The pathophysiological mechanisms of brain edema development have been reviewed by I. Klatzo, who described 2 main causes of cerebral edema — vasogenic and cytotoxic. According to Klatzo, vasogenic edema is caused by an increase in capillary permeability, while cytotoxic edema develops without such changes. An increase in vascular permeability during brain edema has attracted the attention of a number of investigators whose experimental results showed that different tracers, which normally did not penetrate the cerebral vascular walls when administered into the blood stream, were detected in the cerebral tissue with different kinds of brain tissue damage and subsequent edema development.

These data do not establish that increased vascular permeability is the crucial mechanism in the development of brain edema. The role of circulatory factors in the development of brain edema is certainly very important, since the edema is defined as excess accumulation of water in brain tissue and a main source of water is the blood circulating in the cerebral vasculature. Also, the level of the systemic arterial pressure plays an important role in the rate of edema development. However, a considerably more important role in the development of brain edema has been shown recently to be played by the systemic venous pressure.

In spite of the significance of circulatory factors, these factors appear to play a secondary role in the development of brain edema since the retention of water within the cerebral tissue seems to be dependent primarily upon tissue changes. Unfortunately, there is still very little knowledge of the nature of the cerebral tissue changes responsible for development of edema. Attention has been focused on 2 kinds of changes. In the early 1960s it was assumed that changes in the mechanical properties of cerebral tissue were important for development of brain edema, but no experimental evidence to prove this assumption has been obtained so far. Second, an increase in osmolarity of...
the cerebral tissue has been considered a factor causing brain edema, and there have been several recent studies on tissue osmolarity in edema.

The aim of the present study was, first, to gain further insight into the contribution of tissue factors in development of brain edema and, second, to add a new dimension to the possible kinds of tissue changes.

Method

Thirty-three adult rabbits of both sexes weighing 2.5 to 3.5 kg were anesthetized with Hexenalum (30 mg/kg body weight i.v.) and, subsequently, further immobilized with tubocurarin chloride (3 mg/kg i.p.).

Preliminary Surgical Procedure

For reliable control of the most important systemic circulatory parameters the experiments were carried out on the “chest-head” preparation in which the blood circulated in the chest (including heart, lungs and thoracic walls), and also in the neck and head of the animal. For this purpose, an incision was made along the sagittal line of the neck, a tracheotomy tube was inserted for artificial ventilation of the lungs, and a large craniotomy was made in the parietal region of the cerebral hemispheres. The dura mater was not opened until the beginning of the experiment. Through an incision along the sagittal line below the occiput the fourth ventricle of the brain was opened for draining the cerebrospinal fluid. The animals were heparinized (1,500 units/kg body weight).

Monitored Parameters

The systemic arterial pressure was recorded by means of a catheter inserted into the common carotid artery. The systemic venous pressure was recorded through a catheter in the jugular vein. The cerebral venous pressure was recorded through a glass canula in the sagittal sinus. The 3 pressure transducers (EMT-35) of the electromanometers of the Mingograf 81 (Elema, Sweden) were set at the same level as the animal’s heart atrium. The mean pressures were determined by electrical integration. Both the systemic arterial and venous pressures were stabilized, or changed, by using 2 independent pressurized reservoir systems, one connected with the abdominal aorta and the other with the vena cava. The reservoir systems were filled with blood-substituting colloids containing either Polyglukin, or Gelatinine (G. Mukhadze Institute of Hematology and Blood Transfusion, Tbilisi).

Brain volume changes were continuously recorded through a strain gauge, one end of which was fastened to the stereotaxic device and the other placed in contact with the brain surface in the parietal region. The contact end was a plate about 5 mm diameter. The strain gauge was switched into a Watson bridge whose signals were amplified by the preamplifiers EMT-12 with the DC-compensator EMT-16 of the Mingograf 81. The device was calibrated before each experiment so that it was possible to evaluate in the record the amount of brain surface expansion above the initial level. The brain, expanding into an almost circular craniotomy (diameter 2r) hole, may be considered as a spheric segment, since the pressure causing its expansion should be equal in all directions. The volume change of such a segment is proportional to change of its height (h) as determined from the following formula:

$$V_s = \frac{1}{6} \pi h (3r^2 + h^2) = \frac{1}{2} \pi r^2 h (1 + \frac{h^2}{3r^2}).$$

The area of the craniotomy hole $\pi r^2 = \text{const.} = S$. Under the present experimental conditions $h$ is always much smaller than the radius of craniotomy hole $r$ and therefore the size of $\frac{h^2}{3r^2}$ should be so insignificantly small that it can be ignored. Even if, for instance, $h = \frac{1}{2} r$, then $V_s = \frac{1}{2} Sh (1.08)$, i.e. $V_s \approx \frac{1}{2} Sh$, then the error would be 8 percent. But actually the changes of brain volume ($\Delta V_s$) are measured by changes of the height of the expanding brain ($\Delta h_b$):

$$V_s = \frac{1}{2} S \Delta h_b.$$ Under these conditions the error would be much smaller, since $\Delta h \ll r$. Proceeding from this proportionality the recorded brain level changes were designated as “the brain volume changes.”

The concentration of sodium and potassium in the extracellular fluid was monitored by sodium and potassium ion-selective electrodes on the surface of the parietal cortex.

All the parameters were recorded on the Mingograf 81 (Elema, Sweden). Since not all the parameters could be recorded simultaneously in rabbits, different combinations were used in individual experiments.

The brain water content was determined as a percentage of wet weight. The brain hemispheres were removed from the skull and all free fluid carefully wiped from the ventricles with filter paper. After we determined the fresh weight of the pieces of the parietal lobe, including cortex and white matter, the pieces were placed in a constant temperature oven for evaporation of water at 100° C until a constant weight was reached.

The experimental results were treated statistically and presented as mean values and standard errors.
FIGURE 1. Changes of the brain level in the craniotomy hole (ΔBrL) which reflect the brain volume changes under conditions of increase and subsequent decrease of the systemic venous pressure (ΔSVP) in a normal rabbit brain.

Testing Brain Resistance to Edema Development

An increase of the systemic venous pressure and, thus, overfilling the brain vasculature with blood, was found to be a factor contributing to the development of brain edema. A controlled artificial elevation of the systemic venous pressure was used to test the extent to which the brain is predisposed to edema development. The systemic venous pressure was gradually elevated by approximately 13 ± 1 mm Hg and then returned to its initial level by use of the pressurized reservoir system connected with the vena cava so that there was a linear progressive rise and then a drop. This procedure, with a progressive elevation and then fall of the systemic venous pressure, lasted approximately 4 minutes (see below). The brain volume changes were simultaneously recorded with the venous pressure changes and the relationship between these 2 parameters was further ascertained by plotting them on Cartesian coordinates. In some experiments an X-Y recorder was used. To determine the comparative magnitude of hysteresis, irrespective of the height of elevation of the systemic venous pressure and the slope of the curve, the area of hysteresis was determined and divided into the distance between the crossing-point of the X-Y axes and the bend point of the curve.

The results of experiments were interpreted as follows: 1) A rise of the curve on the plot meant an increase of blood volume in the brain vasculature and/or an increase in the brain tissue volume caused by edema; 2) a fall of the curve meant reversal of the above process; 3) hysteresis indicated that in spite of a decrease of the intravascular pressure the blood volume in the brain and/or the brain tissue volume remained increased (the latter indicated edema); 4) if the descending curve lowered under the ascending one it indicated that an active process caused the withdrawal of the blood from the brain and/or of water from cerebral tissue into the blood stream; 5) the slope of the ascending curve indicated the extensibility of the brain tissue.

The criteria for the appearance of edema in the brain at the end of the present experiments were: a) an increased brain volume when the systemic venous pressure was no longer increased; b) an increase in water content in the cerebral tissue as compared with the control; c) a considerable decrease in the slope of the ascending curve of brain volume changes during an increase of the systemic venous pressure; d) significant simultaneous increase in the potassium ion concentration and a decrease in the sodium ion concentration of extracellular fluid, indicating a disturbance of cell membrane function in the cerebral cortex.

FIGURE 2. Rise in the brain level in the craniotomy hole (ΔBrL). This reflects the increase of the brain volume changes and the decrease in the concentration of the sodium ions ([Na⁺]) with no detectable changes of the potassium ([K⁺]) in the extracellular fluid of the cerebral cortex during a short increase of the systemic venous pressure (SVP). The systemic arterial pressure (SAP) remained unchanged. These results indicated that the increase in the brain volume is, at least partly, dependent on the enhanced water filtration from the capillaries into the tissue spaces resulting in dilution of the extracellular fluid in it.
Results

In the tests designed to estimate brain resistance to development of edema, the systemic venous pressure (SVP) was raised gradually over 111.6 ± 9 sec by 13 ± mm Hg, and then lowered during the subsequent 113.2 ± 9 sec reaching its initial level as a rule. These changes in the venous pressure were followed by a temporary rise of the brain level at the recording site by 0.9 ± 0.01 mm, reflecting a change of the brain volume. At the onset of most experiments, a parallel relationship between the SVP and the brain level (i.e. volume) was observed. A rise of the SVP was followed by a brain volume increase, and an SVP decrease along with a brain volume decrease until they reached their initial values. These 2 parameters in the plots showed that, usually, there was no hysteresis initially (fig. 1).

The SVP affected the brain volume through an increase of the cerebral venous pressure. There was a linear relation between an increase of venous pressures in the cranial vena cava and in the sagittal sinus of the brain. The correlation coefficient varied from 9.900 to 9.993, and the regression coefficient varied from 0.66 to 1.72 in different experiments. The adequate regression equation was: $y = (0.776 \pm 0.45)x + 4.63$.

The results showed that simultaneously with the increase of the SVP, and hence of the cerebral venous pressure, there was a decrease in $[Na^+]$ with no marked change in $[K^+]$ in the extracellular fluid of the brain (fig. 2). The data obtained in all experiments are summarized in figure 3: the mean decrease of sodium in the tissue was 13 ± 1.4 mEq/l ($P > 0.001$) while decreases of potassium were insignificant: $- 0.28 \pm 0.44$ mEq/l ($P > 0.5$). As the cerebral intravascular pressure regained its starting value the sodium ion concentration in the extracellular fluid also showed a trend to return to its initial level. During later experiments when brain edema developed, the sodium ion concentration continued to decrease but at that time the changes were more marked, the decrease was 47 ± 13.4 mEq/l. This occurred simultaneously with an increase in potassium ion concentration in the extracellular spaces of the cerebral cortex by 48.5 ± 12.3 mEq/l (fig. 4).

In the course of testing the SVP increase and the brain surface level, and hence of the brain volume, the
response gradually changed. Initially the brain and the SVP changes were usually parallel in the plots*, as in figure 1 (these periods lasted up to one hour or even more in some experiments). Later, a delay in the decrease in brain volume during the drop of the SVP took place, i.e. the hysteresis remained increased despite the decrease of the SVP (and, thus, of the cerebral venous pressure). The brain volume increased only slightly during the rise of the SVP. The water content increased in the cerebral tissue. There was a considerable decrease of \([\text{Na}^+]\) simultaneously with an increase of \([\text{K}^+]\) in the extracellular fluid of the cerebral cortex.

**Discussion**

The methods in the present study made it possible to monitor important physiological parameters necessary for a better understanding of the experimental results relating to the development of brain edema. The parameters were: a) the systemic arterial and venous pressures, and cerebral venous pressure, all of which could be changed arbitrarily or stabilized at any level; b) the intracranial and the intraventricular pressures remained stabilized during the experiments because of a large trephin opening of the skull and draining of the fourth ventricle of the brain; c) the brain volume changes, which were continuously recorded, were thought, first, to represent changes of the blood volume in the cerebral vessels and, second, to result from the amount of water in the cerebral tissue. The latter was monitored also by continuous recording of the concentrations of pNa and pK in the extracellular fluid of the cerebral cortex.

The brain was widely exposed and had prolonged contact with the atmosphere during the experiments which produced changes in cerebral tissue, promoting edema development. In addition, there was a repeated increase in the systemic venous pressure (during the tests) causing blood stagnation in the cerebral vessels and, hence, some cerebral hypoxia. The increase in the blood volume and in blood pressure in the cerebral vasculature are probably the major determinant factors in the development of brain edema.

Draining the fourth ventricle made it unlikely that the volume changes of the brain were dependent upon volume changes of the cerebrospinal fluid. Nor was brain volume influenced by changes of intrathoracic pressure (the lungs were artificially ventilated at a constant rate and volume throughout the experiments). Thus, it was reasonable to believe that the increase of the brain volume during every rise of the systemic venous pressure was caused, first, by an increase in blood volume in the cerebral vasculature (especially in the venous and in the capillary systems) and, secondly, by excessive water filtration into the cerebral tissue. The present studies provided evidence for both of these phenomena: a) the linear increase of the cerebral venous pressure when the systemic venous pressure rose and b) the concentration of the sodium ions fell with almost no detectable change in the concentration of the potassium ions.

Abundant water filtration from blood into the cerebral tissue might be explained by the fact that water easily penetrates the capillary membranes. The data obtained in the present experiments made it possible to calculate the amount of water that can pass from blood into cerebral tissue during periods of increased intravascular pressure.

The existing data suggest that the extracellular spaces in the brain constitute about 13 percent of its volume, i.e., 1 cm³ tissue contains about 130 microliters of extracellular fluid. A decrease of sodium concentration in the fluid, detected in the present experiments when the potassium ion concentration did not increase or else decreased, indicated that this was a result of extracellular fluid dilution by water passing from the blood vessels. If this were a result of sodium ion escape into neuronal cell cytoplasm, the potassium ion concentration should be considerably increased simultaneously.

These experiments show that the amount of water in the brain from the blood stream was increased by about 10 percent, that is, by approximately 0.1 microliter for each microliter of tissue fluid. Therefore, the extracellular fluid was also increased by approximately 10 percent, and the whole brain volume by about 1.3 percent. The fact that the increase of the brain volume was considerably greater during an increase of systemic venous pressure led us to believe

*However, sometimes hysteresis was in evidence from the very beginning of the experiments, indicating that the brain was predisposed to edema development in these cases.
that volume changes are largely caused by the increase of the blood volume in the cerebral vasculature.

At the beginning of our experiments the brain volume increased and decreased in parallel with the systemic venous pressure and the initial concentration of the sodium ions was found in the extracellular fluid of the cerebral tissue. This proved the reversibility of the processes, i.e., when the blood volume in the cerebral vessels is decreased it is followed by a return of the extracellular fluid into the capillaries.

In the course of the individual experiments the brains became edematous, i.e., predisposed to edema development, the hysteresis was observed in the plots of brain volume changes against systemic venous pressure changes. This phenomenon was assumed to depend on the delay of the return of excess blood from the cerebral vessels and on the delay in removal of excess fluid from the extracellular tissue spaces. Water also may be transferred into the cell cytoplasm because a disturbance in the active transport of sodium and potassium ions was evident in this period with a considerable increase in potassium ion concentration in the extracellular fluid. The main source of potassium is cell cytoplasm.10

Because of the large channels connecting intra- and extracranial venous systems, and the linear relationship of the pressures in them, shown in the present experiments, the detention of blood in the cerebral venous system under these conditions may be explained by changes in the mechanical properties of cerebral tissue, and an increase in its compliance and a decrease in its elasticity.9, 11, 12 Further, the retention of water inside the tissue spaces might be explained by the changes in the mechanical properties of cerebral tissue since this would cause a comparative decrease of the pressure inside the tissue spaces under these conditions. On the other hand, the retention of water in the tissue spaces could depend on an increase in osmolarity of cerebral tissue.13

In the light of these considerations it is reasonable to conclude that the changes in the mechanical properties of the cerebral tissue play an important role in the control of blood volume in the cerebral vasculature and in the water exchange between blood and tissue spaces. Furthermore, the present experiments have shown that the properties of cerebral tissue may change in both directions and, thus, may cause not only disturbances, but may also contribute to the active draining of blood from the cerebral vasculature and/or of water from the cerebral tissue spaces, hence compensating for the edema development.

Together with the circulatory factors investigated previously14 the present study demonstrates an important role for tissue factors responsible for the development of edema. These factors seem to be largely the changes in the mechanical properties of cerebral tissue, and changes of the osmolarity of the tissue.

Acknowledgment

The authors are indebted to Prof. Dr. med. Manfred Kessler, Max-Planck-Institut für Systemphysiologie, Dortmund, Bundesrepublik Deutschland, for kindly supplying the potassium ion-selective electrodes.

References

Pathophysiological mechanisms of brain edema development: role of tissue factors.
G Mchedlishvili, L Nikolaishvili and M Itkis

Stroke. 1979;10:52-57
doi: 10.1161/01.STR.10.1.52
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/10/1/52