



Role of Bile Acids and the Biliary HCO_3^- Umbrella in the Pathogenesis of Primary Biliary Cholangitis

Jorrit van Niekirk, MD¹, Remco Kersten, MSc¹, Ulrich Beuers, MD^{*}

KEYWORDS

• PBC • Bile salts • Bicarbonate • Bicarbonate umbrella • Pathogenesis

KEY POINTS

- In primary biliary cholangitis, defects of the biliary HCO_3^- umbrella leading to impaired biliary HCO_3^- secretion have been identified.
- Current therapies stabilize the putatively defective biliary HCO_3^- umbrella in patients with primary biliary cholangitis improving their long-term prognosis by different molecular mechanisms of action.
- Biliary HCO_3^- secretion is thought to be pivotal in humans protecting cholangiocytes against uncontrolled entry of glycine-conjugated bile acids, sustaining bile flow and facilitating disposal of xenobiotics and endobiotics.

INTRODUCTION

The pathogenesis of primary biliary cholangitis (PBC), but also other chronic fibrosing cholangiopathies, remains incompletely understood.¹ In search of a possible pathophysiologic explanation, evidence from experimental, clinical, and genetic studies led us to introduce the biliary HCO_3^- umbrella hypothesis,² stating that cholangiocytes (and hepatocytes) create a protective apical alkaline barrier stabilized by the glycoalkal³ by secreting bicarbonate (HCO_3^-) into the bile duct lumen. This alkaline

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Department of Gastroenterology and Hepatology, Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands

¹ Contributed equally.

^{*} Corresponding author. Department of Gastroenterology and Hepatology, Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, C2-327, Meibergdreef 9, Amsterdam 1100 DE, The Netherlands.

E-mail address: u.h.beuers@amc.uva.nl

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barrier would retain bile salts in their polar, membrane-impermeant state. A defective apical HCO_3^- secretory apparatus would weaken the alkaline barrier, leading to partial protonation particularly of glycine-conjugated (pK_a 4) rather than taurine-conjugated (pK_a 1–2) bile salts in humans, rendering the resulting glycine-conjugated bile acids apolar and capable of crossing the cholangiocyte membrane independent of bile salt transporter activity,⁴ thereby inducing apoptosis and senescence in cholangiocytes.^{4,5} In support of the biliary HCO_3^- umbrella hypothesis, we showed in vitro that bile salt toxicity is pH dependent and that knockdown of the anion exchanger 2 (AE2) sensitizes human cholangiocytes to bile salt-induced apoptosis.⁴ In PBC, expression of cholangiocellular AE2, the apical $\text{Cl}^-/\text{HCO}_3^-$ exchanger, and type III inositoltrisphosphate receptor ($\text{InsP}_3\text{R3}$), both crucial for adequate biliary HCO_3^- secretion, are defective.^{6–9} Consequently, biliary HCO_3^- secretion in PBC is impaired.⁸

Herein, we critically review the most recent evidence regarding the biliary HCO_3^- umbrella hypothesis by assessing biliary HCO_3^- transport mechanisms of cholangiocytes and different factors that affect the biliary HCO_3^- umbrella. We discuss apical and basolateral cholangiocyte membrane transporters and channels that might be involved in the formation of the HCO_3^- -rich layer at the apical membrane of biliary duct epithelia in cooperation with local neurohormonal and nuclear factors. Their possible role in the pathogenesis of PBC and other fibrosing cholangiopathies is also discussed. Therapeutic interventions stabilizing the biliary HCO_3^- umbrella are described.

BILE FORMATION AND MODIFICATION

Bile formation is a complex biological process that is primarily performed by hepatocytes, whereas cholangiocytes facilitate and modify biliary bile by secretory and absorptive mechanisms.¹⁰ Bile salts are the major solutes in bile and are synthesized from cholesterol via 17 enzymatic steps in different intracellular compartments including the cytosol, endoplasmic reticulum, mitochondria, and peroxisomes. The major pathway of bile salt synthesis is initiated by hydroxylation of cholesterol by cholesterol 7 α -hydroxylase (CYP7A1), a member of the cytochrome P450 family. Human hepatocytes conjugate bile salts before secretion into bile mainly with glycine and to a lesser amount with taurine.⁴ Notably, the glycine/taurine ratio of conjugated bile salts is shifted toward membrane-impermeable taurine conjugates in bile of untreated patients with PBC readapting to the glycine/taurine ratio of healthy individuals after effective treatment with ursodeoxycholic acid (UDCA).¹¹

Other compounds excreted in bile are phospholipids, cholesterol, and potentially harmful lipophilic endogenous and exogenous substances, such as bilirubin or xenobiotics. The adenosine triphosphate (ATP)-dependent secretion of bile salts and these organic compounds is followed by osmotic passage of water and electrolytes. Canalicular bile is modified downstream, by adjusting the levels of HCO_3^- , Cl^- , water, and pH by periportal hepatocytes and cholangiocytes. Bile formation is regulated by a complex interplay of numerous intracellular signaling pathways and membrane receptors, transporters, and channels in hepatocytes and cholangiocytes.¹⁰

Biliary HCO_3^- secretion is pivotal in humans and is thought to serve a number of functions: (1) to sustain bile flow, (2) to facilitate disposal of xenobiotics and endobiotics, (3) to generate an alkaline tide for digestion of nutrients in the intestine, and (4) to form a 'biliary HCO_3^- umbrella'.^{2–4} Biliary HCO_3^- secretion is tightly regulated by cellular signaling pathways and membrane receptors, transporters, and channels.¹⁰ Recruitment of transporters is mediated by microvesicles, multivesicular bodies, and exosomes.¹² Additionally, nuclear receptors and microRNAs (miRNAs) regulate expression of numerous genes to enhance or decrease expression of

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