REGIONAL REDISTRIBUTION OF BLOOD AT THE CLIMAX AND DURING DECLINE OF THE FEBRILE RESPONSE IN RATS

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Fever was induced by intravenous injection of rabbit leukocytic pyrogen and also by intravenous injection of pyrogenal. Leukocytic pyrogen led to a greater rise of temperature. In all series of experiments multivariate statistical analysis revealed the predominant influence of two factors. One reflected responses leading to a relative reduction in blood volume in the brain, myocardium, lungs, and liver and to its increase in some abdominal organs, the skin, muscular and bony tissues of the limbs, abdomen, and pelvis. The other factor reflected influences aimed at the redistribution of blood chiefly from the organs and tissues of the head, neck, and thorax into the liver.

KEY WORDS: fever; circulation.

The system regulating the circulation takes part in the mechanism of development of the febrile response [2, 10]. Besides this, a high temperature affects the heart and blood vessels. The boundary line between these two factors is difficult to draw [2]. Recently a method of simultaneous recording of changes in regional blood volume [3] in a large number of organs and tissues, among which changes in the lumen not only of the resistive, but also of the capacitive vessels play a significant role [11, 13], has been developed for use in experiments on rats. The method allows multivariate analysis of the data with separation of the integral changes in the experiment compared with the control into factors. The results obtained by this method at the climax and during the decline of the febrile response are described below.

METHOD

Experiments were carried out on noninbred unanesthetized male rats weighing 180-220 g. The rats were accustomed to the laboratory situation, to the experimenter, to being carried in the hand, and to having their temperature measured. A catheter was implanted permanently in the external jugular vein 4 days before the experiment. Twice a day the catheter was washed out, so that the animals became accustomed to this manipulation also. These preparations for the experiment ensured minimization of nonspecific effects which, in rats, make it difficult to estimate responses due to stress on the mechanisms of temperature regulation [12].

Fever was induced by intravenous injection of 1 ml rabbit leukocytic pyrogen, obtained from the Department of General Pathology, Institute of Experimental Medicine [9], and also by intravenous injection of 1 ml pyrogenal, containing five minimal pyrogenic doses. Animals in the control group received an intravenous injection of 1 ml leukocytic pyrogen inactivated by heating to 90°C for 30 min.

Changes in the regional blood volume were determined at the height of the fever (30 min after injection of leukocytic pyrogen and 1 h after injection of pyrogenal) and also as the temperature fell (3 h after injection of leukocytic pyrogen). The experiments were carried out at room temperature (about 20°C). In the control series and each of the three principal series 14 rats were used.

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TABLE 1. Changes in Relative Blood Volume (% of CBV/% of body weight) in Organs and Tissues during Fever

Organs and tissues	Estimate of changes compared with control								
	leukocytic pyrogen						pyrogenal		
	30 min (series I)			3 h (series II)			1 h (series III)		
	P	f_1	f_2	P	f_1	f_2	P	f_1	f_2
Head									
Skin	>.50+	+.077	—.340	>.25—	—.019	—.534	>.25+	+.295	—.553
Muscles and bones	>.10	—.358	—.799	>.50+	+.328	—.717	>.50—	—.114	—.893
Brain	>.50+	—.241	—.285	>.05—	—.602	—.420	>.25—	—.507	—.679
Neck									
Skin	>.50—	+.172	—.639	>.50—	+.055	—.482	>.05+	+.291	—.148
Muscles and bones	>.25—	—.198	—.750	>.10—	—.509	—.440	>.50—	—.014	—.812
Chest									
Skin	>.50—	+.081	—.816	>.25—	—.157	—.689	>.05+	+.232	—.580
Muscles and bones	>.25—	+.302	—.590	>.10—	+.152	—.072	>.50—	+.315	—.128
Myocardium	>.10—	—.526	—.504	>.50—	—.510	—.178	>.10—	—.463	—.712
Lungs	>.50+	—.327	—.348	>.50+	—.277	—.419	<.05—	—.570	—.266
Abdomen									
Skin	>.50—	+.570	—.263	>.50—	+.503	+.007	>.10—	+.700	—.023
Muscles and bones	>.25+	+.824	—.013	>.50+	+.848	—.027	>.10+	+.841	+.204
Liver	>.25—	—.591	+.618	>.50—	—.709	+.314	<.05—	—.836	+.126
Small intestine	>.25—	+.403	+.133	<.05+	+.181	+.380	>.50—	+.340	+.141
Large intestine	>.25+	+.256	+.097	>.50—	+.316	+.128	>.50+	+.420	+.154
Stomach	>.25+	+.163	—.086	>.50—	+.110	—.065	>.50+	+.195	—.354
Kidneys	>.10+	—.037	+.144	>.25+	—.275	+.278	>.10—	+.123	—.223
Adrenals	>.05+	+.210	+.133	>.25+	+.494	—.194	<.02+	+.546	+.099
Spleen	>.25+	+.158	+.089	>.25—	+.166	+.276	>.10+	+.236	+.258
Pancreas	<.05+	+.391	+.015	>.50+	+.257	+.260	>.50+	.431	—.028
Bladder	>.25+	+.092	+.099	>.10+	+.326	—539	>.50+	+.033	—.246
Testes	>.10+	+.747	—.151	>.50+	+.705	—.369	>.25+	+.169	+.144
Forelimbs									
Skin	>.10+	+.693	—.286	>.25—	+.396	—.041	>.05+	+.808	—.183
Muscles and bones	<.05+	+.683	+.101	>.25+	+.464	—.208	<.01+	+.717	—.051
Hind limbs									
Skin	>.50+	+.769	—.068	>.50+	+.583	+.073	>.25+	+.809	—.099
Muscles and bones	>.25+	+.792	+.030	>.25+	+.206	+.263	>.10+	+.882	—.064
Tail	>.05+	+.659	+.140	>.25+	+.233	+.205	<.05+	+.757	—.082
Weight of factor, %	—	23,4	21,1	—	20,9	15,7	—	31,8	18,8

The method of recording the regional redistribution of blood and the method of multivariate statistical analysis of the results were explained and described previously [3, 5]. They were based on the use of radioactive indicators of the blood components and a special modification of factor analysis in accordance with the method of chief components.

RESULTS AND DISCUSSION

The rectal temperature 30 min after injection of leukocytic pyrogen rose from 36.4 ± 0.07 to 38.5 ± 0.18°C ($P < 0.001$). After 3 h it had fallen to 37.0 ± 0.12°C, but was still higher than initially ($P < 0.001$). After injection of pyrogenal, the greatest rise of temperature occurred within the first hour from 36.6 ± 0.10 to 37.6 ± 0.14°C ($P < 0.001$). In the control group the rectal temperature at the beginning of observation was 36.6 ± 0.10°C; its values 30 min and 1 and 3 h after injection of inactivated leukocytic pyrogen were 36.8 ± 0.08°C ($P > 0.1$), 36.7 ± 0.07°C ($P > 0.25$), and 36.8 ± 0.18°C ($P > 0.5$) respectively.

The circulating blood volume (CBV) in the control group was 58 ± 4.33 mg blood/g body weight and showed no significant change after injection of leukocytic pyrogen. In the experiments with pyrogenal a tendency was observed for CBV to increase and its value reached 64 ± 2.07 mg/g body weight ($0.1 > P > 0.05$).

The absolute blood volume did not change significantly after injection of leukocytic pyrogen in any of the vascular regions studied. Injection of pyrogenal was followed by a significant increase in the absolute blood volume in the adrenals ($P < 0.01$), skin of the neck ($P < 0.02$), chest ($P < 0.02$), and forelimbs ($P < 0.05$), and in the muscular and bony

tissues of the forelimbs ($P < 0.002$) and hind limbs ($P < 0.02$). No statistically significant decrease in the absolute blood volume could be found in the organs or tissues.

Changes in the relative blood volume in the organs and tissues are shown in Table 1. In column P differences between arithmetic means for the control and experimental series are assessed by Student's t-test, whereas in columns f_1 and f_2 the loads of the first and second factors, which are measures of differences relative to a given factor, respectively are assessed. The contribution of the corresponding factor to the integral assessment of the changes is determined by its weight, which is given in Table 1. The plus sign of the factor load and after the value of P means a probable increase in blood volume, a minus sign a decrease. The factor load is statistically significant ($P < 0.05$) if its absolute magnitude exceeds or is equal to 0.360. Significant values of the probability of differences by the t-test (P) and of the factor loads (f_1 and f_2) are shown distinctively in Table 1 in bold type.

The data in Table 1 show that assessment of differences by Student's t-test in the experiments with leukocytic pyrogen does not reflect the details of regional redistributions of blood. Statistically significant changes, only as a relative increase in blood volume, were found only in certain vascular regions. After injection of pyrogenal the decrease in the relative blood volume reached significance in the liver and lungs, whereas a significant increase was found in the adrenals, muscular and bony tissues of the forelimbs, and in the tail.

Subdivision of the integral assessment of the changes into factors gave the following results. In all three series the structures of the loads of the principal (first and second) factors were similar. Loads of the first factor (Table 1) reflected influences leading to a decrease in the relative blood volume in the brain, myocardium, lungs, and liver and to its increase in certain abdominal organs and also in the skin and muscular and bony tissues of the limbs, abdomen, and pelvis.

Opposite effects on changes in the relative blood volume in the organs and tissues were revealed by the load structure of the first factor during exposure of intact rats to cold air [7]. The load structure of the first factor during fever, moreover, had a similarity to changes in the circulation in various vascular regions under the influence of hyperthermia [14, 16] or local heating of the hypothalamus and spinal cord [15]. These observations suggest that the first factor in fever characterizes changes in regional blood volume associated with a rise of body temperature.

The load structure of the second factor in fever (Table 1) reflected influences directed toward redistribution of blood chiefly from the organs and tissues of the head, neck, and chest into the liver.

Redistribution of blood into the liver has been found following exposure to cold [7], blood loss combined with anesthesia and fixation stress [4], in the initial phase of various models of traumatic shock [8], 24 h after laparotomy [1], and during transfusion of an excess of blood, associated with its displacement into the spleen [6]. However, under all the conditions listed above the blood was redistributed into the liver from the skin and muscular and bony tissues of different parts of the body, and also from some abdominal organs. Mobilization of blood from the vascular regions of the head, neck, and chest is thus a special feature observed during fever. Nevertheless, the increase in the relative percentage of blood in the liver was evidently a nonspecific response characteristic of fever also. This response may perhaps reflect augmentation of the hepatic blood flow to provide for increased functional activity of the liver, which helps to provide energy for the responses of the body; the mobilization of blood from the liver revealed by the load structure of the first factor is connected with constriction of the regional capacitive vessels. It will, however, be evident that this explanation requires further experimental justification.

The similar load structures of the first and second factors after injection of leukocytic pyrogen and pyrogenal are evidence that their effects on the body are basically qualitatively similar. However, the pyrexial effect of leukocytic pyrogen is greater than that of pyrogenal

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CHANGES IN SOMATOTROPHIC AND LACTOTROPHIC FUNCTIONS OF THE ADENOHYPOPHYSIS IN RATS WITH ACUTE ALLOXAN DIABETES

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By electrophoresis followed by colorimetric study of the stained gels an increased content of growth hormone and prolactin was found in the pituitary of rats during the development of alloxan diabetes. The STH and prolactin levels 4-5 days after injection of alloxan were higher by 45-58 and 38-43% respectively than in intact animals. Experiments on primary cell cultures using [^{14}C]-L-leucine as labeled precursor revealed increased secretory activity of the somatotrophs and lactotrophs of rats with alloxan diabetes.

KEY WORDS: alloxan diabetes; culture of adenohypophysis; secretion of growth hormone and prolactin.

Despite considerable progress in recent years in the study of the pathogenesis of diabetes many aspects of this problem are still far from understood. During the development of diabetes changes take place in the functions of several endocrine glands. These changes may be compensatory in character, but at certain stages of the disease they aggravate its course. The problem of whether the insular function of the pancreas can be controlled by the pituitary gland has not yet been solved. On the other hand, there is evidence that the pituitary plays a definite role in the pathogenesis of diabetes mellitus. Removal of the pituitary from dogs and other animals [12] has been shown to alleviate the course of experimental diabetes included by subtotal pancreatectomy. Meanwhile pituitary hormones such as growth hormone (STH) and prolactin, under certain conditions, can have a diabetogenic action [8].

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