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Review

# Bile acids and their receptors

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ABSTRACT

Primary bile acids are synthetized from cholesterol within the liver and then transformed by the bacteria in the intestine to secondary bile acids. In addition to their involvement in digestion and fat solubilization, bile acids also act as signaling molecules. Several receptors are sensors of bile acids. Among these receptors, this review focuses on the nuclear receptor FXRα and the G-protein-coupled receptor TGR5.

This review briefly presents the potential links between bile acids and cancers that are discussed in more details in the other articles of this special issue of Molecular Aspects of Medicine focused on "Bile acids, roles in integrative physiology and pathophysiology".

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## 1. Bile acid synthesis and enterohepatic circulation

Bile acids form a group of molecular species with similar, but not identical, chemical structures, and detergent properties. They play an essential role in the transport, digestion and absorption of nutrients, fat and vitamins. Their synthesis and excretion is the most important mechanism of cholesterol catabolism in mammals. The immediate products of the hepatic synthesis pathway are referred to as the primary bile acids, which structurally differ between vertebrate species. For example, cholic acid (3α,7α,12α-trihydroxy-5β-cholanoic acid, CA) and chenodeoxycholic acid (3α,7α-dihydroxy-5β-cholanoic acid, CDCA) are the primary bile acids in humans, whereas in rodents chenodeoxycholic is metabolized into muricholic acids which are more hydrophobic and less toxic to cells than CDCA. The chemical diversity of the bile acid pool is further increased by the actions of the intestinal bacterial flora, which converts primary bile acids into dozens of secondary bile acids. In humans, deoxycholic acid (3α, 12α-dihydroxy-5β-cholanoic acid) and lithocholic acid (3α-dihydroxy-5β-cholanoic acid) represent the major secondary bile acid species that are derived from cholic and chenodeoxycholic acids respectively. The circulation of this wide variety of bile acid species in the enterohepatic tract ensures the complete solubilization and digestion of hydrophobic nutrients in the small intestine. The importance of bile acids actions in humans is highlighted by the pathologies due to polymorphisms within the DNA sequences of the genes encoding enzymes involved in bile acid synthesis and or their transporters.

### 1.1. Hepatic synthesis of primary bile acids

Primary bile acids are synthesized in the liver through a multistep enzymatic process, involving 17 enzymes localized in different intra-cellular compartments of the hepatocytes (microsomes, mitochondria, cytosol, peroxysomes). These enzymatic reactions lead to modifications of the cholesterol steroid ring structure, followed by side chain oxidation and shortening. Two distinct synthesis pathways can produce bile acids: the classical (or neutral) pathway, and the alternative (or acidic) pathway; they differ from each other by the metabolic intermediates and the

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enzymes involved in the first steps of the synthesis.

The classical pathway is initiated by the conversion of cholesterol into 7α-hydroxycholesterol by the microsomal cytochrome P-450 CYP7A1 (cholesterol 7α-hydroxylase), which is the rate-limiting enzyme of this biosynthesis pathway (Myant and Mitropoulos, 1977). The complex regulation of its activity is of great importance for cholesterol and bile acids homeostasis. A homozygous mutation in the gene encoding Cyp7a1 has been identified in three patients (Pullinger et al., 2002). This mutation leads to a frameshift that abolishes the enzyme activity. These patients show hyperlipidemia and premature gallstone disease.

Experimental models highlight the physiological relevance of this enzyme activity, and of bile acids synthesis in general, is evident from the phenotype of CYP7A1-deficient mice (Ishibashi et al., 1996) (Schwarz et al., 1996). About 85% of these mice die within the first 3 postnatal weeks as a consequence of liver failure, vitamin deficiency and lipid malabsorption. These mice produce only small amounts of hepatotoxic monohydroxy-bile acids. Thought the alternative BA synthesis pathway, in which oxysterols, rather than cholesterol, serves as substrates for 7α-hydroxylation. The contribution of this pathway to the total bile acids synthesis has been estimated at 25% in the mouse.

The alternative pathway involves the hydroxylation of cholesterol at three different positions of the side chain leading to the formation of 24-hydroxycholesterol, 25-hydroxycholesterol and 27-hydroxycholesterol. This reaction is catalyzed respectively by the cholesterol 24-hydroxylase (CYP46A1) expressed mainly in the brain, the cholesterol 25-hydroxylase and the cholesterol 27-hydroxylase (CYP27A1). For further conversion into bile acids, oxysterols undergo 7α-hydroxylation by the microsomal cytochrome P-450 enzymes CYP39A1 for 24(S)-hydroxycholesterol and CYP7B1 for 25-hydroxycholesterol and 27-hydroxycholesterol. The 7α-hydroxy intermediates generated by the classical and the alternative pathways are then converted into their 3-oxo,$\Delta^4$ form, by the action of the microsomal 3β-hydroxy-$\Delta^5$-C27-steroid oxidoreductase (HSD3B7). The products of this enzymatic step can be subsequently altered by two pathways to complete the synthesis of primary bile acids: if the 3-oxo,$\Delta^4$ intermediate is metabolized by the microsomal sterol 12α-hydroxylase (CYP8B1), the end product will be cholic acid; if this 12α-hydroxylation does not occur, the resulting product will be converted ultimately into chenodeoxycholic acid in humans, or into muricholic acid in mice. The ratio in which the two primary bile acids are formed and therefore the final composition of the bile acid pool, is thus determined by the activity of CYP8B1.

Following this step all bile acids are subjected to the actions of two cytosolic enzymes which are members of the aldo-keto reductases family: $\Delta^4$-3-oxosteroid 5β-reductase (AKR1D1) and 3α-steroid dehydrogenase (AKR1C4). These proteins catalyze respectively the reduction of the Carbone 4 double bond, and of the 3-oxo group to an alcohol. The next steps in the biosynthesic process involve the progressive oxidation and shortening of the sterol side chain. First, mitochondrial CYP27A1 introduces an hydroxyl group at carbon 27, before oxidizing this group to an aldehyde and then to a carboxylic acid. The ensuing oxidized intermediates are finally transferred from mitochondria to peroxisomes where the side chain shortening takes place. This process leads to the removal of the three terminal carbons, by a series of reactions analogous to those involved in fatty acid β-oxidation, involving the action of five peroximal enzymes: the bile acid coenzyme A ligase, the 2-methylacyl-coenzyme A racemase, the branched chain acyl-coenzyme A oxidases (ACOX1 et ACOX2), the D-bifunctional enzyme and the peroxisomal thiolase 2.

Prior to their secretion into the bile canalicular lumen, primary bile acids are conjugated at their terminal side chain carboxylic acid with the amino acids taurine or glycine, leading to the tauro- or glyco-conjugated bile salts. This reaction is catalyzed by the peroxisomal enzyme bile acid coenzyme-A: amino acid *N*-acyltransferase (BAAT) which is highly efficient as more than 98% of bile acids excreted from the liver are conjugated. The ratio in which taurine and glycine conjugates are formed (3:1 in physiological conditions in humans) depends on the availability of taurine as BAAT has a greater affinity for this amino acid. Conjugation of bile acids is necessary for their solubilization and secretion into bile, and confers to these molecules their amphipathic nature. This property is essential for the role of bile acids in emulsification of a meal during digestion. Conjugation decreases bile acid toxicity, preventing there passive reabsorption from the enterohepatic tract.

### *1.2. Intestinal bio-transformation of primary bile acids into secondary bile acids*

During the intestinal transit, primary bile acids are subjected to a series of structural modifications by the bacterial flora, including their deconjugation and 7α-dehydroxylation. The first one is catalyzed by the bile salt hydrolase (BSH) belonging to the family of choloyl hydrolases (Ec 3.5.1.24) and expressed by several bacterial species. Some of these deconjugated bile acids are absorbed by the enterocytes and are taken up in the liver where they will be reconjugated. The deconjugation is a prerequisite for the 7α-dehydroxylation, which is restricted to free bile acids. This enzymatic reaction gives rise to the secondary bile acids namely deoxycholic and lithocholic originating respectively from cholic and chenodeoxycholic acids. This combined action increases hydrophobicity and pKa of the bile acids, allowing their absorption by passive diffusion across the colonic epithelium. This hydrophobicity increased is associated with a higher toxicity. Thus high secondary bile acid concentrations in feces, blood and bile may involved in the onset of gallstones and colon cancer.

The bile acid pool is thus composed of a wide variety of primary and secondary bile acids with different physical and chemical properties. This combination of bile acids is necessary for the complete solubilization and absorption of dietary fats during the enterohepatic cycle.

### *1.3. Enterohepatic cycle/circulation of bile acids*

The hepatic neo-synthesized bile acids are actively secreted by the hepatocytes into the bile canalicular lumen by the action of the membranous transporter *Bile Salt Export Pump* (BSEP/ABCB11), a member of the ATP binding cassette superfamily. Bile acid secretion is concomitant with the secretion of other bile components such as phospholipids and cholesterol, which depends on the action of transporters including the *Multi Drug Resistance 3* (MDR3/ABCB4) and the ABCG5/ABCG8 heterodimer respectively. This co-secretion allows the formation of micelles within bile that protect the biliary system from the detergent actions of high bile acids concentrations.

The resulting bile is stored in the gallbladder and will be discharged into the intestinal lumen upon ingestion of a meal through gallbladder contraction induced in response to cholecystokinin (CCK). In the small intestinal lumen, bile acids act as detergents to solubilize and thus facilitate the digestion of dietary fats and vitamins.

Bile acids are then actively and very efficiently reabsorbed at the apical membrane of epithelial cells in the terminal ileum *via* the activity of the Apical Sodium-dependent Bile Acid Transporter (ASBT). Bile acids are bound to the cytoplasmic Ileal Bile Acid Binding Protein (I-BABP) and transported from the apical face to the baso-lateral membrane of the enterocytes where they are exported in the portal vein *via* the action of the heterodimer *Organic Solute*

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