



## Modern Views and Approaches to Pathophysiological Bases of Endogenous Intoxication

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**ABSTRACT:** Recently, many scientific works have been devoted to the study of endogenous intoxication (EI) in various pathological diseases and conditions, since EI is one of the most important criteria that determine the severity of a person's condition. EI (endotoxicosis) is a pathophysiological process characterized by the formation and accumulation of various compounds and metabolites in tissues and body fluids in excessive concentrations or forms that are not characteristic of normal metabolism. In the development of EI among biochemical processes, much attention is paid to the activation of proteolysis with a violation of the general enzymatic homeostasis of the body. The metabolic level of endotoxicosis is characterized by excessive accumulation of products of normal and pathologically perverted metabolism and is detected using biochemical and other laboratory methods. The clinical level of endotoxicosis includes both metabolic disorders and various clinical manifestations in the form of complications in the course of the underlying disease and side effects of therapy.

**Key words:** endogenous intoxication, pathophysiology, lipid peroxidation.

### Relevance

As we know, the modern concept of endogenous intoxication (EI) is associated primarily with the development of multiple organ failure (POF) against the background of xenobiotic or activation of pathological endogenous agent and as a consequence of one-time or consecutive onset of failure of heart, lung, liver, kidney, brain, which leads to high mortality - from 60 to 80% [10,25,29, 32]. It is an established fact that liver, kidney and digestive tract failures play a significant role in the outcome of

PON (60%, 56% and 53% of cases, respectively). However, it should be noted that the clinical picture of metabolic disorders in hepatic-renal dysfunction is not as pronounced as respiratory and circulatory disorders, especially in the early stages of its progression [22,25,26]. Therefore, the diagnosis of impaired metabolism, as a rule, is late and often leads to the statement of facts in far advanced or already irreversible changes, determining the outcome of diseases. Most clinicians define EI "as a syndrome unspecific in most clinical, biochemical and immunological manifestations between the formation and excretion of both 'normal' metabolic products and substances of impaired metabolism"[10,13,27]. C.Ince (2005) [16,17,19] suggests that the essence of EI is based on the concept of presenting it as reflecting the consequences of disturbances in macrocirculation and micro hemolympho circulation, gas exchange and oxygen budget, immunity and anti-infective "protection" with a failure to manage the integration of these processes. In this case, according to the author, metabolic disorders proceed in accordance with the nature of the damaging factor and the response to it the system of macro- and microcirculation in accordance with the disruption of transport and extraction of tissue oxygen, activation of the sympathetic-adrenal system, which results in hyper metabolism syndrome, typical of a critical state - tissue need for various substrates to provide compensatory-adaptive mechanisms of energy conservation, prevention of protein breakdown, decreased utilization of fatty acids, increased gluconeogenesis and glucose tolerance, intensification of endothelium permeability.

Depending on the predominance of the mechanism of EI formation, the following forms are conventionally distinguished: retentive, exchange, and resorptive. The retentive mechanism involves mainly a violation of the natural removal mechanism, usually the end products of metabolism of low molecular weight compounds (molecule size - less than 10 nm, molecular weight [MM] - less than 500 daltons). The main route of elimination is renal filtration and excretion. The metabolic mechanism is characterized by the accumulation of metabolic intermediates (molecular size greater than 10 nm, MM less than 500 dalton), which are eliminated by the liver and through the food channel [5]. Depending on the predominance of the mechanism of EI formation, the following forms are conventionally distinguished: retentive, exchange, and resorptive. The retentive mechanism involves mainly a violation of the natural removal mechanism, usually the end products of metabolism of low molecular weight compounds (molecule size - less than 10 nm, molecular weight [MM] - less than 500 daltons). The main route of elimination is renal filtration and excretion. The metabolic mechanism is characterized by the accumulation of metabolic intermediates (molecular size greater than 10 nm, MM less than 500 dalton), which are eliminated by the liver and through the food channel [5]. According to [1], EI develops either as a result of an imbalance in the components of the detoxification system, or in the failure of one of its parts, or simultaneously all of its components. This determines the essence of EI, its general and distinctive features depending on the underlying cause, i.e. the etiology of the disease, as well as its severity according to the number of detoxification organs and components involved in the pathological process [2, 3,21].

The study of the toxicity and potential risks of engineered nanoparticles is of particular importance in nanomedicine [25, 29]. According to the authors, endotoxin, a common contaminant of bacterial origin, has biological effects that can mask the true biological effects of nanoparticles if its presence is not considered. In their publications, the authors report the features of endotoxin contamination of nanoparticles and the different biological effects of endotoxin-contaminated nanoparticles. The authors have analysed various ways to remove endotoxin contamination from

nanoparticles. Although there is no universal method for effectively removing endotoxin from nanoparticles, specific solutions can be found in each case. The main body detoxification organ (involved in the neutralization of endogenous toxic products of cellular metabolism or substances produced by microbes in the gut) is the liver, which in addition to this function performs many other functions to maintain homeostasis. When the liver is damaged, it is known to accumulate toxic substances and decay products of the organ, represented by water-soluble (ammonia, phenylalanine, tyrosine) and albumin-bound toxins (fatty acids, endogenous benzodiazepines, bile acids, bilirubin, aromatic compounds, endogenous vasodilators) [6,23,28]. These substances cause toxic cholestasis, angiocholithiasis and, in many cases, PID, hepatorenal encephalopathy (PE), hepatorenal syndrome (HRS), cardiovascular dysfunction and PID. [2,3,4,11,14,17,18].

The pathogenetic aspects of PE and acute liver failure are poorly understood. The most widespread theories are related to dysfunction of neurotransmitter systems: toxic, false neurotransmitter theory, theory of impaired  $\gamma$ -aminobutyric acid (GABA) metabolism [7,12].

For example, the toxic theory links the development of PE to the excessive formation of ammonia in the colon from protein breakdown products by microflora. Normally, ammonia via the portal vein enters the liver, where urea is formed, but as a result of damage to the latter, the metabolic activity of ammonia is significantly reduced and free ammonia entering the general bloodstream through the porto-caval ducts and penetrates the blood-brain barrier, contributes to the penetration of neurotoxic aromatic acids into the central nervous system, leading to edema and damage to astrocytes. [16,30,31].

Another false neurotransmitter theory explains the development of PE and fulminant liver failure by a decrease in amino acids due to increased protein catabolism and the accumulation of aromatic amino acids (phenylalanine, tyrosine, tryptophan) in the blood, which enter the brain causing inhibition of the enzyme system. The result is suppression of the nervous system and the development of PE [12,22]. A further theory is the hypothesis of enhanced GABAergic transmission. As a result of hepatic insufficiency, GABA produced in the intestine travels by shunts into the bloodstream and then into the brain, leading to the development of PE.

Thus, univariate and multivariate studies conducted as part of the development of multiple organ dysfunction have shown that infection or toxic breakdown products or insufficient utilisation in the liver are independent predictors of adverse outcome (death or transplantation) [20,24,30].

### **Types and classification of endotoxins**

Toxic concentrations in the body can be dozens of names, and the list of substances of autointoxication can be increased by hundreds of thousands of times [8,29]. Conventionally, five classes of endotoxins can be distinguished: substances of normal metabolism in non-physiological concentrations (urea, lactate, glucose, creatinine, bilirubin, etc.); products of impaired metabolism (aldehydes, ketones, acids); immunologically foreign substances (glyco- and lipoproteins, phospholipids); enzymes; inflammatory mediators, including cytokines, biogenic amines, antibodies, circulating immune complexes, adhesion molecules, protein degradation products and others [10]. Endotoxins can also be classified according to the causal relationship leading to endogenous intoxication, namely:

- Bacterial endotoxins;
- Products of normal metabolism in high concentration;

- Activated enzymes that can damage tissue;
- Mediators of inflammation;
- Products of peroxidation;
- Medium molecular substances of various nature;
- Ingredients of non-viable tissues.

Clinicians thus identify a number of conditions in which the body may be affected by endotoxins. These include all types of shock, burns, thyrotoxicosis, peritonitis and others. An interesting hypothesis is that of the effect of endotoxin on neurodegeneration, suggesting that endotoxin causes or contributes to neurodegeneration. Endotoxin is a lipopolysaccharide (LPS) that forms a large part of the outer membrane of Gram-negative bacteria and is present in high concentrations in the gut, gums, skin and other tissues during bacterial infection. Plasma levels of endotoxin are usually low but rise during infections, intestinal inflammation, gum disease and neurodegenerative diseases. The addition of endotoxin in such amounts to the bloodstream of healthy subjects causes systemic inflammation and activation of brain microglia. The addition of high levels of endotoxin to the blood or body of rodents causes microglia activation, priming and/or tolerance, memory deficits and loss of synapses and brain neurons. Endotoxin promotes  $\beta$ -amyloid and tau protein aggregation and neuropathology, suggesting the possibility that endotoxin synergizes with various aggregating proteins to cause various neurodegenerative diseases. Endotoxin levels in the blood and brain are elevated in Alzheimer's disease, which is accelerated by systemic infections, including gum disease. Endotoxin binds directly to APOE, and the APOE4 variant increases endotoxin sensitivity and predisposes to Alzheimer's disease. Gut permeability is increased in the early stages of Parkinson's disease, and injection of endotoxin into mice causes alpha-synuclein production and aggregation, as well as loss of dopaminergic neurons in the substantia nigra. Changes in the gut microbiome in Parkinson's disease and changes in the species of endotoxin-producing bacteria can affect the disease in patients and mice. Blood endotoxin is elevated in amyotrophic lateral sclerosis, and endotoxin contributes to TDP-43 aggregation and neuropathology. Peripheral diseases that increase endotoxin levels in the blood, such as sepsis, AIDS and liver failure, also lead to neurodegeneration. Endotoxin directly and indirectly activates microglia, which damage neurons via nitric oxide, oxidants and cytokines, and by phagocytosis of synapses and neurons. The endotoxin hypothesis is unproven, but if it is true, neurodegeneration may be reduced by reducing endotoxin levels or endotoxin-induced neuroinflammation. Endotoxin directly or indirectly activates microglia, which damage neurons via nitric oxide, oxidants and cytokines, and by phagocytosis of synapses and neurons. The endotoxin hypothesis is unproven, but if true, neurodegeneration may be reduced by reducing endotoxin levels or endotoxin-induced neuroinflammation. Endotoxin directly and indirectly activates microglia, which damage neurons through nitric oxide, oxidants and cytokines, as well as through phagocytosis of synapses and neurons. Indicators reflecting the state of the detoxification system can be divided into two categories:

- biochemical markers of AI;
- immunological markers of EI;
- Integral markers of EI.

The most important pattern in the formation of metabolic disorders in PON should be considered combined hypoxia and its consequences as a reflection of the disorder of the interconnection of the most important homeostasis systems: respiratory, circulatory, metabolic [21].

Therefore, an EI marker is the partial pressure of oxygen as a criterion of compliance of the volumetric blood flow with tissue oxygen requirements. And moderate acidosis has a protective effect, inhibiting the activity of phospholipases, the formation of cAMP, activating succinate oxidation in the mitochondria of muscle, liver, kidneys, brain [19]. Severe acidosis has damaging effects on cellular processes, including inhibition of glycolysis enzymes, increased energy deficiency, activation of lipid peroxidation (LPO) with consequent deterioration of myocardial contractility. Lactic acid (LA), pyruvic acid (PVA) and cellular adenosine triphosphatase (ATP) are universal markers of AI, reflecting the level of energy deficiency and oxygen deficiency. Thus, an accumulation of MK of 2.1 mmol/l and above is considered to be a prognostically unfavourable sign. The triad: an increase in the concentration of sugar, lactate and pyruvate reflects the energy failure of the cell. An increase in the concentration of MC without an increase in PVK is indicative of damage to enzymatic cellular processes [16,21].

Hypoxia results in a chain of pathological events of protein, carbohydrate and lipid metabolism disorder. Among these processes, protein metabolism disorders are central, because protein provides oncotic, transport, osmotic, esterase, endopeptidase functions, as well as the regulation of enzyme systems activity [9].

Therefore, plasma albumin concentration can be considered as an important marker of EI, and the decrease in total protein concentration at the expense of the albumin fraction - as a reflection of the use of albumin as a major factor in plasma detoxification, binding and removal of toxins. A decrease in total protein levels to 45 g/l (65080 g/l in controls) is considered an unfavourable prognostic sign, indicating severe endogenous intoxication.

Medium molecular weight oligopeptides (SM) - substances with a mass between 500 and 5000 daltons - are considered to be universal markers of endogenous intoxication. By their nature, SM are protein toxins with a high content of dicarboxylic and low content of aromatic acids. The peculiarity of the toxic action of medium molecules is that they have a direct membrane toxic effect and initiate the manifestation of peptides, the structure of which is similar to that of bioregulators. Among them, "hepatocerebral", "uremic", "ischemic", and "burn" medium molecular oligopeptides are distinguished. [5].

80% of medium molecular weight oligopeptides. - are proteins and products of their disturbed metabolism, including products of fibrinogen hydrolysis, globulins, glycoprotein catabolism, oligosaccharides, nucleotides, and hormones and their fragments (ACTH, angiotensin, endorphins, enkephalins). Medium molecular oligopeptides include a number of biologically active substances such as parathormone, neurotoxins X, inhibitors of phagocytosis, haemopoiesis, erythrocyte membrane fragility; glucose utilisation and amino acid transport; factors of respiration and phosphorylation decoupling. This determines the toxicity of medium molecules as a result of impaired erythropoiesis, reduced rosette formation and inhibition of mitochondrial respiration; impaired DNA synthesis in hepatocytes and lymphocytes; impaired glucose synthesis and utilization, enzyme activity, creatinine excretion. Neuro- and psychotoxic effects of medium molecular oligopeptides are associated with formation of false neurotransmitters (SM concentration in control is 0.15-0.24 conventional units) [25].

Thus, EI as a component of a critical condition of any origin develops due to the failure of the main components of the detoxification systems: monooxygenase, excretory and immune systems to utilise and eliminate both products of normal and disturbed metabolism and microbial toxins [10,15].



### Conclusions

Thus, endogenous intoxication is mainly due to the concept of multiple organ failure and there is consecutive failure of the heart, lungs, liver, kidneys and brain. In multiple organ failure syndrome, circulatory and respiratory disorders are important, occurring in 60% and 65% of cases, respectively. Metabolic homeostasis failure due to liver and kidney failure is as common as heart failure. In general, EI is based on the concept of its representation as a reflection of the consequences of disturbances in macrocirculation and microhemolymphocirculation, gas exchange and oxygen budget, immunity and anti-infective "protection" with a failure to manage the integration of these processes. In this case, metabolic disorders proceed in accordance with the nature of the damaging factor and the response of the macro- and microcirculatory system to it in accordance with the disruption of transport and extraction of oxygen by tissues, activation of the sympathetic-adrenal system. This leads to the syndrome of hypermetabolism, typical for the critical state - the need of tissues in various substrates providing compensatory-adaptive mechanisms of energy conservation, prevention of protein breakdown, reduced utilization of fatty acids, increased gluconeogenesis and glucose tolerance, intensification of endothelial permeability. In view of the above, the diagnosis of EI can be considered to be not a simple and not fully solved problem. Therefore, some researchers suggest using all possible indicators for endotoxemia diagnosis, counting dozens of samples and tests. Another direction in the diagnosis of endotoxemia is the choice of universal markers for diagnosing intoxication of any etiology, which hardly reflects the essence of the ongoing events. The development and investigation of new, effective methods of diagnosing endogenous intoxication of various etiologies is currently an urgent medical task.

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