Letter to the Editor: Blocking Sodum-Taurocholate Cotransporting Polypeptide Stimulates Biliary Cholesterol and Phospholipid Secretion in Mice

TO THE EDITOR:

The recent report[1] that the increased cholesterol and lecithin content of hepatic bile after administration of the complex lipopeptide, myrcludex B, is attributable to its binding to the sodium taurocholate cotransporting polypeptide (NTCP), which causes a redistribution of canalicular bile transport to the pericentral zone, appears to conflict with a previous study.[2] After partial hepatectomy, NTCP expression significantly decreases in the remaining liver along with increased in hepatic bile flow and no change in cholesterol or lecithin output, findings that were also attributed to a shift in bile acid transport to the pericentral zone of the canaliculus.

Given that in the earlier study[2] no drugs were administered, it seems more likely that myrcludex B also affects other aspects of cholesterol and lecithin transport, including not only the carriers, but also pertubations in the canalicular membrane that affect paracellular and/or transmembrane water flow. Currently, very little data exist on the metabolism and excretion of this potentially very useful drug for the management of hepatitis B.

Although bile acid excretion is essential for the generation of cholesterol-lecithin vesicles[3] and their transition to mixed micelles, a second requirement is their canalicular concentration, which is regulated by the rate of trans- or paracellular water flow[4] as evident from the findings in the Claudin-2 knockout mouse[5] Thus, canalicular concentration of bile acids, rather than residence time within the canaliculus, is probably the major determinant of cholesterol and lecithin concentration in canalicular fluid.

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Potential conflict of interest: Nothing to report.

REPLY:

We sincerely thank Dr. Javitt for his interest in and perspective on our article.[1] He indicates that aspecific effects of Myrcludex B should be considered an explanation for increased biliary cholesterol and phospholipid secretion after Myrcludex B treatment as partial hepatectomy (PH) also leads to an increased contribution of pericentral hepatocytes to bile salt uptake and secretion, but biliary cholesterol and phospholipid secretion are not affected. In our opinion, nonspecific Myrcludex B–induced activation of canalicular or sinusoidal transporters seems unlikely given the absence of Na^+-taurocholate cotransporting polypeptide (NTCP) homology with these transporters and our data from experiments with scavenger receptor class B member 1 or adenosine triphosphate

binding cassette subfamily G member 8 null mice. Myrcludex B is an NTCP-specific peptide showing minimal uptake by hepatocytes.

In contrast to the situation of Myrcludex B–mediated NTCP inhibition, PH acutely leads to a higher flow per gram liver; and periportal hepatocytes thus face a large influx of bile salts, close to their maximal transport capacity. As the bile salt to cholesterol/lecithin curve tends to plateau at higher bile salt concentrations, this explains a relatively low biliary cholesterol/lecithin secretion despite increased bile salt transport.[1,2] Another major adaptation upon PH is that the liver is reprogrammed toward rapid restoration of liver mass. This includes reduced cholesterol synthesis in periportal hepatocytes. Cholesterol and phospholipids are also pivotal for membrane formation in newly generated hepatocytes. The pool of hepatic cholesterol/lecithin available for biliary secretion is thus likely decreased after PH. Finally, PH leads to activation of the nuclear bile salt receptor farnesoid X receptor (FXR), stimulating hepatic regeneration. This is in contrast to Myrcludex B–treated mice, in which hepatic FXR activation is unaffected or even reduced and expression of FXR-regulated proliferative genes is repressed.

Dr. Javitt concludes his letter by stating that the canalicular concentration of bile salts is a major determinant of biliary cholesterol and phospholipid secretion. We partially agree with this notion but note that the amount of lipid secreted per bile acid molecule is variable[2] and that the location matters. Not hampered by adaptations occurring during liver regeneration, we have directly investigated zonation-related differences in bile formation using a very specific NTCP inhibitor combined with monitoring the distribution of a fluorescent bile salt.[1] The results are in line with a shift of hepatic bile salt uptake from predominantly periportal toward more pericentral hepatocytes, leading to increased canalicular exposure and more cholesterol and phospholipid excretion in bile while total biliary bile salts are not increased or are even decreased. It is not known to what extent such a shift occurs in the regenerating liver after PH, and given the complex adaptive changes after PH, this is difficult to predict without experimental data.

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