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Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: Affinity to the mammalian thyroid hormone receptor, and effect on tadpole metamorphosis

Shigeyuki Kitamura[a,*], Teruhisa Kato[b], Mitsuru Iida[b], Norimasa Jinno[a], Tomoharu Suzuki[a], Shigeru Ohta[a], Nariaki Fujimoto[c], Hideki Hanada[d], Keiko Kashiwagi[d], Akihiko Kashiwagi[d]

[a]*Graduate School of Biomedical Sciences, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan*
[b]*EDC Analysis Center, Otsuka Pharmaceutical Co., Ltd., Japan*
[c]*Research Institute for Radiation Biology and Medicine, Japan*
[d]*Laboratory for Amphibian Biology, Graduate School of Science, Hiroshima University, Japan*

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Abstract

The thyroid hormone-disrupting activity of tetrabromobisphenol A (TBBPA), a flame retardant, and related compounds was examined. TBBPA, tetrachlorobisphenol A (TCBPA), tetramethylbisphenol A (TMBPA) and 3,3′-dimethylbisphenol A (DMBPA) markedly inhibited the binding of triiodothyronine (T_3; 1×10^{-10} M) to thyroid hormone receptor in the concentration range of 1×10^{-7}–1×10^{-4} M, while bisphenol A and 2,2-diphenylpropane were inactive. TBBPA, TCBPA, TMBPA and DMBPA did not exhibit thyroid hormonal activity in a thyroid hormone-responsive reporter assay using a Chinese hamster ovary cell line (CHO-K1) transfected with thyroid hormone receptor α1 or β1, but TBBPA and TCBPA showed significant anti-thyroid hormone effects on the activity of T_3 (1×10^{-8} M) in the concentration range of $3 \times 10^{-6} - 5 \times 10^{-5}$ M. The thyroid hormone-disrupting activity of TBBPA was also examined in terms of the effect on amphibian metamorphosis stimulated by thyroid hormone. TBBPA in the concentration range of 1×10^{-8} to 1×10^{-6} M showed suppressive action on T_3 (5×10^{-8} M)-enhancement of *Rana rugosa* tadpole tail shortening.

* Corresponding author. Fax: +81 82 257 5329.
E-mail address: skitamu@hiroshima-u.ac.jp (S. Kitamura).

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These facts suggest that TBBPA, TCBPA, TMBPA and DMBPA can act as thyroid hormone-disrupting agents.

Keywords: Thyroid hormone-disrupting activity; Antagonist of thyroid hormone; Hamster ovary cell line CHO-K1; EcoScreen assay; Tadpole; Tail shortening; Amphibian metamorphosis; Tetrabromobisphenol A; Tetrachlorobisphenol A; Tetramethylbisphenol A

Introduction

Tetrabromobisphenol A (2,2-bis(3,5-dibromo-4-hydroxyphenyl)propane; TBBPA) is a brominated derivative of bisphenol A (BPA), a prototypical estrogenic xenobiotic. The brominated compound is widely used throughout the world as a flame retardant for building materials, paints, rubbers, synthetic textiles and plastic products, including epoxy resin, and electronic equipment, to prevent or retard the initial phase of a developing fire. TBBPA is the most widely used flame retardant in electric equipment such as televisions, computers, copying machines, video displays and laser printers. TBBPA is generally regarded as safe as a flame retardant because it is not readily accumulated in the environment, nor is it highly toxic (Helleday et al., 1999). Global use of TBBPA was about 120,000 tons per year in 1999, and TBBPA currently accounts for about half of the total usage of flame retardants in Japan (de Wit, 2002). About 90% of total used TBBPA is covalently bound to polymers as a reactive flame retardant, but about 10% is used as an additive (unbound form). Unbound TBBPA may leak into the environment and possibly accumulate in biological systems (de Wit, 2002; Herrmann et al., 2003; Sjödin et al., 2003). However, limited information concerning the toxicological impact of this retardant is available. TBBPA and its dimethoxylated derivative have been found in river sediment in Osaka, Japan at concentrations of 0.5–140 μg/kg dry weight (Watanabe et al., 1983). These compounds were also detected downstream from a plastics production facility at 270 ng/g dry weight as TBBPA and at 1500 ng/g dry weight as its dimethoxylated derivative, and also in sewage sludge samples in Sweden (Sellström and Jansson, 1995). Oberg et al. (2002) also detected TBBPA in sewage sludges in Sweden, but reported that the amounts varied greatly. Tetrachlorobisphenol A (2,2-bis(3,5-dichloro-4-hydroxyphenyl)propane; TCBPA) was also detected in waste paper recycling plants (Fukazawa et al., 2002). Thomsen et al. (2002) detected TBBPA in human plasma lipids at the level of 0.44–0.71 ng/g lipids. The halogenated derivative of bisphenol A was also found in air samples at an electronics recycling plant (Sjödin et al., 2001). In addition, tetramethylbisphenol A (TMBPA) and dimethylbisphenol A (DMBPA) have been used as materials for plastic resins.

Accumulating evidence suggests that some natural and synthetic chemicals which are widely distributed in the environment are able to mimic the biological activity of hormones. Among these endocrine-disrupting chemicals are various estrogenic compounds, include chlorinated insecticides, such as dieldrin and methoxychlor, and products used in the plastics and detergent industries, such as alkylphenols and BPA (Andersen et al., 1999). In contrast, *p,p′*-DDE, antifungal vinclozolin, and insecticidal fenitrothion and fenthion are known to have anti-androgenic activity (Chen et al., 1997; Kelce et al., 1995; Kupfer and Bulger, 1987; Kitamura et al., 2003). Hydroxy-PCBs such as 4,4′-dihydroxy-3,3′,5,5′-tetrachlorobiphenyl show anti-thyroid hormonal activity in addition to estrogenic activity (Korach et al., 1988; Lans et al., 1994; Connor et al., 1997; Cheek et al., 1999). Interactions of estrogenic and anti-androgenic compounds