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MINIREVIEWS

Secondary bile acids and the biliary epithelia: The good and the bad

Ilaria Lenci, Martina Milana, Alessandro Signorello, Giuseppe Grassi, Leonardo Baiocchi

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Abstract

The biliary tract has been considered for several decades a passive system just leading the hepatic bile to the intestine. Nowadays several researches demonstrated an important role of biliary epithelia (*i.e.* cholangiocytes) in bile formation. The study of biliary processes therefore maintains a continuous interest since the possible important implications regarding chronic cholestatic human diseases, such as primary biliary cholangitis or primary sclerosing cholangitis. Bile acids (BAs), produced by the liver, are the most represented organic molecules in bile. The physiologic importance of BAs was initially attributed to their behavior as natural detergents but several studies now demonstrate they are also important signaling molecules. In this minireview the effect of BAs on the biliary epithelia are reported focusing in particular on secondary (deriving by bacterial manipulation of primary molecules) ones. This class of BAs is demonstrated to have relevant biological effects, ranging from toxic to therapeutic ones. In this family ursodeoxycholic and lithocholic acid present the most interesting features. The molecular mechanisms linking ursodeoxycholic acid to its beneficial effects on the biliary tract are discussed in details as well as data on the processes leading to lithocholic damage. These findings suggest that expansion of research in the field of BAs/cholangiocytes interaction may increase our understanding of cholestatic diseases and should be helpful in designing more effective therapies for biliary disorders.

Key Words: Cholangiocytes; Biliary secretion; Cholestasis; Bile acids; Secondary bile acids; Ursodeoxycholic acid; Lithocholic acid

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Core Tip: The biliary epithelia present important physiologic activities that are of interest with regard to chronic cholestatic liver diseases. Secondary bile acids (BAs) are derived by bacterial manipulation of the primary BAs produced by the liver. This review summarizes the most important recent findings with regard to secondary BAs interaction with biliary epithelia.

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INTRODUCTION

The biliary system is composed of a delicate structure of anastomosing ducts, leading the bile from the liver toward the intestine[1]. While for several years this anatomical apparatus was considered just as an inert route for bile transport, recently several studies have demonstrated that important qualitative/quantitative bile changes occur within the biliary tract. The isolation and characterization of the biliary epithelia (composed of bile duct cells or cholangiocytes) has deepened our understanding of several important molecular process involving the biliary tree, also shedding some light on the mechanisms leading to chronic cholestatic liver diseases.

Bile acids (BAs) are the main organic molecules secreted in bile[2]. Their physiological importance, which in the beginning was identified only with regard to the physicochemical processes leading to micelle formation[3], nowadays has been expanded by the evidence that BAs are also essential signaling molecules[4]. In this minireview, the most important findings involving secondary BAs and biliary epithelia will be reported together with the possible implications of these mechanisms in human liver diseases.

SECONDARY BAS

BAs are synthesized by the liver starting from cholesterol and are the most represented lipidic component in bile[5]. Taurine or glycine conjugation, occurring after synthesis, confers increased water solubility to these molecules in bile. BAs are traditionally classified as primary (produced by the liver) or secondary (derived by primary BAs after bacterial dehydroxylation in the intestine)[6]. In humans, the primary BAs are cholic (CA) and chenodeoxycholic (CDCA) acid, while the most represented secondary ones are deoxycholic (DCA) and lithocholic (LCA) acid. The removal of a hydroxyl group (C-7 position) in general determines reduced water solubility and increased detergency in comparison with primary precursors. The hydrophilic or hydrophobic character of a specific BA has been put in relation with its potential cytotoxicity and damaging effects[7]. In this perspective, secondary BAs are generally regarded as possibly damaging molecules when they reach adequate concentrations since their detergent/destabilizing effect on cell membranes. Being the bile a mixture of different (primary and secondary) BAs, the concept of hydrophilic/hydrophobic balance of the bile (and so the net concentration of secondary BAs) has been related with possible liver injury in some conditions[8]. The most hydrophobic human BA is the monohydrate LCA. Sulfation of this molecule by the liver greatly reduces its intestinal absorption (also enhancing its hydrophilicity and urine elimination) and the consequent damage induced by LCA enterohepatic recirculation[9]. It in fact represents less than 5% of total BAs in human bile[6]. The number of hydroxyl groups, however, is not the only determinant of the specific hydrophilic/hydrophobic character of a specific BA. In fact, another secondary BA, ursodeoxycholic acid (UDCA), despite having an equal number of OH groups (two) in comparison with CDCA and one less than CA, is more hydrophilic in comparison with the latter molecules. This physico-chemical characteristic is related to the fact that, differently from CDCA (3α, 7α), in UDCA, the two hydroxyl groups are not on the same plane (3α, 7β). See Table 1 for a quick reference on hydroxyl group number and position, together with some other features, of the principal BAs found in human bile. On Figure 1 the approximate amount of each individual BA in human bile is reported.

BILIARY EPITHELIA

Together with hepatocytes, cholangiocytes constitute the liver epithelial compartment. These latter cells, lining the intrahepatic and extrahepatic biliary ducts, despite representing less than 10% of liver mass, are able to support nearly 50% of bile volume under stimulation[10]. They in fact contribute almost

Table 1 Some physico-chemical features of the most relevant primary and secondary bile acids in human bile

	Hydroxil groups number and position	Solubility in water (protonated form, μM)[1]	Critical micellar concentration (sodium salt, mM)[1]	Hydrophobicity index (taurine conjugated)[2]
Primary bile acids				
Cholic acid	3 (3, 7, 12)	273	13	0
Chenodeoxycholic acid	2 (3, 7)	27	9	0.46
Secondary bile acids				
Deoxycholic acid	2 (3, 12)	28	10	0.59
Lithocholic acid	1 (3)	0.05	0.9	1
Ursodeoxycolic acid	2 (3, 7)	0.9	19	-0.47

[1]Values assessed in water as reported by Hofmann *et al*[44].
[2]Cholic acid and Lithocholic acid were assumed to have (by definition) a value of 0 and 1 respectively[8].

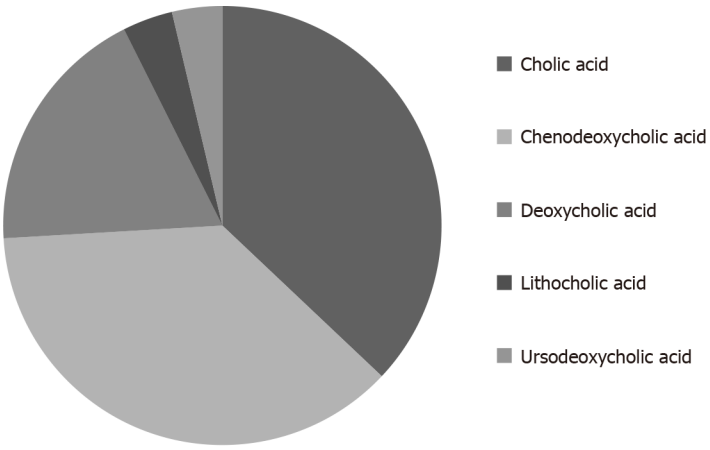

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Figure 1 The relative amount of individual bile acids in human bile is depicted. For each bile acid the extent of conjugation with glicine *vs* taurine is approximately 3 to 1.

exclusively to the so-called BA-independent bile flow. Cholangiocytes are heterogeneous in size and function; the larger ones represent the physiologically functional compartment, while smaller cells (harboring small branches) may replace large ones when the latter are injured[11]. The most studied mechanism of bile duct secretion concerns the interaction between secretin (Sec) and a specific Sec receptor (SR) expressed by cholangiocytes only within the liver. The subsequent downstream molecular mechanisms are characterized by increased intracellular cAMP in bile duct cells, followed by PKC phosphorylation, extrusion of Cl^- by the cystic fibrosis transmembrane regulator and finally its reabsorption and exchange with bicarbonate operated by the Cl^-/HCO_3^- exchanger (AE2)[12]. With this process, a bicarbonate-enriched choleresis is obtained. See Figure 2 for a schematic representation of this mechanism. However, several hormones and neuropeptides (such as somatostatin, histamine, melatonin, gastrin and others) may regulate bile duct cell activity, as these cells have been demonstrated to express the corresponding receptors[13]. BA receptors and transporters are also present on cholangiocytes. They are responsible for important physiological mechanisms.

BAS/BILIARY EPITHELIA INTERACTIONS

The biliary epithelium is constantly exposed to significant concentrations (mM) of BAs. This strict connection is at the basis of important processes under both normal and pathological conditions. As previously stated, BAs are mainly present in bile as glycine or taurine conjugates; however, more than 30 years ago, the possibility that unconjugated BAs may cross the biliary epithelium and recirculate in the liver (the so-called chole-hepatic shunt) was hypothesized, thereby inducing increased choleresis with multiple passages[14]. Later, uptake of BAs by the biliary epithelium was demonstrated by the

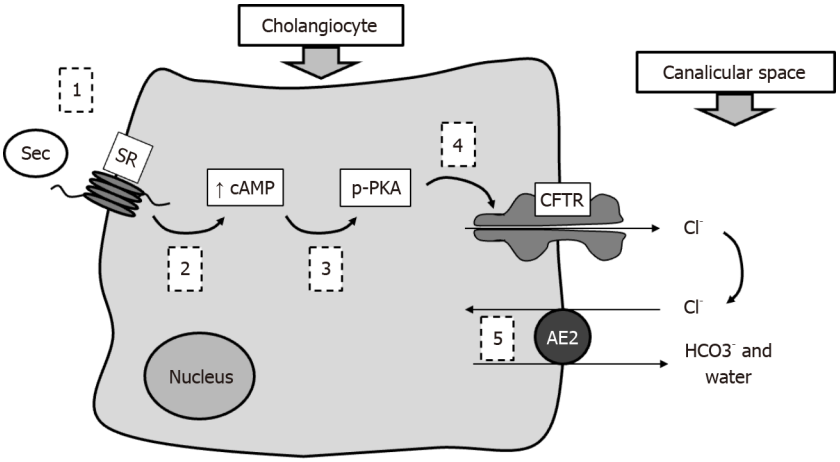

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Figure 2 A step by step representation of secretin-induced biliary secretion is depicted. 1: Secretin (Sec) bind to specific Sec receptor on cholangiocytes; 2 and 3: Increased intracellular levels of cAMP stimulate formation of p-PKA; 4: Cystic fibrosis transmembrane regulator is opened determining Cl- efflux; 5: chloride-bicarbonate exchanger (AE2) favors reuptake of Cl- and releases HCO_3- (osmotically recalling water) in the canalicular space. CFTR: Cystic fibrosis transmembrane regulator; Sec: Secretin; SR: Secretin receptor.

identification of the apical sodium-dependent BA transporter (ASBT) on cholangiocytes[15]. ASBT in the same study was demonstrated to be expressed only by cholangiocytes within the liver and to prompt unidirectional BA transport from the apical to the basolateral cellular domain. ASBT is also expressed in the small intestine, actively reabsorbing BAs and having a major role in maintaining the appropriate entero-hepatic recirculation of these molecules. Gene disruption of this transporter, in fact, nearly completely abolished intestinal recovery of BAs[16], even if a reduced proportion of unconjugated protonated BAs is absorbed by passive uptake in the colon[17]. ASBT function in cholangiocytes, however, remains less clear. In one study, it was demonstrated that Sec stimulation of cholangiocytes was able to increase choleresis, also promoting the transfer of ASBT from the plasma membrane to the apical domain and supporting the original concept of the BA cholehepatic shunt[18]. In another study, a relationship between biliary BAs concentration and ASBT expression was found, suggesting a possible regulatory mechanism of this transporter in maintaining an appropriate biliary BAs concentration[19]. At present, ASBT inhibitors are under study to reduce the BA pool in diseases possibly related to its pathological increment, such as primary biliary cholangitis (PBC)[20].

Further information regarding BAs and cholangiocyte molecular interactions came after the identification of the TGR5, specific for BAs[20]. While in the liver the FXR is mainly expressed in the hepatocyte nucleus where it regulates the transcripts for the synthesis of these molecules[21], on the other hand, TGR5 is prevalently found on the cholangiocyte apical domain[22]. Studies on TGR5(-/-) mice showed an effect on body weight, the immune system and glucose homeostasis[23]. With regard to the biliary tree, TGR5 seems to be an important regulator of cell proliferation with the opposite effect when it is activated in ciliated *vs* non-ciliated cells[24]. In fact, activation of TGR5 on cholangiocyte cilia depresses cAMP formation and proliferation while the same signal in non-ciliated cholangiocytes enhances intracellular cAMP and cell growth. The important role of TGR5 as a possible regulator of biliary mass suggests that this receptor is a possible target in human diseases characterized by uncontrolled cholangiocyte growth, such as cholangiocarcinoma[25] or polycystic liver disease[26]. More recently, other BA receptors, such as the S1PR2, have been identified on cholangiocytes[27]. These signals enhance biliary growth upon stimulation with taurocholic acid (TCA), employing an ERK1/2 dependent mechanism. In conclusion, accumulating evidence demonstrates that the role of BAs in bile is not restricted to lipid dissolution. In fact, BAs are also important molecular signaling molecules.

SECONDARY BAS AND THE BILIARY EPITHELIA

As previously reported, secondary BAs originate from manipulation of the original molecules synthesized by the hepatocytes, by intestinal bacteria. However, within this family, molecules with opposite physicochemical and biological characteristics cohabit. The extremities of this class of organic compounds, in terms of heterogeneity, are represented by UDCA and LCA. At the same time, these two BAs seem particularly interesting and relevant with regard to human biliary diseases, as evidenced by several studies.

UDCA (the good one)

UDCA was first detected as primary BA in Chinese black bear bile, and later also identified in human bile as a secondary BA, in small amounts (≤ 3%)[28]. Interest in UDCA was first focused on its therapeutic potential for cholesterol gallstone dissolution[29,30]. However, its clinical efficacy for gallstone treatment is: (1) Limited to small (≤ 1 cm) non-calcified stones; and (2) affected by frequent recurrent disease when UDCA is withdrawn. On the other hand, early studies on gallstone dissolution, conducted in patients with concurrent chronic hepatitis, also demonstrated the capabilities of UDCA in improving liver function[31].

UDCA beneficial effects on biliary epithelia (general)

Some clinical studies specifically underscored the UDCA beneficial effects in diseases targeting biliary cells and causing an impaired biliary secretion (*i.e.* cholestasis), such as PBC[32]. UDCA (oral dose 13 to 15 mg/kg/day) is in fact, nowadays, a first line treatment for this disease[33,34]. Several mechanisms seem responsible for the improved clinical picture when UDCA is employed in biliary cholestasis[35]. First, due to its intrinsic hydrophilicity, UDCA seems able to reduce the cytotoxicity/hydrophobicity of the total BA pool against bile duct cells. Second, increased biliary secretion is observed if UDCA enrichment occurs in bile. Finally, immune-modulatory and antiapoptotic effects have been demonstrated[32]. Moreover, also regarding PBC, impairment of AE2 and consequent inadequate formation of a delicate bicarbonate film in the canalicular biliary space (the so-called bicarbonate umbrella) has been suggested to facilitate biliary damage by protonated BAs. In this setting, UDCA seems to be able to reconstitute adequate bicarbonate secretion, thus mitigating PBC injury[36] and also reducing the endoplasmic reticulum stress and autophagy acting as a chaperone[37]. With regard to the biliary epithelium, experimental studies have elucidated some important mechanisms.

Molecular basis of UDCA beneficial effects

In early research, conducted in the cholestatic model of the bile duct ligated (BDL) rat (a condition inducing a hyperplastic growth of the biliary tree), UDCA feeding was able to attenuate biliary mass proliferation[38]. A subsequent study using the same model (BDL) clarified that both pathologically enhanced proliferative and secretive processes of cholangiocytes were mitigated by UDCA, as demonstrated by reduced H3 histone, protein cellular nuclear antigen (PCNA) and SR gene expression, and decreased Sec-induced choleresis[39]. Decreased proliferation was not related to cholangiocyte apoptosis and was dependent (as was decreased secretion) on PKCα activation. Another molecular aspect characterizing the effects of UDCA was the decreased ASBT cholangiocyte expression leading to reduced intracellular BA influx. These findings were extended in a more complex model combining rat BDL and vagotomy. In fact, when vagotomy was performed in the BDL rat, the consequent lack of cholinergic stimuli impaired the hyperplastic cholangiocyte response to cholestasis and led to apoptosis in bile duct cells[40]. When UDCA was administered in this model, it was able to counterbalance bile duct cell loss and apoptosis by a PKCα/Ca^{2+} dependent mechanism[41].

UDCA effects in animal model of human biliary disease

Further information regarding UDCA and biliary epithelia came from the Mdr2(-/-) mice model. This mouse is not able to transport phospholipids in bile and develops a chronic cholestasis, resembling the human primary sclerosing cholangitis (PSC), with similar scars and strictures within the biliary tree[42]. In Mdr2(-/-) mice UDCA attenuated reactive cholangiocyte proliferation as well as inflammatory and fibrotic processes. These effects were in part related to the inhibition of mast cells, which are activated during experimental and human PSC[43].

LCA (the bad one)

LCA is a monohydrate secondary BA that is known for its particular hydrophobicity, remaining water insoluble in its free form while it presents a very low critical micellar concentration (concentration at which micelles are spontaneously formed) in saline[44]. According to its physico-chemical properties, LCA has longer been known as a cholestatic and injurious agent in animal experiments[45,46] and, in parallel with this, increased levels of this BA have been found in human with chronic liver disease[47].

General mechanisms of LCA-induced cholestasis

Several mechanisms were identified at the basis of LCA-induced cholestasis such as: (1) Impairment of bile secretion (both BAs dependent and independent)[48]; (2) bile salt export pump translocation from apical membrane to cytosol with its consequent reduced activity[49]; (3) changes in apical membrane fluidity and tight junction permeability[50]; and (4) impairment of canalicular contraction[51].

LCA effects on biliary epithelia

With regard to biliary epithelia, a study on LCA feeding in Swiss albino mice evidenced interesting features[52]. After 4 d of a 1% LCA diet, destructive cholangitis characterized by stenosis of biliary ducts, solid crystal precipitation and bile infarcts was observed. Neutrophil infiltration surrounded the

Table 2 Main findings regarding secondary bile acids and biliary epithelia

Model	Administration route	Main results	Main molecular, immunologic findings	Ref.
Ursodeoxycholic acid				
BDL rat	Feeding (both the unconjugated and taurine-conjugated form)	Decreased biliary proliferation and secretion. No apoptosis	Decreased H3-histone. PCNA, SR and ASBT expression. No apoptosis. Increased PKC α expression	[38, 39]
BDL + vagotomy rat	Feeding (both unconjugated and taurine-conjugated form)	Reversal of duct loss and apoptosis induced by vagotomy	PKCα/Ca^{2+} dependent mechanism	[41]
Mdr2(-/-) mice	Feeding	Decreased proliferation, inflammation and fibrosis	Inhibition of mast cells activity	[43]
Lithocolic acid				
Mouse	Feeding	Destructive cholangitis, bile duct stenosis, bilary infarcts	Damage related to direct toxic effect and not to neutrophil infiltration	[52, 53]
In vivo rat and isolated cholagiocytes	Feeding (cholic acid or Lithocholic acid both taurine conjugated)	Similar effect in increasing proliferation and secretion	Effect restricted to large cholangiocytes	[54, 55]
In vivo rat and isolated cholagiocytes	Feeding (cholic acid or Lithocholic acid both taurine conjugated)	Cholangiocytes proliferation	Dependent by PKA-mediated ASBT expression	[56]
Deoxycholic acid				
Human gallbladder cancer (specimens and cell lines)	*In vitro* exposure	Increased concentration associated with inhibition of tumor growth	Reduced miR-92b-3p inhibits PI3K/AKT activity	[60]

ASBT: Apical sodium bile acids transporter; BDL: Bile duct ligated; PCNA: Protein cellular nuclear antigen; SR: Secretin receptor.

small biliary branches and periductal fibroblast activation with collagen deposition was reported. A subsequent study, conducted in the same experimental system, helped to clarify that LCA-related biliary damage was dependent on direct toxicity of this BA and not to the immune response since neutrophil inhibition did not significantly change the pathological picture[53]. With regard to secretive and proliferative cholangiocyte activities, *in vitro* experiments demonstrated that LCA and CA (taurine conjugated) had similar effects in promoting biliary growth and Sec-stimulated bile output[54]. These results were observed with the large cholangiocyte population, which is well-known as the main functional pool in the biliary tree. Similar results were later confirmed in *in vivo* experiments[55]. In fact, TCA or TLCA rat feeding (1% diet, 1-4 wk) both similarly increased biliary mass and enhanced cholangiocyte biliary secretion. Further experiments suggested that the TLCA stimulation of cholangiocytes function (similarly to TCA) was associated with increased ASBT activity and consequently enhanced intracellular (PKCα/Ca^{2+} dependent) BA trafficking[56]. This process, with regard to LCA, due to the changes in Ca^{2+} flux, was also related to impaired gap junction permeability and consequent cholestasis [57].

Other secondary BAs

With regard to other secondary BAs that may play a role in human biliary physio-pathology, DCA is the only one possibly reaching significant concentrations (10%-35% of total BAs pool) in human bile[58]. DCA liver toxicity has been well-established since the early 1990s and, in a study on rat feeding, this was enhanced in comparison to LCA due to its increased intestinal reabsorption and bile enrichment [59]. Despite this and concerning the biliary epithelia, one study has raised interest by showing the suppression of gallbladder cancer growth by DCA, possibly due to interference with miR-92b-3p[60]. This miR in fact would be responsible of the activation PI3K/AKT pathway that is enhanced in several tumors and also represents a target for anticancer treatment[61]. Several other secondary BAs may be found in different species[62]. For instance in rodents the main represented primary BA is β-muricholic acid (β-MCA; 3α, 6β, 7β)[63]. Bacterial manipulation of β-MCA may give origin to different secondary BAs including HDCA (3α, 6α)[64]. HDCA is reported as the strongest regulator of BA-sensitive ion channel (BASIC) that is normally expressed in brain, intestine and cholangiocytes only, within the liver [65]. While the exact physiologic function of cholangiocyte BASIC has not been well established, evidences demonstrate enhanced activity of this channel, with increased trans-epithelial ion transport, after exposure to HDCA[66]. This suggests BASIC as a further possible regulator of biliary secretion. Table 2 summarizes the main findings regarding secondary human BAs and biliary epithelia.

CONCLUSION

BAs are important organic molecules. For several decades, researchers have focused on their physico-chemical characteristics, due to their reported detergent properties. From this perspective, the hydrophilic or hydrophobic character of a BA has been considered in the past as the main determinants of physiologic effect. This preliminary view is clearly challenged nowadays, with many studies demonstrating the important molecular signaling systems activated by BAs, not only in the hepatocytes but also in the biliary epithelium. Artificial manipulation of native BA molecules, moreover, has led to the discovery of new agents, such as obeticholic acid, that may be helpful for human therapy[67]. Given all the above, it is clear that the original classification of BAs as primary and secondary compounds only expresses aspects of their synthesis and not necessarily beneficial or negative physiologic effects. Similarly, the division of secondary BAs as good or bad ones (as reported in this review) is questionable, since this does not adequately recapitulate the multitude of effects (probably discovered just in part at the present stage) these molecules may have. In fact, UDCA (generally supposed as beneficial) has been demonstrated to be detrimental in experimental obstructive cholestasis as it can lead to bile infarcts and should not be administered in this clinical condition[68]. On the other hand, LCA has shown interesting curative properties and anti-tumoral and anti-inflammatory effects on intestinal environment, in some studies[69]. In conclusion, UDCA and LCA clearly represent the extremities of a field in which research may growth and a revision in our present beliefs regarding these secondary BAs remains therefore possible in the near future. With regard to normal human physiology and in practice, however, LCA accumulation is prevented by a detoxification system while UDCA is formed only in trace amounts. However, bile enrichment is possible when BAs are exogenously administered to manipulate the BAs pool for therapeutic purposes.

FOOTNOTES

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