

Mechanisms of the Endogenic Intoxication Syndrome at the Traumatic Shock

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Abstract

The condition of the basic components of antioxidant-prooxidant system and the role of revealed disturbances in origin and progressing of the endogenic intoxication syndrome (EIS) were estimated. Three components of EIS were investigated: the toxemia, the tissue hypoxia and the antioxidant protection. The level of average molecules in plasma and erythrocytes, ALT, AST, LDH, SOD, malonic dialdehyde, ceruloplasmine, catalase, glutathione reductase, glutathione peroxidase, lactate were studied by biochemical method; the biophysical parameters of blood, myocardium, liver, kidney by Electronic-Paramagnetic-Resonance methods. The disbalance between different links of antioxidant protection, insufficiency of major antioxidants, intensification of free radical oxidation, oxidative stress play a leading pathogenic role in EIS development during traumatic shock. Major sources of production of oxygen active forms are a mitochondrial respiratory chain, hypoxantine - xantineoxidase system, microsomal P-450 oxidase system, excess of Fe^{2+} ions, Mn^{2+} ions and NO. Oxidant stress can determine expressiveness of endotoxicosis and appearance of polyorganic insufficiency in presence of tissue hypoxia and energy-deficiency.

Keywords: *Endogenic Intoxication Syndrome (EIS), average molecules, ceruloplasmine, catalase, glutathione reductase, glutathione peroxidase, SOD, malonic dialdehyde, lactate, EPR, traumatic shock*

Introduction

The endogenic intoxication syndrome (EIS) belongs to a number of widespread syndromes in clinical practice and is observed at the most various etiologic and pathogenic urgent conditions [1,2,3,4]. EIS is considered, as one of the main part of inflammatory-destructive pathological process in an organism, it is characterized by accumulation of endogenic biological substances in a tissue and biological liquids of organism - products of the normal or perverted metabolism or cellular reaction [5]. Original conception of EIS is based on systemic inflammatory response syndrome (SIRS). According to the nomenclature SIRS associated with a documented infection is sepsis in most current studies of the etiology and outcome of SIRS have focused on severely ill patients with little or no systemic inflammation treated at intensive care units [12]. Modern representations about pathogenesis of EIS are based

on recognition of EIS as a leading part in membrano-destructive processes [6,7,8]. Membrane-destructive processes in many respects are connected to intensification of the free - radical oxidation [9] caused by reduction of antioxidant protection, tissue hypoxia and energy-deficiency; and consequently intensity of oxidant stress can determine expressiveness of endotoxicosis and appearance of polyorganic insufficiency, as extreme degree of endotoxicosis. EIS is an indispensable and determining part of pathogenesis of traumatic illness [10,11] and a shock of any etiology [12,13], however peculiarities of origin mechanisms and progressing of EIS, and also an establishment of criteria of severity of endotoxicosis at dynamics of a traumatic shock is not established yet.

The purpose of work was the estimation of basic components of antioxidant-prooxidant system and a role

of the revealed disturbance in the mechanism of endotoxycosis during traumatic shock.

Materials and Methods

Experiments have been carried out on pubertal white rats (male, weight 150-200 g). A heavy traumatic shock modeled by Cannon [14]. Animals were divided on three groups (10 animal in each group): the control; a traumatic shock - the period of stabilization of functions; a traumatic shock - the terminal period. The basic links of EIS were estimated: parameters of toxemia and antioxidant-prooxidant system, tissue hypoxia. Object of research were blood and organs (a myocardium, a liver, kidneys, a brain). A level of average molecules in blood (at length of a wave of 282 nanometers in plasma and in erythrocytes 258 nanometers by Malahova M.J.'s method of spectrophotometry [15]. for an estimation of toxemia was defined.

The content of lactate (by enzymatic spectrophotometry method) and activity of lactatedehydrogenase, ALT, AST-aminotransferase (by kinetic spectrophotometry methods) with use of sets of reagents of firm Boehringer Mannheim [16] were studied. Activity of super oxide dismutase (SOD), glutathione peroxidase, glutathione reductase, catalase and concentration of ceruloplasmine were measured by the spectro-photometry technique; respectively [17,18,19, 20]. The intensity of Electronic-Paramagnetic signals were studied by the electronic-paramagnetic-resonance (EPR) method (radiospectrometer PE-1307). Material from blood and organs were placed in polyethylene tubes and kept in liquid nitrogen (-180°C). Malonic dialdehyde in plasma and erythrocytes determined by a method [21].

Results and Discussion

The increase of the extinction in the spectrogram of plasma and erythrocytes in the period of stabilization of functions at a traumatic shock has been observed; however more significant in erythrocytes (*Tab.1*). The increase of the extinction in 1,6 times in plasma with the decreasing (more than 2 times) in the erythrocytes, during the terminal period of a shock. Value of optical density of plasma and erythrocytes reflect the contents of biologically active substances of low and average molecular weight, and oligopeptide, which is related to the level of an intoxication and toxemia [5,7,8,10,15]. Character of the spectrogram of plasma and erythrocytes allows to reveal a phase of EIS [5,15].

The increase in a level of average molecules in plasma and erythrocytes, during stabilization of functions at a traumatic shock, specifies the presence of the second phase of an intoxication - phase of toxemia (the phase of accumulation of toxic products in blood from the focus of aggression).

There is a reduction of the peak of extinction in the erythrocytes up to norm and below during the terminal period of a shock, due to the damage of erythrocyte's membranes. The growth of amount of optically active substances in plasma can testify development of severe endotoxycosis (phase of an inconsistency of systems of a homeostasis, significant damage of membranes, irreversible changes, and occurrence of polyorgan insufficiency) at a traumatic shock.

Period of traumatic shock	Plasma, $\lambda=282$ nm	Erythrocytes $\lambda=258$ nm
Control	0,16±0,02	0,46±0,06
Stabilization of the function	0,22±0,02*	0,85±0,08*
Terminal period	0,36±0,04*	0,37±0,05*

* p<0.05

Tab.1 Changes of extinction of plasma and erythrocytes during traumatic shock.

Group \ Parameter	Control	Traumatic shock, period	
		Stabilization of the function	Terminal period
Ceruloplasmine, u. opt. dens.	0,26±0,02	0,13±0,07*	0,025±0,07*
Lactate, mmol/ml	1,9 ± 0,3	2,1±0,4*	4,3±0,5*
ALT, mckat/l	0,19±0,03	0,37±0,07*	0,82±0,13*
AST, mckat/l	0,39±0,08	0,67±0,07*	1,2±0,3*
LDH, mckat/l	1,09±0,18	1,67±0,17*	1,98±0,13*
MDA, mcmol/ml (plasma)	0,9±0,2	1,3±0,2*	2,3±0,3*
MDA, mcmol/ml (erythrocytes)	1,4±0,2	2,8±0,4*	5,3±0,4*

* p<0.05

Tab.2 Biochemical parameters of blood during traumatic shock.

Parameter		Period	Organ		
			myocardium	liver	brain
antioxidant defense	SOD, con.u./min/mg of protein	Control	2,3 ± 0,3	2,8 ± 0,2	1,8 ± 0,2
		I	1,6 ± 0,2*	1,15 ± 0,25*	1,2 ± 0,2*
		II	1,4±0,3*	0,46 ± 0,05*	1,0 ± 0,1*
	Catalase, nmol H ₂ O ₂ ⁻ /mg of protein/min	Control	5,8 ± 0,2	6,8±0,4	4,8 ± 0,2
		I	5,1 ± 0,6	4,1±0,2*	1,1±0,3*
		II	0,70± 0,05*	3,4±0,5*	0,6±0,1*
	Glutathione reductase cmol NADPH mg min ΓP, mcmol/g s.	Control	3,3±0,3	2,8 ± 0,2	2,8 ± 0,2
		I	80±11*	115 ± 0,25*	15 ± 0,25*
		II	46 ± 5*	6 ± 1*	0,8 ± 0,1*
	Glutathione peroxidaze mcmol FSH mcmol ml min	Control	3,9±0,2	4,5±0,3	2,9±0,2
		I	1,8±0,2*	1,6±0,2*	0,8±0,2*
		II	1,2±0,1*	0,8±0,1*	0,2±0,1*
	MDA, mcmol/mg	Control	1,0 ± 0,2	1,2±0,2	0,9 ± 0,2
		I	1,8 ± 0,25*	2,8±0,3*	2,0±0,2*
		II	2,4 ± 0,5*	3,5±0,4*	4,0±0,1*

*p<0.05; I - Stabilization of the function; II - Terminal period

Tab.3 Parameters of enzymatic antioxidant defense and MDA during traumatic shock.

Group	Parameter	Intensity of EPR-signals, mm/mg	
		Control	Traumatic shock
Oxidized Ceruluplasmine, g=2,06		30,0±1,6	64,8±2,6*
Fe ³⁺ -transferrine, g=4,3		63,4±1,4	29,4±0,4*
Met- Hb, g=6,0		absent	2,6±0,1*
Signal of inactive receptors g=2,01		absent	presence

*p<0.05

Tab.4 Change of intensity of EPR-signals of blood at the traumatic shock.

Group	Parameter	Intensity of EPR-signals, mm/mg			
		Control		Traumatic shock	
		Myocardium, ventricles		Myocardium, ventricles	
		Left	Right	Left	Right
Free radicals, I Intency, g=2,00		23,4±1,6	22,4±1,3	36,3±0,5*	37,0±0,7*
ΔH half-width		13,3±0,2	13,3±0,2	10,1±0,4*	9,9±0,2*
FeS g=1,94		106±5	104±5	126±3*	126±2*
Mn ²⁺ , g=2,14		2,0±0,1	2,0±0,1	5,2±0,2*	5,7±0,1*

*p<0.05

Tab.5 Change of intensity of EPR-signals of myocardium at the traumatic shock.

Group	Parameter	Intensity of EPR-signals, mm/mg			
		Control		Traumatic shock	
		Liver	Kidney	Liver	Kidney
Free radicals, g=2,00		30,2±0,1	30,0±0,3	51,8±1,3*	48,2±0,9*
ΔH half-width		13,3±0,1	12,5±0,2	9,9±0,1*	9,9±0,1*
FeS, g=1,94		97±3	88±1	128±4*	117±2*
Mn ²⁺ , g=2,14		2,2±0,1	1,8±0,1	9,5±0,3*	5,1±0,3*
Mo ⁵⁺ , g=1,97		8,8±0,3	4,6±0,4	22,8±0,7	16,0±0,3*
FeS-No, g=2,03		absent	absent	3,3±0,1*	absent
Cytochrom P ₄₅₀ , g=2,25		48±1	15,2±0,1	28,8±0,7*	9,7±0,3*

*p<0.05

Tab.6 Change of intensity of EPR-signals of liver and kidney at the traumatic shock.

Alongside with change of optical density at a traumatic shock there is a progressing increase in activity and contents of other biochemical parameters testifying to development of an intoxication, such as, activity ALT, AST, LDH, lactate and MDA (*Tab.2*). The changes of the specified parameters related to cytolysis, activation of the lipid peroxidation, accumulation of products of degradation of lipids, activation anaerobic glycolysis, correlates to the severity of a traumatic shock. It is suggested, that the accumulation of blood lactate may be due to enhanced glycolysis, pyruvate production and inadequate pyruvate metabolism via Krebs cycle, as might occur in hypoxic tissue secondary to organ hypo perfusion. During traumatic shock there are various triggers that can activate inflammatory cascade, including ischemia, necrotic tissue, endotoxic substances. It was observed the release of various kinds of cytokines and oxygen-derived free radicals. The resultant increase in capillary permeability with free radical release into the tissues reduces circulating blood volume. Initial attempts to maintain blood pressure and vital organ perfusion are at the expense of other vascular beds, which lead to regional ischemia. In this situation anaerobic glycolysis predominates with the accumulation of metabolites such as lactic acid and a fall in the pH. This may lead to vasodilation, hypotension and organ dysfunction. Accumulation of lactate during hypoxia originates from impaired mitochondrial oxidative function that reduces the availability of ATP and NAD^+ in the cytosol. [22,23,24]. In turn, these changes cause cytosolic accumulation of pyruvate as a consequence of both: increased production and decreased utilization. Increased production of pyruvate occurs because the reduced cytosolic supply of ATP stimulates the activity of 6-phosphofructokinase, thereby accelerating glycolysis. Decreased utilization of pyruvate reflects the fact that both pathways of its consumption depend on mitochondrial oxidative reactions: oxidative decarboxylation to acetyl coenzyme A, a reaction catalyzed by pyruvate dehydrogenase, requires a continuous supply of NAD^+ ; and carboxylation of pyruvate to oxaloacetate, a reaction catalyzed by pyruvate carboxylase, requires ATP. The increased NADH/NAD^+ ratio shifts the equilibrium of the lactate dehydrogenase reaction (that catalyzes the inter conversion of pyruvate and lactate) to the right. In turn, this change coupled with the accumulation of pyruvate in the cytosol results in increased accumulation of lactate. Despite the prevailing mitochondrial dysfunction, continuation of glycolysis is assured by the cytosolic regeneration of NAD^+ during the conversion of pyruvate to lactate. Provision of NAD^+ is required for the oxidation of glyceraldehydes 3-phosphate, a key step in glycolysis. Thus, lactate accumulation can be viewed as the toll paid by the organism to maintain energy production during hypoxia. [22,23]. Accumulation of lactate is not only due to the increasing of its production and also due to the failure of the hepatic metabolism and renal excretion (in our investigation was shown that

hepatic and renal dysfunction takes place). Many authors feel that the concentration of blood lactate correlates with the degree of hypo perfusion and severity of shock and could be of prognostic value [25] but other authors indicate that a raised blood lactate not associated with the same degree of mortality [26].

Studying of antioxidant parameters shows, that activity of SOD and catalase is reduced at the traumatic shock in the period of stabilization of function (*Tab.3*). The most expressed reduction is marked: SOD activity in a liver (by 43%), and activity catalase in a brain (by 77%). As for glutathione link of antioxidant defense, glutathione peroxidase activity reduces (especially in a liver and a brain), and glutathione reductase activity rises. In the terminal period of shock, reduction of activity of SOD, catalase, and glutathione peroxidase become more expressed (falls by 40, 45, 84%, 88, 50, 87,5% and by 70, 83, 32% in a myocardium, liver and brain accordingly). It is necessary to note, that activity glutathione reductase remains increased in a liver and a myocardium, but in a brain is reduced by 70 %. Antioxidant defense is unable to neutralize active forms of oxygen and does not stop activation of lipid peroxidation that is confirmed by increased contents of MDA.

During traumatic shock, on the background of decreased of enzymatic antioxidant defense, the double increase of intensity of EPR signal of oxidized ceruloplasmin was observed (*Tab.4*). Ratio of oxidized ceruloplasmin to entire the ceruloplasmin concentration was increased, which points on elevation of quota of inactive ceruloplasmin, reduction of antioxidant ability of organism and activation of lipid peroxidation. At the same time, intensity of signal Fe^{2+} -transferrin decreases. EPR spectrum of blood reveals failure of antioxidant defense and activation of lipid peroxidation that causes destruction of membrane structures and erythrocytes in particular, leading to hemolysis and production of methemoglobin. This last is confirmed by appearance of Met-Hb intensive signal ($g=6,0$). Increased signal of oxidized ceruloplasmin in blood and decreased signal of Fe^{2+} -transferrin indicate elevation of free iron ions. It is well know that free iron ions are the powerful promoters of free radical oxidation (Fenton and Haber-Weiss reactions - OH formation). Besides tissue injury and erythrocytes damage during traumatic shock may also release hemoglobin from erythrocytes and myoglobin from red muscles and myocardium, both are potentially dangerous proteins. During traumatic shock, it has been suggested, that release of free hemoglobin and myoglobin takes place, which at the presence of excess H_2O_2 causes hem degradation and release of iron ions. In addition, hemoglobin and myoglobin react with H_2O_2 to form oxidizing species capable of stimulating lipid peroxidation. The reaction of H_2O_2 with the protein probably generates a hem ferryl species plus

an amino acid radical [27]. Thus, iron dependent free radical oxidation may play the important role in pathogenesis of the toxemia during traumatic shock.

In the presence of activated lipid peroxidation as a result of membrane destruction, inactivation of adrenoreceptors signal ($g=2,0$) is obvious. It is probably the result of exaggerated production and/or release of catecholamines, desensitization of adrenoreceptors and disconnection of adrenoreceptors from system of adenylylase due to oxidative stress. *Tab.5* and *Tab.6* show the changes of metabolic paramagnetic centers of the organs during the traumatic shock. In the EPR spectrum of myocardium (left and right ventricles) the intensity of Mn^{2+} -containing complexes increased, that reveals membrane structures destruction and inactivation of mitochondrial SOD. At the same time the intensity of the FeS-centers ($g=1,94$) and free radical signal ($g=2,00$) increased, but its half width decreased, that reveals disorder of mitochondrial respiration at NADH: ubiquinon oxidoreductase locus and generation ubisemiquinons and oxygen free radicals. In hepatocytes in comparison with the myocardium reveals the intensive signal of FeS-NO complexes ($g=2,03$), which indicates the activation of NO synthesis. Also the signal of Mo-containing complexes in hepatocytes and kidneys are increased, that indicate elevation of xantinoxidase activity. The decreasing of the signal of cytochrom P-450 reveals intoxication. It should be mentioned, that excess amount of NO revealed by the intensive signal of FeS-NO in the presence of superoxide radicals and inactivated SOD, converts into

peroxinitrit, which is known as high active free radical, thereby makes favorable conditions for further activation of lipid peroxidation and intoxication.

Conclusions

1. Character of the spectrogram of plasma and erythrocytes allow revealing a phase of EIS. The increase in a level of average molecules in plasma and erythrocytes, during stabilization of functions at a traumatic shock, reflect the presence of the second phase of intoxication - phase of toxemia. The growth of optically active substances in plasma with the decrease in erythrocytes can testify severe endotoxiosis at a terminal phase of traumatic shock. Presence of toxemia during traumatic shock is detected also by changes of biochemical parameters such as, activity ALT, AST, LDH, lactate and MDA.

2. The disbalance between different links of the antioxidant protection, the insufficiency of major antioxidants, the intensification of free radical oxidation, and oxidative stress play a leading pathogenic role in EIS development during traumatic shock. Oxidant stress can determine expressiveness of endotoxiosis and appearance of polyorganic insufficiency in presence of tissue hypoxia and energy-deficiency.

3. A major sources of oxygen active forms' production are mitochondrial respiratory chain, hypoxantine-xantineoxidase system, and microsomal P-450 oxidase system, excess of Fe^{2+} ions, Mn^{2+} ions and NO.

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Механизмы развития синдрома эндогенной интоксикации при травматическом шоке

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Р Е З Ю М Е

Оценено состояние основных компонентов прооксидантно-оксидантной систем и роль выявленных расстройств в возникновении синдрома эндогенной интоксикации (СЭИ) при травматическом шоке. Изучены три компонента СЭИ - токсемия, гипоксия, антиоксидантная защита. Определяли уровень средних молекул в плазме и эритроцитах, лактата, малонового диальдегида, церулоплазмينا, активность ферментов супероксиддисмутазы (СОД), каталазы, глутатионредуктазы, глутатионпероксидазы биохимическими методами. Оценивали также биофизические параметры крови и органов, характеризующие состояние прооксидантно-оксидантной систем ЭПР методом. Установлено, что в развитии синдрома эндогенной интоксикации при травматическом шоке существенную патогенетическую роль играет дисбаланс между активностью различных звеньев антиоксидантной системы, недостаточность основных ее компонентов, активация перекисного окисления липидов, развитие оксидационного стресса, усугубляющего деструктивные и некротические процессы. На фоне тканевой гипоксии и энергодефицита оксидационный стресс поддерживает порочные круги прогрессирования эндогенной интоксикации и возникновения полиорганной недостаточности и гибели.

Ключевые слова: синдром эндогенной интоксикации, СОД, каталаза, глутатионпероксидаза, глутатионредуктаза, церулоплазмин, средние молекулы, ЭПР сигналы, МДА, травматический шок