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EFFECT OF HEPARIN ON PROSTACYCLIN ACTIVITY IN THE AORTIC WALL

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KEY WORDS: heparin; platelets; aggregation; prostacyclin.

The mechanism of the anticoagulant activity of heparin is explained chiefly by its ability to block thrombin and fibrin formation. However, although heparin delays blood clotting, at the same time it induces intravascular platelet aggregation [1, 4]. The platelet-aggregating action of heparin is a substantial obstacle in the way of its use in an artificial circulation and in thrombophilic states due to activation of the adhesive and aggregating function of the platelets. The mechanism of intravascular platelet aggregation after injection of heparin has not been finally studied. The important role of prostacyclin (prostaglandin I_2), synthesized by the endothelium of the vascular wall, in regulation of aggregating activity of platelets has recently been established [13]. The inhibition of prostacyclin synthesis observed in diabetes, ischemic heart disease, and other diseases is accompanied by increased platelet aggregation [2, 9, 10, 15].

The object of this investigation was to study the effect of heparin on prostacyclin activity in the aortic wall.

EXPERIMENTAL METHOD

Experiments were carried out on 25 Wistar rats weighing 200 g. A solution of heparin (from Richter, Hungary) was injected into the caudal vein of the animals in a dose of 750 Units/kg. Prostacyclin activity was determined in the aortic wall by the method in [11] 15 and 60 min after injection of heparin. Segments of the abdominal aorta were removed under pentobarbital anesthesia (50 mg/kg). Platelet-enriched plasma was obtained from blood of donor rats taken from the abdominal aorta and stabilized with 3.14% sodium citrate solution in the ratio of 9:1. Aggregation was studied by the method in [3]. The disodium salt of ADP (from Serva, West Germany), in a final concentration of 10^{-5} M, was used as inducer of aggregation. The statistical analysis was carried out by Student's t test.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that ADP-induced platelet aggregation in healthy animals averaged 90 ± 2.1%, its lag period was short (30-50 sec), the mean value of the angle α was 66 ± 2.8°, and as a rule deaggregation did not develop. After incubation of platelet-enriched plasma with aortic wall taken from intact control animals, platelet aggregation was reduced on average to 20 ± 1.7%, the lag period was lengthened to 100-120 sec, and the angle

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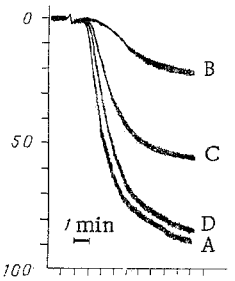

Fig. 1. Effect of heparin on antiaggregating activity of wall of abdominal aorta. A) ADP-induced aggregation of platelets from intact animals. B) Aggregation of platelets during incubation of platelet-enriched plasma for 5 min with 9 mg of wall of abdominal aorta from intact animals. C) Platelet aggregation on incubation for 5 min with aortic wall obtained from animals 15 min after injection of heparin. D) Platelet aggregation on incubation for 5 min with aortic wall obtained from animals 60 min after injection of heparin.

α was reduced to 35-40°, evidence of inhibition of the process. Intravenous injection of heparin caused practically total uncoagulability of the blood (the blood clotting time was over 30 min compared with 1.5-5 min in the control rats) and it inhibited the antiaggregating action of the aortic wall. For instance, after incubation of platelet-enriched plasma with aortic wall from animals receiving an injection of heparin 15 min before removal of the aorta, platelet aggregation was reduced by only 50%, the lag period was 60-80 sec, and 1 h after the injection the vascular wall had completely lost its property of preventing platelet aggregation. Intravenous injection of heparin induced intravascular platelet aggregation; the aggregation index of the platelets under these conditions was increased on average to 1.4 from the normal level of 1.1 ($P < 0.05$).

When injected intravenously, heparin thus blocks the antiaggregating properties of the vascular wall, which in the modern view are principally due to synthesis of prostacyclin by the endothelium of the vascular wall and its constant circulation in the blood stream [10-12, 14]. The mechanism of the inhibitory action of prostacyclin on platelet aggregation is connected with activation of adenylate cyclase and with elevation of the endogenous cAMP level in the platelets [2, 9, 15] and, possibly, with prostacyclin blockade of platelet phosphodiesterase [10].

In the light of these results, the formation of intravascular aggregates of platelets following injection of heparin may be linked with a disturbance of the synthesis of activity of prostacyclin. As a result, the homeostatic balance is upset between the thromboxane-generating system of the platelets, activation of which by various inducers and, in particular, by heparin, leads to platelet aggregation, and the prostacyclin-generating system of the vascular wall. Depression of prostacyclin activity or synthesis abolishes the antiaggregating action, and this may lead to aggregation.

From this standpoint it is easier to understand the cause of the ineffectiveness of heparin in preventing the formation of a thrombocytic thrombus after microscopic injuries to the vascular wall observed in certain cases [5-8, 12, 14]. This is probably because heparin, as a powerful polyanion, initiates the process of platelet aggregation on the one hand, but on the other hand it inhibits the antiaggregating prostacyclin activity of the vascular wall.

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MECHANISM OF THE MODULATING ACTION OF HISTAMINE ON EXCITATION AND CONTRACTION OF SMOOTH-MUSCLE CELLS OF THE URETER

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KEY WORDS: smooth muscles; ureter; histamine; phencarol; Na^+, Ca^{++}, and R^+ ions.

In previous investigations the writers showed that histamine increases the duration of the action potential (AP) plateau of smooth muscle cells (SMC) of the ureter, and it was postulated that lengthening of the AP plateau by histamine was due to increased potential-dependent sodium conductance of the membrane [6].

The object of the present investigation was to continue the study of this phenomenon.

EXPERIMENTAL METHOD

Experiments were carried out on segments of the whole ureter or segments of the circular layer of the ureter from guinea pigs by a double sucrose gap technique, with simultaneous recording of electrical activity and contractions [1]. The original Krebs' solution had the following composition (in mM): NaCl - 120.4, KCl - 5.9, $NaHCO_3$ - 15.5, $MgCl_2$ - 1.2, NaH_2PO_4 - 1.2, $CaCl_2$ - 2.5, glucose - 11.5. In sodium-free Krebs' solution all the NaCl was replaced by equivalent amounts of sucrose. Tetraethylammonium (TEA) was used in a concentration of 8 mM, histamine 10^{-6} g/ml, and phencarol* 10^{-6} g/ml.

EXPERIMENTAL RESULTS

APs and contractions of SMC of the ureter in Krebs' solution during the action of a depolarizing current on the strip (whole preparation), and anelectrotonic responses to the action of a hyperpolarizing current are shown in Fig. 1: Ia and IIIa. Addition of histamine (10^{-6} g/ml) to the Krebs' solution caused a very small decrease in membrane resistance, slight depolarization of SMC, and the appearance of anode-opening APs. The most characteristic features of the action of histamine in Krebs' solution were lengthening of the AP plateau and an increase in the amplitude and duration of contractions Fig. 1: Ib, c; IIIb, c. The increase in the duration of the AP plateau under the influence of histamine was not due to depolarization of SMC, for a shift of resting potential to the same level by the polarizing current caused only a negligible lengthening of the AP plateau. In addition, during repeated application of histamine depolarization of SMC was not always present, but the effect on the AP plateau remained.

To study the role of Ca^{++} ions in the histamine effect, in the next series of experiments the action of histamine on SMC of the ureter was studied in sodium-free Krebs' solution. The writers showed previously that AP of SMC of the ureter in sodium-free Krebs' solution on the addition of TEA, to inhibit potential-dependent outward potassium currents, consists of a spike component and a plateau, the amplitude of which is a direct logarithmic

*Quinuclidyl-3-diphenylcarbinol.

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