MECHANISM OF THE ADAPTIVE ACTION OF HEPARIN IN POSTHEMORRHAGIC HYPOTENSION

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Experiments on dogs with posthemorrhagic hypotension (arterial pressure 30-35 mm Hg) showed that the character of changes in the hexokinase activity and intensity of tissue respiration of homogenates from various parts of the brain differ sharply in animals heparinized (400 i.u. heparin/kg body weight, intravenously) and not heparinized before bleeding. The heparinized animals were more resistant to hypotension. In unheparinized dogs the hexokinase activity was reduced while in the heparinized animals it was increased, especially in the posterior parts of the brain. Meanwhile heparin increases the degree of inhibition of respiration of brain tissue taking place in posthemorrhagic hypotension. A higher survival rate was observed after bleeding in the heparinized animals.

The hexokinase activity and tissue respiration of various parts of the brain and the effect of heparin on these indices were investigated in animals with posthemorrhagic hypotension.

EXPERIMENTAL METHOD

The arterial pressure in dogs was lowered to 30-35 mm Hg in dogs by Wiggers' method [6]. The pressure was kept at a low level for 2.5 h. Nine animals received heparin intravenously (400 i.u./kg body weight) before bleeding. The animals were killed by exsanguination, the brain was removed, cut into sections, and different parts of it were homogenized. The hexokinase activity was determined by Long's method [4], respiration by the direct Warburg's method in an atmosphere of air, and the protein content of the homogenates by Lowry's method [5].

EXPERIMENTAL RESULTS AND DISCUSSION

The results are given in Table 1. Acute blood loss and subsequent hypotension led to a significant decrease in hexokinase activity in the cerebral cortex, cerebellar cortex, and caudate nucleus of the animals not receiving heparin. This parameter was unchanged in the parts of the hind brain which were studied. The character of the changes in the activity of this enzyme corresponded to that described in the literature [1]. The intensity of tissue respiration fell in posthemorrhagic hypotension in all parts of the brain studied except the cerebellar cortex.

After administration of heparin the character of the changes in these parameters of energy metabolism showed sharp changes. Instead of a decrease in hexokinase activity, a statistically significant increase was observed in all parts of the brain tested. However, the degree of inhibition of tissue respiration increased. These changes were most marked in the hind brain, where the hexokinase activity rose by 97% but respiration was reduced by 56%. The increase in hexokinase activity is evidence of activation of the glycolytic pathway of energy metabolism, the one most suited to hypoxia. Depression of respiration may be caused by increased hexokinase activity through the Pasteur effect [3]. The effect of heparin was thus exhibited during adaptation of the brain and posthemorrhagic hypotension, accompanied by hypoxia. The most marked changes were recorded in the hind brain, which carries the principal functional load after acute

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TABLE 1. Hexokinase Activity (HKA; in μg glucose) and Respiration (in μl oxygen) of Tissue Homogenates of Various Parts of the Brain from Dogs with Hypotension

Group of animals	Cerebral cortex		Cerebellar cortex		Caudate nucleus		Superior part of floor of rhomboid fossa		Medulla	
	HKA	absorption of oxygen	HKA	absorption of oxygen	HKA	absorption of oxygen	HKA	absorption of oxygen	HKA	absorption of oxygen
Intact (normal)	138±9,45 (21)	7,94±0,52 (13)	126±8,17 (21)	6,3±0,29 (13)	89±7,46 (22)	6,81±0,3 (13)	72±6,0 (22)	3,69±0,22 (11)	73±5,8 (22)	3,64±0,19 (11)
After hypotension for 2.2 h: without heparin										
P	95±9,9 <0,004 (12)	5,73±0,5 <0,007 (11)	93±11,0 0,02 (12)	5,74±0,23 <0,15 (11)	70±5,9 0,05 (12)	5,76±0,43 0,05 (11)	70±6,8 0,04 (12)	2,99±0,24 0,04 (11)	65±7,8 0,37 (11)	2,48±0,22 <0,001 (11)
With heparin (400 i.u./kg)	183±19,0	4,80±0,81	158±11,0	4,74±0,68	121±8,0	4,57±0,87	143±13,0	1,64±0,34	144±12,0	1,53±0,36
P	0,05 (9)	<0,005 (8)	0,03 (9)	0,05 (8)	0,007 (9)	0,03 (8)	<0,001 (9)	<0,001 (9)	<0,001 (9)	<0,001 (9)

Note. Number of tests in parentheses

blood loss [2]. Heparin, by changing the conditions of tissue metabolism, evidently increases the resistance of the animal to hypoxia. The survival rate of the animals receiving heparin was in fact more than twice as high as the survival rate of the unheparinized dogs: of 12 dogs not receiving heparin, 3 (25%) survived posthemorrhagic hypotension, whereas of the 9 which received heparin, 5 (55%) survived.

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