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Review

Bile acid-activated receptors in the treatment of dyslipidemia and related disorders

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ABSTRACT

Dyslipidemia is a metabolic disorder that constitutes a major risk factor for cardiovascular diseases and stroke and is often associated with diabetes mellitus and atherosclerosis. In recent years a number of ligand-activated receptors have been found to exert a role in integrating essential steps of lipid and glucose metabolism. Bile acid-activated receptors are a defined subset of nuclear and G-protein coupled receptors mainly expressed in entero-hepatic tissues for which bile acids function as signaling molecules. Primary bile acids (chenodeoxycholic acid and cholic acid) are physiological ligands/activators of farnesoid-X-receptor (FXR), pregnane-X-receptor (PXR) and constitutive androstane receptor (CAR), while litocholic acid is a ligand for the Vitamin D receptor (VDR) and the G-protein coupled receptor TGR5. Despite FXR demonstrates a high selectivity for bile acids, PXR and CAR are relatively promiscuous receptors integrating lipid homeostasis with xenobiotic metabolism. FXR, PXR, CAR and TGR exert synergistic activities in regulating lipid and glucose homeostasis and energy expenditure and liver and peripheral insulin sensitivity. Ligands for these receptors hold promise in the treatment of dyslipidemic conditions as revealed by results of a number of preclinical models but carry a defined risk for potential side effects.

Contents

Abbreviations: ABCA1, ATP-binding cassette transporter-1; ABCG5, ATP-binding cassette (ABC) transporters G5; ABCG8, ATP-binding cassette (ABC) transporters G8; AKT, serine/threonine protein kinase PKB; ApoA-I, apolipoprotein A-I; ApoC-II, apolipoprotein C-II; ApoC-III, apolipoprotein C-III; Apo A-IV, apolipoprotein A-IV; Apo A-V, apolipoprotein A-V; ApoE, apolipoprotein E; BSEP, bile-salt export pump; BAT, brown adipose tissue; CA, Cholic Acid; cAMP, Cyclic adenosine monophosphate; CAR, constitutive androstane receptor; CE, cholesterol ester; CTE, cytosolic Acyl-CoA thioesterase; CHD, coronary heart disease; CDCA, chenodeoxycholic acid; CEH, cholesterol ester hydrolase; CRE, cAMP Response Element-Binding; CREBP, cAMP Response Element-Binding Protein; CPT1, Carnitine Palmitoyl Transferase 1; CYP7A1, cholesterol 7α-hydroxylase; CYP8B1, sterol 12β-hydroxylase; CYP39A1, oxysterol-7-alpha-hydroxylase; CYP3A4, Cytochrome P450 3A4; Cyp3a11, Cytochrome P450 3A11; D2, type II iodothyronine deionidase; db/db, diabetic mice; Dio2, type II iodothyronine deiodinase gene; DCA, deoxycholic acid; DM, diabetes mellitus; DR, direct repeat; ECI, enoyl CoA isomerase; 6-ECDCA, 6alpha-ethyl-chenodeoxycholic acid; ERK1/2, extracellular-regulated kinase 1 and 2; FAS, fatty acid synthase; FC, free cholesterol; FBP1, fructose 1,6 bisphosphatate 1; FFA, free (non-esterified) fatty acid; FGF15, fibroblast growth factor 15; FGF19, fibroblast growth factor 19; FGF receptor 4, fibroblast growth factor receptor 4; Foxa2, forkhead box A2; Foxo1, forkhead box O1 transcriptional factor; FXR, farnesoid X receptor; GLUT4, glucose transporter 4; G6Pase, glucose-6-phosphatase; GPCR, G protein coupled receptor; HDL, high density lipoprotein; HMG-CoA, 3-hydroxymethyl-3-glutaryl coenzyme A; HMGCoAS, hydroxy-methylglutaryl CoA synthase; HMGCoAR, hydroxymethylglutaryl CoA reductase; HNF, hepatocyte nuclear factor; IRS, insulin responsive substrate; JNK, Jun N-terminal Kinase; LCA, lithocholic acid; LCAT, lecithin-cholesterol acyl transferase; LDL, Low-density lipoprotein; LDL-r, Low-density lipoprotein receptor; L-PK, L-pyruvate kinase; LPL, lipoprotein lipase; LRH, liver–related homolog-1; Mdr, Multi-Drug Resistance; Mrp1 Mrp2 Mrp3 and Mrp4, Multidrug Resistance Associated Protein-1,2,3,4; NTCP, Na+ taurocholate cotransport peptide; Oatps, organic anion transporting proteins; ob/ob, obese mice; Ostα/β, organic solute transporter α and β; PNC, pregnenolone-16 α-carbonitrile; PCSK9, Pro-protein convertase subtilisin/kexin 9; PEPCK, phosphoenolpyruvate carboxykinase; PGC1α, Peroxisome proliferator-activated receptor- coactivator (PGC)-1α; PKA, protein kinase A; PKC, protein kinase C; PPARa, peroxisome proliferator–activated receptor-α; PPARγ, peroxisome proliferator–activated receptor-γ; PXR, pregnane X receptor; SCP, sterol carrier protein; SHP, short heterodimer partner; SR B1, scavenger receptor B1; SREBP1c, sterol-regulatory-element-binding protein-1c; SREBP2, Sterol regulatory element-binding protein 2; Sult2a1, sulfotransferase 2A1; T3, triiodothyronine; T4, thyroxine; TLCA, taurolithocholic acid; TLR-4, toll like receptor-4; TGR5 or M-BAR or GP-BAR1 or BG37, membrane bile acid receptor; TGF-β1, transforming growth factor-β1; TNFα, tumor necrosis factor α; TG, Triacylglycerols; UCP-1, uncoupling protein 1; UCP-2, uncoupling protein 2; UCP-3, uncoupling protein 3; UGT2Bs, UDP-glucuronosyltransferase-2B7; VLDL, very-low-density lipoprotein; VLDL-R, VLDL receptor; VDR, vitamin D receptor.

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1. Introduction

Dyslipidemia is a broad term that refers to a number of lipid disorders. The majority of lipid disorders (80%) are related to diet and lifestyle, although familial disorders (20%) are important as well. The basic categories of dyslipidemias include: elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), excess lipoprotein(a), hypertriacylglycerolmia, atherogenic dyslipidemia, and mixed lipid disorders. A well defined complication of dyslipidemia is atherosclerosis, a pathogenic condition of the arterial vessel wall, characterized by lipid deposition, leukocyte infiltration and intimal thickening [1]. Atherosclerosis is a leading cause of illness and death. Myocardial infarction and cerebrovascular accidents are life-threatening complications of atherosclerosis. Prevention of atherosclerotic plaque formation and prevention or treatment of complication of atherosclerotic plaque rupture represents a major therapeutic goal. In this context therapeutic strategies aimed at reducing cholesterol plasma levels have been shown effective in reducing atherosclerosis-related mortality. The relationship between dyslipidemia, atherosclerosis and cardiovascular diseases and stroke appears to be clear and direct. A number of clinical trials have demonstrated the efficacy of 3-hydroxymethyl-3-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) for both secondary and primary prevention [1].

2. Bile acids homeostasis

Bile acids are the end product of cholesterol breakdown and represent the predominant pathway for eliminating excess cholesterol from the human body (Fig. 1) [2,3]. Bile acids are synthesized in the liver and secreted into the intestine where they are essential to the absorption, transport and distribution of dietary lipids, lipid-soluble vitamins and steroids. Bile acids are then reabsorbed in the ileum and transported via the enterohepatic circulation to the liver, where they inhibit their own synthesis. In addition to their role in regulating dietary lipid absorption, bile acids are signalling molecules acting on nuclear and cell surface receptors (Fig. 1) [2–7].

2.1. Bile acid-activated nuclear receptors

In 1999, bile acids were discovered to function as endogenous ligands for the nuclear receptor FXR-α (farnesoid X receptor-α, NR1H4) [see Ref. [2] for structure, 8–11]. Since then other nuclear receptors: the pregnane-X-receptors, NR1I2 (PXR), the constitutive androstane receptor, NR1I3 (CAR) and the vitamin D receptor, NR1I1 (VDR) have been shown to be activated by primary and secondary bile acids at micromolar concentrations [2,3,11]. In addition to nuclear receptors, bile acids activate also G-protein coupled seven trans-membrane receptors (GPCRs). One of these receptors, TGR5, also known as M-BAR, was identified in 2002 as a bile acid-activated GPCR [6]. Bile acids activate or regulate a number of additional signalling pathways that are involved in lipid and glucose homeostasis [2,3]. The present review is focused on the role that bile acid-activated receptors play in regulating lipid and cholesterol homeostasis and will provide an updated view of the pharmacological relevance of these signalling pathways in the treatment of dyslipidemic conditions and their complications [2].

Cholesterol is metabolized to bile acids by two different pathways. The "classic" bile acid biosynthesis pathway is exclusively found in the liver and results in the formation of the primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA). The "alternative" pathway is ubiquitous and produces oxidized cholesterols which have to be transported to the liver in order to be converted into bile acids. Under normal conditions, the classic pathway is the main bile acid biosynthetic pathway in the liver [11]. This pathway is highly regulated, predominantly at its first enzymatic step, the cholesterol 7a-hydroxylase (CYP7A1). CYP7A1 expression is under the transcriptional control of a variety of regulatory factors including hormones, oxysterols, bile acids, and xenobiotics, and has a circadian rhythm (Fig. 1) [11,12]. The feedback regulation of bile acid synthesis is primarily achieved in hepatocytes through the transcriptional modulation of CYP7A1 [11]. Bile acid-activated FXR induces the expression of the small heterodimer partner (SHP, NR0B2), an atypical nuclear receptor that lacks the ligand binding domain [2,11,12]. SHP interacts with the liver-related homologue-1 (LRH-1, NR5A2) and hepatocyte nuclear factor 4α (HNF4α; NR2A4) removing the positive regulatory effects of these nuclear receptors on CYP7A1 [2,3,11]. However, because bile acid feeding of *Shp* knockout mice still reduces CYP7A1 mRNA levels to the same extent of that observed in wild-type mice, the requirement of SHP for this inhibitory effect appears to be dispensable [13,14]. This finding indicates that SHP-independent pathway(s) are involved in the repression of CYP7A1 by bile acids.

Activation of intestinal FXR increases the expression and secretion of fibroblast growth factor (FGF)-15 (FGF-19 in humans) from enterocytes [15–17]. Secreted FGF15 subsequently binds to the