Effect of Desmopressin on Erythrocyte Aggregation

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Experiments on rats showed that desmopressin in doses recommended for single injections to humans increased erythrocyte aggregation. A close correlation between erythrocyte aggregation index and blood viscosity, on the one hand, and plasma content of acid glycosaminoglycans on the other was detected.

Key Words: *erythrocyte aggregation; desmopressin; blood rheology; glycosaminoglycans*

Despite almost 30-year experience gained in the use of desmopressin (1-deamino-8-D-arginine vasopressin; DP), a synthetic analog of vasopressin, in the treatment of blood clotting disorders, the exact mechanisms of its hemostatic effect remain not quite clear [10]. Numerous mechanisms are involved in the maintenance of finely balanced hemostasis system, and rheological factors, along with a great number of biochemical reactions, play an important role in modulation of blood response to damaging stimuli [14]. Primary hemostasis takes place in flowing blood, where the conditions of the flow largely regulate the interactions of blood cells between each other and with the vascular wall [8,12]. In turn, an important factor, determining the hemodynamic parameters, particularly in microcirculation, is aggregation of the largest blood cell population, erythrocytes [7]. Though the relationship between erythrocyte aggregation and pathological clotting is acknowledged [11], its modulating effect on physiological hemostatic processes is often neglected.

We studied erythrocyte aggregation and factors determining it after single injection of DP.

MATERIALS AND METHODS

Experiment was carried out on 19 male albino rats (290-320 g) receiving subcutaneously 0.02 μg DP (adiuretin; Ferring-Leciva). After 4 h, the animals were narcotized with sodium ethaminal, decapitated, and the blood was collected. Control group consisted of 15 rats.

Erythrocyte aggregation index (AI) was determined using a MA1 semiautomated aggregometer (Myrenne); the method is based on the analysis of light beam passing through the blood or cell suspension in a plasma-substituting solution [13]. The blood sample was rotated at a shear rate of 600 sec^{-1} and after stop the AI was measured automatically for a 10-sec interval. After high-shift rotation the AI was measured at low shear rate (3 sec^{-1}) for the same time interval. Hematological parameters (hematocrit, hemoglobin concentration, erythrocyte count) were evaluated by universal methods. Fibrinogen concentration was measured by gravimetry. Serum content of acid glycosaminoglycans (GAG) was measured by carbazole color reaction [2]. Plasma and blood viscosities at shear stress of 3.90 and 0.39 N/m^2 were measured on a capillary viscosimeter.

The results were statistically processed using parametric tests.

RESULTS

Injection of DP led to pronounced changes in erythrocyte aggregation characteristics. A significant (more than 10-fold; $p<0.001$) increase in AI in comparison with the control was detected in stasis after high shear rate and low shear rate rotation modes

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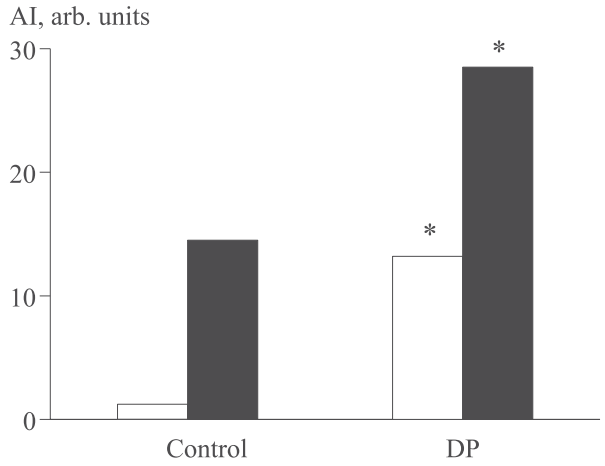

Fig. 1. Erythrocyte AI under DP effect. Light bars: rotation at high shear rate, dark bars: rotation at low shear rate. *p<0.001 compared to the control.

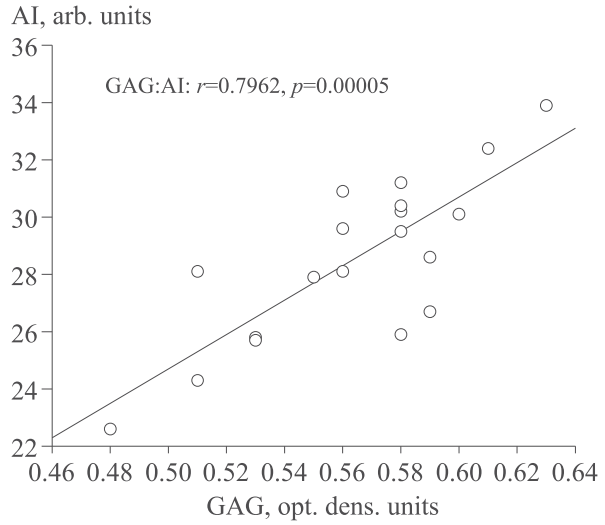

Fig. 2. Correlation between erythrocyte AI evaluated at low shear rate and plasma concentration of acid GAG.

(almost 2-fold; p<0.001) (Fig. 1). This virtually ruled out the relationship between aggregation and completeness of aggregate dispersion during the previous high shear rate rotation and between aggregation and viscosity of the dispersion medium [13].

The increase in fibrinogen concentration in the blood is traditionally regarded as the main cause of increased erythrocyte aggregation (fibrinogen molecules form bridges between the cells) [11]. We observed a trend to an increase in fibrinogen level, but the differences were statistically insignificant and it is hardly possible that this parameter is decisive for high aggregation. The absence of intensive generation of fibrinogen in the circulating blood is an important factor in clinical use of DP excluding the need in fibrinolytic drugs. Since the process of erythrocyte accumulation in aggregates should be in principle governed by common regularities of cell-cell interactions with participation of connective tissue matrix components [1], we analyzed the content of acid GAG in the plasma. Injection of the drug led to an almost 2-fold increase of their concentration (p<0.001), which can be explained by DP (and vasopressin [6]) capacity to activate macrophages and modify secretion of bioactive substances initiating destruction of tissue proteoglycans and GAG release into the blood through the lymph drainage. The proaggregant properties of GAG are also confirmed by the close correlation between their blood concentration and degree of erythrocyte aggregation (Fig. 2).

Since the extracellular matrix is highly sensitive to stress exposure, hormonal and metabolic shifts [3-5], we can hypothesize that its components play an important role in the regulation of blood rheology and largely determine physiological characteristics of this mobile tissue. Taking into account high molecular weight, elongated conformation, and hydrophilia of GAG, and their capacity to bind plasma proteins [10], their effects on blood fluidity can be explained by direct modification of plasma viscosity (Table 1). Coefficients of correlation between GAG and plasma and blood viscosities are 0.731 and 0.687, respectively (p<0.001).

Hence, DP is characterized by pronounced proaggregant effect and hemorheological activity. The detected relationship between erythrocyte aggregation and changed content of connective tissue components in the plasma can be important not only for explaining the hemostatic effect of DP, but also for understanding common mechanisms of hemorheological restructuring in different functional states.

TABLE 1. Effect of DP on Blood Rheology and Biochemistry in Rats (M±s)

Group	Blood viscosity, mPa×sec		Plasma viscosity, mPa×sec	Hematocrit	Fibrinogen, g/liter	GAG, opt. dens. units
	3.90 N/m^2	0.39 N/m^2				
Control (n=15)	3.43±0.18	5.20±0.57	1.17±0.04	43.7±1.1	1.56±0.3	0.28±0.05
DP (n=19)	3.86±0.24*	5.91±0.38*	1.29±0.03*	43.9±1.9	1.68±0.4	0.56±0.04*

Note. *p<0.05 compared to the control.

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