HEPATIC LEVELS OF PROSTAGLANDINS $F_{2\alpha}$ AND I_2 (PROSTACYCLIN) AND OF THROMBOXANE A_2 IN DOGS DEVELOPING HEMORRHAGIC SHOCK

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In patients surviving severe shock of varied etiology, including hemorrhagic, the course of the recovery period is often complicated by acute hepatic failure (AHF), which is the immediate cause of death in 48-67% of cases [6].

Among the many factors involved in the pathogenesis of AHF a special place is occupied by the derived metabolic cascade of polyunsaturated essential fatty acids (chiefly arachidonic acid – AA), namely prostaglandins (PG), thromboxanes (TX), and leukotrienes (LT). Interacting with many hormones, mediators, and enzymes at the cyclic nucleotide level with the involvement of Ca^{2+} ions, the eicosanoids modulate or regulate processes of cell metabolism under both normal and pathological conditions. It has been shown that PG of different groups (D, E, F, I), TXA_2 and LT (A_4, B_4, C_4, D_4, E_4) are synthesized in the liver; playing the role of autocoids in maintenance of the homeostatic functions of the liver, these substances are characterized by the diversity of their effects [3, 14]. It has been suggested that a disturbance of equilibrium between the action of eicosanoids and, in particular, between that of PGI_2 and TXA_2 in favor of the latter, leads to aggravation of shock [12].

EXPERIMENTAL METHOD

Experiments were carried out on 6 adult mongrel dogs of both sexes weighing 21.3 ± 1.7 kg. All painful procedures associated with isolation of the femoral vessels and their catheterization, were performed under local anesthesia with 0.5% procaine solution. A model of hemorrhagic shock was created by one-stage rapid bleeding from the femoral artery until the systolic arterial pressure (BP) had fallen to 40 mm Hg (volume of blood loss 31.9 ± 1.6 ml/kg). To determine eicosanoids in the liver tissue, an oblique incision was made in the right hypochondrial region under local anesthesia with 1% procaine solution, through which one lobe of the liver, used continuously for the investigations, was exteriorized into the operation wound. After resection of part of the liver tissue, the wound in its parenchyma was closed by U-shaped sutures and the lobe was buried in the peritoneal cavity. Samples of liver tissue were taken before and immediately after blood loss, during periods of relative compensation (BP 97.0 ± 31.6 mm Hg) and late (BP 30.0 ± 0.0 mm Hg) shock, namely 134.0 ± 28.3 min and 201.0 ± 43.8 min respectively after blood loss. Concentrations of $PGF_{2\alpha}$, PGI_2, and TXA_2 in the liver were determined by radioimmunoassay using kits from the Institute of Isotopes (Hungary). Concentrations of the two latter prostanoids were judged by the levels of their stable metabolites, specifically 6-keto-$PGF_{1\alpha}$. The radioactivity of the test samples was determined from a "Tesla" γ-counter (Czechoslovakia). The results, subjected to statistical analysis by Student's t test, were expressed in picograms (pg)/0.3 g.

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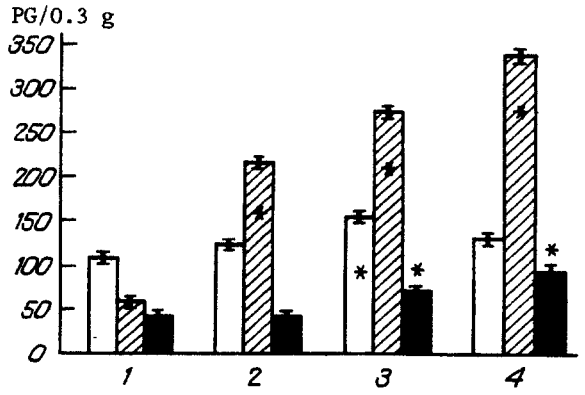

Fig. 1. Changes in PG_2, PGI_2, and TXA_2 levels in liver of dogs developing hemorrhagic shock. Abscissa, concentration of PGI_2, TXA_2, $PGF_{2\alpha}$, in PG/0.3 g; unshaded columns – PGI2, obliquely shaded – TXA_2, shaded black – $PGF_{2\alpha}$. 1) Period of blood loss, 2) immediately after blood loss, 3) period of relative compensation of shock, 4) late period of shock, *) values differing significantly from initial data at $p < 0.001$.

EXPERIMENTAL RESULTS

The fall of BP induced by blood loss from 141.7 ± 3.3 mm Hg to 40.0 ± 0.0 mm Hg led to the development of hemorrhagic shock, in which three periods could be distinguished: early, relative compensation, and late. The last, as a rule, passed suddenly into the phase of secondary hemorrhagic collapse, which culminated in the development of a terminal state and death of the animals. A similar phasic course of the posthemorrhagic reaction was described previously by other workers [2]. The length of survival of the animals after blood loss was 212.2 ± 46.0 min.

Analysis of changes in $PGF_{2\alpha}$, PGI_2, and TXA_2 concentrations in the dog liver showed that acute massive blood loss is a powerful stimulus for synthesis and release of all the eicosanoids studied. However, whereas the concentrations of $PGF_{2\alpha}$ and PGI_2 immediately after blood loss exceeded the initial levels by only 0.2% ($p > 0.5$) and 13% ($p < 0.05$) respectively, the TXA_2 concentration increased by 289% ($p < 0.001$, Fig. 1). This sharp rise of the TXA_2 concentration must be attributed to an emergency adaptive reaction of the body to acute blood loss and to the liver damage preceding it. This effect is manifested as activation of the blood clotting and fibrinolysis system, in which the leading role in the realization of primary hemostasis is played by the adhesive-aggregating function of the platelets [1]. As a result of the action of aggregation inducers (adenosine diphosphate, collagen, catecholamines, etc.) and mobilization of intracellular Ca^{2+}, phospholipase A_2 activity rises sharply, and this results in rapid conversion of AA into TXA_2 [13].

As shock developed progressively the eicosanoid concentrations continued to rise. For instance, in the period of relative compensation of shock the concentration of $PGF_{2\alpha}$, PGI_2, and TXA_2 in the dogs' liver exceeded the initial levels by 64.5%, 42%, and 390% respectively ($p < 0.001$; Fig. 1). However, in the late period of shock, together with the continuing increase in $PGF_{2\alpha}$ and TXA_2, whose levels exceeded the initial values by 127% and 499% respectively ($p < 0.001$), the PGI_2 concentration fell by 14% ($p > 0.1$), but it was 22% above the initial values ($p < 0.02$, Fig. 1).

The shift observed in the relative concentrations of the three eicosanoids heralds the appearance of damaging effects of the action of TXA_2 and $PGF_{2\alpha}$ in a most undesirable form. TXA_2, whose continued release is due to a second wave of aggregation [13], is the most powerful natural vasoconstrictor, and its aggregating effect is so strong that it may lead to widespread thrombosis [10, 11]. By causing destruction of the lisosomal membranes, TXA_2 also induces release of LT, which are nowadays identified as mediators of ischemia and shock [10]. $PGF_{2\alpha}$, increased production of which in the liver is caused by hypoxia [4], not only stimulates platelet aggregation, but also increased vascular resistance in the system of the portal circulation [10].

Meanwhile PGI_2, a disturbance of whose formation is linked with damage to the vascular endothelium in shock, whose cells are the main source of prostacyclin synthesis displays the physiological antagonist TXA_2 [5, 11]. Since the half-life of PGI_2 in the blood is 2-3 min, the effects of its action are also linked with the active metabolite 6-keto-PGE_1, formed during degradation of prostacyclin in the liver [15]. Nevertheless, while preventing aggregation and inducing vasodilatation, exogenous PGI_2 increases the hepatic blood flow in man [9], reduces the degree of necrosis of the liver induced in mice by acetaminophenol [8], and stabilizes lysosomal membranes [10]. Injection of PGE_1 into rats 3 h after induction of hemorrhagic shock almost doubles the ATP concentration in the liver of animals [7].

The results of the present investigation, allowing for the mechanisms of action of PGI_2, are thus experimental evidence in support of the use of prostacyclin or its synthetic analog in the combination treatment of patients with acute hepatic failure.

LITERATURE CITED

1. Z. A. Barkagan, Hemorrhagic Diseases and Syndrome [in Russian], 2nd ed., Moscow (1988).
2. V. D. Bratus' and D. M. Sherman, Hemorrhagic Shock: Pathophysiological and Clinical Aspects [in Russian], Kiev (1989).
3. M. Birmelin and K. Decker, Eur. J. Biochem., **42**, No. 1, 219 (1984).
4. J. T. Flynn, Prostaglandins, **17**, No. 1, 39 (1979).
5. N. Frendenberg, Path. Res. Pract., **162**, No. 1, 105 (1978).
6. D. E. Fry, L. Perlstein, R. L. Fulton, et al., Arch. Surg., **115**, No. 2, 136 (1980).
7. S. S. Ghuman, B. F. Rush, Jr., G. W. Machiedo, et al., J. Surg. Res., **32**, No. 5, 484 (1982).
8. F. Guarner, N. K. Boughton-Smith, G. J. Blackwell, and S. Moncado, Hepatology, **8**, No. 2, 248 (1988).
9. S. Hassan and H. Pickles, Prostagland. Leukotr. Med., **10**, 449 (1983).
10. A. M. Lefer, Fed. Proc., **44**, No. 2, 275 (1985).
11. S. Moncado and J. R. Vane, Brit. Med. Bull., **34**, 129 (1978).
12. C. Moschetta, G. Montanari, G. Corbucci, et al., Minerva Anest., **45**, No. 7-8, 601 (1979).
13. H. Patscheke, Prostaglandins and Thromboxanes, Jena (1981), pp. 333-335.
14. Y. Sakasami, Y. Mizogushi, S. Seki, et al., Biochem. Biophys. Res. Commun., **156**, No. 1, 217 (1988).
15. P. Y.-K. Wong, W. H. Lee, C. P. Quilley, and J. C. McGiff, Fed. Proc., **40**, No. 7, 2001 (1981).