DEVELOPMENT OF FEBRILE AND LEUKOCYTIC RESPONSES DURING ASEPTIC INFLAMMATION IN DIABETIC RABBITS

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A statistically significant decrease in the febrile index compared with the control was found in diabetic rabbits. Some delay was observed in the development of the leukocytic response, although there was no significant difference in the degree of leukocytosis in diabetic and control rabbits. Leukopenia, most marked in the control 18-20 h after the beginning of observation, was absent in some of the diabetic rabbits. No significant differences were found in the intensity of leukocytic infiltration of the inflammatory focus in the diabetic and control rabbits. Depression of the febrile response to aseptic inflammation in the diabetic rabbits was evidently connected with weakening of the ability of the leukocytes in the inflammatory focus to liberate pyrogenic products producing fever.
KEY WORDS: diabetes; aseptic inflammation; fever; leukocytes.

On account of the profound metabolic disturbances in diabetes, the development of various pathological processes and, in particular, of inflammation is modified. For instance, weakening of the leukocytic response to aseptic irritation of the tissues has been observed in diabetic patients [13] and migration of leukocytes is inhibited after intradermal injection of Staphylococcus aureus into rabbits [10]. A reduction in the phagocytic activity of the leukocytes in diabetic patients [9] and animals with diabetes [3, 4, 14] has also been reported.

Considering the close connection between inflammation and the febrile reaction it was decided to study the development of this reaction in response to aseptic inflammation in diabetic animals.

EXPERIMENTAL METHOD

Experiments were carried out on 32 rabbits of both sexes weighing 1.8-2.5 kg, of which 19 were diabetic and 13 were controls. Diabetes was produced by intravenous injection of alloxan in a dose of 150 mg/kg. The rabbits were used in the experiments 15-30 days after injection of alloxan when their blood sugar level was not lower than 250 mg %. Inflammation was produced by subcutaneous injection of 0.3-ml turpentine into the lateral surface of the thigh. The body temperature was measured in the rectum three times at half-hourly intervals to establish the original background, and again every hour during the 24 h after injection of turpentine. The temperature curves thus obtained were analyzed planimetrically and the febrile index was calculated and expressed in conventional planimetric units [8]. The blood leukocytes were counted in a Goryaev's chamber. Pieces of skin at the sites of injection of the turpentine were cut out 24 h after the injection, and from them histological sections were prepared and stained with hematoxylin–eosin and with Sudan-α-naphthol by Goldman's method. Native leukocytic pyrogen was obtained from the Department of General Pathology, Institute of Experimental Medicine.

EXPERIMENTAL RESULTS

The body temperature of all the control rabbits was raised 3-8 h after injection of turpentine, and the increase was maximal (by 1.3-2.4°C) after 11-14 h. In half of the rabbits the body temperature remained raised by more than 1°C 24 h after injection of turpentine, whereas in the rest the temperature fell gradually and regained its initial level 20-24 h after the injection of turpentine.

By contrast with the controls, no febrile reaction to injection of turpentine occurred in 5 of the 19 experimental rabbits. In the other 14 animals the rise of body temperature began a little later than in the controls,

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TABLE 1. Temperature Response of Rabbits to Aseptic Inflammation

Group of animals	Control rabbits	Maximal increase in temperature, °C	Febrile index	
			+	−
Control rabbits (n = 13)	38,5±0,1	1,7±0,11	662,8±58,8	26±9,4
Rabbits with diabetes (n = 19)	38,6±0,12	1,0±0,10	334,5±36,8	10,9±2,5
P	>0,05	<0,01	<0,01	>0,05

TABLE 2. Temperature Response of Rabbits to Injection of Leukocytic Pyrogen

Group of animals	Initial temperature, °C	Maximal increase in temperature, °C	Febrile index
Control rabbits (n = 10)	39,0±0,07	0,8±0,09	49,9±2,5
Rabbits with diabetes (n = 14)	38,9±0,06	0,8±0,04	57,3±2,7
P	>0,05	>0,05	>0,05

namely 6-10 h after injection of turpentine. The highest febrile response in this case was lower and it was observed 11-17 h after injection of turpentine. The normal body temperature was restored in 7 rabbits after 21-24 h; in the rest it remained raised on average by 1°C.

As Table 1 shows, the greatest rise of body temperature and the highest value of the febrile index in the rabbits with diabetes were statistically significantly less than in the control. In some rabbits hypothermia was observed after injection of turpentine, but this was followed by elevation of the body temperature. This hypothermia, evidently connected with the emotional response of the rabbits to the pain produced by the turpentine itself, was expressed as a febrile index with negative sign.

Counting the peripheral blood leukocytes of the control animals for 24 h showed leukocytosis in 11 of the 13 rabbits 2-6 h after injection of turpentine, followed by leukopenia, which was most marked 18-20 h after the investigation began. By 24 h the leukopenia was still present in six rabbits, whereas in the rest the leukocyte count was almost back to its original level. No increase in the leukocyte count was observed in two of the 13 control rabbits, although they gave a marked temperature reaction. These observations agree with those of other workers who did not detect the development of leukocytosis in some febrile rabbits after injection of turpentine [1].

The leukocytosis developed later in the experimental rabbits than in the controls, namely 4-8 h after injection of turpentine. Leukopenia was observed in half of the rabbits and was most marked after 16-20 h; in the remaining animals the leukocyte count was increased at these times. By 24 h the leukopenia still continued in seven rabbits, in five the leukocyte count had returned to its initial level, and in four rabbits leukocytosis was present.

Of the five rabbits with no febrile response to turpentine, the leukocyte count in the blood was not increased after injection of turpentine in only one.

Some delay in the development of the leukocytic response was thus observed, although no significant quantitative difference in the degree of leukocytosis was observed in the experimental and control rabbits. A special feature of the leukocytic response in diabetes was the absence of leukopenia in some of the animals.

Depression of the febrile response to aseptic inflammation in diabetic rabbits could be attributed to changes in the reactivity of the central temperature regulating mechanism to pyrogenic stimuli. To eliminate this possibility, a series of experiments was carried out in which a preparation of native leukocytic pyrogen (NLP) was injected into experimental and control rabbits. The temperature response of the diabetic rabbits to NLP was indistinguishable from that in the control (Table 2). It can be concluded from these results that the reactivity of the temperature regulating centers to pyrogens is unchanged in diabetes.

According to recent data leukocytes are the main source of endopyrogens responsible for producing infectious and aseptic fever [2, 7]. Accordingly, besides the leukocytic response in the peripheral blood, the local leukocytic response in the focus of inflammation was investigated. Histological examination of the focus of inflammation 24 h after injection of turpentine showed no significant difference in the intensity of the leukocytic infiltration of the tissues in the experimental animals compared with the controls. In rabbits which did not develop fever in response to injection of turpentine the leukocytic response in the focus of inflammation also was well marked.

Depression of the febrile response in diabetes is thus associated not with a change in the number of leukocytes in the focus of inflammation, but with changes in their qualitative features. The liberation of leukocytic pyrogen is determined by the state of metabolism in the leukocytes and requires energy [12]. It can tentatively be suggested that in connection with the marked disturbances of the energy metabolism of the leukocytes in diabetes [5, 6, 11] and a change in their reactivity under the unfavorable conditions for their vital activity in the inflammatory focus, their ability to secrete pyrogenic products is weakened.

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CHANGES IN SOME INDICES OF LIPID METABOLISM AFTER LETHAL EXSANGUINATION AND RESUSCITATION

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The lipolytic activity of adipose tissue (LAAT), the concentration of nonesterified fatty acids (NEFA) in the blood and adipose tissue, and the concentrations of ketone bodies and β-lipoproteins in the blood of dogs were determined after lethal exsanguination and in the postresuscitation period. During agony activation of lipolysis was found in the adipose tissue, the levels of NEFA and β-lipoproteins were lowered, and the concentration of ketone bodies in the blood was increased. At the end of the third minute of clinical death inhibition of lipolysis developed and the NEFA concentration in the adipose tissue increased. The blood levels of NEFA and β-lipoproteins fell 1 h after resuscitation, whereas the level of ketone bodies rose; these changes were accompanied by some decrease in LAAT. In the late postresuscitation period (1st, 3rd, and 7th days) LAAT and the blood levels of NEFA, ketone bodies, and β-lipoproteins all increased. The NEFA concentration in the adipose tissue was low in the postresuscitation period.

KEY WORDS: lipid metabolism; terminal relationships; postresuscitation period.

Many studies of metabolic changes during terminal states and in the recovery period after resuscitation have been published. Particular attention has been paid to the study of carbohydrate–phosphorus [1, 6-8], protein [1, 2, 9, 10] and electrolyte and mineral [2] metabolism. Yet lipid metabolism in these states has hardly been studied at all. Considering the important role of lipids in energy metabolism [3, 11], it was decided to

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