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TOPIC HIGHLIGHT

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Endocrine and paracrine role of bile acids

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Abstract

Bile acids are not only important for the absorption of dietary lipids and fat soluble vitamins but are signalling molecules with diverse endocrine and paracrine functions. Bile acids regulate bile acid, lipid and glucose metabolism and modulate temperature and energy homeostasis. Furthermore, bile acids can not only promote cell proliferation and liver regeneration but can also induce programmed cell death. Bile acid functions are mediated through different pathways which comprise the activation of nuclear hormone receptors, of intracellular kinases and of the plasma membrane-bound, G-protein coupled bile acid receptor TGR5/Gp-bar-1.

Key words: Bile acids; Farnesoid X receptor; TGR5; Glucose metabolism; Lipid metabolism

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INTRODUCTION

Bile acids are synthesized from cholesterol in the liver and secreted into bile and the small intestine, where they enable the absorption of dietary lipids and fat soluble vitamins. Most of the bile acids are reabsorbed in the terminal ileum, carried through the enterocytes into the portal blood and returned to the liver, where uptake into the hepatocytes and subsequent transport into bile completes their enterohepatic circulation[1,2]. However, bile acids are not only important for the absorption of dietary lipids but are also signalling molecules, which regulate bile acid synthesis, conjugation and transport and modulate lipid, glucose and energy homeostasis. Bile acids can activate nuclear hormone receptors, such as the farnesoid X receptor (FXR)[3,4], which is a ligand-activated transcription factor[5]. FXR is highly expressed in liver, intestine and kidney[6], and regulates the expression of proteins involved in bile acid synthesis, detoxification and secretion in these organs thereby maintaining bile acid homeostasis[7-9].

Bile acid effects can also be mediated by transcription-independent pathways through the activation of intracellular protein kinases, such as mitogen-activated protein kinases and protein kinase C[10-15]. Furthermore, bile acids can modulate ion fluxes leading to an increase in intracellular ceramide levels, activation of NADPH oxidase, cell shrinkage and apoptosis[16,17]. Recently, the first plasma membrane bound, G-protein coupled bile acid receptor TGR5 (Gpbar-1, M-Bar) has been described[18,19]. *TGR5* mRNA was detected in many tissues, the highest expression being present in macrophages/monocytes, placenta, gallbladder, liver and intestine[18-20]. While FXR has been identified as important regulator of bile acid, lipid and glucose homeostasis, the role of TGR5 in bile acid mediated signalling is largely unclear. However, it has been suggested that bile acids *via* TGR5 induce energy expenditure in brown adipose tissue and skeletal muscle[21], modulate hepatic microcirculation[22], and suppress cytokine release in macrophages[18].

BILE ACIDS REGULATE BILE ACID HOMEOSTASIS

Sustained elevation of bile acid levels leads to severe liver damage and may promote the development of liver tumors. Patients with progressive familial intrahepatic cholestasis type 2 (PFIC-2), which is caused by mutations in the bile salt export pump (BSEP, ABCB11)[23], as well as FXR knockout mice[24] have chronically elevated

serum bile acid levels and spontaneously develop hepatocellular carcinomas[25-27]. In order to prevent bile acid-dependent liver damage and carcinogenesis the bile acid pool size needs to be tightly regulated.

It is well established that bile acids regulate their own biosynthesis, detoxification and transport both in the liver and the intestine. The identification of bile acids as natural ligands for the FXR[3,4] led to the discovery that FXR is essential for the maintenance of bile acid homeostasis, and protects the organism from the accumulation of potentially toxic bile acids (for reviews see[7,28-30]).

In the liver bile acids suppress the transcription of the CYP7A1, the rate-controlling enzyme of bile acid synthesis in the neutral pathway, and of the CYP8B1, the enzyme controlling the production of cholic acid[30]. This repression is mediated through several distinct, mainly FXR-dependent pathways. Activation of FXR by bile acids leads to an upregulation of the small heterodimer partner-1 (SHP)[31,32], which in turn interacts with several transcription factors, including hepatocyte nuclear factor-4α (HNF-4α) and liver receptor homolog-1 (LRH-1), which both bind to the bile acid-response elements (BAREs) in the promoters of the *CYP7A1* and *CYP8B1* genes[31-35]. Using SHP knockout mice, it has become apparent that the bile acid-dependent repression of CYP7A1 is mediated through several redundant pathways, since loss of SHP impaired but did not abolish bile acid-dependent feedback repression of CYP7A1 in these mice[36,37]. Activation of FXR by bile acids leads to the increased expression of fibroblast growth factor 19 (FGF-19) in hepatocytes, which is subsequently secreted and binds its receptor FGFR4 on adjacent hepatocytes. Stimulation of FGFR4 by FGF-19 leads to receptor dimerization, autophosphorylation and activation of the c-Jun N-terminal kinase (JNK) pathway resulting in the repression of CYP7A1 transcription[38]. Therefore FXR can inhibit bile acid synthesis through tow independent pathways. The importance of the FXR-dependent feedback mechanisms on bile acid synthesis is underscored by the finding, that FXR knockout mice failed to downregulate CYP7A and CYP8B in response to bile acid feeding, resulting in an elevation of serum bile acid levels and death of 30% of knockout mice by day 7[24]. Besides the FXR-dependent feedback regulation, bile acid signalling through the G-protein coupled bile acid receptor TGR5 (Gpbar-1) may also contribute to the regulation of bile acid synthesis and bile acid homeostasis. TGR5 knockout mice showed a significantly reduced bile acid pool size[39] and feeding of cholic acid to these mice did not repress the expression of CYP7A1 as observed in wild type littermates[20], indicating that TGR5 may play a role in the regulation of bile acid synthesis and bile acid pool size.

Conjugation of bile acids with taurine and glycine is mediated by the enzymes bile acid coenzyme A (CoA) synthetase and bile acid-CoA amino acid N-acetyltransferase and controlled by FXR[40]. Bile acids are secreted from the hepatocyte into bile across the canalicular membrane by the BSEP. Bile acids induce transcription of BSEP through FXR thereby promoting their own excretion[41,42]. Besides BSEP, two other canalicular transport proteins MDR3 (ABCB4), which is a phospholipid flippase, and MRP2 (ABCC2), which excretes bilirubin and organic anions, are also positively regulated by FXR[43,44]. Thus FXR facilitates bile flow and excretion of cholephilic compounds from hepatocytes. Short-term regulation of canalicular bile secretion occurs through exocytic insertion and endocytic retrieval of transport proteins into and from the plasma membrane and is differentially regulated by hydrophobic and hydrophilic bile acids (for reviews see[45-49]). Hydrophobic bile acids such as taurolithocholylsulfate (TLCS), glycochenodeoxycholate (GCDC) and taurochenodeoxycholate (TCDC) induce NADPH oxidase-dependent hepatocyte shrinkage[16]. Hepatocyte shrinkage is known to lead to the rapid retrieval of MRP2 and BSEP from the canalicular membrane and thus impairs bile formation[50-54]. On the contrary, taurocholate induces hepatocyte swelling and subsequent choleresis, which in the presence of increased hepatocyte bile acid load may serve as a feed-forward regulation leading to the insertion of BSEP into the canalicular membrane and enhanced bile acid excretion[52,54,55]. The choleretic effect of tauroursodeoxycholate, which is widely used for the treatment of cholestatic liver diseases, is mediated through integrins and Src, which trigger the downstream activation of mitogen-activated protein kinases resulting in the recruitment of BSEP to the canalicular membrane[12,13]. Therefore bile acids can alter bile flow both on the long-term scale on the transcriptional level *via* activation of FXR as well as on the short-term scale at the posttranscriptional level through alteration in hepatocyte hydration and subsequent translocation of transporter proteins.

In the intestine bile acid uptake is mediated by the apical sodium dependent bile salt transporter (ASBT, SLC10A2)[56]. While marked interspecies differences in the regulation of ASBT exist[7], human ASBT expression is controlled by FXR[57,58]. The ileal bile acid binding protein (IBABP) binds bile acids within the enterocytes and transfers them to the basolateral membrane for secretion into the portal blood. Despite the regulation of IBABP by FXR[3,59] and the downregulation of IBABP in FXR knockout mice[24], the enterohepatic circulation of bile acids in these mice is increased[60], suggesting the existence of further, FXR-independent pathways for the regulation of bile acid absorption in the ileum.

In the liver bile acids are taken up from the portal blood into hepatocytes across the sinusoidal membrane by several transport proteins. The sodium-dependent sodium taurocholate cotransporting peptide (NTCP, SLC10A1) accounts for the uptake of more than 80% of conjugated bile acids into hepatocytes. Similar to CYP7A1 and ASBT, bile acids repress the expression of NTCP *via* FXR-SHP-dependent mechanisms[61,62]. However, further SHP-independent mechanisms for the regulation of NTCP expression must exist, since *NTCP* mRNA levels in SHP knockout mice were unchanged[36]. Bile acid uptake by NTCP may also be regulated posttranslationally at the protein level, in an FXR-

independent way, since livers from patients with PFIC showed a significant downregulation of the NTCP protein, while *NTCP* mRNA levels were similar to control livers[63]. The other bile acid uptake transporters in the liver belong to the family of organic anion transporters (OATPs). While OATP1B1 expression is downregulated by FXR[64,65], OATP1B3 expression is enhanced[66]. The repression of bile acid uptake transporters (NTCP, OATP1B1) may protect hepatocytes from accumulation of toxic bile acids, while the upregulation of OATP1B3 may help to maintain excretion of xenobiotics under cholestatic conditions[66]. Upregulation of the basolateral bile acid export pumps multidrug resistance protein 4 (MRP4, ABCC4) and the organic solute transporter α/β (OSTα/β) is also observed under cholestatic conditions in humans and rodents[63,67,68]. While the expression of Ostα/β is induced by bile acids *via* FXR[69], the upregulation of MRP4 by bile acids is independent of FXR and is observed both on the translational and posttranslational level[63,67,69]. Bile acids increase the expression of different detoxification enzymes through FXR, such as the UDP-glucuronosyltranserase UGT2B4 and the sulfotransferase SULT2A1[40,70,71]. In hepatocytes, bile acids activate FXR, which in turn induces suppression of de novo synthesis, enhances conjugation and detoxification and increases efflux both across the canalicular as well as the basolateral membrane thereby preventing hepatic accumulation of bile acids and liver damage. This is supported by the finding that administration of a synthetic FXR agonist (GW4064) reduced liver injury in rat models of cholestasis[72].

BILE ACIDS MODULATE GLUCOSE HOMEOSTASIS

A link between bile acids and glucose homeostasis was recognized when patients with type Ⅱ diabetes were treated for dyslipidemia with cholestyramine, a bile acid sequestrant[73]. Besides lowering total cholesterol and LDL cholesterol, cholestyramine also improved glycemia and reduced blood glucose levels by 13%[73]. Treatment of isolated rat hepatocytes with glucose increased *FXR* mRNA levels and target gene expression through activation of the pentose phosphate pathway[74] and thus may interfere with bile acid metabolism. Insulin counteracted the glucose effects in these experiments[74]. Vice versa, several recent studies indicate that bile acids modulate hepatic gluconeogenesis, however, the data are controversial. While the expression of the rate-limiting enzyme of gluconeogenesis phosphoenolpyruvate carboxykinase (PEPCK) was upregulated by bile acids *via* FXR in both primary hepatocytes and hepatoma cell lines in one recent study[75], bile acids repressed PEPCK expression in an FXR-dependent and FXR-independent, SHP-dependent mechanism in both HepG2 cells and mouse liver in several other studies[76-79]. Other enzymes involved in gluconeogenesis, such as the glucose-6 phosphatase (G6Pase) and the fructose 1,6-bisphosphatase (FBP1) were also downregulated by bile acids through SHP[77]. Furthermore, activation of FXR may not only reduce gluconeogenesis, but also increase glycogen synthesis the liver, thereby lowering blood glucose levels[80]. These findings are supported by studies with FXR knockout mice, which show increased gluconeogenesis in the liver and reduced glucose uptake in the skeletal muscle, resulting in elevated blood glucose levels[79]. Inhibition of gluconeogenesis by bile acids was ameliorated in FXR knockout mice but observed in wildtype mice, however, a synthetic FXR agonist (GW4064) failed to repress gluconeogenesis in wildtype animals[79]. The authors give two possible explanations for these observations. Either, the *in vivo* pharmacokinetics of the synthetic agonist prevented long term effects on glucose homeostasis, or bile acids alter gluconeogenesis not only through activation of FXR but also through additional signalling pathways, which together lead to the suppression of gluconeogenesis[79]. The later seems more likely and it has recently been described that bile acids stimulated secretion of glucagon-like peptide 1 through activation of the membrane bound bile acid receptor TGR5[81] and thus may lower serum glucose levels and improve insulin resistance in non-insulin dependent diabetes[82].

Furthermore, bile acids can modulate glucose homeostasis through alteration of the cellular hydration state. Hypo-osmotic hepatocyte swelling, which can be induced by taurocholate[52], stimulates within minutes glycogen synthesis[83] as well as flux through the pentose phosphate pathway[84] and inhibits glycolysis and glycogenolysis[85-87]. Besides these rapid mechanisms, cell swelling leads to an increase in *PEPCK* mRNA expression thus linking hepatocyte hydration to carbohydrate metabolism[88]. Hydrophobic bile acids, such as taurolithocholylsulfate (TLCS) and glycochenodeoxycholate (GCDC), can confer insulin resistance in hepatocytes through inhibition of insulin-dependent phosphorylation of the insulin receptor and impaired recruitment of phosphoinositide-3 (PI-3) kinase as well as protein kinase B activation[89]. Tauroursodeoxycholate (TUDCA) restored insulin signalling under these conditions[89]. Cell shrinkage induced by hydrophobic bile acids independently contributes to insulin resistance since hepatocyte shrinkage itself has insulin-antagonistic effects, stimulating glycogenolysis, proteolysis and inhibiting glycogen and protein synthesis[46,85,86,90,91]. However, hyper-osmolarity does not affect insulin-dependent activation of the insulin receptor but rather acts on the level of or downstream to the PI-3 kinase[92]. These data suggest that hydrophobic bile acids confer insulin resistance in the liver through several distinct pathways.

Taken together, these data demonstrate that bile acids through FXR regulate gluconeogenesis, glycogen synthesis and insulin sensitivity[93], therefore FXR agonists may be useful in the treatment of type Ⅱ diabetes. Apart from FXR, the bile acid receptor TGR5 may also influence glucose metabolism and insulin sensitivity *via* GLP-1 secretion, but additional *in vivo*

studies are required to elucidate the role of TGR5 for glucose homeostasis. Furthermore, hydrophobic bile acids confer insulin resistance in the liver, which may be ameliorated by TUDCA treatment.

BILE ACIDS AFFECT LIPID HOMEOSTASIS

The existence of an inverse relationship between bile acid and triglyceride levels has been recognized over three decades ago, when patients with cholesterol gallstones were treated with chenodeoxycholic acid (CDCA)[94]. The administration of CDCA was accompanied by a reduction in plasma triglyceride levels, which was more pronounced in patients with endogenous hypertriglyceridemia[94], therefore CDCA has been suggested for treatment of hypertriglyceridemia[94-96]. The opposite effect was observed in patients who took bile acid binding resins, which lead to an increased production of very low density lipoproteins (VLDL) and an elevation of serum triglyceride levels[97,98]. The mechanisms underlying this bile acid effect on lipid metabolism remained largely unknown, however, the recent findings that FXR knockout mice have elevated liver and plasma triglyceride levels[24,99] and that the expression of a variety of lipid homeostasis-modulating proteins is regulated by FXR (summarized in[7,100]) suggest, that bile acids modulate lipid homeostasis mainly through activation of FXR.

The triglyceride lowering effect of bile acids involves different pathways downstream of FXR. Activation of FXR increases the expression of SHP, which in turn inhibits the liver X receptor (LXR) mediated upregulation of the sterol regulatory element-binding protein-1c (SREBP-1c) and its target gene expression[100]. SREBP-1c serves as master regulator of fatty acid and triglyceride synthesis[101,102]. Both, basal and inducible expression of SREBP-1c is controlled by LXR[101]. Activation of SREBP-1c positively regulates the expression of genes involved in fatty acid synthesis, such as acetyl CoA synthetase, acetyl CoA carboxylase and fatty acid synthetase[102]. Bile acids inhibit SREBP-1c mediated lipogenesis in an FXR-SHP dependent manner, since the effect was also observed after administration of a synthetic FXR agonist and was attenuated in SHP knockout mice[100]. Besides the inhibition of fatty acid and triglyceride synthesis, bile acids can also stimulate the triglyceride clearance from serum through activation of lipoprotein lipase and subsequent hydrolysis of triglycerides in VLDL and chylomicrons. Bile acids activate FXR and subsequently induce the expression of the apolipoprotein CⅡ (ApoC Ⅱ)[103], which serves as an activator of lipoprotein lipase[104,105]. Furthermore, the expression of another apolipoprotein, ApoCⅢ, which is known to inhibit LPL activity[106], is repressed by activation of FXR[107], thus enhancing the hydrolysis of triglycerides from VLDL. The expression of angiopoetin-like protein 3 (Angptl3), which can also inhibit lipoprotein lipase function[108], was decreased by bile acids[100] and may contribute further to bile acid induced triglyceride hydrolysis. Bile acids, such as CDCA, repressed the expression of the microsomal triglyceride transfer protein (MTP) and ApoB[109], which are essential for the assembly of chylomicrons and VLDL particles[110]. A synthetic FXR agonist failed to lower MTP levels[109] and MTP expression in FXR knockout mice was reduced[100] suggesting a FXR-independent action of bile acids on MTP.

Bile acids may also influence lipid metabolism through cross-talk with peroxisome proliferator-activated receptor α (PPARα)-dependent pathways. PPARα is a nuclear receptor, which plays an important role in lipid and lipoprotein metabolism and controls several enzymes critical for fatty acid oxidation[111]. Expression of human PPARα is directly regulated by bile acids and a synthetic FXR agonist, however, murine PPARα expression is not responsive to bile acids[112]. Furthermore, expression of pyruvate dehydrogenase kinase-4 (PDK4) is upregulated by bile acids *via* FXR, which leads to inactivation of the pyruvate dehydrogenase complex with subsequent suppression of glycolysis and increased fatty acid oxidation[113]. Thus, bile acids may lower triglyceride levels *via* FXR-dependent activation of PPARα and PDK4 eventually leading to increased fatty acid oxidation.

Not only VLDL synthesis and turnover is affected by bile acids, but also HDL clearance is modulated through activation of FXR. FXR knockout mice have increased serum VLDL, LDL and HDL levels[24,99]. Reduced expression of the scavenger receptor BI (SRBI) and subsequent delay in hepatic uptake of HDL cholesterol esters account for the increase in plasma HDL in FXR knockout mice demonstrating that SRBI is a target gene of FXR[99].

In summary, bile acids reduce triglyceride levels through several mechanisms. Besides inhibition of triglyceride and VLDL synthesis *via* SREBP-1c-dependent mechanisms and FXR-independent repression of MTP and ApoB, bile acids also promote VLDL clearance *via* effects on ApoCⅡ, ApoCⅢ and Angptl3 and induce fatty acid oxidation *via* PPARα and PDK4. Furthermore, the close connection between bile acid synthesis and cholesterol elimination, underscores the important role of bile acids in the regulation of triglyceride and cholesterol homeostasis.

BILE ACIDS INCREASE ENERGY EXPENDITURE

Bile acids not only regulate lipid and glucose homeostasis but also modulate energy metabolism *via* the membrane-bound bile acid receptor TGR5 (Gpbar-1). TGR5 is coupled to stimulatory G-protein and activation of the receptor by bile acids increases intracellular cyclic AMP levels[18,19]. Administration of bile acids to mice increased energy expenditure in brown adipose tissue and prevented development of obesity and insulin resistance[21]. The stimulation of TGR5 induced an increased expression of the cAMP-dependent iodothyronine deiodinase type 2 (D2), which converts inactive thyroxine (T4) to active 3,5,3'-triiodothyronine and is crucial for adaptive

thermogenesis in brown adipose tissue. The observed metabolic effect of bile acids was abolished in D2 knockout mice. In isolated brown adipocytes and human skeletal myocytes bile acids stimulated TGR5, increased intracellular cAMP, activated deiodinase D2 and lead to an increase in oxygen consumption[21]. Tissues important for thermogenesis, such as brown adipose tissue in rodents and skeletal muscle in humans co-express TGR5 and deiodinase 2 and the TGR5-cAMP-D2 pathway may be activated in these tissues in response to plasma bile acid levels, which rise after food intake, and may therefore regulate diet induced thermogenesis[21]. The important role of TGR5 for energy homeostasis was confirmed by studies with TGR5 knockout mice. Administration of a high fat diet to TGR5 knockout mice led to a significant accumulation of adipose tissue and increase in body weight as compared to wild type littermates[39].

FURTHER ENDOCRINE EFFECTS OF BILE ACIDS

Bile acids have immunomodulatory functions as oral administration of bile acids successfully reduced endotoxin-related complications following surgery in patients with obstructive cholestasis[114-116]. This beneficial effect of bile acids was attributed to inhibition of endotoxin-induced TNF-α production[117].

The bile acid receptor TGR5 is highly expressed in CD14-positive monocytes, alveolar macrophages[18] and Kupffer cells[118], which are resident macrophages in the liver. Bile acids can alter macrophage function by affecting phagocytic activity as well as cytokine production[119-123]. Bile acids inhibited LPS-induced cytokine production in alveolar macrophages and Kupffer cells in a TGR5-cAMP-dependent manner[18,118], thus supporting the hypothesis that TGR5 plays an important role for macrophage function. Activation of TGR5 in Kupffer cells may prevent excessive cytokine production in sepsis-associated or obstructive cholestasis thereby alleviating liver injury.

Bile acids can prevent bacterial overgrowth and mucosal injury in the small intestine of mice. Subsequently, in mice elimination of bile acids from the intestine through bile duct ligation resulted in bacterial propagation, disruption of the epithelial barrier and translocation of bacteria across the mucosa into lymph nodes. These effects could be prevented by the administration of a synthetic FXR agonist, revealing a novel mechanism of bile acid dependent enteroprotection[124]. The antibacterial action of the FXR agonist (GW4064) were indirect since no bacteriostatic effects were observed when ileal contents were cultured in the presence of GW4064[124].

Bile acids may also interfere with interleukin-6 (IL-6) signalling in hepatocytes. IL-6 has hepatoprotective properties and can ameliorate liver injury induced by obstructive cholestasis[125,126]. It has been shown recently, that the hydrophobic bile acid glycochenodeoxycholate (GCDC) impairs IL-6 induced activation of the signal transducer and activator of transcription (STAT) 3 through caspase-dependent cleavage of the IL-6 receptor glycoprotein 130 as well as through MAP kinase-dependent inhibition of STAT3 phosphorylation, thus contributing to the bile acid-induced liver injury[127,128].

Taken together, bile acids may influence immune functions in the intestine and the liver through activation of FXR-, TGR5-, MAP-kinase- and caspase-dependent pathways.

A role for bile acids in regulation of hepatic microcirculation has also been recently suggested. TGR5 is localized in the plasma membrane of sinusoidal endothelial cells of rat liver and is responsive to bile acids[22]. Stimulation of TGR5 increased cAMP levels, activated protein kinase A and lead to a serine phosphorylation of endothelial NO synthetase and subsequent elevation of NO production[22]. Furthermore, activation of TGR5 resulted in an enhanced serine phosphorylation of the CD95 receptor[22], which may promote the internalization of the receptor from the plasma membrane thereby preventing CD95-induced apoptosis as it has been observed in hepatocytes[129].

A role for bile acids in liver regeneration has also recently been identified[130]. Increased bile acid levels after partial hepatectomy promoted liver regeneration which was attenuated in FXR knockout mice, suggesting that these effects are mediated by FXR[130]. Bile acids have been shown to affect cell proliferation, survival and cell death. These effects of bile acids are reviewed in another article in this issue.

Protein metabolism in the liver can also be affected by bile acids *via* alterations in cell hydration. Taurocholate can induce hepatocyte swelling, which is sensed by integrins and leads to the activation of Src-type kinases and mitogen-activated kinases and subsequent inhibition of autophagic proteolysis at the level of autophagosome formation[131-133] (for reviews on hydration-dependent pathways see[46,86,90,91]).

PARACRINE ROLE OF BILE ACIDS

After excretion into bile, bile acids are in close contact with cholangiocytes, the bile duct forming epithelial cells. Bile acids modulate cholangiocyte secretion, proliferation and survival in a paracrine manner (for a recent review see[134]). Taurocholic acid and taurolithocholic acid increased secretin stimulated intracellular cAMP levels and Cl^-/HCO_3^- exchanger activity thus promoting ductal secretion and bile flow[135,136]. These effects were dependent on bile acid uptake into the cholangiocytes and led to an activation of phosphatidylinositol 3-kinase (PI3-K), followed by an increase in cAMP[135,137]. Ursodeoxycholic acid induced ductal secretion through CFTR-dependent secretion of ATP into bile, which in turn activated apical purinergic P_{2Y} receptors and stimulated chloride efflux and fluid secretion[138]. While taurocholic and taurolithocholic acid stimulated proliferation of bile ducts and increased bile duct mass up to 3-fold[135,136], ursodeoxycholic acid has been shown

to inhibit cholangiocyte proliferation in bile duct ligated rats[139], and to prevent cholangiocyte apoptosis in vagotomized, bile-duct ligated rats[140].

Recently, TGR5 has been detected in cholangiocytes of rat liver[118]. Among the endogenous bile acids taurolithocholic acid represents the most potent TGR5 agonist with an EC_{50} of 0.29 μmol/L[141]. The finding that hydrophobic bile acids, such as taurolithocholic acid, increase cAMP in cholangiocytes[135] suggest, that TGR5 may play a role in cholangiocyte secretion and proliferation and prevention of apoptosis[22].

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