Cellular Signalling 20 (2008) 2180–2197

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Bile acids and signal transduction: Role in glucose homeostasis ☆

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ARTICLE INFO

Article history:
Received 10 June 2008
Accepted 23 June 2008
Available online 27 June 2008

Keywords:
Bile acid signaling
Glucose metabolism
Receptors
Cholesterol derivatives

ABSTRACT

Bile acids are mainly recognized for their role in dietary lipid absorption and cholesterol homeostasis. However, recent progress in bile acid research suggests that bile acids are important signaling molecules that play a role in glucose homeostasis. Among the various supporting evidence, several reports have demonstrated an improvement of the glycemic index of type 2 diabetic patients treated with diverse bile acid binding resins. Herein, we review the diverse interactions of bile acids with various signaling/response pathways, including calcium mobilization and protein kinase activation, membrane receptor-mediated responses, and nuclear receptor responses. Some of the effects of the bile acids are direct through the activation of specific receptors, i.e., TGR5, CAR, VDR, and FXR, while others imply modulation of the hormonal, growth factor and/or neuromediator responses, i.e., glucagon, EGF, and acetylcholine. We also discuss recent evidence implicating the interaction of bile acids with glucose homeostasis mechanisms, with the integration of our understanding of how the signaling mechanisms modulated by bile acid could regulate glucose metabolism.

Contents

Abbreviations: CDCA, chenodeoxycholic acid (3α,7α-dihydroxy-5β cholan-24-oic acid); CA, cholic acid (3α,7α,12α-trihydroxy-5β cholan-24-oic acid); DCA, deoxycholic acid (3α,12α-dihydroxy-5β cholan-24-oic acid); LCA, lithocholic acid (3α-monohydroxy-5β cholan-24-oic acid); cAMP, cyclic AMP; PKC, protein kinase C; GPCR, G protein-coupled receptor; EGF, epidermal growth factor; TLCA, taurolithocholic acid; UDCA, ursodeoxycholic acid (3α,7β-dihydroxy-5β cholan-24-oic acid); TUDCA, tauroursodeoxycholic acid; TLCA-S, taurolithocholic acid 3-sulfate; IP_3, inositol trisphosphate; TCDCA, taurochenodeoxycholic acid; TCA, taurocholic acid; FPR, formyl peptide receptor; PI_3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; TDCA, taurodeoxycholic acid; BDL, bile duct ligation; AC, adenylyl cyclase; GFP, green fluorescent protein; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; JNK, Jun-N-terminal kinase; GLP-1, glucagon-like peptide-1; EGFR, epidermal growth factor receptor; GS, glycogen synthase; ROS, reactive oxygen species; FXR, farnesoid X receptor; RXR, retinoid X receptor; CYP, cytochrome P450; SHP, small heterodimer partner; FGF, fibroblast growth factor; BSEP, bile salt export pump; PFIC, progressive familial intrahepatic cholestasis; PPAR, peroxisome proliferator-activated receptor; FBG, fibrinogen; PXR, pregnane X receptor; VDR, vitamin D_3 receptor; GP, glycogen phosphorylase.

☆ Financially supported by National Institutes of Health grant DK56108 (to B.B.).

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doi:10.1016/j.cellsig.2008.06.014

1. Introduction

Bile acids are synthesized in the liver from oxidation of cholesterol and stored in the gallbladder as the main constituent of bile. The bile is predominantly composed of cholesterol, phospholipids, bilirubin and bile acids. Chenodeoxycholic acid (CDCA) and cholic acid (CA) are the two primary bile acids in humans and are conjugated mainly to glycine (G) and taurine (T) [1]. Upon the chyme reaching the intestine and the release of cholecystokinin (CCK), the gallbladder contracts and the bile is released into the duodenum. The amphipathic chemical structure of bile acids is essential for the solubilization of dietary lipids. More than 95% of the bile acid pool is reabsorbed from the intestine, predominantly by an active sodium-dependent apical bile acid transporter (ASBT) in the terminal ileum and transported back to the liver bound mainly to albumin and to a lesser extent to lipoproteins [2,3]. A limited pool of bile acids that is not reabsorbed in the small intestine undergoes dehydroxylation and deconjugation in the large intestine by bacterial enzymes, leading to the formation of the secondary bile acids, deoxycholic acid (DCA) from CA, and lithocholic acid (LCA) from CDCA. These bile acids are reabsorbed passively from the colon and return to the liver through the portal circulation to exert feedback control on bile acid synthesis.

Bile acids are mainly recognized for their role in dietary lipid absorption and cholesterol homeostasis. However, recent progress in bile acid research suggests that bile acids are also signaling molecules. Bile acids have been shown to affect multiple cellular signaling pathways involving calcium mobilization, cyclic AMP (cAMP) synthesis, and protein kinase C (PKC) translocation and activation. In addition, a membrane G protein-coupled receptor (GPCR) for bile acids, named TGR5, has recently been discovered. Bile acids also appear to modulate other GPCR-associated pathways, including that of the epidermal growth factor (EGF), insulin, muscarinic, and glucagon receptors. Furthermore, some bile acids interact with muscarinic receptors, promoting cell proliferation, and modulate tyrosine kinase receptor pathways by inducing phosphorylation and activation of kinases. These signaling pathways could contribute to the overall responses induced by bile acids, which could impact systemic endocrine functions [4] as well as tumor promotion [5,6]. Indeed, bile acids have been identified as tumor promoters, particularly in combination with other factors like a high-fat diet, stimulating a cellular proliferative response. However, these effects are not induced by all bile acids as the responses are affected by the respective bile acid's degree of hydrophobicity and/or level of hydroxylation.

The current review focuses on recent developments in bile acid-mediated signaling. Although few papers are available that specifically address bile acid signaling, there are many review articles that cover the topics of nuclear receptor signaling, apoptosis, and carcinogenic effects of bile acids. This review will focus on studies pertaining to mechanisms of bile acid signaling and the impact of the signal transduction on glucose homeostasis. Recent developments in bile acid signaling will be covered in detail, while where new data are lacking earlier data will be addressed. Areas that have been extensively covered in previous review articles will not be repeated here. In this event, the reader is referred to previous review articles for additional details. Bile acid transport, while recognized as a critical feature in the regulation of bile acid signaling and, ultimately, the abundance of bile acids available for modulation of various signaling pathways has been previously reported in detail (e.g., [4,7]) and will not be discussed presently.

2. Bile acid signaling mechanisms

2.1. Cellular signaling response

Few general review papers are currently available that specifically highlight the mechanisms of bile acid signaling [4,7]. This subsection will discuss various mechanisms of bile acid signaling, including modulation of receptors in signaling pathways affecting ions, cAMP, PKC, GPCRs, such as glucagon receptor and TGR5, muscarinic receptors, and receptor tyrosine kinases (RTKs).

2.1.1. Cellular Ca^{2+}/Na^{+} mobilization

The fact that bile acids induce cytosolic calcium mobilization in hepatocytes has been known for over 15 years [7–11]. However, the role that bile acids play in the mobilization of calcium in other tissues is less clear. Recent studies have provided additional evidence that disruption of normal biliary function may contribute to a range of medical complications through alteration of normal calcium and sodium signaling and mobilization by bile acids. As previously reviewed [7], bile acids stimulate calcium mobilization through extracellular calcium influx and/or calcium release from intracellular organelles, including the endoplasmic reticulum (ER). Fig. 1 summarizes the effects of bile acids on calcium mobilization. Bile acids induce calcium mobilization to different degrees: CDCA and taurolithocholic acid (TLCA) induce calcium efflux from isolated hamster and rat hepatocytes, however, ursodeoxycholic acid (UDCA) and TUDCA do not demonstrate this effect (see [7] for review). Furthermore, mobilization of calcium from intracellular storage sites varies for different bile acids. As an example, the half-maximal effective concentration (EC_{50}) of UDCA for calcium mobilization was approximately 100 μM at 30 s of stimulation, as compared with the half-maximal effective concentration for TLCA, which was approximately 26 μM [7]. Table 1 summarizes the respective ability of bile acids to stimulate cellular calcium mobilization. Although the significance of altered bile acid levels and effects on calcium signaling has not been fully elucidated, Voronina et al. (2002) recently pointed out that the calcium-releasing properties of bile acids indicate that calcium toxicity may be an important factor for bile acid-induced cellular damage [12]. Abnormally prolonged calcium signals induced by cholecystokinin (CCK) stimulation in pancreatic acinar cells have been shown to induce intracellular trypsinogen activation, a key step for induction of acute pancreatitis [12–14]. That altered calcium signals lead to acute conditions suggests that altered calcium signaling induced by bile acids could play a role in acute pancreatitis and other pancreatic illnesses.

Biliary disease is a major cause of acute pancreatitis, thus, recent studies have focused on the contribution of bile acids to the development of pancreatitis [15]. In one such study, the effect of taurolithocholic acid 3-sulfate (TLCA-S), the conjugated, sulfated form of LCA, was investigated in mouse pancreatic acinar cells. TLCA-S (25–500 μM) induced calcium mobilization, with global cellular calcium oscillations and transients, as well as localized calcium signals occurring in the secretory granule (apical) region of mouse pancreatic acinar cells. Increased calcium mobilization was