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Review

The interrelationship between bile acid and vitamin A homeostasis

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ABSTRACT

Vitamin A is a fat-soluble vitamin important for vision, reproduction, embryonic development, cell differentiation, epithelial barrier function and adequate immune responses. Efficient absorption of dietary vitamin A depends on the fat-solubilizing properties of bile acids. Bile acids are synthesized in the liver and maintained in an enterohepatic circulation. The liver is also the main storage site for vitamin A in the mammalian body, where an intimate collaboration between hepatocytes and hepatic stellate cells leads to the accumulation of retinyl esters in large cytoplasmic lipid droplet hepatic stellate cells. Chronic liver diseases are often characterized by disturbed bile acid and vitamin A homeostasis, where bile production is impaired and hepatic stellate cells lose their vitamin A in a transdifferentiation process to myofibroblasts, cells that produce excessive extracellular matrix proteins leading to fibrosis. Chronic liver diseases thus may lead to vitamin A deficiency. Recent data reveal an intricate crosstalk between vitamin A metabolites and bile acids, in part via the Retinoic Acid Receptor (RAR), Retinoid X Receptor (RXR) and the Farnesoid X Receptor (FXR), in maintaining vitamin A and bile acid homeostasis. Here, we provide an overview of the various levels of "communication" between vitamin A metabolites and bile acids and its relevance for the treatment of chronic liver diseases.

1. Introduction

Efficient absorption of fat-soluble nutrients in the intestine requires the action of bile acids. Bile acids are synthesized in the liver and actively secreted into bile. Bile is collected in the gallbladder, which contracts upon intake of a meal and releases bile in the proximal small intestine. Bile acids form mixed micelles with phospholipids and these structures incorporate fat-soluble nutrients to allow their absorption in the intestine. Simultaneously, bile acid-phospholipid micelles also carry fat-soluble metabolites, like cholesterol, and toxins that need to be secreted from the body. One group of nutrients that depend on bile acids for their efficient absorption are the fat-soluble vitamins A, D, E and K. In contrast to water-soluble vitamins (B, C), the fat-soluble vitamins can be stored in various tissues to buffer periods of low intake. Vitamin A is predominantly stored in the liver and humans can maintain adequate levels of serum retinol for months to years even if intake is minimal. Still vitamin A deficiency is the most common micronutrient deficiency in the world, particularly in many third-world countries because intake is too low.

Abbreviations: ATGL, Adipose triglyceride lipase; ADH, Alcohol dehydrogenase; ALD, Alcoholic liver disease; atRA, All-trans retinoic acid; ASBT/SLC10A2, Apical sodium-dependent bile salt transporter; ABCA1, ATP-binding cassette transporter member 1; BCMO1, Beta-carotene 15,15′-monooxygenase 1; AIH, Autoimmune hepatitis; BAAT, Bile acid coenzyme A: amino acid N-acyltransferase; BSEP/ABCB11, Bile Salt Export Pump; BACS, Bile acid CoA synthase; CEL, Carboxyl ester lipase; CYP7A1, Cholesterol 7-alpha-hydroxylase; CRBP, Cellular retinol-binding protein; CRABP, Cellular retinoic acid-binding protein; CA, Cholic acid; CMs, Chylomicrons; CD36, Cluster Determinant 36; CYP26A1/B1, Cytochrome P450 26 A1/B1; DBD, DNA-binding domain; DHRS3, Dehydrogenase Reductase 3; DCA, Deoxycholic acid; DGAT1, ARAT, ARGP1, DIAR7, Diacylglycerol O-acyltransferase 1; DGAT2, ARAT, Diacylglycerol O-acyltransferase 2; DR, Direct repeat; FXR, Farnesoid X Receptor; I-BABP, Ileal Bile Acid Binding Protein; FGF15/19, Fibroblast growth factor 15/19; HSPG, Heparin sulfate proteoglycan; HCV, Hepatitis C virus; ISX, Intestinal transcription factor; IR, Inverted repeat; LDLR, Low-Density Lipoprotein Receptor; LRAT, Lecithin:retinol acyl tranferase; LCA, Lithocholic acid; NTCP/SLC10A1, Sodium/taurocholate co-transporting polypeptide; MDR, Multidrug resistance protein; MRP, Multidrug Resistance-associated Protein; NR, Nuclear receptor; NALFD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NPC1L1, Niemann-pick C1-like 1; OATP, Organic anion transporting polypeptide; OSTα/β, Organic solute transporter dimer α/β; PTL, Pancreatic triglyceride lipase; PNPLA3, Patatin-like phospholipase domain-containing 3; PLB, Phospholipase B; RPE, Retinal pigment epithelium; RARE, Retinoic acid response element; REH, Retinyl ester hydrolase; RAR, Retinoic Acid Receptor; RXR, Retinoid X Receptor; RARE, Retinoic acid response element; RALDH, Retinaldehyde dehydrogenase; RRD, Retinaldehyde reductases; RBP4, Retinol binding protein 4; RBPR2, RBP4 receptor 2; RDH, Retinol dehydrogenase; RDH16, Rdh2, RODHII, Retinol dehydrogenase 16; PBC, Primary biliary cholangitis; PSC, Primary sclerosing cholangitis; SR-BI, Scavenger receptor class B member 1; SDR, Short chain dehydrogenases/reductases; SHP/NR0B2, Small heterodimer partner; CYP8B1, Sterol 12-alpha-hydrolase; CYP27A1, Sterol 27-hydroxylase; SDC1, Syndecan-1; STRA6, Stimulated by Retinoic Acid gene 6 homolog; SDR, Short chain dehydrogenases/reductases; TTR, Transthyretin; ER, Everted repeat; UDCA, Ursodeoxycholic acid; nor-UDCA, *Nor*-Ursodeoxycholic acid; 9cRA, 9-cis retinoic acid; 9cDHRA, 9-cis-13,14 dihydroretinoic acid.

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Vitamin A deficiency is also a common condition in patients with liver disease, especially if this includes impairment in bile flow, e.g. cholestasis. Not only is vitamin A uptake affected under cholestatic conditions, but chronic liver injury also leads to loss of hepatic vitamin A stores that disappear from hepatic stellate cells when they transdifferentiate to myofibroblasts that leads to liver fibrosis. Bile acids and vitamin A-metabolites, in particular retinoic acids, are high-affinity ligands for the transcription factors Farnesoid X Receptor (FXR), Retinoid X Receptor (RXR) and Retinoic Acid Receptor (RAR), which act, in part as obligate partners in regulating bile acid, lipid and glucose metabolism. There is a wealth of information and excellent reviews that specifically focus on the function, metabolism and signaling functions of vitamin A-metabolites, e.g. retinoic acids, on the one hand or on bile acids on the other hand [1–3]. By no means, this review can cover all the details of the physiological actions of these molecules. Here, we aim to provide an overview of how bile acid and vitamin A metabolism are interrelated and may have implications for the treatment of (chronic) liver diseases.

1.1. Function of vitamin A and its active metabolites

The term "vitamin A" is a generic descriptor for compounds that have the biological activity of retinol or its metabolic products. Vitamin A-derivatives fulfill numerous important functions in the mammalian body, including roles in vision, maintenance of epithelial surfaces, immune competence, reproduction and embryonic growth and development. Dietary sources of vitamin A are provitamin A carotenoids (mainly β-carotene, from plant sources), preformed vitamin A (retinyl esters from animal sources) and precursors of retinol [4]. Mammals depend on dietary intake of (pro-)vitamin A as they cannot synthesize this vitamin themselves. The recommended daily intake of vitamin A is approximately 700 and 900 μg for adult women and man, respectively. Dietary intake of solely β-carotene may be inadequate to maintain normal levels of vitamin A. Retinyl esters should therefore be considered as an essential component of a healthy diet [5]. Approximately 80% of the total body pool of vitamin A is stored in the liver as retinyl esters

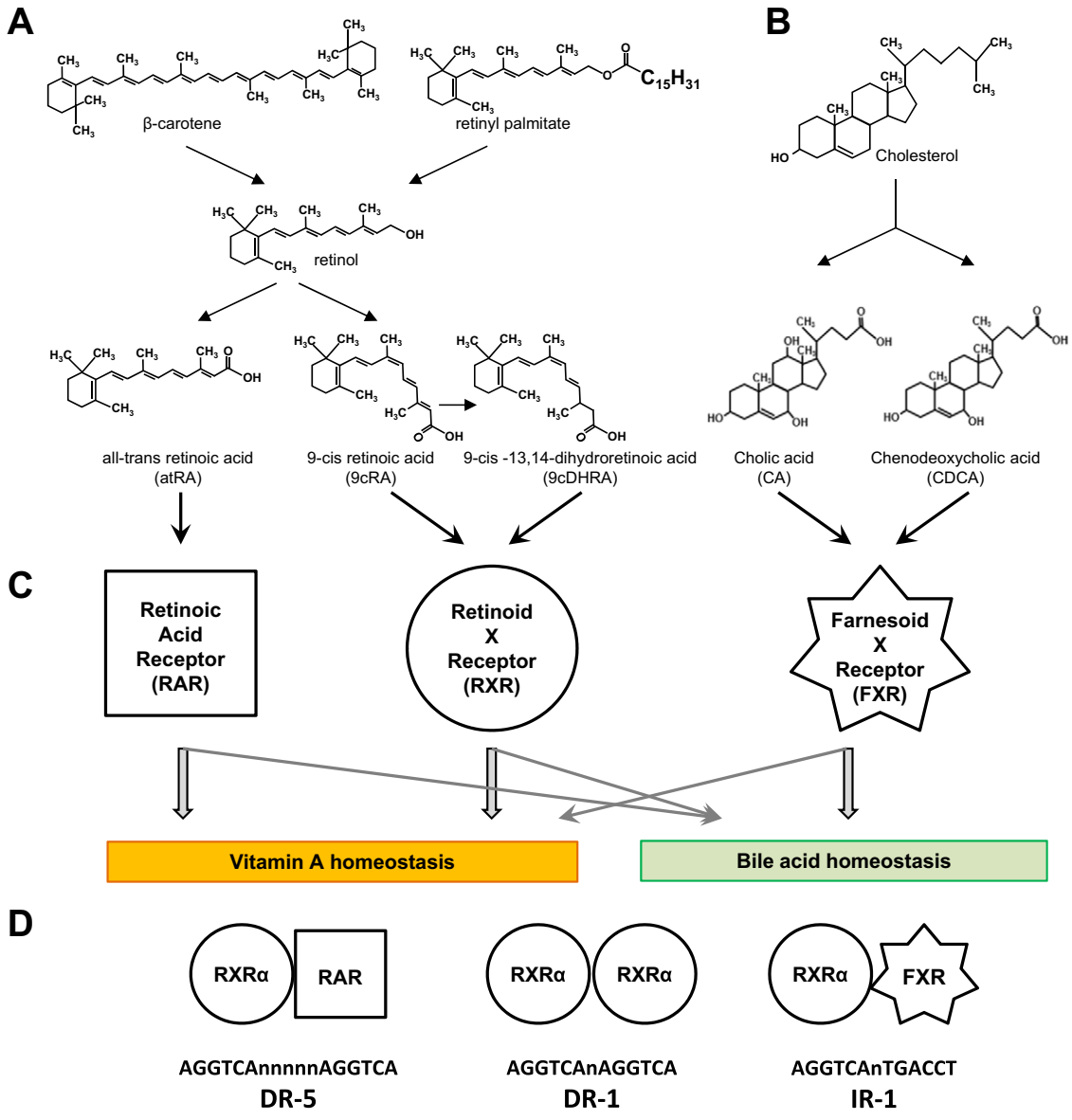

Fig. 1. Chemical structures of key compounds in vitamin A and bile acid homeostasis and their effect on the nuclear recepotors RAR, RXR and FXR. **A**) Structure of retinoids (β-carotene, retinyl-palmitate, retinol, *all-trans* retinoic acid, *9-cis* retinoic acid, and *9-cis*-13,14 dihydroretinoic acid, **B**) structure of cholestrol and primary bile acids (cholic acid, chenodeoxycholic acid), **C**) nuclear receptors RAR, RXR and FXR cross talk to regulate vitamin A homeostasis and bile acid synthesis and/or transport. **D**) RXRα forms homodimers and is an obligate partner for RAR and FXR. Each of those dimers binds to specific DNA sequences as indicated in panel D.