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MINI REVIEW

An important intestinal transporter that regulates the enterohepatic circulation of bile acids and cholesterol homeostasis: The apical sodium-dependent bile acid transporter (SLC10A2/ASBT)

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Summary The enterohepatic circulation of bile acids (BAs) is governed by specific transporters expressed in the liver and the intestine and plays a critical role in the digestion of fats and oils. During this process, the majority of the BAs secreted from the liver is reabsorbed in intestinal epithelial cells via the apical sodium-dependent bile acid transporter (ASBT/*SLC10A2*) and then transported into the portal vein. Previous studies revealed that regulation of the ASBT involves BAs and cholesterol. In addition, abnormal ASBT expression and function might lead to some diseases associated with disorders in the enterohepatic circulation of BAs and cholesterol homeostasis, such as diarrhoea and gallstones. However, decreasing cholesterol or BAs by partly inhibiting ASBT-mediated transport might be used for treatments of hypercholesterolemia, cholestasis and diabetes. This review mainly discusses the regulation of the ASBT by BAs and cholesterol and its relevance to diseases and treatment.

Abbreviations: ASBT, apical sodium-dependent bile acid transporter; BAs, bile acids; PEPT1, peptide transporter 1; OCT1, organic cation transporter 1; OST alpha/beta, organic solute transporter alpha/beta; NTCP, Na+/taurocholate-cotransporting polypeptide; DDIs, drug—drug interactions; SD, Sprague-Dawley; FXR, farnesoid X receptor; SHP, short heterodimer partner; LRH-1, liver receptor homologue 1; RAR/RXR, retinoic acid receptor/retinoid X receptor; SREBP2, sterol response element-binding protein-2; HNF1-alpha, hepatocyte nuclear factor-1-alpha; PPAR-alpha, proliferator-activated receptor-alpha; GR, glucocorticoid receptor; VAD, vitamin D receptor; SHP, small heterodimer partner; EPEC, enteropathogenic *Escherichia coli*; HMGR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; PATD, polyacrylic acid-tetraDOCA conjugate; GCs, glucocorticoids; UDCA, ursodeoxycholic acid; Glp-1, glucagon-like peptide-1; PC, phosphatidylcholine; IBD, inflammatory bowel disease.

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Introduction

The apical sodium-dependent bile acid transporter (ASBT) plays a key role in the enterohepatic circulation of bile acids (BAs) and is expressed at the apical membrane of enterocytes in the ileum, colon, jejunum and, to a lesser extent, duodenum [1]. Regarding the expression of all transporters in the small intestines, the ASBT accounts for 6%, followed by peptide transporter 1 (PEPT1) and organic cation transporter 1 (OCT1) [2]. Mechanistically, the ASBT is electrogenic, requiring the cotransport of two sodium ions together with a bile salt molecule, and the driving force is the inwardly directed Na+ gradient, which is maintained by both the basolateral Na+/K+-ATPase and the negative intracellular potential [3,4]. In addition, the ASBT preferentially transports conjugated BAs (both taurine and glycine) compared with unconjugated BAs [5].

The human *SLC10A2* gene is localized on chromosome 13q33 and is composed of six coding exons spanning approximately 24 kb of DNA [6,7]. A study in *Neisseria meningitidis* demonstrated that the Neisseria ASBT comprises ten transmembrane helices that form two inverted repeat units [8]. A core domain of six helices contains two sodium ions, and the other helices form a panel-like domain [9]. Genetic variants of the ASBT have been identified, including *pP290S* in a patient with Crohn's disease; however, the relationship between genetic variants of the ASBT and clinical diseases or functional consequences is unclear [10].

The enterohepatic circulation of BAs is fundamentally composed of biosynthesis, secretion and reabsorption. BAs are synthesized in the liver from cholesterol by a cascade of enzymes that perform oxidation and conjugation reactions, and the majority of BAs are stored in the gall bladder. After being triggered by food intake, BAs are released into the intestine through the bile duct and further metabolized by gut bacteria into secondary BAs. Approximately 95% of BAs are reabsorbed into intestinal epithelial cells via the ASBT, enter the hepatic portal vein via organic solute transporter alpha/beta (OST alpha/beta) and then enter the liver sinusoids, where they are efficiently transported to the liver [11]. Each bile acid is reabsorbed approximately 20 times on average before being eliminated [11]. ASBT disorders will disrupt the enterohepatic circulation of BAs or some drugs, thus possibly altering the half-life of the drug [12].

The Na+/taurocholate-cotransporting polypeptide (NTCP; *SLC10A1*) is the other transporter of the *SLC10* family that transports BAs from blood to hepatocytes. Compared with NTCP, the ASBT has a considerably narrower substrate specificity. In general, the probability of drug-drug interactions (DDIs) is low for the ASBT [13]. Of note, as one of the handful of transporters suitable for prodrug design in the intestine, the ASBT plays a vital role in enhancing the bioavailability and tissue-selective distribution by transporting BA-drug conjugates [14]. For example, in ASBT-transfected MDCK cells, the ASBT promotes the absorption of the insulin/deoxycholyl-l-lysyl-methylester (DCK) complex [13].

The studies of ASBT performed to date are relatively insufficient, and it is important to pay close attention to the function and regulation of the ASBT. The proper functioning of the ASBT is crucial for the enterohepatic circulation of BAs and cholesterol homeostasis. However, some endogenous compounds or diseases may indirectly affect the ASBT by altering BAs and cholesterol levels. As a consequence, the ASBT is a novel target in these diseases. The current review summarizes the impact of various factors on the ASBT and their mechanisms. We also analyzed the relationship between the ASBT and some diseases involved in BAs or cholesterol dysregulation.

Regulation of the ASBT

ASBT and BAs

The effects of BA homeostasis on ASBT expression and function are complex. Previous results indicated that after common bile duct ligation in Sprague-Dawley (SD) rats, the presentation of BAs to the apical surface of the terminal ileum was reduced, but the expression of ileal ASBT was not altered [15]. However, a different study revealed the negative feedback regulation of BAs on ASBT in mice [16]. Another study showed that ASBT expression is stimulated by the ingestion of cholic acid in rats, potentially through a mechanism that protects the organism from the effects of excessive secondary bile acid production [17].

To maintain BA homeostasis, excessive BAs need to be removed, and BA reabsorption must be decreased. Thus, although the consequences of the BA effect on the ASBT are controversial, the downregulation of this transporter by excessive BAs is more credible. Subsequent investigations analyzed the potential mechanism of this action in different species. In mice, bile acid regulation of the *SLC10A2* gene is mediated by farnesoid X receptor (FXR)-dependent upregulation of short heterodimer partner (SHP) expression [18]. SHP subsequently represses liver receptor homologue 1 (LRH-1)-dependent activation of ASBT expression [18]. FXR-activating ligands downregulate rabbit ASBT expression through the regulatory cascade FXR-SHP-FTF (alpha-fetoprotein transcription factor) [19]. Similarly, in humans, the effects of BAs occur through FXR- and SHP-mediated repression of retinoic acid receptor/retinoid X receptor (RAR/RXR)-induced activation of the ASBT [20].

Different investigators have observed that the *SLC10A2* gene is upregulated, downregulated, or neither by BAs [15–17,21–24]. The difference not only in the various investigated species, but in the lack of unification among experimental models that assess the effects of changes in the BA level on the expression and function of the ASBT might account for the discrepancies that have been observed [15,18,20,25,26].

ASBT and cholesterol

Similar to BA, cholesterol exerts effect on ASBT that varied in different studies. After cholesterol ingestion, the expression of ASBT is upregulated in rabbits, but no change has been observed in rats [27]. However, different studies in mice demonstrated that a cholesterol-enriched diet triggers downregulation of ASBT expression (mRNA and protein) [28].

In humans, circulating ASBT levels vary based on cholesterol levels to properly regulate the cholesterol level of the body. Low levels of cholesterol result in the cleavage