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Minding the calcium store: Ryanodine receptor activation as a convergent mechanism of PCB toxicity

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ABSTRACT

Chronic low-level polychlorinated biphenyl (PCB) exposures remain a significant public health concern since results from epidemiological studies indicate that PCB burden is associated with immune system dysfunction, cardiovascular disease, and impairment of the developing nervous system. Of these various adverse health effects, developmental neurotoxicity has emerged as a particularly vulnerable endpoint in PCB toxicity. Arguably the most pervasive biological effects of PCBs could be mediated by their ability to alter the spatial and temporal fidelity of Ca^{2+} signals through one or more receptor-mediated processes. This review will focus on our current knowledge of the structure and function of ryanodine receptors (RyRs) in muscle and nerve cells and how PCBs and related non-coplanar structures alter these functions. The molecular and cellular mechanisms by which non-coplanar PCBs and related structures alter local and global Ca^{2+} signaling properties and the possible short and long-term consequences of these perturbations on neurodevelopment and neurodegeneration are reviewed.

Contents

1. Introduction

1.1. Polychlorinated biphenyls: Occurrence and concerns to public health

Polychlorinated biphenyls (PCBs) are synthetic chlorinated aromatic hydrocarbons that are non-flammable, chemically stable and have high boiling points. In the United States, PCBs were synthesized and marketed primarily as Aroclor® mixtures whose degree of chlorination was identified by a four-digit designation (*e.g.*, 1248, 1254, 1260, etc.), with the first two digits identifying the mixture as PCBs and the last two digits identifying the percent of chlorine used during synthesis. A higher degree of PCB chlorination increases melting point and lipophilicity, whereas lower chlorination increases vapor pressure and water solubility. Similar PCB mixtures were synthesized worldwide and identified under several trade names such as Clophen® and Kanechlor®. PCB mixtures, especially those of intermediate chlorination, such as Aroclor 1248 and Aroclor 1254, were widely used in several industries for their insulation and heat dissipating properties. PCBs were also broadly incorporated into a variety of common products such as pesticide extenders, plastics, varnishes, adhesives, carbonless copy paper, newsprint, fluorescent light ballasts and caulking compounds (Ross, 2004).

By 1977, when PCBs were banned, more than 600,000 tons were manufactured in the United States, and global production is estimated at over 1.5 million tons (Breivik et al., 2002). Because of their extensive industrial use and chemical stability, PCBs have accumulated in the environment and biota. PCBs have been identified in approximately one third of the sites listed on the National Priorities List (NPL) and Superfund Sites (Anonymous, 2007). The average PCB levels in the environment and human blood have steadily declined since 1977. However, geographic "hotspots" of relatively high PCB contamination persist due to improper disposal, and mobilization of PCBs from

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historical end uses in and around urban environments (legacy PCBs). Specific examples of PCB hotspots in the United States that contribute to higher human exposures include the San Francisco Bay watershed (Davis et al., 2007), the Hudson River watershed (Schneider et al., 2007; Asher et al., 2007), Chicago air (Sun et al., 2006; Hu et al., 2008; Zhao et al., 2009), and regions of Lake Erie near urban centers (Sun et al., 2007; Robinson et al., 2008). Thus, chronic low-level PCB exposures remain a significant public health concern since results from epidemiological studies indicate that PCB burden is associated with immune system dysfunction (Heilmann et al., 2006; Selgrade, 2007; Park et al., 2008a,b), cardiovascular disease (Hennig et al., 2005; Humblet et al., 2008; Dziennis et al., 2008; Everett et al., 2008; Helyar et al., 2009), and impairment of the developing nervous system (Jacobson et al., 1992; Chen et al., 1992; Koopman-Esseboom et al., 1996; Schantz et al., 2003; Grandjean & Landrigan, 2006; Roegge & Schantz, 2006; Rogan & Ragan, 2007; Stewart et al., 2008). Of these various adverse health effects, developmental neurotoxicity has emerged as a particularly vulnerable endpoint in PCB toxicity. Whether neurological, immunological and cardiovascular impairments are interrelated by one or more convergent mechanisms, or arise independently from biologically distinct mechanisms continues to be debated. Furthermore, which PCB structures confer specific health risks to the general public or to a susceptible population, remains unclear.

1.2. Non-dioxin-like polychlorinated biphenyl structures—convergent mechanisms mediated by ryanodine receptors

Of the 209 possible PCB congeners that were synthesized as commercial mixtures, most of the scientific and regulatory attention has been directed toward the so-called dioxin-like PCBs that lack at least two chlorines in the *ortho*-positions. The phenyl rings of dioxin-like PCBs, for example PCB 77 (3,3′,4,4′-tetrachlorobiphenyl) and PCB 126 (3,3′,4,4′,5-pentachlorobiphenyl), assume a coplanar orientation that mimics the planar structure of dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDD), the archetypical agonist for the arylhydrocarbon hydroxylase receptor (AhR) (Fig. 1). Coplanarity and lipophilicity are arguably the two most important physicochemical parameters for optimizing tight binding to AhR, although the position of *para* and *meta* substituents influences apparent binding affinity. A growing number of environmental chemicals are known to activate or inhibit AhR, thereby regulating its translocation to the nucleus where it dimerizes with AhR nuclear translocator (ARNT) (Denison & Nagy, 2003). The AhR–ARNT complex binds to the DNA core sequence 5′-GCGTG-3′ in the promoter region of dioxin-responsive genes to regulate their expression. Prolonged activation of AhR and its responsive genes has been implicated in diverse toxicological sequelae associated with chronic, low-level exposures to TCDD, polycyclic aromatic hydrocarbons (PAHs), and coplanar PCBs (Carpenter, 2006; Mitchell & Elferink, 2009). Thus, the risk to human, fish and wildlife associated with PCB exposures is assessed by assigning an equivalence factor (TEF) that reflects the AhR activity of any individual PCB congener relative to TCDD, which is arbitrarily assigned a TEF of 1.0.

Several limitations of the TEF concept have been identified (Van den Berg et al., 2006). Arguably the most important limitation for predicting PCB toxicity based solely on an AhR-based TEF is the fact that PCBs having one or more chlorines in the *ortho*-positions are non-coplanar structures with very low or no activity towards the AhR yet they exhibit significant toxicological activity. In vitro studies have identified PCB 95 (Fig. 1) among the most biologically active non-coplanar structures and its occurrence in human and environmental samples has been recently scrutinized using improved analytical methods. PCB 95 has been detected in human tissues (Covaci et al., 2002; Chu et al., 2003a; DeCaprio et al., 2005; Jursa et al., 2006), and in environmental samples including indoor and outdoor air, top soil, tidal marsh sediments, grass, diets, and human feces (Robson & Harrad, 2004; Harrad et al., 2006; Hwang et al., 2006; Zhao et al., 2009; Wong et al., 2009). Recent studies indicate that non-coplanar PCBs currently predominate in biological and environmental samples. For example, PCB 153 (Fig. 1) has been identified as a major contributor to total PCB burden in humans (Longnecker et al., 2003; Moon et al., 2009; Agudo et al., 2009; Axelrad et al., 2009).

The *ortho*-rich PCBs and metabolites of both *ortho*-rich and *ortho*-poor PCBs have a number of actions independent of the AhR that have

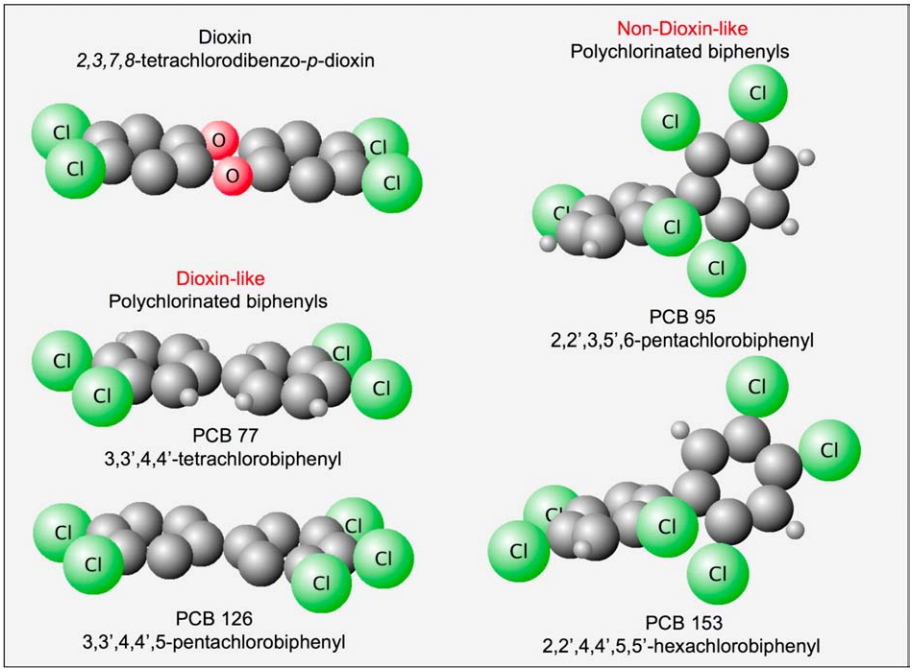

Fig. 1. Coplanar structure of dioxin and two examples of dioxin-like PCBs. Non-dioxin-like PCBs have >2 chlorine substitutions in the ortho-position that introduce steric hindrance thereby promoting non-coplanar geometry, as typified by PCB 95 and PCB 153. 3-D projections were calculated using the Molecular Dynamics Tool of ChemIDplus Advanced (Nat. Lib. Med.).