Bile Acids, Nuclear Receptors and Cytochrome P450

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Summary
This review summarizes the importance of bile acids (BA) as important regulators of various homeostatic mechanisms with detailed focus on cytochrome P450 (CYP) enzymes. In the first part, synthesis, metabolism and circulation of BA is summarized and BA are reviewed as physiological ligands of nuclear receptors which regulate transcription of genes involved in their metabolism, transport and excretion. Notably, PXR, FXR and VDR are the most important nuclear receptors through which BA regulate transcription of CYP genes involved in the metabolism of both BA and xenobiotics. Therapeutic use of BA and their derivatives is also briefly reviewed. The physiological role of BA interaction with nuclear receptors is basically to decrease production of toxic non-polar BA and increase their metabolic turnover towards polar BA and thus decrease their toxicity. By this, the activity of some drug-metabolizing CYPs is also influenced what could have clinically relevant consequences in cholestatic diseases or during the treatment with BA or their derivatives.

Key words
Bile acids • FXR • PXR • Cytochrome P450

Introduction
The essential physiological role of bile and bile acids (BA) in digestion is to neutralize chyme and serve as emulsifiers of fat in small intestine. Thanks to their amphiphilic nature, BA are emulsifiers which enable absorption of lipids and lipid soluble vitamins. The production and secretion of bile is regulated by intestinal paracrine hormones cholecystokinin and secretin and moreover autoregulation via negative feedback exists, too. BA and phospholipids stabilize micellar dispersion of cholesterol in the bile and facilitate cholesterol excretion as well as excretion of hydrophobic metabolites of xenobiotics, toxins and metals. In past decade, it has been postulated that bile acids may also regulate lipid and glucose homeostasis, thermoregulation, and immune response (Claudel et al. 2011). Especially the role of BA in immune response is undoubtedly involved in the therapeutic effects of some BA in cholestatic liver diseases (Roma et al. 2011, Buryova et al. 2013).

The most common human BA (Fig. 1) are cholic acid (CA), chenodeoxycholic acid (CDCA), in much less proportion also glycocholic acid, taurocholic acid (TCA), lithocholic acid (LCA), deoxycholic acid (DCA), and ursodeoxycholic acid (UDCA). BA and oxysterols are natural ligands of several nuclear receptors (NRs), membrane receptors and regulators of metabolism of lipids and glucose (Chiang 2004, Chiang 2009). At least, some of BA regulate above mentioned pathways via their farnesoid X receptor (FXR) agonistic activity. In particular, FXR agonists probably via production of glucagon-like peptides 1 and 2 increase insulin sensitivity, glucose uptake, and adipogenesis in extrahepatic tissues. Meanwhile, they increase fatty acid oxidation, decrease triglyceride, fatty acid, and cholesterol synthesis in the liver and increase insulin production in beta cells (Camilleri and Gores 2015, Adorini et al. 2012). BA as FXR agonists also decrease...
activity of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase and thus, together with all above mentioned effects increase glucose tolerance and insulin sensitivity (Chiang 2013). BA also promote gut motility through TGR5 activation (Camilleri and Gores 2015) which is in agreement with reported adverse effects of therapeutically used BA (American Society of Health System Pharmacists 2016a, American Society of Health System Pharmacists 2016b). Primary BA are deconjugated and dehydroxylated by microflora, and these BA metabolites exert antimicrobial properties (Begley et al. 2005). Another physiological consequence of BA binding on FXR is increased synthesis of fibroblast growth factor-19 (FGF-19), which may reduce glycolysis and lipogenesis, improved insulin sensitivity, and reduce bile acid synthesis (Camilleri and Gores 2015).

Fig. 1. Unconjugated primary and secondary bile acids in humans.

In agreement with above mentioned physiological roles of BA, some BA may be also exploited or tested as therapeutic agents, mostly in cholestatic liver diseases, inflammatory bowel disease (Gadaleta et al. 2010), diabetes mellitus and metabolic disorders (part Therapeutic use of BA).

This review summarizes the importance of BA as important regulators of various homeostatic mechanisms with detailed focus on cytochrome P450 (CYP) enzymes.

Synthesis, metabolism and circulation of bile acids

BA are synthetized in the liver from cholesterol ("classical pathway") in multiple steps catalyzed via CYPs, hydroxy-delta-5-steroid dehydrogenase (HSD3B7), Δ⁴⁻³-oxosteroid-5β-reductase (AKR1D1) and 3α-hydroxysteroid dehydrogenase (AKR1C4) to form 5β-cholestan-3α,7α,12α-triol. Biosynthetic pathway of CDCA leads directly to 5β-cholestan-3α, 7α-diol via AKR1D1 and AKR1C4. Subsequently, those by products are hydroxylated in the position 27 and the hydroxylic group is then oxidized to aldehydic and carboxylic group. The products are further ligated to coenzyme A (CoA) and the side chain is shortened by β-oxidation to release – propionyl-CoA and choyl-CoA or chenodeoxycholyl-CoA. Under physiological conditions, CA and CDCA occurs as Na⁺ salts ("bile salts") (Chiang 2004). Then, primary BA are conjugated with glycine and taurine. UDCA is 7-epimer of chenodeoxycholic acid and therefore is more hydrophilic than its structural analogue CDCA (Fig. 1) and forms about 4 % of BA pool (Roma et al. 2011). Hydroxylation in the positions 6α/β or 7β increases water solubility and decrease toxicity of BA (Chiang 2013).

Apart from this "classic pathway", alternative ("acidic") biosynthetic pathway exists in humans, which forms less than 10 % of total BA. In this pathway, which is believed to occur also in extrahepatic tissues, cholesterol is hydroxylated by series of steps (e.g. CYP27A1, CYP46A1, HSD3B7, 3βHSD), but finally has to be transported into the liver to complete synthesis of CA and CDCA (Chiang 2004, 2009; Russell 2000).

Conjugated BA are stored in gall bladder and secreted into the duodenum in response to ingestion of meal. Then, about 95 % of BA is reabsorbed in ileum, mostly by apical Na⁺-dependant bile salt transporter (SLC10A2 or ASBT) (Camilleri and Gores 2015b). Resorbed BA are transported to the liver in blood through vena portae (Chiang 2013). BA which are not reabsorbed undergo deconjugation and dehydroxylation by intestinal flora to form secondary BA, LCA, and DCA, of which the most is excreted in faeces (Chiang 2009, Chiang 2013).

Bile acids – ligands of nuclear receptors

For many years, BA were thought to be fat emulsifiers and digestive surfactants as the only function of
the BA in the human body. However, recent observations in the last decade documented that BA are involved in the regulation of more complex processes including bile production, glucose and lipid metabolism, and in the modulation of immune response (Renga et al. 2013, Trauner et al. 2010, Claudel et al. 2005). The regulatory role of BA is a result of their interaction with various types of receptors including both intracellular nuclear receptors (NR) and cell surface membrane receptors (MR). BA acids vary in their ability to bind and activate different types of receptors. CDCA together with DCA are the most potent activators of FXR (Parks et al. 1999, Makishima et al. 1999), while LCA is the most potent activator of membrane G-protein coupled receptor TGR5 (Sato et al. 2008). Except of regulation of energy metabolism and immune system reactions, stimulation of different NRs and MRs by BA helps to maintain bile acid homeostasis via targeting the processes of their synthesis, release, reabsorption or metabolism (Copple and Li 2016).

Table 1. Bile acids, their derivatives and metabolites as ligands of nuclear receptors.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligands</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FXR</strong></td>
<td>CDCA&gt;DCA=LCA&gt;CA&gt;UDCA</td>
<td>Makishima et al. 1999, Parks et al. 1999</td>
</tr>
<tr>
<td></td>
<td>Bile alcohols, 6α-ethylCDCA</td>
<td>Pellicciari et al. 2002</td>
</tr>
<tr>
<td></td>
<td>5β-cholanoic acid, 5β-norcholanoic acid, and 5α-cholanoic acid</td>
<td>Sepe et al. 2016</td>
</tr>
<tr>
<td><strong>PXR</strong></td>
<td>3-keto-LCA&gt;CDCA&gt;DCA&gt;CA</td>
<td>Taudinger et al. 2001</td>
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<tr>
<td></td>
<td>7α-OH-4-cholesten-3-one</td>
<td>Goodwin et al. 2003</td>
</tr>
<tr>
<td><strong>VDR</strong></td>
<td>LCA, 3-keto LCA</td>
<td>Makishima et al. 2002</td>
</tr>
<tr>
<td><strong>LXR</strong></td>
<td>Cholestenoic acid</td>
<td>Song and Liao 2000</td>
</tr>
<tr>
<td></td>
<td>6α-hydroxylated BA</td>
<td>Song et al. 2000</td>
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</table>

**Farnesoid X receptor (FXR; NR1H4)**

There are two genes (FXRa and FXRβ) coding the FXR. FXRβ represents a functional NR in mammalian species except of primates and humans, where the gene encodes the non-functional protein (Otto et al. 2003). FRXα encodes four isoforms of FXR different either in the use of promoters or in alternative splicing (Zhang et al. 2003). The structure of FXR corresponds with the general structure of NR with the LBD allowing receptor heterodimerization with retinoid X receptor (RXR) and interactions with co-regulators. After interaction with agonist, FXR binds with FXR response elements as heterodimer FXR/RXR or as a monomer and regulates the gene expression (Ding et al. 2015).

FXR is mainly found in hepatocytes, enterocytes (Forman et al. 1995) and acts as a sensor in the enterohepatic system regulating BA homeostasis. BA are potentially toxic and their levels have to be strictly controlled. In the hepatocytes, FXR controls BA synthesis (via CYP7A1, CYP8B1), sinusoidal uptake, and canalicular secretion of BA. In the intestine, FXR regulates the absorption, trafficking from the apical to the basolateral membrane and basolateral efflux (Modica and Moschetta 2006). FXR plays a protective role against BA toxicity by feedback inhibition of CYP7A1, CYP8B1, and
Pregnane X receptor (PXR; NR1I2)

PXR acts mainly as a xenobiotic sensor. It is activated by steroidal substances including glucocorticoids and its main role is to form a barrier protecting inner environment from xenobiotics. Therefore, its highest expression was found within liver and intestine (Kliewer et al. 1998).

The PXR LBC is substantially larger than in other NRs and is poor in the number of polar groups. Such characteristic explains the high promiscuity and variability of its ligands (Handschin and Meyer 2005). PXR is activated for example by glucocorticoids, steroids, macrolide antibiotics, antifungals, and some herbal extracts (Jones et al. 2000, Lehmann et al. 1998, Ihunnah et al. 2011). From bile acids the most potent ligand of FXR is CDCA with the EC[50] approximately 10 μmol/l (Ding et al. 2015). Other endogenous BA bind to FRX with lower affinity as follows: CDCA>DCA≈LCA>CA>UDCA (Makishima et al. 1999, Parks et al. 1999).

BA can activate the FRX in their free and conjugated forms. The most powerful ligand of FXR is LCA with the EC[50]~10 μmol/l (Ding et al. 2015). Other endogenous BA bind to FRX with lower affinity as follows: CDCA>DCA=LCA>CA>UDCA (Makishima et al. 1999, Parks et al. 1999).

Vitamin D receptor (VDR; NR1I1)

In spite of the fact that hepatocytes do not express VDR, its significant levels are found in non-parenchymal liver cells such as Kupffer cells or sinusoidal endothelial cells (Gascon-Barré et al. 2003). The typical ligand of VDR is cholecalciferol, while most of the BA including CDCA, CA, DCA, or muricholic acid does not activate VDR. Similarly to ligands of PXR, VDR can be activated by LCA and its metabolite 3-keto-LCA with the EC[50]=8 μM and 3 μM, respectively (Makishima et al. 2002). It could be of clinical importance that therapeutically used UDCA can be converted to LCA (VDR and PXR agonist) by intestinal microflora (Xie et al. 2001, Staudinger et al. 2001).

Table 2. The role of NRs in the regulation of CYP genes expression.

<table>
<thead>
<tr>
<th>CYP</th>
<th>FXR</th>
<th>PXR</th>
<th>VDR</th>
<th>CAR</th>
<th>LXR</th>
<th>Reference</th>
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</table>

The role of VDR to promote calcium and phosphate absorption is well known. Its protective role against BA toxicity similar to PXR or against infection of bile duct was documented in the past decade. Stimulation of VDR by both vitamin D and LCA induces production of antimicrobial peptide cathelicidin in the bile duct epithelial cells (D’Aldebert et al. 2009). Both ligands can also increase the expression of CYP3A4 leading to elevated BA clearance (Makishima et al. 2002) while the expression of CYP7A1 can be reduced through VDR activation (Han et al. 2010). Moreover, there is documented interaction between VDR and LXRα with antagonizing effects on the CYP7A gene, too (Jiang et al. 2006).

Liver X receptor alpha (LXRα; NR1H3)

This NR can be found in the tissues with high metabolic activity such as liver, small intestine, kidney or adipocytes (Sato and Kamada 2011), in comparison to LXRβ, which is ubiquitously expressed in all tissues (Teboul et al. 1995). LXR binds to its responsive elements as heterodimer associated with RXR and its influence on gene expression is tissue specific (Moschetta 2015).

Its known endogenous ligands are oxysterols and its physiologic role is the regulation of cholesterol, fatty acid, and glucose homeostasis (Zelcer and Tontonoz 2006). Oppositely to other mentioned NR, LXR activation leads to increased activity of CYP7A1, thus the formation of BA is increased. Together with increased cholesterol transport to bile via specific transporters and restriction of its absorption from intestine, the level of total plasma cholesterol is decreased. However, reduction in cholesterol levels via activation of LXR is associated with fatty liver and hypertriglyceridemia development (Moschetta 2015).

LXR is activated by cholestenoic acid with ED₅₀ of 200 nmol/l (Song and Liao 2000) and also by different oxysterols (Lehmann et al. 1997, Janowski et al. 1996) and 6α-hydroxylated BA (Song et al. 2000) within the range of their physiologic levels.

Constitutive androstane receptor (CAR; NR1I3)

CAR is closely related to PXR, this NR acts similarly as xenobiotic sensors which regulate expression of genes significant for biotransformation and excretion of exogenous compounds. Both receptors are activated by toxic derivatives of endobiotic metabolism, too. However, CAR seems to be more sensitive to endogenous stimuli (Bing et al. 2014). Typical exogenous ligands of CAR represent phenobarbital, 3,3′,5,5′-Tetrachloro-1,4-bis(pyridyloxy)benzene (TCOBOP) (Timsit and Negishi 2007). When activated, it is translocated into nucleus via protein phosphate PP2A and association with RXR precede to binding to DNA (Timsit and Negishi 2007). BA do not seem to be direct ligands of CAR, nevertheless activation of this receptor increases activity of enzymes producing more hydrophilic and thus less hepatotoxic metabolites of BA (Beilke et al. 2009) and activates their excretion from hepatocytes (Wagner et al. 2005).

The genome-wide screening in the liver cells of human donors treated by CAR prototype ligand CITCO (6-(4-Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carboxaldehyde O-(3,4-dichlorobenzyl)oxime) revealed 11 CYP genes among top 25 influenced genes. In all cases CITCO increased gene expression in the range between 2.8-fold and 2.19-fold in ascending order as follows: 2C9<1A2<3A7<3A4<2C8<2A6<2A13<1A1<2A7<2B6<2B7 (Kandel et al. 2016). On the other hand, CYP2E1 was downregulated with 0.86-fold decrease of its expression (Kandel et al. 2016).

Besides binding to nuclear receptors, BA are also ligands of other types of receptors, including membrane G protein-coupled receptors. The first G-protein coupled receptor known to interact with BA was TGR5, GP-BAR1, or M-BAR. This receptor is widely distributed in different tissues and stimulation leads to different effects depending on the tissue and signalling cascade mediating the signal (Duboc et al. 2014). TGR5 is involved in energy metabolism; it protects liver and intestine from inflammation and steatosis, and improves insulin sensitivity (Chiang 2013, Li and Chiang 2015). The influence of some of BA on the immune response is also essential in their therapeutic effect in cholestatic liver diseases (Poupon 2012, Poupon 2014). This effect is in case of UDCA probably mediated by interaction with toll-like receptors TLR4 and TLR9 and glucocorticoid receptors (Poupon 2012).

Regulation of CYP enzymes involved in the metabolism of bile acids

The synthesis of BA is limited mainly through activity of cholesterol 7α-hydroxylase (CYP7A1), which is believed to be the only rate-limiting step in BA synthesis (Chiang 2013). The protein content and metabolic activity of CYP7A1 is regulated by variety of
factors. CYP7A1 metabolic activity is limited mainly by availability of its substrate cholesterol. Feeding the experimental animals with cholesterol lead to increase expression of CYP7A1, suggesting the stimulatory effect of substrate (“Km effect”) on CYP7A1 (Chiang 2013). On the other hand, negative feedback exists and most of BA are negative regulators of CYP7A1 (Gupta et al. 2001). CDCA, DCA and with much lesser potency also other BA, such as UDCA and LTA, inhibit transcription of CYP7A1 gene. Minor BA, UDCA, which is used therapeutically, increases expression of murine CYP3A11, CYP2B10 and human CYP3A4 – these enzymes catalyze hydroxylation of primary BA towards less toxic (hydrophilic) BA (Roma et al. 2011, Schuetz et al. 2001).

As mentioned above, BA are ligands of several NR, including FXR and it seems that BA downregulate CYP7A1 probably through activation of RXRα/FXR (Chiang 2013). FXR decreases CYP7A1 expression by several indirect mechanisms, by induction of SHP, which in turn inhibits transactivation of CYP7A1 and CYP8B1 by hepatocyte nuclear factor 4α (HNF4α) and liver-related homolog-1 (LRH-1). This is in line with finding of Peng et al. (2016), who reported that CYP7A1 is upregulated in young FXR nullizygous mice.

Moreover, activation of FXR further decreases intracellular BA content by increase of expression of canalicular BSEP (bile salt efflux pump, ABCB11). These feedback mechanisms seem to protect inner environment of hepatocytes from BA toxicity and liver damage. Taurodeoxycholic acid also downregulates CYP27A1 via activation of HNF1α (Rao et al. 1999).

The regulation of BA synthesis and metabolism seems to be very complex and some pathways are anticipatory, since activation of VDR may trigger decrease of SHP and this leads to induction of CYP7A1 (Chow et al. 2014). The expression of VDR itself in rat ileum and liver is regulated (among others) by some of BA (at least by CDCA), but not LCA. The VDR activation by 1,25-dihydroxycholecalciferol or LCA then leads to increase in transcription of CYP3A1 and CYP3A2 genes as well as CDCA treatment. However, when combined together with LCA the expression of CYP3A1 and CYP3A2 is reduced (Khan et al. 2010). It was also reported by the same team of authors that CDCA decreases expression of CYP3A1, CYP3A2, and CYP3A9 mRNA in rat liver, whereas the expression of CYP3A1 in the rat ileum is increased and CYP3A2 and CYP3A9 are not influenced within the whole rat intestine (Khan et al. 2009). This means that unlike UDCA, CDCA could decrease the metabolism and increase the liver toxicity of hydrophobic BA (Khan et al. 2010). In another study with the primary culture of human hepatocytes, CDCA decreased expression of CYP3A4, CYP7A1, CYP2C8, CYP1A1, CYP2E1 and CYP1A2 genes after 48 hours of incubation, as well as it decreased expression of the AHR and PPARγ gene (Krattinger et al. 2016). The overview of BA influence on CYP enzymes is summarized in the Table 3. The results of experiments focused on the regulatory role of BA in the CYP expression seem to be highly variable and dependent on the model used. Moreover, the effects of hydrophobic and hydrophilic BA may differ, as there are differences in

<table>
<thead>
<tr>
<th>Bile acid</th>
<th>1A1</th>
<th>1A2</th>
<th>3A1</th>
<th>3A2</th>
<th>3A4*</th>
<th>CYP</th>
<th>1A7</th>
<th>3A9</th>
<th>7A1</th>
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<tbody>
<tr>
<td>CDCA</td>
<td>↓7</td>
<td>↓7</td>
<td>↑5,6↓6*</td>
<td>↑5↓6*</td>
<td>↑3,6↑7</td>
<td>↓6*</td>
<td>↓1,7</td>
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</tr>
</tbody>
</table>

their selectivity and affinity to nuclear receptors (Table 1). This is also resembled by different clinical effects of DCA and CA on one hand and UDCA, TUDCA and nor-UDCA on the other hand. While CA and CDA appear to be hepatotoxic, UDCA prevents from liver damage. Surprisingly, the genetic polymorphisms of CYP7A1 do not seem to influence the production of BA (Xiang et al. 2012).

Other endogenous regulators seem to play a significant role in BA synthesis, such as blood glucose levels, insulin, thyroid hormone, glucocorticoids and glucagon (Siljevik Ellis 2006, Twisk et al. 1995, Chiang 2009, Xiao et al. 2016). Glucose increases both CYP7A1 transcription (Li et al. 2010) and CYP7A1 metabolic activity by histone acetylation of gene promoter. The latter mechanism is also mediated by insulin (Li et al. 2012). Glucagon inhibits BA synthesis via block of CYP7A1 expression (Song and Chiang 2006). In overall, fasting state seem to downregulate CYP7A1, while elevated glucose and insulin seems to increase expression or metabolic activity of CYP7A1 (Chiang 2009, Chiang 2013).

Bile acids as regulators of CYP enzymes involved in the metabolism of xenobiotics

Through activation of FXR and PXR, BA are regulating rate-limiting step in their biosynthetic pathway (CYP7A1), as well as several transporters involved in BA elimination from hepatocytes, as mentioned above.

BA may also influence CYP enzymes, which are primarily involved in the drug metabolism, such as CYP3A4, CYP2C8, CYP2E1 or CYP1A2.

Although PXR and CAR are primary regulators of CYP enzymes, other nuclear receptors of different types are also known to be involved in their regulation.

With respect to the proposed binding ability to the nuclear receptors, namely FXR, it is not surprising that BA may induce expression of CYP3A4 (Schuetz et al. 2001), SULT2A1 and UGT2B4 genes (Poupon 2012) and increase CYP3A4 metabolic activity (Schuetz et al. 2001).

In particular, FXR nullizygous mice exhibit downregulation of bile salt export pump and thus increase hepatocellular BA content, which in turn, may activate PXR and upregulate CYP3A (involved in their metabolism), but also CYP2B and some ABC transporters (Schuetz et al. 2001). It is also note of worth, that BA are not equipotent ligands of FXR (Table 1). Hydrophilic BA are not considered to be agonists of FXR (Chiang, 2013) and sometimes are reported to be partial agonists, and sometimes also partial antagonists of FXR, such as UDCA (Modica et al. 2010).

It was reported that UDCA may induce the enzymes of CYP3A subfamily (Schuetz et al. 2001) and thus decrease concentrations of substrates of CYP3A4 (such as cyclosporine A (CsA)) after UDCA treatment (Yan et al. 2008, Becquemont et al. 2006, Kurosawa et al. 2009, Uchida et al. 2014).

Interestingly, the rate of CsA elimination was not changed (Caroli-Bose et al. 2000), what implies for decreased bioavailability through induction of intestinal CYP3A4 and P-glycoprotein by activation of PXR (Schuetz et al. 2001). PXR is known as potent inducer of phase I metabolic enzymes, phase II conjugation enzymes and phase III drug transporters (Chiang 2013). Among BA, both taurine-conjugate of UDCA (TUDCA) and UDCA were reported to be the most effective inducers of CYP3A4 in primary human hepatocytes (Schuetz et al. 2001) which corresponds with their ability to decrease toxicity of more hydrophobic BA.

Information on the influence of UDCA on bioavailability of CsA is inconsistent and controversial, since there were published studies documenting decreased dosing of CsA when combined with UDCA, when AUC of CsA were increased twice (Gutzler et al. 1992). Similarly, the bioavailability of CsA was increased with either combination with TUDCA or CsA-TUDCA micellar solution (Balandraud-Pieri et al. 1997). This report may be explained in part by effect of excipient-based increase ion CsA bioavailability, since other micellar dispersions of CsA may also increase the bioavailability and AUC of CsA (Balandraud-Pieri et al. 1997).

Therapeutic use of BA

Dried bile of Chinese black bear was used as a remedy already during the dynasty of Tang in China (approximately 600-900 A.D.) (Guarino et al. 2013). Evidence-based use of bile acids as drugs dates about 30 years back (Beuers et al. 2015). In particular, CDCA was utilized as a treatment for gallstone dissolution, which was later displaced by UDCA due to the better safety profile and efficacy. CDCA caused diarrhea, increased serum total cholesterol and LDL-cholesterol, among other adverse effects (American Society of Health System Pharmacists 2016a). UDCA is currently the only drug approved by FDA for the treatment of primary
biliary cirrhosis (PBC, stage I. and II.) (Roma et al. 2011). UDCA delays progression and need for liver transplantation, increases survival and is well tolerated in PBC at the doses of 10-20 mg/kg/day (American Society of Health System Pharmacists 2016b, Poupon 2014, Roma et al. 2011). In some countries, UDCA is also recommended in primary sclerosing cholangitis (PSC) but evidence on benefit from treatment with UDCA is not as convincing as in PBC. Nevertheless, UDCA is reported to improve biochemical characteristics of disease, ameliorate inflammatory component of the disease, but it probably does not influence overall survival, liver histology nor time to the transplantation at the doses of 10-15 mg/kg/day (EASL 2009). UDCA is also registered for the dissolution of radiolucent, noncalcified gallbladder stones smaller than 20 mm in diameter at the doses of 10-114 mg/kg/day (American Society of Health System Pharmacists 2016b). UDCA is also recommended in the treatment of intrahepatal cholestasis in pregnancy (10-20 mg/kg/day). It alleviates pruritus and improves liver biochemical parameters in up to 80% of patients (European Assoc Study 2009, Gabzdyl and Schlaeger 2015). Another use of UDCA is cystic fibrosis liver disease (CFLD, syn. CFALD – Cystic Fibrosis Associated Liver Disease, syn. CFAHD – Cystic Fibrosis Associated Hepatobiliary Disorders). UDCA improves biochemical parameters in cystic fibrosis patients, but not overall survival (Staufer et al. 2014). Concerning off-label use, UDCA is recommended by European Society for Blood and Marrow Transplantation (ESBMT) as protective agent in Hepatic Veno-Occlusive Disease after hematopoietic stem cell transplantation (RR=0.34) (Dalle and Giralt 2016). Due to the hepatoprotective effect of UDCA, there are some reports that UDCA improves biochemical parameters in non-alcoholic steatohepatitis (NASH), notably in higher doses (Xiang et al. 2013), but in overall there is not enough evidence for routine use of UDCA in NASH (Ratziu 2012, Georgescu and Georgescu 2007). UDCA in low doses may also prevent from colorectal cancer in patients with concomitant inflammatory bowel disease and PSC (Singh et al. 2013).

Some other derivatives of natural BA – “bile mimetics” – in particular FXR and TGR5 agonists, such as nor-UDCA and obeticholic acid, have been suggested to treat cholestatic liver disease (Poupon 2012, Adorini et al. 2012). Obeticholic acid (6α-ethyl-chenodeoxycholic acid) is a semisynthetic derivative of CDCA and potent FXR agonist (Neuschwander-Tetri et al. 2015). It was used in the treatment of PBC and NASH in patients non responding to UDCA (Camilleri and Gores 2015). Obeticholic acid also improved liver histology in NASH patients, but 23% of the patients developed pruritus compared to 6% in placebo group (Neuschwander-Tetri et al. 2015). Moreover, obeticholic acid (25 mg/day) improved liver enzymes, increased low density lipoproteins and decreased markers of fibrosis in patients with type II diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) (Mudaliar et al. 2013). In another study, increase of total cholesterol with simultaneous decrease of HDL cholesterol was reported upon obeticholic acid treatment (Neuschwander-Tetri et al. 2015).

BA and BA sequestrants are currently investigated as possible adjustment to the treatment of diabetes mellitus (notably Type II) due to their ability to increase insulin sensitivity, and decrease gluconeogenesis (in particular through increase of glucagon like peptide 1) (Camilleri and Gores 2015).

Conclusions

BAs are essential physiological factors preserving homeostasis through their influence on nutrition, metabolism and excretion of both endo- and xenobiotics and their metabolites. BAs have also an important role in pathogenesis of cholestatic diseases and drug induced liver injury. Some of BA, their analogues and so called bile mimetics seem to be promising drugs. Apart of the effects of lipid absorption and xenobiotic excretion based on physico-chemical properties of BA, most of their regulatory and signalling properties are mediated through the nuclear receptors FXR, PXR CAR, LXRs and VDR, as well as membrane bound receptors TGR5 and S1PR2 (Copple and Li 2016). The physiological role of interaction of BA with NRs is probably to decrease production of toxic hydrophobic BA and to increase their metabolic turnover towards polar and hydrophilic BA, to increase their excretion and thus decrease their toxicity in the hepatocytes. By this, the activity of some drug-metabolizing CYPs is also influenced since these are regulated by the same NRs, what could have clinically relevant consequences in cholestatic diseases or during the treatment with BA or their derivatives.

Conflict of Interest

There is no conflict of interest.
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