Molecular Aspects of Medicine 37 (2014) 57–76

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Clinical application of transcriptional activators of bile salt transporters ☆

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ARTICLE INFO

Article history:
Available online 12 December 2013

Keywords:
Nuclear receptors
ATB-binding cassette transporters
Cholestasis

Chemical compounds studied in this article:
24-*nor*UDCA (PubChem CID: 192254)
Bezafibrate (PubChem CID: 39042)
Budesonide (PubChem CID: 5281004)

ABSTRACT

Hepatobiliary bile salt (BS) transporters are critical determinants of BS homeostasis controlling intracellular concentrations of BSs and their enterohepatic circulation. Genetic or acquired dysfunction of specific transport systems causes intrahepatic and systemic retention of potentially cytotoxic BSs, which, in high concentrations, may disturb integrity of cell membranes and subcellular organelles resulting in cell death, inflammation and fibrosis. Transcriptional regulation of canalicular BS efflux through bile salt export pump (BSEP), basolateral elimination through organic solute transporters alpha and beta (OSTα/OSTβ) as well as inhibition of hepatocellular BS uptake through basolateral Na^+-taurocholate cotransporting polypeptide (NTCP) represent critical steps in protection from hepatocellular BS overload and can be targeted therapeutically. In this article, we review the potential clinical implications of the major BS transporters BSEP, OSTα/OSTβ and NTCP in the

Abbreviations: ABC, ATP-binding cassette; AE2 (SLC4A2), anion exchanger 2; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; ALP, alkaline phosphatase; ASBT (SLC10A2), apical sodium-dependent bile acid transporter; ASCOM, activating signal cointegrator-2-containing complex; BCRP (ABCG2), breast cancer resistance protein; BRIC2, benign recurrent intrahepatic cholestasis type 2; BS, bile salt; BSEP (ABCB11), bile salt export pump; CA, cholic acid; cAMP, cyclic adenosine monophosphate; CARM1, co-activator-associated arginine methyltransferase 1; CBDL, common bile duct ligation; CCl4, carbone tetrachloride; CDCA, chenodeoxycholic acid; CtBP, C-terminal binding protein; DCA, deoxycholic acid; DILI, drug-induced liver injury; GCA, glycocholic acid; GGT, gamma-glutamyl transpeptidase; GR (NR3C1), glucocorticoid receptor; GRE, glucocorticoid response element; HNF1α, hepatocyte nuclear factor 1 alpha; HNF4α, hepatocyte nuclear factor 4 alpha; ICP, intrahepatic cholestasis of pregnancy; IL-1β, interleukin-1 beta; IL-6, interleukin 6; IR-1, inverse repeat 1; FGF19/FGF15, fibroblast growth factor 19/15; FXR, farnesoid X receptor (NR1H4); FXRE, FXR response element; JNK, c-Jun N-terminal kinase; LCA, litocholic acid; LRH1 (NR5A2), liver receptor homologue 1; LPS, lipopolysaccharide; LXR (NR1H3), liver X receptor; MAF, musculo-aponeurotic fibrosacroma; MARE, MAF recognition element; MCL-1, myeloid cell leukemia factor 1; MDR1 (ABCB1), multidrug resistance protein 1; MDR2 (ABCB4), multidrug resistance protein 2; MRP2 (ABCC2), multidrug resistance-associated protein 2; MRP3 (ABCC3), multidrug resistance-associated protein 3; MRP4 (ABCC4), multidrug resistance-associated protein 4; NDRG2, NMYC downstrean-regulated gene 2; NF-κB, nuclear factor kappa-B; NRF2, nuclear factor erythroid 2-related factor 2; NTCP (SLC10A1), Na^+-taurocholate cotransporting polypeptide solute carrier family 10 member 1; OATP, organic anion transporting polypeptide; OCA, obeticholic acid; OSTα/OSTβ (SLC51A/SLC51B), organic solute transporter alpha/beta; PBC, primary biliary cirrhosis; PFIC2, progressive familial intrahepatic cholestasis type 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PL, phospholipid; PPARα (NR1C1), peroxisome proliferator-activated receptor alpha; PPARγ (NR1C3), peroxisome proliferator-activated receptor gamma; PSC, primary sclerosing cholangitis; PXR (NR1I2), pregnane X receptor; RARα (NR1B1), retinoic acid receptor; RXRα (NR2B1), retinoid X receptor; SHP (NR0B2), short heterodimer partner; SRC2, steroid receptor co-activator 2; SREBP1, sterol regulatory element-binding protein 1; STAT-5, signal transducer and activator of transcription 5; TαMCA, α-tauromuricholic acid; TβMCA, β-tauromuricholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TUDCA, tauroursodeoxycholic acid; TGR5, G protein coupled bile acid receptor; TNF-α, tumor necrosis factor alpha; TPN, total parenteral nutrition; UDCA, ursodeoxycholic acid; VDR (NR1I1), vitamin D receptor; VPAC-1, vasoactive intestinal polypeptide activated receptor.

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http://dx.doi.org/10.1016/j.mam.2013.12.001
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Fenofibrate (PubChem CID: 3339)
FXR-450/WAY-362450 (PubChem CID: 10026128)
GW4064 (PubChem CID: 9893571)
Ursodeoxycholic acid/UDCA/ursodiol (PubChem CID: 31401)
Obeticholic acid/INT-747/6alpha-ethylchenodeoxycholic acid (PubChem CID: 447715)
Phenobarbital (PubChem CID: 4763)
Rifampicin (PubChem CID: 5381226)

pathogenesis of hereditary and acquired cholestatic syndromes, provide an overview on transcriptional control of these transporters by the key regulatory nuclear receptors and discuss the potential therapeutic role of novel transcriptional activators of BS transporters in cholestasis.
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Contents

1. Introduction

Cholestatic liver injury comprises a wide range of genetic or acquired disorders of bile formation and/or flow ultimately resulting in intrahepatic and systemic accumulation of bile salts (BSs) (Lindblad et al., 1977; Setchell et al., 1997). Primary or secondary dysfunctions of specific hepatocellular transport systems as well as mechanical obstruction/destruction of the bile duct system are central mechanisms causing impaired elimination of biliary constituents. Elevated levels of BSs may cause liver damage due to their lipid solubilizing, proinflammatory and proapoptotic properties (Allen et al., 2010; Faubion et al., 1999; Graf et al., 2002; Guicciardi and Gores, 2002; Krahenbuhl et al., 1994; Reinehr et al., 2003). Since intracellular BS content is regulated by complex mechanisms involving BS uptake, synthesis, detoxification and export, transcriptional stimulation or inhibition of specific transport mechanisms may be critical in limiting intrahepatic retention of BSs and hepatocyte damage. The canalicular BS export pump (BSEP), basolateral efflux transporter organic solute transporters alpha and beta (OSTα/OSTβ) as well as the BS uptake system Na^+-taurocholate cotransporting polypeptide (NTCP) are the major regulators of intracellular BS load and have emerged as promising drug targets in cholestasis.

2. Functional role of BSEP in health and disease

Canalicular excretion of BSs constitutes the rate-limiting step in hepatic BS excretion and represents the driving force for their enterohepatic circulation (Stieger and Beuers, 2011). BSEP (ABCB11), previously also known as sister of p-glycoprotein (sPgp) is a member of the canalicular ATP-binding cassette (ABC) transporter superfamily and represents the major canalicular BS export system (Childs et al., 1995; Gerloff et al., 1998; Nishida et al., 1991; Stieger and Beuers, 2011). Conjugated monovalent BSs are the major substrate for BSEP (Byrne et al., 2002; Gerloff et al., 1998; Hayashi et al., 2005; Noe et al., 2002; Stieger et al., 2000), among which taurochenodeoxycholic acid (TCDCA) is the preferred substrate followed by taurocholic acid (TCA), tauroursodeoxycholic acid (TUDCA) and glycocholic acid (GCA) (Noe et al., 2002).

Various *BSEP* mutations differently impact on transporter activity leading to a wide variety of clinical manifestations in humans (Ho et al., 2010; Kagawa et al., 2008). Complete loss of function *BSEP* mutations manifest as severe cholestasis in progressive familial intrahepatic cholestasis type 2 (PFIC2) (Jansen et al., 1999; Strautnieks et al., 1998, 2008) and patients carry a considerable risk for development of hepatobiliary malignancies (Knisely and Portmann, 2006; Knisely et al., 2006; Scheimann et al., 2007; Sheridan et al., 2012; Strautnieks et al., 2008) likely due to persistent cell injury by elevated concentrations of intracellular BSs and impairment of cell repair mechanisms (Knisely et al., 2006; Palmeira and Rolo, 2004; Sokol et al., 2006; Souza et al., 2008). In contrast, *BSEP* variants with mildly impaired transporter function manifest in form of benign recurrent intrahepatic cholestasis type 2 (BRIC2) (Kubitz et al., 2006; van Mil et al., 2004) and may have a pathogenetic role in

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