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Special Section on Bile Acids, Drug Metabolism, and Toxicity—Minireview

Environmental Chemical Contribution to the Modulation of Bile Acid Homeostasis and Farnesoid X Receptor Signaling

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ABSTRACT

Maintaining bile acid (BA) homeostasis is important and regulated by BA activated receptors and signaling pathways. Farnesoid X receptor (FXR) and its regulated target networks in both the liver and the intestines are critical in suppressing BA synthesis and promoting BA transport and enterohepatic circulation. In addition, FXR is critical in regulating lipid metabolism and reducing inflammation, processes critical in the development of cholestasis and fatty liver diseases. BAs are modulated by, but also control, gut microflora. Environmental chemical exposure could affect liver disease development. However, the effects and the mechanisms by which environmental chemicals interact with FXR to affect BA homeostasis are only emerging. In this minireview, our focus is to provide evidence from reports that determine the effects of environmental or therapeutic exposure on altering homeostasis and functions of BAs and FXR. Understanding these effects will help to determine liver disease pathogenesis and provide better prevention and treatment in the future.

SIGNIFICANCE STATEMENT

Environmental chemical exposure significantly contributes to the development of cholestasis and nonalcoholic steatohepatitis (NASH). The impact of exposures on bile acid (BA) signaling and Farnesoid X receptor-mediated gut-liver crosstalk is emerging. However, there is still a huge gap in understanding how these chemicals contribute to the dysregulation of BA homeostasis and how this dysregulation may promote NASH development.

Introduction

The goal of this minireview is to provide an update on the regulation of bile acid (BA) homeostasis by the nuclear receptor Farnesoid X receptor (FXR) and the effects on this regulation by exposure to environmental or therapeutic agents. BAs are critical molecules for life, and disruption of BA homeostasis has been closely linked to hepatic, intestinal, and systemic diseases, including cholestasis, fatty liver diseases, and hepatic and colon tumors. Identifying the underlying molecular mechanisms by which BA regulation is disrupted by endogenous and/or xenobiotic factors will aid in not only understanding disease pathogenesis, but also providing novel strategies to prevent and/or treat diseases associated with BA dysregulation.

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BAs and FXR Regulation of BA Homeostasis

BA synthesis in the liver is the primary form of cholesterol catabolism (Fig. 1). In the liver, two major pathways carry out BA synthesis,

ABBREVIATIONS: AHR, aryl hydrocarbon receptor; ASBT, apical sodium-dependent bile acid transporter; BA, bile acid; BDE-47, 2,29,4,49-tetrabromodiphenyl ether; BDE-99, 2,29,4,49,5-pentabromodiphenyl ether; BPA, bisphenol A; BPAF, bisphenol AF; BPS, bisphenol S; BSEP, bile salt export pump; CA, cholic acid; CAR, constitutive androstane receptor; CDCA, chenodeoxycholic acid; CYP27A1, sterol 27-hyroxylase; CYP7A1, cholesterol 7α hydroxylase; CYP8B1, sterol 12alpha-hydroxylase; DCA, deoxycholic acid; DDI, drug-drug interaction; EDC, endocrine disrupting chemical; FDA, US Food and Drug Administration; FGF, fibroblast growth factor; FXR, Farnesoid X receptor; GM, gentamicin; HCH, hexachlorocyclohexane; HNF4α, hepatocyte nuclear factor 4-alpha; IFALD, intestinal failure-associated liver disease; LCA, lithocholic acid; MCA, muricholic acid; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NTCP, sodium taurocholate cotransporting polypeptide; OATP, organic anion transporter; OCA, obeticholic acid; OCP, organochlorine pesticide; PBDE, polybrominated diphenyl ether; PBDE-28, 2,4-Dibromo-1-(4-bromophenoxy)benzene; PCB, polychlorinated biphenyl; PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonate; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; p,p'-DDE, p,p'-dichlorodiphenyldichloroethylene; PXR, pregnane X receptor; SHP, small heterodimer partner; TCDD, 2,3,7,8-tetrachlorodibenzo para dioxin; TCDF, 2,3,7,8-tetrachlorodibenzofuran; TCS, triclosan; TLCA, taurolithocholic acid; VM, vancomycin; WT, wild-type.

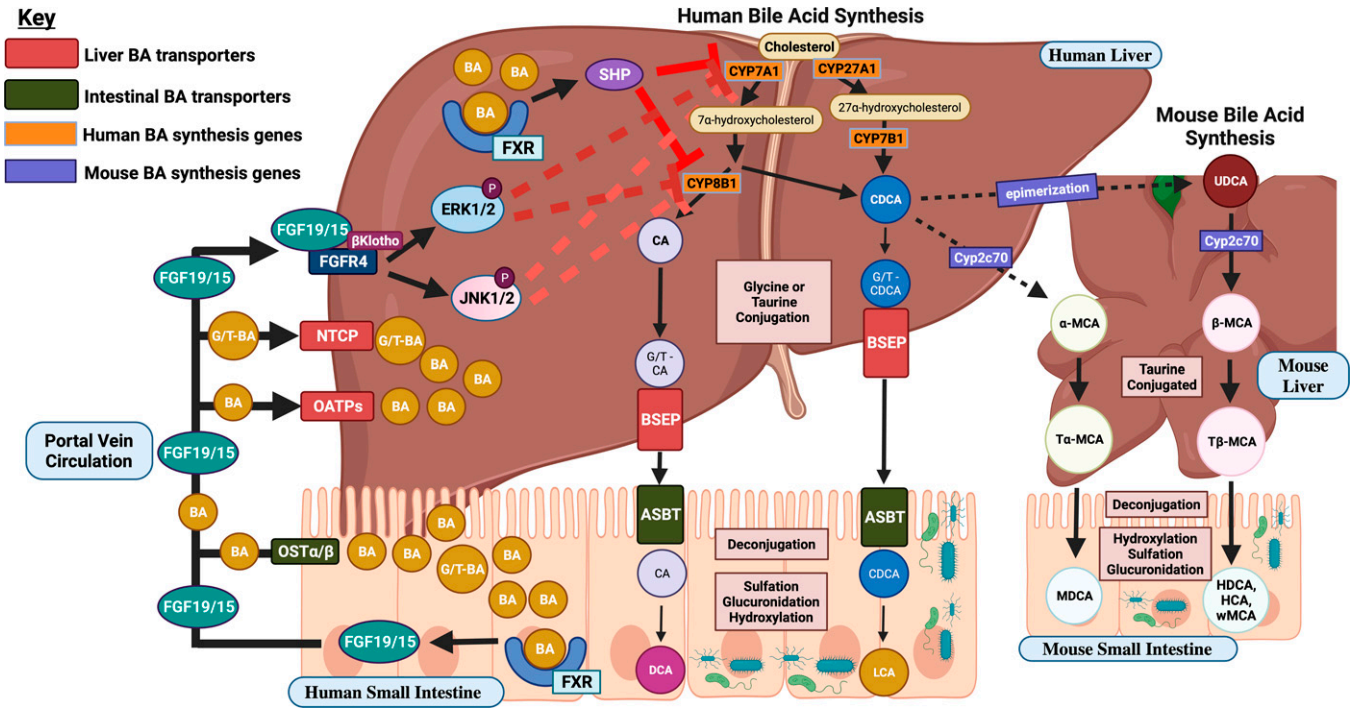

Fig. 1. Suppression of BA Synthesis Mediated by FXR Signaling. Primary BAs are synthesized in hepatocytes by two pathways: the classic pathway initiated by CYP7A1 and the alternative pathway initiated by CYP27A1. CA and CDCA are the most prevalent primary BAs in humans. In mice, primary BAs are CA and α/β-MCA. CDCA is the precursor for α-MCA as well as the precursor for the ursodeoxycholic acid, which is then synthesized to β-MCA via CYP2C70. Primary BAs are conjugated, and in humans, BAs undergo both glycine and taurine conjugation, with a preference for glycine conjugation. In mice, almost all BAs are taurine conjugated. After conjugation, BAs are transported out of the liver via BSEPs to the gallbladder and then to the small intestine. BAs are taken up in the small intestine by way of the transporter ASBT. Once in the small intestine, BAs are deconjugated and undergo additional modifications facilitated by bacterial microbiomes in the gut. The resulting BAs are secondary BAs, DCA, and LCA in humans and murideoxycholic acid in mice. BAs are also integral signaling molecules. BAs are endogenous ligands for many receptors, the best-known receptor being FXR. In the liver, FXR induces its target gene SHP to inhibit gene expression of *CYP7A1/Cyp7a1* and *CYP8B1/Cyp8b1*, acting as negative feedback regulation for BA synthesis. In the small intestine, FXR induces FGF19 in humans and FGF15 in mice. FGF19/15 then enters portal vein circulation to activate fibroblast growth factor receptor 4/βKlotho complex in hepatocytes, which activates the extracellular signal-regulated kinase 1/2 and c-Jun N-terminal kinase 1/2 pathways to inhibit gene expression in classic pathway of BA synthesis. BAs also enter portal vein circulation, leaving the intestine via the transporter dimer organic solute transporter alpha/beta. NTCP transports conjugated BAs back to the liver whereas OATPs transport unconjugated BAs back to the liver. Figure was made with biorender.com.

the classic and the alternative pathway. The classic pathway is the predominant pathway, with the first and rate-limiting reaction catalyzed by a cytochrome P450 enzyme, cholesterol 7α-hydroxylase (CYP7A1). Subsequent enzymatic reactions catalyzed by sterol 12α-hydroxylase (CYP8B1) and sterol 27-hyroxylase (CYP27A1), respectively, yield the primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA). Whereas in the alternative pathway, reactions carried out by the first enzyme, CYP27A1, followed by 25-hydroxycholesterol 7α-hydroxylase, produces CDCA (Russell and Setchell, 1992; Russell, 2003). Interestingly, small amounts of BAs were still detected in mice with both *Cyp7a1* and *Cyp27a1* gene deletion, suggesting minor BA synthetic pathways are present, at least in mice (Rizzolo et al., 2019; Rizzolo et al., 2021). In rodents, CDCA is converted to muricholic acid (MCA), and the enzyme responsible for this conversation has been identified as CYP2C70 (Takahashi et al., 2016; Honda et al., 2020).

Most BAs are either taurine or glycine conjugated in the liver, increasing their solubility (Fig. 1) (Li and Chiang, 2014). Conjugated BAs are effluxed by bile salt export pump (BSEP) into bile canaliculi and stored in the gallbladder. During postprandial release, the gallbladder contracts, releasing BAs into the duodenum. Upon reaching the small intestine, BAs function as physiologic detergents that aid in the absorption of dietary triglycerides, cholesterol, and lipid-soluble vitamins (Hofmann, 1999). In the ileum, most conjugated BAs enter enterocytes via apical sodium-dependent bile acid transporter (ASBT). BAs are transported across ileocytes by the intestinal bile acid-binding protein and taken to portal circulation by the transporter heterodimer, organic solute transporters (OST) α/β). BAs recirculate to the liver via portal circulation and are uptaken into hepatocytes by either the sodium taurocholate cotransporting polypeptide (NTCP) or organic anion transporters (OATPs) (Hagenbuch and Meier, 1994; Jacquemin et al., 1994; Wong et al., 1994; Dawson et al., 2005; Csanaky et al., 2011). Approximately 95% of BAs are recycled through enterohepatic circulation (Fig. 1). When very small amounts of conjugated BAs escape the ileal reabsorption and reach the colon, gut bacteria deconjugate and further metabolize the primary BAs to form more hydrophobic and cytotoxic secondary BAs, including lithocholic acid (LCA) from CDCA and deoxycholic acid (DCA) from CA, through dehydrogenation, dehydroxylation, and epimerization reactions. BAs in the large intestine are passively reabsorbed or excreted into feces.

BA synthesis is tightly regulated through a gut-liver negative feedback loop. In the distal small intestine, FXR induces an endocrine fibroblast growth factor (FGF) 19 in humans and FGF15 in mice. FGF19/15 then enters portal vein circulation to activate fibroblast growth factor receptor 4/βklotho complex in hepatocytes, resulting in activation of the extracellular signal-regulated kinase 1/2 and c-Jun N-terminal kinase 1/2 pathways to repress the expression of genes in classic pathway of BA synthesis. In the liver, activation of FXR induces small heterodimer partner (SHP), which functions to mainly suppress gene expression of *CYP8B1/Cyp8b1* and, to a lesser extent, *CYP7A1/Cyp7a1* (Goodwin et al., 2000; Lu et al., 2000; Inagaki et al., 2005; Song et al., 2009; Kong et al., 2012).

BAs are endogenous signaling molecules that activate various nuclear receptors including FXR, vitamin D receptor, and the pregnane X receptor (PXR), as well as G-protein coupled membrane receptors, including Takeda G-protein-coupled receptor 5, muscarinic receptors 1 and 2, and the Sphingosine-1-phosphate receptor 2 (Xie et al., 2001; Makishima et al., 2002; Raufman et al., 2002; Katsuma et al., 2005; Studer et al., 2012; Liu et al., 2014). Activation of FXR by BAs regulates BA homeostasis including synthesis, transport, metabolism, and detoxification (Parks et al., 1999; Li et al., 2010; Thomas et al., 2010; Kong et al., 2012; Zhan et al., 2014). FXR is crucial in the regulation and checkpoints of many genes and pathways spanning from BA enterohepatic circulation to lipid and glucose metabolism. These pathways regulate cell-signaling pathways involved in regulating lipid, glucose and energy metabolism, metabolic homeostasis, and inflammation. Therefore, any perturbation to BA levels and/or the composition, or regulators will have a cascade of effects on a multitude of pathways. Currently, FXR is a novel target for the therapeutic treatment of nonalcoholic steatohepatitis (NASH) (Oseini and Sanyal, 2017; Helmstädter et al., 2021; Sanyal et al., 2021; Wang et al., 2021). Nonalcoholic fatty liver disease (NAFLD) is a worldwide clinical epidemic that is most notably seen in Western countries with an estimated prevalence affecting 20%–30% of the population (Satapathy and Sanyal, 2015; Younossi et al., 2016). NAFLD is a spectrum of liver diseases that range from simple steatosis to inflammation. Left unattended, NASH may progress to fibrosis, cirrhosis, and even hepatocellular carcinoma (Pierantonelli and Svegliati-Baroni, 2019). NASH-derived cirrhosis is currently the second leading etiology of liver disease among adults waiting for liver transplantation in the United States (Satapathy and Sanyal, 2015). NASH is characterized by histopathological presence of macrovesicular steatosis, lobular inflammation, hepatic ballooning, Mallory bodies, and perisinusoidal fibrosis (Brunt, 2001). NASH is a multifactorial disease with pathogenesis not fully determined (Armstrong and Guo, 2017; Oseini and Sanyal, 2017). Confirmed diagnosis of NASH relies on an invasive and highly undesirable biopsy, and there currently is no US Food and Drug Administration (FDA) approved therapy for NASH (Sanyal et al., 2015).

FXR seems critical in NAFLD/NASH development. Activation of FXR may repress NASH development, which is suggested by the increase in NASH development in FXR knockout mice in a high-fat diet induced NASH model (Kong et al., 2009). During NASH development, FXR has been shown to be downregulated (Wang et al., 2008; Zhang et al., 2009a; Zhang et al., 2009b; Bjursell et al., 2013; Porez et al., 2013; Armstrong and Guo, 2017). Due to the accumulated evidence that FXR plays an important role in modulating lipid homeostasis and suppressing inflammation in NASH development, FXR emerges as a major drug target to treat NASH (Sanyal et al., 2015; Chow et al., 2017; Oseini and Sanyal, 2017; Maliha and Guo, 2021).

Environmental Chemicals Contribute to Modulation of BA Homeostasis

Exposure to environmental chemicals has been demonstrated to be a significant contributor to NASH development (Cave et al., 2007). The impact of the environmental exposures on BA signaling and FXR-mediated gut-liver crosstalk has been emerging in recent years. However, there is still a huge gap in understanding how these chemicals impact and contribute to the regulation of BA homeostasis. The purpose of this minireview is to focus on the recent reports of the effects and mechanisms by which environmental chemicals, including pesticides, industrial plastics, per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), and dioxins, alter BA homeostasis and FXR-mediated gut-liver crosstalk that may collectively contribute to NASH development in humans (Table 1).

Pesticides: Herbicides, Fungicides, Insecticides

Pesticides are a broad class of chemicals used for the prevention, destruction, or control of any pests, including herbicides, fungicides, and insecticides (EPA, 2021a).

Organochlorine Pesticides

Organochlorine pesticides (OCPs) are chlorinated hydrocarbons that were manufactured and used worldwide from the 1940s through the 1960s in agriculture and mosquito control. OCPs were successful in controlling malaria and typhus but are banned in most advanced countries for their adverse health effects. OCPs are resistant to environmental degradation and persistently bioaccumulate in the body; exposure to them are known to lead to reproductive disruption (Saxena et al., 1981; Beard et al., 1999), cancer (Stellman et al., 2000; Wolff et al., 2000), neurobehavioral disorders (Tilson et al., 1985; Saeedi Saravi and Dehpour, 2016), immunologic toxicity (Miranda et al., 2008; Thompson et al., 2019; Shah et al., 2020), and metabolic disease (Park et al., 2010; Lee et al., 2011; Cano-Sancho et al., 2017; Han et al., 2020). The most well-known OCPs are DDT and hexachlorocyclohexane (HCH), and their major metabolites are p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) and βHCH (Salihovic et al., 2016).

Exposure to p,p'-DDE and βHCH may alter BA homeostasis via both gut- and liver-mediated mechanisms. Chronic low dose p,p'-DDE and HCH exposure to adult male C57BL/6 mice for 8 weeks resulted in modulation of gut microbiota abundance and composition most notably in enhanced *Lactobacillus* with bile salt hydrolase activity (Liu et al., 2017). Chronic low dose OCP exposure significantly induced mRNA levels of BA synthesis genes *Cyp7a1, Cyp8b1*, and *Cyp27a1* and hepatic transporters multidrug resistance-associated protein 2, multidrug resistance-associated protein 3, *Ntcp* and *Bsep* (Liu et al., 2017). In the ileum, OCP exposure decreased mRNA expression of genes *Asbt,* Ostα/b, and *Fgf15*. To test if OCP exposure directly affected hepatic BA synthesis, HepG2 cells treated with OCPs were found to significantly induce mRNA levels of CYP7A1, CYP8B1, CYP27A1, and BSEP (Liu et al., 2017).

Metabolomics profiling of Atlantic salmon hepatocytes exposed to 0.1, 1, 10, and 100 μM p,p'-DDE for 48 hours led to the upregulation of BA synthesis, decreased secretion of Bas, and the reduction of glucuronidation metabolites (Olsvik and Søfteland, 2018). The proposed mechanism for increased BA synthesis is due to the very hydrophobic nature of p,p'-DDE, BA synthesis may be increased to conjugate and secrete more p,p'-DDE.

In developed countries where malaria and typhuria are well managed, the use of OCPs are banned while its derivatives continue to biomagnify; however, in developing countries, these pesticides are still widely used and therefore it is important to elucidate the potential of OCPs to cause and contribute to metabolic disease. It is known that derivatives of DDT and HCH alter BA homeostasis, and more research is needed to understand the larger implications of exposure to OCPs.

Endocrine Disrupting Chemicals

Bisphenols. Bisphenol A (BPA) is a known endocrine disrupting chemical (EDC) used in the production of phenol resins, polyacrylates, polyesters, epoxy resins, and polycarbonate plastics. BPAs are composed of two phenol rings connected by a methyl bridge containing two methyl groups (Murata and Kang, 2018). BPA exposure leads to carcinogenesis, reproductive toxicity, perturbed immune response, and neurodevelopmental disorders (Murata and Kang, 2018). BPA exposure is widespread and has been detected in water, air, and soil.

TABLE 1

Environmental chemicals known to modulate bile acid signaling

Exposure to environmental chemicals has been demonstrated to be a significant contributor to NASH development, and the impact of the exposures and how these chemicals impact and contribute to BA homeostasis remain unclear. The recent reports on the effects and mechanisms by which environmental chemicals, including pesticides; industrial plastics; PFAS; PCBs and dioxins, alter BA homeostasis are included.

Chemical	Model	Exposure	Physiologic and Molecular Endpoint	Citation
p, p'-DDE *β*-HCH	C57BL/6 mice	p, p'-DDE 1 mg/kg bw/day *β*-HCH 10 mg/kg bw/day; 8 weeks	↑ Cyp7a1, Cyp8b1, Cyp27a1 mRNA ↓ileal BA reabsorption ↑hepatic BA synthesis modulation of gut microbiota abundance and composition	Liu et al., 2017
	HepG2 cells	p, p'-DDE 10 ng/mL *β*-HCH 100 ng/mL; duration unknown	↑ CYP7A1, CYP8B1, CYP27A1, BSEP mRNA	
p, p'-DDE	Atlantic salmon hepatocytes	0.1, 1, 10, 100 *μ*M; 48 hrs	↑ BA synthesis, albumin synthesis ↓ secretion of BAs, glucoronidation metabolites	Olsvik & Søfteland, 2018
BPA	C57BL/6 mice	10 *μ*g/ kw bw, 10 mg/kg bw; during pregnancy	gestational glucose intolerance in F0 pregnant mice metabolic abnormalities in F1 male offspring ↔ Cyp7a1, Cyp8b1 mRNA 10 mg/kg bw: altered lipid metabolism, ↑ hepatic BA levels, ↓ *Fxr, Shp* mRNA	Susiarjo et al., 2017
BPA BPS BPAF	Primigravida pregnant Institute of Cancer Research mice	100 ng/g bw/day; duration of pregnancy until postnatal day 21	BPS and BPAF: ↑ glucose, glycogen in liver ↑ mRNA of Fxr, Shp, and genes related to glucose and lipid metabolism	Meng et al., 2018
BPS	CD-1 mice	0.2 mg/kg/day; gestational day 8 through postnatal day 21	Adult male pups: ↑ fecal BAs ↓ *β*-diversity of Ruminococcaceae family ↑ Lactobacillus ↔ Cyp7a1 mRNA ↓ IL-2, IL-12p35, IL-12p40, Nqo1 mRNA	Gomez et al., 2021
PFAS	Human	—	positive association between PFAS and BAs for LCA, GLCA, TLCA negative association between PFAS and BAs for GDCA	Salihović et al., 2020
PCB	C57BL/6 mice Conventional Germ free	6 mg/kg daily, 30 mg/kg daily; 3 days	altered gut microbiome composition, modulated BA homeostasis at 30 mg/kg increased hepatic efflux transporter expression, ileal Fgf15	Cheng et al., 2018
PBDE-47 PBDE-99	C57BL/6 mice	BDE-47 100 *μ*mol/kg/daily BDE-99 *μ*mol/kg/daily; 4 days	↑ Akkermansia muciniphila and Erysipelotri- chaceae Allobaculum spp., ↓ BA-synthesizing enzymes BSEP, NTCP, OATP1B2 Protein levels ↑ Cyp7a1 mRNA	Li et al., 2018

TABLE 1 *continued*

Chemical	Model	Exposure	Physiologic and Molecular Endpoint	Citation
PBDE-47	CD-1 mice	0.2 mg/kg/day; gestational day 8 through postnatal day 21	↑ Cyp7a1 mRNA ↑ abundance of CA, T-DCA and DCA BA metabolites ↑ abundance of the genus Blautia, Ruminococcus genus, and Lachnospiraceae	Gomez et al., 2021
PBDE-28	Human	—	altered infant gut microbial composition ↓ abundance of Veillonella	Iszatt et al., 2019
TCDD	Sprague-Dawley rats	TCDD 0.1 μg/kw bw, 40 μg/kg bw; 6 hrs, 24hrs, 7 days	at 40 μg/kg: ↓Cyp7a1, Shp, Fxr, Ntcp, Oatp2 mRNA widespread changes in cell signaling, cellular adhesion, cytoskeletal and membrane transport protein pathways	Fletcher et al., 2005
	C57BL/6 mice	0.01-30 μg/kg; every 4 days for 28 days	↓ Cyp7a1 mRNA systemically altered enterohepatic circulation ↑ hepatic and serum BA pools ↓ fecal BA levels ↑ ileal transporters Asbt, Ostα	Fader et al., 2017
	Ahr-null mice	37 μg/kg/ daily; 5 days	↓ hepatic BA pool ↔ Cyp7a1 mRNA ↓ biliary TCA, TDCA, CA and DCA; hepatic T-αMCA, TUDCA	Csanaky et al., 2018
TCDF	Ahr-null	24 μg/kg; 5 days	↑ *Cyp7a1, Bacs* mRNA ↑ TCDCA and TβMCA shifted gut microbiota ratio of Firmicutes to Bacteroidetes	Zhang et al., 2015

Bacs, bile acid-coenzyme A synthetase; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TUDCA, tauroursodeoxycholic acid

BPA may increase BA levels through altered FXR signaling, but the exact mechanism is unclear. Dietary exposure to BPA at 10 mg/kg and 10 mg/kg body weight per day during pregnancy in C57BL/6J mice induced metabolic abnormalities in F1 male offspring, and gestational glucose intolerance was also induced in pregnant mice (Susiarjo et al., 2017). At 10 mg/kg body weight per day, BPA altered lipid metabolism and increased hepatic BA levels. The altered hepatic BA levels due to BPA dietary exposure were associated with a significant decrease in *Fxr* and *Shp* mRNA expression (Susiarjo et al., 2017). Interestingly, BPA exposure did not change *Cyp7a1* or *Cyp8b1* gene expression, suggesting that the elevated BA levels were not due to an increase in BA synthesis; instead, it is likely that fetal transport of BAs were disrupted, leading to the accumulation of BAs in the liver.

Bisphenol S (BPS) and Bisphenol AF (BPAF) are BPA analogs that are commonly used in place of BPA to comply with restrictions and regulations. In another pregnancy study, low doses of BPA, BPS, and BPAF were administered at 100 ng/g body weight per day and dams were exposed until postnatal day 21. Interestingly, BPS and BPAF exposure resulted in significant increases in glucose and glycogen contents in the liver, which is associated with increased mRNA levels of Fxr and Shp, but the exact role of FXR in increased glycolysis and the inhibition of gluconeogenesis by these environmental chemicals is unclear (Meng et al., 2018). In an early life exposure study, CD-1 mouse dams were orally administered 0.2 mg/kg BPS daily from gestational day 8 through postnatal day 21. This exposure to BPS in adult male pups led to an increase in fecal BAs, a decrease in beta-diversity of fecal microbiome content; specifically, there was a decreased relative abundance of a taxon in the Ruminococcaceae family and persistent increase in Lactobacillus in adult male pups. This genus is known to have bile salt hydrolase activity (Gomez et al., 2021). Interestingly, BPS exposure in early life did not significantly alter mRNA expression of *Cyp7a1* (Gomez et al., 2021). To our knowledge, this is the first study to show the effect of BPS on gut microbiome composition. These findings suggest that exposure to BPS may have a profound effect on

the gut-liver axis to affect BA homeostasis (Gomez et al., 2021). Currently, there remains a large gap in understanding how these EDCs disrupt BA homeostasis, glucose, and lipid metabolism, and more research is needed to further elucidate the effects and mechanisms of bisphenols on these signaling pathways.

Polyflourinated Chemicals. PFAS are a class of synthetic chemicals and EDCs that have been used worldwide dating back to the 1950s. PFAS include perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), GenX chemicals or fluoropolymers, and more. PFAS can be found widely in food packaging, commercial household products, production facilities or industries, drinking water, and living organisms including fish, animals, and humans (EPA, 2021b). Overwhelming research shows that PFOS and PFOA can cause reproductive and developmental, immunologic, kidney and liver toxic effects in vivo. PFAS structurally resemble long-chain fatty acids with fluorine in place of hydrogen. PFOS and PFOA chemicals stay persistently in the environment and human body, as they do not break down and can accumulate over time.

PFAS may alter BA homeostasis. There is strong evidence that some PFAS may undergo enterohepatic circulation. Transporter studies conducted suggest that perfluorobutane sulfonic acid, perfluorohexane sulfonate (PFHxS), and PFOS are substrates of human and rat NTCP; furthermore, human ASBT can transport PFOS, and human organic solute transporter alpha/beta can transport PFHxS and PFOS (Zhao et al., 2015). This study hypothesized that the combined BA transporter network aids in the enterohepatic recycling of PFHxS and PFOS, which may contribute to the extensive serum elimination of PFAS in humans (Zhao et al., 2015). According to the European Food Safety Authority) and US Environmental Protection Agency (EPA), the most consistent finding of PFAS was increased cholesterol levels among exposed populations (EFSA, 2018; EPA, 2021b). PFAS have been shown to decrease fecal BA excretion (Bijland et al., 2011). This reduction of fecal BA excretion may be due to the fact that PFAS reduced the mRNA levels of Cyp7a1 and led to an increased reuptake of BAs via enhancing the FXR-mediated negative feedback loop, which subsequently reduces de novo BA synthesis (Bijland et al., 2011; Beggs et al., 2016).

PFAS may also reduce BA synthesis through reducing hepatocyte nuclear factor 4-alpha (HNF4α) levels. HNF4α is a master transcriptional regulator in differentiated hepatocytes, regulating liver specific processes including BA synthesis, lipid metabolism, and maintenance of hepatocellular quiescence and differentiation. Research suggests that PFOA exposure decreases HNF4α expression in hepatocytes (Watt et al., 2003). Human hepatocytes treated with occupationally relevant concentrations of PFOA and PFOS at 10 μM significantly decreased HNF4α protein expression, which is associated with reduction of the expression of HNF4α target genes, including *CYP7A1*/*Cyp7a1* (Beggs et al., 2016).

Emerging evidence suggests that PFAS may alter human BA homeostasis. In a human study, levels of PFAS and BAs were measured in 20 healthy humans (Salihović et al., 2020). In this study, the results found significant associations between plasma PFAS and BA levels. Furthermore, correlation analyses between PFAS and BA concentrations reveal a positive association with LCA, glycolithocholic acid, and taurolithocholic acid (TLCA) and a negative association with glycodeoxycholic acid. However, the majority of circulating BAs was negatively associated with PFAS, suggesting that the de novo synthesis of BAs is reduced, which is in agreement with published literature (Salihović et al., 2020). Increased levels of LCA and its conjugates could indicate a variety of scenarios including increased reuptake of BA in the gut, decreased clearance from blood, increased production of conjugated BA in the liver, or decreased deconjugation by host microbiota (Salihović et al., 2020).

Polychlorinated Biphenyls. PCBs are a subgroup of synthetic organic chemicals that were previously manufactured and marketed around the world under the commercial name Aroclor in the early to mid-1990s for their coolant and electrical insulating properties (Faroon and Olson, 2000; Christensen et al., 2021). Waste containing PCBs before 1977 was placed in landfills and accidentally spilled and leaked in transport. As a consequence, PCBs have entered the environment and bioaccumulated (Faroon and Olson, 2000). Like PFAS, PCBs are known EDCs and do not readily break down; they can easily cycle among air, water, and soil, therefore, ongoing exposure to these chemical mixtures is extremely problematic. PCBs exist as mixtures in the environment, which makes measuring and evaluating toxicological endpoints in biologic tissues of these mixtures extremely difficult (Christensen et al., 2021). The multitude of toxicities incited by PCB exposure observed in humans and animals include carcinogenicity (Dorgan et al., 1999; Stellman et al., 2000; Wolff et al., 2000), perturbations of reproductive and developmental processes (Jonsson et al., 1975–1976; Faqi et al., 1998), and cardiovascular and metabolic functions (Choi et al., 2003; Arsenescu et al., 2008).

It is known that PCB exposure is associated with fatty liver disease; however very little is known regarding the impact that this chemical class has on the gut microbiome, and in relation to that, how BA signaling is impacted. In one recent study conducted in adult female conventional and germ-free mice, Fox River mixture, a PCB mixture, were orally administered at 6 or 30 mg/kg daily for 3 days. These treatments showed that PCBs not only alter BA gut-liver crosstalk but also bacterial involved in BA metabolism (Cheng et al., 2018).

Polybrominated Diphenyl Ethers. Polybrominated diphenyl ethers (PBDEs) are environmentally persistent organobromine compounds that may alter BA composition and levels. PBDEs were previously manufactured as flame retardants incorporated in plastics, textiles, furniture, rubber, and electronic devices. Over recent years, health concerns about exposure to PBDEs has grown as they have been found to cause developmental and reproductive toxicity, disruption in thyroid hormone homeostasis, liver toxicity, and carcinogenesis in rodent models (Gascon et al., 2011; Linares et al., 2015; Pohl et al., 2017). There are 209 PBDE congeners, and two of the most predominant congeners detected environmentally and in human specimens are 2,29,4,49-tetrabromodiphenyl ether (BDE-47) and 2,29,4,49,5- pentabromodiphenyl ether (BDE-99) (Erratico et al., 2011). BDE-47 and BDE-99 are known to activate constitutive androstane receptor (CAR) and PXR in rodents and humans, two major xenobiotic sensing nuclear receptors, and therefore inducing expression of cytochrome P450s, which may lead to the modulation of BA signaling (Pacyniak et al., 2007).

A well conducted study for the effects of PBDE on BA homeostasis was done in 9-week-old male conventional and germ-free mice with oral administration of BDE-47 at 100 μmol/kg or BDE-99 at 100 μmol/kg once daily for 4 days, followed by extensive analysis of microbiome, transcriptome, and BA profiling (Li et al., 2018). This study revealed that PBDEs altered the expression of genes involved in BA synthesis and transport at mRNA and protein levels. Specifically, the treatment of PBDEs increased Cyp7a1 mRNA levels but generally reduced the protein levels of BA synthetic enzymes and transporters. Furthermore, PBDEs changed hepatic and gut BA species, with a significant increase in unconjugated BA species, likely due to alteration of gut microbiome that are involved in BA deconjugation. This study suggests that PBDEs are not FXR modulators and presumably regulate BA homeostasis via activating CAR and/or PXR. In a study with early life PBDE exposure, BDE-47 was orally administered to CD-1 mouse dams at 0.2 mg/kg once daily from gestational day 8 through the end of lactation at postnatal day 21. The results from this study showed that exposure to BDE-47 in early life led to an increase in expression of Cyp7a1, a general trend of increase in abundance of

CA, taurodeoxycholic acid, and DCA BA metabolites and increased the abundance of the microbiome for secondary BA synthesis (Gomez et al., 2021).

PBDE exposure may lead to alternation of human microbiome. Norwegian mothers and their 1-month-old babies were analyzed for 28 environmental chemicals including 2,4-Dibromo-1-(4-bromophenoxy)-benzene (PBDE-28). In the breastmilk of mothers and gut bacteria in the babies, it was found that exposure to PBDE was associated with an altered infant gut microbial composition. PBDE-28 was associated with 4% less Shannon diversity, and infants highly exposed to PBDE-28 had relatively less abundance of *Veillonella* (Iszatt et al., 2019).

These initial discoveries suggest that PBDE exposure can alter BA homeostasis, which may subsequently affect physiology and pathology associated with altered BA and lipid metabolism.

Dioxins. Dioxins and dioxinlike compounds are a group of polychlorinated dibenzo para dioxiychlorinated dibenzofurans chemicals collectively called persistent organic pollutants that are grouped together for their shared mechanism of action. Dioxins bind and activate aryl hydrocarbon receptor (AHR) and subsequently elicite toxicity in rodents and humans (Gillner et al., 1985; Kolluri et al., 2017). Activation of AHR is widely known to mediate the expression of genes, resulting in toxic responses including immune suppression, hepatotoxicity, tumor production, dermal lesions, teratogenicity, and wasting dependent on sex, age, and tissue (Denison et al., 2011). This is of great concern as dioxin persistent organic pollutants are mainly byproducts of industrial processes in the production of PCBs and other chlorinated organic chemicals. Dioxins are known to occur naturally to a lesser degree by the incomplete combustion of organic material by forest fires or volcanic activity (Pohl, 2000). Upon entering the body, dioxins are stored in adipose tissues and their estimated half-life in the body is 7 to 11 years (Pohl, 2000).

2,3,7,8-Tetrachlorodibenzo Para Dioxin. There are 75 polychlorinated dibenzo para dioxins congeners with the most toxic one being 2,3,7,8-tetrachlorodibenzo para dioxin (TCDD). TCDD is historically well known as a contaminant in some batches of herbicide of Agent Orange, a defoliant used during the Vietnam War, and extensively studied to date. TCDD has been well studied for its role in AHR activation and its role in eliciting hepatotoxicity.

TCDD is known to alter expression of genes involved in cholesterol metabolism and BA biosynthesis, increase serum BA levels, decrease biliary flow, and induce bile duct epithelial cell proliferation (Pohl, 2000; Fletcher et al., 2005). In an acute study, male rats were administered a single oral dose of TCDD at 0.4 or 40 mg/kg and global analysis of gene expression was performed at 6 hours, 24 hours, and 7 days after the treatment. At 40 mg/kg dosage, widespread changes in gene expression were observed in cell signaling proteins, cellular adhesion, cytoskeletal, and membrane transport protein pathways (Fletcher et al., 2005). Additionally, at the high dose, there was a significant decrease in the mRNA levels of Cyp7a1, Shp, Fxr, Ntcp ,and Oatp2 (Fletcher et al., 2005). The observed changes suggest TCDD exposure resulted in a major disruption of BA synthesis and transport (Fletcher et al., 2005). In a sub-acute TCDD exposure, male mice were administered TCDD by oral gavage every 4 days for 28 days at concentrations ranging between 0.01-30 mg/kg, the treatments resulted in the repression of genes involved in BA synthesis and cholesterol metabolism including *Cyp7a1* (Fader et al., 2017). TCDD exposure systemically altered enterohepatic circulation, despite the repression of *Cyp7a1* gene expression. There was an observed increase in hepatic and serum levels of BAs, while fecal BA levels decreased, which indicates the treatment enhanced intestinal resorption as there were observed increases in ileal expression of transporters ASBT and OSTα (Fader et al., 2017).

Furthermore, TCDD increased fecal levels of bile salt hydrolase and the bile acid-inducible operon, suggesting there was increased gut microbiota deconjugation and dehydroxylation activity, which is consistent with the accumulation of TLCA and other secondary BAs (Fader et al., 2017). A similar disruption on BA homeostasis in male and female mice by TCDD was observed when it was administered to wild-type (WT) and AHR-null mice at 37 mg/kg for 5 days (Csanaky et al., 2018). In WT mice, TCDD decreased the concentration of total hepatic BAs without decreasing *Cyp7a1* expression and altering the FXR-gut-liver axis (Csanaky et al., 2018). The amount of 12-OH BAs, including taurocholic acid, taurodeoxycholic acid, CA, and DCA in bile and its metabolites in the liver, tauro-α-muricholic acid, tauroursodeoxycholic acid, were decreased upon exposure to TCDD (Csanaky et al., 2018). The observed decreases in 12-OH BAs are possibly due to the decrease in *Cyp8b1* mRNA expression in the liver. The observed changes were not found in AHR-null mice, suggesting an AHR-dependent mechanism.

2,3,7,8-Tetrachlorodibenzofuran. 2,3,7,8-tetrachlorodibenzofuran (TCDF), a dioxin congener with a short half-life, was found to inhibit FXR signaling via an AHR dependent manner. TCDF was administered in diet to 6-week-old male WT and AHR-null mice for 5 days at 24 mg/kg and this dietary exposure to TCDF seemed inhibit FXR signaling in WT mice resulted in a 10-fold induction in Cyp7a1 mRNA levels (Zhang et al., 2015). The mRNA levels were also increased for bile acid-coenzyme A synthetase, an important enzyme involved in conjugating BAs with taurine, which was coupled with subsequent increases in taurochenodeoxycholic acid and tauro-β-muricholic acid (Zhang et al., 2015). Dietary exposure to TCDF altered gut microbiota, shifting the ratio of Firmicutes to Bacteroidetes; these changes are attributed to the perturbed BA homeostasis (Zhang et al., 2015).

Bile Acids in Drug Development. The abovementioned environmental chemicals including pesticides and industrial plastics commonly known as EDCs used in industrialization processes are known to dysregulate BA homeostasis by perturbation of BA synthesis and transport as well as by altering gut microbiome composition (Table 1). Endogenous substrates such as BAs are crucial biomarkers that are increasingly being studied to better inform drug development with respect to the prediction of drug-drug interactions (DDI)s. In the recent years, BAs and some of their conjugates glycochendodeoxycholate-3-sulfate and chenodeoxycholate-24-glucoronide have been proposed as endogenous biomarkers of hepatic transporter Solute carrier organic anion transporter family member 1B1, Solute carrier organic anion transporter family member 1B3, BSEP, and NTCP in drug development (Watanabe et al., 2015; Takehara et al., 2017; Chu et al., 2018; Neuvonen et al., 2021). The use of conjugated BAs as endogenous biomarkers to inform potential DDIs is a huge stride toward better informing risk assessment in drug development and could also potentially inform DDI management strategies. These environmental chemicals may have a potential to alter endogenous metabolism and contribute to the development of chronic liver diseases. The scientific community must develop an appreciation for BAs as more than just signaling molecules, but also explore their potential to tell us more about liver disease. More research is urgently needed to elucidate the mechanisms by which these chemicals disrupt BA homeostasis and lipid metabolism.

FXR Modulation by Environmental Contaminants

There are few environmental chemicals known to modulate FXR signaling directly; however, several of the known chemicals to alter FXR signaling are FDA-approved therapeutics that can be found in the environment in a likely unappreciable amount (Table 2). We have to point out that certain populations may be exposed to these chemicals at high amounts, e.g., occupational workers.

TABLE 2

Environmental chemicals known to modulate FXR signaling

Very few environmental chemicals are known to modulate FXR signaling, however the majority of them are FDA approved therapeutics.

Chemical	Model	Exposure	Physiologic and Molecular Endpoint	Citation
Gliquidone	U2-OS cells; nucleoBAS FRET	10 μM; 30 mins	45% FXR activation compared with GW4064	van de Wiel et al., 2019
Nicardipine			33% FXR activation compared with GW4064	
Fluticasone			60% FXR activation compared with GW4064	
Avermectin			84% FXR activation compared with GW4064	
Ivermectin			74% FXR activation compared with GW4064	
Triclosan			69% FXR activation compared with GW4064	
Ivermectin	COS-7 cells; reporter assay	0.5 μM; 24 hrs	Ivermectin activates FXR in a concentration dependent manner; EC50 ~200 nM	Jin et al., 2013
	C57BL/6 andFXR-null mice	1.3 mg/kg/day; 14 days	WT-mice only: ↓ serum glucose, insulin, cholesterol ↑ Hepatic Shp mRNA ↓ Cyp7a1, Cyp8b1 mRNA	
Ivermectin GW4064	KK-Ay mice	Ivermectin 1.3 mg/kg/ dayGW4064 30 mg/kg/day; 14 days	Ivermectin only: ↓ bw, serum glucose and insulin ↓ Ldlr, Pepck mRNA GW4064 only: ↓ Hmgcr, Sr-Bi mRNA Both: ↓ serum cholesterol ↓ Cyp7a1, Cyp8b1, G6Pase mRNA ↑ Bsep mRNA	
Ivermectin Doramectin Abamectin GW4064	KK-Ay mice	Avermectin analogs 1.3 mg/kg/ dayGW4064 30 mg/kg/day; 14 days	Avermectin analogs only: ↓ LW:BW, serum triglycerides, cholesterol ↓ Cyp8b1, Srebp-1c, Scd-1 mRNA ↑ Shp, Bsep, Akr1b7 mRNA	Jin et al., 2015
Triclosan CDCA	Huh7 cells	Triclosan 10 μMCDCA 50 μM;24 hrs	Triclosan either very weak agonist or partial antagonist competing with CDCA for binding of FXR	van de Wiel et al., 2019
Gentamycin Vancomycin	Human Intestinal Failure Patients with cholestasis	—	Disrupted FXR signaling ↓ ASBT, OSTα/B mRNA ↓ serum FGF19 ↑ CYP7A1, CYP8B1, CYP27A1 mRNA	Xiao et al., 2018
	C57BL/6 mice	Gentamycin 2 g/LVancomycin 500 mg/L	Antibiotic treatment altered BA transport in liver and ileum ↑ TβMCA = ↓ Fgf15 mRNA ↑ Cyp7a1, Cyp27a1, Mrp3, Mrp4, Mdr3 mRNA	

AKR1B7, aldo-keto reductase family 1, member 7; FRET, Fluorescence Resonance Energy Transfer; G6Pase, glucose 6-phosphatase; MRP3, multidrug resistance-associated protein 3; nucleoBAS, nuclear bile acid sensor; PEPCK, phosphoenolpyruvate carboxykinase; Scd1, stearoyl-CoA desaturase; SREBP-1c, sterol regulatory element binding protein-1c.

FDA-Approved Therapeutics

FXR is an attractive therapeutic target for the treatment of several metabolic diseases including NASH (Ding et al., 2015; Chávez-Talavera et al., 2017; Oseini and Sanyal, 2017; Wang et al., 2018; Chiang and Ferrell, 2019). Currently, there are no FDA-approved therapeutics for the treatment of NASH, and researchers are utilizing high throughput biochemical screening technology to identify chemicals that activate FXR to advance in the direction of finding FXR modulator(s) as potential therapy for NASH (van de Wiel et al., 2019).

In a study utilizing a nuclear BA sensor, Fluorescence Resonance Energy Transfer technology, the FXR-activating potential of several drugs used in clinical practice was assessed utilizing WT and transfected U2-OS cells. Fifteen drugs were tested positive for FXR activation and six of the drugs found to activate FXR also induced FXR

target gene expression (van de Wiel et al., 2019). These six drugs are currently widely used in clinical practice: gliquidone for the treatment of type 2 diabetes, nicardipine to treat hypertension, fluticasone proprionate for anti-inflammation, avermectin and ivermectin as antiparasitics, and triclosan for its antibacterial properties (van de Wiel et al., 2019). Exposure to these therapeutics implies that there may be a greater effect on downstream FXR target proteins, and the probability of these orally administered drugs to reach the enterocytes in the intestine and activate FXR is extremely high. Exemptions to this are the topical drugs such as avermectin and ivermectin, as their ability to penetrate the skin epithelial barrier to reach enterocytes is considerably low (van de Wiel et al., 2019).

Avermectin and Its Derivatives. Avermectin and its derivative ivermectin are a series of 16-membered macrocyclic lactone derivatives generated as fermentation products by soil actinomycete for their potent insecticidal properties and widely used as an antiparasitic in animals and humans (Jin et al., 2015). Ivermectin is structurally similar to GW4064 and CDCA, and interestingly, has been found to notably induce the recruitment of nuclear receptor corepressor 2 by FXR (Jin et al., 2013). In a reporter gene assay utilizing COS-7 cells, ivermectin was found to activate FXR in a concentration-dependent manner with an EC50 of ∼200 nM (Jin et al., 2013). Ivermectin was administered intraperitoneally for 14 days to WT and FXR KO mice fed a high-fat diet to assess the effects on glucose and cholesterol metabolism in vivo. Ivermectin treatment led to a decrease in serum glucose, insulin, and cholesterol levels in WT but not FXR KO mice, suggesting that ivermectin may reduce serum glucose levels by improving insulin sensitivity in an FXR-dependent manner (Jin et al., 2013). Ivermectin treatment also induced hepatic mRNA levels of Shp while reduced those of Cyp7a1 and Cyp8b1 in WT but not in FXR KO mice (Jin et al., 2013). Diabetic KK-Ay mice were fed a high-fat diet and administered GW4064 or ivermectin daily by intraperitoneal injection for 14 days to further elucidate the role of ivermectin's improvement of hyperglycemia and hyperlipidemia. Ivermectin and GW4064 significantly lowered serum cholesterol levels, and interestingly, significantly reduced Cyp7a1 and Cyp8b1 mRNA expression (Jin et al., 2013), suggesting other mechanisms are involved in reducing cholesterol levels. Ivermectin treatment did not elicit significant alterations in mRNA levels of genes involved in cholesterol synthesis and was found to regulate glucose 6-phosphatase and phosphoenolpyruvate carboxykinase more favorably compared with GW4064 (Jin et al., 2013). These data suggest ivermectin could potentially have an advantage over the novel GW4064 ligand with respect to regulating glucose homeostasis.

Doramectin and abamectin are other avermectin analogs that have shown to reduce hepatic lipid accumulation, decrease serum cholesterol and glucose levels, and improve insulin sensitivity in an FXR-dependent manner. Ten-week-old KK-Ay male mice were fed a high-fat diet and administered avermectin analogs including doramectin, abamectin, ivermectin, and GW4064 by intraperitoneal injection for 14 days (Jin et al., 2015). Administration of doramectin, abamectin, and ivermectin to obese diabetic mice decreased liver to body weight ratios, lowered serum triglyceride and cholesterol levels, improved insulin sensitivity, and significantly decreased hepatic mRNA levels of sterol regulatory element binding protein-1c and Stearoyl-CoA desaturase while inducing mRNA levels of a direct FXR target gene Aldo-keto reductase family 1, member 7 (*Akr1b7),* suggesting a potential mechanism in reducing de novo lipid synthesis in the liver (Jin et al., 2015). Avermectin and similar analogs have been used for decades for the treatment of parasitic infection in animals and humans. Perhaps this class of environmental chemicals can be repurposed as a potential therapeutic for the treatment of fatty liver diseases.

Triclosan

Triclosan (TCS) is chlorinated phenoxyphenol widely used as an antibacterial in personal care products, including toothpaste, detergents, first aid products, mouthwash, soap, and technical equipment until recently banned by the FDA in both Europe and the United States. Due to the versatile nature of TCS, consumers may be exposed to this FXR activator. This is of great concern as TCS is known to be rapidly absorbed dermally and can reach systemic circulation. In the study conducted by Van de Wiel et al. (2019), TCS was found to moderately activate FXR; however, short-term treatment of TCS did not result in any changes on intestinal bile acid-binding protein promoter activity nor did it induce FXR target genes (van de Wiel et al., 2019). In another experiment determining the effect on FXR activation with 50 μM CDCA, TCS was found to be either a very weak agonist or a partial antagonist possibly competing with CDCA for binding of FXR (van de Wiel et al., 2019). More research is needed to fully understand the molecular mechanism by which TCS interacts with FXR and subsequent biologic outcomes when interacting with gut BA pathways.

Antibiotics

The link between oral antibiotic treatment and reduced colonic microbial diversity has been well established. It is also well known that the consequence of reduced intestinal microbial diversity is associated with major shifts in the BA composition, as the gut microbiome is responsible for the generation of secondary BAs and subsequent alterations in FXR signaling. In a single population-based cross-sectional study in pediatric patients with intestinal failure-associated liver disease (IFALD), patients were administered oral antibiotics gentamicin (GM) or vancomycin (VM) to prevent bacteremia and the consequences of GM and VM treatment in patients with IFALD and cholestasis led to significantly lower abundance of BA-biotransforming bacteria compared to patients with IFALD (Xiao et al., 2018). Specifically, the reduction in bacteria by antibiotics was associated with BA dysmetabolism and modulation of FXR signaling (Xiao et al., 2018). As a result, these patients on antibiotics presented with increased primary and decreased secondary BAs in the serum (Xiao et al., 2018). Patients with intestinal failure and cholestasis exhibited disrupted FXR signaling with significant decreases in the expression of FXR target genes, *Asbt* and *Ost α/β*, in ileum and a decrease in serum FGF19 (Xiao et al., 2018). FGF19 is critical to the negative-feedback regulation of BA synthesis in the liver, and in these patients with cholestasis, hepatic mRNA expression of *Cyp7a1*, *Cyp8b1*, and *Cyp27a1* was significantly increased (Xiao et al., 2018). The effects of oral antibiotics were further determined in 6-week-old C57BL/6 mice administered GM 2 g/L or VM 500 mg/L in drinking water for 2 weeks. BA metabolism in mice administered GM and VM was significantly impaired with marked alterations in intestinal microbiota composition (Xiao et al., 2018). Specifically, the antibiotic treatment increased tauro-*β*-muricholic acid in the colonic content of treated mice, a known FXR antagonist, which is associated with a decrease in *Fgf15* and increases in *Cyp7a1* gene expression (Xiao et al., 2018).

Antibiotic usage evidently plays a major role in the modulation of BA metabolism, and understanding the molecular mechanisms by which antibiotics alter FXR signaling is needed as patients with NASH and other hepatic disease are likely to be administered antibiotics during their treatment regimes.

Perspective on Future Directions. Research from the last two decades has clearly shown the importance of maintaining BA homeostasis, regulating various biologic processes by BA activated receptors and signaling pathways. However, the role of individual BAs in these processes is not entirely clear, and the effects of environmental chemicals on modulating BA homeostasis remains unclarified.

There has been an emerging appreciation for BAs as not only signaling molecules, but also potential therapeutics and biomarkers in disease initiation, progression, and treatment. Furthermore, activation of FXR by synthetic ligands may not be as specific as desired. For example, a BA mimetic, obeticholic acid (OCA), is a strong synthetic FXR agonist. OCA is currently approved for the treatment of primary biliary cholangitis/cirrhosis and may be approved for NASH therapy (Neuschwander-Tetri et al., 2015). However, a very recent study showed that OCA treatment in mice led to CAR activation, which induced intestinal UGT1A1 expression and resulted in increased elimination of serum bilirubin in humanized UGT1 mice (Weber et al., 2021). Even this effect may be beneficial in treating neonates with hyperbilirubinemia, the non-therapeutic effects of FXR activation in other patient populations may need to be evaluated. Furthermore, BAs and their conjugates have also been explored for their role as endogenous biomarkers as substrates for transporter DDI (Watanabe et al., 2015; Takehara et al., 2017; Chu et al., 2018; Neuvonen et al., 2021).

The BA-FXR axis is a critical target in NASH therapeutic development as the global epidemiologic burden of NASH is projected to steadily increase. Understanding how exposure to environmental chemicals modulate BA signaling and homeostasis and how these exposures may contribute to liver disease pathogenesis such as NASH will greatly provide insight into NASH prevention and/or treatment.

Conclusion

In this minireview, we have focused on discussing the effects on BA homeostasis and FXR regulation with exposure to environmental chemicals or therapeutic agents. Revealing the interface between endobiotic homeostasis and xenobiotic exposure will provide mechanistic insight and preventative strategies to improve human health in the future.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Taylor, Bhattacharya, Guo.

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