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APPROACHES TO PHARMACOLOGICAL CORRECTION OF ENDOTHELIAL DYSFUNCTION ASSOCIATED WITH METABOLIC ENDOTOXEMIA

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Received on 03-06-2016

Accepted on 27-06-2016

Abstract

The article considers possible pathogenetic mechanisms of cardiovascular and metabolic diseases and potential ways of early prevention and correction them. A special place in the article have been paid to the role of proinflammatory cytokines and Toll-like receptor 4 type and a review of the main groups of drugs (monoclonal antibodies to proinflammatory cytokines and antagonists of Toll-like receptor type 4) for carrying out targeted high-tech treatment of metabolic endotoxemia .

Keywords: Endothelial dysfunction, Metabolic endotoxemia, Chronic inflammation, Comorbidity.

Introduction: In the modern view, a chronic low-grade inflammation is one of the leading pathogenetic component of the socially important chronic non-communicable diseases associated with endothelial dysfunction, such as atherosclerosis and arterial hypertension [1-3], preeclampsia [4], diabetes, obesity, chronic obstructive pulmonary disease [1, 5], chronic kidney disease [6]. A metabolic endotoxemia may be inducer of this inflammation.

Metabolic endotoxemia: biological role

Metabolic endotoxemia is an important aspect in the search for pathogenetic links and ways of pharmacological correction of cardiometabolic disorders. The growing interest of scientists to this problem is reflected in Figure 1.

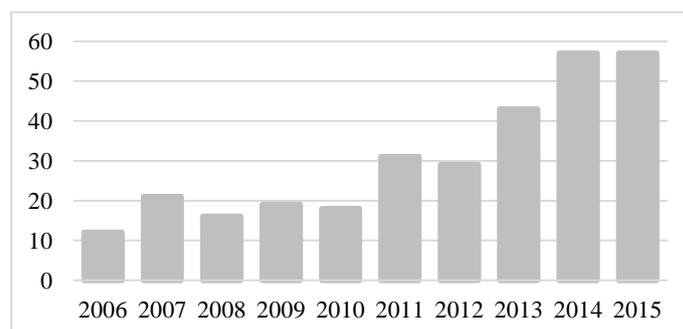


Figure 1. Dynamics of the number of publications on request «metabolic endotoxemia» in PubMed.

Overview of clinical studies on this issue is presenting in Table 1.

Table 1: The results of clinical studies of metabolic endotoxemia association with a variety of pathological conditions.

References	Participants	Assays	Correlation
Varma, M.C., 2016 [7]	Children (n = 60)	Systemic levels of tumour necrosis factor- α , interleukin-1 β , 6, 8 and 10, plasminogen activator inhibitor-1, soluble intercellular adhesion molecule type-1, matrix metalloproteinase-9, myeloperoxidase and vascular endothelial growth factor as well as endotoxin levels.	Inflammation, vascular injury and atherogenesis
Wong, V.W., 2016 [8]	Adults (n=920)	Endotoxemia(using the limulus ameocyte lysate), systemic levels of lipopolysaccharide-binding protein (LBP) and endogenous endotoxin-core antibody immunoglobulin G	Non-alcoholic fatty liver disease in the general population
Tremellen, K., 2015[9]	Women (n=45)	Systemic levels of LBP and follicular fluid interleukin – 6; progesterone	Plasma C-reactive protein and inflammation within the ovary, progesterone reduction.
Kallio, K.A., 2015 [10]	Adults (n = 2,452)	Systemic levels of LBP	Obesity, metabolic syndrome and coronary heart disease events
Liu, X., 2014 [11]	Adults (n = 2,529)	Systemic levels of LBP	Increased risk of developing metabolic syndrome
Hawkesworth, S., 2013 [12]	Middle-aged women (n=93)	Systemic levels of bacterial lipopolysaccharide, endotoxin-core IgM and IgG antibodies, interleukin-6	Obesity and diabetes
Mehta, N.N.,	Healthy human	Systemic levels of cytokines, C-	Adipose tissue

2012 [13]	volunteers (n=10)	reactive protein, insulin and glucose; serial whole blood & subcutaneous adipose tissue mRNA expression	inflammation and systemic insulin resistance in the absence of overt clinical response
Lassenius, M.I., 2011 [14]	Type 1 diabetic patients (n = 904); patients with IgA glomerulonephritis (n = 98); nondiabetic subjects (n = 345)	Serum lipopolysaccharide activity	Components of the metabolic syndrome (higher serum triglyceride concentration, earlier onset of diabetes, increased diastolic blood pressure)
van der Crabben, S.N.,2009 [15]	Healthy male volunteers (n=18)	Hepatic and peripheral insulin sensitivity	Peripheral and hepatic insulin sensitivity increase

Metabolic endotoxemia is a complex of pathological changes that occur in the body in two-three times increase in the level of circulating endotoxins [5]. Endotoxins are obligate structural component of the membrane of Gram-negative bacterium and having a lipopolysaccharide structure. Normally, about 5% of endotoxins intestinal microbiota enter the blood system and play an important role in support the normal function of the immune system (activating components of the inborn immunity), the liver and the sympathetic-adrenal system [1]. Increase in the circulating endotoxins level can be associated with classic risk factors for cardiovascular and metabolic diseases: an increase in carbohydrate and fat intake [1, 5, 16]; chronic stress [17], smoking and alcohol abuse [5], rheumatoid arthritis [1], chronic kidney disease [1, 16].

Pharmacological correction of the metabolic endotoxemia and chronic low-grade inflammation

The increase in the number of patients with comorbid disorders, namely cardiovascular disease, may be associated with common pathogenetic components of cardiovascular disease formation, such as metabolic endotoxemia, chronic low-grade inflammation and endothelial dysfunction [18-21]. Such a close pathogenetic relationship of these diseases has led to the emergence of the term «cardiometabolic continuum» [22]. And the role of metabolic endotoxemia in the development of this condition allows us to call it a new cardiometabolic target for pharmacological correction and early prevention of cardiovascular disease, obesity and diabetes mellitus type II.

The search for such pharmacological targets has been started with medicines and biologically active additive that normalize the function of the gastrointestinal microflora: probiotics, prebiotics, pectin and polyunsaturated fatty acids [1, 23, 24]. Preclinical and clinical studies have shown that normalization of the gastrointestinal microflora contributes to the inhibition of growth of pathogenic microorganisms, reduce the intestinal permeability and immunomodulatory action. A close relationship of metabolic endotoxemia and cardiovascular disease has allowed to continue the search among the known drugs with endothelium protective action. Reducing the severity of endotoxemia and low-grade chronic inflammation has been identified with the use of statins and angiotensin-converting enzyme inhibitors [1]. Pressing issue is to study endothelium protective action of macrolides in the pathology [25] and combined pharmacotherapy endothelial dysfunction, associated with metabolic endotoxemia and low-grade chronic inflammation [26-32].

Targeted therapy

A promising direction of experimental and clinical pharmacology is a targeted therapy. To identify potential targets, it is necessary to consider the sequence of formation of physiological and pathological changes in the human body in response to the entry of endotoxins into the systemic circulation.

Endotoxins realize their effects through activation of innate immunity receptors – Toll-like receptors [5, 6]. Receptor binding leads to activation of nuclear factor NF- κ B, which stimulates the transcription of genes encoding the synthesis of proinflammatory cytokines (tumor necrosis factor- α , interleukin-6, interleukin-1 β) [33].

Proinflammatory cytokines are one of the potential targets for pharmacological correction. The effectiveness of high-tech targeted therapy with monoclonal antibodies to proinflammatory cytokines (interleukin-6 and interleukin-1 β) is currently not only a promising area of rheumatology and oncology, but also occupies an important place in the treatment and prevention of cardiovascular and metabolic diseases. So, the effectiveness of monoclonal antibodies to proinflammatory cytokines to reduce the inflammatory response and normalization of metabolic parameters in atherosclerosis, metabolic disorders, comorbid disorders has been showed in clinical studies [34-36]. A potential mechanism for the effectiveness of this group of drugs may be associated with a decrease in inflammatory response associated with metabolic endotoxemia and normalization of endothelial function by reducing the negative effects of proinflammatory cytokines on the vessel wall.

Toll-like receptor can be another potential target for the development and creation of new groups of drugs. As the lipopolysaccharides cause the activation of 4 subtypes of these receptors, we will focus on pharmacological groups,

inhibiting this receptor and, thus, depress the cascade activation of the nuclear factor NF- κ B and resulting in the elimination of the imbalance effects of the system of proinflammatory and anti-inflammatory cytokines.

Vildagliptin is a drug for the treatment of diabetes mellitus type II from the group of DPP-4 inhibitors and it's one of the known inhibitors of Toll-like receptors type 4. The ability of the dipeptidyl peptidase to dose-dependently increase the expression of Toll-like receptors type 4 and disrupt the balance of proinflammatory and anti-inflammatory cytokines has been showed in preclinical studies [37]. Vildagliptin neutralized the effects of the dipeptidyl peptidase, inhibited the activity of inducible NO synthase and had anti-inflammatory effects. Thus, it is necessary to further study the effectiveness of vildagliptin on the prevention and correction of metabolic endotoxemia and the normalization of the functions of the endothelium.

The opportunity of development and creation of innovative high-tech drugs have contributed to the emergence of TAK-242 (Resatorvid). It's the experimental drug, specific antagonist of Toll-like receptors type 4. Numerous preclinical studies have showed that TAK-242 significantly reduces the synthesis of the nuclear factor NF- κ B and proinflammatory cytokines in the immune competent cells, including reducing the inflammatory response of endothelial cells by acting on Toll-like receptors type 4 [38, 39]. Thus, it is possible to talk about a potential endothelium protective action of this drug. Besides, there were also identified other its effects, such as reduce the insulin resistance [40], reduce the frequency of cardiorenal complications at an elevated level of aldosterone [38], a neuroprotective effect in various neurologic diseases [41, 42]. The question remains about the effectiveness of TAK-242 in atherosclerosis and comorbid disorders.

Conclusion

Thus, the development, creation and further preclinical and clinical studies of targeted therapies for the correction of metabolic endotoxemia and associated with it endothelial dysfunction is an important step in the development and implementation of preventive services and correction of cardiovascular and metabolic diseases.

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