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EDITORIAL

Quantifying the Complexities of Bile Acid Metabolism in Man: Continued Progress

Bile acids are multifunctional end products of cholesterol metabolism that have long been known to facilitate the intestinal absorption of dietary lipids by micellar solubilization. In the past decade, bile acids have had renewed interest because of the discovery of their signaling properties as well as the marketing of a modified bile acid (obeticholic acid) for the treatment of primary biliary cholangitis. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, a physiology-based pharmacokinetic (PBPK) model of bile acid metabolism in health and in certain disease conditions is described by Voronova et al.[1] She has led a consortium of investigators from Russia, Oman, and Sweden, coming from both industry and academia, whose aim was to develop the most complete PBPK description of bile acid metabolism in human beings that is currently available. Their work was stimulated by a similar effort nearly 40 years ago by Molino and Hofmann together with colleagues from the Politechnico University in Torino, Italy.[1,2] The effort of Voronova et al[1] extends the earlier work, however, by also including the pharmacodynamic effects resulting from activation of the nuclear receptor Farnesoid X receptor by bile acids. Their model also includes changes in the plasma level of C4, an early intermediate in bile acid biosynthesis, whose plasma level correlates linearly with the rate of bile acid synthesis. The PBPK model of Molino and Hofmann has also been used to characterize the metabolism of obeticholic acid in health and in cirrhosis.[3]

Bile acid chemistry is complex, and its understanding is thwarted by a lamentable nomenclature that is based on studies of bile acids from nearly 2 centuries ago. Chenodeoxycholic acid is the default bile acid, with its hydroxy group at carbon (C)-3 deriving from cholesterol, its precursor, and its hydroxy group at C-7 resulting from 7-hydroxylation by *cyp7A1*, the committed step in bile acid biosynthesis. In vertebrates, 1 more OH group usually is added to form a trihydroxy bile acid. Generally, this is at C-12, to form cholic acid, but other common sites of additional hydroxylation are at C-6 (mice and swine) or at C-16 (birds).[4]

Bile acid metabolism is complex because bile acids are exposed to the intestinal microbiome, which converts primary bile acids to secondary bile acids. These, in turn, may be absorbed, join the circulating primary bile acids, and undergo further metabolism. Voronova et al[1] included deoxycholic acid in their simulation, which is reasonable because it is a major bile acid in human beings. Lithocholic acid, which is formed by bacterial 7-dehydroxylation of chenodeoxycholic acid, was not included in their model because it is esterified with sulfate (at C3) in the liver after absorption from the colon; sulfated lithocholate does not undergo intestinal absorption and rapidly is lost from the circulating bile acids.

Early work on bile acid physiology led to the hypothesis that bile acids themselves down-regulate their own synthesis. Investigators were puzzled when intravenously infused bile acids did not down-regulate bile acid biosynthesis, but intestinally infused bile acids did. The protein fibroblast growth factor (FGF)19 was identified as the regulatory signal coming from the intestine. Uptake of FGF15 by the hepatocyte was mediated by FGFR4 and B-Klotho, and led to down-regulation of bile acid synthesis. Thus, this pathway of down-regulation of bile acid biosynthesis involves multiple participants, and impairment in any one of their activities should lead to up-regulated bile acid synthesis manifest clinically as diarrhea.

Voronova et al[1] also simulated the effects of decreasing ileal bile acid transport by pharmacologic inhibition of ASBT, the ileal apical sodium-dependent bile acid transporter. Such blockage results in decreased FGF19 release, increased hepatic synthesis of bile acids, and increased passage of bile acids into the colon where they undergo deconjugation. They noted that cholic acid is too polar to undergo appreciable passive absorption. Therefore, the bacterial conversion of cholic acid (membrane-impermeable) to deoxycholic acid (highly membrane-permeable) becomes important for bile acid conservation. Another insight from their modeling is that bile acid synthesis increases during the fasting state because of decreased Farnesoid X receptor activation causing decreased FGF19 release. The increase in bile acid synthesis is signaled by an increase in plasma C4 levels.

Investigators whose research is concerned with bile acids should be grateful for the comprehensive PBPK model of bile acid metabolism in human beings by Voronova et al[1] that substantially advances our understanding of human hepatobiliary physiology.

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References

1. Voronova V, Sokolov V, Al-Khaifi A, Straniero S, Kumar C, Peskov K, Helmlinger G, Rudling M, Angelin B. A physiology-based model of bile acid distribution and metabolism under healthy and pathologic conditions in human beings. Cell Mol Gastroenterol Hepatol 2020;10:149–170.
2. Hofmann AF, Molino G, Milanese M, Belforte G. Description and simulation of a physiological pharmacokinetic model for the metabolism and

enterohepatic circulation of bile acids in man. I. Cholic acid in healthy man. J Clin Invest 1983; 71:1003–1022.
3. Hofmann AF, Hagey LR, Krasowski MD. Bile salts of vertebrates: structural variation and possible evolutionary significance. J Lipid Res 2010; 51:226–246.
4. Edwards JE, LaCerte C, Peyret T, Gosselin NH, Marrier JF, Hofmann AF, Shapiro D. Modeling and experimental studies of obeticholic acid exposure and the impact of cirrhosis stage. Clin Transl Sci 2016;51:226–246.

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Conflicts of interest
The author discloses no conflicts.


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