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ROLE OF PROSTACYCLINE IN ANTIAGGREGATING ACTIVITY OF THE VASCULAR WALL

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KEY WORDS: prostacycline; antiaggregating activity of the vascular wall; platelets.

The antiaggregating activity of the vascular wall is the factor which is largely responsible for preventing the development of intravascular thrombus formation and atherogenesis. A decrease in this activity, under the influence of catecholamines or stress, for example, may be the main cause of development of thrombosis and tissue necrosis [7]. It has been suggested that antiaggregating activity is due to the formation of prostacycline (PGI_2), which has extremely powerful antiaggregating and vasodilator effects [7], in the vascular wall. However, many physiologically active substances which may also affect platelets are formed in a system with such complex organization as the vascular wall. It has been shown, for example, that fibroblasts and smooth-muscle cells release substances which potentiate aggregation [3]. Views ascribing the antiaggregating activity of vessels essentially to PGI_2 synthesis alone may therefore be excessively oversimplified. The aim of the present investigation was to clarify the role of PGI_2 in the realization of the antiaggregating effect of the vascular wall.

EXPERIMENTAL METHOD

Platelet-enriched plasma (PEP) was obtained from fresh citrate-stabilized blood from healthy blood donors. The PEP sample was separated into two parts, to one of which was added crystalline prostacycline (from Upjohn Co., USA) to a final concentration of 1 μg/ml, whereas a segment of a blood vessel was incubated in the other part (5 min, 37°C). The total area of the segment was chosen so that the antiaggregating effect of the isolated vessel corresponded to that in the sample with prostacycline. Samples of 0.5 ml were taken at definite time intervals from these two original samples, and the degree of aggregation induced by ADP (10^{-6} M) was determined in them. Aggregation was measured on an aggregometer of the writers' own design [1]. The vessels for investigation were taken from cadavers of 12 persons with no history of cardiovascular diseases during life, and dying accidentally. The vessels were

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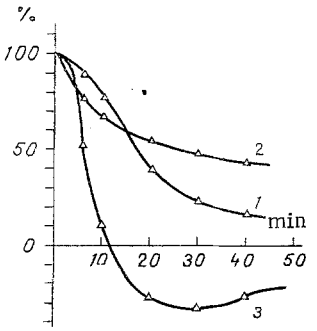

Fig. 1

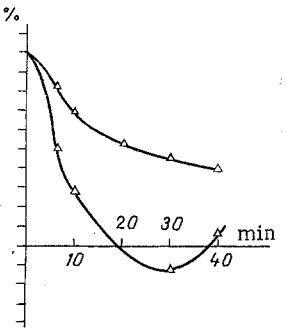

Fig. 2

Fig. 1. Changes in antiaggregating effect of crystalline PGI_2 in PEP (1) and different versions of changes in antiaggregating effect of vascular segments (2, 3).

Fig. 2. Dynamics of changes in antiaggregating effect of vascular segment before (1) and after (2) incubation with adrenalin.

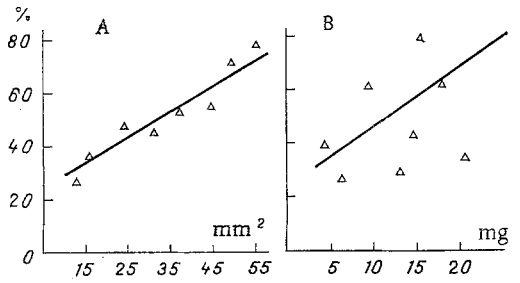

Fig. 3. Changes in antiaggregating effect of vascular segment depending on area of intima (A) and weight (B).

taken within 8 h after death. Some experiments were conducted on segments of the aorta from Wistar rats.

EXPERIMENTAL RESULTS

In the course of the experiments graphs showing the decrease in antiaggregating effect of crystalline PGI_2 and of the vascular segment with incubation time were obtained (Figs. 1 and 2). The decrease in the antiaggregating effect of PGI_2 was associated with its breakdown in the plasma, and it was characterized by the shape of the graph of falling activity and the time taken for activity to be reduced by half ($T_{1/2}$) [5]. Assuming that the antiaggregating effect of the vascular segment was due principally to prostacycline released from it, the graph of its declining antiaggregating effect ought to correspond to that obtained with crystalline PGI_2, incubated in the same sample of PEP. However, according to the results actually obtained, such a parallel was by no means always observed between them. The two principal types of changes in the antiaggregating effect of the vascular segment in samples of PEP, in which the decline of activity of PGI_2 did not differ from normal, are illustrated in Fig. 1. The first type is characterized by the appearance of a period of prolonged stabilization of the antiaggregating effect after the initial rapid decline; depression of platelet aggregation, moreover, continued to be observed even when the effect of PGI_2 in the same sample had disappeared virtually completely. Conversely, the second type was characterized by much faster disappearance of the antiaggregating effect of the vascular segment than that of PGI_2; after a certain time interval, moreover, a definite proaggregating effect could often be observed.

It is evident that this disparity can be explained by assuming that the antiaggregating effect of the vascular wall is due not only to PGI_2, but also to a combination of substances which affect platelets unequally and which also differ in their stability in plasma. In the course of decomposition of unstable agents liberated from the vascular segment in PEP, the

TABLE 1. Relations Between Initial Antiaggregating Activity of Vessels and Character of its Decline During Incubation

Character of decline of antiaggregating effect	Antiaggregating activity, % inhibition of aggregation/mm² of intima		
	<1,5	1,5–4,0	>4,0
I variant	1	4	4
II variant	3	6	1
III variant	5	2	1

effect of the more stable compounds begins to be exhibited. Under these circumstances both the character of the initial effect and the trend of its changes with time will depend on the ratio between the concentrations of the different agents in the total complex substances released by the vessel wall into PEP. For example, the first type of changes in the antiaggregating effect of the vascular segment was characterized by a high content of antiaggregant substances in the secretion of the vascular wall, whose effect on platelets predominated throughout the period of observation. Besides PGI_2, large quantities of a more stable antiaggregant, which may have been adenosine [6], were evidently liberated also. Conversely, in this case a large quantity of proaggregants was secreted, and after breakdown of the PGI_2 their effects began to be exhibited in the form of an increase in the degree of aggregation. This is all the more probable because proaggregants such as thromobxane A_2 and $PGF_{2\alpha}$ can be synthesized in the vascular wall [4]. Under these circumstances the possibility cannot be ruled out that the total combination of agents released from the vascular wall may contain many other substances, some of them not yet identified.

From this standpoint changes in antiaggregating activity of the vessels under the influence of various factors can be examined not only as changes in PGI_2 synthesis, but also as a complex change in the relation between different agents in the whole combination of substances released by the vessel into PEP. This may explain the varied character of the action of many physiologically active agents on antiaggregating activity of the vessel wall. Under the conditions of this present investigation a phenomenon of this kind was found in the case of catecholamines, especially adrenalin, which induced a decrease, which varied considerably in degree, in antiaggregating activity in different vascular segments, and in some cases (18%) actually increased such activity. The study of the time course of changes in the antiaggregating effect of the vascular segment before and after incubation with adrenalin (5 µg/ml, 3 min) showed that in this case its effect is very variable. The first version of changes in the antiaggregating effect of the vascular segment was observed most frequently, and was followed by the second version (Fig. 2). This can be explained both by a decrease in PGI_2 synthesis and by an increase in the synthesis of proaggregants, even if PGI_2 synthesis remained unchanged or was at a higher level.

It is interesting to compare the character of changes in the antiaggregating effect of the vascular segment with its initial antiaggregating activity. This is a somewhat difficult task in view of the uncertainty of methods of standard evaluationg of antiaggregating activity of blood vessels. Usually it is recommended that segments of vessels of equal weight are incubated in PEP, but in our opinion this cannot be regarded as a sufficiently adequate approach because the endothelial layer accounts for only a negligible fraction of the vascular segment by weight, whereas it accounts for a large proportion of PGI_2 synthesized. It is evidently more correct to characterize the antiaggregating effect in relation to the area of intima through which compounds synthesized not only in the endothelium, but also in the underlying layers, are released. A convenient method of comparing the antiaggregating activity of different segments is thus to express it per unit area; for example, it can be expressed as percentage inhibition of aggregation per square millimeter of intima. Investigations showed that the increase in antiaggregating effect of the vascular segment depends much more clearly on an increase in the area of its intima than on its mass (Fig. 3).

To compare the initial antiaggregating activity of vascular segments and the time course of the decline in their antiaggregating effect, principal variants of these parameters were distinguished (Table 1). Analysis of the ratio between these variants showed that rapid decline with the appearance of a proaggregant effect is most characteristic of low initial antiaggregating activity, and conversely, when initial activity was high it declined slowly (Table 1). Consequently, it can be postulated that high initial activity is determined by

the formation predominantly of antiaggregant substances in the vessel, whereas low initial activity is determined by the formation of very small quantities of antiaggregants but by a high content of agents with the opposite effect on platelets.

It can thus be concluded from these results that antiaggregating activity of blood vessels cannot be justifiably reduced simply to the effect of PGI_2 synthesized in them. More probably a whole range of agents, differing in their effects on platelets and their stability in plasma, is released from the vessels into the blood stream. Under ordinary conditions the effect of antiaggregants predominates in secretion from the vascular wall, but the possibility naturally cannot be ruled out that the vascular wall may be in a state in which proaggregants will be predominant in the combination of substances secreted by it. This view is confirmed by the cases of initial proaggregating activity of segements from the middle cerebral artery, removed from the zone of a brain infarct, described previously [2]. The complex nature of antiaggregating activity of the vascular wall, which can be more accurately defined as the platelet-active properties of the vessels, must evidently be taken into account both during interpretation of experimental results and during analysis of the importance of this phenomenon in regulation of the circulation and development of its disorders.

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TIME COURSE OF RECOVERY OF THE MICROCIRCULATION AFTER STRESS

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KEY WORDS: microcirculation; vascular permeability; stress; mast cells.

The writer showed previously that immobilization and generalized electrical stimulation induce changes in the terminal blood flow and vascular permeability in the rat mesentery [1, 2]. However, the time course of recovery of the microcirculation and of the state of the microvascular wall and mast cells (MC) after stress has not been studied. The investigation described below was devoted to the study of these problems.

EXPERIMENTAL METHOD

Experiments were carried out on 185 male Wistar rats weighing 200-250 g. Immobilization for 24 h or electrical stimulation for 6 h were used as extremal stimuli. An apparatus based on the Docuval (Carl Zeiss, East Germany) microscope was used for biomicroscopic study of the mesenteric microcirculation. Vascular permeability in the mesentery was studied by luminescence contact biomicroscopy followed by quantitative photometry on a LYUMAM KF-1 microscope. Fluorescein isothiocyanate-labeled globulin was used as indicator of disturbances of vascular permeability. The morphological and functional state of the MC was assessed by biomicroscopy and also by examination of mesenteric preparations. The latter were obtained after intravital fixation of the mesentery by intraperitoneal injection of 15 ml of Carnoy's fixing solution.

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