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Review Article

Bile acid receptors link nutrient sensing to metabolic regulation

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a common liver disease in Western populations. Non-alcoholic steatohepatitis (NASH) is a more debilitating form of NAFLD characterized by hepatocellular injury and inflammation, which significantly increase the risk of end-stage liver and cardiovascular diseases. Unfortunately, there are no available drug therapies for NASH. Bile acids are physiological detergent molecules that are synthesized from cholesterol exclusively in the hepatocytes. Bile acids circulate between the liver and intestine, where they are required for cholesterol solubilization in the bile and dietary fat emulsification in the gut. Bile acids also act as signaling molecules that regulate metabolic homeostasis and inflammatory processes. Many of these effects are mediated by the bile acid-activated nuclear receptor farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5. Nutrient signaling regulates hepatic bile acid synthesis and circulating plasma bile acid concentrations, which in turn control metabolic homeostasis. The FXR agonist obeticholic acid has had beneficial effects on NASH in recent clinical trials. Preclinical studies have suggested that the TGR5 agonist and the FXR/TGR5 dual agonist are also potential therapies for metabolic liver diseases. Extensive studies in the past few decades have significantly improved our understanding of the metabolic regulatory function of bile acids, which has provided the molecular basis for developing promising bile acid-based therapeutic agents for NASH treatment.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic fat accumulation (steatosis) that is not caused by alcohol consumption.[1,2] NAFLD is a common liver disease and affects ~30% of the Western population.[1,2] Currently, simple hepatic steatosis does not require clinical treatment. However, in some patients it may progress to nonalcoholic steatohepatitis (NASH), which is a more debilitating form of NAFLD characterized by the presence of hepatocellular injury and inflammation. Patients with NASH have a significantly increased risk of developing fibrosis, cirrhosis, liver cancer and liver failure. In addition, patients with NASH have a significantly higher risk of cardiovascular diseases (CVD), which are the leading cause of morbidity and mortality among these patients.[3,4] NASH pathogenesis is incompletely understood and is considered a result of complex interactions between genetic and environmental factors. Patients with NASH are often obese and diabetic and commonly possess other features of metabolic syndrome, such as insulin resistance, dyslipidemia and hypertension. It is thought that over-nutrition and obesity cause adipocyte stress and dysfunction, leading to inflammatory infiltration and adipose insulin resistance. As a result, uncontrolled lipolysis causes increased free fatty acid release and fatty acid lipotoxicity in non-conventional fat storage tissues, such as the skeletal muscle, pancreas and liver.[2,5] Adipose-derived fatty acids serve as a major source of hepatic fat in NAFLD.[2,5] Increased hepatic fat accumulation in the presence of insulin resistance further promotes hepatic triglyceride overproduction, which is a key contributing factor to dyslipidemia and higher CVD risk. Unfortunately, there are no approved therapies for NASH. Patients who develop end-stage liver disease require a liver transplantation. New therapeutic interventions that treat both liver-related and cardiovascular-related complications in patients with NASH are still needed.

Bile acids are cholesterol derivatives produced only in the hepatocytes of the liver.[6] Hepatic bile acid synthesis represents the only quantitatively significant route for cholesterol elimination. Bile acids are amphipathic physiological detergents that facilitate dietary cholesterol, lipid and fat-soluble vitamin absorption in the

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small intestine.[6,7] Studies over the past couple decades have demonstrated that bile acids act as signaling molecules that regulate intracellular signaling pathways. Many of these pathways are critically involved in the regulation of lipid, glucose and energy metabolism. In addition, bile acid synthesis and plasma bile acid concentrations are sensitive to circadian and nutrient regulation, which suggests that bile acid signaling integrates nutrient sensing to the maintenance of metabolic homeostasis. Drugs targeting bile acid metabolism and signaling have been used clinically to treat patients with hypercholesterolemia and hyperglycemia.[6] New therapies targeting bile acid signaling pathways are currently being developed to treat fatty liver diseases. In this review, we will summarize the current knowledge of bile acid synthesis regulation and the mechanisms underlying bile acid signaling regulation of metabolic homeostasis. These comprise the molecular basis for the development of bile acid-based therapies for fatty liver disease.

2. A brief introduction on bile acid metabolism

Cholesterol conversion into bile acids involves several enzymatic and non-enzymatic reactions (Fig. 1A). Hepatocytes are the only cell type that expresses all the required bile acid synthetic enzymes, which are located in different intracellular compartments, including the endothelium reticulum (ER), cytosol, mitochondria and peroxisomes. Cholesterol 7α-hydroxylase (CYP7A1), which is a cytochrome P450 (CYP) enzyme residing in the ER, catalyzes the first and rate-limiting step in the classic bile acid synthesis pathway to convert cholesterol to 7α-hydroxycholesterol. 7α-hydroxycholesterol is subsequently converted to two primary bile acids, chenodeoxycholic acid (CDCA) and cholic acid (CA) (Fig. 1A). CA synthesis involves the C-12 hydroxylation of 7α-hydroxy-4-choesten-3-one to 7α, 12α-dihydroxy-4-cholesten-3-one, which is catalyzed by another cytochrome p450 enzyme sterol 12α-hydroxylase (CYP8B1) that is located in the ER (Fig. 1B). As displayed in Fig. 1A, CDCA can also be produced via the alternative bile acid biosynthesis pathway, in which cholesterol is first converted to 27-hydroxycholesterol by the mitochondrial sterol 27-hydroxylase (CYP27A1). Newly synthesized bile acids are conjugated to the amino acids glycine or taurine on the side chain to form N-acyl amidates, a process that is catalyzed sequentially by two enzymes, bile acid-CoA ligase and bile acid-CoA:amino acid N-acyltransferase.[8,9] Conjugation of bile acids increases bile acid water-solubility under physiological pH and decreases bile acid toxicity. The bile of human patients with defective bile acid-conjugating enzymes contains high levels of unconjugated bile acids, which causes fat-soluble vitamin malabsorption, growth retardation and liver injury.[10,11] Human bile contains glycine- and taurine- conjugated bile acids in a roughly 3:1 ratio, while mouse

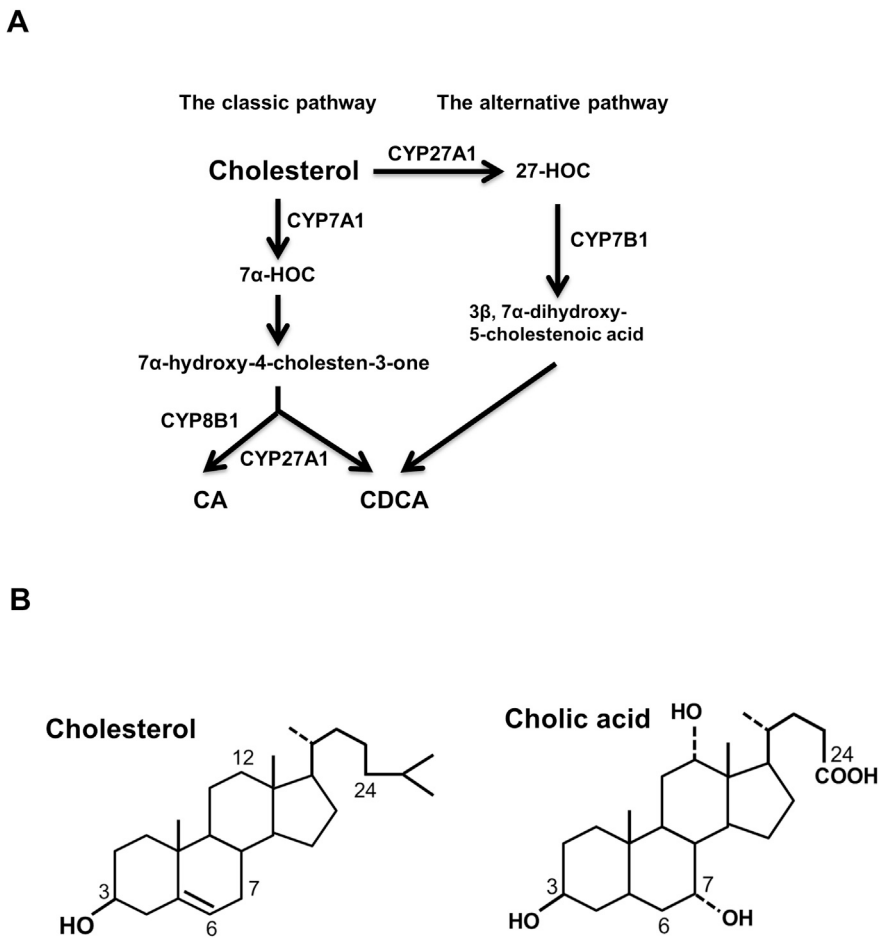

Fig. 1. Bile acid synthesis. **A**. Primary bile acids can be synthesized by two pathways in hepatocytes. The classic bile acid synthesis pathway is considered the primary pathway in humans. In this pathway, cholesterol is first converted to 7α-hydroxycholesterol (7α-HOC) by the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1) in the endoplasmic reticulum. 7α-hydroxy-4 cholesten-3-one (C4) is a common precursor for chenodeoxycholic acid (CDCA) and cholic acid (CA). Sterol 12α-hydroxylase (CYP8B1) catalyzes the C-12 hydroxylation of C4, which leads to the synthesis of CA. In the alternative pathway, cholesterol is first converted to 27-hydroxycholesterol (27-HOC) by mitochondrial sterol 27-hydroxylase (CYP27A1). Oxysterol 7α-hydroxylase (CYP7B1) then catalyzes C-7 hydroxylation. The alternative pathway only produces CDCA. **B**. Cholesterol and cholic acid molecular structures.

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