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INFLUENCE OF INTESTINAL MICROBIOTA ON THE METABOLISM OF MAIN CARDIOTROPIC DRUGS

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ВЛИЯНИЕ МИКРОБИОТЫ КИШЕЧНИКА НА МЕТАБОЛИЗМ ОСНОВНЫХ КАРДИОТРОПНЫХ ПРЕПАРАТОВ

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The intestinal microbiota is one of the most important pathogenetic links in the development of cardiovascular diseases. Every year the world scientific community finds new interactions at the level of signaling molecules, metabolites and microorganisms, identifying more and more patterns and cause-and-effect relationships which indicate the commonality of the intestinal microbiota (GM) and cardiovascular diseases. The state of the host's intestinal community, its qualitative and quantitative composition, directly and indirectly affects the fundamental pathogenetic mechanisms of the development of cardiovascular diseases.

Despite the fact that there are scientifically based methods of treatment, cardiovascular diseases remain the leading cause of death in the world. This phenomenon is partly due to wide variations in individual response to cardiovascular drugs. The pharmacological effects of cardiotropic drugs are quite different even within groups of patients comparable in age and gender. Every year intestinal microbiota is more and more evident to be responsible for this intraspecific variability.

Gut microbes influence drug metabolism in several pharmacokinetic ways, and conversely, drugs can have significant effects on the microbiome and therefore pharmacodynamic processes. Drugs can alter the gut microenvironment and microbial metabolism, influence bacterial growth, thereby changing the composition and functions of the microbial community.

One of the most important functions of GM, related to “intestinal-cardiovascular system”, is participation in the metabolism of major cardiotropic medications, such as digoxin, statins, ezetimibe, antithrombotic drugs, calcium channel blockers (CCBs), beta blockers (BB), gliflozins and inhibitors of the renin-angiotensin-aldosterone system (RAAS).

Keywords. Gut microbiota, alpha diversity, beta diversity, short-chain fatty acids, statins, ezetimibe, gliflozins, *Bacteroides*, *Firmicutes*.

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Микробиота кишечника является одним из важнейших патогенетических звеньев в развитии сердечно-сосудистых заболеваний. С каждым годом научное мировое сообщество находит новые взаимодействия на уровне сигнальных молекул, метаболитов и микроорганизмов, выявляя все больше закономерностей и причинно-следственных связей, указывающих на общность микробиоты кишечника и сердечно-сосудистых заболеваний. Состояние кишечного сообщества хозяина, его качественный и количественный состав напрямую и опосредованно влияет на фундаментальные патогенетические механизмы развития кардиоваскулярных заболеваний.

Несмотря на существование научно обоснованных методов лечения, сердечно-сосудистые заболевания остаются ведущей причиной смерти во всем мире. Частично этот феномен обусловлен широкими индивидуальными различиями в реакции на сердечно-сосудистые препараты. Фармакологические эффекты кардиотропных препаратов проявляются по-разному у людей, страдающих от сердечно-сосудистых заболеваний, даже внутри сопоставимых по возрасту и полу групп. С каждым годом появляется все больше данных о том, что за эту внутривидовую изменчивость ответственна микробиота кишечника.

Кишечные микробы влияют на метаболизм лекарств посредством нескольких фармакокинетических путей, и наоборот – лекарства могут оказывать значимое влияние на микробиом и, следовательно, на фармакодинамические процессы. Лекарственные препараты могут изменять микроокружение кишечника, микробный метаболизм и влиять на рост бактерий, тем самым изменяя состав и функции микробного сообщества.

Одной из важнейших функций микробиоты кишечника, представляющей интерес в плоскости «кишечник – сердечно-сосудистая система», является участие в метаболизме основных кардиотропных препаратов, таких как дигоксин, статины, эзетемиб, антитромботические препараты, блокаторы кальциевых каналов (БКК), бета-блокаторы (ББ), глифлозины и ингибиторы ренин-ангиотензин-альдостероновой системы (РААС).

Ключевые слова. Микробиота кишечника, альфа-разнообразие, бета-разнообразие, короткоцепочечные жирные кислоты, статины, эзетимиб, глифлозины, *Bacteroides*, *Firmicutes*.

INTRODUCTION

Despite the existence of evidence-based treatments, cardiovascular disease remains the leading cause of death worldwide. This phenomenon is due in part to wide individual differences in response to cardiovascular drugs. For example, genetic variations in metabolic enzymes such as cytochrome P-450 have been shown to alter the metabolism, transport, and even the site of drug application and can be used to predict individual responses, personalizing drug therapy [1; 2].

The pharmacological effects of cardiotropic drugs manifest themselves differently in people suffering from cardiovascular diseases, even within age- and gender-matched groups. Every year, more and more data are emerging that the intestinal microbiota (IM) is responsible for this intraspecific variability.

Gut microbes influence drug metabolism through several well-known pharmacokinetic pathways, including the production of microbial enzymes that transform drug molecules, the production of microbial metabolites that interfere with drug metabolism, the alteration of inflammatory pathways that alter host gene expression, and the modification of host genes or enzymes that metabolize drugs [3]. Conversely, drugs can have significant effects on the microbiome and, consequently, on pharmacodynamic processes. Drugs can alter the gut microenvironment, alter microbial metabolism, and influence bacterial growth, thereby altering the composition and function of the microbial community.

One of the most important functions of MC, which is of interest in the "gut – cardiovascular system" plane, is participation in the metabolism of the main cardiotropic drugs, such as digoxin, statins, ezetimibe, antiplatelet agents, anticoagulants, calcium channel blockers (CCB), beta-blockers (BB), gliflozins and renin-angiotensin-aldosterone system (RAAS) inhibitors [4–6].

ACETYLSALICYLIC ACID

A large number of studies have found that antibiotic use can alter the pharmacological effects of aspirin. These changes are due to the ability of the gut microbiota to metabolize acetylsalicylic acid, converting it into an intermediate substance, salicylic acid. The first studies [7] showed a connection between the increase in the antithrombotic activity of aspirin in rats and the intake of ampicillin. Limiting the intestinal microbial landscape changed the pharmacokinetics of acetylsalicylic acid. Antibacterial therapy significantly reduced the activity of intestinal microbial metabolism and thereby prolonged the bleeding time in rats receiving aspirin. These data suggest that concomitant use of antibiotics and antiplatelet agents may mutually modulate metabolism and pharmacokinetics by suppressing the metabolic activity of intestinal microbiota, which may enhance therapeutic efficacy. Another study found that rats given aspirin and amoxicillin had reduced counts *of Helicobacter pylori* and *Prevotella copri*. These parameters affected metabolic activity by reducing the rate and amount of aspirin converted to the metabolite salicylic acid [8], which in turn led to increased plasma aspirin concentrations. In 2020, Zhao et al. found that *Lysinibacillus sphaericus* affected the bioavailability of aspirin by destroying it [9]. Germ-free mice fed *L. spaericus* had lower plasma aspirin levels than controls. The study [10] found that the type of medication taken has a much greater impact on the gut microbiome than the amount of medication taken. NSAIDs, particularly aspirin, were particularly associated with distinct microbial populations. Four operational taxonomic units (OTUs) (*Prevotella, Bacteroides, Ruminococcaceae, Barnesiella*) distinguished aspirin users from nonusers.

CLOPIDOGREL

Clopidogrel was nominally associated with multiple gut microbiota profiles in the United Kingdom Twins cohort, suggesting potential interactions between clopidogrel and the gut microbiome [11]. In another large population metagenomic analysis, clopidogrel was classified as a class of platelet inhibitors that was associated with increased microbial diversity. Finally, metabolomic analysis of plasma metabotypes (groups of metabolically similar metabolites) revealed a potential role of dysbiotic MC in inducing adverse drug events causing high platelet reactivity, which hinders the achievement of therapeutic outcome. Plasma metabotypes contained metabolites associated with dysbiotic MC, such as choline, trimethylamine, and L-phenylalanine. Although high platelet reactivity during treatment is multifactorial, it is associated with gut microbiome dysbiosis [12].

STATINS

The efficacy of statins has been demonstrated in numerous randomized trials, but there is evidence that their use increases the risk of developing type 2 diabetes [13]. Type

2 diabetes is a multifactorial disease, and recent studies have highlighted the importance of the gut microbiome in its development [14]. A study investigating statin treatment in a mouse model revealed profound changes in the gut microbial composition. The composition of the microbial landscape of the microbiota was altered, increasing the proportion of *Bacteroides* and decreasing the presence of the gram-positive phylum *Firmicutes*. This shifts the microbiota toward a higher energy production capacity (from butyrate to acetate, lactate, and succinate), similar to what is observed in MC associated with diet-induced obesity [15]. Statin therapy, in addition to its primary effect of inhibiting HMG-CoA reductase, is supported by a number of pleiotropic properties. On the one hand, there is a growing literature demonstrating a reduced risk of bacterial infection in patients taking statins. Retrospective studies have shown that statins can reduce mortality in patients with pneumonia and sepsis, and reduce the risk of postoperative infections [16]. One study in hospitalized patients found a reduced risk of developing Clostridial C. *difficile* (a member of the *Firmicutes* phylum) infection in those taking statins [17]. Atorvastatin increased bacterial diversity in rats fed a high-fat diet compared with levels observed in controls fed a normal diet [18]. Conversely, MC has been shown to influence the cholesterol-lowering effect of atorvastatin. In antibiotic-induced microbiome-depleted mice, the lipid-lowering effect of atorvastatin was reduced and the expression of genes regulating cholesterol levels in the liver and intestine (*Ldlr, Srebp2, and Npc111*) was altered [19]. In addition to the effects on cholesterol levels, mouse models show changes in intestinal bile acid levels that the authors suggest are related to MC. Bacteria are required to enzymatically catalyze bile acid deconjugation so that bile can be passively absorbed from the intestine into the systemic circulation [20]. In hypercholesterolemic humans treated with atorvastatin, the drug helped restore the relative abundance of several dominant and important taxa, such as *Faecalibacterium prausnitzi* and *Akkermansia muciniphila*, which were significantly reduced at baseline in hypercholesterolemic individuals [21]. Incubation of lovastatin with human and rat fecalase preparations revealed four metabolites: the demethylbutyryl metabolite, the hydroxylated metabolite, the active metabolite of the hydroxy acid M8, and the hydroxylated M8 [22]. In rats concomitantly treated with antibiotics, the systemic concentration of the active metabolite M8 was lower. These results suggest that gut microbes may be involved in the metabolism of lovastatin, and antibiotic treatment may reduce the biotransformation of orally administered lovastatin by gut bacteria. In a mouse study, rosuvastatin treatment significantly affected bile acid metabolism [23]. In rats, dysbiosis was associated with decreased efficacy of rosuvastatin, as reflected by a smaller reduction in blood LDL levels [24]. These studies showed that rosuvastatin affects the microbial composition of the gut, prompting further studies in humans. The first study found that the efficacy of rosuvastatin was associated with microbial variations in the community composition. Sixty-four patients with hyperlipidemia were treated with rosuvastatin (10 mg / day) and divided into rosuvastatin responders and non-respon-

ders based on blood lipid levels above or below normal. The gut microbiome from collected feces differed significantly, with rosuvastatin responders having higher abundance of *Firmicutes*, butyrate-producing bacteria such as *Ruminococcaceae, Lachnospiraceae, Clostridiaceae*, and lower abundance of *Bacteroidetes* [25]. The second study presents conflicting data, as faecal samples from a randomized control trial of 66 participants receiving rosuvastatin (20 mg / day) or placebo did not reveal any significant changes in microbial composition. However, changes in the expression of microbial genes encoding proteins associated with the choline / betaine – TMA pathway were detected, suggesting that rosuvastatin affects gut microbial metabolism [26]. In a systematic evaluation of small molecules, Kaddurah-Daouk et al. examined the correlation between baseline metabolite levels and therapeutic efficacy of simvastatin in 100 subjects to predict response to statin treatment [27]. The results indicate that microbial-derived secondary bile acids, including taurocholic and glycocholic acids, as well as coprostanol, can predict the LDL-lowering effect of simvastatin, indicating a microbial effect on the gut. Coprostanol, used as a biomarker for the presence of human feces, is produced by intestinal bacteria by hydroxylation of cholesterol [28]. Results suggest that patients with higher levels of coprostanol-producing bacteria before treatment will respond better to statins. In addition, simvastatin appears to have antibacterial activity against many Gram-positive bacteria such as staphylococcus and streptococcus, making the drug a good candidate for future studies as an antimicrobial resistance breaker [29].

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Comparative use of captopril and lisinopril in an experiment on mice allowed us to establish that animals that received captopril for a week had a significant decrease in body weight. Weight loss is associated with changes in their intestinal microbiome with a predominance of the anaerobic metabolic pathway. In the work [30], captopril therapy decreased vascular wall permeability, reduced fibrosis, caused reverse remodeling of the muscle layer, and even partially restored the length of intestinal epithelial villi in rats with spontaneous and angiotensin-II-induced arterial hypertension. In animal experiments, benazepril increases the species diversity of microflora, bringing its composition closer to the normoflora, in contrast to the flora characteristic of "hypertensive" rats. However, enalapril therapy in the experiment did not reveal reliable differences in the intestinal microbiome of rats, but at the same time, a decrease in the concentration of the toxic metabolite TMAO, which is associated with an increase in cardiovascular risk, was recorded in blood samples. Captopril was shown to modulate the intestinal microbiota in rats. Another study in rats revealed an increase in the number of bacteria during captopril treatment even after its discontinuation [31]. The authors suggest that these results demonstrate that long-term exposure to captopril is associated with changes in MC. In addition to the long-term effect of captopril, another study in rats shows that maternal treatment with this drug reduces hypertension in male offspring by altering microflora, particularly the orders *Clostridiales* and *Erysipelotrichales* [32]. Thus, captopril has been shown to affect MC with

long-lasting and potentially transgenerational effects. Similar changes in MC were observed in a rat study with benazepril, where the authors noted changes in the ratio of *Firmicutes* to *Bacteroidetes*, as well as *Coccus* to *Bacillus* [33].

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers as a class have evidence of effects on MC. Telmisartan reduced colonic inflammation in rats with colitis [34]. The finding that telmisartan reduced colonic inflammation led to investigation of the drug's effects on atherosclerosis [35]. In mice, a high-fat diet was associated with lower colonic microbial diversity. However, telmisartan treatment restored the induced dysbiotic *Firmicutes* / *Bacteroidetes* ratio, leading to subsequent beneficial effects. In fact, telmisartan was more effective than the probiotic *Lactobacillus rhamnosus* in altering MC. Candesartan and losartan treatment in hypertensive mice similarly restored the altered *Firmicutes* / *Bacteroidetes* ratio and protected against hypertension-induced intestinal pathophysiological changes [36]. Irbesartan improves stress-induced microbiota changes. Stress markedly reduces the percentage of faecal taxa, whereas irbesartan treatment corrects these changes in community structure [37]. In contrast, olmesartan has a unique side effect called sprue-like enteropathy, which is characterized by chronic diarrhea, weight loss, and biopsy revealing villous atrophy and mucosal inflammation. In patients followed at the Mayo Clinic, discontinuation of olmesartan improved symptoms and resulted in histologic recovery [38]. It is unclear why the gastrointestinal effects of olmesartan differ from those of other ARBs such as telmisartan, candesartan, losartan, and irbesartan, which have beneficial effects on MC.

CALCIUM CHANNEL BLOCKERS

Amlodipine is a dihydropyridine calcium channel blocker that is commonly prescribed for the treatment of hypertension and coronary heart disease. A study by Yoo et al. reported the metabolism of amlodipine upon incubation with human fecalase, indicating the involvement of gut microbiota in amlodipine metabolism [39]. Unchanged amlodipine was reduced by 9 % upon 24-hour incubation with human fecalase. In addition, it was found that antibiotic administration can increase the bioavailability of amlodipine in rats. At ampicillin doses of 10 and 20 mg/kg, the concentration of amlodipine in plasma increased by 42 and 133 %, compared with the corresponding data of the control group. Amlodipine itself also has bactericidal properties. Of the 504 bacterial strains tested, amlodipine had varying degrees of antimicrobial activity, most notably against *Staphylococcus aureus, Vibrio cholerae, Vibrio parahemolyticus*, *Shigella* species, *Salmonella* species, and *Bacillus* species [40]. Song et al reported a reduction in gastrointestinal side effects with amlodipine plus probiotics. Amlodipine, like bacterial dysbiosis, is associated with diarrhea. The known side effect and the association between dysbiosis and diarrhea prompted the authors to investigate amlodipine and probiotics in a rat model. The probiotic mixture alleviated intestinal complications and induced changes in MC composition in rats. An et al. investigated what metabolite changes occurred due to induced changes in microbiota composition in mice treated with amlodipine compared

to amlodipine and probiotics [41]. The lipid metabolic profile was altered in mice treated with amlodipine, with cholesterol, phosphatidylcholines, and triglycerides with a high number of double bonds increased in total. The amlodipine group also showed a reduction in triglycerides with few double bonds. The authors believed that amlodipine alters the composition and balance of metabolites produced by bacteria that ultimately contribute to gastrointestinal side effects. Similarly, nifedipine and nimodipine, the calcium channel blockers, have been investigated for antimicrobial properties. Due to the high permeability of nimodipine through the gastrointestinal tract, the study examined its bacterial degradation in dilutions with human feces. Using colonic bacteria as a model, Vertzoni et al. observed rapid degradation of nimodipine in feces [42]. More recently, Zhang et al. demonstrated that gut microbes are involved in the metabolism of nifedipine *in vitro.* After 24-hour incubation in rat fecal suspensions, nifedipine concentrations decreased by more than 50 %, indicating that gut microbes are involved in the metabolism and biotransformation of nifedipine and nimodipine.

AMIODARONE

Organ toxicity, induced by amiodarone, is potentially serious due to the long half-life of the drug, so its bioavailability is of particular importance. Amiodarone has been shown to affect typical strains of intestinal bacteria. Co-administration of the probiotic *Escherichia coli* Nissle 1917 demonstrated an increase in the bioavailability of amiodarone (43 %) and its metabolite N-desethylamiodarone in rats [43]. The authors suggest that the modulation of amiodarone metabolism is associated with the administration of *E. coli* Nissle 1917, resulting in better absorption of the drug in the gastrointestinal tract. Another study showed that amiodarone has bactericidal activity *in vitro* against pathogenic human strains such as *S. epidermidis*, *E. coli*, and *Klebsiella* [44]. Both studies reflect that amiodarone therapy has a microbiome component, albeit through different mechanisms.

BETABLOCKERS

Metoprolol is the most commonly prescribed beta-adrenergic blocker used to treat cardiovascular diseases including coronary artery disease, hypertension and heart failure. Metoprolol is metabolized via a saturable pathway, namely hepatic cytochrome 2D6 (CYP2D6). This drug is primarily metabolized to O-desmethylmetoprolol and α-hydroxymetoprolol. Approximately 85 % of metoprolol and related metabolites are excreted in the urine, making it an ideal target for monitoring. Brocker et al. analyzed the urine of patients taking metoprolol using metabolomics data. They found increased levels of methyluric acid, hydroxyhippuric acid, and hippuric acid in the urine of hypertensive patients after oral metoprolol administration. These three compounds are considered to be gut microbiome metabolites [45]. Hippuric acid is formed by the conjugation of glycine and benzoic acid by gut microbial metabolism, and hydroxyhippuric acid is a microbial end product, both of which arise from the metabolism of polyphenols in the gut microbiota. These compounds reflect the composition of the gut microbiota [46]. This indicates that long-term metoprolol treatment may affect the microbial composition and diversity of the gastrointestinal tract.

Moreover, metagenomic analysis of feces samples from patients with atherosclerotic cardiovascular disease showed that metoprolol treatment was positively correlated with changes in the metagenomic linkage group (MLG) [47]. Therefore, the drug may affect the microbiome by affecting gene expression in the gut microbiome. As mentioned above, metoprolol therapy appears to alter the gut microbiome, indicating that metoprolol may directly or indirectly influence the composition of the gut microbiota.

EZETEMIBE

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption that acts on the brush border of the small intestinal mucosa, specifically binds to the C1-like Niemann-Pick transporter 1 on the intestinal mucosa and selectively inhibits the absorption of exogenous cholesterol. This drug is currently the second line in the treatment of dyslipidemias accompanied by elevated LDL levels [48]. In a study by Jin Jin et al., a group of mice were exposed to a high-fat diet for 20 weeks with and without ezetimibe. Ezetimibe intervention significantly reduced serum TC and HDL-cholesterol levels. In addition, after long-term treatment with the cholesterol absorption inhibitor, the alpha diversity of the gut microbiota was significantly reduced. Ezetimibe caused changes only in some low-abundance bacteria, which was expressed as a decrease in Proteobacteria and *Desulfovibrio* and an increase in *Bacteroides* [49].

GLIFLOZINS

The SGLT-2 class inhibits glucose reabsorption in the proximal convoluted tubule of the nephron, resulting in glucosuria and concomitant natriuresis. In addition to its well-known effects on glucose control in patients with type 2 diabetes, it has been shown to improve many conditions such as NAFLD, CHF independent of EF, and chronic kidney disease. In mouse studies, dapagliflozin, empagliflozin, and canagliflozin have shown beneficial effects on the microbiota, regardless of the underlying disease that is the primary indication for the drug [50–53]. The researchers used different categories of rats, ranging from mice fed a high-carbohydrate diet to animals with nephropathy, and this heterogeneity made it difficult to analyze the effects of SGLT-2 on the microbiota. In other animal studies, dapagliflozin treatment altered the microbial diversity in type 2 diabetic mice, particularly *Bacteroidetes* and *Proteobacteria*. Moreover, the *Firmicutes* to *Bacteroidetes* ratio was significantly lower ($p < 0.05$) in diabetic mice than in controls [54].

In a study [55], empagliflozin significantly altered the structure and composition of gut microbiota in patients with type 2 diabetes and cardiovascular risk factors after three months of treatment: empagliflozin was found to increase levels of short-chain fatty acid-producing bacteria such as *Roseburia, Eubacterium*, and *Faecalibacterium* species and to decrease levels of some harmful bacteria including *Escherichia-Shigella, Bilophila*, and *Hungatella*.

CONCLUSIONS

Knowledge gained from the synthesis of clinical studies demonstrates that the influence of the gut microbiota and its metabolites on the major classes of cardiotrophic drugs continues to be studied in depth. The characteristics of the individ-

ual's gut microbiota can be used as a factor to personalize therapy, directly influencing the choice of dose, a specific drug within a class, or even the class of drugs themselves.

Further studies of specific mechanisms that determine changes in intestinal diversity and biochemical iterations within the "intestinal" pharmacokinetics of the drug are needed. Managing the quantitative and qualitative composition of the intestinal microbiota and its metabolites may become a new therapeutic target and will allow direct and indirect influence on the prognosis of patients with cardiovascular diseases.

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