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MECHANISM OF THE FALL IN INTRACRANIAL PRESSURE DUE TO THE ACTION OF FUROSEMIDE

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KEY WORDS: intracranial pressure; furosemide; brain electrolytes; cerebral edema.

Furosemide is widely used in clinical practice for the treatment of cerebral edema and to lower the intracranial pressure. The mechanism of its action is attributed to its direct effect on water and electrolyte metabolism in brain tissue [4], to a decrease in CSF formation [6, 8], and to dehydration of brain tissue caused by a rise in the osmotic pressure of the blood as a result of loss of salts and water by the kidney [1, 7]. The writers showed previously that after injection of polyethyleneglycol-400 dehydration of brain tissues is accompanied by an increase in the blood volume of the brain, maintaining a stable fluid level in the airtight cranial cavity [3]. It could accordingly be postulated that the cause of the fall in CSF pressure after administration of furosemide was a reduction in the intracranial blood volume due to loss of extracellular fluid as a result of intensive diuresis. The aim of the present investigation was to study this possibility.

EXPERIMENTAL METHOD

Experiments were carried out on 70 mongrel dogs weighing 5-15 kg and 17 female albino rats weighing 150-200 g. Under pentobarbital anesthesia (25-35 mg/kg) siliconized catheters were introduced into the femoral vein and artery and jugular vein of the dogs; the cisterna magna was punctured and the urinary bladder catheterized at the same time. The arterial blood pressure was measured by the direct method with a mercury manometer, and the pressure in the inferior vena cava and jugular vein and the cisternal CSF pressure were measured with a water manometer. Furosemide was injected intravenously in a dose of 10 mg/kg.

Under pentobarbital anesthesia the rats' skulls were trephined above the right cerebral hemisphere and brain trauma was inflicted by a mechanical method. On the 3rd day after trauma, when cerebral edema was most marked, furosemide was injected intraperitoneally into the animals; 60 min later they were decapitated, blood and the cerebral hemispheres were removed for investigation, dried at 105°C to constant weight to determine the water content, after which concentrated HNO_3 was added and, after the organic matter had dissolved, the Na^+ and K^+ concentrations were determined by flame photometry, Fe by atomic absorption spectrophotometry, the serum protein concentration on a refractometer, and osmolarity by a cyroscopic method.

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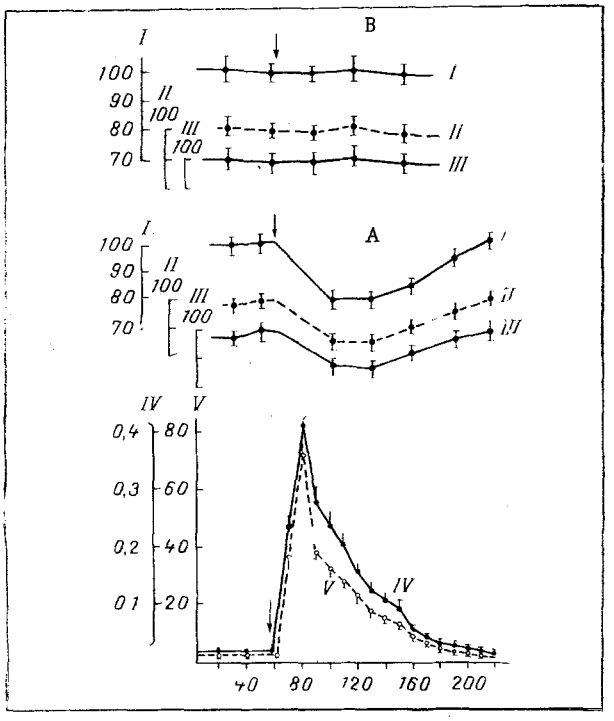

Fig. 1. Effect of furosemide on kidney function and CSF pressure in dogs. Abscissa, time (in min); ordinate: I) CSF pressure; II) pressure in jugular vein; III) central venous pressure (in % of initial level); IV) diuresis (in ml/min/kg body weight); V) Na^+ excretion (μeq/min/kg body weight). A) Animals with both kidneys; B) nephrectomized dogs. Arrow indicates injection of furosemide.

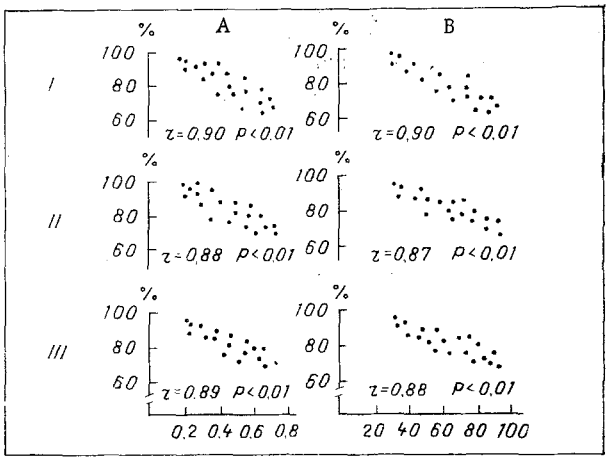

Fig. 2. Relationship between maximal fall of CSF pressure (I), central venous pressure (II), pressure in jugular vein (III), and maximum of diuresis and sodium excretion after injection of furosemide. A) Diuresis (in ml/min/kg body weight); B) sodium excretion (in μeq/min/kg body weight).

EXPERIMENTAL RESULTS

Intravenous injection of furosemide into the dogs caused the development of diuresis and salt excretion, to reach a maximum after 20-30 min, and continuing for over 2.5 h (Fig. 1). Synchronously with the development of diuresis, pressure in the inferior vena cava and jugular vein fell by 25% and the CSF pressure fell by 20% of the initial level (Fig. 1). Distinct correlation was found between the fall of central venous pressure and of CSF pressure and the increase in diuresis and sodium excretion (Fig. 2). Loss of fluid by the kidney evidently leads to a decrease in the extracellular fluid volume and a decrease in CSF pressure. This hypothesis was confirmed in experiments on nephrectomized animals: their CSF pressure did not fall after injection of furosemide (Fig. 1). The dominant role of excretion of large volumes of fluid by the kidney rather than a change in osmolarity of the

TABLE 1. Effect of Injection of Furosemide on Composition of Blood Serum and CSF (M ± m)

Test object	Parameter	Group of animals	Time after injection of furosemide, min				
			0	60	120	180	240
Blood serum	Na^+, mM	1	148±2	149±2	149±3	146±2	148±2
		2	145±2	145±2	148±2	147±2	146±2
	K^+, mM	1	4,1±0,2	4,0±0,1	4,0±0,2	4,2±0,1	4,1±0,1
		2	4,0±0,2	4,1±0,2	4,2±0,2	4,1±0,1	4,0±0,1
	Osmolarity, millios-moles/liter	1	297±2	296±2	299±3	298±2	297±2
		2	296±3	299±3	295±3	296±2	298±2
	Protein, g/liter	1	73,2±7,1	87,3±1,7*	81,4±1,5*	74,1±1,3	74,0±1,1
		2	73,1±1,3	73,1±1,6	74,3±1,4	73,5±1,0	73,1±1,2
CSF	Na^+, mM	1	141±3	143±2	140±3	143±2	143±2
		2	142±3	141±2	141±2	143±2	141±2
	K^+, mM	1	3,0±1,7	2,8±0,2	2,9±0,2	2,8±0,2	2,9±0,2
		2	2,9±0,2	3,0±0,2	2,0±0,2	2,9±0,2	3,0±0,2
	Osmolarity, millios-moles/liter	1	290±3	293±4	289±4	291±2	291±3
		2	290±4	290±2	291±3	290±3	291±2

Legend. Group 1 consisted of animals with intact kidneys, group 2 of animals with bilateral nephrectomy. *P < 0.01 compared with period before injection of furosemide.

TABLE 2. Effect of Furosemide on Content of Water, Sodium, and Iron in Rat Cerebral Hemispheres (M ± m)

Test object	Parameter	Brain trauma (8)	Brain trauma + furosemide (9)
Cerebral	Water, kg/kg dry substance	3,72±0,03	3,50±0,09*
	Na^+, μmoles/kg dry substance	211±1	160±16*
	Iron, μmoles/kg dry substance	3,35±0,18	3,77±0,32*
Blood	Iron, μM	14,5±0,43	17,5±0,6*

Legend. Number of animals given in parenthesis. *P < 0.05 compared with trauma without furosemide.

blood or its ionic composition is demonstrated by the stability of the Na^+ and K^+ concentrations and osmolarity of the blood serum observed in dogs after injection of furosemide (Table 1). Rapid excretion of large volumes of fluid by the kidney leads to a decrease in the circulating blood volume, as shown by the increase in its serum protein concentration (Table 1). In that way the conditions are created for increased outflow of venous blood from the intracranial cavity, and this leads to a fall in CSF pressure. This conclusion is confirmed by data showing that even small changes in central venous pressure are reflected in the intracranial pressure [2, 5].

This hypothesis was confirmed by experiments to measure the iron concentration in the brain. The greater part of the iron is concentrated in erythrocytes, and in acute experiments changes in its content in a tissue reflect the blood volume in that tissue. Under the influence of furosemide, because of the abundant diuresis, hemoconcentration took place, with an increase of 19% in the protein concentration and 21% in the iron concentration, but concentrations of ions remained unchanged (Table 1; Table 2). The iron concentration in brain tissue increased by a lesser degree than in the blood volume of the brain. This explanation is supported by the decrease in the Na^+ concentration in the dehydrated brain; Na^+ is the main cation of the extracellular fluid, its serum concentration does not change and, consequently, a decrease in the volume of blood in the brain led to a fall in the Na^+ level in the brain substance (Table 2).

A leading role in the mechanism of action of furosemide on intracranial pressure is thus played by its diuretic effect. Reduction of the blood volume and extracellular fluid

volume leads to a decrease in the intracranial volume of fluid and to a decrease in CSF pressure. The presence of correlation between the fall of CSF pressure and the rise of diuresis is evidence that the effect of furosemide on the kidney can be regarded as a criterion of the magnitude of the effect of the drug on the intracranial pressure.

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CHANGES IN LIVER CYTOCHRONE P-450 CONCENTRATION IN CONGENEIC RESISTANT MICE DURING CHRONIC ALCOHOLIZATION

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KEY WORDS: congeneic resistant mice; principal mouse histocompatibility system (H-2); cytochome P-450; ethanol.

The adaptive increase in ethanol oxidation during chronic alcoholization takes place mainly through induction of a microsomal ethanol-oxidizing system (MEOS). Activation of MEOS is accompanied by qualitative and quantitative changes in its terminal component, namely cytochrome P-450, on which ethanol is oxidized to acetaldehyde [5, 8, 9, 12, 14]. Despite the important role of MEOS in adaptation of the organism to ethanol, no investigations devoted to the study of its particular features in animals with marked differences in their response to alcohol have been undertaken.

In the investigation described below the concentration of cytochrome P-450 was studied in the liver of two pairs of congeneic resistant (CR) mice, with simultaneous recording of differences in their level of ethanol consumption. The use of CR mice, differing genotypically only in relation to the H-2 system, as the model was determined by existing observations indicating functional unity of the immune and metabolic systems [2] and participation of the principal histocompatibility system in the regulation of metabolic, endocrine, and neurotransmitter processes when disturbed by chronic alcoholization [2, 3, 6, 13].

EXPERIMENTAL METHOD

Experiments were carried out on male mice of two pairs of CR lines (B10.R111 and B10.R107; A/Sn and A.SW) weighing 20-35 g and kept on a standard laboratory diet. The pure-strain ancestors of these lines of mice were generously provided by the Research Laboratory of Experimental Biological Models, Academy of Medical Sciences of the USSR. During chronic alcoholization the animals received a 10% ethanol solution as the sole source of fluid; control animals received water. The level of alcohol consumption was expressed as the ratio of the quantity of alcohol consumed by the experimental animals to the quantity of water consumed by the control mice. The animals were kept in cages six at a time. The duration of alcoholization was 69 days. From the 42nd through the 48th days of the experiment ethanol

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