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Pathogenetic role of circulatory factors in brain edema development

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Abstract

Sufficient experimental evidence has been accumulated at present, proving that changes in cerebral blood circulation are largely involved in brain edema development. On the one hand, they might be an immediate cause of edema, e.g., a significant rise of the systemic arterial pressure surpassing the limits of cerebral blood flow autoregulation, or cerebral ischemia damaging brain tissue and the blood-brain barrier. On the other hand, circulatory changes, e.g., systemic arterial and venous pressure variations, as well as changes in cerebrovascular resistance or in the microcirculation of cerebral tissue, might be the factors which affect in different ways the development of edema of various etiologies. The effects of these circulatory changes may have dual implications, being either malignant, i.e., aggravating edema development, or compensatory, i.e., restricting or in some cases even eliminating brain edema. Knowledge of the circulatory changes is an essential tool in neurosurgical practice, providing for effective treatment of this severe pathological process in the brain.

Keywords: Arterial and venous pressures, brain edema, cerebral blood flow, cerebrovascular resistance active changes, disturbance of cerebral microcirculation.

1 Introduction

From the pathogenetic point of view, there may be pointed out three factors, which play the most important part in brain edema development [12]:

- circulatory factors, among which the primary role is played by the blood flow rate in microvessels (since blood is the actual source of edematous fluid) and the intravascular blood pressure level (driving water with solutes from blood to tissue compartments)*;
- specific structural and functional properties of microvascular walls (the blood-brain barrier), which control both passive and active transport of substances from blood to tissue space, and vice versa; and
- tissue factors, involving osmotic properties of interstitial fluid, mechanical properties of tissue elements, transport of substances across astrocytic and neuronal plasma membranes, etc., which are responsible for retaining the excessive amount of extra- and intracellular fluid in brain tissue.

Circulatory changes, just as any other changes in the body, which are involved in brain edema development, may in principle operate in two diametrically opposite directions. On the one hand, they may be pathological, i.e., provoking structural and/or functional alterations in the brain or outside it and thereby leading to brain edema development. On the other hand, the changes may play a compensatory role, i.e., restricting pathological alterations and thus preventing from brain edema development. Such kind of compensatory changes regularly occur in the living organism in response to any pathogenic effect and are nothing but physiological regulating mechanisms triggered by deviations from homeostasis. Both from the theoretical and practical points of view, it is highly important to differentiate between, and appraise correctly, these two kinds of changes during brain edema development, in order to choose only those therapeutic means which reduce or delete pathological changes and at the same time activate compensatory events. However, it is not always an easy task to point out precisely, which of the changes can be considered noxious, and which – beneficial, since all of the changes are complexly interrelated in the body and what is more: some of them might have dual implications, i.e., being positive from one point of view, and negative from the other.

During investigations into brain edema development, various experimental models were applied. In

* A significant part is also played by the osmolarity of blood plasma, which counteracts the water transfer from blood to interstitial spaces, but this factor will not be considered in the present article.

the present author's view it is not so much necessary to look for models maximally approaching natural conditions of human pathology, as to apply in the first line those experimental conditions, which provide accumulation of maximum amount of new knowledge on the functional processes in the body bringing about brain edema development or its elimination.

When any edema-producing factor, or factors, affect the brain, edematous changes in it develop within various time spans. This period was found to be rather different even when analogous or "standard" (in cases of experimental work) pathogenic factors affect the brain. Within this "latent" period, there occur certain changes in the brain, which ultimately lead to the development of edema. These changes, although not sufficiently identified as yet, might be edema type-specific. The state of the brain preceding the occurrence of obvious signs of edema was termed as preedema [7]. It would be most essential to identify the preedematous changes, since it is just they that make brain tissue predisposed to edema development, and to eliminate them, in order to "nip in the bud" this pathological process.

2 Circulatory changes in the brain during edema development

The majority of data considered below belong to the author's experimental research. This is bound to the fact that the involvement of circulatory changes in brain edema development has been the subject of detailed analysis performed throughout the recent 25 years in this laboratory. Studies by other researchers concentrate mostly on blood-brain barrier and tissue factors, rather than on the role of pure circulatory changes in the brain during edema development.

Cerebral blood flow was assessed using various techniques and in different experimental models of brain edema. In the majority of studies blood flow was found to be reducing with the development of edema in cerebral tissue [5, 16, 17, 18]. Such circulatory changes have been most often interpreted by researchers as a result of elevated interstitial pressure causing compression of minute blood vessels in the brain.

Figure 1 illustrates the dynamics of cerebral blood flow changes with gradual development of osmotic

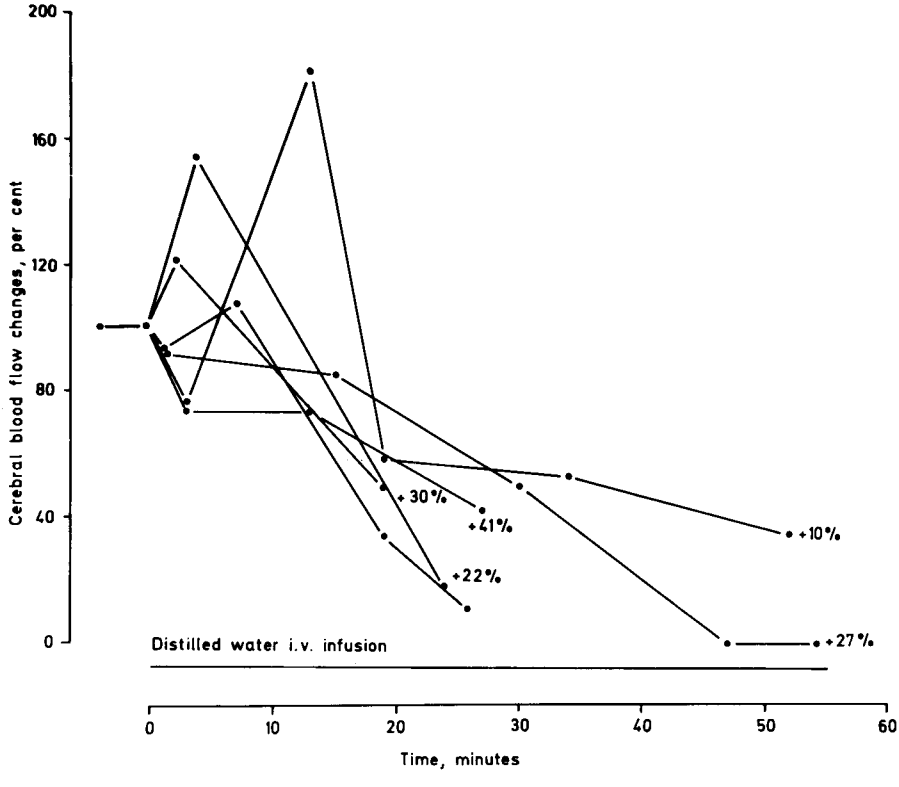

Figure 1. Cerebral blood flow assessed using hydrogen clearance technique in the course of osmotic brain edema development in six rabbits. Figures indicate increase in water content of brain tissue at the offset of individual experiments (experiments by SIKHARULIDZE and MCHEDLISHVILI [19]).

edema in the brain: following initial, though not regular, increase of cerebral blood flow, the latter undergoes regular reduction, progressing with the increase of brain edema.

Systemic arterial pressure affects brain edema development in a significant way, especially in cases when it exceeds the limits of cerebral blood flow autoregulation. Its rise brings about the elevation of blood pressure in cerebral microvessels, resulting in the enhanced fluid transudation from blood to brain tissue compartments and may even become the direct cause of hypertensive brain edema [1, 3]. The spreading of cold injury-induced and ischemic edemas was found to be directly dependent upon the level of the systemic arterial pressure [2, 6]. Even in animals with no brain edema, a rise in the arterial pressure caused considerable fluid filtration to cerebral tissue spaces across the blood-brain barrier, so that brain volumetric increase was found dependent by 50% on the enhancement of intravascular blood volume, and by another 50% on the increase of brain tissue volume due to fluid transfer to extracellular compartments [15].

Conversely, lowering of the systemic arterial pressure reduces blood pressure level in cerebral microvessels and causes the decrease of fluid transfer from blood to brain tissue, thereby restricting brain edema development. In experiments with rabbits, during the development of postischemic brain edema systemic arterial pressure level showed a regular decrease (Figure 2). This presumably indicates a physiological mechanism operative in the body under natural conditions, serving to reduce edema development.

Systemic venous pressure has a very significant effect upon blood pressure level in cerebral microvessels, inasmuch as there seems to be no "autoregulation" mechanism in the cerebral venous bed (in contrast to the arterial bed): a linear relationship was found between the systemic and cerebral venous pressures [14]. Therefore, the effect of elevated systemic venous pressure is considerably greater than that of arterial pressure. This was demonstrated in experiments detecting the dependence of cerebral blood volume on the respective rises of either the systemic venous or arterial pressure (Figure 3). It follows that the elevation of the systemic venous pressure in patients should have an especially noxious effect, from the point of view of brain edema development.

Resistance to blood flow in the cerebral arterial bed was found to undergo specific changes in the course of brain edema development. In this case, particular

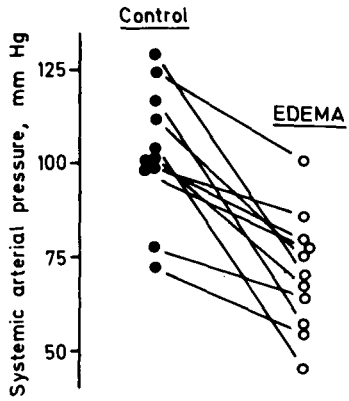

Figure 2. Lowering of systemic arterial pressure level after development of postischemic brain edema in rabbits (reproduced from MCHEDLISHVILI et al. [13]).

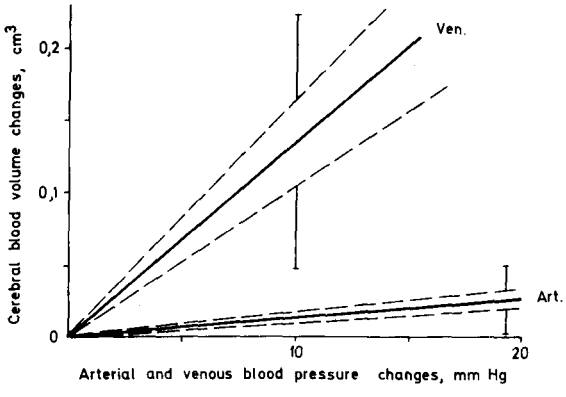

Figure 3. Effects of systemic arterial (Art.) and venous (Ven.) pressures upon cerebral blood volume and, hence, blood pressure rise in cerebral microvessels under open skull conditions in rabbits. Mean (solid lines), mean errors (dotted lines), and standard deviations (vertical lines) are presented.

emphasis should be put on two, functionally most active parts of the cerebral arterial bed, i.e., the major arteries (internal carotid and vertebral arteries) and the pial arterial network, since it is just these arterial portions that were found to be most actively involved in the regulation of specific types of cerebral blood flow [8]. Resistance changes in the major arteries, assessed by simultaneous recording of the arterial pressure gradient along these vessels, evidenced for their dilatation following brain trauma (in the preedematous period), but this vascular response changes to constriction as soon as edema has already developed in the brain (Figure 4). The diameter of pial arteries (investigated directly under open skull conditions where extravascular pressure

remained constant) displayed a similar vascular response, i.e., dilatation during preedema after trauma, and constriction after the occurrence of edema (Figure 5). However, these data were quantitatively incomparable to each other, because of the specificity of the applied techniques. In recent experiments, the vascular resistance was assessed so as to compare it in various parts of the cerebral vascular bed in the course of osmotic brain edema development. The most prominent increases in resistance were found in the major arteries of the brain, in contrast to smaller cerebral vessels, and were shown to be directly dependent upon the extent of edema (Figure 6). It seems to arise no doubt, from the point of view of the anatomical arrangement of the major and pial arteries, and specific experimental conditions, that the constriction of both of these arterial

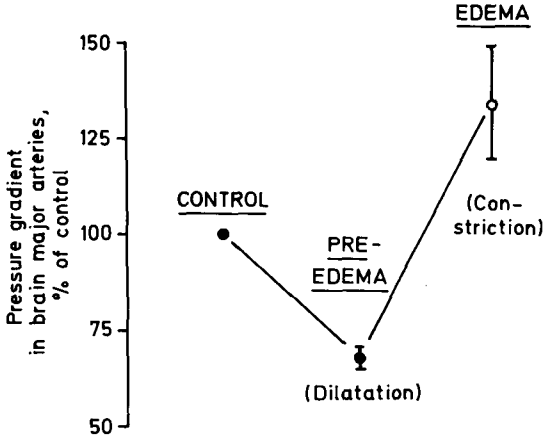

Figure 4. Functional behaviour of brain major arteries (internal carotids and vertebrals) in the course of edema development following standard mechanical brain trauma in dogs (data from MCHEDLISHVILI and AKHOBADZE [10]).

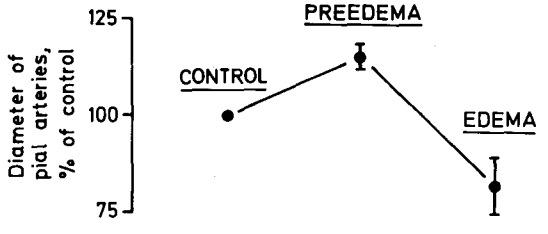

Figure 5. Diameter changes of pial arteries in the course of brain edema development following standard mechanical brain trauma in rabbits. The arteries are located at a sufficient distance from the locus of trauma and studied under open skull conditions (data from MCHEDLISHVILI and AKHOBADZE [10]).

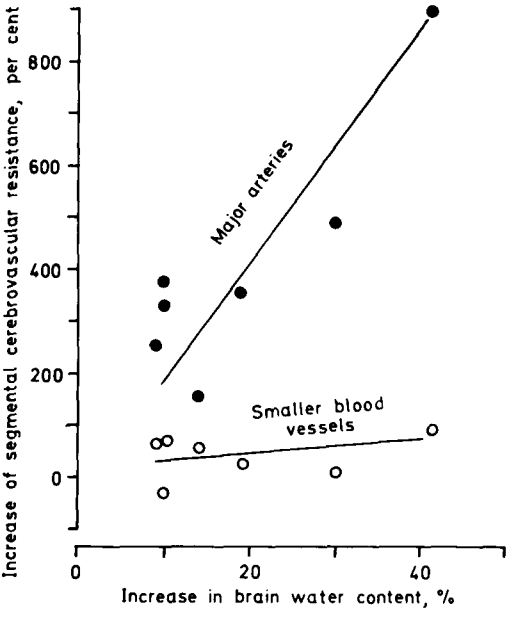

Figure 6. Segmental resistance changes in various parts of the cerebral vascular bed against the extent of osmotic brain edema (diverse water contents in cerebral tissue) in rabbits (reproduced from SIKHARULIDZE and MCHEDLISHVILI [19]).

segments of brain vasculature during edema is an active vascular response decreasing the blood flow, pressure, and volume in the brain. As for intracerebral arteries, in particular the radial arteries penetrating the cerebral cortex, there has been obtained as yet no conclusive evidence on their behavior in the course of brain edema development.

The increase of cerebrovascular resistance related to naturally developed active constriction of cerebral arteries, which causes reduction of cerebral blood flow, can be interpreted as a compensatory event, since it necessarily results in restraining the transudation of edematous fluid from microvessels to brain tissue interstitial compartments, thereby restricting brain edema development.

Thus, proceeding from the available experimental results on the arterial behavior of the brain, we concluded that cerebrovascular resistance underwent active increase during the development of brain edema. In generalized edema in the brain, the vasoconstriction was especially pronounced in brain major arteries and was most probably due to a neurogenic reflex, like the one observed during the increase of cerebral blood volume [8]. It may be conjectured that in case of edema development the vasoconstrictor reflex is triggered by mechanorecep-

tors of the cerebral meninges. However, the particularities of this physiological regulatory mechanism remain as yet open to detailed studies.

Cerebral microcirculation was found to undergo specific changes during edema development. These changes were investigated in rabbit parietal cortex under conditions of traumatic, as well as postischemic, brain edemas [11, 16]. The number of active capillaries (i.e., those with flow of red cells and plasma in their lumina), estimated in thick microscopic preparations after cerebral tissue in situ fixation, was found to be reduced, preferentially in cases with a well-pronounced edema. The diameter of such capillaries was altered only slightly and showed narrowing mainly when the accumulation of water in edematous tissue became very considerable (Figure 7). The diameter of plasmatic capillaries (i.e., those filled only with blood plasma, without red cells) was regularly found much smaller than that of active capillaries and displayed actually no alterations with the progress of edema in the cerebral cortex (Figure 7). There were found no significant variations in the number of plasmatic capillaries, whereas the capillaries with stases regularly increased in number, along with the enhancement of edema (Figure 8). Direct evidence has been obtained that the aggregability of red blood cells in cerebral vessels increases regionally during the development of traumatic and postischemic brain edemas [9, 11]. In addition, the deformability of red blood cells studied inside cerebral capillaries was found to decrease during brain edema, this being detectable in the narrowest capillaries [16].

Consequently, specific changes have been detected in the microcirculation of the cerebral cortex during edema development: transformation of a significant part of blood capillaries into the plasmatic form, with a smaller diameter, thus indicating a reduced local hematocrit in the cerebral microcirculation. Formation of stases in a great number of capillaries due to intravascular red blood cell aggregation, and the lowering of these latter's deformability, certainly results in the disturbance of normal blood fluidity in the cerebral microvascular bed.

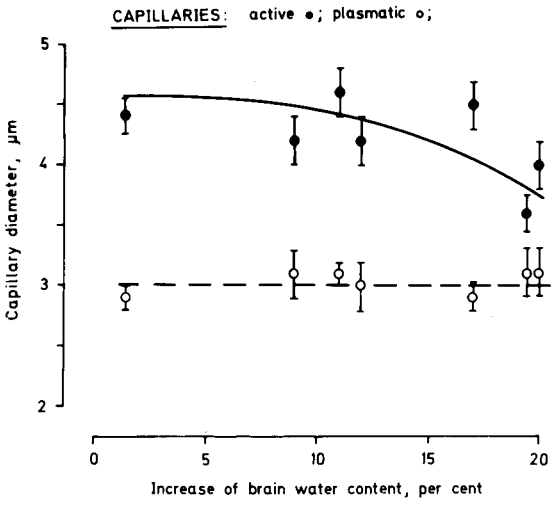

Figure 7. Diameters of active (•) and plasmatic (o) capillaries in the neocortex under conditions of postischemic brain edema of various extent, judged from diverse water contents in the cerebral cortex (modified from MCHEDLISHVILI [9]).

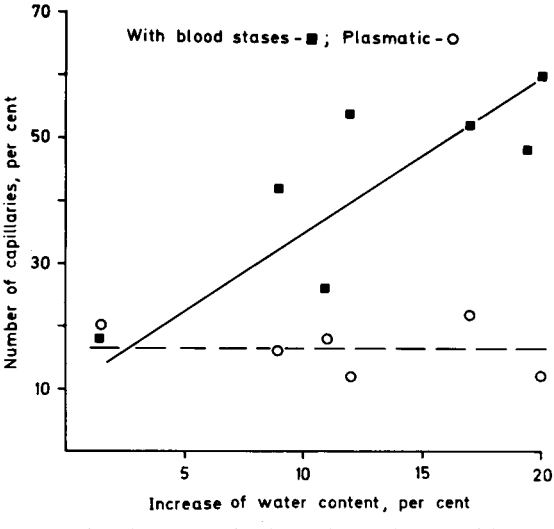

Figure 8. Amount of plasmatic capillaries (o) and capillaries with stases (■) in the neocortex during postischemic brain edema of various extent, judged from diverse water contents in the cerebral cortex (modified from MCHEDLISHVILI [9]).

3 Conclusion

Among the principal pathogenic factors involved in the development of brain edema circulatory changes play a crucial role from the point of view of provokation of, and compensation for (reduction or elimination), brain edema. The effect of circulatory changes might be rather complex. Thus, a remarcable increase of the systemic arterial pressure (during acute or chronic arterial hypertension simultaneously with the insufficiency of cerebral blood flow autoregulation) or of the systemic venous pressure (during extreme and noncompensated venous blood stagnation, both local and systemic), as well as the de-

crease of cerebrovascular resistance (observed, e.g. following brain trauma in the preedematous period) might provoke brain edema by elevating blood pressure in cerebral microvessels. Furthermore, a temporary extreme insufficiency of blood supply to brain tissue during ischemia of various origin, entailing functional and/or strucutral damage of cerebral tissue elements ("cytotoxic brain edema" according to KLATZO [4]), might also provoke brain edema.

In addition, the development of brain edema of any origin might be affected by secondary circulatory changes of pathological character, provoking further damage of vascular walls of cerebral tissue elements. Among circulatory changes considered in the present article those are microcirculatory disturbances in the brain related to changes of rheological properties of blood in microvessels, namely the enhanced intravascular red blood cell aggregation entailing the formation of stases in capillaries, as well as the lowered red cell deformability, which becomes especially critical under the conditions when a tendency is in evidence of reducing microvascular lumina in the brain during edema.

While considering presently available data on circulatory changes occurring systemically in the living organism or locally in the cerebral circulation, we saw that there might occur inherent changes, which are to be interpreted as compensatory ones, since they tend to reduce brain edema formation. All the possible normal physiological mechanisms operative in the body serve to compensate for, i.e., reduce, the development of edema in the brain. Such are the lowering of the systemic arterial pressure and the elevation of cerebrovascular resistance, as well as the decrease of blood flow rate in cerebral microvessels. These circulatory changes reduce the transport of fluid with various substances dissolved in it across the walls of microvessels to cerebral tissue compartments, and thus serve to restrict edema formation.

However, circulatory changes might as well exert a negative effect, which is certainly the case with the just described changes in the circulatory bed. For instance, if blood flow reduction is superfluous, it can clearly lead to the deficiency of blood supply to, and the damage of, brain tissue elements. Therefore, the scope of compensatory effects, occurring intrinsically in the body, has to be, and certainly is, always controlled by feedback regulatory mechanisms (provided, the natural state and hence the normal physiological mechanisms of the patient have not been damaged by pathological disturbances). This problem becomes even more complicated when clinicians try to activate the body's natural compensatory effects by using various therapeutic means, particularly under conditions when the outcome is not sufficiently controlled by the appropriate techniques. In such cases the artificial changes produced, might prove qualitatively or quantitatively ina dequate and will therefore exert negative, rather than positive effects on the patient.

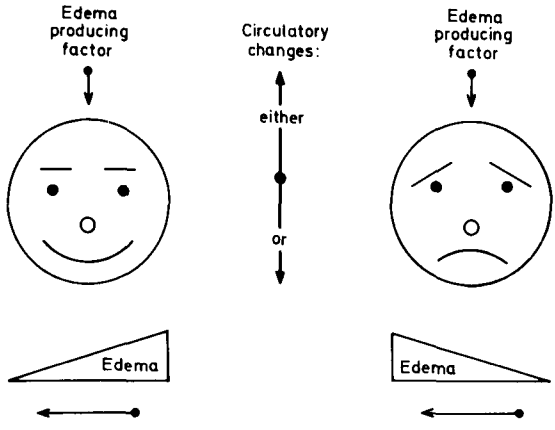

Figure 9. Possible effects of circulatory changes on brain edema development.

Consequently, the knowledge of the effects of circulatory changes upon brain edema development is an indispensable tool for clinicians in treating this severe pathological process of the brain, since the circulatory changes can be comparatively more easily controlled than the blood-brain barrier or tissue factors.

Proceeding from the present-day knowledge, and taking into account that each of the circulatory parameters, both systemic and cerebral, might be changed, naturally or artificially, in two opposite directions (i.e., increase or decrease), it may be conjectured that under specific conditions each of them can either provoke or restrict brain edema development. This conclusion is schematically presented in Figure 9.

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