bacteroidetes and Firmicutes [26, 27].

Microbial products produce a certain effect on the activity of natural immunity as well and promote maturation and activation of intestinal monocytes/macrophages [28]. An increased amount of mucosal CD11b+ monocytes in mice-recipients of microbiota after MCAO, and migration of monocytes into the brain during an acute phase after stroke were demonstrated [29, 30].

After MCAO in GF-mice with transplanted microbiota of animals with previously simulated focal ischemia of the brain, peripherally activated and/or polarized T-cells migrate into the peri-infarction tissue – at least 25 % T-cells, coming to the brain during an acute

phase of stroke originate from the intestinal immune system [23, 24]. Grafting of fecal microbiota from healthy animals improves the course of stroke – the volume of cerebral infarction 3 days after MCAO decreases, and the amount of Foxp3+Treg cells in the ischemic hemisphere and spleen increases in comparison with that of the control [23]; the effect of this procedure is mediated by lymphocytes.

Meanwhile, not all the researchers share the opinion concerning a negative role of dysbacteriosis in the course of ischemic-reperfusion brain injury. Recently intestinal dysbacteriosis induced by antibiotics has been found to possess a neuroprotective effect followed by a decreased area of infarction and improvement of the CNS functional state parameters through the accent of polarization of Th cells into the side of Treg induction [31]. This research describes a new mechanism of interaction in the «intestinal microbiota-brain» axis, based on the bacterial priming of the intestinal dendritic cells (DC) resulting to a local growth of Treg cells in the small intestine and inhibition of effect produced by T-cells IL-17+γδ. Effector T-cells migrate from the intestine to the brain, where they are localized in the pia mater of the brain and intensify ischemic neuroinflammation by means of IL-17 secretion, increasing production of chemokines in the brain parenchyma and its infiltration by cytotoxic immune cells. Selecting bacterial samples of the intestinal content DC migrate into the mesenteric lymph nodes, where they represent antigens inducing Treg polarization [32], inhibiting activity of T-cells IL-17+γδ. The authors consider that leptomeninx during post-ischemic inflammation performs the function of a specific filter, since under the described experimental conditions γδ T-cells after stroke did not enter the brain, their migration was limited by the pia mater, and an increased amount of these cells in the injured brain was explained by their extravasate entrance from the compromised meningeal vessels [33]. Due to this fact meningeal T-cells IL-17+γδ control penetration of monocytes and neutrophils, the main leukocyte populations being recruited into the ischemic brain, into the brain parenchyma. This suggestion was evidenced by reduction of IL-17+γδ T-cells in the pia mater of the brain after stroke in mice with intestinal dysbacteriosis associated with lowered expression of IL-17-sensitive chemokine in the brain parenchyma.

Conclusion. Literary data are indicative of disputable scientific opinions existing nowadays concerning the role of dysbacteriosis (neuroprotective or neurodegenerative) in the course of ischemic brain injuries. Meanwhile, the studies are in common concerning the evidenced role of the intestinal microbiota in disturbances of T-cell homeostasis, ratio changes of their Treg-Th17 subpopulations, and migration of intestinal lymphocytes to the ischemic brain.

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