Impact of Febrile Reactions on the Distribution of Carbohydrate and Protein Metabolic Products in Body Fluids

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It is shown that in rabbits with fever the lymphatic system is involved together with the circulatory system in the resorption of metabolic products from intercellular spaces of organs and tissues and in the transport of these products to the general circulation. In cases of a long-lasting febrile reaction, the toxicity of lymph greatly increases as a consequence of a rise in its content of creatinine and urea.

Key Words: *lymph; febrile reaction; pyruvic and lactic acids; urea; creatinine*

In studies concerned with the pathogenesis of febrile responses, much attention is given to metabolic changes in the body and particularly to disorders of protein and carbohydrate metabolism. However, the distribution pattern of various metabolites in body tissues and fluids during a febrile reaction remains unexplored. It is therefore interesting to speculate what role the lymphatic system may play in the resorption and transport from organs and tissues to the general circulation of metabolic products, i.e., in processes of their redistribution in the body during a febrile reaction.

In this comparative study on rabbits, we measured levels of glucose, pyruvic and lactic acids, creatinine, and urea in the lymph drained from various body regions and in blood serum during febrile reactions of varying duration.

MATERIALS AND METHODS

For the experiments, 63 Chinchilla rabbits weighing 2.5 to 4.2 kg were used. A febrile reaction was produced by intravenous injection of a lipopolysaccharide pyrogen (Pyrogenal) as described previously [5]. Lymph was collected from the thoracic lymphatic duct, postnodal portion of the hepatic lymphatic duct, and the intestinal lymphatic trunk; blood was taken from the femoral vein. Lymph and blood samples were assayed for levels of glucose (enzymatically), pyruvic and lactic acids [1,8], and urea and creatinine [4]. Euthanasia after the tests was performed with a lethal dose of a narcotic substance.

RESULTS

As can be seen in Table 1, in the control group there were no major differences in the levels of glucose and urea between the body fluids assayed; creatinine, lactic acid, and pyruvic acid levels in the blood were higher than in the lymph.

The febrile reaction was accompanied by elevation of glucose in the body fluids, particularly in the hepatic lymph, where its level rose 3.3-fold. The levels of pyruvic and lactic acids also rose, the rise in lactic acid being higher, indicating that excess lactate was accumulating in the body. Elevations of lactic acid in all three kinds of lymph

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were greater than in the blood (2.6-4.5 times vs. 1.4-3.3 times). Pyruvate and lactate remained elevated in the body fluids after the 5th Pyrogenal injection (on day 10). Creatinine and urea levels rose regardless of the duration of fever, the rise in the lymph being higher than in the blood. The contents of metabolites in the body fluids increased as the duration of fever increased.

We believe that during a febrile reaction glycogenolysis intensifies and the blood sugar level rises (particularly in the blood drained from the liver) under the influence of elevated catecholamine concentrations [4]. On the other hand, insulin activity falls, which is conducive to glucose accumulation in the blood [2]. Elevated blood sugar may be a result not only of enhanced glycogenolysis but also of slowed glucose utilization at the periphery, especially because an increase in epinephrine secretion may be accompanied by inhibition of glucokinase activity in tissues and by decreased glucose utilization therein. A high glucocorticoid concentration in the blood of feverish animals is a prerequisite for the emergence of hexokinase inhibitors in excessive amounts and for inhibition of glucokinase activity in the myocardium and skeletal muscles. Moreover, the activation of glucocorticoids leads to inhibition of insulin secretion and lowers the tolerance of tissues for this hormone and also for glucose. The elevation of glucose may in turn contribute to the persistence and intensification of the febrile reaction as a result of glucose interaction with the endogenous pyrogen generated [9].

Of particular interest appear to be the results we obtained in measuring glucose levels in the lymph drained from various organs and body regions during a febrile reaction. The glucose produced as a result of glycogenesis in the liver is absorbed not only into the blood but also directly into the lymph, as is indicated by the marked rise of its level in the hepatic lymph. Since the biochemical composition of thoracic duct lymph is largely determined by liver function, variations of glucose concentration in the lymph are likely to

TABLE 1. Lymph and Blood Levels of Glucose and Carbohydrate and Protein Metabolic Products during Febrile Reactions ($M \pm m$)

Parameter	Control rabbits	Number of Pyrogenal injections							
		one		three			five		ten
		after 2.5 - 3 h	after 5 - 5.5 h	day 4	day 6	day 10	day 6	day 10	day 11
Thoracic duct lymph									
Pyruvic acid, μmol/liter	115.8±7.3	188.8±12.8*	210.2±16.1*	263.7±21.2*	129.5±13.5	111.9±13.5	220.6±21.2*	170.6±11.7*	235.7±25.5*
Glucose, μmol/liter	3.7±0.7	10.2±1.5*	9.2±1.3*	6.7±1.7*	3.7±1.0	3.6±0.5	10.6±0.9*	3.6±0.4	11.2±1.2*
Lactic acid, mmol/liter	1.3±0.1	4.6±0.4*	3.5±0.4*	5.8±0.4*	1.3±0.1	1.3±0.1	5.3±0.3*	2.9±0.3*	5.7±0.3*
Creatinine, μmol/liter	62.9±9.1	180.8±21.4*	208.7±38.7*	199.3±22.4*	152.8±12.6*	78.6±8.9	142.3±3.5*	155.1±12.1*	254.0±22.4*
Urea, mmol/liter	2.7±0.4	7.1±0.9*	9.0±1.0*	8.8±0.8*	2.3±0.6	3.2±0.7	8.4±0.6*	6.0±0.5*	10.1±1.6*
Hepatic lymph									
Pyruvic acid	112.0±7.3	189.3±11.8*	224.1±19.4*	271.0±21.1*	112.9±7.9	115.2±12.0	198.4±9.9*	161.5±10.8*	248.5±25.7*
Glucose	3.4±0.5	11.9±1.1*	8.9±1.9*	10.4±0.9*	4.0±0.9	3.6±0.7	10.1±0.8*	3.6±0.8	11.1±1.5*
Lactic acid	1.3±0.1	4.9±0.3*	4.3±0.4*	4.3±0.2*	1.2±0.1	1.3±0.1	5.1±0.3*	2.8±0.3*	5.9±0.3*
Creatinine	64.8±9.1	209.7±21.4*	216.9±38.7*	245.5±22.4*	144.3±12.6*	65.7±8.9	157.8±3.5*	167.3±12.1*	207.2±22.4*
Urea	2.4±0.3	11.7±0.8*	8.9±0.6*	8.6±0.8*	2.2±0.4	2.6±0.2	8.1±0.9*	6.3±0.5*	9.4±0.4*
Intestinal lymph									
Pyruvic acid	112.1±5.4	212.2±21.9*	211.3±15.3*	238.6±20.5*	121.2±12.1	114.9±10.6	179.6±17.4*	154.0±12.1*	218.5±19.9*
Glucose	3.2±0.6	9.5±1.9*	9.5±1.5*	8.2±1.7*	3.4±0.3	3.1±0.2	10.1±1.1*	4.0±0.6	9.8±1.1*
Lactic acid	1.3±0.1	3.8±0.2*	3.4±0.4*	3.8±0.5*	1.3±0.1	1.4±0.1	4.4±0.3*	2.5±0.2*	4.8±0.2*
Creatinine	82.6±8.4	202.2±18.6*	242.4±56.8*	173.4±14.7*	133.4±10.1*	88.8±10.2	177.5±25.8*	173.1±15.4*	256.9±33.2*
Urea	2.3±0.3	8.1±0.8*	10.3±1.8*	8.2±1.0*	2.2±0.5	2.6±0.4	11.1±0.9*	8.8±0.8*	12.2±0.6*
Blood serum									
Pyruvic acid	173.3±10.2	273.3±24.4*	345.7±16.1*	351.2±29.5*	220.1±14.1*	165.6±11.0	323.5±35.1*	173.1±15.2	347.2±35.0*
Glucose	3.5±0.9	8.6±1.0*	5.4±0.3*	6.1±0.9*	4.1±0.7	3.6±0.5	10.1±1.0*	5.0±0.5	5.6±0.6*
Lactic acid	1.6±0.1	4.2±0.2*	2.9±0.3	4.2±0.3*	2.0±0.2	2.1±0.2*	4.7±0.2*	3.0±0.3*	4.8±0.2*
Creatinine	122.9±12.2	163.7±7.7*	146.3±11.1	147.4±8.0	195.6±15.2*	102.8±16.2	171.8±21.6*	168.6±7.5*	264.6±25.2*
Urea	3.4±0.3	5.4±0.6*	10.6±1.0*	7.6±1.0*	5.5±0.3*	3.8±0.4	7.2±0.6*	5.6±0.5*	9.8±0.6*

Note. The asterisk indicates a significant difference from the control group.

reflect the glucose-forming function of the liver more accurately than its variation in the blood. Possibly, the increases in glucose concentration in the lymph and hyperglycemia would be more pronounced in the absence of the "restraining" influence exerted by kinins which stimulate glucose transport and utilization through the biosynthesis and release of prostaglandins [7].

The appreciable elevations of lactic and pyruvic acids observed in the blood and particularly in the lymph attest to an activation of glycolytic processes. As a result of the activation of these processes in muscles during a febrile reaction, the blood and lymph receive large quantities of lactate, which is again converted into glucose in the liver. On the other hand, it may well be that lactic acid accumulation in the body up to a certain concentration is beneficial, being a physiological measure designed to combat the development of oxygen deficiency during the febrile reaction.

The elevation of pyruvic acid in body fluids in fever may be due, first, to the generation of this acid in excess in the process of lactic acid oxidation and, second, to its enhanced resorption from tissues. Pyruvic acid is known to be readily oxidizable under aerobic conditions, passing through the tricarboxylic acid cycle. For this reason a rise in its level in body fluids during fever is an indication that the further oxidation of this acid is impaired because of inhibited activity of the enzymes involved in the Krebs cycle.

Fever steps up protein catabolism in the body. The amino acids formed during protein breakdown undergo deamination in the liver. The major pathway by which the ammonia released in this process is detoxified is urea production in the mitochondria of liver cells. Therefore, the elevation of urea in the lymph and blood observed in our experiments appears to indicate that the urea-forming function of the liver was preserved during the febrile reaction. As urea is the main fraction of residual nitrogen, we believe that in the first stage of the febrile reaction there is probably a productive azotemia, associated with enhanced production of nitrogenous waste, to which a relative (dehydration) azotemia is added later. In our view, the elevations of creatinine in the lymph and blood during fever result from increased breakdown of protoplasmic proteins and the entry of creatinine into the lymph and blood from the muscle tissue where it is synthesized.

It follows, then, that during a febrile reaction, the lymphatic system is involved together with the circulatory system in the resorption of glucose, carbohydrate metabolic products, and nonprotein nitrogenous components from intercellular spaces of organs and tissues and in their transport to the general circulation. However, in cases of a long-lasting fever (5 or 10 days), the toxicity of the central lymph greatly increases as a consequence of the excessive production of toxic metabolites and the development of functional, resorptive, and transporting insufficiency of the lymphatic system - despite some intensification of lymph production. This is manifested not only in increased creatinine and urea levels in the lymph, but also in an increased lymphocytic index of intoxication, as we have shown earlier [6].

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