Metabolic and Physiological Characteristics of Immediate Response to Overheating in Man

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Intensified catabolism with activated proteolysis caused by stress and high temperature as a physical and chemical factor was found to be the typical response of the human body at the first stage of acute overheating. The data on the glutathione, which detoxifies lipid peroxides and protects proteins from oxidation, showed that hyperthermia strained the body antioxidant mechanisms. The body resistance to overheating depended on its initial status characterized by specific metabolic conditions.

Key Words: *humans; overheating; glutathione system; proteolysis*

The research interest in the problem of overheating has not decreased in recent decades [2,6,7,15]. The biochemical and molecular mechanisms underlying the compensatory and adaptive reactions to overheating are not well understood. These regulatory mechanisms seem to determine the variability of the human body resistance to external overheating. Our objective was to study general characteristics of physiological and metabolic processes occurring in human body exposed to acute overheating and to analyze individual characteristics which determine the body resistance to hyperthermia.

MATERIALS AND METHODS

The study involved 49 healthy volunteers in the age range of 20-25 years. After their functional conditions and working capacities had been assessed at comfort temperature, they were exposed to heat in a Tabaj climatic complex (45°C air temperature at a 45% humidity and a 1-2 m/sec air flow rate). During the test the subjects were dressed in isolating water-proof clothes and performed veloergometric exercise with a controlled workout to accelerate hyperthermia. Rectal temperature and cardiovascular indices were recorded during the test. Rectal temperature of 39.5°C or the subject's discomfort with the refusal to continue the test were taken as the threshold endurance. Samples of venous blood and urine were taken for biochemical analysis 1 h prior to the exposure and 10-20 min after it.

The index of thermosensitivity (ITS) was calculated to assess the level of strain in a thermoregulatory system. It was determined as the index of thermal strain divided by the time of exposure. The index of thermal strain (IS) was calculated from the following formula [9]:

$$IS=2.5\times dT+0.125\times dW+0.012\times dPs,$$

where dT is the increase in rectal temperature, °C, dW is the rate of water loss, g/min, and dPs is the increase in heart rate (HR), beats/min.

The subjects were divided into three groups in accordance with low, medium, and high indices of ITS that reflect the level of strain in their thermoregulatory systems.

The concentration of TBA-reactive products in blood plasma was determined in the samples taken with heparin [1]. The total content of low- and medium-molecular-weight compounds and oligopeptides

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with molecular weight no less than 10 kD was determined in plasma and erythrocytes [10,11]. The content of reduced glutathione (RG) and thiol groups [16], as well as the activities of glutathione peroxidase [3] and glutathione-S-transferase [17], were measured in the whole blood samples. The activity of superoxide dismutase (SOD) [5] and the concentrations of lactate and pyruvate [14] were determined in blood plasma. The concentration of 17-oxycorticosteroids in urine was calculated according to [13]. Blood plasma cortisol, thyrotropin, and thyroxin were assayed radioimmunologically. All the other biochemical indices were measured by a Spectrum automatic biochemical analyzer. The data were analyzed statistically using Statgraphics and BMDP software.

RESULTS

Individual responses to external overheating in healthy humans were determined by different autonomic reactions. The groups with the extreme ITS values differed in a variety of indices, and the most important of them proved to be the time of staying in the climatic complex and HR increase. A minor HR increase and a relatively slow rise of rectal temperature combined with less intensive perspiration were typical of subjects with low ITS. These characteristics predetermined their longer stay in the climatic chamber (Table 1).

It should be noted that with a few exceptions similar changes in most biochemical parameters were observed in all the subjects, irrespective of their ITS (Table 2). As seen from Table 3, the more endurable subjects with low ITS revealed an initially higher metabolism, as judged by the malonic dialdehyde (MDA) indices in the presence of Fe^{2+} (Fe^{2+}-MDA) and the blood plasma concentration of oligopeptides and low- and medium-molecular-weight compounds. In contrast to subjects with high ITS, their responses to overheating were not accompanied by an increase in Fe^{2+}-MDA content and changes in SOD activity, although the glutathione system reacted in a similar way in both groups. However, the decrease in RG content and the increase in glutathione peroxidase activity in the subjects with high ITS were less pronounced than in those with low ITS, and their initially more active glutathione-S-transferase became more suppressed. This can imply the predominance of different metabolic pathways of RG transformation in persons with different responses to overheating. It also suggests the importance of the protective antioxidant glutathione system for an immediate response to the activation of free radical oxidation under conditions of overheating. During this process RG is reversibly oxidized by glutathione peroxidase and irreversibly conjugates with the products of lipid peroxidation in the glutathione-S-transferase reaction. Therefore, a persistent decrease in glutathione-S-transferase activity, which is probably due to inhibition or deactivation of this enzyme by hyperthermia, is an unfavorable factor. Glutathione-S-transferase is an enzyme with a relatively low catalytic activity. Under conditions of RG deficiency it can be inhibited even by oxidative substrates as well as by bilirubin and bile acids [8].

Presumably, specific features of neurohumoral regulation, which manifested themselves in different autonomic reactions in the two extreme groups of the

TABLE 1. Physiological Indices in Subjects with Different Values of then Index of Thermosensitivity, ($X \pm m$)

Index	ITS		
	low (n=10)	intermediate (n=30)	high (n=9)
ITS, arb. units	35.8±1.4	49.5±0.6	60.7±0.9***
Exposure time, min	102±8	78±2	76±2**
Rise of rectal temperature, °C	2.2±0.2	2.3±0.1	2.7±0.1+
Water loss, kg	1.2±0.1	1.3±0.1	1.8±0.2+
Heart rate, beats/min			
initial	71.6±3.9	67.9±1.4	66.2±1.9
after exposure	93.4±5.1	104.0±3.2	114.7±5.7*
Systolic pressure, mm Hg			
initial	115.3±2.4	120.1±2.0	117.2±1.8
after exposure	115.7±3.1	113.1±2.7	108.9±3.7
Diastolic pressure, mm Hg			
initial	67.4±2.1	71.8±2.0	72.1±2.3
after exposure	57.9±4.4	60.3±1.6	62.8±2.8

Note. +$p<0.1$; *$p<0.05$; **$p<0.01$; ***$p<0.0001$ in comparison with the low ITS subjects.

TABLE 2. Biochemical and Hematological Blood Indices of Healthy Men before and after Heat Exposure ($X \pm m$, n=49)

Index	Before exposure	After exposure
Erythrocytes, $\times 10^{12}$/liter	4.66±0.03	4.87±0.03***
Hemoglobin, g/liter	148.1±1.3	155.8±1.0***
Segmented neutrophils, %	57.4±1.3	62.9±1.4**
Eosinophyls, %	2.3±0.3	2.0±0.3
Monocytes, %	5.0±0.4	3.7±0.3**
Basophils, %	0.3±0.1	0.3±0.1
Lymphocytes, %	32.7±1.2	27.9±1.2**
Cortisol, nmol/liter	346±18.6	796±41.0***
Thyrotropin, μunits/ml	1.44±0.09	2.17±0.13***
Thyroxin, pmol/liter	14.7±0.2	15.4±0.2**
17-oxycorticosteroids, mg/100 ml urine	1.87±0.14	2.04±0.13
Glucose, mmol/liter	5.00±0.16	5.69±0.17**
Pyruvate, mmol/liter plasma	0.18±0.01	0.19±0.01
Lactate, mmol/liter plasma	2.25±0.17	1.54±0.07***
Total protein, g/liter	75.3±1.1	76.2±0.7
Albumins, g/liter	47.2±1.0	46.9±1.3
Globulins, g/liter	26.2±0.9	27.4±0.5
Urea, mmol/liter	4.15±0.18	4.72±0.18**
Creatinine, μmol/liter	77.5±3.1	86.4±2.6**
Compounds with low and medium molecular weights, OD units		
in blood plasma	10.5±0.4	12.0±0.4***
in erythrocytes	22.6±0.4	22.5±0.5
Oligopeptides, μg/ml		
in blood plasma	413±9	508±11***
in erythrocytes	872±25	731±17***
Triglycerides, mmol/liter	0.97±0.11	0.74±0.04***
MDA, nmol/ml plasma	5.24±0.20	5.34±0.19
MDA with Fe^{2+}, nmol/ml plasma	7.11±0.22	7.46±0.22*
SOD, conv. units/mg plasma proteins	1.06±0.01	1.00±0.02***
RG, mmol/liter blood	0.70±0.02	0.64±0.01**
Thiol-groups, mmol/l blood	5.33±0.10	5.71±0.14*
Glutathione peroxidase, mmol RG/minxliter blood	201.6±1.7	225.5±5.5***
Glutathione-S-transferase mmol/RG/minxliter blood	0.99±0.03	0.78±0.02***
Calcium, mmol/liter	2.45±0.03	2.52±0.03*
Phosphate, mmol/liter	1.51±0.06	1.22±0.05***

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison with the pre-exposure values.

subjects, strongly determine individual variations of metabolic responses to overheating.

The dynamics of responses to hyperthermia of heating in healthy humans varies with the conditions. In previous studies, where these conditions were similar to those employed in our study, significant changes in physiological, hematological, immunological, and biochemical parameters were revealed immediately after the exposure [4,12]. The conditions of heating in our study were not as severe as previously, but the subjects had to perform more intense physical work in a moisture-proof outfit, which increased overheating due to the metabolic heat production. The perspiration was more intense (Table 1) and the critical rectal temperature 39.5°C was achieved after 76-102 min (depending on individual resistance) which was 20 min

TABLE 3. Group-Specific Changes in Biochemical Indices Before and After Heat Exposure ($X \pm m$)

Index	ITS			
	low (n=9)		high (n=10)	
	before exposure	after exposure	before exposure	after exposure
Fe^{2+}-MDA, nmol/ml blood plasma	7.6±0.5	7.4±0.6	6.3±0.3°°	7.0±0.2°
SOD, conv. units/mg plasma protein	1.05±0.02	1.04±0.03	1.05±0.03	1.00±0.04+
RG, mmol/liter blood	0.75±0.06	0.58±0.02++	0.72±0.04	0.64±0.04°
Glutathione peroxidase, mmol RG/minxliter blood	194.6±2.5	248.4±9.2*	203.6±4.2°	233.3±10.0++°
Glutathione-S-transferase, mmol RG/minxliter blood	0.88±0.10	0.78±0.04	1.11±0.07°	0.82±0.04*
Low- and medium-molecular compounds in blood plasma, OD units	13.8±2.7	15.6±3.2++	9.9±2.2°°	11.2±1.3+°°°
Oligopeptides in blood plasma, μg/ml	425±32	527±66*	376±43°°	501±52**

Note. +p<0.1, ++p<0.05, *p<0.01, **p<0.001 in comparison with the pre-exposure values; °p<0.1; °°p<0. 05; °°°p<0.001 in comparison with the low ITS group.

later than in the above-mentioned studies. Judging by the increased absolute concentration of blood cells and hemoglobin in our study, blood viscosity increased, but nod decreased, as reported by others [4]. These processes are very close in time during overheating: blood is usually diluted by tissue fluids, but further loss of water results in blood thickening. Despite the variations in the circulating blood volume, unilateral shifts were observed in many biochemical parameters: an increase in glucose concentration, a decrease in lactate concentration due to its active removal in sweat [6] and, possibly, its increased utilization in the liver, an increase in blood concentration of urea and creatinine, and a decrease in SOD activity. Blood cortisol and urinal 17-oxycorticosteroid concentrations increased considerably (Table 2).

The catabolic effect of heat exposure manifested itself in elevated plasma content of low- and medium-molecular-weight metabolites. Increased plasma concentration of oligopeptides was indicative of intensified proteolysis during acute hyperthermia. It was specific for heating, since no changes in plasma concentration of oligopeptides were observed during exposure to cold (387±22 μg/ml before cooling against 397± 14 μg/ml after it, n=24). Thus, the reactions of healthy subjects to external overheating were characterized by general physiological and biochemical regularities, which were independent of heating conditions, and by individual features, which were due to the different capacities of their autonomic nervous systems. This difference manifested itself in the time course of body overheating and predetermined different heat endurance in nonadapted subjects. It should be noted that the subjects which were classified into groups according to different changes in their physiological parameters in the process of overheating were initially distinguished by a number of biochemical indices (Table 3), which should be taken into account when the basic criteria for the preliminary assessment of human endurance under conditions of overheated environment are developed.

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