Dioxin in Kidney Disease

Subjects: Developmental Biology

Contributor: Xing Zhang , Jodi A. Flaws , Michael J. Spinella , Joseph Irudayaraj

Endocrine disrupting chemicals (EDCs) are a class of hormone-like chemicals that exist in the environment and interfere with the production, transport, metabolism, regulation, degradation, and/or action of hormones. The kidney is one of the most important organs in the urinary system and an accumulation point. Dioxins were identified as toxic compounds in the 1960s. Dioxins are a group of structurally related chemicals composed of two coplanar benzene rings.

endocrine disrupting chemicals kidney diseases renal cell carcinoma

1. Introduction

Endocrine disrupting chemicals (EDCs) are a class of hormone-like chemicals that exist in the environment and interfere with the production, transport, metabolism, regulation, degradation, and/or action of hormones. The ability of EDCs to interfere with endogenous hormones can lead to adverse effects on development, reproduction, immune, endocrine, and nervous systems of the organism. The cascade of events can also result in endocrine and metabolic imbalances in offspring as well [1][2]. EDCs are present in wastewater, textiles, cosmetics, waste residues produced by industrial and agricultural processes and in several domestic and household goods [3][4][5], and ultimately end up in landfills. Common contaminants include per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), dioxins, bisphenol A (BPA), and phthalates, as well as heavy metals such as Cd, Pb, Hg [6]. Upon entry into the human system, EDCs often indirectly interact to cause endocrine imbalance in the organism by affecting the formation, secretion, transport, and metabolism of hormones in the organism, and thus, affecting growth, development, and reproduction.

Due to the environmental persistence of EDCs and their mobility in water bodies, these chemicals can migrate for a long distance along with water bodies [7][8][9]. At present, EDCs such as PFAS, BPA, PCBs and PAHs have been found in main water bodies worldwide [10][11]. Due to the limitations in existing wastewater treatment technologies, EDCs from livestock and poultry as well as domestic and industrial wastewater enter natural water bodies with wastewater discharge and continue to migrate and transform. EDCs in the environment can also be enriched through the food chain and accumulate in organisms at all trophic levels. The higher the trophic level, the higher the accumulation, eventually leading to toxicity [12][13][14]. There are several standard methods for extracting and estimating the concentration of EDCs in biological and environmental samples, including solid-phase extraction (SPE) [15], liquid chromatography-mass spectrometry (LC-MS) [16], gas chromatography-mass spectrometry (GC-MS) [17][18] and high-performance liquid chromatography (HPLC) [15][19]. It is important to use appropriate sample extraction and estimation methods for accurate and reliable detection of the levels of EDCs in different types of

samples. With extensive advances in the chemical industry and the ubiquitous presence of plastics, EDCs entering the environment are on the rise both in terms of quantity and variety (new materials), and consequently, their hazards to humans and animals have attracted increased attention by societal and regulatory agencies (**Figure 1**).

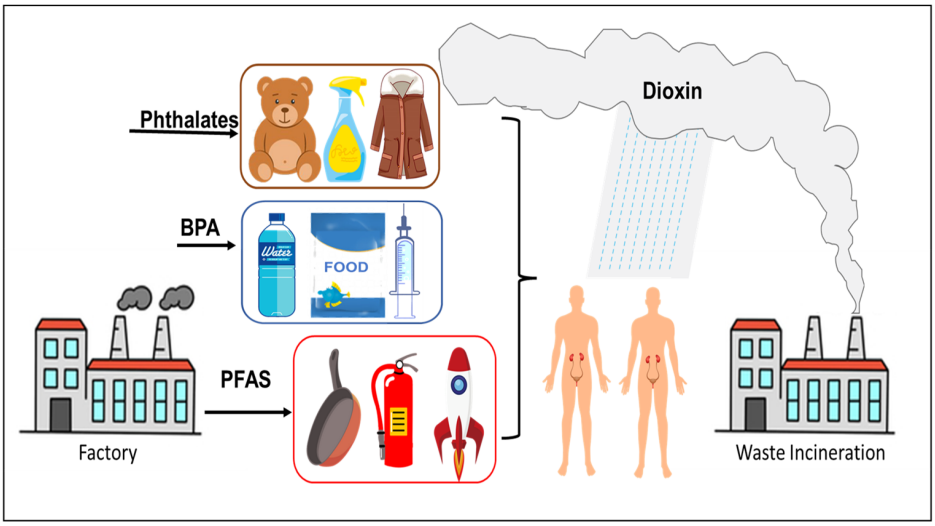

Figure 1. Common sources of EDCs.

The kidney is one of the main target organs of EDCs for accumulation. Patients with kidney disease usually show decreased renal function and proteinuria, which affects recovery from the disease [20]. Common renal diseases include chronic nephritis, renal calculi, renal failure, and renal cysts. These diseases are usually associated with the glomerular filtration rate (GFR) of the kidney, pathological damage, and abnormal blood or urine composition [21][22].

2. Dioxin

Dioxins were identified as toxic compounds in the 1960s. Dioxins are a group of structurally related chemicals composed of two coplanar benzene rings (**Figure 2**a). These compounds induce a similar spectrum of toxic phenotypes, with a wide range of potency. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is one of the most toxic compounds in this group of chemicals [23]. Incineration is the largest source of dioxin emissions in the environment [24][25]. Dioxins enter the ambient air through chimneys, spread continuously, and accumulate in the surrounding area of the incineration plant. Routes of exposure to dioxins include inhalation, dust ingestion, and skin contact. Dioxins accumulate in the tissues of various animals [26][27][28][29][30][31] and cause chloracne, embryotoxicity [32][33] and nephrotoxicity [34].

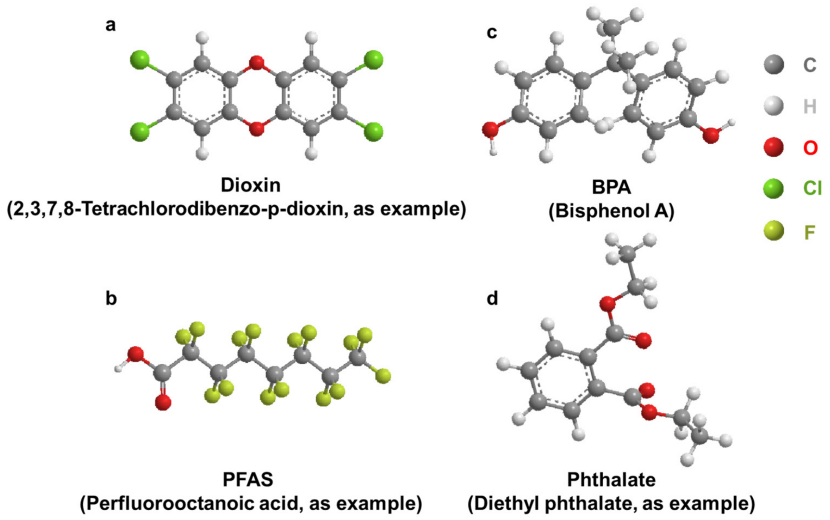

Figure 2. General structure of select EDCs. (**a**): Dioxin; (**b**): BPA; (**c**): PFAS; (**d**): Phthalate.

2.1. Accumulation of Dioxins in the Kidney

Animal studies: Several studies, but not all, suggest that TCDD may accumulate in the kidney to impart toxicity. Examination of aquatic organisms by analyzing ten-year-old fish in heavily polluted lakes in China showed that a large amount of dioxin accumulated in the kidneys [35]. Numerous studies have indicated that the accumulation of TCDD can cause the ballooning degeneration or even necrosis of the renal tubules of zebrafish [36]. Polybrominated diphenyl ethers (PBDEs), which have similar structures to PCB, have also been associated with renal histopathological changes [37] and significantly reduced catalase activity [38]. Exposure of infant mice to PCB caused hyperuricemia in adults, leading to secondary nephrotoxicity such as renal hypertrophy and fibrosis [39]. After 12 days of exposure, the combined exposure to TCDD and PCB was more likely to induce nephrotoxicity through high expression of *CYP1A1* (Cytochrome P450 Family 1 Subfamily A Member 1), compared with the control group (equivalent volume of olive oil). TCDD and PCB exposure also significantly increased serum creatinine and blood urea nitrogen levels, renal oxidative stress and histopathological changes compared to control in rats [40]. Further studies will shed light on TCDD and PCDD mediated carcinogenesis [41].

Human studies: Shalat et al. [42] reported that three young male utility workers developed kidney cancer after chronic exposure to PCB-containing transformers. Residents from an e-waste dismantling area showed increased accumulations of PCB, which could have contributed to abnormal changes in markers of kidney injury [43]. The screening of environmental chemicals in the soil of an e-waste recycling area and human cancer risk assessment calculations showed that dioxins have the highest potential cancer risk to residents, followed by PCBs [44]. Through a multiple linear regression model analysis of 150 pregnant women, it was found that exposure to environmental pollutants may have negative effects, while exposure to greenspace may have positive effects on fetal renal function during pregnancy [45]. Epidemiological evidence indicated that the development of diabetes and chronic kidney disease was also associated with long-term exposure and accumulation of dioxins [46][47][48]. Jain [48] analyzed data from US adults from 1999 to 2004 to investigate concentration changes of four dioxin homologs and

four separate furan homologs at various stages of renal function decline and found that renal dysfunction was associated with high dioxin/furan concentrations.

2.2. Effect of Dioxin on AHR Regulation/Activity and RCC

The **AHR** is a ligand activated transcription factor that mediates the toxic effects of TCDD. The **AHR** is mostly expressed in the nucleus of advanced clear cell renal cell carcinoma (RCC) and tumor infiltrating lymphocytes, and its expression is related to the stage and histological grade of pathological tumors [49]. Numerous studies have shown a complex association between the **AHR** and cancer characteristics, including increased malignant cell invasion, migration, metastasis, and survival [50][51][52]. The primary structure of the **AHR** is considered to be critical to determining the sensitivity and specificity of animal responses to dioxins.

Animal studies: In a constructed adenine diet model of chronic kidney disease, female **AHR** knockout mice showed inflammatory and pro-fibrotic gene expression and acute tubular injury [53]. After exposure to TCDD, 9 renal function was significantly reduced in wild-type male mice, indicating that the **AHR** plays a major role in mouse kidney development [54]. Due to poor renal excretion in patients with chronic kidney disease, the accumulation of toxic substances was found to increase *CYP1A1* expression. Because of the higher inducibility of polymorphic genotypes, the pathway may become more deleterious in individuals with homozygous mutant alleles [55].

TCDD-induced fetal hydronephrosis (TiFH) is a type of obstructive hydronephrosis characterized by the presence of dilated ureter or ureteral effusion. The relationship between TiFH and **AHR** was investigated in both rats and mice. In mice, *Cox-2* (cyclooxygenase-2) plays a key role in TiFH [56][57]. The induction effect of TCDD in the mouse kidney does not require translocation of **AHR** to the nucleus. TCDD induction of *Cox-2* in mouse kidney is primarily mediated by a non-genomic pathway that activates **AHR**. In rats, TiFH is also induced and may be an endogenous ligand for **AHR** and/or a protein interacting with **AHR**. In contrast to rats, mice lacking **AHR** did not develop hydronephrosis or hydronephrosis in the absence of TCDD [58]. To better explore the role of **AHR** in normal development and chemical response, **AHR** knockout (**AHR**-KO) models were created in rats and mice, respectively. However, in **AHR**-KO rats, hydronephrosis and hydroureter were observed and **AHR** was found to play significantly different roles in tissue development and virulence in rodent species [59].

Human studies: In a study of more than 300 chronic kidney disease (CKD) patients and healthy controls, overexpression of polymorphic variants of *CYP1A1* were associated with free radical production related enzymes after exposure to environmental pollutants, and with induction of renal dysfunction. Because of the different effects of **AHR** in rats and mice, it was not possible to directly use animal models to verify the effect of TCDD in the human kidney. To better detect the effects of dioxins on human health and reduce the differences between species, the mouse **AHR** was replaced with human **AHR** cDNA by knock-in strategy. Human **AHR** can be expressed in mice to mediate the development of TCDD-induced hydronephrosis [60]. Transcriptional analysis of human **AHR** was performed and compared in the liver and kidney, but dioxin exposure in the kidney altered only 17 genes, including many **AHR** target genes [61].

Overall, the relationship between *CYP1A1*, TCDD, and the **AHR** is complex and involves the metabolism of TCDD by *CYP1A1* and the activation of the **AHR** by TCDD. The activation of the **AHR** by TCDD may lead to the expression of various genes that could contribute to nephrotoxicity, including genes involved in inflammation and oxidative stress. *CYP1A1* is involved in the metabolism of TCDD, and the activation of the **AHR** by TCDD may also lead to the expression of *CYP1A1*. More research is needed to fully understand the mechanisms by which TCDD causes adverse health effects.

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