How Microbiome Impact on the Cardiovascular System
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Abstract
Humans are known to have constant symbiosis with microorganisms. Non-pathogenic microbial associations participate in vital functions of a host macroorganism and in maintenance of homeostasis. There is some data that our microflora may negatively influence on host macroorganism. Gut flora metabolism of phosphatidylcholine may promote cardiovascular disease [1,2]. However, Lactobacilli and products of their metabolism, being administered with a food, have positive impact on the cardiovascular system. Bioactive peptides produced during Lactobacillus fermentation are favorable for the treatment of hypertension. Probiotic bacteria have demonstrated the ability to reduce blood cholesterol by several mechanisms including assimilation of cholesterol. Metabolic products of lactobacilli may stimulate intracellular calcium signaling in cells of cardiovascular system. We should use complete potential of proteolytic activity of Lactobacilli, their ability to produce high concentration of favorable metabolites to receive unique pharmprobiotic products for prophylaxis and probably for the treatment of life-threatening diseases.

Keywords: Lactobacillus fermentation; Probiotics; Microbiome; Cardiovascular system; Vascular smooth muscle; Heart; Hypertension; Cholesterol

Abbreviation
ACE: Angiotensin-converting enzyme; CVD: Cardiovascular disease; SHR: Spontaneously hypertensive rats; TMAO: Trimethylamine-N-oxide

Humans are known to have constant symbiosis with microorganisms (microbiota/microflora). Non-pathogenic microbial associations participate in vital functions of a host macroorganism and in maintenance of homeostasis. Actually, microflora may be considered as an endocrine organ of a host macroorganism[3]. It has morphokinetic influence, participate in a metabolic activity and produce biologically active compounds, including important neuromediators regulating mental activity of human, such as glutamate and γ-aminobutyric acid [3].

The indigenous microflora in duodenum intestinal one, colonizing the sites of macroorganism and connecting to the external environment, is separated from the internal environment of a macroorganism by corresponding barriers. However, metabolic products of our microflora in gastrointestinal tract can rather easily penetrate into the blood, thereby influencing the macroorganism physiology.

There are some data that our microflora may negatively influence on host macroorganism. There is some evidence of microbe-induced human malignancies [4]. There is some interconnection of the gut violation and cardiac diseases [5]. Recently it was shown that gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. An increased plasma level of trimethylamine-N-oxide (TMAO), a product of the intestinal microbial metabolism of dietary phosphatidylcholine is associated with an increased rate of major adverse cardiovascular events. A major adverse cardiovascular event was defined as death, myocardial infarction, or stroke. Actually, fasting plasma TMAO levels predict the risk of incident major adverse cardiovascular events independently of traditional cardiovascular risk factors [1,2]. However, there is no the mechanistic link between TMAO and cardiovascular risk, because of an efficient kidney excretion mechanism [2]. An association between infectious organisms and atherosclerosis has previously been postulated [6]. However, anti-microbial therapy in preventing disease progression has been disappointing [6,7]. In their latest study, published in the New England Journal of Medicine [2] suggested therapeutic modulation of microbiota with functional food containing probiotics [8] and with nonsystemic antibiotics reduction of TMAO producing microbes. However, potency of probiotic to reduce TMAO is strain dependent [8]. Additionally, macroorganism may have non-toxic bacteria involved in its microflora, which are able to reduce TMAO. For example, E.coli TMAO reduction was associated with an anaerobic respiration [9].

Authors [2] recommend avoiding excessive consumption of dietary phosphatidylcholine and choline. Choline intake can be reduced with a vegetarian or high-fibre diet, but choline is a semiessential nutrient, so should not be entirely eliminated from the diet [2].

I think that consumption of non-fat food fermented with Lactobacilli may be effectively used for prophylaxis of cardiovascular disease. Lactobacilli and products of their metabolism, being administered with a food, have positive impact on the cardiovascular system [10]. Lactobacilli are able to produce biologically active peptides inhibiting Angiotensin-
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Converting Enzyme (ACE). Hypertension arises from the conversion of Angiotensin-I to the potent vasoconstrictor Angiotensin-II by the ACE. Dairy products fermented with Lactobacilli contain bioactive peptides known to inhibit the activity of ACE and thus alleviate hypertension. Oral administration of Calpis sour milk to spontaneously hypertensive rats (SHR) was able to lower systolic blood pressure [11]. Similar results were seen with oral administration of milk fermented with L. helveticus CP790 [12]. Studies in humans have shown that in persons who fed milk fermented with Lactobacilli a significant lowering of blood pressure was observed [13,14]. Thus, bioactive peptides produced during Lactobacillus fermentation are favorable for the treatment of hypertension. The ACE-inhibitory peptides produced during the fermentation of milk are already on the market, such as Calpis (Calpis Co., Ltd., Japan) and Evolus® (Valio, Finland) [15].

Hypertension is often associated with hypercholesterolemia or lipid abnormality and obesity [16]. Hypercholesterolemia is another significant risk factor for cardiovascular disease. Cholesterol is depositing in the arteries restricting blood flow to the heart. Probiotic bacteria have demonstrated the ability to reduce blood cholesterol by several mechanisms including assimilation of cholesterol [17], binding cholesterol and bile acids to the cell surface thus inhibiting absorption from the small intestine [18], and suppression of bile acid absorption by deconjugation of bile salts by the bacterial bile salt hydrolase activity [19,20] and may reduce oxidized low-density lipoproteins [21], thereby reducing cardiovascular complications. Cholesterol-lowering effect of probiotics was observed in hypercholesterolemic hamsters [22] and in rat [23]. In humans, hypercholesterolemic patients fed probiotics yogurt containing L. acidophilus and B. lactis were able to reduce their cholesterol levels compared to cohorts who consumed ordinary yogurt [24, 25]. Nevertheless, some authors did not observe cholesterol-lowering effect of probiotics [15].

At last, administration of Probiotics and products of their metabolism improves gastrointestinal barrier, thereby reducing complications in patients with chronic heart insufficiency [5]. Administration of Probiotics in intensive care units improved the immunity state, decreased overall mortality, and reduced such symptoms as diarrhea and sepsis [26].

At the cellular level it was shown that some products of a bacterial fermentation and organic acids, such as lactate, acetate, propionate, and butyrate caused contraction of colon smooth muscle via calcium influx into the cells [27]. It was shown that a bacterial supernatant E. coli Nissle 1917 increases colon contraction via non-identified metabolites in addition to acetate [28]. However, there is the data showing that acetate, propionate and butyrate do not increase intracellular calcium in colon smooth muscles [29]. Recently, it was shown that Lactobacilli are able to increase intracellular calcium in cardiomyocytes, thereby increasing contractility of myocardium [30], in contrast to bacterial DNA and RNA of pathogenic microorganisms (S. aureus and E. coli) and LPS, which suppressed contractility of rat cardiomyocytes significantly [31]. In neurons probiotic metabolic products stimulated protein kinase-C activity and partly activated ryanodine receptors [32]. In vascular smooth muscles probiotic metabolic products also stimulated protein kinase C [33], stimulated heart mitochondria respiration and exerted a mild uncoupling effect on electronic transport and oxidative phosphorylation in mitochondria [30].

Earlier it was shown that intravenous administration of the cultural milieu of lactic bacteria was able to protect myocardium from ischemia [34]. From the data provided it is clear that components of the cultural solution of Lactobacillus bulgaricus-51 cause hypotension, poorly influencing heart beating [34]. These data are in accordance with our experiments, in which lactobacilli can suppress considerably the thapsigargin-induced calcium influx in vascular smooth muscle cells [30]. In the conditions of sepsis, steady hypotension is observed and the agonist-induced calcium influx is considerably suppressed, which worsen the situation. Endotoxins also inhibit both phases of the calcium response considerably, namely, calcium release from intracellular stores and, to a great extent, agonist-induced calcium influx in endothelial cells of blood vessels [35]. Thus, during sepsis, when considerable bacterial translocation is observed, a large amount of lactic bacteria in the blood may aggravate a septic disease by increasing hypotension.

Despite the fact that lactic bacteria practically do not cause infectious diseases, nevertheless, there are some data where Lactobacillare associated with cardiovascular infections [36]. Moreover, it was shown that after single intraperitoneal injection of the Lactobacillus caseicellular extract in mice, the inflammation of coronary arteries, similar to the Kawasaki disease, is developed [37]. In Europe, North America, and Japan the Kawasaki disease is considered to be the main reason of the acquired cardiovascular sickness in children [38].

However, various fermentative products of Lactobacilli have long save history of administration for thousands of years, in the form of fermented milk and vegetable products such as yogurt and pickles [39]. Such low fat fermented products may be used for the prophylaxis of some cardiovascular diseases, mentioned above. The problem is that yogurts at modern market generally contain high amount of carbohydrates. Consumption of the latter has been shown to increase the risk to develop CVD [40]. Thus, positive effect of fermented probiotic products may be annihilated, if not more, by negative effect of carbohydrates.

Fermentation of food products is very promising method of receiving biologically active natural products, which have positive impact on the cardiovascular system. Such products contain metabolites of proteolytic activity of fermenting bacteria. There are huge fermentative products: Bulgarian yogurt, kefir, koumiss, Italian cheeses, Swedish and Finnish fermented milk, Russian ryazhenka and prostokvasha, Sour Cream, French Creme fraiche, etc. National food of Japan, New Zealand, Africa (cassava) and many othersmost fermented food products, such as yogurt, fermented beverages or juices and cheese, are taken only through the first stage of fermentation, intended simply to pre-digest or
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preserve the food (with organic acids, etc. produced by bacteria), while most organic matter remains in complex form. We should use complete potential of proteolytic activity of Lactobacilli, their ability to produce high concentration of favorable metabolites to receive unique pharmpriodic products for prophylaxis and, probably, for the treatment of life-threatening diseases.

References


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