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TOXIC PROPERTIES OF SERUM OF RABBITS AND DOGS EXPOSED TO CONTROLLED HYPERTHERMIA

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KEY WORDS: hyperthermia; toxicity of serum; mast cells.

Under the influence of excessive heat the blood serum acquires pathological properties connected with the appearance of burn toxins and physiologically active substances [3, 7, 8], disturbance of the lysosomal apparatus of the cells [1], and changes in the physicochemical parameters of the blood [5, 6]. The diversity of the changes in composition of the blood suggests parallel activation of various pathological and physiological mechanisms forming the response of the body as a whole.

In the investigation described below the toxic properties of the blood serum of dogs and rabbits and the degranulation reaction of mast cells, with particular reference to the system of peritoneal mast cells of rats, were studied in order to determine the relationship between the severity of the reaction of the body and the functional state of the mast cell system, one of the physiological mechanisms of immediate defense [9], in a model of heat stress.

EXPERIMENTAL METHOD

Dogs and rabbits were exposed to hyperthermia on the 22 PG-01 apparatus, intended for creating controlled temperature conditions in man and warm-blooded animals [4]. The assigned body temperature (rectal, 42°C) was maintained automatically for 1 h in rabbits and 2 h in dogs through a system of feedback between body temperature and the heat carrier used in the apparatus. The dogs were overheated in the unanesthetized state and also under thiopental sodium anesthesia; the rabbits were unanesthetized. Serum for investigation of toxicity was collected 5-10 min after the end of the experiment and also on the 1st, 3rd, 5th, 7th, 11th, and 15th days in rabbits and dogs exposed to hyperthermia without anesthesia. The toxicity of the serum was determined by biological testing on mice with blockage of the reticuloendothelial system [2]. To estimate toxicity the serum from each experimenatl animal was injected into ten noninbred albino mice. The state of the mast-basophilic system was assessed by the degree of degranulation of the mast cells on films stained with toluidine blue. Mast cells were obtained by centrifugation of rat peritoneal washings on the 1st, 3rd, 7th, 11th, and 13th days after hyperthermia for 1 h. The cells were divided into five groups depending on the number and staining of the granules, shape of the cells, and integrity of the membrane. Round cells with clear edges, filled with many stained granules, were placed in group I. The cells of group II contained a few translucent cavities due to commencing degranulation. The cells of group III had uneven edges and paler cytoplasm because of considerable degranulation. Group IV consisted of cells with fragmented cytoplasm, including cells of "shot" type in cells of group V the membrane was absent and granules were located at the site of the former cell.

The data were subjected to statistical analysis by Student's t-test.

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TABLE 1. Survival Rate of Mice with Blockade of Reticuloendothelial System after Injection of Serum from Hyperthermic and Intact Dogs and Rabbits (M ± m)

Serum	Number of animals	Time after injection of serum, days					
		1	2	5	6	7	8
Intact rabbits	3	10	10	10	10	10	10
Hyperthermic rabbits	11	6.5±0,75	6,3±0,68	6,2±0,67	6,0±0,69	5,9±0,6	5,7±0,6
Dogs after anesthesia	6	10	10	10	10	10	10
Dogs exposed to hyperthermia under anesthesia	14	7,2±0,68	6,4±0,7	6,4±0,7	6,2±0,68	6,2±0,68	6.2±0,68
Dogs exposed to hyperthermia without anesthesia	10	8,2±0,56	7,7±0,52	7,3±0,55	7,3±0,55	7,3±0,55	7,1±0.44

Legend. Significance of differences compared with initial value in each group of mice in experiments with hyperthermic serum $P < 0.001$.

TABLE 2. Survival Rate of Mice with Blockade of Reticuloendothelial System during First Three Days after Injection of Serum Taken at Different Times after Hyperthermia from Dogs and Rabbits (M ± m)

Time elapsing after hyperthermia, days	Number of animals	Species of animal		Significance of differences in toxicity of serum from dogs and rabbits
		dog	rabbit	
1	5	7,7±0,24	4,8±1,13	<0,01
3	5	8,5±0,61	7,0±0,38	<0,05
5	5	10,0	8,4±0,45	<0,01
7	5	10,0	9,2±0,45	<0,01

TABLE 3. Time Course of Degranulation of Peritoneal Mast Cells of Rats after Hyperthemia (M ± m)

Group of cells	Number of animals	Before hyperthermia	Time elapsing after hyperthermia, days				
			1	3	7	10	13
I	5	9,4±1,03	1.4±0.37‡	23,6±1,56†	43,6±1,68†	10,0±1.05	8,8±1.04
II	5	48,6±3,52	5,6±0,4*	19,0±1.32	23,6±1,21	33.0±1,92	63,6±2.01
III	5	29,6±1,63	5,0±1,07‡	17.0±1.34*	20.0±1,24*	40.6±1.8	21,6±1,77
IV	5	12.3±0,81	36,4±2.1†	12,4±1,33	12,0±0,86	10.3±1,26	5,4±0,94
V	5	0.0	51,5±3,28‡	28,2±1,83‡	0.8	5,6±0.72‡	0.0

*P < 0.05.
†P < 0.01.
‡P < 0.001.

EXPERIMENTAL RESULTS

Serum of healthy rabbits and dogs had no toxic properties (Table 1). After hyperthermia the most pathogenic sera were those from rabbits and anesthetized dogs. Changes in the blood of dogs exposed to hyperthermia without anesthesia were probably less marked because the survival rate of the mice was higher than in the other series of experiments. In all cases the largest number of mice died on the 1st day after injection of serum from hyperthermic animals. Rabbit serum was the most pathogenic. Most mice in the series using serum from anesthetized hyperthermic dogs died on the 2nd day. No mice died on the 3rd or 4th day, but a second wave of mortality occurred on the 5th-8th days: Its duration was longer when rabbit serum was used and shorter when dog serum was used. It can be tentatively suggested that metabolic disturbances were more severe in the rabbits, with a smaller body weight, than in dogs. The toxicity of the serum from dogs exposed to hyperthermia without anesthesia was less marked, and this emphasizes the role of the CNS in the mechanism of the response of the body during exposure to heat stress.

The stronger toxic properties of the rabbit serum was confirmed by injection of serum obtained from rabbits and dogs on the 1st, 3rd, 5th, 7th, and 11th days after hyperthermia.

Data on survival of the mice in Table 2 are given for the first 3 days after injection of the serum, for the number of mice was unchanged on the following days. Dog serum remained pathogenic for the first 3 days, rabbit serum for 7 days.

The data in Table 3 are evidence of active involvement of the mast cell system in the general reaction of the organism and of the rapid decline in activity of this system during hyperthermia by the scheme adopted. This is shown by the presence of a large number of cells which had completely or partly exhausted their functional powers. The evident predominance of cells of group I until the 7th day, subsequently giving way to a tendency for restoration of the initial ratio between them, suggests that hyperthermia has a stimulating action on mast cell production.

This demonstration of the toxic properties of the serum and considerable exhaustion of one of the physiological mechanisms of immediate defense are evidence of the systemic character of the pathogenesis of hyperthermia.

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HYPOCLYCEMIC EFFECT OF EXCESS OF THYROID HORMONES IN INSULIN-DEFICIENT RATS

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The view is widely held that hyperthyroidism aggravates the course of diabetes mellitus [1, 7, 9]. However, it has been shown that experimental thyrotoxicosis is accompanied not only by inhibition of insulin secretion, with "disinhibition" of hepatic glucose production, but also by an insulin-independent acceleration of glucose utilization by extrahepatic tissues and, in particular, by muscles [4, 11]. This effect is manifested particularly clearly when the liver is "excluded" from the circulation [3, 10].

Assuming that the aggravating effect of an excess of thyroid hormones on the course of diabetes mellitus may be connected with inhibition of the residual secretion of insulin, it

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