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Mini-Review

Function of Bile Acid Associated with Gut Microbiota

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ABSTRACT

The human gut microbiota involve in metabolism of carbohydrates, proteins and bile acids. Primary bile acids Cholic acid (CA) and Chenodeoxycholic acid (CDCA) are synthesized in the liver and conjugated with the amino acids glycine or taurine, stored in the gall bladder. Glycine and taurine conjugates of CA and CDCA are transformed into the secondary bile acids deoxycholic acid (DCA), lithocholic acid (LCA) and a small amount of urosodeoxycholic acid (UDCA) by microbiol actions. The bile acids have a unique relationship with the gut microbiota. Although a great deal of work has shown that different bile acids play different roles in maintaining the intestinal barrier according to their uniqueness, the underlying mechanisms are complex and need to be further studied.

Keywords: Gut microbiota; Primary bile acids; Secondary bile acids; Bio-Functions

INTRODUCTION OF BILE ACIDS

The human colonic microbiota is a large and complex microbial community, which involved in metabolism of carbohydrates, proteins and bile acids. It plays an important role in human health [1-3].The undigested dietary carbohydrates can be converted into the short chain fatty acids by gut microbial fermentation [2]. Human gut microbiota can produce metabolites by protein fermentation which have beneficial or harmful physiological effects on humans [3]. There is no evidence that a fraction of ingested lipids is degraded by the microbiota. However, ingestion of lipids is linked to bile acids secretion [4].

Bile flow is generated mainly by bile acids which converted into from cholesterol. About 50% of cholesterol in the body is excreted in the form of bile acids. This is the important way of cholesterol metabolism. Primary bile acids Cholic Acid (CA) and Chenodeoxycholic Acid (CDCA) are synthesized in the liver and conjugated with the amino acids glycine or taurine, stored in the gall bladder. Following a meal, they are secreted into the small intestine where they play an important role in digestion of fat and fat-soluble vitamins. About 97% of bile acids are reabsorbed in the ileum and return to the liver, 3% enter the large intestine. Glycine and taurine conjugates of CA and CDCA are transformed into the secondary bile acids deoxycholic acid (DCA), lithocholic acid (LCA) and a small amount of urosodeoxycholic acid (UDCA) by microbiol actions. According to the hydrophobic property, bile acids is in the order of LCA>GCDCA>DCA>CDCA>CA. Less hydrophobic bile acid CA has no cytotoxic effects [5].

Bile acids are known for their role in promoting lipid absorption and maintaining cholesterol balance, but they also act as messenger to regulate their own synthesis and play an antibacterial role to protect intestinal mucosa [6]. Bile acids also damage gut barrier. In conclusion, the interaction between bile acids and intestinal mucosa is unique. Each bile acid plays a different role due to its different physiological characteristics.

INTERACTION BETWEEN UDCA AND INTESTINAL MUCOSA

UDCA is a hydrophilic dihydroxycholic acid first found in bile duct of the Chinese black bear [7]. It is formed by differential isomerization of hydroxyl groups at C7 of primary bile acid CA under gut microbial activities [8,9]. It's a physiologic cholic acid that is low in humans. UDCA plays an important role in protecting gut barrier. It plays an immunomodulatory role by downregulating the secretion of IL-8 in intestinal epithelial cells [10]. It can protect colon epithelial cells from DCA [11]. In indomethacin-induced enteropathy, a model of Crohn's disease, UDCA has a protective effect by reducing epithelial permeability and decreasing oxidative stress [12-15]. When different concentrations of UDCA were applied to trinitrobenzenesulfonic acid-induced colitis, it was found that 50 mg/kg of UDCA had therapeutic effect, with the increase of s100A8, a neutrophil/monocyte marker, and augmentation of IL-1β expression [13]. Primary biliary cirrhosis patients who treated with UDCA has higher expression of BCRP an apical ATP-dependent efflux pumps of intestinal epithelia, than normal. BCRP plays a key role in extruding toxins and carcinogens from enterocytes into the intestinal lumen often after glucuronidation or sulfation. It is believed that UDCA stabilizes the small intestinal detoxification machinery through the upregulation of BCRP [14].

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INTERACTION BETWEEN DCA AND INTESTINAL MUCOSA

DCA is a potentially toxic secondary bile acid. It is converted from CA which is modified by deconjugation followed by dihydroxylation at C-7 by bacterial enzymes [15]. High concentration of DCA in the large intestine has been found to be particularly harmful to colon epithelial. Not only can DCA induce DNA damage in the colonocyte cell line HT29 [16], but also cause DNA damage and apoptosis in the HCT-116 human colon adenocarcinoma cells [17]. While DCA is suspected to have mutagenic and carcinogenic effects because of its genetic toxicity [18]. DCA in the physiological concentration range inhibited intestinal epithelial cell proliferation via an FXR-dependent mechanism that may include downstream inactivation of the EGFR/Scr/ERK pathway [19] and inhibited colonic epithelial wound healing by activation of FXR, with down regulation of CFTR expression [20]. In patients with collagenous colitis in remission, normal concentration of DCA exacerbated the already impaired mucosal barrier function by increasing bacterial uptake fourfold [21]. DCA is also a pro-inflammatory factor. One study has shown that colitis can be induced in rats by giving them a diet containing DCA [22].

INTERACTION BETWEEN LCA AND INTESTINAL MUCOSA

LCA is formed by deconjugation of CDCA followed by dihydroxylation at C-7 by bacterial enzymes [15]. Recent studies suggested that LCA can be used as one of potential biomarkers to assist diagnosis of disease [23]. LCA can destroy the integrity of colonic mucosal membrane and cause mucosal hyperplasia, but also has mutagenic effect. LCA and 3KCA can bind and transactivate the vitamin receptor, the pregnane X receptor and farnesoid X receptor. These receptors are highly expressed in the intestine. LCA regulate bile acid synthesis, metabolism and transport through its interaction with PXR, VDR and FXR [24]. One study suggested that PXR-mediated repression of NF-κB target genes in the colon is a critical mechanism by which PXR activation decrease the susceptibility of mice to DSS-induced IBD [25].While LCA is a direct agonist ligand for the human PXR receptor [26].

INTERACTION BETWEEN CDCA AND INTESTINAL MUCOSA

It has been evidenced that the genotoxicity of chenodeoxycholic acid CDCA has DNA damage [27]. CDCA can induce apoptosis and upregulate expression of COX-2 in a concentration- and time-dependent manner [28,29]. A research indicated that CDCA promoted tumor growth through decrease of MCT1- and SMCT1-mediated butyrate absorbed in intestinal epithelial [30]. Another study gave an information that in people with oral CDCA the colonic transit accelerated significantly, stool frequency increased and stool consistency decreased [31]. To Irritable bowel syndrome (IBS), some researchers found that the concentration of fecal primary BA was dramatically higher and the percentage of fecal secondary BA was lower in patients with diarrhea-predominant IBS (IBS-D) than in healthy subjects (HS) [32]. This may explain the reason of diarrhea in IBS caused by increase of concentration of primary BA.

BILE ACIDS AND GUT MICROBIOTA

Intestinal flora plays an important role in maintaining host health. It not only obtains nutrition and energy from food, but also produces some related metabolites such as bile acids that can regulate host metabolism. The biotransformation of bile acids is accomplished by the action of intestinal flora, which is mainly regulated by FXR receptor and TGR5 receptor related signaling pathways [33]. Similarly, bile acids can also affect the survival and growth of bacteria by regulating the expression of FXR receptors. There is interaction between bile acids and intestinal flora [34]. The level of intestinal bile acid is related to the overgrowth and inflammation of intestinal bacteria [35,36].

BA is one of the host factors that regulate composition of gut microbiota, and oral bile acids (BAs) induce changes in gastrointestinal bacterial populations [37]. Gut bacterial species is important for bile acids diversity. A research showed that the rats lack of intestinal microbiota had decreases of secondary BAs and increases of conjugated Bas [38]. In patients with ulcerative colitis, concentration of secondary BA was lower in the presence of intestinal microdysbiosis and exacerbated gut inflammation [39].

The different bile acids play some different important roles in the intestinal tract and gastrointestinal diseases. The interaction between bile acids and intestinal flora affects the maintaining homeostasis.

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