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Interaction of Bile Acids and Intestinal Microbiota and Its Role in the Etiology of Some Diseases of the Digestive System (Literature Review)

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Abstract: Bile acids (BA) are synthesized in the liver from cholesterol and enter the duodenum through the common bile duct. Participating in digestion, most of the BA are adsorbed in the terminal section of the small intestine into the blood again and enter the liver. A small part of the fatty acid (FA) from the small intestine enter the large intestine, where, in contact with microbiota, it changes its physical and chemical state, while simultaneously affecting the composition of the microbiota of this environment. Bile acids are synthesized in the liver from cholesterol and enter the duodenum through the common bile duct. Participating in digestion, most of the BA are adsorbed in the terminal section of the small intestine into the blood again and enter the liver. A small part of the BA from the small intestine enter the large intestine, where, in contact with microbiota, it changes its physical and chemical state, while simultaneously affecting the composition of the microbiota of this environment. Violation of the interaction between microbiota and fatty acids is the cause of the development of *Clostridioides difficile*, *Salmonella* Typhimurium infections, as well as inflammatory bowel diseases, type 1 diabetes, bronchial asthma, various skin diseases, metabolic syndrome, obesity, Parkinson's disease, schizophrenia and epilepsy. In this review, we tried to consider current literature data on the physiological and pathogenic interaction of the intestinal microbiota and BA metabolism in the liver-intestinal-liver chain and their participation in the etiopathogenesis of some diseases of the digestive tract.

Key words: Bile acids, gut microbiota.

1. Introduction

According to the prevailing ideas, the human body is a complex microecological system with evolutionarily established relationships with the microorganisms inhabiting it. It is an antagonist of pathogenic and opportunistic microbes, participates in the metabolic processes of the human body, biosorption and microbial transformation of toxic compounds, performs a morphokinetic function, participates in the immunobiological reactivity of the macroorganism, etc. One of the constituent parts of the microecological system of the human body is the microbiocenosis of the gastrointestinal tract (GIT). It has a complex structure and is represented by mucosal (parietal) and cavity (luminal, fecal) fractions, which differ from each other in quantitative and qualitative parameters.

The development and function of the human body is greatly influenced by the tissue environment, metabolic processes in its own cells and colonizing microbial commensals. Along with the course of normal physiological processes, the intestinal microbiota and its metabolites regulate several physiological processes and play an important role in maintaining normal physiological processes. The existing gut microbiota affects not only neighboring tissues, but also distant organs and tissues in the body, for example, through the brain-gut axis to the brain, through the liver-gut axis to the liver, as well as the immune and hormonal systems of the body [1]. At the same time, in turn, the organism itself re-forms the intraluminal microbiota. In this complex interrelated reaction, genetic features, specificity of the

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microenvironment and the dietary habits of the host play an important role [2]. In this process, the selective influence of the commensal microbiota remains poorly understood.

Inflammatory processes in the intestine are accompanied by a violation of the intestinal microbiota. In this aspect, various complex pathogenetic changes are associated with the disruption of microbiota metabolites and host tissue products [3]. However, the etiology of these pathological processes is multifactorial and they develop due to improperly functioning parameters [4, 5]. Therefore, a multifaceted host-microbiota interaction is critical to maintaining physiological homeostasis. An example of such an interaction is the frequent regulation of the same pool of intraluminal metabolites by host and microbiota enzymes [6]. Most physiological and metabolic processes require a synchronous interaction between the host and the microbiota. The biosynthesis of bile acids (BA) is a classic example of the general alternating enzymatic reactions between the liver and the microbiota: the liver synthesizes primary BAs, which are subsequently transformed into secondary FAs in the intestine under the influence of the microbiota. This circulation of fatty acids plays an important role in many physiological and pathophysiological processes in the liver-gut axis.

The aim of this work is to analyze the literature data on the role of the interaction of bile acids and intestinal microbiota in physiological and pathophysiological processes in the liver-gut axis.

2. Methods

About 250 articles on this topic available in PubMed resources were studied and analyzed, of which 40 sources are included in the review.

Bile acids are monocarboxylic hydroxy acids from the class of steroids; they are synthesized in liver peroxisomes from cholesterol [7] and excreted as bile into the duodenum, reabsorbed in the intestine, transported by the bloodstream to the liver, and reused in bile secretion. In the liver, fatty acids combined with glycine (Gly), taurine (Tau) or sulfate are called primary fatty acids. They consist of cholic acid (CA) and chenodeoxycholic acid (CDCA) or their tauro- and glycoconjugated versions. During the day, the total synthesis of primary bile acids is 400-600 mg/day. No more than 10% of the newly synthesized bile acids in the liver enter the intestine, the remaining 90% are the product of the enterohepatic circulation of bile acids (from the intestine to the blood and to the liver). Under the influence of intestinal microflora in the colon, secondary bile acids are formed from primary bile acids, such as deoxycholic, lithocholic, ursodeoxycholic, allocholic, etc. Deoxycholic acid, secreted by the liver as part of bile, is absorbed into the blood. Lithocholic acid is absorbed much worse than deoxycholic acid. The ratio of cholic, chenodeoxycholic and deoxycholic acids in human bile is normally 1: 1: 0.6.

Typically, 95% of primary CAs are reabsorbed in the terminal ileum and transported via the portal vein back to the liver (enterohepatic circulation); Primary fatty acids returned to the liver, inhibiting cholesterol biosynthesis, are used in the biosynthesis of fatty acids. At the same time, a small amount of primary fatty acids also pass into the large intestine, where, under the influence of some intestinal bacteria, by deconjugation, oxidation/epimerization, 7-α-dehydroxylation and esterification, they are converted into secondary fatty acids - deoxycholic acid (DCA), ursodeoxycholic acid (UDCA) and lithocholic acid (LCA) [8]. It should be noted that secondary FAs exhibit strong antimicrobial activity and cytotoxicity in the gut, regulating gut bacteria composition and host physiology [9]. The antimicrobial properties of CAs are enhanced by immunoglobulin A (IgA), located on the surface of the mucous membranes of the large intestine. Thus, both FAs and IgA, by inhibiting the growth and adhesion of bacteria, subsequently protect the biliary tract from

ascending infections. In addition, fatty acids remove bilirubin from the body with feces. Primary and secondary FAs, by activating the receptors of nuclear and plasma membranes (the nuclear farnesoid X receptor -FXR or the G protein-coupled receptor -TGR5), have a biological effect on the host cells [10]. These receptors control the synthesis and metabolism of fatty acids. However, the involvement of these receptors allows CAs to contribute to the regulation of glucose homeostasis, lipid metabolism, and energy expenditure [11]. In addition, CAs regulate immune responses by ligation of these two receptors, which are located at the interface between the host immune system and the intestinal microbiota. Both receptors are highly expressed on cells of the innate immune system, including macrophages, dendritic cells, and natural killer T cells (NKT) [12]. In particular, TGR5 and FXR regulate macrophage polarization and may also save mice from severe colitis [13].

Thus, the main functions of FAs include (a) emulsification and digestion of fat, (b) regulation and elimination of cholesterol, (c) antimicrobial action, and (d) removal of bilirubin from the body [14]. However, since there are many microbes that are resistant to bile, the antimicrobial action of bile (acid) selectively inhibits certain types of microbes, which subsequently affects the composition of the entire intestinal or biliary microflora [15, 16].

The digestive tract is inhabited by a diverse composition of multiple microorganisms that form mutually beneficial relationships with the host [17]. The specified microflora performs some enzymatic functions that are beyond the capabilities of the host. In turn, diet significantly affects the composition of the microbiota. Products produced by the gut microbiota are involved in homeostasis and affect host immunity through nutrient and metabolite dependent mechanisms. A change in the composition of the intestinal microbiota (dysbacteriosis) is the cause of many intestinal and extraintestinal disorders in the body.

In addition to the intestines, the gallbladder also has a complex microbiota, which is relatively less studied. However, unlike the gut, the biliary tract microbiota contains relatively low levels of Bacteroidetes, while Proteobacteria, Tenericutes, Actinobacteria, and Cyanobacteria are higher than in the gut. Both in the intestine and in the gallbladder, the composition of the microbiota can be disturbed [18]. One example of the regulation of the FA pool is the intervention of the microbial metabolism of the body. The biochemical reactions that occur, such as deconjugation, oxidation, 7-α-dehydroxylation, and esterification of FAs in the gut microbiota, can drastically alter their physicochemical properties and subsequently affect their function (including microbial toxicity) and intestinal absorption rates. For example, numerous enzymes present in all major types of bacteria, having an effect on FAs (deconjugation), enhance their reabsorption in the intestine, promote colonization of the intestine by microbiota, and can serve as a nutrient source of sulfur, nitrogen, and carbon [19].

In general, representatives of the bacteria Firmicutes, Clostridium or Eubacterium have 7-α-dehydroxylation activity. Primary fatty acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are converted to secondary fatty acids deoxycholic acid (DCA) and lithocholic acid (LCA) by 7-α-dehydroxylation. This process is quantitatively the most important and most physiologically significant conversion of fatty acids in the human body. At the same time, the content of deoxycholic acid can reach up to 25% of the total FA pool.

The impact of the gut microbiota appears to go beyond FA composition and biotransformation. In mice, intestinal sterility induced by antibiotic therapy is detected by a decrease in faecal excretion of fatty acids. At the same time, together with increased FA secretion and reabsorption from the intestine and a general change in the metabolic homeostasis of the host, the BA pool increases [20]. Under the influence of the microbiota, the fluidity of FAs, the permeability

and functions of cell membranes and membrane-bound proteins change. On the other hand, FAs cause DNA damage and oxidative stress, and also affect the formation of RNA and proteins [21].

The use of fatty acids promotes the reproduction of Firmicutes at the expense of Bacteroidetes in the intestine. Along with this, lower intraluminal levels of FAs help the growth of gram-negative bacteria, affect the integrity of intestinal epithelial cells and mucosal immune responses, and thus indirectly regulate the composition of microbial communities. Secondary FAs can also exhibit toxic effects and lead to the development of infectious, inflammatory or malignant diseases [22].

Disruption of normal interactions between FA and microbiota can lead to many functional disorders. However, the corollary-causal relationship between the compositional alteration of the gut microbiota and associated individual diseases remains unclear. However, dysbacteriosis is present in inflammatory bowel disease (IBD).

2.1 Infectious Diseases

The composition of fatty acids in the intestine is significantly affected by microbial metabolism. At the same time, products derived from the microbiota confer resistance to colonization of the intestinal mucosa against many pathogenic microbes. Usually, the composition of the microbiota is formed by the FAs themselves and the habitual diet [23]. It has been established that a decrease in the volume of secondary fatty acids leads to an increase in susceptibility to pathogenic bacteria.

Fatty food increases the primary concentration of fatty acids and creates the conditions for the subsequent colonization of the intestine by *Salmonella* enteritidis serovar Typhimurium (*S.* Typhimurium), as this flora adapts to bile, increases the expression of virulence genes and, thus, exhibits a much higher resistance to bile than intestinal microbiota.

Pathogenic strains of *Escherichia coli* (*E. coli*) have been used to trigger various bile resistance mechanisms, including enhancing gene responses to stress, promoting DNA repair or membrane damage, inducing efflux pumps, or activating toxin/antitoxin systems to remove compounds. bile [24].

The virulence of *Shigella flexneri* and *Shigella dysenteriae* is increased by bile in the small intestine before they reach the site of infection in the large intestine.

The life cycle of *Clostridioides difficile* (*C. difficile*), antibiotic associated diarrhea (AAD) pathogens, and spore-forming Gram-positive bacteria are significantly affected by bile and microbiota. Under the influence of antibiotic therapy, the commensal microbiota involved in the transformation of primary FAs into secondary FAs is destroyed. The latter, in turn, inhibit the germination of *C. difficile* spores into vegetative bacteria [25]. As a result, due to the accumulation of primary FAs, *C. difficile* spores germinate, bacteria replicate and produce enterotoxins that mediate colitis.

Clostridium (C.) scindens can actually convert cholic acid into toxic secondary fatty acids, deoxycholic acid [26]. Synthesized metabolites from host bile salts inhibit *C. difficile* and increase resistance to this infection.

An analysis of the literature data shows that the intestinal microbiota also modulates intestinal viral infections. For example, FA modification by commensal bacteria initiates a type III interferon response and subsequently inhibits norovirus infection of the proximal small intestine [27].

Based on the data obtained on primary and secondary FAs and their derivatives, they have recently been proposed as a therapy for SARS-CoV-2 infection due to their properties of inhibiting virus binding to host cells and suppressing the cytokine

storm caused by COVID-19 [28].

2.2 Inflammatory Bowel Disease (IBD)

Ulcerative colitis (UC) and Crohn's disease (CD) are characterized by immune-mediated inflammation in the gastrointestinal tract. Despite the absence of a generally accepted definitive etiology of these 2 chronic diseases, clinicians agree that both disorders are the result of a complex interaction of microbial, genetic, geographical and habitual factors, which leads to an imbalance in the interaction of symbiotic microorganisms, intestinal epithelium and the immune system.

Both in preclinical models of experimental enterocolitis and in people with IBD, intestinal absorption of fatty acids is impaired. At the same time, in patients with IBD, the altered content of fatty acids in the composition of faeces does not support remission [29].

An increase in the intraluminal FA pool in the colon often manifests as diarrhea. Importantly, restoration of the intestinal AD pool not only improves clinical symptoms, but also increases the number of regulatory T cells and reduces host susceptibility to inflammatory colitis [30]. Elevated levels of secondary FAs have also been associated with remission in UC patients after faecal microbiota transplantation. Thus, secondary FAs are associated with remission and improved clinical outcome of IBD, presumably reflecting a richer and more diverse microbiota.

2.3 Immune-mediated Liver Disease

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) progress slowly to obliterative fibrosis and eventually cirrhosis. Due to biliary obstruction, impaired bile flow alters the commensal gut microbiota, susceptibility to infection, and integrity of the intestinal epithelial layers [31].

In patients with PSC, elevated concentrations of taurolithocholic acid (a pro-inflammatory and potentially carcinogenic agent) accompany biliary dysbiosis.

Patients with both PSC and IBD show different correlations between microbiota and stool GI compared with IBD patients without concomitant PSC [32].

It has been proven that in contrast to patients with UC, in patients with PSC (without concomitant PSC), the relative number of Clostridiales II and the total bacterial diversity are lower. It is likely that microbial modifications of FAs alter the host's metabolism, which can lead to changes in immune signals through FA receptors and to modified immune responses.

Because microbial triggers play an important role in the pathogenesis of both diseases, altered FA compositions in PBC and PSC may allow even uncommon bacteria to proliferate and/or perpetuate ascending infections in the biliary tree.

Thus, there is strong evidence that microbial agents and/or changes in the gut/biliary microbiota, as well as an altered metabolite profile, including FAs, are involved in the pathogenesis of PBC and PSC.

Because pathogenic bacteria can use the bile duct as a route of infection and ursodeoxycholic acid (UCDA, one of the secondary bile acids) is the only drug currently available for the treatment of PBC, its mechanism of action may include antimicrobial activity against *C. difficile* infections [33].

2.4 Hepato-intestinal Carcinogenesis

It is well known that the gut microbiota affects the efficacy of tumor immunotherapy [34]. In addition, there is increasing evidence that FAs and gut microbiota contribute to gut and liver carcinogenesis [35]. Often, representatives of the genus Clostridiales are involved in these processes, presumably due to their ability to convert primary to secondary FAs by 7-α-dehydroxylation.

Cholecystectomy disrupts the outflow of bile into the intestine and enterohepatic circulation of bile and can cause dysbacteriosis [36]. The subsequent dysfunction of FA metabolism presumably puts

patients at an increased risk of developing colorectal cancer (CRC). Thus, the absence of a distinct intestinal microbiota contributed to the accumulation of secondary FAs in the intestinal lumen, which may be the leading cause of CRC incidence in patients with cholecystectomy. The subsequent absence of surfactant protein D, which is synthesized in the gallbladder, contributes to the manifestation of intestinal dysbacteriosis [37]. Secondary dysbacteriosis caused by GI for other medical reasons also contributed to intestinal carcinogenesis [38] and adenomatous polyps. In this context, primary FAs significantly inhibit cellular responses following exposure to Bacteroides fragilis toxin (BFT or fragilysin), a metalloprotease encoded by enterotoxigenic Bacteroides fragilis (ETBF) that (leads to oncogenesis in susceptible experimental mice) is abundant in the intestinal mucosa of patients with CRC. The probiotic Clostridium butyricum (butyrate-producing), inhibits gut tumor development by modulating Wnt signaling and gut microbiota [39]. Through cell cycle arrest and apoptosis, butyrate inhibits the proliferation of deoxycholic acid resistant colon cells. The question arises whether this is due to altered FA metabolism, which is currently unknown.

In order to remove Clostridium species, the use of antibiotics such as vancomycin promoted the accumulation of primary bile acid chenodeoxycholic acid (CDCA). CDCA triggers the production of the chemokine CXCL16 by sinusoidal liver endothelial cells, resulting in the accumulation of natural killer T lymphocyte cells.

In an experiment in mice, a change in the composition of the intestinal microbiota involved in the metabolism of bile acids contributed to the progression of hepatocellular carcinoma. A similar effect is observed in patients with non-alcoholic steatohepatitis [40].

3. Conclusions

According to the literature data, enterohepatic circulation of fatty acids along the intestine-liver axis is involved in the pathogenesis of many disorders. The use of antibiotics for the selective destruction of individual microbiota or FA sequestrants may be an alternative therapeutic option for the treatment of immune diseases of the liver, biliary tract and intestines. Thus, the choice of drugs, their duration of use, their bile permeability and their availability must be carefully evaluated, especially in connection with the fact that many types of microbes and their functions in maintaining immune tolerance are not yet well understood. It is necessary to carefully consider therapeutic regimens, identify targets and approaches that can be used to develop effective treatments for dysbiosis and disorders of bile acid metabolism.

Conflict of Interest

The authors state that there are no apparent or potential conflicts of interest in the work.

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