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REVIEW

Understanding the Multiple Effects of PCBs on Lipid Metabolism

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Qiuli Shan[1,2]*
Hongmei Li[1]*
Ningning Chen[1]*
Fan Qu[1]
Jing Guo[1]

[1]College of Biological Science and Technology, University of Jinan, Jinan 250022, People's Republic of China; [2]State Key Laboratory of Environmental Chemistry and Eco-Toxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, People's Republic of China

*These authors contributed equally to this work

Abstract: Polychlorinated biphenyls (PCBs) are a typical class of environmental contaminants recently shown to be metabolism-disrupting chemicals. Lipids are a highly complex group of biomolecules that not only form the structural basis of biofilms but also act as signaling molecules and energy sources. Lipid metabolic disorders contribute to multiple diseases, including obesity, diabetes, fatty liver, and metabolic syndromes. Although previous literature has reported that PCBs can affect lipid metabolism, including lipid synthesis, uptake, and elimination, few systematic summaries of the detailed process of lipid metabolism caused by PCB exposure have been published. Lipid metabolic processes involve many molecules; however, the key factors that are sensitive to PCB exposure have not been fully clarified. Here, we summarize the recent developments in PCB research with a focus on biomarkers of lipid metabolic disorders related to environmental exposures.

Keywords: PCBs, metabolism-disrupting chemicals, hepatocytes, lipid metabolism

Introduction

Polychlorinated biphenyls (PCBs) are a group of chlorinated hydrocarbons that were widely produced and used in electrical equipment, building materials and other industrial applications in the 1930s–1970s.[1] Although the production of PCBs was banned worldwide by the Stockholm Convention in 2001 because of concerns about their risks to human health and the environment, a total of 1.3 million tons of PCBs was manufactured during this time, including 209 different PCB congeners.[2] PCBs are lipid-soluble and resistant to biodegradation, which enables them to persist in various environmental media, including air, soil, and water, and they are even biologically amplified through the food chain.[3–5] In addition, unintentional releases of PCBs from old electrical equipment have recently increased in various countries, particularly in China.[6] Therefore, environmental and health issues caused by PCBs are still a matter of concern.

Previous studies showed that PCBs have been classified as metabolism-disrupting chemicals (MDCs).[7] The liver is known to be the main site of metabolism and is an important detoxifying organ in the body. Thus, hepatocytes are exposed to high concentrations of chemicals, and the subsequent occurrence of liver metabolism damage induced by PCBs has become a growing issue.[8,9] For example, existing evidence from animal and human cell studies showed that PCB exposure could cause glucose and lipid metabolic disorders in the liver, thus initiating the onset of chronic systemic metabolic disorders, such as obesity, type 2 diabetes, fatty liver disease, cardiovascular disease and cancer.[10–14] In fact, in addition to acting directly on the

Correspondence: Qiuli Shan
Email bio_shanql@ujn.edu.cn

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target organ, most PCBs that enter the body through breathing, drinking water and the diet can be stored in the liver and adipose tissue.[15] When metabolic processes are disrupted in the body-especially, lipid metabolism-PCBs stored in adipose tissue are released into the blood circulation, potentially exposing the individual to various known adverse health effects for a second time.[16,17] Therefore, it is important to understand the health risks of PCBs by assessing the effect of PCB exposure on lipid metabolism homeostasis.

In this paper, we summarize recent evidence that PCB exposure alters lipid metabolism and its underlying mechanisms in the livers of humans and rodents. We aim to elucidate the specific molecular mechanisms responsible for PCB-induced disruption of lipid metabolism and identify the related targets of PCB exposure. Our hope is that this paper will provide a therapeutic strategy in the treatment of PCB intoxication.

Mechanisms by Which PCBs Affect Hepatic Lipid Accumulation

Lipids are hydrophobic biomolecules that can be broadly divided by their chemical composition into three main categories: simple lipids (eg, triglycerides, TGs), compound lipids (eg, sphingolipids) and derived lipids (eg, cholesterol).[18] However, most lipids are stored in adipose tissue in the form of the simple lipid TG. There are two main sources of lipids in the body: dietary intake and in vivo synthesis. Dietary lipids need to be broken down and resynthesized in the small intestine, while in vivo, hepatocytes have the strongest ability to synthesize and release lipids.[19] Generally, lipids receive less attention in the life sciences than do other biomolecules, such as proteins and nucleic acids. However, lipids represent a complex group of biomolecules that play a vital role in a variety of biological processes, including cell composition, signal transduction, energy storage, and hormone production.[20] Currently, the roles of lipids in different tissues have been extensively studied, and the results (as shown in Figure 1) show several adverse effects such as disordered energy homeostasis, including proinflammatory effects, proapoptotic effects, and dyslipidemia.[21–26] Thus, lipid metabolism homeostasis is also vital to life.

It is well recognized that disturbances in lipid metabolism homeostasis can be attributed to the imbalance of lipid acquisition and removal.[27–29] The lipid acquisition process usually involves free FA uptake from blood by hepatocytes and de novo lipogenesis. The lipid removal process generally involves mitochondrial FAs oxidation and export as a component of VLDL particles. Therefore, PCB exposure-induced dysregulation of lipid

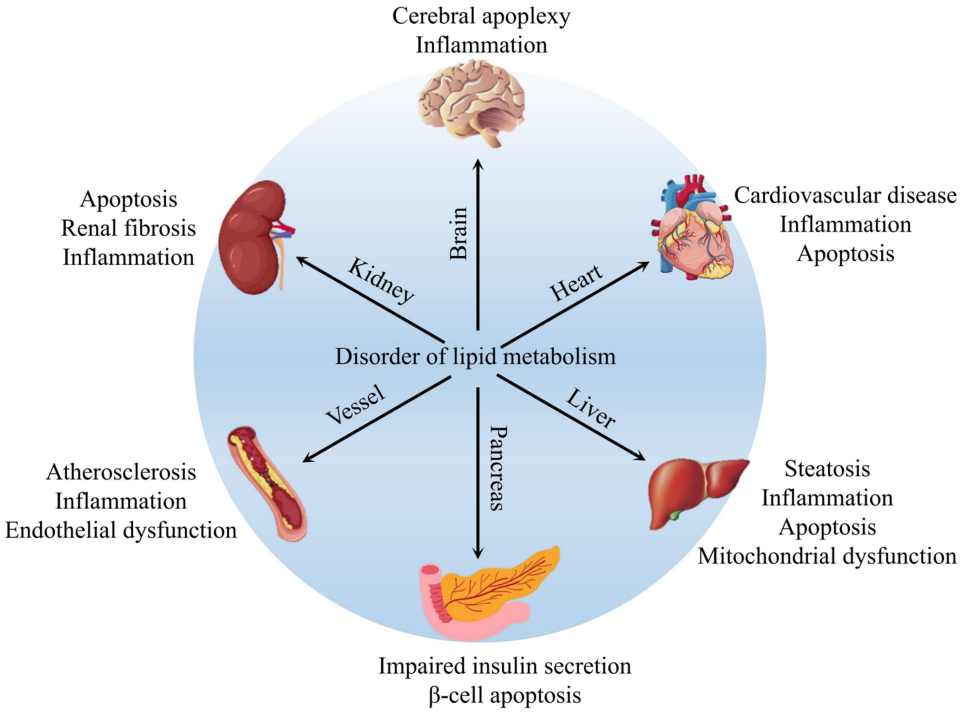

Figure 1 The relationship between lipid metabolic disorders in different organs and tissues.

metabolism homeostasis is also closely related to changes in these processes.

Effects of PCBs on de novo Lipogenesis

De novo lipogenesis refers to the incorporation of non-esterified FAs derived from glucose into TG synthesis within the liver.[30] Although many cells and tissues still rely on lipid intake to meet survival requirements, numerous studies have demonstrated that de novo lipogenesis plays a substantial role in the pathogenesis of metabolic diseases-for example, 26% of TGs arise from de novo lipogenesis in Nonalcoholic fatty liver disease (NAFLD) patients.[31] De novo lipogenesis is regulated by a variety of transcription factors, such as SREBP-1, ChREBP, LXRs, AhR and PXR, and ACC and FASN. However, available evidence suggests that PCB exposure only interferes with lipid metabolism by affecting the expression of some nuclear transcription factors and enzymes.

Nuclear Transcription Factors

AhR

The toxicity of PCBs often depends on their interaction with a variety of cellular receptors.[32,33] PCBs have been classified as either dioxin-like or nondioxin-like based on whether they activate the AhR.[34] Thus, AhR is a typical nuclear receptor of dioxin-like PCBs that has attracted widespread attention. Under normal physiological conditions, AhR is present in the cytoplasm in the form of non-activated protein compounds. Upon binding to various exogenous agonists, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), dioxin-like PCBs, and benzo[a]pyrene (BaP), AhR is activated and then translocated into the nucleus, where it dimerizes with ARNT and binds to specific enhancer sequences adjacent to target promoters.[35] It has been reported that the expressions of various AhR targets involved in detoxification metabolism and antioxidant defense, such as Phase I metabolic enzyme genes (*Cyp1a1, Cyp1a2, Cyp1b1*, and *Cyp4* family), Phase II metabolic enzyme genes (*GST*), and antioxidant enzymes (SOD), are significantly induced by PCBs[33,36,37] (Figure 2). Interestingly, even though the expression of AhR was reduced in mice exposed to Aroclor 1260 (PCB mixture, reduced 3.3-fold) and PCB 126 (reduced 3.2-fold), the transcriptional activity of AhR was not affected, as indicated by the increased expression of the AhR target gene *Cyp1a2*.[32] Recent studies using AhR$^{-/-}$ mice have revealed that AhR deficiency can protect against high-fat diet (HFD)-induced obesity, hepatic steatosis, insulin resistance and inflammation.[38] Additionally, Boverhof et al[39] have shown that C57BL/6 mice treated with an AhR agonist (TCDD) for 7 days experienced lipid accumulation in their liver tissues. These results show that AhR is involved not only in the metabolism of xenobiotics but also in energy metabolism.

In fact, of all the target genes, *Cyp1a1* is most strongly induced by AhR,[40] and its coded enzymes are localized to

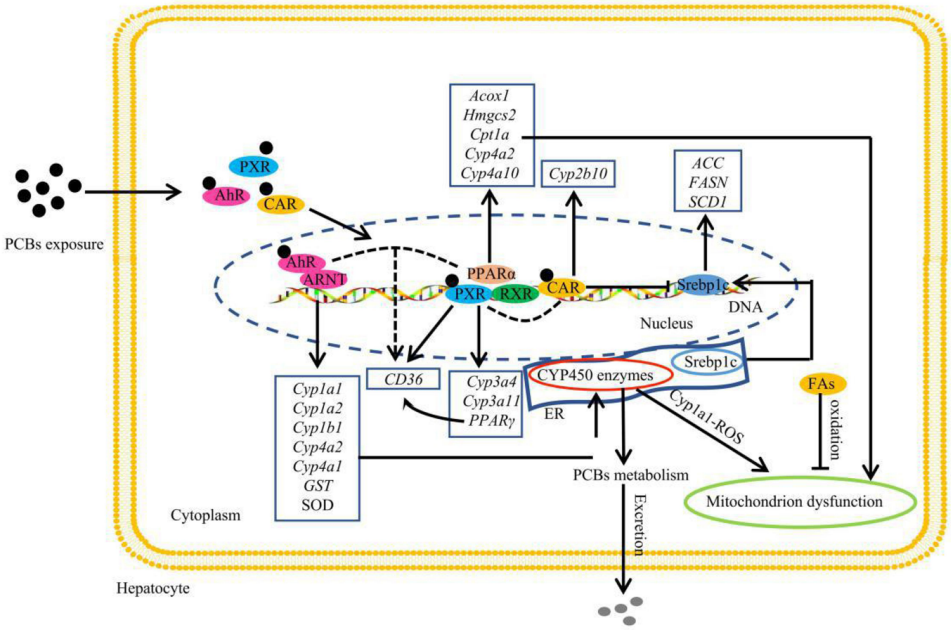

Figure 2 Effect of PCB156 exposure on nuclear receptors in hepatocytes.

the endoplasmic reticulum. *Cyp1a1* can directly hydroxylate or oxidize PCBs that can then be secreted.[41] On the other hand, PCBs have been shown to increase ROS primarily through a Cyp1a1 uncoupling-mediated mechanism.[42] The increased ROS can damage biofilm structures and cause mitochondrial dysfunction, which causes the main FA oxidation pathways to be blocked in cells (Figure 2). In addition, Kawano et al[43] previously reported that AhR activation significantly increased the levels of TGs and six long-chain monounsaturated FAs in the livers of mice by enhancing the expression of FAT/CD36, thus resulting in hepatic microvesicular steatosis. However, FAT/CD36 is not a direct target gene of AhR, and the AhR-induced activation of FAT requires other mediators, such as the reported PPARs.[43] Interestingly, the upregulation of FAT/CD36 was also observed in the PCB-induced AhR and PPAR activation pathways.[32,44] Together, these results further confirm that AhR plays an important role in PCB-induced lipid metabolism disorder.

PXR and CAR

PXR and CAR are two other xenobiotic receptors that regulate the expression of phase I and phase II metabolic enzyme systems.[45] Non-dioxin-like PCBs may act as ligands of some nuclear receptors other than AhR, such as CAR and PXR.[46] After PCB exposure, the expressions of the nuclear receptors PXR and CAR and their downstream genes *Cyp3a4, Cyp3a11* (PXR target) and *Cyp2b10* (a CAR target) were also obviously dysregulated in cells and animal models[32,44,47,48] (Figure 2). Similar to the mechanism of action of AhR, ligand binding to PXR and CAR induces the translocation of these receptors to the nucleus. Subsequently, PXR and CAR enter the nucleus and form isodipolymers by binding with RXR, thus inducing the expression of *Cyp3a* or *Cyp2b* family members.[49,50] In addition, PXR can dimerize with PPARα and induce the expression of Cyp3a subfamily members. Recently, PXR and CAR have also been considered as emerging new regulators of hepatic energy metabolism that connect sensing the chemical environment with metabolic health issues.[51,52] Specifically, PXR activation mediates lipid accumulation, and its potential mechanisms most likely involve increased hepatic FA uptake by activating CD36. Moreover, in the same study, it was found that PXR also induced the expression of PPARγ, which is another positive regulator of CD36, suggesting that PXR can regulate CD36 directly or through the activation of PPARγ to increase the flow of FAs into hepatocytes[53] (Figure 2). However, available evidence suggests that there is coordination between PXR and CD36 expression in PCB-induced steatosis, but the mechanism still requires further study.[48]

Unlike the activation of PXR, the activation of CAR may reduce lipid levels by interacting with Srebp1[54] (Figure 2). Although CAR has been proposed as a potential therapeutic target for lipid metabolic disease, some barriers exist for the clinical use of its agonists, and CAR also interacts with PPAR to regulate lipid and glucose homeostasis.[50,51] Moreover, there is a complex relationship between CAR and PXR in PCB-induced metabolic disorders. For example, Aroclor 1260 could induce CAR and *Cyp2b10* expression in wild-type mice, and CAR and Cyp2b10 expressions were significantly induced in PXR$^{-/-}$ mice.[55] However, the presence of both PXR and CAR is required for Aroclor 1260 to induce NASH.[55]

PPARs

PPARs are another crucial type of PCB-activated nuclear transcription factor superfamily and include PPARα, PPARβ/δ, and PPARγ. PPARs can form heterogenous dipolymers with retinol-type X receptors and then bind to DNA to regulate target gene transcription. A great deal of research has been done on the gene distribution and functional characteristics of this family.[56–59] Therefore, a brief introduction is provided here. PPARα is most prominently expressed in hepatocytes, muscle and cardiomyocytes. PPARα is known to be the master regulator of β-oxidation, and it controls the expression of enzymes for FA oxidation in peroxisomes, mitochondria and the endoplasmic reticulum (microsomes). However, the exclusive effects of PCBs on PPARα-mediated FA oxidation are ambiguous. In male Sprague-Dawley (SD) rats, PCB 126 reduced the expressions of hepatic *PPARα* and its transcriptional targets, such as *Acox1* and *Hmgcs2*.[44] In the same study, other transcriptional targets of PPARα, such as *Cpt1a* and *Cyp4a2*, which are involved in mitochondrial and microsomal FA oxidation, were not decreased. Moreover, in C57BL/6 mice, *PPARα* and *Cpt1a* expressions were also significantly decreased in the HFD +PCB 153 group.[13] But the expressions of *PPARα, Cpt1α*, and *Cyp4a10* were significantly increased in PCB 126- or Aroclor 1260-exposed mice.[32,44,55] Together, these results show that PPARα pathway disorders caused by PCB

exposure play an important role in PCB-induced lipid metabolic disorders.

PPARβ/δ is expressed ubiquitously and is similar to PPARα in promoting FA oxidation in metabolic tissues such as the skeletal muscle, liver and heart. Compared to what is known about PPARα and PPARγ, there is currently less research on the effects of PCBs on PPARβ/δ. Only two papers have reported a reduction in PPARβ/δ in Aroclor 1260-treated mice and in PCB 156-treated hepatocytes.[60,61] In contrast, it has been extensively shown that exposure to PCBs, such as PCB 126 and PCB 77, can induce PPARγ expression in the livers of mice.[11,62] PPARγ is expressed predominantly in adipose tissue and the immune system. PPARγ plays an important role in increasing insulin sensitivity, as well as in promoting FA uptake by adipocytes and adipocyte differentiation, and the net effect of these processes is an increase of TG storage in adipocytes. Importantly, studies have shown that PPARγ responds differently to PCBs in different liver pathological states. For example, in normal mice, increased PPARγ levels were observed in PCB 126-induced NAFLD,[11] while PPARγ was downregulated in the PCB 126-induced liver injury group.[63] In any case, PPARγ is likely to be one of the key factors in PCB-induced lipid disorders. The role of PPAR in PCB-induced lipid metabolism disorders is shown in Figure 2.

SREBPs

SREBPs and ChREBP are major nuclear transcription factors that regulate cellular lipid homeostasis. However, the current study focused on the effects of PCB exposure on SREBPs, and less information is known about ChREBP. SREBPs are composed of three major isoforms: Srebp1a, Srebp1c and Srebp2. The expression of Srebp1c, but not Srebp1a or Srebp2, is significantly induced by PCB exposure.[9] Srebp1a and Srebp1c are isoforms of the same gene, Srebp1. Unactivated Srebp1c is usually bound to the membrane of the ER and is then cleaved to generate the mature active forms, which translocate to the nucleus to upregulate the expression of enzymes involved in the biosynthesis of FA and TG, such as *ACC, FASN*, and *SCD1*[64,65] (Figure 2). Aroclor 1260 is a mixture of PCBs that has demonstrated robust effects on the progression of steatohepatitis in models of obesity and NAFLD. C57BL/6 mice treated with Aroclor 1260 for 12 weeks had increased *Srebp1c* expression, especially compared to that produced with a HFD alone, and Aroclor 1260 promoted the development of steatohepatitis via the induction of *Srebp1c* mRNA in a dose-dependent manner.[48] In addition, hepatic lipid deposition induced by PCB 126[9] or PCB 153[66] was also related to the induction of *Srebp1c* expression (Figure 2). The roles of all the nuclear transcription factors in PCB-induced lipid metabolism disorder are shown in Table 1.

Lipogenic Enzymes

Enzymes are one of the most critical factors that can be directly involved in lipid metabolism. Thus, changes in lipogenic enzyme activity have long been considered one of the key mechanisms involved in lipid metabolism disorders caused by PCBs. In de novo lipogenesis, pyruvate generated by glycolysis first enters mitochondria and participates in the TAC, thus producing the FA synthesis precursor acetyl-CoA. Acetyl-CoA is then catalyzed to malonyl-CoA under Acc, initiating FA synthesis (Figure 3). Finally, FAs that have been synthesized from acetyl-CoA or taken up from the blood are involved in the biosynthesis of TGs by sn-glycerol-3-phosphate (G3P) or monoacylglycerol (MAG). Notably, the G3P pathway is dominant in the liver, whereas the MAG pathway is essential for the biosynthesis of TGs in the small intestine. In this paper, we only focused on the G3P pathway of TG synthesis.

Effect of PCB Exposure on Enzymes Associated with FA de novo Synthesis

Acc is a key rate-controlling enzyme in de novo FA lipogenesis, and there are two isoforms of *Acc* in rodents and humans: *Acc1* and *Acc2*. *Acc1* is highly expressed in hepatocytes and adipocytes, whereas *Acc2* is mainly associated with the heart and skeletal muscle. It has been reported that inhibition of both *Acc1* and *Acc2* reduces hepatic TGs and insulin resistance in rat models.[67] In addition to Acc, *Fasn* catalyzes the last step in the FA biosynthetic pathway, in which malonyl-CoA is converted to palmitic acid. Once fatty acyl-CoA synthetase-mediated activation occurs, palmitic acids are either incorporated into TAG or broken down through a series of mitochondrial β-oxidation processes into acetyl-CoA. After PCB exposure, the mRNA levels of *Acc* and *Fasn* are significantly induced at the same time in AML-12 hepatocytes and 3T3-L1 preadipocytes of mice.[66] In addition, PCB exposure affects the structure of *Scd1*. Previous studies have shown that *Scd1* is a microsomal enzyme that can catalyze the synthesis of monounsaturated long-chain FAs from saturated FAs.[68] The formation of unsaturated fatty acids is a key factor involved in important physiological

Table 1 The Roles of Nuclear Transcription Factors in PCB-Induced Lipid Metabolism Disorder

Roles in Lipid Metabolism	Target Gene	Nuclear Transcription Factors	Expression	Reference
FAs ω-oxidation	*Cyp1a1* *Cyp1a2* *Cyp1b1* *Cyp2b10* *Cyp3a4* *Cyp4a2* *Cyp4a10*	AhR AhR AhR CAR PXR AhR/PPARα AhR/PPARα	Up Up Up Down Up Up Up	Wahlang et al[13] Shi et al[32] Wahlang et al[33] Ruan et al[37] Nebert et al[40] Newsome et al[41] Wahlang et al[47]
Elimination of active oxygen	*GST* *SOD*	AhR AhR	Up/- Up/-	Wahlang et al[33] Ruan et al[37]
The first enzyme of the FAs β-oxidation pathway, which catalyzes the desaturation of acyl-CoAs to 2-trans-enoyl-CoAs	*Acox1*	PPARα	Down	Wahlang et al[44]
A mitochondrial enzyme that catalyzes the first reaction of ketogenesis	*Hmgcs2*	PPARα	Down	Wahlang et al[44]
A mitochondrial enzyme that catalyzes the formation of acylcarnitine from acyl-CoA and free carnitine	*Cpt1a*	PPARα	Down	Wahlang et al[13]
FAs uptake	*CD36*	PXR/PPARγ	Up	Chi et al[11] Shi et al[32] Wahlang et al[44] Chi et al[62] Wahlang et al[63] Wahlang et al[83]
Converts Acetyl-CoA to malonyl-CoA	*Acc*	Srebp1c	Up	Wu et al[66]
Promotes the formation of palmitic acid from malonyl-CoA and acetyl-CoA	*Fasn*	Srebp1c	Up	Wu et al[66]
Promotes the formation of monounsaturated fatty acids	*Scd1*	Srebp1c	Up	Chi et al[11] Chi et al[62]

metabolic processes for TG synthesis. In PCB-induced steatosis, the expression of *Scd1* is always significantly induced[11,62] (Figure 3).

Effect of PCB Exposure on Enzymes Associated with the G3P Pathway

In the G3P pathway, G3P is converted to DAG under the action of GPAT, AGPAT, and PAP (Figure 3). Recent studies have shown that PCB exposure can interfere with the gene expression of the above mentioned enzymes by affecting the expression of the core rhythm genes in the liver.[69] The final step in TG synthesis requires *Dgat*, which is the rate-limiting enzyme in TG synthesis. *Dgat* exists in two isoforms: *Dgat1* and *Dgat2*. Experimental evidence suggests that *Dgat1* knockout mice have 50% less TG in their tissues, and *Dgat2* knockout mice die shortly after birth because of severe lipopenia.[68,70] However, it has been recently reported that *Dgat* inhibition increased the hepatic free FA levels and exacerbated hepatic oxidative damage and hepatocyte death, thereby promoting the progression from steatosis to fibrosis.[71] Interestingly, PCB 126 exposure could induce *Dgat1* and *Dgat2* expression in the livers of mice fed a control diet.[11] However, in the MCD diet-induced liver injury, PCB 126 significantly reduced *Dgat2* expression in the livers of mice.[63] Thus, the effect of PCBs on *Dgat* may be associated with the liver condition (Figure 3).

Effects of PCB Exposure on the Uptake of Hepatic Nonesterified FAs

FAs are a group of molecules consisting of long hydrocarbon chains of different lengths (carbon atoms) and saturation levels (double bond numbers). Within the cell,

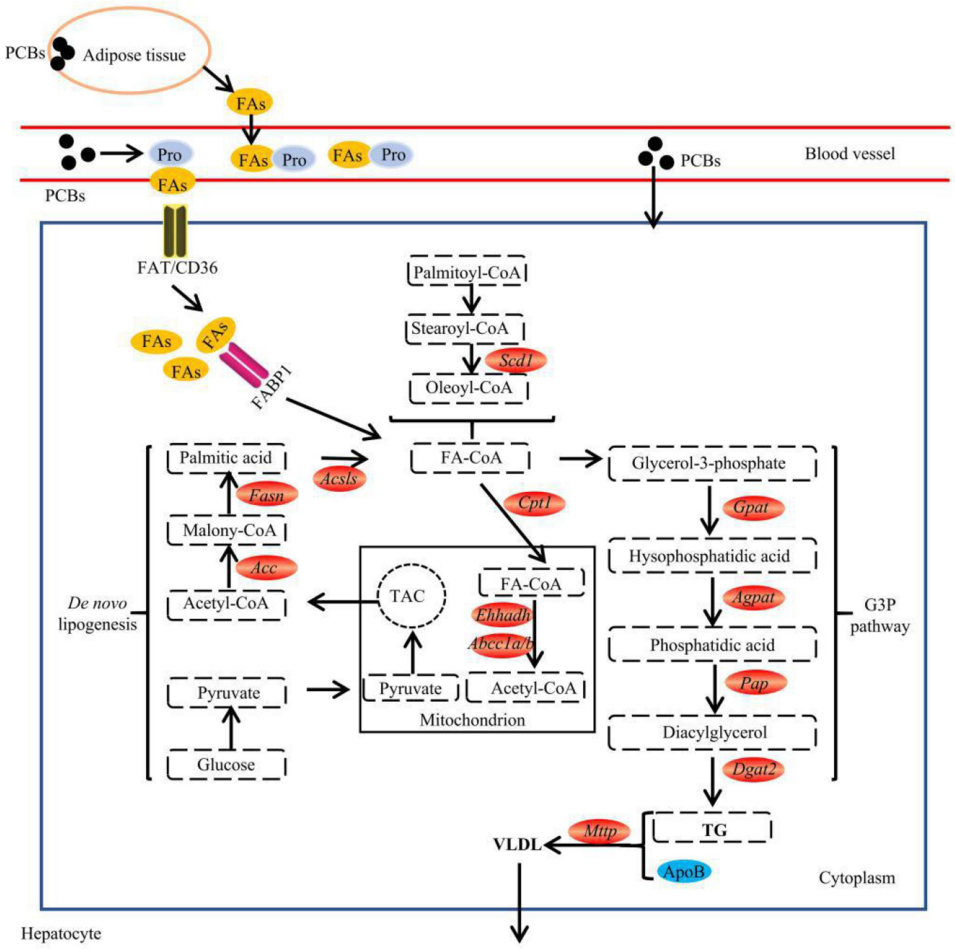

Figure 3 Effect of PCB156 exposure on lipid metabolism-related enzymes.

FAs are one of the most important raw materials for lipid synthesis.[19,72] Generally, there are two sources of FAs: glycolysis and plasma. However, FAs derived from glycolysis were introduced in the lipogenic enzyme section, and the primary discussion here will be FAs derived from plasma. Donnelly et al[31] demonstrated that approximately 60% of hepatic TGs in human subjects are derived from nonesterified fatty acids in the plasma. Importantly, PCBs have been reported to accelerate steatosis or worsen diet-induced steatosis by promoting hepatic FA uptake from plasma.[11,32,62] In fact, increased plasma FAs are due to increased FA release from adipose tissue. Moreover, the increased fat mass directly contributes to increased FA release from adipose tissue.[73] FAs are poorly soluble in blood and are mainly present bound to proteins such as albumin.[74] Therefore, FAs need to be separated from the albumin to which they are bound before entering the cell. Subsequently, FAs diffuse to the membrane surface, either binding with receptors on the membrane surface or inserting directly into the lipid bilayer.[75] It is now clear that the main transporters involved in FA transmembrane translocation are caveolins, FATPs, FAT/CD36 and FABPs.[28,59] Interestingly, available experimental evidence shows that PCB exposure increases FA intake mostly through FAT/CD36 and FABPs[33] (Figure 3).

FAT/CD36

FAT/CD36 is an 80 kD membrane protein with heavy glycosylation. FAT/CD36 can be expressed in a wide range of cells, such as microvascular endothelial cells, immune cells, adipocytes and myocytes.[76] In 1993, Abumrad et al[77] first found that FAT/CD36 promotes cell intake of FAs. This role was then well demonstrated in rodents and humans.[78,79] FAT/CD36 can accelerate FA dissociation from albumin and catalyze the integration of protonated FAs into the outer phospholipid bilayer of the plasma membrane, promoting the intake of FAs in cells.[59] Therefore, multiple findings suggest that increased FAT/

CD36 activity may be critical for the development of steatosis.[80–82] Interestingly, mice that were administered the PCB mixture Aroclor 1260 had increased *CD36* expression.[32,44,48,55,83] Moreover, treatment with individual congeners (eg, PCB 126, PCB 77 or PCB 156) has also been found to increase *CD36* expression in mice or cells.[11,32,44,62,63,83]

FABPs

In parallel with the increase in *CD36*, PCB exposure also increases the gene expression of FABPs.[32] FABPs are another highly expressed protein superfamily that facilitates the transport of FAs and other lipid mediators across cellular membranes. In fact, FABPs are mainly located in the cytoplasm, where they may facilitate the transport of FAs from the cytoplasm to their nuclear receptors, thus controlling the transcription of downstream target genes.[59] FABPs include nine different members (FABP1, 2, 3, 5, 6, 7, 8 and 9), and PCB exposure mainly increases the expression of *FABP1*,[32,83] which is also known as L-FABP and is primarily expressed in the liver, small intestine, pancreas, and kidney. Exposure to both Aroclor 1260 and PCB 126 increases the expression of *FABP1* in the livers of mice.[32] Furthermore, 1 week after an acute injection of PCB 126 in rats, the hepatic gene and protein levels of FABP1 were higher than those in the corn oil group.[84] A summary of the effects of PCBs on fatty acid intake is shown in Figure 3.

FA Oxidative Pathways

FA oxidation, especially mitochondrial FA β-oxidation, is a crucial pathway of aerobic ATP production in mammalian organisms. PPARα is known as the master regulator of β-oxidation and controls the expression of enzymes for FA oxidation in mitochondria. In the de novo lipogenesis section, we summarized the effects of PCB exposure on PPARα. In this section, we mainly analyze the effect of PCB exposure on the expression of key factors that are directly involved in the β-oxidation process. FAs that enter cells are first converted into acyl-CoA under the action of long-chain ACSLs and then transported to mitochondria by CPT1 for oxidation. CPT1 has been confirmed as a rate-limiting enzyme in the oxidation of FAs. Available literature has shown that PCB exposure reduces FA oxidation mainly by decreasing CPT1 expression.[13,44,63,85] After acyl-CoA enters the mitochondrial matrix, an oxidation cycle that includes oxidation, hydration, dehydrogenation, and thiolytic cleavage occurs with the assistance of acyl-CoA oxidases, hydratase, 3-hydroxyacyl-CoA dehydrogenase, and peroxisomes harboring the D-bifunctional enzymes L-bifunctional enzyme (Ehhadh) and 3-ketoacyl CoA thiolase A/B (Acaa1a/b). Emerging transcriptomics evidence supports that PCBs could lead to the dysregulation of Ehhadh and Acaa1a/b expressions. These results showed that PCB exposure-induced diseases may be closely related to abnormal lipid oxidative processes (Figure 3).

In addition, some special oxidation pathways especially, ω-oxidation are carried out in the endoplasmic reticulum in hepatocytes and require cytochrome P450 enzymes. Interestingly, cytochrome P450 enzymes are mostly downstream effectors for AhR, PXR or CAR, which are widely involved in the metabolism of xenobiotics, including PCBs. Thus, PCB exposure is also closely related to FA ω-oxidation through effects on the expression of CYP450 enzymes.[32]

TG Secretion

Hepatocytes can synthesize lipids using glucose and then form VLDL particles to transport lipids to peripheral tissues, including skeletal muscle, cardiac muscle and adipose tissue. In hepatocytes, each VLDL particle is composed of apolipoprotein B 100 (apoB 100), which is assembled with TG and cholesteryl esters. These constituents are then delivered to peripheral tissues when VLDL is converted by lipoprotein lipase to higher-density and smaller-sized atherogenic particles, including LDL and IDL. There is growing evidence that PCBs block hepatic VLDL secretion, and the corresponding mechanism may be related to the dysregulated expression of MTTP.[9] The key event responsible for hepatic VLDL metabolism is the lipidation of apoB 100, and this process is known to be regulated by Mttp, which is an ER resident protein that has both apoB 100 binding and lipid transfer domains.[59] A small quantity of TG is first transferred to apoB 100 in the ER by MTTP. The apoB then continues to bind with larger droplets of TG to form VLDL particles. Therefore, a decrease in Mttp expression hampers VLDL assembly, preventing liver lipids from being secreted. Furthermore, the results of experimental studies using animal or cell models support the hypothesis that reduced Mttp activity is sufficient to induce hepatic steatosis. In particular, a significant decrease in Mttp was also observed in PCB-induced hepatic lipid accumulation in rats,[9,63,84] further indicating that PCBs causes hepatic lipid metabolic dysfunction (Figure 3).

Table 2 The Mechanisms of PCBs in Lipid Metabolism

Category	Mechanisms	Reference
De novo lipogenesis	(1) Nuclear transcription factors: AhR, PXR, CAR, PPARs, and Srebp1c (2) Factors associated with FAs de novo synthesis: *Acc, Fasn* and *Scd1* (3) Factors associated with the G3P pathway: *Gpat, Agpat, Pap* and *Dgat2*	Boucher et al[9] Chi et al[11] Shi et al[32] Wahlang et al[33] Newsome et al[41] Lim et al[42] Shen et al[69]
FAs uptake	*FAT/CD36, FABP1*	Boucher et al[9] Wahlang et al[48] Wu et al[66]
FAs β-oxidation	*CPT1a/b, Ehhadh* and *Acaa1a/b*	Wahlang et al[13] Wahlang et al[44] Wahlang et al[63] Gadupudi et al[85]
TG secretion	*MTTP*	Boucher et al[9] Wahlang et al[63] Chapados and Boucher[84]

Conclusions

During the past two decades, numerous studies have suggested that PCB exposure is significantly associated with disturbances in lipid metabolism. However, the pathogenesis of hepatic lipid metabolism disorders induced by PCBs is very complex and only partially understood. Based on existing evidence, the present review focused on the specific mechanisms by which PCB exposure is involved in lipid metabolism. Overall, the key events responsible for PCB-induced lipid accumulation are (i) increased lipid influx due to the upregulated expression of CD36 and Fabp1; (ii) increased lipogenesis due to the activated expression of AhR, CAR, PXR, Srebp1c, Acc, Fasn and Scd1; (iii) decreased FA oxidation due to the downregulated expression of PPARα; and (iv) decreased lipid efflux due to the reduced expression of Mttp. These key factors and mechanisms are summarized in Table 2. Although further research is needed, the elucidation of each of these steps will offer novel therapeutic options in the field of PCB-induced metabolic diseases in the coming years.

Abbreviations

Acaa1a/b, 3-ketoacyl CoA thiolase A/B; ACC, acetyl CoA carboxylase; Acox1, acyl-CoA oxidase 1; ACSLs, acyl-CoA synthetases; AGPAT, acylglycerol-3-phosphate acyltransferase; AhR, aryl hydrocarbon receptor; ARNT, AhR nuclear translocator; CAR, Constitutive androstane receptor; ChREBP, carbohydrate-responsive element binding protein; Cpt1a, carnitine palmitoyltransferase 1A; CYP450, cytochrome P450; DAG, diacylglycerol; Ehhadh, L-bifunctional enzyme; ER, endoplasmic reticulum; FATPs, FA transport proteins; Fas, fatty acids; FASN, FA synthase; FAT/CD36, fatty acid translocase; FMO3, flavin-containing dimethylaniline monoxygenase 3; G3P, glycerol-3-phosphate; Gpat, glycerol-3-phosphate acyltransferase; GST, glutathione S transferase; Hmgcs2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; LXRs, liver X receptors; MCD, methionine-choline deficient; MTTP, microsomal triglyceride transfer protein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic-steatohepatitis; PAP, phosphatidic acid phosphatase; PPARs, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; SCD1, stearoyl CoA desaturase-1; SOD, superoxide dismutase; TAC, tricarboxylic acid cycle; SREBP-1, sterol regulatory element binding protein-1 SREBP-1; VLDL, very low-density lipoprotein.

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Disclosure

The authors have no potential conflicts of interest to disclose.

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