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**IMMUNE CHANGES IN THE PATHOLOGY OF FORMATION ALLERGIC DISEASE
CHARACTERISTICS, AT A TIME OF BRAIN AND ISCHEMIC STROKE**

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**იმუნური ძვრები ალერგიული დაავადების ფორმირების პათოლოგიაში, თავის ტვინისა
და იშემიური ინსულტის დროს**

ა. წერეთლის სახელმწიფო უნივერსიტეტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი,
საქართველო

რეზიუმე

ჩვენი კვლევის მიზანი იყო ისეთი სპეციფიკური მონაცემების მოპოვება, რომელიც დააზუსტებდა ცერებრალური ქსოვილის პროცესში (როგორც იშემიურ ფოკუსში, ასევე პენუმბრაში) ფოკალური დარტყმის ფორმირების პროცესს: 1. ადგილობრივი სისხლის მიმოქცევა და უანგბადის ნაწილობრივი წნევის ცვლილებები და აზოტის ოქსიდის დონე სხვადასხვა დროის ინტერვალებით; 2. სისხლის რეოლოგიური თვისებების და თავისუფალი რადიკალების ცვლილების როლი ორივე, გეომეტრიული განზომილებებისა და სისხლის მიმოქცევის დონის განსაზღვრაში პენუმბრაში; 3. ფოკალური იშემიის ცენტრისა და პენუმბრას ქსოვილებში მორფოლოგიური ცვლილებების ანალიზის შედეგები.

Introduction: In cases of brain focal strokes, optimal use of so called “therapeutic window” is of critical significance, with respect of the treatment outcome. First of all, this deals with maintenance of penumbral area of infarction developed in the neural tissue and its saving from involvement into the ischemic process and, certainly, relieving of the processes developed in the ischemic focus, through minimization of the volume of necrotic tissue [4,8,9]. For the purpose of obtaining of this extremely significant information, first of all, for the research, supposedly, we should select the experimental model that is as close as possible with the pattern of ischemic stroke development, where the relevant processes develop in the organism, without external impact (whether medial or traumatic nature). [1,2,3]. And, certainly, we should study the processes developed in the course of the external intervention, where such intervention is necessary for the patient and is directly related to the possibility of formation of the ischemic stroke in the brain. Regarding the literary materials and own experience, as such models, we have selected non-invasive photochemical method for development of the focal ischemia in the brain and local hyperthermia exposition that is used for treatment of the cancer tissues, together with radio- or chemotherapy. In both cases, the status of blood rheological properties actively influences formation of the ischemic stroke, as well as free radicals bound with oxygen and nitrogen oxide [5,6,7,10].

Research goals and objectives: regarding all above, the main goal of our research was obtaining of such specific data that would specify the following, in the process of cerebral tissue (both, in ischemic focus and penumbra) in the process of formation of focal strike and upon its completion: 1. Dynamics of local blood circulation and oxygen partial pressure changes and level of nitrogen oxide at different time intervals; 2. Role of change of blood rheological properties and free radicals in determination of both, geometrical dimensions and blood circulation level in penumbra; 3. Results of analysis of the morphological changes in focal ischemia center and penumbra area tissues.

Scientific novelty of the obtained results: in the brain, in both processes of ischemic stroke development processes that we have used, the most significant complications are caused by thrombosing

of the cerebral vessels, in development of which the rheological properties of blood are of primary significance. In case of increased viscosity of the blood, the injury induced in the cerebral tissue is more prominent. By using of antioxidants and such powerful scavenger of free radicals as DMSO and/or by changing of the concentration balance of nitrogen oxide and oxygen radicals (in favor of nitrogen oxide), reduction of the scale and severity of injury induced by the focal infarction (by relevant morphological changes) is possible. Cerebral tissue is characterized with extremely high sensitivity to hyperthermia impact developed in the tissue itself, rather than in the environment.

Statistical analysis of the obtained results was provided by the software package of variation statistics (ANOVA), implementation of which was provided by means of Excel program. Statistical reliability of the differences was checked by Student-t criterion.

Obtained results: as evidenced by the provided data, increase of temperature to 41 degrees cause growth of local blood flow and its level, in 20-30 minutes, achieve 150 percent of the initial level. Further increase of temperature to 43 degrees initially cause drastic growth, actually doubling of local blood flow, compared with the initial level but after 20-30 minutes its level falls dramatically, to 60 percent of the initial level. As for high temperature hyperthermia, where there was used heating of the cerebral cortex surface to 45 degrees, local blood flow falls significantly and in 20-30 minutes its measurement became impossible.

Prior administration of Dextran provided significant difference (compared with the normal rats) at 43 degrees, in 20-30 minutes from beginning of hyperthermia, local blood flow in cerebral cortex reduced significantly and approached to 40 percent of initial level. With further increase of temperature, blood flow could not be measured and this means that it has stopped.

Administration of such powerful scavenger of free radicals as dimethyl sulfoxide (DMSO) has dramatically changed the picture, in 20-30 minutes after beginning of 43-degree hyperthermia, local blood flow actually returned to the initial level and, unlike the dextran-treated group, at 45 degrees, initially, the local blood flow was measurable (for 5-10 minutes of hyperthermia) and in 20-30 minutes, blood flow in this group of the animals became unmeasurable as well.

Thus, administration of scavenger of free radicals, dimethyl sulfoxide provides practical opportunity to reduce, at least partially, the scale of brain injury caused by hyperthermia.

Conclusion: immediately upon beginning of illumination (i.e. ischémisation) of cerebral cortex great quantities of active forms of oxygen and nitrogen oxide form; emergence of the complexes of NO and hemic iron takes place as well. In the process of ischemia, nitrosylation of the proteins containing mitochondria iron-sulfur centers takes place and due to this, suppression of electrons transport and oxidizing phosphorylating. It was established that similar processes develop in penumbra area of cerebral infarction as well, though, with certain delay and lower intensity. And this allows prevention of cytotoxic effect of nitrogen oxide in the therapeutic window. For this, it is necessary to suspend reduction of nitrogen oxide quantity in penumbra and break concentration balance between nitrogen oxide and oxygen radicals, in favor of the former. Thus, nitrogen oxide acquires the function of antioxidant and protects the cells from destructive action of the oxygen radicals. Extremely high sensitivity of the tissues of central nervous system to local hyperthermia exposition is established even at 41°C, necessitating urgent preventive measures, if in normal cerebral (non-cancer) tissue the temperature achieves 41°C limit that would inevitably cause formation of ischemic stroke. In the conditions of local hyperthermia, one of the most significant causes of central nervous system tissues injury is emergence of micro thrombi in the cerebral vessels. Stopping of blood flow, together with the other outcomes, worsens thermal clearance, where the tissue maintains high temperature. This amplifies destructive action of hyperthermia and contributes to formation of ischemic stroke. Growth of blood viscosity decelerates blood flow and create favorable conditions for thrombus formation, especially in the venous system. Worsening of blood rheological properties causes intensification and increase of dimensions of cerebral tissue injury induced by both, photochemical method and local hyperthermia. For the purpose of prevention and stopping of such development of the processes, permanent control of the rheological properties of the blood flowing from the cerebral system is necessary. Administration of

the free radicals scavenger DMSO (dimethyl sulfoxide) significantly delays development of the ischemic stroke induced in the cerebral tissue and also significantly improve functional condition of penumbra area, thus reducing its size and contributing to increase of so called therapeutic window.

Theoretical and practical significance. We regard that the results of this work would, primarily, contribute to more exact specification of general principles of hyperthermia therapy and at a time of its use at oncological clinics, the limit of thermal tolerance of the central nervous system tissues and the roles of blood rheological properties and free radicals in prevention of possible injury induced by hyperthermia of the normal (non-cancer) tissue will be duly taken into consideration.

Within the therapeutic window, in penumbra area of focal cerebral infarction, cytotoxic effect of nitrogen oxide should be avoided and for this, reduction of the quantities of nitrogen oxide in penumbra area must be stopped (as demonstrated in our experiments) and break the concentration balance between nitrogen oxide and oxygen radicals, in favor of the former. In this way, nitrogen oxide acquires the antioxidant function and protects the cells from destructive effect of the oxygen radicals.

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SUMMARY

The main goal of our research was obtaining of such specific data that would specify the following, in the process of cerebral tissue (both, in ischemic focus and penumbra) in the process of formation of focal strike and upon its completion: 1. Dynamics of local blood circulation and oxygen partial pressure changes and level of nitrogen oxide at different time intervals; 2. Role of change of blood rheological properties and free radicals in determination of both, geometrical dimensions and blood circulation level in penumbra; 3. Results of analysis of the morphological changes in focal ischemia center and penumbra area tissues.

Keywords: allergic disease, immune changes, brain, ischemic stroke