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Potential Health Risks from Persistent Organic Pollutants (POPs) in Marine Ecosystem

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Abstract A wide-spread contamination of persistent organic pollutants (POPs) such as dioxins, PCBs, PBDEs in the aquatic ecosystem has generated a great concern over the potential risk for these substances to impact marine biotas and food web. Since a major exposure route of these substances to the humans is through the consumption of food including fish and marine byproducts, the consumption of contaminated products has been a great public health concern. Exposure to POPs has been associated with a wide spectrum of adverse effects including reproductive, developmental, immunologic, carcinogenic, and neurotoxic effects. This review covers the background information of key POPs substances and the recent development of toxicity studies including the mode of action. Because neurotoxic effects of some POPs have been observed in humans at low concentrations, polychlorinated biphenyl (PCB), a representative chemical of POPs, is focused to discuss the possible mode(s) of action for the neurotoxic effects. This review provides the updates of toxicity studies on POPs and paves ways to discuss a possible implication of contaminated marine biota over the human health among the marine biotechnology researchers.

Keywords : Persistent Organic Pollutants (POPs), PCBs, Neruotoxicity, Marine, Ecosystem

Introduction

Numerous chemicals are now produced in our industrial society. Some of these chemicals are produced unintentionally as unwanted byproducts in the course of their manufacturing processes. Many studies demonstrated that these chemicals are harmful to humans if present in excessive amounts in our food web or ecosystems. Persistent organic pollutants (POPs) are long-lived toxic organic compounds such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), organochlorine pesticides, and dioxins. POPs are major concern for human health and ecosystem due to their high degree of persistence and bioaccumulation in the environment. These POPs could be released with time, remain in the aquatic environment for long period of time due to their high persistence, and bioaccumulate in the food web [20,27].

The presence of POPs in marine environments is a legacy of industrial chemical production and management. Due to the long half-life of POPs in the environment, marine life such fish can become contaminated at concentrations many times higher than those of the marine sediments. The bioaccumulation of POPs, in particular PCBs, in fish has been particularly

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well documented and numerous studies have reported elevated concentrations of PCBs in fish from various aquatic environments [3] The issue of PCB-contaminated fish and potential human exposure has elevated concern over human health.

Polychlorinated biphenyls (PCBs) are ubiquitous environmental contaminants resulting from intensive industrial use and inadequate disposal over past decades [25]. PCB mixtures as well as congeners possess a surprising array of biological activity leading to toxicity. It is known that some PCBs and other halogenated hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) produce some of their biological effects through a receptor-mediated response by binding to the cytosolic aryl hydrocarbon (Ah) receptor followed by induction of a number of genes [22]. Since PCBs represent a significant group of POPs, the focus of this review will be on this group of chemicals discussing the neurotoxic effects and possible mode(s) of action.

Sources of Persistent Organic Pollutants (POPs)

PCBs

Polychlorinated biphenyls were used in electrical transformers, capacitors and heat transfer and hydraulic systems. PCBs were also used in paints, polymers and adhesives, as lubricants, plasticizers, fire retardants and immersion oils, vehicles for pesticide application [24]. Due to the widespread use, PCBs were detected in most of environmental media including aquatic ecosystem. Although commercial use of PCBs is no longer allowed in the most of countries, they are still present in the global environment. About a million ton of PCBs is still in use in older electric equipment and other products [32].

PCDDs and PCDFs

Polychlorinated dibenzo-p-dioxins (PCDDs) and Polychlorinated dibenzo-p-furans (PCDFs) are by-products that are formed during the synthesis of certain industrial halogenated aromatic chemicals, and by-products of combustion [24]. PCDDs and PCDFs have been identified in effluents, wastes and pulp samples from the paper industry. Emissions from municipal waste incinerators as well as backyard burning contain PCDDs and PCDFs [12,24].

PBDE

Polybrominated diphenyl ethers (PBDEs) were manufactured for use as flame retardants in industrial and consumer products. These chemicals were used for carpet, clothes, holster, radios, televisions, thermostats, and various automotive parts [11].

Toxic equivalency factors (TEFs)

The structural relationship between PCDD, PCDF and PCB congeners and their toxicity is the computational fundamentals of toxicity equivalency factors (TEFs) and the toxic equivalency (TEQ) approach (Table 1). The TEQ approach is applied to estimate the toxic potency from mixtures of PCDDs, PCDFs and PCBs found in the environmental samples. Based on the assumption that these chemicals have a similar mechanism of action of binding to the AhR, the toxic potency of each chemical in a mixture is expressed as a fraction of 2,3,7,8-TCDD toxicity to cause the same effect. TEF value of 2,3,7,8-TCDD is assumed to be 1. In another word, the TEF is EC50 ratio of TCDD-like compounds/TCDD. The toxic potency of a mixture of PCDDs, PCDFs and/or PCBs is estimated by multiplying the concentrations of individual congeners by their respective TEFs and summing the products to yield a total TEQ. The total TEQ expresses the toxicity as if the mixture were pure 2,3,7,8-TCDD [24,26,27,33]. Although several assumptions are required to generate TEF values, the TEQ approach have been agreed in the international community of risk assessment as the most plausible way to estimate the potential toxic effects of mixtures of 2,3,7,8-TCDD-like chemicals [27].

Common mechanism of action for Dioxin-like compounds

The aryl hydrocarbon receptor (AhR) is involved in regulating the metabolic enzymes of xenobiotics as well as genes involved in cell growth regulation and differentiation [7,20,22]. The

AhR plays an important role in the species- and tissue-specific toxicity of PCBs and PCDD and PCDF isomers. It is generally agreed that most of the toxic effects of 2,3,7,8-TCDD (namely dioxin) and dioxin-like compounds require activation of the AhR. The toxicity of individual isomers is closely associated with the affinity that these compounds bind to the AhR. The most toxic compounds tend to show the highest binding affinity

Table 1. Summary of World Health Organization (WHO) 2005 Toxic Equivalency Factor (TEF) values.

Compound	WHO 2005 TEF
Chlorinated dibenzo-p-dioxins	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003
Chlorinated dibenzofurans	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,6,7,8,9-HpCDF	0.01
OCDF	0.0003
Non-ortho-substituted PCBs	
3,3′,4,4′-tetraCB (PCB 77)	0.0001
3,4,4′,5-tetraCB (PCB 81)	0.0003
3,3′,4,4′,5-pentaCB (PCB 126)	0.1
3,3′,4,4′,5,5′-hexaCB (PCB 169)	0.03
Mono-ortho-substituted PCBs	
2,3,3′,4,4′-pentaCB (PCB 105)	0.00003
2,3,4,4′,5-pentaCB (PCB 114)	0.00003
2,3′,4,4′,5-pentaCB (PCB 118)	0.00003
2′,3,4,4′,5-pentaCB (PCB 123)	0.00003
2,3,3′,4,4′,5-hexaCB (PCB 156)	0.00003
2,3,3′,4,4′,5′-hexaCB (PCB 157)	0.00003
2,3′,4,4′,5,5′-hexaCB (PCB 167)	0.00003
2,3,3′,4,4′,5,5′-heptaCB (PCB 189)	0.00003

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of the AhR [22]. The receptor affinity may be responsible for species and strain differences in sensitivity to 2,3,7,8-TCDD and related chemicals may be responsible. Species differences in sensitivity to 2,3,7,8-TCDD and related chemicals in bird could be due to differences in amino acid composition of the ligand-binding domain [17]. Effects of dioxin-like compounds are also mediated through the AhR in fishes. Fishes possess AhRs that can be grouped within at least three distinct clades (AhR1, AhR2, AhR3). AhR2 has been shown to be the active form in most teleosts, with AhR1 not binding dioxin-like compounds [8]. However, there is still a controversy over explaining different responses in species susceptibility to dioxin and dioxin-like compounds.

The AhR is a basic helix-loop-helix (bHLH) and Per-Arnt-Sim (PAS)-containing transcription factor [7]. hsp90 (a heat shock protein of 90 kDa), the X-associated protein 2 (XAP2) and p23 are the chaperon proteins that are required for the activation of AhR. When dioxin ligand passes through the plasma membrane and binds to the AhR, the ligand AhR complex undergoes a conformational change for a nuclear localization (Figure 1). The complex translocates into the nucleus and the chaperone proteins dissociate from the complex. The AhR−ligand then binds to the bHLH-PAS nuclear protein, AhR nuclear translocator (Arnt). This heterodimer binds to DNA called the dioxin responsive element (DRE). Binding of the ligand−AhR−Arnt complex to the DRE initiates transcription of genes encoding ctyochrome P450 enzymes (notably CYP1A1 and other AhR-responsive genes [7]. Abrupt modulation of gene expression may be responsible for a series of biochemical, cellular and tissue changes following exposure to dioxin and related compounds [6,20].

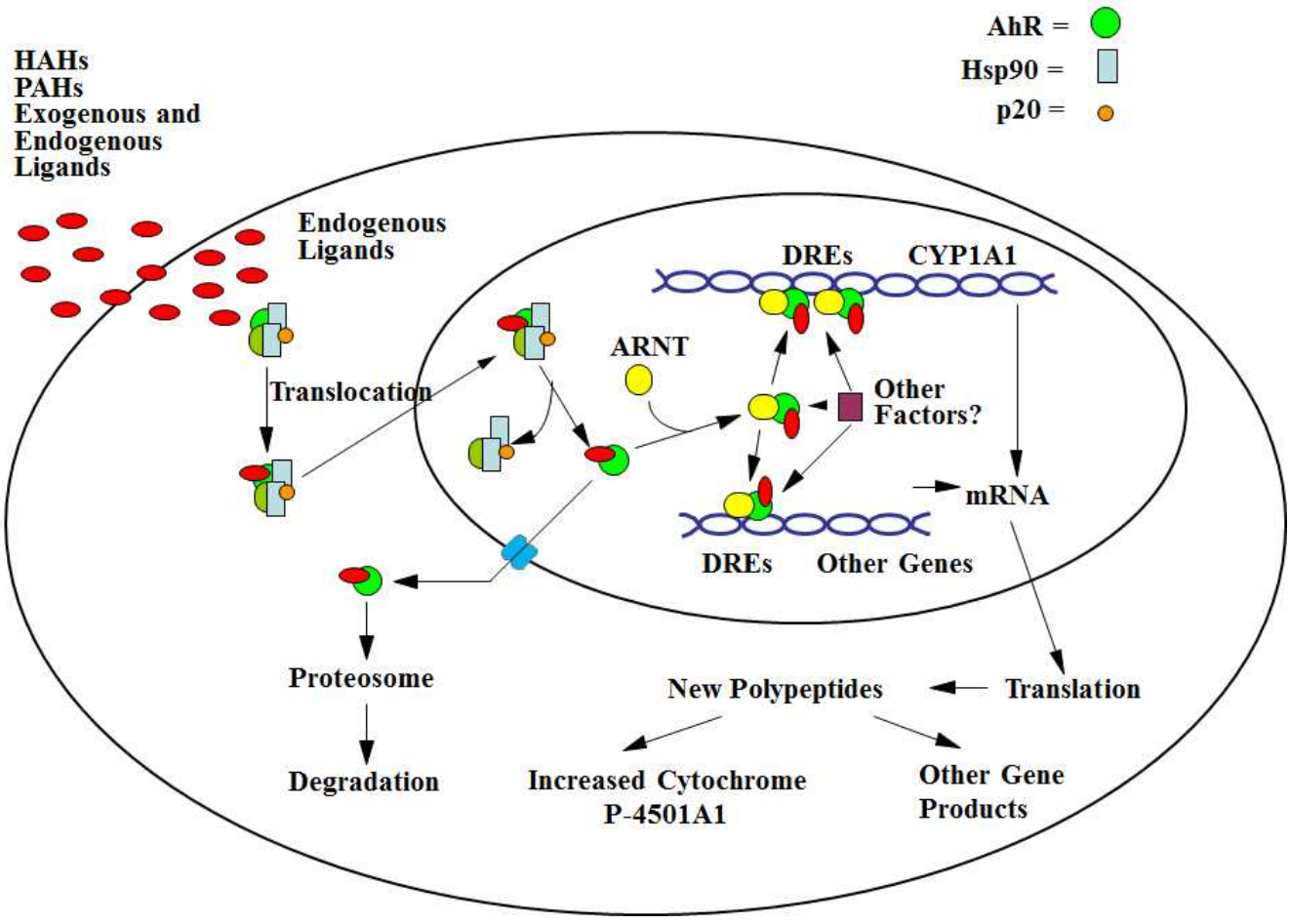

Figure 1. Schematic drawing of AhR-mediated mechanism of action for dioxins and related compounds (Denison and Nagy, 2003)

Evidence of neurotoxicity following exposure to PCBs.

There is much evidence that PCBs can cause neurotoxicity in humans and that in utero exposure is more important than lactational exposure in causing the neurotoxic effects. It is reported that children born to mothers, who had ingested fish contaminated with PCBs, tend to have learning and memory deficits [15]. Prenatal PCB exposure was associated with poorer performance on the Psychomotor Index in children from general population in US [23]. It is also indicated that PCB exposure is associated with deficits in mental and motor scores in children up to 7-months of age [34]. These studies suggest that the nervous system, especially during development, is sensitive to exposure to PCBs and related chemicals.

Neurochemical effects

There is extensive evidence for an association between exposure to dioxin-like chemicals and adverse effects on behavior and cognition. Neurotransmitters are major targets of these compounds [10]. In addition, signal transduction enzymes such as protein kinase C (PKC) as well as alterations in Ca^{2+} homeostasis may play pivotal roles in expression of neurochemical effects following PCB exposure[30].

It has been shown that PCBs can reduce dopamine (DA) concentrations in the brain when an animal is exposed during developmental stage [28]. PCB-induced abnormality in cognitive function is related with the alteration of cholinergic neurotransmitter system [9]. PCB also altered N-methyl-D-aspartic acid (NMDA) receptor binding sites in the visual cortex area when exposed during the pregnancy [1]. PCB-induced alteration in the regulation of glutamate may lead to excess activation of excitatory neurons, which may result in neuronal death.

PCB congeners, in particular coplanar dioxin-like PCBs, are known to alter Ca^{2+} homeostasis in the brain. Disruption of Ca^{2+} homeostasis by PCBs can result in various adverse effects such as the production of reactive oxygen species (ROS), long-term potentiation (LTP) and synaptic plasticity [21]. It is generally accepted that PCB exposure increase an influx of extracellular Ca^{2+} from a variety of routes. The routes of extracellular Ca^{2+} into cells include entry via L-type voltage-sensitive calcium channels, the endoplasmic reticulum (ER), glutamate receptors channels [13].

Protein kinase C (PKC) has been shown to have an important role in PCB-induced toxicity [19]. Isoforms of PKC play pivotal roles in modulation of neurotransmitter release, neuronal apoptosis, long-term potentiation (LTP), and neurological diseases [4]. It is demonstrated that PCBs increase PKC translocation from membrane fraction to cytosolic fraction and affect the second messenger molecules such as inositol phosphate in cerebellar granule cells in vitro [19]. For classic PKC isoforms, extracellular calcium is required for their translocation. However, Yang and Kodavanti [35] reported that ortho-substituted PCBs (non-coplanar PCBs) induce translocation of the calcium-dependent isoform, PKC-α, as well as the calcium-independent isoform, PKC-ε. In a later study with rats exposed to 6 mg Aroclor 1254/kg body weight/day from GD 6 to PND 21, three different isoforms of PKC (-α, -ε, -γ) in subcellular fractions of brain preparations were altered [36]. Brain NOS activity is also inhibited by PCB exposure [16,37]. NOS is involved in both long-term potentiation and oxidative stress [31]. Thus, inhibition of NOS could influence the level of LTP which may result in learning and memory deficits.

Intracellular signal transduction is a key pathway by which extracellular signals are transferred to the cytosol and nucleus of the cell. Any interference with these processes would have the potential for profound effects on the function of neuron as well as their development. Thus, any alteration of signaling pathway by PCB exposure may lead to abruption of normal activity of growth factors and neurotransmitters. For future studies, cross talk between the receptor signals and second

messengers will be warranted to further elucidate PCB-induced neurotoxicities.

Discussion

Marine ecosystems are constantly threatened by contaminants produced by the rapid industrialization and other human activities on the grounds. The potential impact on marine organisms and human health is now a growing concern and becomes a global issue [14]. Persistent organic pollutants (POPs), such as polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), brominated flame retardants (BFRs) can pose a great threat on marine fauna and human health, considering their high toxicity and persistence in the environment [29].

Recent increase in the incidence of developmental disabilities may be related with the environmental contamination in our surroundings. Although genetic factors have a key role in developmental disabilities, environmental chemicals may also be a factor responsible for various developmental disorders of the brain, such as Attention Deficient Hyperactive Disorder (ADHD) and autism [5]. Developmental neurotoxicity is associated with abnormality in behavior, neurophysiology, and neurochemistry of the nervous system occurring in the offspring, in particular when toxic chemicals are exposed in utero and during lactation. Compared to adult brain, the developing nervous system in early life is known to be more sensitive to toxicants, due to the presence of rapid growth period of the brain, known as “brain growth spurt” [9]. In humans, the “brain growth spurt” begins from the third trimester of pregnancy to the first one or two years of life. During this period, the brain goes through pivotal developmental stages such as neurogenesis, migration, and differentiation. Toxicant exposure during any of these stages could have detrimental effects on the normal brain development in early life. Intracellular signaling is a crucial biochemical pathway for the normal function and development of the nervous system. The alterations of intracellular second messengers in this process by toxic chemicals may be key steps for developmental neurotoxicity of a number of chemicals including PCBs. Understanding of neurotoxic mechanism of action for POPs may provide good scientific basis for more accurate human health risk assessment from environmental contaminants.

Conclusion

Human demands on marine resources are ever increasing. However, biodiversity on marine life is in jeopardy due to the off-shore contamination from the inlands [29]. Since consumption of contaminated products is a major route of the persistent toxic chemical exposure to the human bodies [38], it is critical to monitor the level of exposure regularly and implement the effective risk assessment over the suspected products. Recently, it is reported that the consumption of blue shark derived products can pose to human health, because the shark samples presented values above the regulatory limits of environmental contaminants [2]. When PCDDs/DFs and PCBs concentrations in fishes, crustaceans, cephalopods, and bivalves collected at markets in Korea were monitored for three years (2007–2009), slightly lowering trends of concentrations were found for fishes but no clear chronological trend was observed for other marine products [18]. Although the trend of contamination for certain marine species is generally in a decline, there is still unknown level of contamination in many other aquatic compartments threatening the health of marine ecosystem.

Fish consumption is one of major exposure routes of PCB accumulation in our body. In particular, because neurotoxic effects of PCBs are more significant when exposed during early life thru lactation or in utero, the critical window of exposure at the early life is a key issue for regulating these chemicals. It is now a great concern that even low background level of contamination may influence developmental neurotoxicicty such as ADHD and autism. Therefore, an extended monitoring of POPs is required in the marine environment as well as byproducts generated from marine biotechnology, to minimize the risk of human health impact.

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