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Conflicts of interest

The author discloses the following: C. Richard Boland has been a co-author on prior articles with members of the EPICOLON consortium as part of large collaborations, but was not involved in any of the planning or execution of this project, or writing of this manuscript, had no prior knowledge of this work, and was not involved in the review or any aspect of this work before being invited to write an editorial to accompany the manuscript.

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When Bile Acids Don't Get Amidated

See "Genetic defects in bile acid conjugation cause fat-soluble vitamin deficiency," by Setchell KDR, Heubi JE, Shah S, et al, on page 945.

Bile acids are attracting increasing attention in the medical community because they do not only fulfill a long-known role of micellar solubilizers,[1] mediating the intestinal uptake of dietary fats and fat-soluble vitamins, but have been unraveled more recently as potent signaling molecules and metabolic integrators both in and outside the liver.[2] Consequently, a number of bile acid analogs are being tested as potential therapeutic agents for hepatic and extrahepatic diseases.[2] Bile acid synthesis[3] as well as secretion and re-uptake of mainly glycine- and taurine-conjugated bile salts[4] represent key functions of the human liver: Conjugated bile salts form two thirds of organic compounds in human bile and are efficiently recycled via the enterohepatic circulation, as first described by Reverhorst and Borelli 3 centuries ago. In liver, bile acids directly modulate their hepatocellular uptake, synthesis, and biliary secretion at both the transcriptional level (via activation of bile acid-sensitive nuclear receptors such as farnesoid X receptor or pregnane X receptor), and at the posttranscriptional and posttranslational levels via modulation of diverse signaling cascades.[5] In extrahepatic tissues, expression of the membrane bile acid receptor TGR5 sensitizes cells to high levels of hydrophobic bile salts.[6]

Bile acid synthesis from cholesterol is restricted to the liver and represents the major catabolic pathway of cholesterol responsible for about 90% of its breakdown. Bile acid synthesis requires 17 enzymatic reactions in different subcellular compartments of the hepatocyte (Figure 1)[3] and its key enzymatic steps are tightly regulated by nuclear hormone receptors, other transcription factors, and posttranscriptional signaling chains.[2] The end products are glycine- and taurine-conjugated bile acids, which are effectively secreted into bile with <2% of bile acids re-

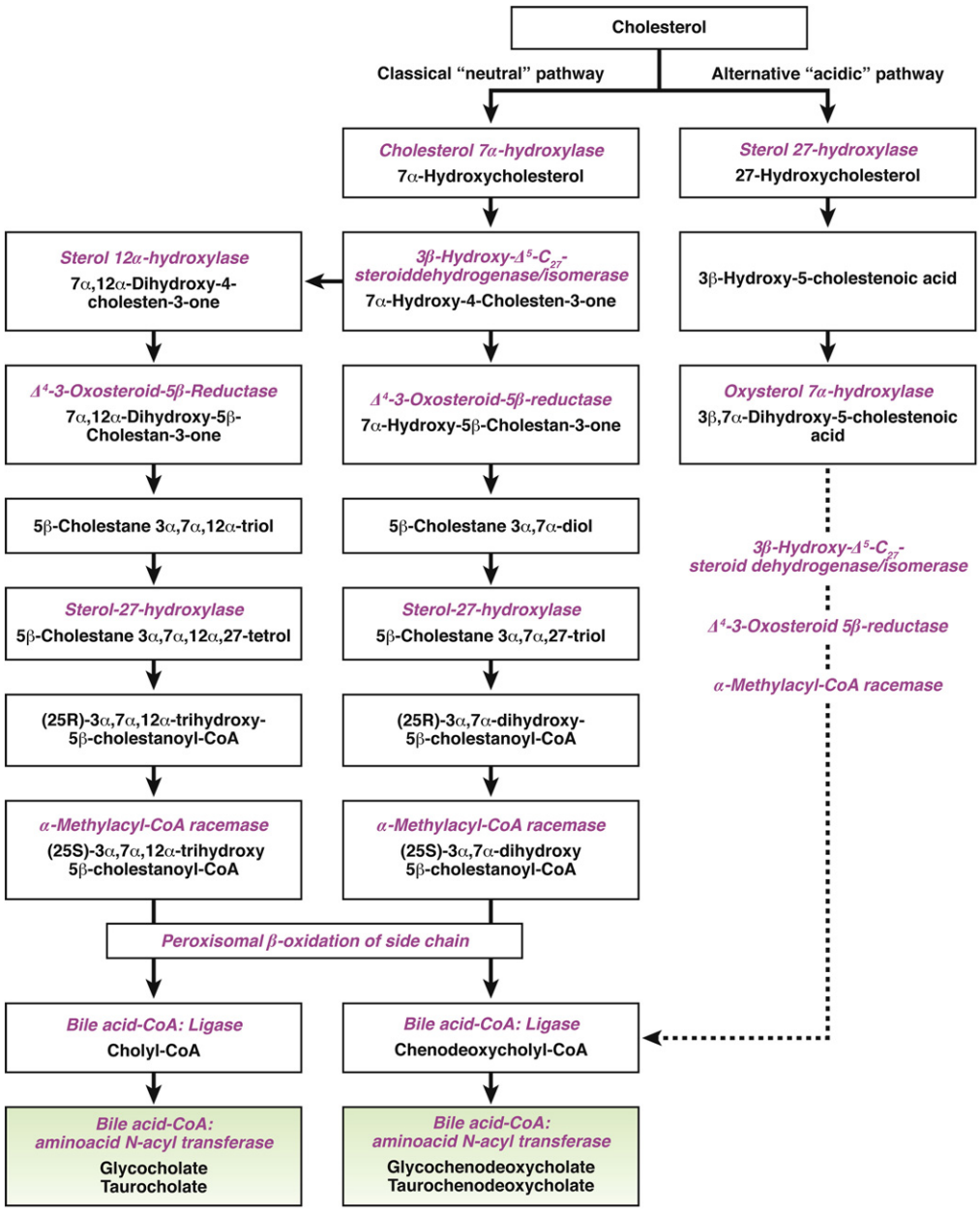

Figure 1. Biosynthesis of bile acids. Primary bile acids chenodeoxycholic acid and cholic acid are synthesized from cholesterol in the human liver via the neutral and to a much lesser extent via the acidic pathway that is of particular relevance in the first period of life. Enzymes for which inborn errors of metabolism have been characterized are given in italics. The diseases are usually named by the defective enzyme, followed by deficiency, namely, 3β-hydroxysteroid-Δ^5-C_{27}-steroid dehydrogenase deficiency. Sterol 27-hydroxylase deficiency causes cerebrotendinous xanthomatosis (CTX). Zellweger syndrome is among the peroxisomal defects. Setchell et al[10] describe patients with mutations in the gene *BAAT* encoding the bile acid-CoA: aminoacid N-acyl transferase (*highlighted in green*). Modified with kind permission from Springer Science and Business Media.[8]

maining in the unconjugated form.[7] Various genetic defects in bile acid synthesis have been identified in the past (Figure 1). Their clinical manifestations may range from liver failure in early childhood to cirrhosis or progressive neuropathy in the adolescent or adult.[8,9]

In the present issue of GASTROENTEROLOGY, Setchell et al[10] describe 10 pediatric patients with a defect of the last step of bile acid synthesis, a peroxisomal bile acid conjugation defect, namely, amidation with glycine or taurine in the C_{24} position of the bile acid molecule (Figure 1). A key clinical finding in these pediatric patients, in whom the diagnosis was made between 3 months and 14 years of age, was the deficit of fat-soluble vitamins and its sequelae, severe coagulopathies and/or rickets in half of them. In contrast with most other defects in bile acid synthesis, serum liver tests and/or liver histology were not regularly affected in those children who had undergone blood testing or liver biopsy.

The biochemical and clinical data clearly show the importance of conjugated bile acids for the absorption of fat-soluble vitamins in the small intestine. Conjugation of bile acids with glycine or taurine, in healthy humans at a ratio of about 3:1,[7] increases the molecular weight and, at least for the taurine conjugate, markedly lowers the pK_a, thereby enhancing aqueous solubility and decreasing carrier-independent uptake into duodenal or jejunal mucosa cells of the negatively charged bile salt molecule at the pH of the small intestine. In contrast, unconjugated proton-