BIOLOGICAL RHYTHMS OF THE HEMOSTASIS SYSTEM IN DOGS

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In the modern view, a set of biological rhythms coordinated with each other in time forms the temporal organization of a biosystem [8, 10]. This view is valid for the hemostasis system [12, 13]. Research in the last two decades has been devoted to the study of internal and external synchronization of the hemocoagulation system, and considerable chronobiological and chronomedical knowledge in this field has been collected in that period [2-7, 9, 11]. The writer previously described the chronobiological norm of individual parameters of the hemostasis system in dogs or of small functional groups of such parameters [12-14], but a more detailed study of the state of the time structure of the hemostasis system, using new techniques, is still essential.

The aim of this investigation was to study biorhythms of parameters of hemostasis, as a system in which they act as interacting elements, and characterize its principal functional blocks.

EXPERIMENTAL METHOD

The hemostasis system was studied in the fall of the years 1984-1987 by methods of instrumental electrocoagulation on the N-334 and AGKM1-01 instruments, and by the traditional tests of test-tube coagulometry (silicone clotting time, plasma heparin tolerance, fibrinolytic activity of blood by the euglobulin method). Experiments were carried out either in the course of 1 day, the dog's blood being tested every 3 h (Series 1) or in the course of 3 consecutive days, testing the blood every 4 h (Series 2). Experiments were conducted on 17 dogs (seven beagles and 10 mongrels), similar in age, weight, and length of stay under standard animal house conditions. Blood for testing was taken from the anterior Skachkov veins, using them in strict order.

The results of the first series of experiments were subjected to statistical analysis by Student's test, and those of the second series by group and individual chronoanalysis by computer, with determination of the period, mesor, amplitude, and acrophase of the sinusoidal rhythms, and by individual cosinor analysis for the data obtained on 1 day and for all measurements in the 3-day series [1, 15].

EXPERIMENTAL RESULTS

The 24-hourly trend of the parameters of the hemostasis system of all the dogs in the fall of 1984-1985 is shown in Table 1 (1780 information units). The parameters of rhythms of the seven beagle dogs in the fall of 1986-1987 are given in Table 2 (126 coagulograms, 882 information units relating to seven parameters of hemostasis).

In the first series of experiments fluctuating changes in the state of hemostasis in the course of the 24-h period were found as regards the majority of the parameters in the dogs: two waves of a tendency toward hypercoagulation — from 6 a.m. to 9 a.m. and from 6 p.m. to 9 p.m., and two waves of hypocoagulation — from noon to 3 p.m. and from midnight to 3 a.m. (differences not statistically significant). The fluctuations were determined by the time course of the intensity of the process of thromboplastin and thrombin formation from procoagulants, i.e., the first two phases of coagulation, reflected in integral parameters of the time of beginning of the process and its duration (T_1 and T), the rate of which depends on activity and concen-

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TABLE 1. Circadian Rhythm of Fluctuations of Parameters of Hemostasis System of Dogs in Fall of 1984-1985

Parameters of coagulogram	statistical parameters	Time cuts 6.00	9.00	12.00	15.00	18.00	21.00	24.00	3.00
Beginning of clotting (sec T_1	M	72,4	90,6	111,09*	137,2*	83,6	91,5	116,1*	127,4*
	m±	8,1	6,05	7,9	12,9	6,6	6,2	8,2	11,8
End of clotting (sec) T_2	M	310,4	321,4	355,7*	343,6	329,9	316,6	347,4	358,4*
	m±	15,26	15,66	16,09	16,15	15,6	15,4	15,2	16,4
Duration of clotting process (sec) T	M	191,4	225,5	249,09*	270*	195	216	238,4	260,2*
	m±	16,2	18,4	14,6	20,1	16	14,4	18,1	17,6
Beginning of retraction and fibrinolysis T_3	M±	837,6	848,3	866,5	926,9*	911,4	870,4	896,6*	916,8*
	m ±	75,9	79,2	76,3	85,9	73,2	80,3	86,4	85,7
Rate of retraction and fibrinolysis during first 5 min	M	0,26	0,29	0,25	0,31*	0,27	0,27	0,29	0,29
	m±	0,1	0,05	0,17	0,08	0,04	0,045	0,06	0,07
Silicone clotting time (sec)	M	596	636	668*	686*	629,5	639,2	657,4	662*
	m ±	14,4	11,4	11,56	8,9	12,5	18,4	17,3	18,2
Plasma heparin tolerance (sec)	M	306,4	303,8	344	436,3*	412,7	374,2	396,7*	388,4
	m±	7,8	8,3	7,3	16,9	14,3	18,4	9,6	11,4
Fibrinolytic activity of blood	M	58,4	75,4	63,1	89,4*	52,8	64,4	92,6*	98,4*
	m ±	2,6	1,8	3,1	3,6	2,8	11,4	11,6	12,1
Number of investigations	n	218	252	212	212	235	218	218	218

— $p<0,05$.

TABLE 2. Parameters of Rhythms of Hemocoagulogram of Dogs in Fall of 1986-1987

Parameters of hemocoagulogram (HCG)	Parameters of rhythms: period	mesor	amplitude	acrophase
Beginning of clotting (sec) T_1	12,3	—	20,1 (12,2—25,9)	—
	24,1	94,78 (86,4—128,6)	15,8 (10,4—24,8)	14,25 (13,00—16,30)
End of clotting (sec) T_2	24,3	362,8 (309,8—421,5)	25,7 (15,8—36,7)	13,3 (12,05—14,35)
Duration of clotting process (sec) T	13,0	—	36,4 (26,1—42,4)	—
	24,6	278,3 (241,6—326,5)	23,6 (13,3—30,1)	13,44 (12,15—16,00)
Beginning of retraction and fibrinolysis T_3	13,3	—	51,33 (32,6—68,8)	—
	26,8	626,83 (468,4—742,3)	56,4 (34,8—76,4)	16,05 (14,45—17,55)
Minimal amplitude of HCG (Am)	12,3	—	0,3 (0,2—0,6)	—
	24,5	3,54 (1,8—5,87)	0,31 (0,2—0,64)	5,1 (4,00—6,22)
Minimal amplitude of HCG (Am)	—	—	0,01 (0,00—0,15)	—
	26,7	0,05 (0,01—0,086)	0,01 (0,00—0,12)	6,2 (5,15—7,13)
Amplitude of HCG 10 min after beginning of fibrinolysis (A10)	12,00	—	0,25 (0,12—1,00)	—
	26,2	0,64 (0,45—0,89)	0,2 (0,1—1,1)	17,05 (16,00—18,30)

Legend: mesors and amplitudes shown as corresponding units of measurement; acrophases in hours and minutes. Ninety-five per cent confidence intervals between parentheses.

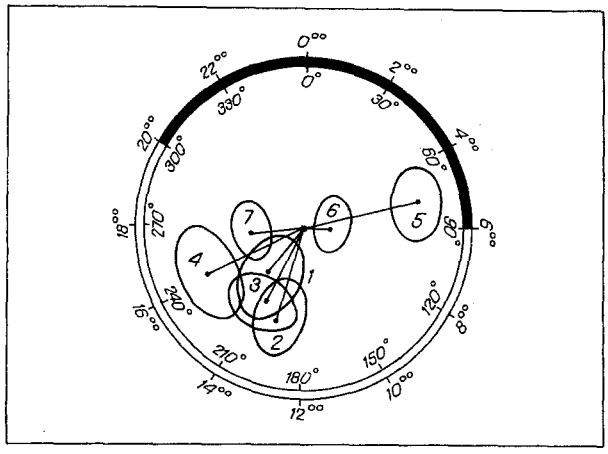

Fig. 1. Diagram of circadian rhythms of time of beginning (1), end (2), and duration (3) of clotting process, beginning of retraction and fibrinolysis (4); and maximal (5) and minimal (6) and 10-min (7) amplitudes of hemocoagulograms of dogs during fall, according to the results of group chronoanalysis.

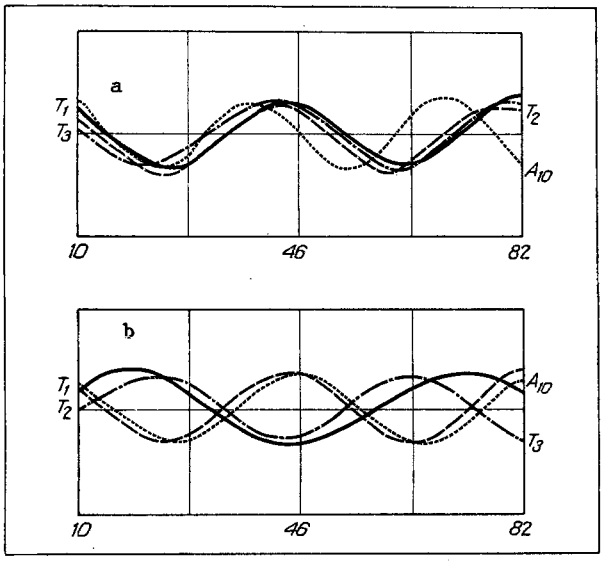

Fig. 2. Sinusoids of individual rhythms of parameters of hemocoagulogram in fall: beginning (T_1) and end (T_2) of clotting, time of beginning of fibrinolysis (T_3) and 10-min amplitude of coagulogram (A_{10}) of dogs "Belka" (a) and "Gerakl" (b).

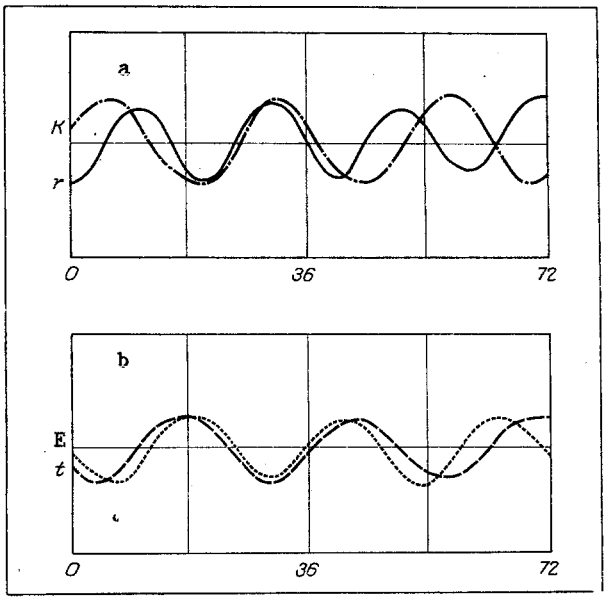

Fig. 3. Sinusoids of individual rhythms of parameters of thromboelastogram of dog "Gerakl" during fall: reaction time (r), beginning of clot formation (K), and its elasticity (E), and constant of specific clotting (t).

tration of thrombin in fibrinogen, and the quantity and quality of the platelets. The time of beginning of retraction and of fibrinolysis (T_3) and the fibrinolytic activity of the blood were in phase; the rate of these processes (C1-5), however, obeyed a circadian rhythm with a single wave, with the maximal fall to 3 p.m., coinciding with a decrease in plasma heparin tolerance.

Analysis of the results of the second series of experiments (Table 2) revealed the presence of significant 12-hourly (ultradian) and circadian rhythms in the beagles, and the parameters of the first and second phases of coagulation were in phase, with five acrophases of the circadian rhythms being located in the second half of the daylight period and two during the early morning hours (Fig. 1). This temporal organization was preserved during two consecutive falls and was found by individual

chronoanalysis. As well as circadian rhythms, the latter also revealed in four dogs significant infradian rhythms with periods of 40.09-60.91 h (p = 0.916-0.991). These rhythms form two versions of temporal organization:

1) With sinusoids of all three stages of the coagulation process (T_1, T_2, T_3, and A_{10}) in phase (Fig. 2a) and 2) with waves that are out of phase, when the rhythm of the parameter of the beginning of retraction and fibrinolysis (T_3) and the 10-min amplitude of the coagulogram, reflecting their intensity and characterizing the postcoagulation phase, is opposite to the rhythms of the first two stages of coagulation (Fig. 2b). It must be pointed out that the second type of temporal relations also is present when there is a circadian temporal organization of the components of coagulation hemostasis with periods of 20.212-26.933 h (p = 0.935-0.992): the reaction time (in h), reflecting the rate of formation of thromboplastin and thrombin and corresponding to the first, invisible phase of coagulation, is in phase in its rhythm with the thromboelastographic constant of thrombin (K), i.e., the second phase, but is out of phase with the rhythms of the specific binding constant (t) and the elasticity of the blood clot (E), characterizing the third, postcoagulation phase of the process (Fig. 3).

The differences found may perhaps be a temporal marker of variance of activation of fibrinolysis: during internal activation, caused by factor XII, which activates blood clotting, the rhythms of parameters characterizing coagulation and the postcoagulation process are in phase; during external activation of fibrinolysis by a protein activator of tissue type from the vascular endothelium or blood cells (erythrocytes, platelets, and leukocytes), their mutual temporal organization can be seen to be out of phase.

The study of biological rhythms of parameters of coagulation hemostasis in dogs in the fall thus showed that they constitute a set that is integrated into a temporal system of ultradian, circadian, and infradian rhythms.

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