CEREBRAL VENOUS PRESSURE, ITS RELATION TO SYSTEMIC VENOUS PRESSURE AND TO THE DEVELOPMENT OF CEREBRAL EDEMA

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KEY WORDS: cerebral edema; venous pressure; arterial pressure.

The important role of circulatory factors in the development of cerebral edema is becoming more and more evident. Previously the effect of systemic arterial pressure (AP) [3, 9] and also of the cerebrovascular resistance [1, 3, 8] was discovered. More recently it has been shown that the systemic venous pressure (VP) makes a much greater contribution to the development of cerebral edema than the arterial pressure [7]. The influence of all these circulatory factors on the development of cerebral edema depends primarily on their effect on the level of the intracapillary pressure in the brain, which determines the filtration of water from the vessels into the brain tissue [4].

Since the effect of the systemic VP on the development of cerebral edema is one of great practical importance in clinical medicine, it was decided to study the relationship between the systemic VP and the cerebral VP, with which, in turn, the intracapillary pressure in the brain and, consequently, the rate of development of the cerebral edema, are connected [7].

EXPERIMENTAL METHOD

Experiments were carried out on 29 adult rabbits of both sexes weighing 2-3 kg, anesthetized with pentobarbital or hexobarbital (30 mg/kg). After the operation, heparin (1500-2000 units/kg) was injected intravenously into the animals.

The systemic VP (through the external jugular vein), the systemic AP (through the common carotid artery), and the cerebral VP (through a glass cannula introduced into the sagittal sinus in the dorsal direction) were recorded simultaneously by electromanometers on the Mingograph-81 instrument (from Elema-Schoenander,

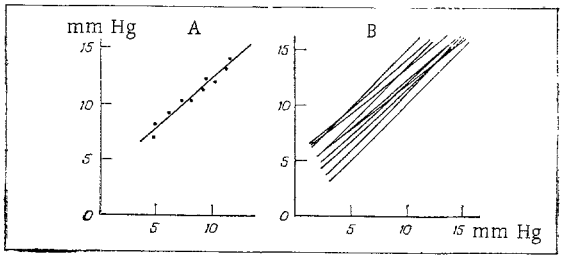

Fig. 1. Cerebral VP (ordinate) as a function of systemic VP (abscissa). A) In one typical experiment; B) family of curves from experiments on different animals.

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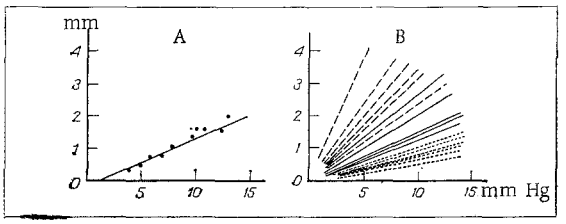

Fig. 2. Changes in brain level (ordinate), reflecting changes in its volume, as a function of systemic VP (abscissa). A) In one typical experiment; B) family of curves from different experiments (rabbits); continuous lines represent normal brain, broken lines respresent brain in pre-edematous state, dotted lines represent brain during edema.

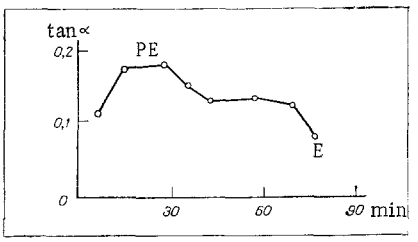

Fig. 3. Changes in tangent of angle of slope of curve showing changes in brain volume (ordinate) as a function of systemic VP throughout one of the experiments (abscissa). PE) Pre-edematous state of brain, E) cerebral edema.

Sweden). The experiments were carried out on a thorax–head preparation [2]. Pressurized reservoirs filled with gelatinine (from the G. M. Mukhadze Blood Transfusion Institute, Tbilisi) and connected with the caudal vena cava and abdominal aorta immediately below the diaphragm, enabled both the systemic VP and the systemic AP to be stabilized or changed.

The skull was widely trephined in the parietal region. Changes in brain volume were recorded in a separate series of experiments simultaneously with the systemic VP and AP. The apparatus for recording these changes consisted of a strain gauge, one end of which was attached to a stereotaxic apparatus, the other end to a rod ending in a disk or sphere (about 5 mm in diameter), which was in contact with the brain surface in the parietal region. The strain gauge was connected to a bridge circuit, the signals from which were amplified by EMT-12 preamplifiers. The instrument was calibrated after each experiment, so that the level of the brain in the burr-hole could be recorded quantitatively. The brain, projecting into an approximately circular hole, could be regarded as approximately the segment of a sphere. The volume of such a segment is calculated by the equation:

$$V = \frac{1}{6}\pi h\,(3a^2 + h^2) = \frac{1}{2}\pi a^2 h\left(1 + \frac{h^2}{3a^2}\right) = \frac{1}{2}Sh\left(1 + \frac{h^2}{3a^2}\right),$$

where: h is the height of the segment, i.e., in this case the level of swelling of the brain; a the radius of the segment, i.e., the radius of the burr-hole; $S = \pi a^2$ the area of the burr-hole. The term $h^2/3a^2$ can be disregarded because $h \ll a$ (the height of swelling of the brain is much less than the radius of the burr-hole); consequently, $V = {}^1/_2\,Sh$. It follows from the above that changes in the level of the brain Δh_b, measured in the experiments, can be interpreted as changes in its volume, for with a high degree of accuracy they are directly proportional: $\Delta V_b = {}^1/_2 - S\Delta h_b$. Hence it follows that the changes recorded in the brain level can be called "changes in brain volume.

The experimental conditions (long-term trephining of the skull and an exposed brain) and the procedures used (repeated venous stasis of blood in the brain) led ultimately to the development of cerebral edema. The criteria of appearance of edema were an increase in brain volume, despite restoration of the normal level of VP, and the considerable increase in the content of water in its tissue (determined by drying it to constant weight).

EXPERIMENTAL RESULTS

The systemic VP was changed by means of the pressurized reservoir on average from 1.5± 1.1 to 13.8 ± 0.9 mm Hg. Under these circumstances VP in the brain was changed from 4.6 ± 0.9 to 15.9 ± 0.8 mm Hg. The relationship between these values was linear (Fig. 1A), as shown by the high coefficients of correlation (the mean value of $r = 0.959 \pm 0.012$). On repetition of the tests, the angles of slope of the curves plotted by joining the experimental points (Fig. 1B) varied. The mean value of the coefficients of regression was $b = 0.869 \pm 0.043$. The mean value of the segment intercepted by the curves of the ordinate (Fig. 1B) was $y_0 = 3.14 \pm 0.39$; it evidently depended on the perfusion pressure for the brain and so correlated with the level of the systemic AP.

This linear relationship between the cerebral VP and systemic VP can evidently be attributed to the fact that the intra-and extracranial venous systems are connected by numerous comparatively wide channels, along the length of which in all probability there are no structures which would considerably modify the resistance to the blood flow. Accordingly, an increase in systemic VP ought to cause a proportional increase in the intravascular pressure in the brain and a corresponding increase in the filtration of water from the vessels into the brain tissue.

However, situations may arise in the body in which there is no complete parallel between the changes in the cerebral and systemic VP. This happens when there is a primary change in the vascular resistance in the cerebral arteries as a result of their constriction or dilatation. Under these circumstances VP in the brain falls or rises, without any reflection on the level of the systemic VP [5, 6]. A rise in the systemic VP evokes an increase in the level (and, consequently, in the volume) of the brain, and the relationship is usually linear (Fig. 2A). The angle of slope of the curve varies during development of cerebral edema in the course of the experiments: It increased considerably in the pre-edematous brain and decreased (it fell below the initial level) when cerebral edema had appeared (Fig. 3).

In the "normal" brain, i.e., at the beginning of the experiments, before there was any tendency toward the development of edema, the regression equation for a typical curve (that, for example, illustrated in Fig. 2A) was as follows: $y = (0.165 \pm 0.001)x - 0.32 \pm 0.14$. In the "pre-edematous" brain, before there were any clear signs of edema, but edema appeared during the next rise or rises of systemic VP, the angle of slope of the curve increased considerably (sometimes twofold) compared with normal (Fig. 2B). When, however, cerebral edema appeared and the quantity of water in the brain was 88.6 ± 4.7% of its weight (79.8 ± 1.7% in control experiments, the differences are statistically significant: $P < 0.001$), the slope of the curve was considerably reduced – to approximately 50% of the initial value (Fig. 2B).

Under conditions when the cerebral VP was a linear function of the systemic VP, the changes in the dependence of the increase in brain volume of the systemic VP (and, consequently, on the cerebral VP) could be connected with the fact that in the pre-edematous state and during actual edema the mechanical properties of the brain are changed and, in particular, the compliance of its tissue. The data obtained show that the compliance of the brain was considerably increased in the pre-edematous state and reduced during edema.

The increase in brain volume in the experiments described above was thus mainly connected with an increase in the blood volume in the brain, i.e., with dilatation of the vessels (especially the capillaries and veins). The lumen of the veins is known to be determined mainly by two factors acting in opposite directions: the intravascular pressure (which rises simultaneously with the systemic VP) and the mechanical properties of the vessel walls and surrounding tissues (which become more compliant in the pre-edematous state). The increase in surface area of the walls of the blood vessels, in turn, increases the filtration surface for water.

Consequently, an increase in systemic VP promotes the development of cerebral edema, first, by considerably increasing the intravascular blood pressure in the brain and, second, by increasing the filtration surface of the vessel walls, which is particularly marked in the pre-edematous state of the brain.

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CYCLIC AMP IN MACROPHAGES, INTESTINAL MUCOSA, AND BLOOD PLASMA OF GERMFREE AND ORDINARY ANIMALS

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In recent years much attention has been paid to the system of cyclic nucleotides in the regulatory mechanisms of immunity of resistance to infection [2, 4, 6]. Germfree animals with their intact immune system constitute an adequate object for studying the role of the microbial factor in the development of the nucleotide-cyclase mechanisms of cellular reactivity of the host organism.

The object of this investigation was to study, in comparative experiments on germfree and ordinary animals, the role of natural microbial contamination of the host organism on ability to form cyclic AMP in the intestinal mucosa and macrophages.

EXPERIMENTAL METHOD

Germfree and ordinary C3H/He mice aged 3-4 months and outbred guinea pigs aged 2-3 weeks were used. The animals were kept in Trexler germfree isolators. During work with animals in germfree isolators, the rules established in [1] were observed. The germfree animals were kept, fed, and subjected to microbiological control in accordance with the general demands of gnotobiological technology [3].

The cyclic AMP content was determined in peritoneal macrophges, the intestinal mucosa, and the blood plasma of intact animals and also in the course of administration of Escherichia coli 055 lipopolysaccharide (LPS). The LPS was isolated by the water–phenol method [8] and purified on a Spinco ultracentrifuge at 105,000g.

The effect of LPS on the adenylate cyclase of the intestinal mucosa was studied by the method of local application in an isolated loop of small intestine of germfree guinea pigs. For this purpose, under ether anesthesia a loop of small intestine was isolated in the animals and 1000 μg of LPS in a volume of 0.5 ml of 0.14 M NaCl was injected into a segment of it (8 cm long), isolated by means of silk ligatures. Only physiological saline was injected in control experiments. The animals were killed after 30 and 60 min and scrapings of intestinal mucosa were obtained together with blood plasma. Weighed samples of the scrapings were homogenized in 1 ml 5% TCA and were extracted 5 times with 2 volumes of ether, after the addition of 0.1 ml 1 N HCl. Cyclic AMP was determined by the competitive binding method [5]. The values obtained for the cyclic AMP content in picomoles were expressed per 100 mg tissue and per milliliter of blood plasma.

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