An In-Depth Analysis of The Human Apical sodium-dependent Bile Acid Transporter and Its Crucial Function in The Movement of Biomaterials In Significant Body Organs

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ABSTRACT
This initiative aims to investigate the transit of bile acids from various organs. Enterohepatic circulation depending on particular transporters is demonstrated by the human apical sodium-dependent bile acid transporter (hASBT). Between the inward-facing state of hASBT and its outward-facing state, a conformational shift takes place as a result of the binding of sodium and substrates in this extracellular pocket. In the present work, computational models of inhibition and hASBT inhibitors will be found. Bicarbonate communicates with the central nervous system both directly and indirectly. Numerous compounds containing bicarbonate can affect the brain directly by binding to the Farnesoid-X and Takeda G protein-coupled receptors. Determining whether the postprandial rise in plasma bile acids is also reflected in greater levels of bile acids in the brain and whether these levels are adequate to activate the bile acid receptors expressed in the brain are therefore crucial. According to study results, hASBT may be essential for the movement of biomaterial in the body's primary organs.

Keywords: Enzyme, efflux, influx, protein, transporter.
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INTRODUCTION

Transporters are integral-membrane proteins that allow various types of molecules to pass through the plasma membrane, including ions, small molecules, and proteins. A Human apical sodium-dependent bile acid transporter (hASBT) transports small molecular bile acids from the apical surface of enterocytes and cholangiocytes to the cytoplasm to maintain enterohepatic bile acid circulation. Membrane transport proteins are involved in the transport of a variety of nutrients, metabolic substances, and signaling molecules within cells. The human genome sequence indicates that approximately 500 to 1200 genes encode transport proteins. Often called

multifunctional transporters, transporters play a vital role in the translocation of endogenous substances such as sugars, lipids, amino acids, bile acids, steroids, and hormones across biological membranes; they also influence drug disposition and toxicity[1]. The central role played by hASBT in the enterohepatic circulation of bile acids (BAs) and conjugates means that defects in protein activity can alter BA signaling via the farnesoid X receptor (FXR) and can result in metabolic and cellular dysfunction, resulting in gastrointestinal disorders[2]. A protein called hASBT (SLC10A2) is crucial for maintaining an enterohepatic circulation of bile acids since it is responsible for reclaiming bile acids from the distal ileum lumen. As evidenced by a large amount of research, hASBT plays a critical role in intestinal bile acid absorption[3].

HISTORY

Cloning of hASBT began at Wake Forest University in the laboratory of Paul Dawson. It was subsequently cloned from mice, rats, rabbits, and humans. It contains 348 amino acids (347 in rabbits) and has a molecular weight of 43 kilodaltons (kDa), which differs from the predicted molecular weight of 38 kDa due to glycosylation. On chromosome 13q33, there is the hASBT gene. With its liver orthologue, sodium taurocholate co-transporting polypeptide (NTCP), it shares 35% identity and 63% amino acid sequence similarity. An electrogenic transporter, coupled with sodium, transports bile acids in a 2:1 sodium-to-bile acid stoichiometry. There are suggestions that hASBT may also be a dimer, although it has been shown to be expressed at high levels in the terminal ileum, renal proximal tubules, and bile duct epithelium. hASBT is thought to be a monomer, though some evidence suggests it may be a dimer as well. It is suggested that hASBT is responsible for intestinal reabsorption of bile acids from inherited mutations in hASBT. It is thought to be transported through various organs, including the BBB, liver, intestine, kidney, and placenta. It may also be transported through the GIT

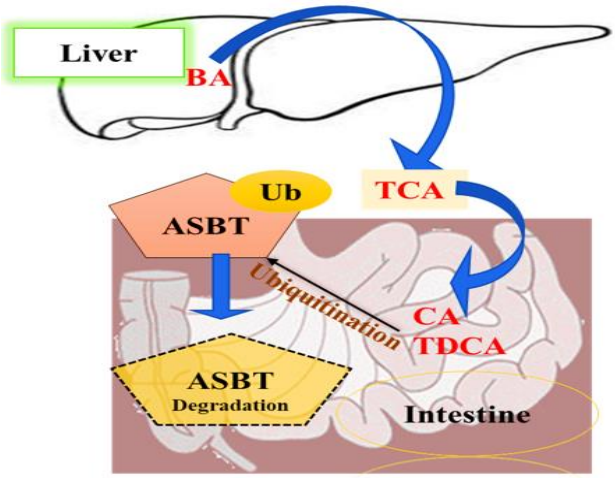

Figure 1: Diagrammatic representation of Bile Acid Synthesis [Apical sodium-dependent bile acid transporter (ASBT); Bile Acid (BA); Tricarboxylic Acid (TCA); Cholic Acid (CA); Taurodeoxycholic Acid (TDCA)]

BILE ACID SYNTHESIS AND RECIRCULATION

There are 17 enzymes that are specifically expressed in the liver that participate in the catabolism of cholesterol into bile salts in the parenchyma. Deficiencies in these mechanisms can result in cholestasis, liver damage, and impaired lipid metabolism, among other problems[4]. BAs can be modified and conjugated to affect their solubility, hydrophobicity, and receptor binding affinity[5]. As bile acids pass through the bile canaliculi, they drain into the bile ducts located in the portal triad. Cholangiocytes line the bile ducts and play a role in BA modification and circulation by cholehepatic shunting, the process by which BAs are reabsorbed from the bile and returned to hepatocytes. As a result of food ingestion, both BAs and fat-soluble vitamins (A, D, E, and K) flow into the intestinal lumen via the common hepatic duct to assist in emulsification, metabolism, and absorption. BAs can also be deposited in the gallbladder to store cholesterol and prevent it from crystallizing. The hASBT reabsorbed approximately 95% of BAs in the distal ileum, and they were then delivered to the liver through the portal system through enterohepatic or portal circulation. Bile acids are deconjugated by the gut microbiome and converted to secondary bile acids prior to absorption or faecal excretion, which affects the gut microbiome community, BA pool, and liver health. Among other compounds, bilirubin, heavy metals, and drug metabolites, bile excretion plays a pivotal role in eliminating endogenous and exogenous compounds. The main components of bile are phospholipids, cholesterol, and bile acids combined into micelles. A bicarbonate molecule is an amphipathic molecule that can form a water-lipid interface. As a result of bile acids, dietary fat is better digested in the small intestine and transported across enterocytes. Bile acids are synthesized in pericentral hepatocytes through the rate-limiting conversion of cholesterol into 7-hydroxycholesterol by cholesterol 7-hydroxylase (CYP7A1). The main primary bile acids, chenodeoxycholic acid (CDCA) and cholic acid (CA), are formed through a complex biosynthesis pathway involving several enzymes (80% of the human bile acid pool). In mice, CDCA is converted into muricholic acid[6]. In the last step of biosynthesis, bile acids are conjugated with glycine (mostly in humans) or with taurine (mostly in rodents). Most sequestered bile acids are in their conjugated state, that is, negatively charged, which prevents passive membrane diffusion. Bacterial modification in the distal intestine produces secondary bile acids from these primary bile acids. The enterohepatic circulation of bile acids is highly efficient (only 3–5% of bile acids are lost through feces), owing to efficient reabsorption by the sodium-dependent bile acid transporter of the terminal ileum (SLC10A2/ASBT) and extrusion into the portal blood by the heterodimeric organic solute transporter of the leukocytes

(SLC51A/B/OST). Physiologically, faecal bile acid loss is compensated for by de novo production of cholesterol in the liver, which increases cholesterol clearance from the body. At the hepatic basolateral membrane, bicarbonate is recycled from portal blood by two transport systems: the sodium-dependent taurocholate co-transporting polypeptide (SLC10A1/NTCP) and the sodium-independent organic anion transporting polypeptide (SLCO/OATP). In the fasting state, human systemic blood bile acid concentrations range from 5 m (fasting) to 3–7 m (postprandial) in the fasting state. Postprandial bile acid is more prominent in portal blood (from 4–27 to 22–55 m). Due to this, bile acid escape from the liver into the general circulation is effectively restricted, with a first-pass extraction fraction varying from 50 to 90%, depending on the bile acid structure[7].

BILE ACID RECEPTOR AGONIST EFFECTS ON THE GUT/LIVER AXIS DURING LIVER DISEASE

BA species influence and regulate gut microbial species composition. Different species and concentrations of *B. aeruginosa* in the gastrointestinal tract may result in increased side effects, including increased intestinal permeability and diarrhea caused by *B. aeruginosa*. Following CDCA treatment, elevated hydrophobic BAs in the colon can be reduced[8], alleviating the toxicity associated with insoluble BA concentrations and mast cell secretory factors (such as histamine or Nerve Growth Factor (NGF)). The gut microbiome of patients with PBC was altered compared to healthy controls, a finding that was partially reversed with Ursodeoxycholic Acid (UDCA)[9].

APICAL MEMBRANE TRANSPORT

Apical membrane transport has also been characterised in some laboratories. The first observations were made on goats in 1974. Sodium Chloride (NaCl) and Potassium chloride (KCl) solutions infused into the teat were absorbed into the bloodstream, while isotonic sucrose solutions infused in the same way drew ions into the milk space. Furthermore, measurements of the effect of changes in the concentrations of Sodium (Na+), Potassium (K+), and Chlorine (Cl) in the milk space of the goat mammary gland on the transepithelial potential difference indicated the presence of a nonselective cation channel and a Cl channel in the apical membrane[10]. Ion transport across membrane vesicles isolated from MFG membranes also supports the existence of K+ and Cl channels. As with the mouse, careful measurements of the basolateral and transepithelial potentials *in vivo* indicated a basolateral potential of 49 Millivolts (mV) and a transepithelial potential of 35 mV. Subtracting the apical potential from the equilibrium potentials across the apical membrane of Na+ and K+ of 26 and 15 mV, the apical potential should be in the range of 14 mV. There is a much higher concentration of Cl in the cell than in the milk of any species where

it has been measured, and the ion is therefore out of electrochemical equilibrium. There is no clear mechanism for maintaining milk's Cl levels[11], but experiments in tissue culture models suggest that Cl transporters may function. On a Transwell support, the cell line 31EG4 forms a monolayer that is satisfactory because it forms a tight monolayer. In line with the *in vivo* mammary gland, glucocorticoids greatly increase the resistance of this monolayer. 31EG4 cells have both the amiloride-sensitive epithelial Na+ channel and the cystic fibrosis transmembrane conductance regulator (CFTR), a Cl channel that is stimulated by cyclic AMP and inhibited by diphenylamine-2-carboxylate. Electrophysiological experiments confirmed that both were located on the apical border of 31EG4 cells by immunostaining[12]. CFTR was also detected at the apical border of the human mammary gland. Cl is transported by this transporter between the milk and the lactating mammary gland cells. This passive channel, however, cannot explain the movement of Cl from the lumen to the cell due to its electrochemical gradient[13]. Women with cystic fibrosis, a cause of defective CFTR, do not have a problem lactating despite the role of CFTR in the ionic composition of milk.

ASBT ON HEPATIC CIRCULATION

To maintain the body's supply of bile acids, enterohepatic circulation of bile acids is essential. The ATP-binding cassette transporter ABCB11 (formerly known as the bile salt export pump "BSEP") transports the bile acids across the hepatic canalicular membrane from the liver. In the small intestine, bile acids solubilize dietary lipids into micelles by transferring them to the lumen of the small intestine. The Human sodium-dependent bile acid transporter (hASBT) in leucocytes is responsible for taking up bile acids upon reaching the ileum. There is little loss of bile acids through faecal excretion, and most of them are reabsorbed in the ileum. Heteromeric organic solute transporters transport bile acids into the portal circulation from the basolateral membrane of the leucocyte[5]. The portal circulation then returns the bile acids to the liver[5]. The enterohepatic circulation of bile acids is highly efficient. However, the liver must synthesize bile acids de novo to replace the small fraction of bile acids that are lost through faecal excretion. A cytochrome P-450 enzyme named cholesterol 7-hydroxylase (CYP7A1) catalyzes the rate-limiting step of the major bile acid synthesizing pathway. The feedback inhibition of hepatic CYP7A1 by bile acids is now well established as the mechanism by which they regulate their synthesis[14]. Leucocytes are stimulated to produce ileal fibroblast growth factor 15/19 by bile acids binding to the farnesoid X receptor (FXR). In the liver, Fibroblast Growth Factor (FGF 15/19) binds to its receptor, FGFR4, causing a yet unknown mechanism to suppress the enzyme CYP7A1. Among the factors limiting hepatocellular transport of bile acids is ABCB11 transport across the

canalicular membrane. Humans have been identified with mutations that cause ABCB11 to stop functioning. If liver transplantation is not performed, the patient develops cirrhosis and dies at a young age due to disruption of the enterohepatic circulation (EHC). ABCB11 is highly polymorphic in humans, with a wide range of expression levels. The impact of this wide variation in the expression of human disease remains unknown. In addition, the effect of ABCB11 overexpression on enterohepatic circulation of bile acids is not fully understood. Humans and rodents produce choleric acid as a primary bile acid. The cholate acid pool size, the fractional turnover rate, and the synthesis rate are the kinetic parameters that allow the description of its production and conservation in the body, such as cycling time and reabsorption efficiency, as well as estimation of relevant enterohepatic cycling parameters[9]. Using radioactive or stable isotope dilution techniques is the preferred method to study bile acid kinetics *in vivo* and has contributed significantly to our current understanding of bile acid physiology in humans. Cholic acid isotope enrichment measurements in small amounts of plasma can now be performed using a microscale stable isotope dilution technique. It is possible to measure the bile salt pool size, fractional turnover rate, and synthesis rate simultaneously in small animals without interrupting the enterohepatic circulation[15].

ASBT ON BLOOD BRAIN BARRIER

Through the internal carotid and vertebral arteries that join in a ring at the base of the brain, bile acids reach the brain via the systemic circulation. Through these arteries, blood reaches the brain. Contrary to other capillaries throughout the body, brain capillary endothelial cells are interconnected by tight junctions, so substances in the blood must travel across the endothelial cell membranes to enter the brain. By protecting the brain from potentially harmful circulating molecules[16], the blood-brain barrier (BBB) is maintained. Several reports indicate that conjugated and unconjugated bile acids can pass through the BBB. It is unclear how this occurs. Since CA, CDCA, and deoxycholic acid (DCA) are phospholipid bilayer-permeable, unconjugated bile acids might diffuse across the BBB. In fact, unconjugated ursodeoxycholic acid crossed the BBB in a dose-dependent manner in patients with amyotrophic lateral sclerosis[17]. Due to their larger structure and amphipathic nature, conjugated bile acids require active transport across the BBB. The BBB and choroid plexus contain multiple xenobiotic and bile acid transporters found in the liver, intestine, and kidney, providing the machinery for bile acid transport across the BBB[18]. They include members of the solute transporter family, such as organic anion transporting polypeptides (OATP) and ATP-binding cassette transporters (ABC), such as multidrug resistance proteins (MRDP). These transporters protect the brain from

potentially harmful molecules by transporting toxic molecules from the brain to the bloodstream. Both basolateral (blood-facing) and apical (brain-facing) transporters facilitate the transport of molecules from the systemic circulation into the CNS. The perfusion of [3H] TCA into the ipsilateral hemisphere of a rat brain in situ failed to produce significant bile acid uptake, indicating that the labelled TCA probably did not cross the BBB. Bile acids are not directly transported across the BBB by their transporters *in vivo*[19].

ASBT ON GUT:

The symbiotic relationship between the human host and the bacteria colonizing the intestinal tract is dynamic. The gut microbiota, also known as gut bacteria, has a variety of effects on the host, ranging from shaping the gut and immune system to altering energy metabolism. Bacteria benefit from living in a nutrient-rich, protected environment. Bile acids (BAs) are also known to be metabolized by intestinal bacteria. Through a complex multi-enzyme process in the liver, BAs are made from cholesterol[20]. By oxidizing and dehydroxylating primary BAs (that is, those synthesized in the liver), intestinal bacteria can convert them into more hydrophobic, so-called secondary BAs. A cycle of enterohepatic circulation occurs when BAs are efficiently reabsorbed by ileal enterocytes and transported back to the liver. BAs reach the colon in relatively small amounts, where some are absorbed and the remainder is excreted in feces. A small number of BAs are synthesized each cycle to maintain a constant circulation, which is equivalent to the loss in faeces under steady-state conditions. In the terminal part of the ileum[21], the hASBT is the main mediator of active BA absorption. The faecal BA excretion of hASBT knockout mice (hASBT-KO) is 10-20 times greater than that of wild-type mice. Despite increased BA synthesis, the BA pool size is significantly reduced, suggesting that alternative (absorptive) mechanisms cannot compensate for the loss of hASBT function. hASBT is negatively regulated in the small intestine by the transcription factor Gata4. In the terminal ileum of adult mice, Gata4 expression is repressed, allowing hASBT expression in enterocytes. Duodenal and jejunal Gata4-iKO knockouts induce hASBT expression[22]. The concentration of BAs in the small intestine is higher in germ-free animals, while germ-free animals excrete fewer BAs faecally. Because germ-free animals have a longer half-life of 14C-labeled taurocholic acid, Comparable results have also been reported for mice treated with antibiotics. The results could be explained by microbial degradation of BAs increasing excretion of BAs in the feces. The faecal BA levels and tracer levels of germ-free rats are not affected by the colonization of a bacterial strain capable of deconjugating BAs. High levels of plasma cholesterol, which is produced by BAs, are a significant cause of cardiovascular diseases. By understanding how bacteria affect BA homeostasis, we

may be able to modulate cholesterol levels in the future. This study compared germ-free mice to conventional mice and treated mice with antibiotics for a short period of time. In this study, we investigated the mechanism by which the absence of gut microbiota affects bile acid metabolism[23]. We found that under normal conditions, gut microbiota strongly regulate enterohepatic recycling of bile acids through a GATA-4 dependent pathway. hASBT expression is regulated spatially and temporally in this process[24].

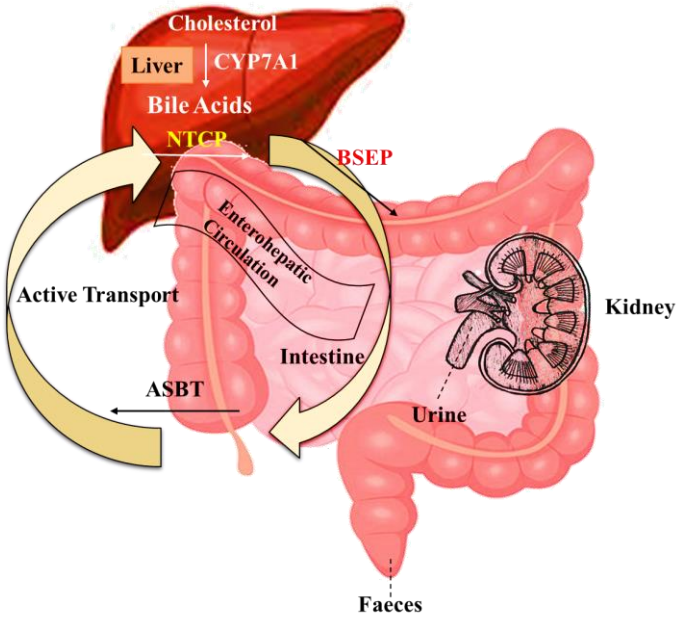

Figure 2: Regulation of hASBT

[Sodium taurocholate co-transporting polypeptide (NTCP); Bile Salt Export Pump (BSEP); Apical sodium-dependent bile acid transporter (ASBT)]

ASBT ON HEART

Cardiovascular tissue also expresses receptors that mediate BA signaling. Farnesoid-X receptors (FXR) are expressed in the vasculature, and their ligands are primary BAs[25]. The activation of vasculature specific FXR improves lipid profiles and influences vascular tension, thereby reducing the risk of atherosclerosis[26]. FXR expression was low in neonatal cardiomyocytes, but these receptors did not appear to be functional. In recent work by Pu et al. on FXR within adult cardiomyocytes and cardiac tissue, activating cardiomyocyte FXR by in vitro CDCA administration significantly induced FXR mRNA expression. CDCA caused dose- and time-dependent apoptosis in these cells when administered in vitro[27]. FXR activation also caused the opening of the Mitochondrial Permeability Transition Pore (MPTP), a protein that plays a role in apoptosis and heart failure[28]. In rats with ischemic heart tissue, FXR expression was significantly upregulated, and inhibition of FXR reduced the severity of the insult,

suggesting that FXR may play a role in cardiac apoptosis and injury. Vitamin D receptors have been found to be localized in the t-tubules of cardiomyocytes[29]. Furthermore, this receptor is known to be liganded by lithocholic acid (LCA), a secondary bile acid. Cardiomyocytes isolated from mice exhibit increased contraction rates, and activation of the receptor causes altered contractility when vitamin D is used rather than LCA[30]. Cardiomyocyte proliferation and morphology were also altered by vitamin D exposure. Cardiomyocytes with VDR deletion are enlarged, hypertrophied, and exhibit systolic and diastolic dysfunction. Therefore, VDR expression and function are relevant to the normal function of cardiomyocytes. However, whether LCA-liganded VDR also affects these pathways has not been demonstrated. In human, rabbit, and bovine heart tissue, as well as mouse tissue and cardiomyocytes, Takeda G protein-coupled receptor-5 (TGR5), also known as G protein-coupled bile acid receptor-1 (GPBAR-1), is expressed at moderate levels by its mRNA. Although TGR5 expression has been demonstrated in the heart, its function remains unknown. It has been shown that BA administration does affect TGR5[31]. The cardiomyocyte-specific TGR5 receptor in mice reduced glycogen synthase kinase-3 (GSK3) and increased protein kinase B following taurochenodeoxycholic acid (TCDCA) and LCA administration. In a dose-dependent manner, taurolithocholic acid (TLCA) administration caused the expression of TGR5 in the endothelium of the bovine aorta to produce nitric oxide in a dose-dependent manner.

CONCLUSION

In this review, we discussed different pathways of bile acid transportation. Abnormal enterohepatic BA circulation and cholesterol homeostasis can undoubtedly alter hASBT expression and function. Cholestasis is typically associated with increased levels of bile salts in the liver and the blood. The clinical implications of this regulatory response may include the pathophysiology and treatment of cholestatic liver disease. Bile salts may contribute to the protection of human cholangiocytes against potentially toxic human hydrophobic bile salts.

ABBREVIATIONS

ABC - ATP-binding cassette transporters
ASBT - Apical sodium-dependent bile acid transporter
BA - Bile Acid
BSEP - Bile salt export pump
CA - Cholic Acid
CDCA - Chenodeoxycholic acid
CFTR - Cystic fibrosis transmembrane conductance regulator
DCA - Deoxycholic acid
EHC - Enterohepatic circulation
FXR - Farnesoid-X receptor
GPBAR1 - G protein-coupled bile acid receptor 1
GSK3 β - Glycogen synthase kinase-3β

hASBT - Human apical sodium-dependent bile acid transporter
kDa - Kilodaltons
MPTP - Mitochondrial Permeability Transition Pore
MRDP - Multidrug resistance protein
mV - Millivolts
NGF - Nerve Growth Factor
NO - Nitric Oxide
NTCP - Sodium taurocholate cotransporting polypeptide
OATP - Organic anion transporting polypeptides
TCA - Tricarboxylic Acid
TCDCA - Taurochenodeoxycholic acid
TDCA - Taurodeoxycholic Acid
TGR5 - Takeda G protein-coupled receptor 5
TLCA - Taurolithocholic acid
UDCA - Ursodeoxycholic Acid
VDR - Vitamin D receptor

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