DYNAMICS OF CHANGES IN BLOOD VESSELS OF THE CEREBRAL CORTEX DURING THE DEVELOPMENT OF POSTISCHEMIC EDEMA

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The results of investigations of the cerebral circulation in edema of different etiology [6,7,8,9] have shown that the vasomotor activity of the arterial system of the brain is responsible for bringing about changes in the circulation which are mainly compensatory in character. On the other hand, much experimental evidence has been obtained suggesting that the blood-brain barrier is disturbed in cerebral edema [1,2,14,15,18,19,20]. Meanwhile, substances injected into the brain tissue are retained and are removed from it much more slowly [13]. It might be suggested that the disturbances of the barrier function of the vascular walls of the brain, on the one hand, and the changes in the properties of the "supporting" tissue, so that fluid passes more easily from the blood into the brain tissue, and less easily out of that tissue, on the other hand, must play an important role in the pathogenesis of edema. It has not yet been explained, however, what changes in the structure of the vessel walls and of the supporting tissue of the brain lie at the basis of these processes.

The object of the present investigation was to study the vascular walls of the cerebral cortex and the surrounding tissue in the process of development of postischemic edema of the brain. Edema of this type regularly develops when the circulation of the blood into the brain is temporarily halted by bleeding, and the cerebral circulation is then restored by the intra-arterial infusion of blood [4,10,12].

EXPERIMENTAL METHOD

Investigations were carried out on 32 adult rabbits, some of which were anesthetized with urethane (1 g/kg), but most of which were given a local (procaine) but not a general anesthetic.

The state of the cerebral circulation was assessed by recording the level of the arterial pressure in the aorta and the circle of Willis. On the basis of the difference between these pressures, the state of the system of the internal carotid and vertebral arteries was judged [3,5]. The pial arteries were investigated by serial microphotorecording [4]. Withdrawal of blood and its reinfusion were carried out by means of a blood pressure compensator [3], the cannula of which was tied into the abdominal aorta below the origin of the renal arteries (in some experiments into the common carotid artery).

The vessels of the cerebral cortex were investigated histologically after intravital fixation. In standard conditions, under a pressure corresponding approximately to normal, 30-40 ml of a mixture of formalin (12%) and isotonic saline, diluted half and half with ethyl alcohol (96°), was injected through one of the internal carotid arteries into the cerebral vessels. The brain was left in this solution for 24 h. Next day the material was transferred into 12% formalin solution (in physiological saline) for 3 days.

The brain was cut on a freezing microtome. Sections 30 μ in thickness were stained by various methods — Van Gieson, Mallory, Bielschowsky, hematoxylin-eosin as modified by Katsnelson — and impregnated with silver by Klosovskii's method. In most cases, however, unstained sections were investigated. In these, the various structures could be clearly seen because of differences in their refractive properties. In this way, the nonelectively stained individual elements of the vessel wall could be obtained and the general picture of the tissue could be seen fully.

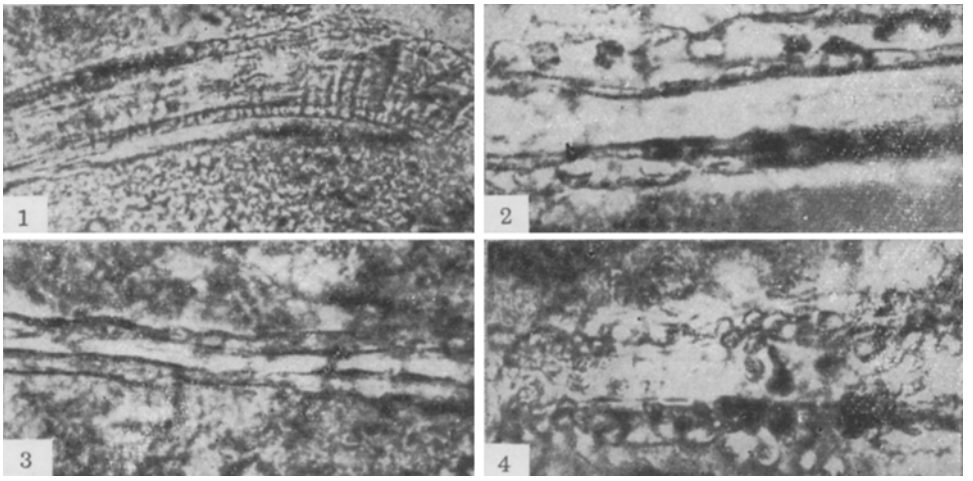

Fig. 1. Changes in the wall of the arteries and veins in the parietal cortex after restoration of its circulation. Duration of ischemia 1-2 min. Intravital fixation. Unstained preparations: 1) artery of the cerebral cortex in normal conditions (control), magnification 40 × 10; 2) swelling of the arterial wall arising during ischemia and leading to constriction of the lumen of the vessel, magnification 40 × 10; 3) separation of the connective-tissue components of the arterial walls into layers, observed after restoration of the circulation, with the formation of intramural spaces in which can be seen erythrocytes which have entered them by diapedesis, magnification 40 × 10; 4) the same, in the veins, magnification 40 × 10.

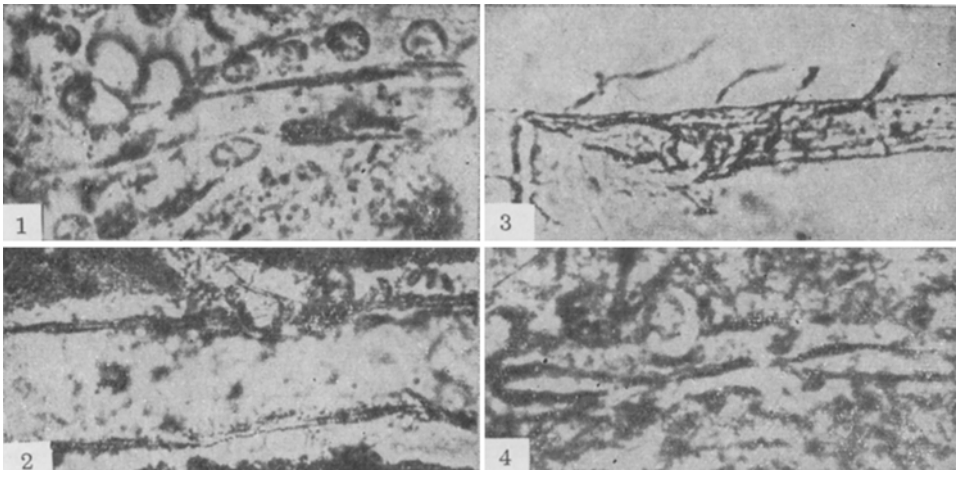

Fig. 2. Changes in the wall of the blood vessels in the parietal cortex in the process of development of postischemic edema of the brain: 1) swelling and separation into layers of the capillary wall, with the formation of intramural spaces in which can be seen erythrocytes which have entered them by diapedesis (pre-edema), magnification 90 × 7; 2) perivascular fissures formed during preparation of the histological sections (pre-edema), magnification 40 × 10; 3) fluffing of the surface of the walls of a vessel isolated from the surrounding tissues in the period of pre-edema, magnification 40 × 10; 4) swelling of the walls and varicose changes in the lumen of a capillary of the cerebral cortex in postichemic edema, magnification 90 × 7.

The degree of visibility of the various structural elements of the vessel walls and of the surrounding tissues in the u stained sections may be judged from the photomicrographs (Figs. 1 and 2). The parietal, temporal, and olfactory regions of the cortex were investigated.

The material for investigation was fixed before bleeding (control), during complete arrest of the circulation to the brain for 1-2 min by bleeding, and at various periods after restoration of the circulation. In this way, the dynamics of the changes in the walls of the cerebral vessels and the surrounding tissue could be followed during the development of postischemic cerebral edema.

EXPERIMENTAL RESULTS

When blood was taken from the abdominal aorta, the general arterial pressure fell progressively. The results of the microscopic investigation of the brain surface showed that the blood flow in the arteries and veins of the pia (and consequently, in the capillaries of the cortex also) gradually slowed and finally stopped completely. When the circulation in the brain was restored after intra-arterial blood infusion, considerable dilatation of the pial arteries took place. This phenomenon was evidently a manifestation of postischemic (reactive) hyperemia in the brain. This vasodilatation of the arteries on the brain surface lasted approximately 20-30 min after restoration of the circulation [4].

When the walls of the cortical vessels were fixed during the period of 1-2 min when the blood flow was arrested, or in the first few minutes after its restoration, increasingly severe morphological changes were found in them. These changes appeared in the stage known as pre-edema [7], i.e., after the action of the etiological factor and before the appearance of clear macroscopic signs of edema. The characteristic changes of pre-edema in the walls of the cerebral vessels were as follows: a) swelling of the structural elements of the walls, which was found in arteries and veins of different caliber, and also in the capillaries, although in the last named these changes were less clearly defined than in the larger vessels (compare Fig. 1,1 and Fig. 1,2); b) separation of the layers of the connective-tissue membrane of the walls of the arteries and veins, appearing slightly later than the swelling of the component parts of the vessel walls themselves. In these circumstances, extensive intramural spaces were formed between the layers in which erythrocytes escaping from the lumen of the vessels could often be seen (Fig. 1,3 and 1,4). This separation of the layers was least marked in the capillary walls, where it took the form of splitting into usually two thin layers (Fig. 2,1). It may be assumed that these layers are of connective-tissue origin, for they stained red by Van Gieson's method, black when impregnated with silver, bright blue by Mallory's method, and green by Matsuura's method. The larger the diameter of the vessel, the more clearly defined the separate layers of its walls.

The swelling and separation into layers of the vessel walls of the cerebral cortex in the stage of pre-edema appeared simultaneously with the changes in their barrier properties; the vessels became permeable even to particles as large as erythrocytes. After restoration of the circulation in the brain, an abundant diapedesis of erythrocytes was always found, not only in the capillaries, but also in the arteries and veins of different caliber (Fig. 1,3 and Fig. 2,1 and 2,2). The preliminary injection of trypan blue intravenously (10 ml of a 2% solution, injected over a period of 30 min) also showed that after temporary ischemia of the brain the permeability of the barrier of the vessels walls in the brain was increased. Macroscopically, the brain was stained blue only when the morphological changes in the vessel walls were detected microscopically in the period of pre-edema. If these changes were absent, the trypan blue did not pass through the barrier of the vessel walls.

On account of the swelling and separation into layers, the walls of the cerebral vessels became much thicker. Their external diameter did not change appreciably along the course of the vessels, but their internal diameter was considerably reduced, to a mean value of 61% of the original diameter (these figures were obtained from measurements of about 1000 vessels by means of an ocular micrometer). It is difficult to decide how this influences the resistance to the blood flow, for narrowing of the lumen of such small vessels is known to cause an increase in the fluidity of the blood (the Foreus–Lindquist phenomenon).

Besides the changes described above in the vessel walls, changes were also observed in the tissue immediately surrounding them. The cerebral vessels are connected to the surrounding tissue mainly by neuroglia and by connective-tissue bands which, according to Camarmayer [17], stretch from one vessel to another and form what may be called the connective-tissue skeleton of the brain. In pre-edema, all these bands were apparently fragmented, as a result of which the vessels easily fell away from the sections or came apart in some places from the brain substance, thus forming perivascular spaces (Fig. 2,2). The surface of the vessels isolated in this way was covered by large numbers of broken bands, resembling villi (Fig. 2,3), among which the conical pedicles of the astrocytic glia and the connective-tissue bands could easily be differentiated.

Hence, in the normal brain, there are no perivascular spaces. They were formed only in the early stages of development of edema, in most cases in connection with mechanical action on the tissue during preparation of the histological sections. The possibility of the postmortem formation of the "perivascular spaces" in edema was also mentioned by Beranek and co-workers [16]. However, the essential condition for their appearance is the development of changes in the functional properties of the connective-tissue and neuroglial elements of the cerebral cortex surrounding the vessels.

When the vessel walls and the surrounding tissue were fixed 5-10 min after restoration of the circulation (sometimes after repeated bleeding), and macroscopic signs of edema had appeared, further changes could be seen in the histological preparations. The walls of the arteries, capillaries, and veins nearly everywhere had become loose and granular. The structural details of the media and adventitia were indistinct, so that it was often difficult to draw the line between them. In most vessels, neither the individual layers nor the intramural spaces could be differentiated, and only in individual cases were traces of the layered pattern still present. Blood cells could no longer be seen in the thickness of the vessel walls or in the surrounding tissues. All the changes enumerated above led to slight condensation of the vessel walls. Although the endothelial cells remained swollen and continued to encroach on the lumen of the vessels, the lumen of the arteries and veins was not substantially reduced, whereas in the case of some of the precapillaries and capillaries the reduction in the lumen was appreciable. Another factor causing this picture was the varicose changes in the width of some of the small vessels (Fig. 2,4). The results of measurements of the lumen of the arteries, capillaries, and veins showed that in edema its mean value was 84% of that in the corresponding vessels in control experiments (as mentioned above, in the stage of pre-edema the degree of constriction was much greater, 61% of the initial diameter). This relative dilatation of the lumen and decrease in the thickness of the walls in postischemic edema might have been determined by the fact that, as a result of dilatation of the afferent pial arteries and the increase in the intravascular pressure, the endothelium and the other layers of the walls of the cortical vessels were displaced to the side; this applied above all to the cortical arteries.

After the development of edema, changes subsequently took place in the tissue immediately surrounding the vessels. These changes took the form, in particular, of changes in the refractive properties of its elements, so that they were less clearly visible in unstained sections; the connective-tissue bands and the neuroglial processes were differentiated with difficulty. The brain became more compact. The walls of the blood vessels were intimately connected with the surrounding tissue and showed no tendency to come apart from it, and no perivascular spaces were formed. This shows that, in cerebral edema, the increase in the "fragility" of the connective-tissue bands and the neuroglial processes which, in the period of pre-edema, led to a disturbance of the connection between the vessel and the surrounding tissues, was no longer observed in cerebral edema. It may be suggested that it is these changes which are in fact responsible for the increase in permeability of the vascular barrier in the period of pre-edema. This permeability was evidently considerably disturbed in the period of pre-edema, and subsequently began to recover. The fact that, in established edema, the vessel walls were condensed and no erythrocytes were found, either in the thickness of the walls or in the surrounding tissue, is further evidence in support of this suggestion.

Most of the changes in the arteries, capillaries, and veins of the cerebral cortex described in this paper were undoubtedly purely pathological and arose as a result of ischemia of the brain tissue, possibly on account of anoxia. The possibility remains, however, that these changes may arise initially as compensatory reactions of the vessel walls to the deficient blood supply to the brain, for the permeability of their barrier is increased and the nutrition of the brain tissue is improved.

If postischemic edema develops throughout the brain, then despite the restoration of the initial level of the general arterial pressure and the considerable dilatation of the pial arteries, the blood supply to the brain may remain low. This is explained, on the one hand, by the compensatory constriction of the system of the internal carotid and vertebral arteries, which lasted for 20-30 min after severe cerebral ischemia in G. I. Mchedlishvili's experiments [4], and on the other hand it may be dependent on the reduction in the lumen of the arteries, capillaries, and veins of the cortex which was discovered in the present investigations. The findings described by B. I. Slovikov [11], who showed that the oxygen tension in the cerebral cortex remained low for 15 min or more after the general arterial pressure had been restored, using a polarographic method, demonstrated a deficiency in the blood supply to the brain following a period of ischemia.

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