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Bile Acids as Receptor Ligands in Metabolic Processes - The FXR Connection

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Introduction

Cell signaling in response to diet and metabolites are important mediators for metabolic outcomes. They are different in the fed and fasted states. In recent years postprandial Bile Acids (BAs), oxysterols, hormones and indeed fatty acids (FAs) that are derived from dietary and human lipids including cholesterol derivatives or its precursors are recognised as differential signaling molecules to interact with an array of two distinct classes of receptors that are central to metabolism: nuclear receptors and G-Protein Coupled Receptors (GPCRs). Two main BA modulated receptors, nuclear receptor Farnesoid X Receptor (FXR) and Takeda G protein coupled receptor 5 (TGR5), are central to lipid and carbohydrate metabolism and in cross talk between the gut to the liver and with other tissues. They also influence the action of other NRs and GPCRs. Table 1 summarizes the characterized BA activated receptors, their ligand agonists, the tissues where they are expressed and the processes that they influence. This review focuses on the FXR, its biochemistry, functions and implications for health and in disease.

Nuclear receptors (NRs) including FXR, are cell membrane, ligand activated, transcription factors with an important role in regulating many physiological pathways within a cell [1] (Table 1). Once activated NRs move to the cell nucleus to alter the transcriptional landscape by binding to recognition elements (REs) in target gene promoter/s [2]. NRs can act as homodimers or heterodimers and can bind to a variety of DNA response elements that are specific for each NR [3]. They influence a range of metabolic processes and this is reflected by their range of ligands (Table 1). Note, that there is considerable overlap among ligands, but that they vary in their relative potency for receptor activation. Importantly, therefore, they appear to cross talk for efficiency and sometimes amplification of function.

FXR, known as the BA receptor (BAR), since it is potently activated by individual BA moieties, it controls BA levels but it is also central to lipid and sugar metabolism in both the liver and the gut. BAs are central for micelle formation and nutrient uptake. GIT FXR is postprandially activated in response to gall bladder BA release and the moieties generated by GIT microbial action [4]. In the liver, recycled BA concentrations alter its expression to regulate the synthesis of BA, and in doing so, alter cholesterol, lipid, and glucose as well as autophagy-mediated lipid catabolism [5-8]. A further layer of regulation is through gut to liver hormone FGF19, shutting off the rate-limiting step in bile acid synthesis through CYP7A1. Its phosphorylation in hepatocytes facilitates its transport to the nucleus to activate non-receptor tyrosine kinase (Src) phosphorylation to further activate FXR (on Y67) [9]. Indeed, these authors report that FXR phosphorylation and signaling appears defective in primary biliary cirrhosis (PBC) sufferers.

While two FXR alleles are present in humans, designated FXRα (NR1H4) and FXRβ(NR1H5) [10], FXRβ is a pseudogene in humans but is active in rats and rabbits [11]. FXRα is conserved across many species from human to fish [12]. Alternative RNA processing identifies two distinct promoters but four different isoforms of this protein. Isoforms 1 and 2 represent the active forms [10,13]. FXRα is differentially expressed in tissues including liver, intestine, kidney and adrenal gland, while low expression is detected in the heart, adipose tissue and skeletal muscle [3,14]. Thus, we can hypothesize that FXR is important for frontline energetics and less so for stored energy. Indeed, FXR is also an important regulator of lipid and glucose metabolism. In the diabetic murine model FXR activation leads to reduced circulating glucose concentrations improving hyperglycaemia [15]. An effect later confirmed in FXR knockout mice [16]. Synthetic FXR agonist fexeramine (FEX), reduces adiposity and weight gain while improving insulin sensitivity, cholesterol levels and reducing the levels of inflammatory cytokines in a DIO mouse model [17,18]. Activation of FXR can also reduce inflammation, seen in cases of diabetic nephropathy [19]. Since FXR activation displays beneficial effects to various metabolic associated diseases, this receptor is targeted for metabolic treatments [20].

The liver has a role in controlling plasma glucose homeostasis through the activation and expression of genes encoding metabolic enzymes including glucokinase, L-type Pyruvate Kinase (Lpk) and Acetyl-coenzymeA carboxylase-1 (Acc-1) mediated by the sterol regulatory element-binding protein-1c (Srebp-1c) and carbohydrate-response elements (ChoREs) [21]. These enzymes maintain a balance between glucose uptake and production during fed and fast states in response to FXR signaling [15,22]. FXR also regulates triglyceride production in the liver. Here, FXR activation, by Cholic Acid (CA), suppresses expression of the transcription factor SREBP-1c causing

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Table 1: Bile acid activated nuclear receptors. The table includes endogenous bile acid ligands, site of action, mechanism of action and downstream effects.

Nuclear Receptor	Cofactors	Bile acid agonists	Site of action	Process	References
FXR	DRIP205, SRC,	CDCA>LCA=DCA>CA	Brain, lungs, liver, kidney, adrenal gland	Regulate glucose and lipid metabolism, ↓inflammation	(Pineda Torra et al., 2004, Bramlett et al., 2000)
RXR	PGC-1, TIF2	Retinoic acid, 7-Hydroxycholesterol	Brain, lungs, liver, kidney, intestine	Maintain glucose and lipid metabolism, bone adevelopment, immunity,	(Delerive et al., 2002, Dawson and Xia 2012, Menendez-Gutierrez and Ricote 2017)
LXR	SIRT1, p160, TRRAP	Oxysterols, 27-hydroxycholesterol, 6α-hyroxy bile acid (HDCA)	Brain, lungs, liver, kidney, intestine, adipose tissue, adrenal glan, spleen	↑cholesterol metabolism and efflux	(Bovenge et al., 2015, Husskonen et al., 2004, Unno et al., 2005)
PXR	PGC-1α, SGK2, PP2Cα, SCR1/ NCOA1, SCR2/ GRIP1	3-KetolCA>LCA.DCA. CA	Intestine, liver	↑detoxification of BA, ↑dysregulation of lipid and glucose metabolism	(Wagner et al., 2005, Hakkola et al., 2016, Hassani-Nezhad-Gashti et al., 2018, Hariprasad et al., 2009)
VDR	SRC-1/TIF2, CBP/ p300, SRA/DRIP/ TRAP	3-oxo-LCA>LCA>DCA>CA	Bone, liver, intestines, kidneys, muscle, brain, and skin	↑detoxification of LCA↑inflammation	(Freedman 1999, Makishima, Lu et al. 2002, Pols, Puchner et al. 2017)
PPAR	PBP/PPARBP, TRAP220/MED1, PGC-1α, SRC-2/ TIF2/GRIP1	Essential Fatty acids, Trans-retinoic acid, eicosanoids	Liver, intestines, adipose tissue, heart, sp;een and skeletal muscle	↑inflammation ↑fatty acid oxidation, maintain energy homeostasis	(Viswakarma et al., 2010, Graham et al., 2005, Wang et al., 2003, Wang et al., 2018

down regulation of enzymes, including Fatty Acid Synthase (FAS), required for lipogenesis [23]. This FXR mediated inhibition of SREBP-1c expression involves interaction with Small Heterodimer Partner (SHP) and interference of Liver X Receptor (LXR) activity [23]. This FXR mediated SREBP-1c repression could prevent lipid synthesis and storage and could alter cholesterol synthesis again reinforcing FXR as a potential therapeutic target [24,25]. FXR mediated regulation of triglyceride levels can also be controlled by coactivator peroxisome-proliferator-activated receptor-γ-coactivator-1α (PGC-1α). PGC-1α upregulates FXR expression by co-activation of peroxisome proliferator-activated receptor (PPARγ) and HNF4α to triglyceride synthesis and secretion [26]. FXR also dictates the flux of lipoproteins carrying lipid back to the liver for processing through activation of a number of surface receptors for low and very low density lipoprotein uptake. It can also determine the level of apolipoprotein levels to tag these and high density lipoproteins that dictate reverse cholesterol transport [27-35]. Taken together activation of FXR [36-40], whether it is phosphorylated or not, may influence different outcomes in different tissues and these outcomes appear dependent on the fed or the fasted state and enterohepatic circulation of dietary defendant hormones and metabolites from the gut [41-44].

Perspective

NRcrosstalk and their responses are modulated in the fed and in the fasted states, in doing so they can alter metabolism and influence immune function. Their relative expression in sustaining health and in contributing to diseases remains unknown and therefore merits further investigation through assessment of their combined therapeutic value.

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