Enzyme Levels in the Lymph of Febrile Animals of Different Age Groups

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Fever in young rabbits was accompanied by more pronounced and longer-lasting changes in the lymph levels of various enzymes than in adult rabbits, suggesting a greater lability of metabolic processes, of cell membrane permeability, and of "enzymic homeostasis" in general in younger animals.

Key Words: *fever; lymph; enzymes*

We showed earlier that enzyme levels in the lymph of febrile animals more accurately reflect the changes in cell membrane permeability and in the extent and severity of damage suffered by the cells than do enzyme levels in the blood [5-7]. However, the question of how enzyme levels in lymph may differ between febrile animals of different age was not addressed. In this study we compared, in rabbits of two age groups, lymph levels of various enzymes differing in their intracellular location.

MATERIALS AND METHODS

A total of 63 adult rabbits (body weight 2.5-4.2 kg) and 58 young rabbits aged 60-90 days (body weight 1.2-1.7 kg) were used. Fever was produced by the pyrogenic drug Pyrogenal as previously described [4]. Lymph was obtained from the thoracic lymph duct and assayed for alkaline [10] and acid [11] phosphatases, 5'-nucleotidase [9], aldolase [1], alanine (ALT) and aspartate (AST) aminotransferases [2], lactate dehydrogenase [8], and creatine phosphokinase [3] at different times during the febrile response. After the assays, rabbits were given a lethal dose of an anesthetic and subjected to histopathological examination.

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RESULTS

The results are presented in Table 1. In the control young rabbits the lymph levels of all enzymes, with the exception of acid and alkaline phosphatases, were lower (the creatine phosphokinase level was 12 times lower) than in the adult controls.

Although fever was, in general, accompanied by considerable elevations of enzyme levels in both age groups regardless of how many Pyrogenal doses were given, the degree and persistence of the elevations differed. For example, the 5'-nucleotidase level rose 5- to 13-fold in the lymph of young rabbits depending on the duration of fever, but only 2- to 5-fold in the lymph of adult rabbits. Elevations of the ALT level in young rabbits were 4.5-fold after one Pyrogenal dose, 6- to 9-fold after three doses, and 10-fold after five and ten doses, while they were 2-, 4-, and 8-fold, respectively, in the adult animals. After five days of fever, the creatine phosphokinase level was elevated 6-fold in the young rabbits but only 2-3-fold in the adults.

The rise of enzyme levels in body fluids during fever appears to occur because of (1) increases in cell membrane permeability in the presence of continuing (perhaps enhanced) enzyme biosynthesis and (2) alterations in the catalytic activity of enzymes both in the cells of the damaged organ(s) and after the enzymes have entered the blood and

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TABLE 1. Enzyme Levels in the Thoracic Duct Lymph of Febrile Rabbits ($M \pm m$)

Enzyme	Control	No. of Pyrogenal doses							
		one		three			five		ten
		after 2.5-3 h	after 5-5.5 h	on day 4	on day 6	on day 10	on day 6	on day 10	on day 11
Young rabbits									
Alkaline phosphatase, μmol/literxsec	0.21±0.03	0.31±0.04*	0.39±0.06*	0.69±0.07*	0.58±0.11*	0.32±0.05	0.83±0.13*	1.07±0.11*	0.89±0.13*
Acid phosphatase, nmol/literxsec	32.39±3.37	44.39±8.17	85.85±10.87*	109.87±11.37*	72.60±10.37*	37.14±6.14	177.65±24.19*	220.59±15.19*	179.17±32.36*
5'-Nucleotidase, nmol/literxsec	15.3±4.3	23.1±11.7	86.6±24.8*	152.4±36.6*	208.7±43.7*	170.2±48.0*	155.5±38.3*	184.5±76.4*	113.3±37.1*
Aldolase, μmol/literxsec	0.06±0.01	0.24±0.04*	0.16±0.03*	0.32±0.03*	0.37±0.03*	0.43±0.02*	0.39±0.04*	0.29±0.03*	0.50±0.04*
AST, μmol/literxsec	0.06±0.01	0.13±0.02*	0.09±0.02	0.22±0.02*	0.24±0.02*	0.06±0.01	0.28±0.03*	0.31±0.03*	0.48±0.04*
ALT, μmol/literxsec	0.06±0.02	0.26±0.01*	0.27±0.04*	0.49±0.07*	0.51±0.05*	0.17±0.03*	0.62±0.09*	0.37±0.05*	0.61±0.04*
LDH, μmol/literxsec	0.64±0.08	1.96±0.18*	1.25±0.12*	1.81±0.18*	0.68±0.07	0.52±0.03	2.14±0.18*	2.03±0.15*	2.36±0.14*
CK, μmol/literxsec	0.07±0.01	0.22±0.03*	0.15±0.03*	0.53±0.05*	0.09±0.05	0.07±0.02	0.24±0.02*	0.15±0.02*	0.29±0.07*
Adult rabbits									
Alkaline phosphatase, μmol/literxsec	0.35±0.03	0.60±0.05*	0.76±0.04*	1.09±0.06*	1.19±0.08*	0.65±0.05*	1.76±0.15*	0.70±0.05*	1.80±0.18*
Acid phosphatase, nmol/literxsec	36.49±5.18	65.96±9.02*	63.10±7.22*	118.61±10.94*	102.50±12.07*	48.65±4.83	112.74±10.14*	90.35±9.85*	193.01±15.04*
5'-Nucleotidase, nmol/literxsec	44.10±11.05	86.16±31.75	85.48±28.44	279.64±37.71*	208.88±45.41*	26.72±8.27	234.22±48.67*	183.95±45.56*	82.54±31.22
Aldolase, μmol/literxsec	0.11±0.01	0.37±0.05*	0.40±0.10*	0.46±0.07*	0.40±0.06*	0.14±0.03	0.51±0.06*	0.39±0.07*	0.63±0.07*
AST, μmol/literxsec	0.10±0.02	0.18±0.02*	0.55±0.07*	0.60±0.06*	0.10±0.02	0.10±0.02	0.68±0.06*	0.61±0.08*	0.68±0.07*
ALT, μmol/literxsec	0.13±0.02	0.21±0.03*	0.34±0.05*	0.56±0.05*	0.10±0.02*	0.13±0.03	0.93±0.08*	0.77±0.06*	0.89±0.10*
LDH, μmol/literxsec	1.05±0.08	1.66±0.27*	1.66±0.11*	1.99±0.09*	1.52±0.10*	0.87±0.13	2.39±0.07*	2.04±0.14*	2.40±0.05*
CK, μmol/literxsec	0.85±0.09	1.99±0.24*	1.55±0.30*	1.63±0.16*	1.30±0.22	0.70±0.15	1.64±0.21*	1.13±0.18	5.92±1.55*

Note. *$p<0.05$ relative to the control group. AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CK = creatine phosphokinase.

lymph. It is also possible that the levels of enzymes rise as a result of depressed activity of their inhibitors or an altered spatial configuration of their molecules.

Intracellular enzymes enter body fluids only when the cell membranes are damaged, and the pattern of their exit from the cells depends on the nature of the damage. In reversible inflammatory conditions characterized by increased cell membrane permeability, the first to be liberated are cytosolic enzymes; in necrotic processes leading to cell destruction, mitochondrial and lysosomal enzymes appear in the peripheral blood and lymph.

Since the Pyrogenal-induced fever was not accompanied by gross destructive changes in the tissues or organs of the test rabbits, the recorded sharp rises in the lymph levels of enzymes widely differing in their intracellular location suggests the existence of a single trigger in the mechanism regulating their activity in tissues or cell membrane permeability under adverse conditions such as fever.

It should be noted that the level of some enzymes (acid and alkaline phosphatases, creatine phosphokinase, and 5'-nucleotidase) following a single Pyrogenal dose was elevated only in the lymph. This indicates that the enzymes were most likely absorbed from the intercellular spaces into the lymphatic system directly. The failure to record similar rises of enzymes in the peripheral blood (data not shown), despite the presence of conditions favoring their accumulation there, may be accounted for by their dilution with large volumes of circulating blood and also by the preservation of adaptational mechanisms operating to maintain the "enzymic homeostasis" in the blood of young rabbits with fever of short duration.

The results of this study suggest that the lymphatic system plays an important part in the maintenance of "enzymic homeostasis" in the intercellular spaces when the liberation of enzymes from tissues is considerable. The age-related reactivity and resistance of the body largely determine the nature and degree of changes in the permeability of cellular and histohematic barriers and the severity of metabolic disorders during fever, which dictates the need for a selective approach to their correction.

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