IMPACT OF PEPTIDE BIOREGULATORS, EXTRACTED FROM WALL OF INFLAMED GALL BLADDER OF PATIENTS WITH CHRONIC CACULOUS CHOLECYSTITIS, UPON HEMOSTATIS WITHIN IN AN EXPERIMENT

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Study of condition of hemostasis system among 30 rabbits after 15-day intramuscular introduction of peptide bioregulators, extracted from wall of inflamed removed gall bladders of patients with chronic calculous cholecystitis (CCC) after laparoscopic cholecystectomy (LCE), has been carried out. The objective of this research is to study impact of peptide bioregulators ($XKXG_1$, $XKXG_2$), extracted from inflamed removed chromic calculous bladders of patients with CCC after LCE, upon homeostasis within an experiment upon rabbits. Peptide bioregulators were extracted via method of acetous extraction. It has been shown that peptide bioregulators $XKXG_1$ and $XKXG_2$ cause multidirectional hyper- and hypocoagulation shifts in organism of experimental animals. It is established that on day 15 an expressed disseminated intravascular coagulation syndrome (DIC-syndrome) is formed within organism of rabbits which is caused by influence of humoral peptide bioregulators, as explained by the authors.

Keywords: chronic calculous cholecystitis, peptides, bioregulators, hemostasis

In recent years is has been established that inflammatory chronic calculous [9], acute catarrhal, acute pultaceous, and acute gangrenous gall bladders of patients with cholecystitis contain biological active humoral factors [1; 11-12].

The study of peptide regulatory mechanisms of multi-cell systems is one of the most important directions in modern biology and medicine [2-3; 8; 13]. Development of this problem enables us not only to understand causes of individual development, but also study deeper physiological processes that undergo within a multi-cell organism, and their changes in conditions of pathology [4-5; 7; 10].

Disturbance in peptide regulation, and, therefore, transition of informational molecules between cells must inevitably result in development of pathologies, including diseases of outer-liver biliary tracts, and it served as object of our research.

The goal of this research is to study influence of peptide bioregulators ($XKXG_1$, $XKXG_2$), extracted from inflamed removed chronic calculous gall bladders of patients with CCC after LCE, upon hemostasis within an experiment on rabbits.

Materials and research methods

In our test breedless rabbits of both sexes with body mass of 2 to 3 kgs were used. Examination of hemostasis was undertaken before the experiment (background), on day 15 of introducing peptide fractions, extracted from inflamed removed chronic calculous gall bladders of patients with CCC after LCE. Peptide fractions in our experiments were introduced to animals intramuscularly in dose of 1 mg/kg of body mass. Before introduction peptide fractions were dissolved in sterile phisiological solution. Preparations were introduced 1 time per day during 15 days. As a control (preparation of comparison) same volume of sterile 0,9 % solution of natrium chloride was introduced over the same period to 10 rabbits, among which condition of hemostasis system was inspected. During the research we used methods that characterise all links of hemostasis system: counting number of thrombocytes in thrombocyte-dense plasma, adhesion of thrombocytes, aggregation of blood plates, retraction of blood clot. Methods that characterize overall coagulative blood activity: period of plasma recalcification, kaolin plasma time, kaolin cephalin clotting time, plasma tolerance against heparin (TPH), auto-coagulative test (ACT), prothrombin time, thrombin time, coagulating fibrinogen, antithrombin III (At III), protaminsulphate test, ethanol test. Methods that characterize fibrinolytic activity of blood: total euglobulin clot dissolution, Hageman-dependent euglobulin clot dissolution. The received material was processed via methods of variational statistics for the related and non-related observations, index of difference reliability (D) was calculated.

Research results and discussion

From chronic calculous gall bladders of patients with CCC after LCE we have extracted via method of acetous extraction 4 peptide fractions that were named $XKXG_1$, $XKXG_2$, $XKXG_3$ and $XKXG_4$. The data of table 1 in blood, taken from a.pulmonalis of experimental rabbits on day 15 of introducing fraction $XKXG_1$ testified for hyper-, hypocoagulative shifts in hemostasis. Thus, number of thrombocytes decreased from $215,6 \pm 18.8$ to $168,6 \pm 2,1 (P < 0,001)$. At the same time

their adhesion decreased from 60,0 ± 3,59 to 38,6 ± 2,1 (P < 0,001), and time of aggregation, on the opposite, increased from 30,0 ± 2,5 to 41,0 ± 2, 51(P < 0,05). Time of whole blood clotting according to Lee-White in non-siliconized and siliconized test tubes decreased from 5,6 ± 0,35 to 2,5 ± 0,08 (P < 0,05) and from 9,4 ± 0,86 to 3,3 ± 1,4 (P < 0,001) correspondingly. Data of electrocoagulogramme also revealed hypercoagulation. Periods of beginning, duration, and end of blood clotting decreased from 592,5 ± 11,6 to 153,0 ± 8,9 (P < 0,001), from 353,0 ± 7,1 to 113,3 ± 4,2 (P < 0,001), from 945,5 ± 17,9 to 266,6 ± 13,1 (P < 0,001) correspondingly. Hypercoagulation is attended to increase in blood viscosity (P < 0,05) and unchanged density of blood clot.

Biochemical indexes of hemostasiogram in blood of a.pulmonalis of experimental rabbits on day 15 if introducing fraction XKXG1 testified for multi-directed hypercoaguative shifts: sharply decreased time of plasma recalcification, kaolin, and kaolin-cephalic time – from 180,0 ± 7,1 to 40,0 ± 1,7 (P < 0,001), from 79,1 ± 6,2 to 23,0 ± 1,7 (P < 0,001), from 67,8 ± 4,4 to 21,0 ± 2,1 (P < 0,001) correspondingly. Time of plasma clot formation, according to the data of autocoagulogram, decreased by 6 min. (P < 0,001), and definition increased by 8 min. (P < 0,001) and 10 min (P < 0,001). In blood of a.pulmonalis rabbits tolerance of plasma against heparin increased sharply from 12,3 ± 0,89 to 2,0 ± 0,4(P < 0,001). However, thrombin time changed unreliably (P > 0,2), and content of free heparin increased from 10,1 ± 0,8 to 12,0 ± 0,89(P < 0,01). Among 5 of 10 experimental animals ethanol tests and among 4 of 10 – protamine sulfate were positive.

Table 1

Indexes of hemostasis in blood, taken from a.pulmonalis of rabbits after 15 days of intramuscular introduction of peptide, received from chronic calculous gall bladders of patients after LCE (fraction –$XKXG_1$)

№	Indexes	Healthy animals (control)	After introduction of fraction $XKXG_1$
1	Number of thrombocytes ($x10^9$/l)	215,5 ± 18,8	168,6 ± 2,1*
2	Adhesion of thrombocytes (%)	60,0 ± 3,59	38,6 ± 2,1*
3	Aggregation of thrombocytes (s)	30,0 ± 2,5	41,0 ± 2,54*
4	Time of clotting according to Lee-White (min) in non-siliconized test tube.	5,6 ± 0,35	2,5 ± 0,08*
	In siliconized test tube	9,4 ± 0,86	3,31 ± 1,4*
5	Beginning of blood clotting (s)	592,5 ± 11,6	153,0 ± 8,9*
6	Duration of blood clotting (s)	353,0 ± 7,1	113,3 ± 4,2*
7	End of blood clotting	945,5 ± 17,9	266,6 ± 13,1*
8	Blood viscosity (units)	5,0 ± 0,35	2,7 ± 0,2*
9	Clot density (units)	0,02 ± 0,0	0,02 ± 0,0
10	Time of plasma recalcification (s)	180,0 ± 7,1	40,0 ± 1,7*
11	Kaolin time of plasma (s)	79,1 ± 6,2	23,0 ± 1,7*
12	Kaolin-cephalic time (s)	67,8 ± 4,4	21,0 ± 2,1*
13	Autocoagulogram (s) on 6 min	15,0 ± 0,7	12,0 ± 1,7*
	On 8 min	9,6 ± 0,89	11,0 ± 1,7*
	On 10 min	7,8 ± 0,7	9,6 ± 0,8
14	TPH (min)	12,3 ± 0,89	2,0 ± 0,4*
15	Prothrombin time (s)	35,0 ± 3,4	43,0 ± 3,4*
16	Trombin time (s)	38,3 ± 3,7	35,0 ± 2,5
17	Free heparin (s)	10,1 ± 0,8	12,0 ± 0,89
18	Ethanol test	10 (-)	5 (+)
19	Protamine sulfate test	10 (-)	4 (+)

Note: * P < 0,05 in comparison to hemostasis indexes among healthy animals.

Table 2

Indexes of hemostasis in blood, taken from v.pulmonalis of rabbits after 15 days of intramuscular introduction of peptide, received from chronic calculous gall bladders of patients after LCE (fraction –$XKXG_1$)

№	Indexes	Healthy animals (control)	After introduction of fraction $XKXG_1$
1	Number of thrombocytes (x10^9/l)	309,1 ± 7,1	165,3 ± 1,8*
2	Adhesion of thrombocytes (%)	30,5 ± 7,1	29,3 ± 0,71*
3	Aggregation of thrombocytes (s)	28,0 ± 2,5	39,6 ± 1,4*
4	Time of clotting according to Lee-White (min) in non-siliconized test tube.	4,6 ± 0,4	4,8 ± 0,1
	In siliconized test tube	7,0 ± 0,3	5,4 ± 0,0
5	Beginning of blood clotting (s)	608,0 ± 7,1	150,0 ± 3,6*
6	Duration of blood clotting (s)	410,0 ± 8,0	109,1 ± 1,8*
7	End of blood clotting	1017,0 ± 14,3	259,1 ± 5,4*
8	Blood viscosity (units)	5,0 ± 0,3	5,0 ± 0,05
9	Clot density (units)	0,02 ± 0,71	0,02 ± 0,0
10	Time of plasma recalcification (s)	210,0 ± 3,23	58,0 ± 0,3*
11	Kaolin time of plasma (s)	130,0 ± 7,1	25,0 ± 0,3*
12	Kaolin-cephalic time (s)	80,0 ± 3,5	23,0 ± 0,7*
13	Autocoagulogram (s) on 6 min	14,0 ± 1,43	9,0 ± 0,35*
	On 8 min	12,0 ± 0,71	8,0 ± 0,3*
	On 10 min	7,0 ± 0,71	7,0 ± 0,35
14	TPH (min)	14,0 ± 0,71	2,5 ± 0,2*
15	Prothrombin time (s)	37,0 ± 0,7	40,1 ± 1,07*
16	Thrombin time (s)	40,0 ± 0,53	30,0 ± 0,35*
17	Free heparin (s)	10,0 ± 0,5	8,0 ± 0,3*
18	Fibrinogen (g/l)	1,6 ± 0,07	1,0 ± 0,01*
19	Total euglobulin fibrinolysis (min)	160,0 ± 3,0	190,0 ± 3,4*
20	Hageman-dependent fibrinolysis (min)	138,0 ± 4,4	200,0 ± 3,2*
21	Ethanol test	10 (-)	10 (+)
22	Protamine sulfate test	10 (-)	10 (+)

Note: * P < 0,05 in comparison to hemostasis indexes among healthy animals.

In blood, taken from v.pulmonalis (table 2) of experimental rabbits on day 15 of introducing fraction $XKXG_1$ number of thrombocytes decreased from 309,1 ± 7,1 to 165,3 ± 1,8 (P < 0,001). Their adhesive function remained almost unchanged (P > 0,2) at the background of increase in time of their aggregation from c 28,0 ± 2,5 to 39,6 ± 1,4 (P < 0,05). Time of whole blood clotting according to Lee-White of hyper-, normal coagulation in hemostasis: in non-siliconized test tube (P > 0,2) time of blood clotting did not increase reliably, and in siliconized tube it decreased (P < 0,001). According to electrocoagulograph, periods of beginning, duration, and end of blood coagulation decreased from 608,0 ± 7,1 to 150,0 ± 3,6 (P < 0,001), from 410,0 ± 8,0 to 109,1 ± 1,8 (P < 0,001), and from 1017,0 ± 14,3 to 259,1 ± 5,4 (P < 0,001) respectively. However, a difference between hemostasis of blood, received from a.pulmonalis (table 1) and v.pulmonalis (table 2) of rabbits at the same period of observation was change in blood viscosity (P > 0,2). Density of blood clot in blood a.pulmonalis (table 1) of the experimental rabbits, as well as in blood v.pulmonalis (table 2) didn't change. The data of biochemical indexes in blood v.pulmonalis among experimental rabbits on day 15 of introducing fraction $XKXG_1$ testified for hyper-, hypocoagulation. Time of plasma recalcification decreased

from 210,0 ± 3,23до 58,0 ± 0,3 (P < 0,001). It was attended by increasing activation of Hageman factor. Thus, kaolin time decreased from 130,0 ± 7,1 to 25,0 ± 0,3(P < 0,001). A decrease in kaolin-cephalic time from 130,0 ± 7,1 to 25,0 ± 0,3(P < 0,001) indicates a coagulational completeness of thrombocytes in blood v.pulmonalis of the experimental rabbits. Autocoagulogramme on 6 min (P < 0,05) and on 8 min (P < 0,05) shortened, and on 10 min (P > 0,2) of determination remained the same. Fraction $XKXG_1$ suppressed anti-coagulative system of rabbit blood on day 15 of introduction in blood v.pulmonalis. Thus, thrombin time decreased from 40.0 ± 0,53 to 30,0 ± 0,35 (P < 0,05). Content of free heparin decreased from 10, 0 ± 0,5 to 8,0 ± 0,3 (P < 0,05). It was confirmed by sharp increase in plasma tolerance against heparin from 14,0 ± 0,71 to 2,5 ± 0.2 (P < 0,001). Content of fibrinogen decreased from 1,6 ± 0,07 to 1,0 ± 0.01 (P < 0,01). We should point out that in blood v.pulmonalis of experimental rabbits on day 15 of introducing fraction $XKXG_1$ total euglobulin fibrinolysis and Hageman-dependent fibrinolysis from 160.0 ± 3,0 to 190,0 ± 3.4 (P < 0,001) and from 138,0 ± 4,4 to 200,0 ± 3,2 (P < 0,001) correspondingly. Among all 10 animals tests on ethanol and protamine sulfate resulted positively.

Table 3

Indexes of hemostasis in blood, taken from a.pulmonalis of rabbits after 15 days of intramuscular introduction of peptide, received from chronic calculous gall bladders of patients after LCE (fraction $XKXG_2$)

№	Indexes	Healthy animals (control)	After introduction of fraction $XKXG_2$
1	Number of thrombocytes (x10^9/l)	215, ± 18,8	114,0 ± 6,65*
2	Adhesion of thrombocytes (%)	60,0 ± 3,59	60,00,35
3	Aggregation of thrombocytes (s)	30,0 ± 2,5	30.0 ± 0.35
4	Time of clotting according to Lee-White (min) in non-siliconized test tube.	5,6 ± 0,35	4,1 ± 0,19*
	In siliconized test tube	9,4 ± 0,86	7,8 ± 0,08
5	Beginning of blood clotting (s)	592,5 ± 11,6	391,0 ± 3,95*
6	Duration of blood clotting (s)	353,0 ± 7,1	350,0 ± 3,59
7	End of blood clotting	945,5 ± 17,9	741,0 ± 7,55*
8	Blood viscosity (units)	5,0 ± 0,35	5,0 ± 0,05
9	Clot density (units)	0,02 ± 0,0	0,02 ± 0,0
10	Time of plasma recalcification (s)	180,0 ± 7,1	80,3 ± 3,23*
11	Kaolin time of plasma (s)	79,1 ± 6,2	60,1 ± 0,35*
12	Kaolin-cephalic time (s)	67,8 ± 4,4	66,8 ± 0,3
13	Autocoagulogram (s) on 6 min	15,0 ± 0,7	12,0 ± 0,35*
	On 8 min	9,6 ± 0,89	11,0 ± 0,3
	On 10 min	7,8 ± 0.7	7,0 ± 0,3
14	TPH (min)	12,3 ± 0,8	9,8 ± 0,10*
15	Prothrombin time (s)	35,0 ± 3,4	20,8 ± 1,79*
16	Thrombin time (s)	38,3 ± 3,7	28,0 ± 1,97*
17	Free heparin (s)	10,1 ± 0,8	10,0 ± 0,3
18	Fibrinogen (g/l)	71,6 ± 3,9	59,8 ± 1,07*
19	Anti-thrombin 3 (s)	1,2 ± 0,07	1,2 ± 0,03
20	Total euglobulin fibrinolysis (min)	123,6 ± 6,6	122,1 ± 4,31
21	Hageman-dependent fibrinolysis (min)	133,3 ± 6,29	132,8 ± 1,79
22	Ethanol test	10 (-)	10 (+)
23	Protamine sulfate test	10 (-)	10 (+)

N o t e : * P < 0,05 in comparison to hemostasis indexes among healthy animals.

Table 4

Indexes of hemostasis in blood, taken from v.pulmonalis of rabbits after 15 days of intramuscular introduction of peptide, received from chronic calculous gall bladders of patients after LCE (fraction $XKXG_2$)

№	Indexes	Healthy animals (control)	After introduction of fraction $XKXG_2$
1	Number of thrombocytes ($x10^9$/l)	309,1 ± 7,1	209,0 ± 3,5*
2	Adhesion of thrombocytes (%)	30,5 ± 7,1	20,0 ± 2,51
3	Aggregation of thrombocytes (s)	28,0 ± 2,5	17,8 ± 0,89*
4	Time of clotting according to Lee-White (min) in non-siliconized test tube.	4,6 ± 0,4	3,4 ± 0,07*
	In siliconized test tube	7,0 ± 0,3	4,9 ± 0,16*
5	Beginning of blood clotting (s)	608,0 ± 7,1	207,0 ± 2,51*
6	Duration of blood clotting (s)	410,0 ± 8,0	199,0 ± 1,79*
7	End of blood clotting	1017,0 ± 14,3	407,5 ± 4,31*
8	Blood viscosity (units)	5,0 ± 0,3	3,8 ± 0,3*
9	Clot density (units)	0,02 ± 0,0	0,02 ± 0,0
10	Time of plasma recalcification (s)	210,0 ± 3,23	109,5 ± 3,59*
11	Kaolin time of plasma (s)	130,0 ± 7,1	30,0 ± 2,51*
12	Kaolin-cephalic time (s)	80,0 ± 3,5	30,0 ± 1,07*
13	Autocoagulogram (s) on 6 min	14,0 ± 1,43	12,0 ± 0,35
	On 8 min	12,0 ± 0,71	9,8 ± 0,35
	On 10 min	7,0 ± 0,71	5,0 ± 0,35*
14	TPH (min)	14,0 ± 0,7	11,0 ± 0,35*
15	Prothrombin time (s)	37,0 ± 0,71	20,0 ± 0,3*
16	Thrombin time (s)	40,0 ± 0,53	39,8 ± 0,53
17	Free heparin (s)	10,0 ± 0,5	10,0 ± 0,3
18	Fibrinogen (g/l)	80,0 ± 3,5	60,0 ± 0,89*
19	Anti-thrombin 3 (s)	1,6 ± 0,07	1,0 ± 0,03*
20	Total euglobulin fibrinolysis (min)	160,0 ± 3,0	159,0 ± 1,97
21	Hageman-dependent fibrinolysis (min)	138,0 ± 4,4	130,0 ± 1,79
22	Ethanol test	10 (-)	10 (+)
23	Protamine sulfate test	10 (-)	10 (+)

Note: * $P < 0,05$ in comparison to hemostasis indexes among healthy animals.

In blood, taken from a. pulmonalis (table 3) on day 15 of introducing fraction $XKXG_2$ number of thrombocytes decreased from 215,5 ± 18,8 to 114,0 ± 6,65 ($P < 0,001$). But, unlike blood, taken from the heart, in lung artery on day 15 of the experiment adhesive ($P > 0,2$) and aggregation ($P > 0,2$) function of blood plates didn't change. Such integral indicator of blood coagulation as Lee-White demonstrated us a clear growth in coagulation potential in blood a.pulmonalis on day 15 of the experiment. Period of blood clot formation decreased from 5,6 ± 0,5 to 4,1 ± 0,19 ($P < 0,05$) in non-siliconized test tubes and from 9,4 ± 0,86 to 7,8 ± 0,08($P < 0,05$) in siliconized tubes. However, data of electrocoagulogram registered multi-directional shifts in hemostasis. Although duration of blood clotting did not change reliably on day 15, periods of beginning and end of clotting shortened correspondingly from 353,0 ± 7,1 to 350,0 ± 3,59 ($P < 0,001$) and from 945,5 ± 17,9до 741,0 ± 7,55 ($P < 0,001$). So how can we explain this multi-directional nature of shifts in hemostasis of a.pulmonalis blood on day 15 of introducing this fraction $XKXG_2$? Analysis of hemostasiogram shows us that kaolin-cephalic time of plasma did not change reliably ($P > 0,2$). In other words, different directions of blood clotting shifts is explained by the fact that fraction $XKXG_2$ in blood a.pulmonalis on day 15 suppresses activity of thrombocyte factor. Besides, this defect of thrombocyte hemostasis, formed under the influence of peptide

$XKXG_2$ is combine with above-mentioned disturbance in thrombocyte adhesion and aggregation. At the same time, activity of Hageman was not suppressed in blood of the studied rabbits, that is proven by decrease in kaolin plasma time from 79,1 ± 6,2 to 60,1 ± 0,35 (P < 0,05). Also, according to shortening in time of plasma recalcification from 180,0 ± 7,1 to 80,3 ± 3,23 (P < 0,001), acceleration of thrombic plates formation takes place. In our discussion multidirectional nature of shifts in autocoagulation tests is supported by shortening in clot formation from 15,0 ± 0,7 to 12,0 ± 0,35 (P < 0,05) on 6 min and its unchanged time on 8 min (P > 0,2) and 10 min (P > 0,2). Considering the fact that TPH shortened from 12,3 ± 0,8 to 9,8 ± 0,10 (P < 0,05) and regardless of the fact that level of free heparin amongst experimental animals didn't change in comparison to control, we can conclude that on day 15 of introducing fraction $XKXG_2$ in blood of a.pulmonalis anti-coagulative system is suppressed. In other words, we should underline that peptide $XKXG_2$ in pool of lung artery forms favourable conditions for clot formation. Danger of clot formation is also increased by the fact that on day 15 of introducing this peptide in the studied blood content of anti-thrombin III is decreased from 71,6 ± 3,9 to 59,8 ± 1,07 (P < 0,001). Regardless of the fact that level of fibrinogen and activity of fibrinogen remained unchanged, FPD tests were positive among all 10 animals.

In blood, taken from v. pulmonalis (table 4) on day 15 of introducing fraction $XKXG_2$ number of thrombocytes decreased from 309,1 ± 7,1 to 209,0 ± 3,5 (P < 0,001), their aggregation strengthened from 28.0 ± 2.5 to 17,8 ± 0,89 (P < 0,001), and adhesion remained unchanged (P > 0,2). Parameters of biochemical hemostasiogram testified synonymously for an expressed hypercoagulation. Time of whole blood clotting decreased from 4,6 ± 0,4до 3,4 ± 0,07 (P < 0,05) in non-siliconized test tube, and from 7,0 ± 0,3 to 4,9 ± 0,16 (P < 0,001) in siliconized tube. According to electrocoagulogramme, beginning of blood clotting shortened from 608,0 ± 7,1 to 207,0 ± 2,51 (P < 0,001), as well as duration and ending – from 410,0 ± 8,0 to 199,0 ± 1,79 (P < 0,001) and from1017,0 ± 14,3 to 407,5 ± 4,31 (P < 0,001) correspondingly. At the same time, according to the data of electrocoagulograph, blood viscosity grew from 5,03 ± 0,3 to 3,8 ± 0,3 (P < 0,001). Biochemical hemostasiogram registered a clear hypercoagulation: time of recalcification shortened (P < 0,001), kaolin time of plasma(P < 0,001) and kaolin-cephalic time of plasma (P < 0,001) was shortened as well. Only according to the data of autocoagulogram, time of blood clot formation did not change reliably on 6 min (P > 0,2) and 8 min (P > 0,2) of observation. However, it shortened from 7,0 ± 0,71 to 5,0 ± 0,35 (P < 0,05) on 10 min. Like in previous tests, fraction $XKXG_2$ suppressed anti-coagulative blood system TPH (P < 0,05), free heparin (P > 0,2), thrombin time (P > 0,2) decreased content of anti-thrombin III from 80,0 ± 3,5 to 60,0 ± 0,89 (P < 0,001) and fibrinogen levels from 1,6 ± 0,7 to 1,0 ± 0,03 (P < 0,01).

Conclusion

Peptide fractions of chronic calculous cholecystitis after 15 days of introducing them intramuscularly into blood, taken from a. and v.pulmonalis formed thrombopenia and increased time of their aggregation.

Thus, 15-days intramuscular introduction of peptide bioregulators, extracted from wall of inflamed removed gall bladders of patients with chronic cholecystitis forms THS-syndrome within organism of experimental rabbits.

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