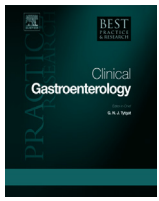
Best Practice & Research Clinical Gastroenterology 28 (2014) 573–583

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology



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Bile acids, obesity, and the metabolic syndrome

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Keywords:
Bile acids
FXR
TGR5
Obesity
Insulin resistance

A B S T R A C T

Bile acids are increasingly recognized as key regulators of systemic metabolism. While bile acids have long been known to play important and direct roles in nutrient absorption, bile acids also serve as signalling molecules. Bile acid interactions with the nuclear hormone receptor farnesoid X receptor (FXR) and the membrane receptor G-protein-coupled bile acid receptor 5 (TGR5) can regulate incretin hormone and fibroblast growth factor 19 (FGF19) secretion, cholesterol metabolism, and systemic energy expenditure. Bile acid levels and distribution are altered in type 2 diabetes and increased following bariatric procedures, in parallel with reduced body weight and improved insulin sensitivity and glycaemic control. Thus, modulation of bile acid levels and signalling, using bile acid binding resins, TGR5 agonists, and FXR agonists, may serve as a potent therapeutic approach for the treatment of obesity, type 2 diabetes, and other components of the metabolic syndrome in humans.

Introduction

Bile is a mixture of bile acids (BAs), cholesterol, phosphatidylcholine, and bilirubin. Of these, BAs are essential constituents and play critical roles in regulation of metabolism in both humans and animal

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http://dx.doi.org/10.1016/j.bpg.2014.07.004
1521-6918/

models. Bile acids have long been recognized to aid in the absorption of fat and fat-soluble vitamins and modulate cholesterol levels. However, recent data indicate that bile acids also play an important role in glucose and lipid homeostasis by activating both the nuclear receptor LXR and the cell surface receptor G protein-coupled bile acid receptor 5 (TGR5) [1–3]. Moreover, modulation of plasma bile acid levels and the total bile acid pool can affect glycaemic control, body weight, and insulin sensitivity [4–6].

In this review, we will focus on the relation between bile acids and regulation of systemic metabolism and the potential for bile acids as a therapeutic approach for obesity, insulin resistance, type 2 diabetes (T2D), and other components of the metabolic syndrome.

Bile acid synthesis and regulation

Bile acid synthesis

BAs are amphipathic molecules with a steroid backbone which are synthesized from cholesterol in hepatocytes. It is estimated that about half of the 800 mg of cholesterol synthesized daily is used for bile acid synthesis, totalling about 200–600 mg daily in humans [7].

Bile acids are synthesized from cholesterol through two dominant pathways: the classic pathway and the alternative pathway (Fig. 1). In the classic (or neutral) pathway, CYP7A1 catalyses the initial and rate-limiting step converting cholesterol into 7α-hydroxycholesterol, with CYP8B1 subsequently regulating synthesis of 12α-hydroxysterols including cholic acid (CA). In the alternative (or acidic) pathway, CYP27A1 first hydroxylates the cholesterol side chain, converting cholesterol into 27-hydroxycholesterol, which is then 7α-hydroxylated by CYP7B1 prior to CYP8B1 action. In humans, the classical pathway produces the primary BA cholic acid (CA) and chenodeoxycholic acid (CDCA) in

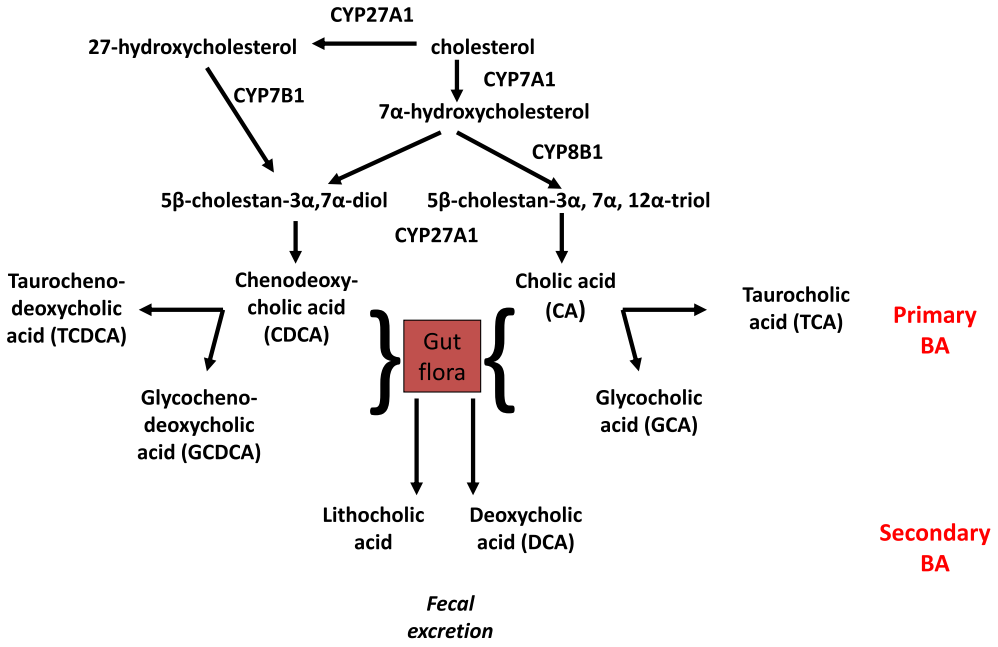

Fig. 1. Bile acid synthesis pathway. Cholesterol is converted to two primary bile acids in human liver, CA and CDCA. Key regulatory enzymes in these pathways include CYP7A1, CYP8B1, CYP27A1, and CYP7B1. CYP7A1 initiates the classic (neutral) biosynthetic pathway, while CYP27A1 initiates the alternative (acidic) pathway in liver and macrophages. CA and CDCA can be conjugated with glycine (G) and taurine (T). In the intestine, conjugated CA and CDCA are deconjugated and then dehydroxylated at the 7α-position to the secondary bile acids DCA and LCA, respectively.