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Structure–activity relationships of 44 halogenated compounds for iodotyrosine deiodinase-inhibitory activity

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ABSTRACT

The aim of this study was to investigate the possible influence of halogenated compounds on thyroid hormone metabolism via inhibition of iodotyrosine deiodinase (IYD) activity. The structure-activity relationships of 44 halogenated compounds for IYD-inhibitory activity were examined *in vitro* using microsomes of HEK-293 T cells expressing recombinant human IYD. The compounds examined were 17 polychlorinated biphenyls (PCBs), 15 polybrominated diphenyl ethers (PBDEs), two agrichemicals, five antiparasitics, two pharmaceuticals and three food colorants. Among them, 25 halogenated phenolic compounds inhibited IYD activity at the concentration of 1×10^{-4} M or 6×10^{-4} M. Rose bengal was the most potent inhibitor, followed by erythrosine B, phloxine B, benzbromarone, 4′-hydroxy-2,2′,4-tribromodiphenyl ether, 4-hydroxy-2,3′,3,4′-tetrabromodiphenyl ether, 4-hydroxy-2′,3,4′,5,6′-pentachlorobiphenyl, 4′-hydroxy-2,2′,4,5′-tetrabromodiphenyl ether, triclosan, and 4-hydroxy-2,2′,3,4′,5-pentabromodiphenyl ether. However, among PCBs and PBDEs without a hydroxyl group, including their methoxylated metabolites, none inhibited IYD activity. These results suggest that halogenated compounds may disturb thyroid hormone homeostasis via inhibition of IYD, and that the structural requirements for IYD-inhibitory activity include halogen atom and hydroxyl group substitution on a phenyl ring.

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1. Introduction

Halogenated compounds, such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) have been widely used throughout the world. They have been detected in wildlife and human adipose tissue, breast milk and serum, presumably due to their lipophilic character (Sandau et al., 2002; Schecter et al., 2003; Inoue et al., 2006; Qiu et al., 2009). These compounds may disrupt thyroid hormone homeostasis, because they are structurally similar to the endogenous hormones. Further, the chemical structures of some agrichemicals, antiparasitics, pharmaceuticals and food colorants also resemble those of thyroid hormones. Although the mechanisms of thyroid disruption by environmental contaminants have not been fully established, several mechanisms have been investigated. For example, PCBs and PBDEs, including their hydroxylated metabolites, bind competitively to the thyroid hormone receptor in mammals (Kitamura et al., 2005, 2008; Kojima et al., 2009). Also, hydroxylated PCBs and PBDEs show high binding affinity for the serum thyroid hormone-binding protein transthyretin (TTR) (Meerts et al., 2002; Hamers et al., 2006). Decreased levels of circulating plasma thyroxine (T4) following exposure to PCBs and PBDEs have been reported in laboratory animals (Szabo et al., 2009). Triclosan, a chlorinated phenolic antibacterial agent, decreases serum T4 concentration in male juvenile rats (Zorrilla et al., 2009). Erythrosine B and rose bengal, which are used as food colorants, were reported to disturb thyroid function in rats (Kurebayashi et al., 1988). In addition, bithionol and closantel, which are used as antiparasitics for animals, exhibit thyroid hormone-like activity in reporter gene assays (Matsubara et al., 2012).

Iodotyrosine deiodinase (IYD) is a dehalogenase that contains flavin mononucleotide (FMN), and is involved in the NADPH-dependent deiodination of 3-iodo-L-tyrosine (MIT) and 3,5-diiodo-L-tyrosine (DIT), which are released along with the thyroid hormones T4 and 3,5,3′-triiodothyronine (T3) during thyroglobulin proteolysis (Fig. 1) (Gnidehou et al., 2004; Friedman et al., 2006). IYD action on MIT and DIT results in the release of iodide and tyrosine, which can be reused for thyroid hormone synthesis (Rokita et al., 2010). A deficiency in IYD activity can result in a lack of adequate iodide retention and ultimately, hypothyroidism

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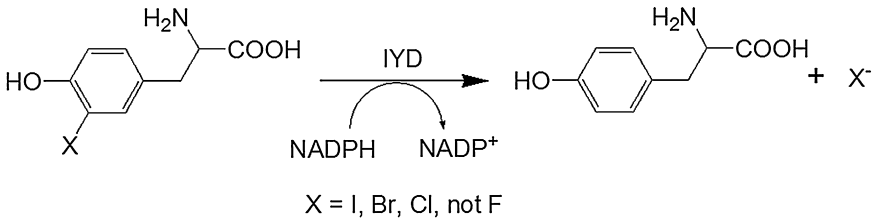

Fig. 1. Reductive dehalogenation of halogenated tyrosines catalyzed by IYD.

(Krause et al., 2007; Moreno et al., 2008). This enzyme has also been discovered to act as a general dehalogenase by promoting reductive dehalogenation of 3-bromo- and 3-chloro-L-tyrosine, though not 3-fluoro-L-tyrosine (McTamney and Rokita, 2009). Thus, compounds that modulate IYD activity may alter levels of thyroid hormones and related compounds, thereby affecting various biological pathways.

Thus, in order to clarify the effects of various halogenated compounds on thyroid hormone metabolism, we investigated the inhibitory effects of 44 chemicals on IYD activity. Specifically, we examined the structure-activity relationships of 17 PCBs, 15 PBDEs, two agrichemicals, five antiparasitics, two pharmaceuticals and three food colorants (Fig. 2) for IYD-inhibitory activity *in vitro* using microsomal fraction from HEK-293 T cells expressing recombinant human IYD.

2. Materials and methods

2.1. Chemicals

The purities and sources of the 17 PCBs and 15 PBDEs tested in the present study are shown in Table 1. The hydroxylated and methoxylated PCBs were synthesized according to the method of Bergman et al. (1994). BDE-47 (B-1) was synthesized according to the method of Teclechiel et al. (2009), and BDE-85 (B-2) and BDE-99 (B-3) following the method of Orn et al. (1996). The hydroxylated and methoxylated PBDEs were synthesized according to the method of Marsh et al. (2003). Bromophenofos (C-1) (>97%), bromoxynil (C-2) (>97%), oxyclozanide (D-1) (>98%), tribromsalan (D-2) (>98%), closantel (D-3) (>99%), nitroxynil (D-5) (>98%), triclosan (E-1) (>98%), rose bengal (F-1) (>98%) and phloxine B (F-3) (>98%) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Benzbromarone (E-2) (>98%) was obtained from Sigma-Aldrich (St. Louis, Mo, USA). Bithionol (D-4) (>97%) and erythrosine B (F-2) (>95%) were purchased from Tokyo Chemical Industries, Co., Ltd. (Tokyo, Japan).

2.2. Plasmid construction

The IYD cDNA was amplified by PCR from a human liver cDNA library using primers 5′-GGATCCATGTATTTCCTGACTCCCATCTTGG-3′ and 5′-CTCGAGCTACACTGTCACCATGATCTGGTC-3′, and inserted into the BamHI-XhoI restriction sites of plasmid pcDNA3.1 (+) to generate pcDNA-IYD.

2.3. Cell culture and transfection

HEK-293 T cells were cultured in Dulbecco's modified Eagle's medium (Invitrogen, Grand Island, NY), supplemented with 10% FCS. pcDNA-IYD was transfected into HEK-293 T cells using FuGENE HD (Roche, Mannheim, Germany). Stable transfectants were selected by the addition of hygromycin (Invitrogen).

Table 1
Purity and source of 17 PCBs and 15 PBDEs examined in this study.

(A) PCBs		
Compound	Purity (%)	Source
(A-1) 2,2′,4,4′-tetrachlorobiphenyl (2,2′,4,4′-TCB)	>98	Accu standard
(A-2) 3,3′,4,4′,5-pentachlorobiphenyl (3,3′,4,4′,5-PCB)	>98	Accu standard
(A-3) 2-hydroxy-3,3′,4,4′-tetrachlorobiphenyl (2-OH-3,3′,4,4′-TCB)	>98	This study
(A-4) 3-hydroxy-2,2′,5,5′-tetrachlorobiphenyl (3-OH-2,2′,5,5′-TCB)	>98	This study
(A-5) 4-hydroxy-2,2′,3,4′,5,5′-hexachlorobiphenyl (4-OH-2,2′,3,4′,5,5′-HxCB)	>98	This study
(A-6) 4-hydroxy-2′,3,4′,5,5′-pentachlorobiphenyl (4-OH-2′,3,4′,5,5′-PCB)	>98	This study
(A-7) 4-hydroxy-2′,3,4′,5,6′-pentachlorobiphenyl (4-OH-2′,3,4′,5,6′-PCB)	>98	This study
(A-8) 4-hydroxy-2′,3,5,5′-tetrachlorobiphenyl (4-OH-2′,3,5,5′-TCB)	>98	This study
(A-9) 4-hydroxy-2,2′,5,5′-tetrachlorobiphenyl (4-OH-2,2′,5,5′-TCB)	>98	This study
(A-10) 4-hydroxy-2′,3,4′,5-tetrachlorobiphenyl (4-OH-2′,3,4′,5-TCB)	>98	This study
(A-11) 4-hydroxy-2′,3,4′,6′-tetrachlorobiphenyl (4-OH-2′,3,4′,6′-TCB)	>98	This study
(A-12) 4-hydroxy-2,3,3′,4′-tetrachlorobiphenyl (4-OH-2,3,3′,4′-TCB)	>98	This study
(A-13) 4-hydroxy-2′,3′,4′,5′-tetrachlorobiphenyl (4-OH-2′,3′,4′,5′-TCB)	>98	This study
(A-14) 4-hydroxy-3,3′,4′,5-tetrachlorobiphenyl (4-OH-3,3′,4′,5-TCB)	>98	This study
(A-15) 4-methoxy-3,3′,4′,5-tetrachlorobiphenyl (4-MeO-3,3′,4′,5-TCB)	>98	This study
(A-16) 4,4′-dihydroxy-3,3′,5,5′-tetrachlorobiphenyl (4,4′-diOH-3,3′,5,5′-TCB)	>98	This study
(A-17) 4-4′-dimethoxy-3,3′,5,5′-tetrachlorobiphenyl (4,4′-diMeO-3,3′,5,5′-TCB)	>98	This study
(B) PBDEs		
(B-1) 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47)	>98	This study
(B-2) 2,2′,3,4,4′-pentabromodiphenyl ether (BDE-85)	>98	This study
(B-3) 2,2′,4,4′,5-pentabromodiphenyl ether (BDE-99)	>98	This study
(B-4) 2,2′,4,4′,6-pentabromodiphenyl ether (BDE-100)	>98	Accu standard
(B-5) 2′-hydroxy-2,4,4′-tribromodiphenyl ether (2′-OH-BDE-28)	>98	This study
(B-6) 2-hydroxy-4,4′-dibromodiphenyl ether (2-OH-BDE-15)	>98	This study
(B-7) 4′-hydroxy-2,2′,4-tribromodipheyl ether (4′-OH-BDE-17)	>98	This study
(B-8) 4-hydroxy-2,2′,3,4′-tetrabromodiphenyl ether (4-OH-BDE-42)	>98	This study
(B-9) 4′-hydroxy-2,2′,4,5′-tetrabromodipheynl ether (4′-OH-BDE-49)	>98	This study
(B-10) 4-hydroxy-2,2′,3,4′,5-pentabromodipheynl ether (4-OH-BDE-90)	>98	This study
(B-11) 2-methoxy-4,4′-dibromodiphenyl ether (2-MeO-BDE-15)	>98	This study
(B-12) 4′-methoxy-2,2′,4-tribromodipheyl ether (4′-MeO-BDE-17)	>98	This study
(B-13) 4-methoxy-2,2′,3,4′-tetrabromodiphenyl ether (4-MeO-BDE-42)	>98	This study
(B-14) 4′-methoxy-2,2′,4,5′-tetrabromodipheynl ether (4′-MeO-BDE-49)	>98	This study
(B-15) 4-methoxy-2,2′,3,4′,5-pentabromodipheynl ether (4-MeO-BDE-90)	>98	This study

Accu standard; Accu standard, Inc. (New Haven, CT, USA).

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