EFFECT OF ACTH, CORTICOSTEROIDS, AND SEX HORMONES ON THE BLOOD CLOTTING SYSTEM

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Experiments on rabbits showed that cortisone, hydrocortisone, 6-methylprednisolone, ACTH, and testosterone increase the activity of the blood clotting system to different degrees, increase retraction of the blood clot, diminish fibrinolysis, and lower the free heparin and antithrombin concentration in the blood. In experiments on rats they increase capillary resistance. Desoxycorticosterone and estradiol lowered the clotting power of the blood and increased its fibrinolytic activity. Desoxycorticosterone reduced and estradiol increased the capillary resistance.

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The effect of the endocrine system, especially the steroid hormones, on the clotting system of the blood has received inadequate study.

The object of the present investigation was to study changes in the blood clotting process after administration of glucocorticoids and desoxycorticosterone acetate to animals, stimulation of the adrenal cortex with ACTH, and after administration of sex hormones. To judge the state of the blood vessels the capillary resistance was investigated.

EXPERIMENTAL METHOD

Experiments were carried out on 136 rabbits weighing 2000-3500 g and on 186 male albino rats weighing 150-200 g. To assess the state of all phases of blood clotting, the thromboelastograms were recorded on a Soviet thromboelastograph and on an apparatus manufactured by the firm "Hellige," using citrated blood. Activity of the prothrombin complex was determined by Quick's method and calculated from dilution curves in percent. For this purpose graphs were plotted on logarithmic paper [3,4]. The fibrinolytic activity of the blood was investigated by Bidwell's method and calculated from the percentage lysis of the incubated clot. The blood heparin concentration was estimated by titration with protamine sulfate, the antithrombin activity of the blood plasma by inactivation of standard thrombin solution added to it, and clot retraction by ability of the blood clot to contract and express serum from it during incubation at a constant temperature. The capillary resistance was measured from the time of appearance of petechiae after creation of a negative pressure (200 mm Hg) in a vessel applied to the rats' skin.

Investigations were carried out under normal conditions and 24, 48, and 72 h after a single injection of the test hormones — ACTH, hydrocortisone, cortisone, 6-methylprednisolone, and prednisolone in doses of 5 mg/kg, desoxycorticosterone in a dose of 1 mg/kg, testosterone in a dose of 2.5 mg/kg, and estradiol in a dose of 0.5 mg/kg.

EXPERIMENTAL RESULTS

After administration of a single dose of glucocorticoids (cortisone, hydrocortisone, prednisolone, 6-methylprednisolone) the clotting power of the rabbits' blood was increased, as shown by shortening of the reaction time (r) and of the time of clot formation (K) on the thromboelastogram. The maximal amplitude was increased but not in every case (Fig. 1). The activity of the prothrombin complex determined by Quick's method showed a significant increase ($P < 0.05$; Table 1). Of the preparations given, cortisone possessed the greatest activity and 6-methylprednisolone the least. These hormones increased clot

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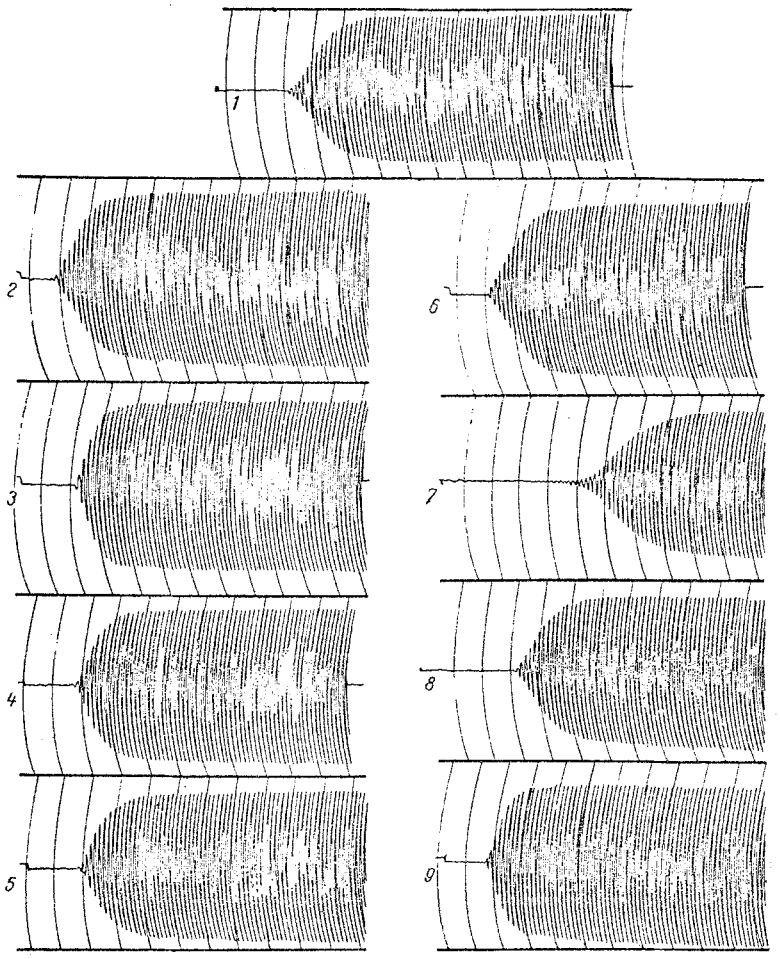

Fig. 1. Thromboelastogram of rabbits. 1) Normal; 2-9) 24 h after injection of cortisone, prednisolone, 6-methylprednisolone, ACTH, desoxycorticosterone acetate, estradiol dipropionate, and testosterone propionate respectively.

retraction, reduced the intensity of fibrinolysis and the heparin concentration and lowered the antithrombin activity in the blood. The capillary resistance was increased (Table 2).

During stimulation of the adrenal cortex with ACTH, the trend of changes in the clotting power of the blood and capillary resistance was similar to that observed after injection of glucocorticoids.

Testosterone propionate, like the glucocorticoid hormones, increased the activity of the blood clotting system (Fig. 1) and increased clot retraction. The capillary resistance was higher than initially. The activity of testosterone was less than that of the glucocorticoids judging by the indices studied. Estradiol dipropionate reduced the clotting power of the blood.

Small amounts of thrombin, converting fibrinogen into fibrin, are known to be constantly formed in the body, regulating the degree of permeability of the blood vessel wall [1]. Blocking the fibrinolytic enzymes with glucocorticoids and testosterone in our experiments was accompanied by an increase in capillary resistance. Fibrinolysis produced in animals by fibrinolysin and streptokinase is accompanied, according to our findings, by a decrease in capillary resistance. Administration of inhibitors of fibrinolysis, such as ϵ-aminocaproic acid, PAMBA, ACTH, cortisone, hydrocortisone, etc., prevented the decrease in capillary resistance and hemorrhagic manifestations arising as a result of injection of knowingly increased doses of fibrinolysin, streptokinase, and other activators of fibrinolysis [2]. Consequently, the state of the fibrinolytic activity is of great importance in the regulation of the permeability and resistance of the capillaries.

TABLE 1. Effect of a Single Dose of Hormones on Activity of the Prothrombin Complex by Quick's Method (24 h after injection of hormones)

Hormone	Number of animals	Activity of prothrombin complex (in percent)		
		Initial index	After 24 h	P
Cortisone acetate	8	100 ± 11	185 ± 17	< 0.05
Hydrocortisone acetate	8	100 ± 10	172 ± 16	< 0.05
Prednisone	8	100 ± 9	167 ± 15	< 0.05
6-methylprednisolone	8	100 ± 10	152 ± 14	< 0.05
ACTH zinc-phosphate	8	100 ± 11	180 ± 17	< 0.05
Desoxycorticosterone acetate	8	100 ± 10	47 ± 5.3	< 0.05
Estradiol dipropionate	12	100 ± 11	68 ± 8.4	< 0.05
Testosterone propionate	12	100 ± 10	118 ± 11.2	

TABLE 2. Effect of a Single Dose of Hormones on Activity of the Prothrombin Complex by Quick's Method (24 h after injection of hormones)

Hormone	Number of animals	Capillary resistance (in min)		
		Initial index	After 24 h	P
Cortisone acetate	15	5.2 ± 0.6	9.0 ± 0.81	< 0.05
Hydrocortisone acetate	15	5.0 ± 0.4	8.1 ± 0.72	< 0.05
Prednisone	15	4.7 ± 0.42	9.2 ± 0.85	< 0.05
6-methylprednisolone	15	4.9 ± 0.51	8.6 ± 0.79	< 0.05
ACTH-zinc-phosphate	15	5.1 ± 0.46	8.4 ± 0.76	< 0.05
Desoxycorticosterone acetate	15	5.3 ± 0.48	3.6 ± 0.27	< 0.05
Control	56	5.1 ± 0.52	4.9 ± 0.36	

The results suggest that steroid hormones are highly active compounds influencing blood coagulation. Glucocorticoids and androgens increase the clotting power of the blood. These changes take place as a result of an increase in activity of individual blood clotting factors, namely I, II, V, VII, VIII, IX, and X, as was previously shown by other authors [3,5,6,7]. In addition they increase the number of platelets and erythrocytes in the blood, and these also contain large quantities of blood clotting factors.

Analysis of the phases of hemocoagulation showed that the formation of active thromboplastin and the change from prothrombin into thrombin and formation of fibrin from fibrinogen are accelerated. At the same time, fibrinolytic enzymes, heparin, and antithrombins are blocked. Such changes in coagulation may bring about thrombus formation. According to some reports [8], the leading factor in the hemostatic action of sex hormones is a decrease in permeability of the vascular wall, and this is in agreement with the present findings.

The steroid hormones thus exert a regulatory effect on all phases of the blood clotting process.

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