

## HEALTHCARE PROFESSIONAL

Inborn errors of bile acid synthesis are now recognized as a category of metabolic liver disease (Setchell & Heubi, 2006). Individuals with inborn errors of bile acid synthesis lack the enzymes needed to synthesize the primary bile acids, cholic acid and chenodeoxycholic acids (CDCA). This deficiency in activity of specific enzymes involved in bile acid synthesis results in diminished production of primary bile that are essential for promoting bile flow and the concomitant production of high concentrations of atypical bile acids and bile acid intermediates (Heubi et al., 2007). The enzyme deficiency allows these bile acid intermediates that are the substrates for a particular enzyme, to accumulate and these can be metabolised to an array of unusual bile acids, several of which have been shown to be hepatotoxic. The absence of primary bile acids causes hepatocytes to continuously metabolize cholesterol in an attempt to establish a normal bile acid pool. The result is the continued production of high concentrations of these hepatotoxic metabolites, which cause a progressive cholestasis. The liver disease associated with these inborn errors in bile acid synthesis is progressive and, if untreated, may lead to death from cirrhosis and liver failure (Heubi et al., 2007). Bile acids belong to the steroid class and are classified as acidic sterols.

In humans, the principal bile acids are synthesised in the liver. Hepatocytes convert cholesterol to two highly polar primary bile acids: cholic acid, a trihydroxy-bile acid with hydroxyl groups at C-3, C-7 and C-12 ( $3\alpha,7\alpha,12\alpha$ -trihydroxy- $5\beta$ -cholanoic acid); and chenodeoxycholic acid, a dihydroxy-bile acid with hydroxyl groups at C-3 and C-7 ( $3\alpha,7\alpha$ -dihydroxy- $5\beta$ -cholanoic acid). These bile acids are extensively conjugated to the amino acids glycine and taurine (Heubi et al., 2007).

Bile acid biosynthesis is complex with synthesis of the full complement of bile acids requiring at least 17 enzymes. The pathway involves the addition of hydroxyl groups to the ring structure of cholesterol and the oxidation and shortening of the cholesterol side-chain (Russell & Setchell, 1992). The Biosynthetic Pathway is depicted in Figure 2.5.1-

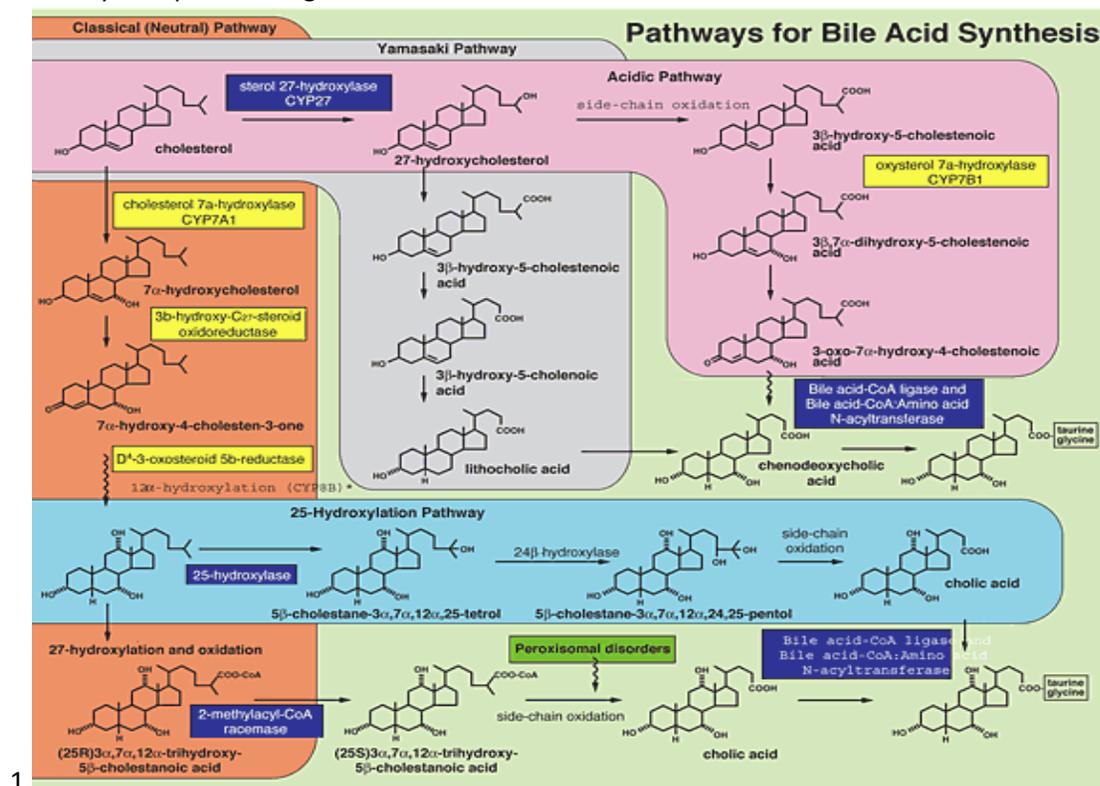


Figure 2.5.1-1: Bile acid synthesis (Bove et al., 2004)

The enzymes required for bile acid biosynthesis are located in different hepatocyte organelles; C-27 hydroxylation occurs mainly in the mitochondria, whereas further ring structure modification is performed in the cytoplasm. Sidechain modification and conjugation are mainly performed in peroxisomes (Bove et al., 2004).

Bile acids perform several important functions (Heubi et al., 2007). They are the major catabolic pathways for the elimination of cholesterol from the body. Bile acids provided the primary driving force for the promotion and excretion of bile and are essential to the development of the biliary excretion route for the elimination of endogenous and exogenous toxic substances, including bilirubin, xenobiotics and drug metabolites. Within the intestinal lumen, the detergent action of bile acids facilitates the absorption of fats and fat-soluble vitamins (Heubi et al., 2007).

Inherited mutations in the genes encoding the enzymes involved in bile acid synthesis cause a spectrum of human disease ranging from life-threatening manifestations such as liver failure in early childhood to progressive neuropathy in adults. The consequences of inadequate bile acid synthesis also include a variable spectrum of fat and fat-soluble vitamin malabsorption syndromes. Nine recognised inborn errors of bile acid metabolism have been identified that lead to enzyme deficiencies and impaired bile acid synthesis in infants, children and adults. Other enzyme defects may occur but have yet to be identified. Patients may present with neonatal cholestasis, neurologic disease or fat and fat-soluble vitamin malabsorption. If untreated, progressive liver disease may develop or reduced intestinal bile acid concentrations may lead to serious morbidity or mortality (Heubi et al., 2007).

Disorders in bile acid synthesis and metabolism can be broadly classified as primary or secondary. Primary enzyme defects involve congenital deficiencies in enzymes responsible for catalyzing key reactions in the synthesis of cholic and chenodeoxycholic acids. The primary enzyme defects include:

- 3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase (also known as 3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid dehydrogenase/isomerase or 3 $\beta$ -HSD or HSD3 $\beta$ 7) deficiency
- $\Delta$ 4-3-oxosteroid 5 $\beta$ -reductase ( $\Delta$ 4-3-oxo-R or AKR1D1) deficiency
- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency
- Defective bile acid amidation due to failure to conjugate with glycine and/or taurine
- 2- (or  $\alpha$ -) methylacyl-CoA racemase (AMACR) deficiency
- Oxysterol 7 $\alpha$ -hydroxylase (CYP7B1) deficiency
- Cholesterol 7 $\alpha$ -hydroxylase (CYP7A1) deficiency
- Trihydroxycholestanoic acid (THCA) CoA oxidase deficiency
- Side-chain oxidation defect in the sterol 25-hydroxylation pathway

The most common enzyme deficiency appears to be 3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase deficiency, followed by  $\Delta$ 4-3-oxosteroid 5 $\beta$ -reductase (AKR1D1) deficiency, sterol 27-hydroxylase (CTX) deficiency and amidation defects (Heubi et al., 2007).

Secondary metabolic defects that impact primary bile acid synthesis include peroxisomal biogenesis disorders such as Zellweger's cerebro-hepato-renal syndrome and related disorders. Generally, these rare genetic autosomal recessive diseases manifest as progressive cholestatic conditions that can lead to liver failure and possibly fat-soluble vitamin malabsorption syndromes (Bove et al., 2004).

Liver diseases due to defects in bile acid synthesis are inexorably characterized by progressive hepatic destruction with impairment of essential function, resulting in either acute or chronic liver failure. Clinical severity is highly variable depending on the defect. Generally, clinical testing reveals deficiency of normal serum bile acids, the presence of atypical bile acids in serum, urine and bile, elevated serum

aminotransferases (indicators of hepatocellular injury), and normal serum  $\gamma$ -glutamyl transferase (GGT) (an indicator, when elevated, of bile duct epithelial injury).

Progression of liver disease is most rapid in defects in sterol nuclear modification that result in the accumulation of toxic monohydroxy or unsaturated oxo-bile acids. Reduced bile flow caused by the combination of atypical bile acids and reduced primary bile acids produces cholestasis in  $3\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase deficiency,  $\Delta$ 4-3-oxosteroid  $5\beta$ -reductase, oxysterol  $7\alpha$ -hydroxylase deficiency, and defects of side-chain oxidation and peroxisomal biogenesis.

Pathological findings may include intralobular cholestasis with giant cell transformation, prevalence of necrotic hepatocytes including giant cell forms, and hepatic injury concentrated at the portal limiting plate where the smallest bile ductules are injured (cholangiolitis). Fibrosis is typically progressive and periportal. Interestingly, pericellular (intralobular) fibrosis, a pattern that is common in other metabolic liver disorders, is minimal or absent. Larger interlobular bile ducts and major bile ducts are spared, an important correlate of the low serum GGT levels that typify defects in bile acid synthesis (Witzleben et al., 1992; Daugherty et al., 1993; Bove et al., 2000; Bove et al., 2004).

Ultrastructure of the liver with defects in bile acid synthesis has thus far revealed nonspecific changes in structure and appearance of trapped bile residue in canaliculi, with the possible exception of unusual canalicular morphology in infants with liver failure due to  $3\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase deficiency (Daugherty et al., 1993).

Some defects in bile acid synthesis manifest with neuropathology rather than liver disease. 2-methylacyl-CoA racemase and D-bifunctional protein, which are localised in peroxisomes, primarily cause neurological defects with or without liver disease (Setchell et al., 2003). It is thought that the bile acid intermediates that are substrates for these enzymes can function as bile acids. Both enzymes are not only involved in bile acid synthesis, but also act on branched-chain fatty acids.

References (representative scientific articles):

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