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CHANGES IN MECHANICAL PROPERTIES OF BRAIN TISSUE AS FACTOR OF BRAIN EDEMA DEVELOPMENT

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The following factors are known to determine water transfer through the microvascular wall, and hence edema development: a) the intravascular blood pressure, b) the blood osmotic pressure, c) the interstitial fluid osmotic pressure and d) its hydrostatic pressure (Haddy et al., 1976). In turn, the major determinants of the interstitial fluid hydrostatic pressure are: 1°, the amount of the fluid and, 2°, the mechanical properties, namely the deformability (mechanical compliance) and plastic behavior of tissue elements surrounding the interstitial compartments. The rise of this pressure was detected upon the influx of water in the extracellular compartments during development of traumatic brain edema (Reulen, 1976). As to the changes in the mechanical properties of the brain tissue elements in the course of brain edema development they have not been investigated so far. However these changes should play an important role in abundant influx of water from blood and in its accumulation in tissue spaces, since both of these events are greatly dependent upon the enlargement of brain interstitial spaces, and this is primarily due to increase in deformability and in mechanical plasticity of the surrounding elements. It has been shown that in the connective tissue these mechanical properties undergo considerable changes under conditions of development of inflammation and edema (Voronin, 1947). Therefore it might be assumed that similar changes may occur in the brain. Of particular importance for the development of brain edema are the cerebral tissue changes which could appear in the preedemic period, i.e. before water accumulation in the tissue.

The suggestion that the changes in mechanical properties of the brain tissue play a role in the development of edema was made about two decades ago (Mchedlishvili, Akhobadze, 1961). However, no evidence of the changes has accumulated so far. The present work illustrates some of the changes of the mechanical properties of the brain tissue in the course of edema development.

MATERIALS AND METHODS

The experiments were carried out on 33 adult rabbits of either sex, weighing about 3 kg, anesthetized with Nembutal or Hexenal in doses sufficient for eliminating pain responses. Besides, local anesthesia with novocaine or polocaine hydrochloride (1%) was applied during surgical procedures. In addition the animals were immobilized with myorelaxants for artificial lung ventilation during the experiments (the ventilation air volume was adjusted as before paralysis).

Sagittal incision was made along the midline of the neck. Tracheotomy was performed for artificial ventilation, and the right common carotid artery and external jugular vein were exposed and ligated. Then polyethylene catheters of the largest available diameter were inserted into these vessels in the thoracic direction: into the artery for recording the systemic arterial pressure and into the vein for recording the systemic venous pressure with electromanometers (Elema-Schönander, Sweden, or Farum, Poland). A thick silk ligature was placed around the contralateral common carotid artery permitting to occlude it when necessary.

The circulation in the forelegs and in the hind part of the body was cut off for carrying out experiments on the „chest-head" preparation (Mchedlishvili, 1962). For that purpose both subclavian arteries and veins were exposed and ligated immediately outside the chest wall; then the abdominal aorta and caudal caval vein were exposed just behind the diaphragm and polyethylene catheters of the largest available diameter were inserted into both vessels towards the heart to connect them with two separate pressurized reservoir systems filled with Gelatinine or Dextran-40 (Fig. 1).

A large craniotomy (approximately 20 mm in diameter) was made over the parietal region of the cerebral hemispheres. The dura mater was not opened until the beginning of the experiments and then was removed from the brain surface over the area of the craniotomy hole. Further, on the animals' back, through an incision along the sagittal line below the occiput, the fourth ventricle of the brain was opened to drain the cerebro-spinal fluid.

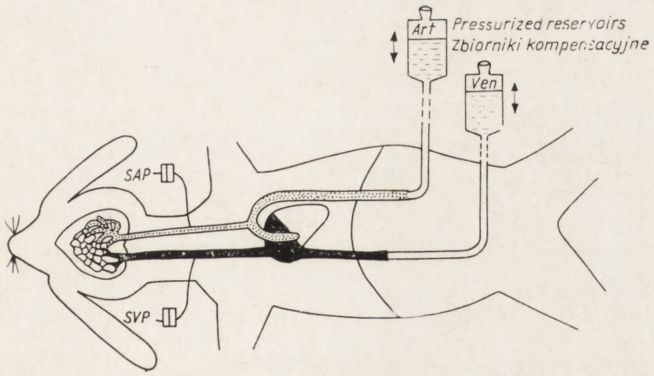

Fig. 1. Schematic set-up of the „chest-head" preparation of rabbit for control of both systemic arterial (SAP) and systemic venous pressures (SVP) by means of an arterial (Art) and venous (Ven) pressurized reservoir systems.

Ryc. 1. Schemat preparatu „klatka piersiowa-głowa" królika służącego do kontrolowania układowego ciśnienia tętniczego (SAP) i żylnego (SVP) przy pomocy ciśnieniowych zbiorników kompensacyjnych (tętniczego — Art i żylnego — Ven).

To prevent blood clotting, heparin was injected intravenously (1,500—2,000 units per 1 kg of body weight) at completing the surgical procedure. Noradrenaline was gradually applied to the circulatory system in a dose of approximately 1—2 μg for 5 min. during the experiments. In a part of experiments the parameters under investigation were recorded on Mingograph 81 (Elema-Schönander, Sweden) and in the other part on Watanabe Mark III Linear recorder (Japan). The results were evaluated statistically and presented as mean (M) and standard deviation (SD).

The displacements of the brain surface level were continuosly recorded by a mechanical device consisting of a strain-gauge, one end of which was fastened to a stereotaxic device and the other having a bearing upon the brain surface in the parietal region. The bearing had a form of a sphere about 5 mm in diameter. The strain-gauge was connected to a Watson bridge, the signals from which were amplified before recording. The whole set-up was calibrated before each experiment so that it was possible to evaluate the height of the brain surface expansion above the initial level. The brain expanding through an almost circular craniotomy hole may be considered as a spheric segment. Volume changes of such a segment are directly proportional to changes in its height, the error being less than 10 per cent (Mchedlishvili et al., 1979a). Accordingly, the recorded brain level changes could be considered as reflecting the brain volume changes.

One series of experiments (21 rabbits) consisted in repeated tests with artificial elevation of the systemic venous pressure by means of the venous pressurized reservoir. The duration of every test was 7—10 min. They were repeated 2—10 times in the course of each experiment on the average every 12 ± 2.16 min. and finally resulted in the development of brain edema.

In another series of experiments (12 rabbits) ischemia was brought about in the hemispheres by two operations: occlusion of the second common carotid artery (the first one was cut off blood flow during the preliminary surgical procedure) and restriction of the collateral blood supply to the hemispheres through the vertebral arteries by lowering the systemic arterial pressure by use of the pressurized reservoir system to a level of ca 25 mm Hg (Mchedlishvili, 1973). The duration of cerebral ischemia was 15—20 minutes and then the cerebral blood flow was recovered. The tests with elevation of the systemic venous pressure were repeatedly carried out in the course of and after ischemia. At last edema developed in the brain.

The criteria for the occurrence of edema in the brain at the end of the experiments were: a) increased brain level, i.e. volume, when the systemic venous pressure was already decreased and b) a significant increase in water content in the cerebral tissue (determined as percentage of its wet weight) in comparison with the control values.

The mechanical properties of the brain tissue were investigated in the following way: a load was temporarily applied to the brain causing its deformation and the response of the brain was recorded during both applying of the load and the following unloading. Thus, the two following kinds of mechanical properties of the brain tissue were revealed, namely, its deformability (i.e. the value of its strain caused by specific load) and its plastic characteristics estimated as area of hysteresis during its cyclic loading and unloading (the size of the area showed the delay of recovery of initial configuration of the brain tissue following its specific loading).

The deformability of the brain tissue was estimated as mean rise (in mm) of the brain surface at increase of the systemic venous pressure by 1 mm Hg. The areas of hysteresis were measured in the plots of relationships of brain level changes against systemic venous pressure (causing respective changes in cerebral intravascular pressure).

RESULTS

First series of experiments. * Repeated increases in the systemic, and thus cerebral, venous pressure have regularly led to the develop-

* The experiments were carried out in Warszawa.

ment of brain edema: the brain level rose by 4.1 ± 1.3 mm * and the water content in the cerebral tissue amounted to 88.6 ± 4.7 per cent while in control animals it was 79.8 ± 1.7 per cent ($P < 0.001$). Though the rate of the edema development varied considerably, in the course of all experiments it was possible to distinguish: 1) „normal" brains with no features of edema, 2) preedematous brains in which specific features of edema were not evident, but it appeared in the subsequent test or tests, and 3) brains with pronounced features of edema.

During the tests the systemic venous pressure rose from 1.2 ± 1.3 to 16.5 ± 7.5 mm Hg and subsequently decreased to almost the initial level. The duration of the increase was 2.84 ± 1.25 min. and that of the subsequent decrease 4.95 ± 2.05 min. The systemic arterial pressure was maintained at a constant level or became insignificantly elevated during the increase of the systemic venous pressure.

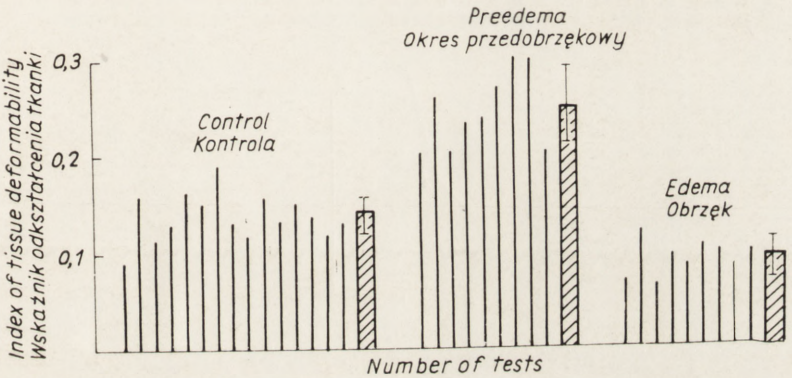

Fig. 2. Index of deformability of brain tissue in the course of brain edema development (caused by repeated venous blood stagnation). The striated columns show mean values and standard deviations.

Ryc. 2. Indeks odkształceń tkanek mózgu w rozwoju obrzęku wywołanego przez powtarzane zatrzymanie odpływu krwi żylnej. Kolumny zakreskowane oznaczają wartości średnie i odchylenia standardowe.

Along with the increase of the systemic venous pressure there was a rise in the brain level, manifesting different degrees of its deformability. The index of brain tissue deformability (i.e. the average pressure by mm Hg) was calculated for the individual tests (Fig. 2). The following values of the index were obtained in different groups of tests: normal brains 0.14 ± 0.02, preedematous brains 0.25 ± 0.04, edematous brains 0.09 ± 0.02 the difference being in all the cases statistically significant ($P < 0.001$). Consequently, when brain becomes

* Here and below: mean and standard deviations.

preedematous, i.e. predisposed to edema development, the deformability of its tissue increases considerably, but while even the first symptoms of edema appear the deformability markedly decreases.

The changes in the brain level, i.e. its volume, were plotted against the increase and subsequent decrease of the systemic venous pressure in individual tests. It appeared that in normal brains (with no features of preedema or edema) there was no considerable hysteresis in the plots (Fig. 3A). However, the latter appeared and inc-

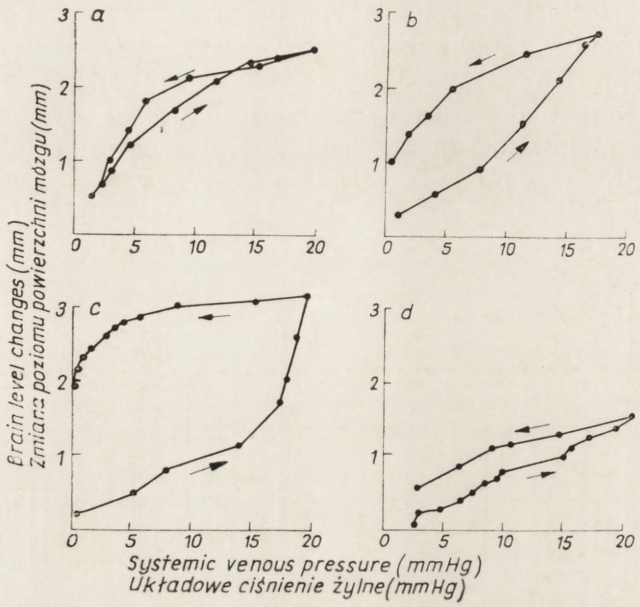

Fig. 3. Patterns of relationship of changes of systemic venous pressure and those of brain surface level, the latter expressing brain volume changes, in the course of experiment. Hysteresis gradually increases in preedematous state (A, B, C), but decreases significantly when edema is already present (D).

Ryc. 3. Wykres zależności między zmianami układowego ciśnienia żylnego i zmianami poziomu powierzchni mózgu, wyrażającymi zmiany jego objętości w przebiegu doświadczenia. Histereza stopniowo wzrasta w okresie przedobrzękowym (A, B, C) i znacznie zmniejsza się po wytworzeniu się obrzęku (D).

reased regularly in the brains becoming preedematous (Fig. 3B, 3C). When edema was already evident the slope of the ascending curve regularly decreased (by 55.3 ± 16.8% in comparison with the initial stages of the experiments) and hysteresis diminished by 59.1 ± 23.9% in comparison with the preedematous state (Fig. 3D). Changes in hysteresis at the beginning of the experiments („normal" brains), during preedematous state of the brains, as well as when edema was in evidence in individual tests are presented in Fig. 4.

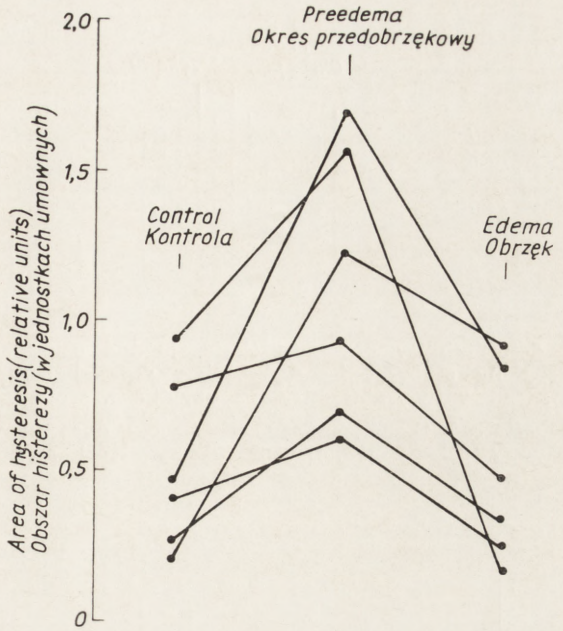

Fig. 4. Patterns of changes of hysteresis in plots of brain level changes against systemic venous pressure in the course of brain edema development (caused by repeated venous blood stagnation).

Ryc. 4. Zmiany histerezy na wykresach obrazujących zmiany poziomu powierzchni mózgu w zależności od układowego ciśnienia żylnego, w rozwoju obrzęku wywołanego powtarzanym zatrzymaniem odpływu krwi żylnej.

Second series of experiments. * Following ischemia the brains were considerably more apt to edema development than following repeated increases in the venous pressure alone. The changes in the mechanical properties of the brain, typical of the preedematous state, appeared already during ischemia. If the index of deformability of the brain was 0.0695 ± 0.026 before ischemia, it became 0.142 ± 0.03 during ischemia, and was 0.056 ± 0.007 when edema was evident following recovery of blood supply to the brain (Fig. 5). ** The area of hysteresis was comparatively small in normal brain but during edema it increased to 0.458 ± 0.386 and decreased again to 0.385 ± 0.258 i.e. by 16% relative to preedemic state of the brain assumed as 100% (Fig. 6).

DISCUSSION

The method used in the reported experiments seems to be adequate for determining the mechanical properties of the brain tissue. The

* The experiments were carried out in Tbilisi.

** The quantitative differences in deformability seen in Figs. 2 and 5 are dependent on different characteristics of the applied sensors.

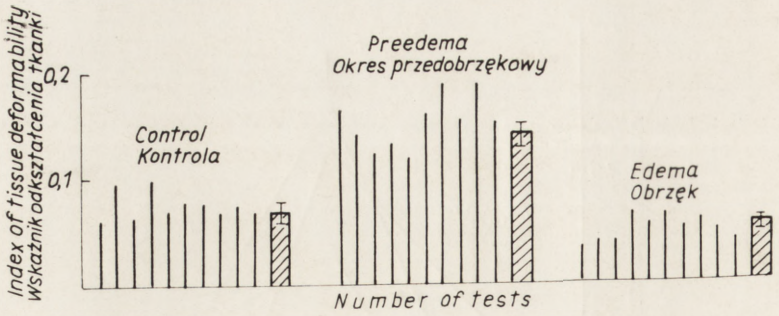

Fig. 5. Index of deformability of brain tissue in the course of brain edema development (caused by cerebral ischemia). The striated columns show mean values and standard deviations.

Ryc. 5. Indeks odkształceń tkanek mózgu w rozwoju obrzęku wywołanego niedokrwieniem. Kolumny zakreskowane oznaczają wartości średnie i odchylenia standardowe.

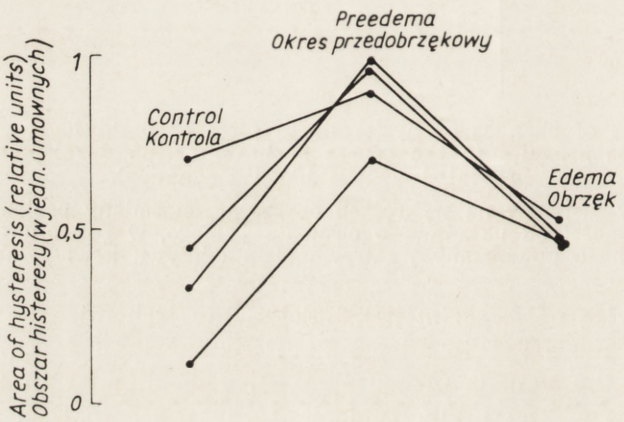

Fig. 6. Patterns of changes of hysteresis in plots of brain level changes against systemic venous pressure in the course of brain edema development (caused by cerebral ischemia).

Ryc. 6. Zmiany histerezy na wykresach obrazujących zmiany poziomu powierzchni mózgu w rozwoju obrzęku wywołanego niedokrwieniem.

load applied to the brain to cause its deformation was the increase in its intravascular pressure by a controlled rising of the systemic venous pressure while the systemic arterial pressure was maintained constant. The „chest-head" preparation (Mchedlishvili, 1962) with separate venous and arterial pressurized reservoir systems provided a possibility to change or to maintain arbitrarily the pressures irrespectively of the heart function.

The dependence of the changes in cerebral venous pressure (in the sagittal sinus) upon those in the systemic venous pressure was found

to be linear, the mean correlation coefficient varied from 9.900 to 9.993 and the regression coefficient varied from 0.66 to 1.72 in different experiments (Mchedlishvili et al., 1979a). This meant that during the increase of the systemic venous pressure by 1 mm Hg the cerebral venous pressure rose by ca 0.87 mm Hg.

The brain volume changes in the present experiments could not depend upon fluctuations of the volume of the cerebro-spinal fluid in the ventricular system because of an effective drainage of the fourth ventricle. Neither were they influenced by intrathoracic volume changes since the lungs were artificially ventilated at a constant rate and volume throughout the experiments. Thus the brain volume changes reflected, first, the blood volume changes in the brain vasculature and, second, the changes in the brain tissue volume, which might vary due to accumulation of water (during the development of edema) or its decrease. The amount of water filtrated from blood to brain tissue was estimated previously in the same experimental conditions and was found to be ca 1.3 per cent of the whole brain volume (Mchedlishvili et al., 1979a).

Two experimental models of brain edema were used in the present studies, the first having been introduced recently (Mchedlishvili et al., 1979a). Repeated venous stagnation within the brain produced brain edema virtually in all the experiments, though at a different rate varying from ten minutes to two hours. Edema development was probably due to the following factors: a) a considerably long exposure of the brain surface to atmospheric air in animals previously subjected to a complicated surgical procedure and existing as „chest-head" preparation throughout the experiments, and b) a repeated increase in the systemic venous pressure resulting in venous blood stagnation in the brain entailing circulatory hypoxia, tissue acidosis, as well as considerable rise in the brain intravascular pressure. The second experimental model used in the present experiments was the controllable brain ischemia (Mchedlishvili, 1973) which was found to be quite suitable for studies of the postischemic brain edema development (Mchedlishvili et al., 1976, 1979b).

The present experiments revealed that the elastic and plastic mechanical properties of brain tissue, estimated from the rate of its protrusion from the craniotomy hole and from the delay of reestablishment of its initial shape became significantly changed: both the deformability and the area of hysteresis increased in the preedemic state of the brain. This should certainly facilitate the transfer of water from the blood microvessels to the interstitial spaces and to distend the latter. However, when the volume of fluid increases consi-

derably in the interstitial compartments (at development of edema) this should affect the interstitial pressure causing its increase (Reulen, 1976). This may in turn change the mechanical properties of the brain, namely decrease considerably both the deformability and the area of hysteresis, as shown in the present studies to occur during edema. Besides, it cannot be excluded that the latter changes may be also active in their nature, and if so they would cause restriction of further transfer of water from blood and, thus, impede the development of brain edema. If this assumption is true such changes should be considered as a compensatory response which force water passage both back to the blood stream as well as to the cerebrospinal fluid spaces. The possibility of an active withdrawal of water from the brain tissue during edema development was suggested in our recent studies (Mossakowski et al., 1980).

The other consequence of the changes in the mechanical properties of brain tissue during the preedematous state is the dilatation of the cerebral blood vessels, namely of capillaries and veins. It is well known that their diameter is determined by two factors: the intravascular pressure and the conversely directed vascular wall tension. The anatomic structure of their walls, unlike that of arteries and arterioles, is such that the latter factor is to a great extent determined by the mechanical properties of surrounding tissue. The index of tissue deformability of the brain obtained in the present experiments showed its increase during the preedematous state of the brain. Such changes seem to be responsible for the tendency shown in our recent studies (Mossakowski et al., 1980) to accumulate excessive amount of blood within the brain vessels during development of edema.

Recent studies (Mchedlishvili et al., 1979a, 1979b) have focused on the tissue changes which seem to be crucial in the pathophysiological mechanism of development of brain edema. Besides the changes in the mechanical properties of the brain tissue, also other abnormalities may be responsible for the excessive hydratation of the brain tissue in the course of edema development, and among them the increase in osmolarity of the tissue due to breakdown of high molecular weight compounds occurring while the tissue is damaged (Hossmann, Takagi, 1976). In addition, disturbance in cellular membrane function entailing disorders in ion and water transport through the membranes during development of brain edema may occur (Bakay, Lee, 1965; Reulen, Brendel, 1967; Mchedlishvili et al., 1979a), as a result of which water easily passes from extracellular to intracellular compartments and therefore the colloid osmotic pressure of the interstital

fluid should respectively increase. In turn, all the tissue changes mentioned above seem to depend on metabolic abnormalities occurring in the brain as a result of hypoxia, hypercapnia, acidosis, etc.

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ZMIANY MECHANICZNYCH WŁAŚCIWOŚCI TKANEK MÓZGU JAKO CZYNNIK SPRZYJAJĄCY ROZWOJOWI OBRZĘKU

Streszczenie

W doświadczeniach przeprowadzonych na królikach wywoływano obrzęk mózgu przy pomocy powtarzanego zatrzymania odpływu krwi żylnej lub przez niedokrwienie. Określano zdolność tkanek mózgu do odkształcenia i ich plastyczność w rozwoju obrzęku. Stwierdzono, że zarówno zdolność do odkształcenia (podatność mechaniczna), jak i plastyczność mózgu, znacznie wzrasta w okresie przedobrzękowym, a zmniejsza się (nawet poniżej wartości wyjściowych) po wytworzeniu się obrzęku. Zmiany mechanicznych właściwości mózgu autorzy uważają za czynnik wpływający na rozwój obrzęku.

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ИЗМЕНЕНИЯ МЕХАНИЧЕСКИХ СВОЙСТВ ТКАНИ МОЗГА КАК ФАКТОР, СПОСОБСТВУЮЩИЙ РАЗВИТИЮ ОТЕКА

Резюме

В экспериментах, проводившихся на кроликах, с помощью повторяющегося венозного застоя крови или исхемии в головном мозгу постоянно развивался отек. В процессе развития отека мозга определяли деформируемость и пластичность его ткани. Было показано, что деформируемость (механическая податливость) и пластичность значительно возрастают в предотечный период, но уменьшаются после развития отека, оказываясь ниже контрольных (исходных) величин. Эти изменения механических свойств рассматриваются как факторы, влияющие на развитие отека головного мозга.

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