EFFECT OF ADENOSINE ON BLOOD PROSTAGLANDIN LEVELS AND PLATELET AGGREGATION IN EXPERIMENTAL MYOCARDIAL INFARCTION

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Myocardial ischemia is accompanied by the release of several compounds affecting vascular tone and the state of aggregation of the blood into the blood stream. Occlusion of the coronary artery causes activation of platelets and stimulates synthesis of thromboxane A_2 (TxA_2) and prostaglandins E_2 and F_{2a} (PGE_2 and PGF_{2a}) [8, 14]. Depending on its concentration, PGE_2 can exert both a proaggregating and an antiaggregating action, and it is usually regarded as a weak antiaggregant (IC_{50} for rabbits is 28 μmoles/liter) [1]. PGF_{2a} and, in particular, TxA_2 are powerful inducers of platelet aggregation [1]. Meanwhile, large quantities of adenosine are released from the cardiomyocytes during ischemia, and this inhibits aggregation and enhances the coronary blood flow [3].

These properties of adenosine and also its cardioprotective effect on the early stages of ischemia [13] suggest that the use of this substance may be worthwhile as an antianginal and cardioprotective agent in myocardial infarction [2].

Meanwhile, we know that adenosine stimulates the formation of prostaglandins and thromboxanes in the heart [16], suggesting that the antithrombocytic effect of adenosine can be weakened in vivo. To test this hypothesis, in the investigation described below the effect of adenosine was studied on concentrations of PGE_2 and TxB_2 (a stable metabolite of TxA_2) and on platelet aggregation in rabbits with myocardial infarction.

EXPERIMENTAL METHOD

Experiments were carried out on 28 male rabbits weighing 2.5-3 kg. Under pentobarbital anesthesia (45 mg/kg) intravenously and with artificial ventilation of the lungs, the descending branch of the left coronary artery (LCA) was ligated in its upper third. Immediately after ligation, physiological saline (PS — control group) was injected into the femoral vein for 30 min with a volume velocity of 0.05 ml/min, or adenosine, dissolved in PS, was injected in a dose of 0.25 mg/kg/min (experimental group). After the end of infusion, the animals remained under observation for 1.5 h. From eight animals in each group, before occlusion of LCA and again at the 30th and 120th minutes of the experiment, 2 ml of blood was taken from the femoral artery. The concentration of 11-deoxy-13,14-dihydro-15-keto-11,16-cycloprostaglandin E_2 (a stable metabolite of TxA) was determined in the plasma with the aid of test kits from "Amersham" (England). The degree of platelet aggregation was estimated in six rabbits in each group at the same times. For this purpose, 5.4 ml of blood was taken from the femoral artery of each rabbit into siliconized test tubes containing 0.6 ml of 3.8% sodium citrate solution. Plasma-enriched platelets were obtained by centrifugation at 160 g for 10 min. The platelet count was adjusted to the

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TABLE 1. Concentrations of PGE_2 and TxB_2 (in μg/ml) in Blood of Rabbits with Myocardial Ischemia

Time, min	Control		Adenosine, 0.25 mg/kg·min	
	PGE_2 (n=8)	TxB_2 (n=8)	PGE_2 (n=8)	TxB_2 (n=8)
0	51±8	16±3	42±8	17±5
30	58±12	45±4**	91±10**	66±10**
120	148±22**	59±15*	177±23**	167±17**

Legend. *$p < 0.01$, **$p < 0.001$.

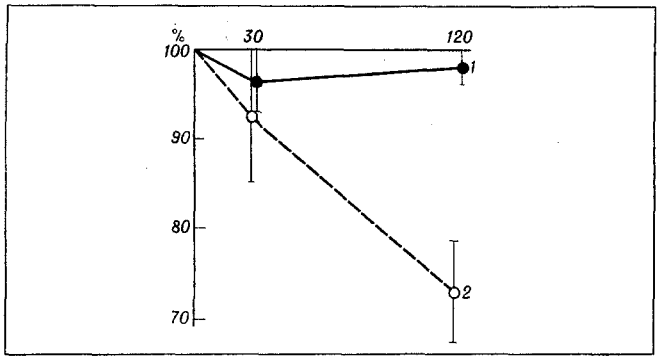

Fig. 1. Change in degree of platelet aggregation in animals of control and experimental groups. Abscissa, time (in min); ordinate, degree of aggregation (in % of initial). 1) Experimental group, 2) control group.

standard level ($5 \cdot 10^5/\mu l$) by diluting the samples with Tyrode buffer. Aggregation was induced by adding ADP to the incubation medium (final concentration 2.5 μM). The degree of aggregation was estimated by Born's optical method on a one-channel FRM-1 aggregometer at 37°C, with mixing of the sample at a speed of 400 rpm. The significance of any observed changes was assessed by Student's test and Wilcoxon's paired test.

EXPERIMENTAL RESULTS

In rabbits with experimental myocardial infarction, immediately after a 30-min infusion of PS an almost threefold increase in the plasma TxB_2 level was found. After 120 min the thromboxane level remained the same, but the concentration of PGE_2 showed a significant (also threefold) increase (Table 1). TxA_2 is known to be an active inducer of platelet aggregation and to be produced by these cells in response to their activation. Meanwhile no significant increase took place in the degree of platelet aggregation. On the contrary, after a 30-min infusion of PS a very weak tendency was observed for aggregation to be depressed, and after 120 min this parameter fell on average by 27.5% below its initial level ($p < 0.05$). Very probably the fall in the level of aggregation by the 120th minute was connected with a significant increase in the PGE_2 concentration at that time, for low concentrations of PGE_2 stimulate aggregation whereas high concentrations, conversely, inhibit it [1, 5, 15]. It can also be tentatively suggested that stimulation of TxA_2 synthesis is compensated by aggregation blockers formed during ischemia: by adenosine and prostacyclin [7, 16].

At the 30th minute after injection of adenosine a twofold increase in the PGE_2 concentration and a fourfold increase in TxB_2 were found in the blood. By the end of the experiment the levels of these compounds in the blood plasma were increased even more — by 4.6 and 10 times respectively compared with their initial values. Moreover, whereas the PGE_2 level, as Table 1 shows, only very slightly exceeded that in the control group, the blood thromboxane level in the rabbits of the experimental group after 120 min was almost 3 times higher than that in the control group. These data are in agreement with the time course of the degree of platelet aggregation (Fig. 1). Unlike in the control group, throughout the experiment the degree of platelet aggregation remained virtually unchanged. In this case the antithrombocytic action of infused adenosine and of high PGE_2 concentrations was evidently weakened by increased TxA_2 synthesis. Possibly interaction between these processes may hold the degree of platelet aggregation at a constant level.

The physiological activity of adenosine is due to its interaction with P_1 and P_2 purine receptors. Both have been identified in the cardiovascular system [8]. Some workers associate prostaglandin formation with excitation of these receptors [3].

The biochemical mechanisms of interaction between adenosine and prostaglandins have not yet been adequately studied. These compounds may behave as antagonists, but only if they induce opposite effects. Thus adenosine, which gives vasorelaxing and negative inotropic effects, abolishes the vasoconstrictor and positive inotropic action of $PGF_{2\alpha}$. Under these circumstances they do not affect the vasodilator and negative inotropic action of PGE_2 and prostacyclin [11].

It has now been suggested that specific interactions of adenosine and prostaglandins of this type are a calcium-dependent process, for both adenosine [5] and prostaglandins [9, 10] actively influence intracellular Ca^{2+} metabolism. However, these suggestions require further analysis.

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