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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

A New Treatment for Chronic Hepatitis B and D Offers Novel Insights Into Obesity and Hepatic Steatosis

Obesity and related nonalcoholic fatty liver diseases (NAFLD) are an increasing health burden in modern Western societies. Obesity facilitates the development of insulin resistance, which is the key driver of metabolic syndrome. Insulin resistance impairs glycogen synthesis and increases hepatic steatosis, leading to the development of NAFLD as hepatic manifestation of metabolic syndrome.[1] Dysfunctional glucose and lipid metabolism along with inflammation and oxidative stress in NAFLD are risk factors for cardiovascular diseases.[1,2] Dietary interventions, exercise, and bariatric surgery are the classic options to treat obesity and NAFLD. Furthermore, the Food and Drug Administration approved pioglitazone and vitamin E for the treatment of biopsy-proven nonalcoholic steatohepatitis (NASH). Both drugs improve insulin sensitivity and histologic features of NASH in the liver. However, pioglitazone is associated with weight gain, and vitamin E increases the risk of prostate cancer.[3] Therefore, research in the fields of obesity, NAFLD, and NASH is increasing, with bile acids and their corresponding signaling as one of the promising targets.

The recent research in NAFLD includes among others farnesoid X receptor (FXR), C-C chemokine receptor types 2 and 5 (CCR2/5), and statins. Research on FXR and the semisynthetic FXR agonist obeticholic acid (OCA) is well-advanced for NAFLD and NASH. OCA has been demonstrated to improve NAFLD activity score in a multicenter, double-blind, placebo-controlled, parallel group, randomized clinical trial[4] and to improve inflammation, fibrosis, and portal hypertension in experimental models of advanced stages of chronic liver disease.[5,6] Nevertheless, OCA treatment leads to increase in cholesterol with its sequelae, and also its tolerability (itching) is questionable.[7] Another option explored lately is the dual antagonist of CCR2/5 cenicriviroc, which seems to decrease hepatic fibrosis in NASH patients in a randomized, double-blind, multinational phase 2b study. However, body weight and NAFLD activity score were not improved under cenicriviroc.[8] In addition, some classic drugs of metabolic syndrome have been tested. Statins beneficially affect the liver phenotype, including steatosis, inflammation, and fibrosis and liver-related complications due to pleiotropic effects.[9,10] Potential hepatotoxicity of statins prevented their use in patients with chronic liver diseases for a long time and was proven false, especially in low doses, lately.[11]

Nevertheless, these drugs do not change obesity. Currently, bariatric surgery is the most effective measure to reduce body weight and seems to be effective on metabolic state and NAFLD, including inflammation and fibrosis,[12] although bariatric surgery is an invasive intervention with corresponding risks.

Donkers et al[13,14] open another promising path for obese patients. Previous and current works describe a novel mechanism using the physiological situation of bile increase and extend circulation time. They targeted Na^+-taurocholate cotransporting polypeptide (NTCP) genetically as well as pharmaceutically. Myrcludex B specifically binds NTCP and prevents receptor stimulation by viruses competitively.[15] Myrcludex B is a chemically synthesized lipopeptide and comprises parts of the preS1 domain of the hepatitis B virus (HBV) large surface protein[16] and represents the first compound of a new class of entry inhibitors for treatment of chronic HBV and hepatitis D virus (HDV) infections. It has been shown to be safe and well-tolerated[17,18] and is currently in phase 2b and phase 3 clinical trials for treatment of HBV and HDV infections, respectively. Because myrcludex B inhibits hepatic bile uptake, it might be potentially used to treat metabolic diseases, which is supported by the current study of Donkers et al.[13] These novel data demonstrate that NTCP inhibition decreases hepatic bile acid clearance and induces glucagon-like peptide 1 (GLP-1) mediated thermogenesis in brown adipose tissue, stimulates fatty acid oxidation, and increases fecal energy excretion, leading to a reduction in body weight and hepatic steatosis. At the same time, thyroid hormone activation and energy expenditure were not affected by myrcludex B.[13] GLP-1 analogues themselves have been already identified as potential targets to treat obesity and NAFLD because they decrease body weight and improve histologic features of NAFLD and NASH[19] and also reduce the risk of cardiovascular diseases.[20]

However, NTCP inhibition might be superior to GLP-1 agonists by using and prolonging the natural meal-dependent bile acid dynamics. The role of reduced NTCP activity was suspected because hepatitis B patients with loss of function mutation of NTCP were less susceptible for cirrhosis or hepatocellular carcinoma.[21] However, drug-drug interactions of myrcludex B need to be investigated more carefully, especially because inhibition of organic anion transporting polypeptides 1B1 has been described already,[22] which could be harmful in concomitant treatment with statins, specifically simvastatin. The present study together with published evidence encourages comprehensive investigation of NTCP inhibition in cirrhosis and complications of portal hypertension, which was beyond the scope of this study.

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Conflicts of interest
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