MECHANISM OF ACTION OF ESTROGENIC AND GONADOTROPIC HORMONES ON THE CLOTTING AND ANTICLOTTING SYSTEMS OF THE BLOOD

Ch. S. Guseinov, L. A. Plodovskaya, N. Ya. Lagutina, and G. A. Chernov

UDC 612.115.3:[612.621.31+612.433.62.018

In recent years, interest in the role of estrogens in the pathogenesis of hemorrhages during menstruation has increased considerably. Soviet and Western authors [3, 4, 6, 12, 14, 15, 17, 18] have reported changes in the clotting and anticlotting systems of the blood during disturbances of the ovarian menstrual cycle. However, no attempt has yet been made to study the influence of sex hormones, notably estrogens, on these indices. In the present paper an investigation of the action of estrogenic and gonadotropic hormones on the coagulation of the blood is described.

EXPERIMENTAL METHOD

Experiments were carried out on 36 sexually immature monkeys (green guenons) and 6 rabbits.

The experimental animals were divided into two groups. The animals of group 1 received a mixture of hormones [chorionic gonadotropin – luteinizing hormone (LH) and human menopausal gonadotropin – follicle-stimulating hormone (FSH) "Humegon"] in doses of 180-380 and 200-500 units chorionic gonadotropin.

In the sexually mature animals, FSH and LH act simultaneously: FSH causes growth and maturation of the follicles, LH causes rupture of the ripe follicle (ovulation), bleeding into the cavity of the follicle, and the formation of the corpus luteum. The proportions between the two hormones differ in different phases of the menstrual cycle.

The animals of group 2 received only large doses of chorionic gonadotropin (LH) – from 2000 to 6000 units.

The functional state of the clotting and anticlotting systems of the blood was investigated in detail in the experimental animals. The plasma recalcification time and the fibrinogen were determined by Rutberg's method [8], the free heparin by Sirmai's method [11], the prothrombin time of the plasma and serum by Quick's method [16], and the fibrinolytic activity of the blood by the method of Kowalski and Niewiarowski [13].

The blood serotonin concentration was determined by the method of Chernov and Lipats [10]. The results obtained were subjected to statistical analysis by the Student–Fisher method.

EXPERIMENTAL RESULTS

Series I included 14 experiments on 24 monkeys. The effect of repeated injection of gonadotropin on the blood clotting system indices of the monkeys is illustrated in the table.

As the table shows, the most marked changes were observed in the blood serotonin metabolism. In all the animals the 5-hydroxytryptamine concentration showed a sharp decrease against the background of an increased gonadotropin level, and varied within limits of 0-0.006 μg/ml (mean 0.015-0.006 μg/ml).

Research Institute of Clinical and Experimental Surgery, Ministry of Health of the RSFSR; Institute of Obstetrics and Gynecology, Ministry of Health of the USSR; Central Institute of Hematology and Blood Transfusion, Ministry of Health of the USSR; Institute of Poliomyelitis and Virus Encephalitis, Moscow
(Presented by Academician B. V. Petrovskii). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 64, No. 9, pp. 24-27, September, 1967. Original article submitted December 10, 1965.

Table 1. Effect of Female Sex Hormones and Gonadotropins on Some Indices of the Blood Clotting System, M ± m

Animals	Experimental conditions	Index of blood clotting system: recalcific. time, sec	thrombin time, sec	free heparin, sec	plasma prothrombin time, sec	serum prothrombin time, sec	thromboplastin, sec	serotonin, μg/ml	fibrinogen, mg%	Blood fibrinolytic activity, min	blood clots retraction, ml
Monkeys (12)	Normal	306,8±31,6	27,4±1,7	7,6±0,4	10,8±1,2	37,4±3,6	7,34±0,74	0,7000±0,10	274,6±5,71	251±1,36	0,39±0,024
	After admin. of leuteinizing hormones	569,0±33,6	35,9±2,8	12,6±2,29	8,9±0,7	45,6±3,5	9,45±0,95	0,0134±0,002	344,0±36,8	235±12,4	0,18±0,05
Monkeys (24)	After admin. of follicle-stimulating hormones	458,8±28,5	25,7±1,2	11,5±0,71	8,0±0,71	26,6±4,4	—	0,015±0,006	232,0±21,6	251±1,36	0,45±0,018
Rabbits (6)	Before injection of hormones	369,0±59,8	26,6±2,1	10,3±2,5	9,6±0,5	33,0±4,1	—	0,055±0,002	249±27	275±13,2	0,26±0,1
	After injection of luteinizing hormones	482,0±42,06	36,0±12	—	8,5±1,5	50,0±25,2	—	0,0137±0,006	155±22	220±13,4	—

Notes: 1. The investigation was carried out 14 days after the end of the course of hormone therapy. 2. The platelet count of the peripheral blood of the animals remained within normal physiological limits before and after hormone therapy. 3. Number of animals in parentheses.

Besides these changes, however, marked changes were also observed in the first phase of blood clotting. The serum prothrombin time was shortened, in association with disturbed prothrombin consumption and an increase in the plasma recalcification time. The results obtained by these methods showed a decrease in the level of platelet 3rd factor, taking part in the thromboplastin formation.

Another noteworthy feature was an increase in the free heparin concentration, reaching 250% in some cases.

Occasionally the fibrinogen concentration was reduced to 88 mg%. The fibrinolytic activity of the blood was increased correspondingly.

The other indices of the blood clotting system were within physiologically normal limits.

Most monkeys of this group had multiple ovulation (from 2 to 12 corpora lutea).

In the experiments of series 2, the changes in the factors of the clotting and anticlotting systems of the monkeys' blood under the influence of FSH and of the rabbits' blood under the influence of folliculin were investigated. The results obtained were similar to those in the experiments of series 1 (see table). At necropsy on the monkeys uniform changes were found: enlargement of the ovaries, hemorrhages into the follicles, and, in most cases, luteinization of the follicles. The changes and disturbances were less marked with a dose of 600 units. Ovulation was never observed.

The results of these investigations of the clotting and anticlotting systems of the blood, and also the serotonin concentrations determined after administration of the hormones, showed that the most marked changes affected the blood 5-hydroxytryptamine level, thromboplastic formation, and also the anticoagulant and fibrinolytic activity of the blood.

Many reports have been published of changes in the permeability and resistance of the blood vessels, both during normal menstruation and during distrubances of ovarian and menstrual function [1, 7]. An increase in the permeability of the blood vessels of the endometrium and their gaping during detachment of the functional layer in the premenstrual and menstrual periods determine the transfer of thromboplastic substances into the general circulation. The penetration of the tissue thromboplastin into the blood stream facilitates the release of the components of the anticlotting and fibrinolytic systems [12], and these are responsible for changes in the anticoagulants during menstruation.

The results obtained thus demonstrate the important role of hormones in the mechanism of neuro-endocrine regulation of blood clotting. In addition, the results reveal the close physiological connection between hormonal regulation and hemostasis during the ovarian menstrual cycle.

LITERATURE CITED

1. E. A. Kost, Hemorrhagic Diatheses, Moscow-Leningrad (1928).
2. B. A. Kudryashov, Klin. Med., No. 3, 19 (1961).
3. A. A. Lebedev, Dysfunctional Uterine Bleeding, Moscow (1960).
4. S. K. Lesnoi, in the book: Textbook of Clinical Endocrinology, Moscow (1958), p. 221.
5. G. P. Pron', Akush. i Gin., No. 1, 45 (1955).
6. A. A. Radionchenko, Akush. i Gin., No. 6, 75 (1959).
7. A. A. Radionchenko, Akush. i Gin., No. 4, 74 (1961).
8. R. A. Rutberg, Lab. Delo., No. 6, 6 (1961).
9. M. K. Stepankina, Akush. i Gin., No. 6, 21 (1946).
10. G. A. Chernov and A. A. Lipats, Byull. éksp. Biol., No. 8, 59 (1959).
11. E. Sirmai, Probl. Gematol., No. 6, 38 (1957).
12. E. Fluckiger and K. Salzmann, Experientia (Basel), 17, 131 (1961).
13. E. Kowalski and S. Niewiarowski, Acta physiol. pol., 9, 295 (1958).
14. C. Maric, Compt. Rend. Soc. Biol., 154, 1638 (1960).
15. H. Pigeand, R. Burthiault, R. Bethoux, et al., Cynec. et Obstet., 57, 415 (1958).
16. A. J. Quick, Am. J. Med. Sci., 213, 272 (1947); Circulation, 24, 1422 (1961).
17. S. Seller, Therapie, 12, 53 (1957).
18. S. Slimane-Taleb, Compt. Rend. Soc. Biol., 153, 788 (1959).