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Review

Bile acids in the colon, from healthy to cytotoxic molecules

Juan I. Barrasa, Nieves Olmo, Mª Antonia Lizarbe, Javier Turnay *

Department of Biochemistry and Molecular Biology I, Faculty of Chemistry, Complutense University, 28040 Madrid, Spain

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ABSTRACT

Bile acids are natural detergents mainly involved in facilitating the absorption of dietary fat in the intestine. In addition to this absorptive function, bile acids are also essential in the maintenance of the intestinal epithelium homeostasis. To accomplish this regulatory function, bile acids may induce programmed cell death fostering the renewal of the epithelium. Here we first discuss on the different molecular pathways of cell death focusing on apoptosis in colon epithelial cells. Bile acids may induce apoptosis in colonocytes through different mechanisms. In contrast to hepatocytes, the extrinsic apoptotic pathway seems to have a low relevance regarding bile acid cytotoxicity in the colon. On the contrary, these molecules mainly trigger apoptosis through direct or indirect mitochondrial perturbations, where oxidative stress plays a key role. In addition, bile acids may also act as regulatory molecules involved in different cell signaling pathways in colon cells. On the other hand, there is increasing evidence that the continuous exposure to certain hydrophobic bile acids, due to a fat-rich diet or pathological conditions, may induce oxidative DNA damage that, in turn, may lead to colorectal carcinogenesis as a consequence of the appearance of cell populations resistant to bile acid-induced apoptosis. Finally, some bile acids, such as UDCA, or low concentrations of hydrophobic bile acids, can protect colon cells against apoptosis induced by high concentrations of cytotoxic bile acids, suggesting a dual behavior of these agents as pro-death or pro-survival molecules.

Contents

Abbreviations: BH, Bcl-2 homology; CA, cholic acid (3α,7α,12α-trihydroxy-5β-cholanoic acid); CDCA, chenodeoxycholic acid (3α,7α-dihydroxy-5β-cholanoic acid); DCA, deoxycholic acid (3α,12α-dihydroxy-5β-cholanoic acid); EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; FXR, farnesoid X receptor; *GADD153*, growth arrest- and DNA damage-inducible gene 153; LCA, lithocholic acid (3α-hydroxy-5β-cholanoic acid); MAPK, mitogen-activated protein kinase; MPT, mitochondrial permeability transition; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLA_2, phospholipase A2; PLC, phospholipase C; PXR, the pregnane X receptor; ROS, reactive oxygen species; TNF, tumor necrosis growth factor; TRAIL, TNF-related apoptosis inducing ligand; UDCA, ursodeoxycholic acid (3α,7β-dihydroxy-5β-cholanoic acid); VDR, vitamin D receptor.

* Corresponding author. Tel.: +34 91 394 4148; fax: +34 91 394 4159.
E-mail address: turnay@bbm1.ucm.es (J. Turnay).

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1. Introduction

The maintenance of the function and structure of the gastrointestinal mucosa requires a strict controlled balance between cell proliferation, differentiation and apoptosis. Cell behavior and survival are influenced by luminal components including several physiological molecules such as butyrate and bile acids (Haza et al., 2000). It is well known that the content of the lumen depends on the diet. A high intake of dietary fiber and low saturated fats is associated with a reduced incidence of colorectal cancer; this protective effect has been attributed to butyrate, an end-product of colonic fiber fermentation and the major natural regulator of the homeostasis of the normal colonic mucosa (Andoh et al., 2003; Velazquez et al., 1997). Other molecules from the intestinal lumen, bile acids and salts among them, may also affect the colorectal epithelium. A proposed mechanism for the influence of a diet with a high content in saturated fats in carcinogenesis is the stimulation of bile discharge; secondary bile acids would alter the growth of the intestinal epithelium acting as tumor promoters (Bernstein et al., 2005; Ou et al., 2012). On the other hand, these molecules induce apoptosis and it has been suggested that a decrease in susceptibility to these agents may correlate with an increased risk for colorectal cancer (Schlottman et al., 2000). In fact, it has been described that bile acids are involved as etiologic agents in cancer of the gastrointestinal tract, including cancer of the esophagus, stomach, small intestine, liver, biliary tract, pancreas and colon/rectum (Baptissart et al., 2012; Bernstein et al., 2009).

Taking into account that most of the data regarding the effect of bile acids in apoptosis, cell signaling and carcinogenesis are mainly restricted to hepatocytes, in this paper we review the available information about the influence of these agents in the colonic homeostasis and colorectal carcinogenesis. Therefore, we first briefly describe the physiology of bile acids, followed by a depiction of the different apoptotic pathways triggered by these agents in colonocytes. Next we discuss their role in oxidative stress and cell signaling, and the relationship between these processes with colorectal carcinogenesis. Finally, we summarize the potential protective role of bile acids, mainly UDCA, on the colonic tract. Thus, the aim of this review is to highlight the dual role of bile acids in the intestinal homeostasis, on the one hand as physiological detergents and regulators of cell fate and signal, and on the other hand as potential tumor promoting agents.

2. Biochemistry and physiology of bile acids

Bile acids are amphipathic and water-soluble end products of cholesterol metabolism; they have 24 carbon atoms and constitute a major part of the bile. Some of their properties are related to their amphipathic nature. They are key molecules involved in digestion whose main physiological role is to facilitate the emulsion and absorption of dietary fats and liposoluble vitamins in the gut, and the excretion of cholesterol into the intestinal tract. At the intestinal level, bile acids modulate pancreatic enzyme secretion and cholecystokinin release, and they are potent antimicrobial agents that prevent bacterial over-growth in the small bowel. Bile acids also stimulate biliary lipid secretion and are able to form mixed micelles together with biliary phospholipids, which allows the solubilization of cholesterol and other lipophilic compounds in bile (Hofmann and Hagey, 2008). On the other hand, bile acids are molecules with potentially membrane-damaging properties and they act as calcium ionophores; these properties have been related to their hydrophobicity.

Primary bile acids are synthesized in the liver from cholesterol through a cascade of reactions catalyzed by enzymes located at the cytosol, microsomes, mitochondria, and peroxisomes. The modification of the sterol nucleus of cholesterol precedes the oxidative cleavage of its side chain; it begins with the hydroxylation of cholesterol at C-7, catalyzed by cholesterol 7α-hydroxylase, the rate-limiting enzyme of the pathway. In humans, the two primary bile acids, cholic (CA) and chenodeoxycholic (CDCA), are synthesized through this pathway. Extensive descriptions of these reactions and enzymes can be found elsewhere (Hylemon et al., 2009; Monte et al., 2009). After their synthesis, CA and CDCA are conjugated with glycine or taurine in the liver, stored in the gall bladder and then released into the intestinal tract. During the intestinal transit, these molecules are mainly absorbed in the ileum, but a small fraction continues its transit into the large bowel where they undergo modifications by intestinal anaerobic bacteria. This biotransformation in the human colon involves mainly deconjugation and oxidation/epimerization of hydroxyl groups at C-3, C-7 and C-12 as well as dehydroxylation at position C-7. Bacterial dehydratases remove the hydroxyl group at C-7 from CA and CDCA yielding the secondary deoxycholic (DCA) and lithocholic (LCA) bile acids, respectively. Ursodeoxycholic acid (UDCA) is formed in the human colon by bacterial epimerization of the hydroxyl group in C-7 of CDCA through the stable intermediate 7-oxo-LCA (Fukiya et al., 2009). In addition, 7-oxo-LCA, among other secondary bile acids, can be reabsorbed in the distal intestine and transported back to the liver, where it is reduced to CDCA and, to a lesser extent, UDCA (Odermatt et al., 2011). The structures of some of the most abundant bile acids are shown in Fig. 1.

The different bile acids exhibit distinct biological effects, although CA does not exert any significant effect on human colon carcinoma cells (Barrasa et al., 2011; Hofmann and Hagey, 2008; Martinez et al., 1998; Pérez-Ramos et al., 2005). Interestingly, whereas the unconjugated bile acid UDCA is considered an hepatocyte protector, CDCA is highly cytotoxic (Amaral et al., 2009; Paumgartner and Beuers, 2002). The only structural difference between them is the configuration of the hydroxyl group at C-7 (β in UDCA and α in CDCA; Fig. 1), revealing the importance of the stereospecificity in the cytotoxic mechanisms of these agents. In contrast to the toxic effects of hydrophobic bile acids, UDCA is hydrophilic and is used as a therapeutic drug for patients with cholestatic liver diseases. Moreover, UDCA has been approved by the FDA for the treatment of primary biliary cirrhosis. Despite its clinical efficacy, the precise mechanism by which UDCA improves liver function is still not entirely understood and controversial results have been reported (Wood, 2011).

3. Programmed cell death

Programmed cell death is an essential physiological process in the homeostasis of the organisms that is triggered by different death stimuli. Rather than necrosis, which is an accidental and non-regulated cell death caused by extreme conditions, programmed cell death is an active process that is governed by