ASBT inhibitors in cholangiopathies – good for mice, good for men?

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Bile acids (BAs) retention in the liver is a potent determinant of liver failure risk in chronic cholestatic diseases. Schematically, these diseases include « inherited » forms resulting from ABCB11, ATPB8, ABCB4, CFTR, JAGGED1 gene defects and acquired immune mediated-pathologies such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Biliary drainage either internally or externally are well-known invasive procedures capable to reduce pruritus or retard the rate of progression to cirrhosis in these disorders (1, 2). The rapid increase in our understanding of the molecular basis and pathophysiology of BA-related disorders provides now many opportunities for development of novel therapeutic approaches (3). One of these is targeting one or several players of the gut-liver axis, namely ASBT, OST alpha/beta, FXR and FGF19 with the aim at reducing hepatic BA concentrations.

Absorption of BAs from the intestinal lumen and export into the portal circulation is mediated by a series of transporters expressed on the enterocyte apical and basolateral membranes (4). The ileal apical sodium-dependent bile acid cotransporter (ASBT; gene symbol, SLC10A2) is responsible for the initial uptake of BAs across the enterocyte brush border membrane. The BAs are then efficiently shuttled across the cell and exported across the basolateral membrane by the heteromeric Organic Solute Transporter, OSTα - OSTβ. In the ileocytes, BAs bind to FXR that
activates FGF19 (fgf 15 in rodents) transcription and then its secretion in the portal blood flow. FGF19 and BAs-activated FXR in hepatocytes suppress the transcription of Cyp7A1, the rate limiting enzyme involved in the conversion of cholesterol to BAs. Under normal physiological conditions about 5% of BAs spill over into the colon. In the colon BAs activate chloride channels and water secretion. Spill over of BAs into the colon stimulates 7alpha-dehydroxylation and formation of secondary BAs that activate TGR5. This enhances GLP-1 secretion which will increase insulin secretion and improve insulin sensitivity. ASBT inhibitors interrupt the enterohepatic circulation of bile salts by blocking the entry of BAs in the ileocytes and this may reduce the circulating BA pool, given that the loss exceeds the upregulated BA synthesis.

Mice with targeted disruption of the Mdr2(Abcb4) gene encoding a canalicular phospholipid floppase (Mdr2 −/− mice) spontaneously develop periductal inflammation and fibrosis. These features are linked to the lack of biliary phospholipid secretion and consequently increased concentration of free non-micellar-bound BAs, regurgitation of bile from leaky bile ducts into the portal tract which subsequently cause liver inflammation and fibrosis. Baghdasaryan et al (5) and Miethke et al (6) examined the effects of specific intestinal ASBT inhibitors in this model of sclerosing cholangitis. In the two studies the results were quite similar. Briefly, Asbt inhibition led to increased fecal secondary BA elimination, decreased taurocholate and tauro-beta-muricholate (the primary BAs in mouse) concentrations in blood, liver and bile, fgf15 was profoundly reduced and BAs synthesis was increased. In parallel, bile duct injury, markers of inflammation and fibrosis were attenuated. Despite the massive increase of BA delivery in the colon no evidence of enhanced secretion of GLP-1 was found and no change in blood lipids was noted. Asbt inhibition appeared safe and did not induce diarrhea or colonic inflammation.

The authors of the two studies suggest that ASBT inhibition could be a promising therapeutic approach for cholestatic liver diseases. Before accepting such a premise the expected bad consequences of interruption of the enterohepatic BA circulation in men need to be underlined. Fat soluble vitamin deficiencies, hyperoxaluria and urolithiasis, increased incidence of pigment and cholesterol gallstone, diarrhea, colonic inflammation and carcinogenesis are potential consequences of long-term BAs malabsorption in men. Vitamins A and D are potent inducers of fgf15 and modulators of BA synthesis in mice (7). Unfortunately, neither the status nor the possible role of these vitamins were explored in mice receiving ASBT inhibitors. Colonic inflammation were not detected in the Baghdasaryan’s study, probably due to the absence of
chenodeoxycholate in mice. However the risk of colorectal cancer associated with ASBT inhibition needs to be evaluated carefully. In a recent study, Asbt-deficient mice challenged with azoxymethane alone to induce aberrant crypt foci (the earliest histological marker of colon neoplasia), or a combination of AOM and dextran sulfate sodium to induce colon tumor formation exhibited a 54% increase in aberrant crypt foci and 70 and 59% increases in colon tumor number and size, respectively, compared to littermate controls. Asbt-deficient mice had a striking, 2-fold increase in the number of colon adenocarcinomas (8).

Bile acid sequestrants are orally administered, non absorbable cationic resins that have been used to treat hypercholesterolemia and bile acid malabsorption for many years. A more recently recognized therapeutic benefit of sequestrants is that they lower blood glucose concentrations in patients with insulin resistance. The sequestrant colesevelam is now approved for treating type 2 diabetes. Like ASBT inhibitors, sequestrants inhibit FXR activity, strongly suppress FGF15/19 expression and activate TGR5 in the colon and thus stimulate the expression and secretion of GLP-1 (9). Because of these effects, it would be of great interest to determine whether sequestrants could alleviate liver injury in mdr2-/- mice as ASBT inhibitors do.

Exploring the possible therapeutic benefit of drugs that decrease FXR and FGF15/19 seems nowadays paradoxical since the use of FXR agonists and the FGF19 derivative NGM282 is already in advanced progress in patients with fibrosing cholangiopathies (3). However, as for many other diseases, it can not be excluded that variable combination therapies targeting BA homeostasis will be the best way to offer a personalized and efficient therapeutic approach in the various inherited and acquired forms of chronic cholestatic diseases.

References


