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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 biphenyls (PCB) exposures remain a significant public health concern since results from epidemiological studies indicate 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.

1. Dioxin-like and non-dioxin-like PCBs

1.1. 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, Sweetman, Pacyna, & Jones, 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 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, Hetzel, Oram, & McKee, 2007), the Hudson River watershed (Asher, Wong, & Rodenburg, 2007; Schneider, Porter, & Baker, 2007), Chicago air (Hu, Martinez, & Hornbuckle, 2008; P. Sun, Basu, & Hites, 2006; Zhao et al., 2009), and regions of Lake Erie near urban centers (S. D. Robinson, Landrum, Van Hoof, & Eadie, 2008; P. Sun, Basu, Blanchard, Brice, & Hites, 2007). Thus, chronic low level PCB exposures remain a significant public health concern since results from epidemiological studies indicate PCB burden is associated with immune system dysfunction (Heilmann, Grandjean, Weihe, Nielsen, & Budtz-Jorgensen, 2006; H. Y. Park et al., 2008; Selgrade, 2007), cardiovascular disease (Dziennis et al., 2008; Everett, Mainous, Frithsen, Player, & Matheson, 2008; Helyar et al., 2009; Hennig et al., 2005; Humblet, Birnbaum, Rimm, Mittleman, & Hauser, 2008), and impairment of the developing nervous system (Y. C. Chen, Guo, & Hsu, 1992; Grandjean & Landrigan, 2006; Jacobson, Jacobson, Padgett, Brumitt, & Billings, 1992; Koopman-Esseboom et al., 1996; Roegge & Schantz, 2006; Rogan & Ragan, 2007; Schantz, Widholm, & Rice, 2003; P. W. 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 PCB structures–convergent mechanisms mediated by RyRs

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). Co-planarity 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 two 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 (Chu, Covaci, & Schepens, 2003; Covaci, de Boer, Ryan, Voorspoels, & Schepens, 2002; DeCaprio et al., 2005; Jursa, Chovancova, Petrik, & Loksa, 2006), and in environmental samples including indoor and outdoor air, top soil, tidal marsh sediments, grass, diets, and human feces (Harrad, Ren, Hazrati, & Robson, 2006; Hwang, Green, & Young, 2006; Robson & Harrad, 2004; F. Wong, Robson, Diamond, Harrad, & Truong, 2009; Zhao 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 (Agudo et al., 2009; Axelrad, Goodman, & Woodruff, 2009; Longnecker et al., 2003; Moon, Kim, Choi, Yu, & Choi, 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 been termed “non-dioxin-like”. Mono-*ortho* substituted PCBs may have dioxin-like and non-dioxin-like activities. However mono-*ortho* congeners commonly detected in tissues, such as PCB 118 (2,3,4,4′,5-pentachlorobiphenyl) and PCB 156 (2,3,3′,4,4′,5-hexachlorobiphenyl), have extremely low TEF values ($\ll$0.0001), and their apparent AhR activity could be largely attributed to coplanar contaminants (Peters, *et al*. 2006). Several biological activities have been experimentally demonstrated with non-dioxin-like PCBs, and these were recently reviewed (Fonnum, Mariussen, & Reistad, 2006; Mariussen & Fonnum, 2006). Endocrine effects include weak estrogenicity (Safe, 2004), enhanced insulin (Fischer, Wagner, & Madhukar, 1999) and arachidonic acid secretion (Bae, Peters-Golden, & Loch-Caruso, 1999), and disruption of the hypothalamo-pituitary-thyroid axis. Two possibly convergent mechanisms actively being investigated include (1) disruption of thyroid hormone metabolism and signaling (Knerr & Schrenk, 2006; Zoeller, 2005; Zoeller, Dowling, & Vas, 2000), and (2) perturbations in cellular Ca^{2+} signaling (Pessah, 2001; Tilson, 1998). 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. The pivotal roles of Ca^{2+} signals in regulating movement, metabolism, growth, proliferation, gene transcription and protein translation in virtually all cell types is well established. Kodavanti and coworkers first reported that exposure non-coplanar PCBs elevate cytoplasmic Ca^{2+} in cultured cerebellar granule neurons (P. R. Kodavanti, Shin, Tilson, & Harry, 1993), and several mechanisms were proposed including disruption of membrane properties (P. R. Kodavanti, Ward, McKinney, & Tilson, 1996). A selective receptor-targeted mechanism was also proposed based on the stringent structure-activity relationship of PCBs for enhancing the activity of ryanodine receptors (RyRs), a family of intracellular Ca^{2+} channels (P. W. Wong & Pessah, 1996). For example, PCB 95 and PCB 153 at concentrations $\leq$10 μM lack detectable AhR activity, yet significantly enhance the activity of type 1 (RyR1) and type 2 (RyR2) isoforms at concentrations $\leq$1 μM (Pessah et al., 2006; P. W. Wong & Pessah, 1996). Figure 2 demonstrates the relative activity of 28 non-coplanar PCBs toward RyR1 and their relative contribution to total PCB burden reported in Fox River fish (52%) (Kostyniak et al., 2005), San Francisco Bay tidal marsh sediments (~50%) (Hwang et al., 2006), and human serum (~45%) (DeCaprio et al., 2005). Because not all the PCBs detected in these studies have been tested for RyR activity, these estimates of the occurrence of RyR-active PCBs are conservative. Therefore, the PCB congeners found in highest abundance in environmental samples and tissues collected from humans and animals are capable of directly and potently interacting with a major family of intracellular Ca^{2+} channels. RyRs are broadly expressed in most cell types where they participate in shaping temporally and spatially defined Ca^{2+} signals that are essential for regulating several aspects of cellular signaling that regulate growth, movement, metabolism, secretion and plasticity.

Significant to the neurotoxic potential of PCBs, RyR channel activity regulates a variety of physiological and pathophysiological processes in the central (Berridge, 2006; Dai, Hall, & Hell, 2009), and peripheral nervous systems (Behringer, Vanterpool, Pearce, Wilson, & Buchholz, 2009; Buchholz, Behringer, Pottorf, Pearce, & Vanterpool, 2007; Jackson & Thayer, 2006). Decrements in neonatal reflexes, cognitive function, motor activity, tremors, changes in autonomic functioning, and hearing impairments are consistent findings with developmental PCB exposures in studies of humans and animals, and are primarily attributed to adverse effects on the developing CNS (Darras, 2008; Fitzgerald et al., 2008; Kenet, Froemke, Schreiner, Pessah, & Merzenich, 2007; Mariussen & Fonnum, 2006; Roegge & Schantz, 2006; P. Stewart, Reihman, Lonky, Darvill, & Pagano, 2000). The possibility that PCBs might directly influence peripheral neurons and their effectors including skeletal, cardiac, and smooth muscle, and cochlear hair cells, all of which express functionally essential RyRs, has not received nearly as much investigation as their influence on the developing endocrine and central nervous systems.

In addition to TH, studies on the endocrine disrupting effects of PCBs and related organohalogens have also focused on estrogen, insulin, and their respective signaling pathways (Carpenter, 2008; Fonnum et al., 2006; Zoeller, 2007). Considering that RyRs have been shown to regulate several aspects of these same endocrine functions (Dillmann, 2002; Islam, 2002; Muchekehu & Harvey, 2008), a common convergent mechanism may contribute to pathological endocrine signaling and abnormal responses in target organs that depend on RyR activity for mediating appropriate Ca^{2+} signals.

This review will focus on our current knowledge of the structure and function of RyRs in muscle and nerve cells and how PCBs and related non-coplanar structures alter these functions. Our current knowledge of how RyRs assemble into arrays and clusters, how they generate local releases of Ca^{2+} termed sparks, and trigger global Ca^{2+} waves is most advanced in studies of skeletal, cardiac and smooth muscle. The topic is reviewed here first to provide context to the molecular mechanisms by which PCBs and related structures influence RyR structure and function. 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 will then be discussed.

2. RyR macromolecular complexes: Significance to PCB-mediated Ca^{2+} dysregulation

As might be predicted by their size and critical contribution to muscle function, multiple factors contribute to the precise regulation of RyR channel activity. In skeletal and cardiac muscle at least 20 protein-protein interactions have been described for the two major isoforms RyR1 (type 1 RyR) and RyR2 (type 2 RyR), respectively (Fig 3), and these interactions influence important aspects of Ca^{2+} channel function that are either essential for excitation-contraction (EC) coupling or fine-tune the spatial and temporal properties of local and global Ca^{2+} signals in the myocyte. Many of these interactions, when disrupted, have been shown to contribute to RyR-mediated susceptibility to muscle damage and to the progression of several muscle disorders. Similar functional and/or physical coupling of RyRs to context-specific proteins have been identified in smooth muscle, neurons and other cells types.

The composition of RyR macromolecular complexes is therefore an important consideration when interpreting the seemingly diverse *in vitro* and *in vivo* actions attributed to non-coplanar PCB congeners and Aroclor mixtures in a wide variety of tissues and cell types. PCBs have been shown to enhance Ca^{2+} release from sarcoplasmic reticulum/endoplasmic reticulum (SR/ER) and mitochondrial stores, and to promote Ca^{2+} entry, but whether these effects stem from

convergent receptor-mediated mechanisms or multiple "nonspecific" influences on membrane integrity has been debated (Inglefield, Mundy, & Shafer, 2001; Pessah, & Wong, 2001). PCBs also alter the activities of RyR "accessory" proteins including the multifunctional protein kinases, PKA (Inglefield, Mundy, Meacham, & Shafer, 2002; Llansola, Piedrafita, Rodrigo, Montoliu, & Felipo, 2009) and PKC (P. R. Kodavanti et al., 1994), calmodulin (Benninghoff & Thomas, 2005; Olivero & Ganey, 2001), and FKBP12 (FK506 binding protein 12 kDa), the major T-cell immunophilin (Gafni, Wong, & Pessah, 2004; P. W. Wong, Garcia, & Pessah, 2001; P. W. Wong & Pessah, 1997). Additionally, PCB toxicity in excitable and non excitable cells appears to be mediated at least in part by oxidative stress and involves biotransformation via quinone and hydroxylated metabolites, and altered activities of key anti-oxidant defense enzymes such as glutathione transferases, NADH/NAD(P)H oxidoreductases, and possibly selenoproteins (Duntas, 2008; Howard, Fitzpatrick, Pessah, Kostyniak, & Lein, 2003; Y. Liu et al., 2009; Murugesan, Balaganesh, Balasubramanian, & Arunakaran, 2007; Wei et al., 2009). Many of these proteins have been directly implicated in redox regulation of RyRs.

2.1. Organization, function and dysfunction of RyR complexes

Ryanodine receptors (RyRs) and inositol 1,4,5-trisphosphate receptors (IP_3Rs) are a family of Ca^{2+} channels that are broadly expressed throughout the central and peripheral nervous systems. The distribution, structure, and function of RyRs are best understood in striated muscle where expression of RyR1 and RyR2 isoforms are essential for engaging the process of EC coupling in skeletal and cardiac muscle, respectively. In mice, targeted deletion of RyR1 results in a birth-lethal phenotype (Buck, Nguyen, Pessah, & Allen, 1997; Takeshima et al., 1994), whereas RyR2 null mice do not survive past embryonic day 9 (Takeshima et al., 1998). These phenotypes are consistent with the failure to engage EC coupling in these tissues at times critical for the animal's survival. A third isoform, RyR3, is not essential for EC coupling although it is transiently expressed in skeletal muscle during embryonic development and is down regulated in most, but not all, fibers postnatally (Conti, Reggiani, & Sorrentino, 2005; Legrand et al., 2008; Tarroni, Rossi, Conti, & Sorrentino, 1997). Targeted deletion of RyR3 does not impair muscle function or survival, but does seem to impact neurobehavioral function (Section 2.5.2).

2.2. RyRs in striated muscle

In striated muscle, RyRs channels are anchored to specialized regions of the SR of the developing myotube and adult fiber, termed junctional regions, where the SR and transverse tubule membranes approach within 10–15 nm of each other (Fig 4). In the context of these junctions, RyRs organize into tetrameric arrays or clusters that span the junctional SR-T tubule space (Di Biase & Franzini-Armstrong, 2005;Franzini-Armstrong, Protasi, & Tijskens, 2005). Each tetramer has four-fold symmetry and constitutes a functional channel of ~2.2 MDa that regulates releases of Ca^{2+} stored within the lumen of the SR into the cytoplasm.

Coordinated gating (activation and inactivation) of multiple RyR channels generates spatially limited and temporally defined release of Ca^{2+} sparks (Cheng & Lederer, 2008; Chun, Ward, & Schneider, 2003; Gonzalez et al., 2000; Gyorke, Hagen, Terentyev, & Lederer, 2007). Thus sparks represent quantal releases of Ca^{2+} from the lumen of junctional SR to a restricted area of the cytoplasm. Although spontaneous and evoked Ca^{2+} sparks are commonly observed in cardiomyocytes, smooth muscle myocytes, and invertebrate skeletal muscle, they are rarely detected in intact adult mammalian skeletal muscle under physiological conditions. The lack of sparks in mammalian skeletal muscle is likely because the L-type Ca^{2+} channel $Ca_V1.1$ confers direct negative regulation of RyR1 (E. H. Lee et al., 2004; Zhou et al., 2006). However, Ca^{2+} sparks can be readily detected in mammalian skeletal muscle under pathophysiological conditions that generate reactive oxygen species (ROS) (Martins, Shkryl, Nowycky, & Shirokova, 2008). This is not unexpected since both RyR1 and RyR2 are exquisitely sensitive

to sulfhydryl modification by compounds that generate ROS (Abramson, Zable, Favero, & Salama, 1995; Favero, Zable, & Abramson, 1995), redox cyclers, and cysteine arylators (Abramson, Buck, Salama, Casida, & Pessah, 1988; Feng, Liu, Xia, Abramson, & Pessah, 1999; J. Gao et al., 2005; Pessah et al., 2001; Pessah, Durie, Schiedt, & Zimanyi, 1990; Pessah, Kim, & Feng, 2002). Highly reactive (hyper-reactive) cysteine residues within the RyR sequence and possibly accessory proteins have been identified, and these confer redox sensing properties to the Ca^{2+} channel complex (Jurynec et al., 2008; G. Liu, Abramson, Zable, & Pessah, 1994; G. Liu & Pessah, 1994; Phimister et al., 2007; Voss, Lango, Ernst-Russell, Morin, & Pessah, 2004). Shifts in RyR activity in response to localized changes of glutathione (GSH/GSSG), nitric oxide, oxygen, and ROS appear to constitute a fundamental physiological and pathophysiological mechanism that adjusts local and global cellular Ca^{2+} signals to the changing local redox environment. The mechanisms appear to involve glutathionylation, nitrosylation, electron delocalization, and oxidation of hyper-reactive cysteines within RyR complexes (Aracena, Sanchez, Donoso, Hamilton, & Hidalgo, 2003; Aracena-Parks et al., 2006; Feng & Pessah, 2002; Sun et al., 2008; Terentyev et al., 2008; Xia, Stangler, & Abramson, 2000; Zable, Favero, & Abramson, 1997). PCBs appear to mediate toxicity, at least in part, by mechanisms involving oxidative stress (Glauert et al., 2008; Howard et al., 2003; Y. Liu et al., 2009; Lyng & Seegal, 2008). Thus, in addition to direct binding of PCBs to RyRs, PCB metabolites that possess redox active moieties, such as quinones and semiquinones (Machala et al., 2004; Spencer, Lehmler, Robertson, & Gupta, 2009), would be expected to confer additional activities toward modifying RyRs and their signaling events. In this regard, site-selective oxidation of RyRs was already demonstrated for naphthoquinones, benzoquinones, and benzo[a]pyrene 7,8-dione (Feng et al., 1999; Gao et al., 2005; Pessah et al., 2001).

As spark frequency and spatial spread of Ca^{2+} increases with physiological (e.g. plasma membrane depolarization) or pharmacological (e.g., caffeine) stimuli, Ca^{2+} waves are initiated that are capable of propagating throughout the cell in which they occur (Cheng & Lederer, 2008). Thus activation of RyRs is a means of eliciting controlled release of SR Ca^{2+} stores and is a major source of both local and global Ca^{2+} signals that are essential for regulating contractility of striated and smooth muscle.

2.2.1. Could non-coplanar PCBs alter RyR function in striated muscle?—Skeletal and cardiac muscle represent major organs for the initial disposition of PCBs following exposure (Matthews & Anderson, 1975; Matthews & Tuey, 1980; Birnbaum, 1983; Brandt, Mohammed & Slanina, 1981). Muscle tissues are therefore considered critical compartments when formulating physiologically based pharmacokinetic models that faithfully reproduce tissue: blood partitioning (Pharam, Kohn, Matthews, DeRosa & Protier, 1997). A recent study of Galapogos sea lions identified the congener profile of PCBs found in muscle biopsies (Alava et al., 2009). Results from this study indicate that the 10 most active congeners identified based on [^{3}H]ryanodine binding analysis (Fig. 2) represented nearly 25% of the total PCB burden found in muscle (Avala et al, 2009). In rodents exposed to PCB 136, the low-dose group displayed significantly higher PCB levels in cardiac and skeletal muscle compared to other tissues, such as adipose tissue and the liver (Kania-Korwel et al., 2008).

Surprisingly, if and how non-coplanar PCBs modify the properties of striated muscle EC coupling has only recently been examined. The physical interactions between $Ca_V1.1$ and RyR1 that trigger skeletal muscle EC coupling provide a relevant experimental model for testing whether non-coplanar PCBs can impair the fidelity of this otherwise tight form of conformational coupling between two Ca^{2+} channels. The amplitude of Ca^{2+} transients in mouse embryonic myotubes elicited by low frequency (0.1 Hz) electrical pulses was significantly enhanced within 2.5 min after initiating perfusion of 5 μM PCB 95 in the external medium compared to the solvent control, and PCB 95 prevented recovery of the Ca^{2+} signal

to its original baseline (Fig 5A&B) (Cherednichenko & Pessah, in review). When higher frequency electrical pulse trains were evoked (2.5 and 5 Hz), PCB 95 not only amplified Ca^{2+} transient amplitudes but also caused ectopic Ca^{2+} transients immediately after electrical stimuli were suspended (arrows, Fig 5C), and these were not observed in the absence of PCB. How non-coplanar PCBs and related structures influence the coupling between RyRs and plasmalemmal Ca^{2+} channels (Fig 4), and their direct impacts on skeletal and cardiac muscle function clearly needs more attention.

2.2.2. RyR associations with plasma membrane proteins—Over the last 15 years major advances have been made in understanding how RyR structure relates to function and identifying key accessory proteins that regulate activation and inhibition of Ca^{2+} release from ER/SR stores. Most of our understanding comes from studies of RyR1 in skeletal muscle and RyR2 in cardiac muscle where they assemble in macromolecular complexes termed Ca^{2+} release units (CRUs). The central component of the CRU is the RyR homotetramer, with a small C-terminal transmembrane assembly anchored within the membrane and a massive cytoplasmic ("junctional foot") assembly spanning the T-tubule SR junction (Di Biase & Franzini-Armstrong, 2005; Franzini-Armstrong et al., 2005) (Fig 4). Although the composition of key proteins comprising the CRUs of skeletal and cardiac muscle are strikingly similar (Fig 3), skeletal muscle does not require Ca^{2+} entry through the L-type voltage gated Ca^{2+} channel ($Ca_V1.1$) to trigger activation of RyR1 and SR Ca^{2+} release. Rather, $Ca_V1.1$ and RyR1 physically interact such that four $Ca_V1.1$ subunits in the T-tubule membrane orient over every second RyR1 anchored to the junctional SR. This structural arrangement engages a form of bidirectional signaling in which T-tubule depolarization is sensed by the S4 segment of $Ca_V1.1$ and transmitted to RyR1 through conformational shifts of the "critical domain" (residues 720–765 of $Ca_V1.1$) residing within the cytoplasmic loop between repeats II and III (Grabner, Dirksen, Suda, & Beam, 1999). RyR1 transmits a retrograde signal to not only enhance L-type Ca^{2+} entry current (Fleig, Takeshima, & Penner, 1996; Nakai et al., 1996; Sheridan et al., 2006), but also affect precise alignment of $Ca_V1.1$ and associated subunits into tetradic arrays within the T-tubule membrane (Protasi, Franzini-Armstrong, & Allen, 1998). In myotubes and some adult fibers, retrograde signaling from RyR1 to CaV1.1 appears to be essential for preventing decrement and ultimate failure of EC coupling during prolonged high frequency (tetanic) electrical pulse trains, through a process termed excitation-coupled Ca^{2+} entry (ECCE) (Cherednichenko, Hurne et al., 2004).

Initial results using pharmacological tools indicated that $Ca_V1.1$ was the voltage sensor that triggers ECCE, and that the L-type Ca^{2+} channel was unlikely to constitute the Ca^{2+} conduction pathway for ECCE. More recent evidence indicates that the L-type channel is a major contributor to ECCE (Bannister, Pessah, & Beam, 2009). Pharmacological agents that influence conformational states of RyR1 influence electrophysiological properties of the L-type Ca2+ current and ECCE in similar ways. For example, experimental conditions that permit the alkaloid ryanodine to lock RyR1 channels in a persistently closed (non-conducting) conformation (Zimanyi, Buck, Abramson, Mack, & Pessah, 1992) also causes significant reduction in the inter-tetrad distances of the $Ca_V1.1$ complex (Paolini, Fessenden, Pessah, & Franzini-Armstrong, 2004) and influences the activation-deactivation kinetics of ECCE (Bannister et al., 2009; Cherednichenko, Hurne et al., 2004). Importantly, missense mutations that affect RyR1 function can dramatically alter the properties of both orthograde and retrograde signaling, modifying channel functions on both side of the junction (Andronache, Hamilton, Dirksen, & Melzer, 2009; Bannister et al., 2009; Cherednichenko et al., 2008; Hurne et al., 2005; T. Yang, Allen, Pessah, & Lopez, 2007).

In contrast to skeletal muscle, conformational coupling between L-type Ca^{2+} channels ($Ca_V1.2$) and RyR2 is not sufficient to trigger EC coupling in the absence of Ca^{2+} entry across the T-tubular membrane in cardiomyocytes. Rather tight functional coupling between L-type

Ca^{2+} entry mediated by $Ca_V1.2$ channels within the T-tubule membrane and RyR2s occurs across narrow 12 nm junctions through the process of Ca^{2+}-induced Ca^{2+} release (CICR) (Bers, 2008). Depolarization of the T-tubule membrane triggers $Ca_V1.2$-mediated localized Ca^{2+} influx (termed sparklets) that in turn triggers RyR2-mediated sparks immediately across the junctional space. Depending on the intensity of stimuli arriving at the T-tubule membrane and other local "environmental" factors that influence RyR2 activity (e.g., phosphorylation state), summation of sparks can produce local and propagated Ca^{2+}waves through the process of CICR (Cheng & Lederer, 2008).

In addition to interactions with voltage-gated channels ($Ca_V1.1$ and $Ca_V1.2$) as described above, RyRs have been shown to directly or indirectly interact with and regulate the function of store-operated Ca^{2+} channels (SOCCs) in some, but not all muscle tissues examined. For example, the transient receptor protein channels TrpC3 (Kiselyov et al., 2000; E. H. Lee, Cherednichenko, Pessah, & Allen, 2006; Woo et al., 2009), TrpM4 (Morita et al., 2007), and TrpV4 (Earley, Heppner, Nelson, & Brayden, 2005) were shown to interact with RyR complexes. However, Trp-RyR interactions may not be the major mechanism responsible for store-operated Ca^{2+} entry (SOCE) in skeletal muscle. Knockdown of STIM and Orai, the essential components of the Ca^{2+}-release activated Ca^{2+} current (I_{CRAC}), greatly suppresses SOCE in skeletal muscle cells without impairing ECCE (Lyfenko & Dirksen, 2008), and SOCE is not dependent on RyR1 expression (Cherednichenko, Hurne et al., 2004; Lyfenko & Dirksen, 2008). However, STIM was recently shown to gate TrpC channels by electrostatic interaction (Zeng et al., 2008).

Homer is a family of proteins shown to regulate signal transduction, synaptogenesis, and receptor trafficking in neurons (Szumlinski, Kalivas, & Worley, 2006; Xiao, Tu, & Worley, 2000). Both short and long forms of Homer interact with RyR1 and RyR2 and regulate channel function in an additive biphasic manner that is highly dependent on their relative concentration, but is independent of multimerization *via* the coiled-coil domains found in Homer long-forms (Feng et al., 2008; Feng et al., 2002; Pouliquin, Pace, & Dulhunty, 2009; Ward et al., 2004). As demonstrated earlier in neurons where Homer links IP_3R responses to mGluR1 signaling, Homer may also play a scaffolding function in striated muscle linking RyR1 and RyR2 to CaV1.1 or CaV1.2, respectively, to regulate the gain of EC coupling (G. Huang et al., 2007; Pouliquin et al., 2009). In skeletal muscle, Homer appears to also link TRPC (Trp or TRP??) channels to the cytoskeletal matrix and function to regulate mechanotransduction (Stiber et al., 2008).

Three important consequences of co-localization and functional coupling of RyRs with Ca^{2+} channels residing in the surface membrane include: (1) it permits local signaling microdomains; (2) it confers a mechanism for reciprocal regulation between channels in the plasma membrane and RyRs anchored within the SR/ER membrane; and (3) it provides direct feedback about the state of Ca^{2+} filling within the SR/ER lumen. Thus chemical agents that interact with RyR and alter its conformation and function are likely to influence not only the properties of Ca^{2+} release from stores, but also Ca^{2+} entry through SOCE and ECCE mechanisms.

2.2.3. RyR associations with cytoplasmic proteins—Two T-cell immunophilins, FK506 binding protein 12 kDa (FKBP12) and its isoform FKBP12.6 (also referred to as calstabins 1 and 2) can tightly bind to RyR1 (Jayaraman et al., 1992) and RyR2 (Timerman et al., 1996). Although up to four FKBPs can bind per functional RyR channel (one per subunit), the ratio of FKBP isoform/RyR is likely to vary according to tissue and with changing physiological or pathophysiological states (Lehnart, 2007; Zalk, Lehnart, & Marks, 2007). Cryo-electron microscopy (EM) reconstruction of frozen hydrated RyR1 tetramers revealed that FKBP12 binds adjacent to cytoplasmic domain 9 of the clamp region complex (Samso, Shen, & Allen, 2006; Serysheva et al., 2008; Wagenknecht et al., 1997) (Fig. 6A, top view of

cytoplasmic “foot” domain). Mutagenesis studies with RyR1 suggest essential contributions of Val-2461-Pro-2462 (corresponding RyR2 residues Ile-2427-Pro-2428) in the binding interaction (Gaburjakova et al., 2001), but the N-terminal residues 305-1937 of RyR2 may also contribute to binding FKBP12.6 (Masumiya, Wang, Zhang, Xiao, & Chen, 2003). Since the first report that FKBP12 stabilizes the functional behavior of RyR1 (Brillantes et al., 1994), disruption of FKBP12/12.6 RyR complexes has been associated with heritable and acquired disorders of cardiac (Gyorke & Carnes, 2008; Zalk et al., 2007), and skeletal (Bellinger, Mongillo, & Marks, 2008; Bellinger et al., 2009) muscle.

PCB-triggered Ca^{2+} release form junctional SR membrane vesicles isolated from skeletal muscle can be selectively negated by pretreatment with either the immunosuppressive drug FK506 or rapamycin (Fig 6B) without inhibiting responses to other RyR1 channel activators such as caffeine (Wong & Pessah, 1997). FK506 and rapamycin tightly bind to the greasy binding pocket of FKBP12 promoting dissociation of the FKBP12/RyR1 complex and possibly preventing rebinding. Rapamycin and FK506 interfere with the actions of PCB 95 (and other active PCBs) in the same concentration range that promotes the dissociation of the FKBP12/RyR1 complex, suggesting that PCBs interact with a binding site formed at the FKBP12/RyR1 complex interface to enhance channel open probability (Fig 6A). However, an allosteric mechanism has not been ruled out.

Nevertheless, the molecular mechanism by which PCB 95 affects the RyR1/FKBP12 is mediated by direct stabilization of the channel in the full open state (Fig 7). Samso and coworkers (2009) recently utilized PCB 95 to better understand the basis for RyR1 conformational transitions between closed and open states. Single-channel biophysical characterization of the two states in bilayer lipid membranes (Fig 7, left and middle panels) and cryoelectron microscopy of frozen single-particles in their hydrated state (Fig 7 right panel) were performed on identical samples and conditions to permit direct correspondence between biophysical state and structural conformation of the channel. PCB 95 appears to invert the thermodynamic stability of the RyR1/FKBP12 channel complex producing extremely long-lived openings interspersed with extremely short-lived transitions to the closed state, although the unitary current is indistinguishable from the native open state. By contrast, the presence of very low Ca^{2+} on the cytoplasmic side ($pCa^{2+}<10^8$ set in the presence of the Ca^{2+} chelator EGTA) after fusion of an actively gating channel completely stabilized the fully closed state of the channel. The corresponding three-dimensional structures at ~10Å resolution provided information about the structure surrounding the ion pathway indicating the presence of two right-handed bundles emerging from the putative ion gate (the cytoplasmic “inner branches” and the transmembrane “inner helices”) (Samso et al., 2009). The PCB 95 modified state causes a precise relocation of the inner helices and inner branches resulting in an approximately 4Å increase in diameter of the ion gate (Fig 7, right panel). Six of the identifiable transmembrane segments of RyR1 have similar organization to those of the mammalian Kv1.2 potassium channel. Upon gating to the PCB 95-induced open state, the distal cytoplasmic domains move towards the transmembrane domain while the central cytoplasmic domains move away from it, and also away from the fourfold axis (Samso et al., 2009).

Similar FKBP12/RyR1 dependent Ca^{2+} release and direct activation of RyR1 channels have been demonstrated with bastadin-5 (Fig 8) and bastadin-10, two members of a family of over 20 bromotyrosine-derived macrolactams that have been isolated from the Verongid marine sponges *Ianthella sp.* (L. Chen, Molinski, & Pessah, 1999;Mack, Molinski, Buck, & Pessah, 1994). Like PCB 95, bastadin-10 (B10) dramatically stabilizes the open conformation of the RyR1 channel, possibly by reducing the free energy associated with closed to open channel transitions. The stability of the channel open state induced by B10 sensitized the channel to activation by Ca^{2+} to such an extent that it essentially obviated regulation by physiological concentrations of Ca^{2+} and relieved inhibition by physiological Mg^{2+}. These actions of B10

were produced only on the cytoplasmic face of the channel, were selectively eliminated by pretreatment of channels with FK506 or rapamycin, and were reconstituted by exogenous addition of human recombinant FKBP12. Bastadin-10 dramatically enhances spark frequency and duration in adult frog skeletal muscle fibers (Gonzalez et al., 2000), whereas bastadin-5 was shown to influence both resting Ca^{2+} and caffeine-evoked transients in cultured myotubes (Pessah et al., 1997;T.Yang, Esteve et al., 2007). The reduced pharmacophore that confers RyR activity resides within the 'eastern' and 'western' non-coplanar bromocatechol ether moieties that resemble hydroxylated brominated diphenylethers defined by the dashed boxes in Figure 8 (Masuno, Pessah, Olmstead, & Molinski, 2006).

The widely used antibacterial triclosan, a non-coplanar chlorocatechol ether (Fig 8), was shown to activate RyR1 and mobilize Ca^{2+} from SR stores of intact primary skeletal myotubes (Ahn et al., 2008). Both non-coplanar PCBs and bastadins also enhance RyR2 activity although the requirement for FKBP12.6 has not been reported.

Calmodulin (CaM) and S100A1 are two widely expressed Ca^{2+} binding proteins that interact with RyR1 and RyR2 isoforms in a Ca^{2+}-dependent manner. Both proteins appear to compete with a common conserved site within the clamp domains corresponding to residues 3614-3643 (Wright et al., 2008). Although ApoCaM can enhance RyR activity, it is thought that Ca^{2+}-CaM provides the major physiological regulatory role, inhibiting RyR channel activity as local Ca^{2+} concentration rises (Meissner, 2002). By contrast Ca^{2+}-S100A1 stimulates RyR channel activity. Competition between Ca^{2+}-CaM and Ca^{2+}-S100A1 on RyRs has been proposed to confer tight but dynamic regulation of EC coupling gain with temporal changes in local Ca^{2+} concentration in skeletal and cardiac muscle (Wright et al., 2008). PCB 95 and bastadin-5 and 10 were shown to dramatically shift the Ca^{2+} dependence of RyR1 channel activation and inhibition independently of exogenously added CaM or SA1001A (L. Chen et al., 1999; P. W. Wong & Pessah, 1996). Whether these compounds shift the dynamic regulation mediated through CaM and S100A1 remains to be investigated.

The Ca^{2+} binding protein sorcin and presenilin 2 (PS2) are ubiquitously expressed in various tissues including neurons and cardiomyocytes and each has been demonstrated to influence RyR function. Sorcin interacts with the C-terminal endoproteolytic fragment of PS2 in a Ca^{2+} dependent manner, but not with full-length PS2 (Pack-Chung et al., 2000), but the interaction may not be essential for modulation of RyR. In heart tissues, PS2 was shown to physically interact with RyR2. Papillary muscle PS2 knockout mice display enhanced peak amplitudes of Ca^{2+} transients and peak tension compared to wild type (Takeda et al., 2005). Sorcin inhibits Ca^{2+} channel activity and attenuates spark activity and was proposed to contribute a physiological means for terminating Ca^{2+} induced Ca^{2+} release in cardiac muscle (Farrell et al., 2004; Farrell, Antaramian, Rueda, Gomez, & Valdivia, 2003; Stern & Cheng, 2004).

At least three Ser residues within the junctional foot assembly of RyR1 (Ser 2844) and RyR2 (Ser 2808, Ser 2814, Ser 2030), can be phosphorylated by PKA (Aydin et al., 2008; Wehrens et al., 2006), Ca^{2+}-CaM kinase II (Currie, Loughrey, Craig, & Smith, 2004; Huke & Bers, 2008) and possibly PKC (Takasago, Imagawa, Furukawa, Ogurusu, & Shigekawa, 1991). Evidence that the scaffolding protein mAKAP tethers PKA in close proximity to protein phosphatase A1 and A2 (PPA1 and PPA2) within the RyR2 complex, possibly through a leucine/isoleucine zipper (LIZ) motif, suggests tight regulation of RyR2 phosphorylation in response to changes in cellular cAMP, such as those that normally occur with β-adrenergic stimulation (Marks, Marx, & Reiken, 2002; Marx et al., 2001). However, RyR phosphorylation is complex in both striated muscle and neurons, and appears to be dynamically regulated with shifting physiological and pathophysiological states (Dai et al., 2009; Zalk et al., 2007).

Altered patterns of RyR phosphorylation are associated with changes in RyR nitrosylation, glutathionylation, and depletion of FKBP12/12.6 from its binding site located within the clamp region. Importantly these changes have been strongly implicated in the etiology of several heritable and acquired disorders of striated muscle, including malignant hyperthermia susceptibility (MHS) and central core disease (CCD) (Durham et al., 2008), Duchenne muscular dystrophy (Bellinger et al., 2009), catecholaminergic polymorphic ventricular tachycardia (CPVT), arrhythmogenic right ventricular dysplasia type 2 (ARVD2), and ischemic heart failure (Blayney & Lai, 2009). Over 120 missense or deletion mutations within RyR1 have been associated with MHS, central core disease (CCD) and/or multiminicore disease (MmD) in skeletal muscle (R. Robinson, Carpenter, Shaw, Halsall, & Hopkins, 2006). Nearly 25 mutations have been identified within RyR2 that contribute to CPVT (Gyorke, 2009; N. Liu, Rizzi, Boveri, & Priori, 2009). Significant increases in RyR Ser phosphorylation and Cys nitrosylation have been associated with an increased Ca^{2+} leak through RyR channels carrying a few of these mutations and these can markedly reduce the Ca^{2+} content of the ER/SR lumen. RyR mutations also alter the fidelity of ECCE (Cherednichenko et al., 2008; T. Yang, Allen et al., 2007) perhaps further compounding SR Ca^{2+} depletion. Whether hyper-phosphorylation, nitrosylation, and/or glutathionylation of RyRs with mutations are common convergence points of CRU dysfunction and progression of these diverse disorders is currently being intensely investigated. Of relevance to the toxicity of PCBs and related chemicals that alter the function of RyRs, it should be noted that RyR mutations may remain phenotypically silent or subclinical until triggered by one or more environmental exposures or stressors. Recently, changes in the phosphorylation state (at Ser 2808 and Ser 2814) were associated with functional impairments in cardiac RyR2 channels in the streptozotocin-induced model of type 1 diabetes (Shao et al., 2009).

Several enzymes and proteins involved in regulating cellular redox status have been also demonstrated to directly regulate RyR channel activity. The *mu* isoform of glutathione-s-transferase (GST *mu*) was shown to promote inactivation of RyR1 and RyR2, whereas its distant relative CLIC-2 that functions as a chloride channel appears to selectively attenuate the activity of RyR2 in the presence of a GSH:GSSG redox buffer (Abdellatif et al., 2007; Jalilian, Gallant, Board, & Dulhunty, 2008; Meng et al., 2009). Selenoprotein N (SepN) is physically associated with RyR1 of skeletal muscle and it appears to be essential for conferring regulation of RyR1 channels by GSH:GSSG redox potential (Jurynec et al., 2008). Importantly the absence of SepN in skeletal muscle appears to contribute to a subset of congenital myopathies and altered redox regulation of RyR1 has been implicated in their etiology.

NAD(P)H oxidases are major sources of superoxide generation in myocytes, especially during arrhythmia and after acute myocardial infarction. For example tachycardia augments the association of the NAD(P)H oxidase cytosolic subunit p47phox to the SR fraction, without modifying the content of the membrane integral subunit gp91phox (Sanchez, Pedrozo, Domenech, Hidalgo, & Donoso, 2005). The enzymatic oxidation of NADH is tightly linked with negative regulation of RyR2 channel activity in cardiac myocytes. Inhibition of NADH oxidase activity with nanomolar rotenone or pyribaben relieves this negative regulation and increases RyR2 channel activity, spark frequency, and Ca^{2+} oscillations in cardiomyocytes (Cherednichenko, Zima et al., 2004).

RyRs are emerging as a central integrator of not only physiological signals, but also of pathophysiological responses to oxidative stress that may arise from mutations in the RyR proteins themselves, their accessory proteins, metabolic imbalances, or insults from xenobiotic chemicals such as PCBs. Whether RyR-active PCBs and related non-coplanar structures influence the phosphorylation, nitrosylation, and/or glutathionylation state of the receptor complex has not been explored.

2.2.4. RyR associations with integral and luminal SR proteins—Within the junctional SR sacks of cardiac and skeletal muscle, RyRs form a protein complex with triadin and junctin (which are anchored within the membrane), and calsequestrin that resides within the SR lumen (Guo, Jorgensen, & Campbell, 1996; G. Liu & Pessah, 1994). Ultrastructural and biochemical evidence supports a model in which triadin and junctin interact directly with RyRs and may act to scaffold calsequestrin (a low affinity SR Ca^{2+} binding protein) near the RyR lumen to control the availability of Ca^{2+} near RyRs thereby providing luminal control (feedback) to the CRU about the local filling state of the Ca^{2+} store (Beard, Wei, & Dulhunty, 2009). Ablation of either triadin or calsequestrin expression in heart results in CPVT. Both PCBs and bastadins were shown to influence the balance of regulated RyR1 channels (i.e., those sensitive to ryanodine) and their ryanodine-insensitive "leak" states in isolated SR and BC3H1 cells, possibly by converting low conductance leak states into high conductance channel states (Pessah et al., 1997; P. W. Wong & Pessah, 1997). More recently, bastadin 5's ability to convert ryanodine insensitive Ca^{2+} leak to ryanodine sensitive channels was shown to lower resting free Ca^{2+} in intact myotubes expressing wild type RyR1 and those expressing MH susceptibility mutations, but only in the presence of RyR1 channel blockers (ryanodine or FLA 365) (T. Yang, Esteve et al., 2007). In this regard, myotubes with MH mutations have significantly higher resting intracellular Ca^{2+} levels than those expressing wild type RyR1, and the reductions afforded by bastadin 5 in the presence of ryanodine are significantly greater (Fig 9).

Junctophilins are integral ER/SR proteins that form non-covalent interactions with membrane lipids through their MORN (*m*embrane *o*ccupation *r*ecognition *n*exus) motifs, and are primarily responsible for stabilizing close apposition of the junctional regions SR/ER and the plasmalemma in both muscle cells and neurons (Kakizawa, Moriguchi, Ikeda, Iino, & Takeshima, 2008; Takeshima, Komazaki, Nishi, Iino, & Kangawa, 2000). Junctophilins are therefore essential for creating a specialized milieu that permits the large junctional foot assembly of RyRs to physically and functionally interact with proteins in the plasma membrane. The importance of proper assembly of junctional assembly has been recently underscored in mice with targeted deletions or mutations in junctophilins. Deletion of junctophilin isoform 1 (JP1), the major form expressed in skeletal muscle, results in weak EC coupling and contractile failure that is lethal shortly after birth (Ito et al., 2001). The lack of JP1 may also negate critical aspects of channel regulation because JP1 and RyR1 interact in a confomationally sensitive manner that involves hyper-reactive Cys residues (Phimister et al., 2007). Deletion of junctophilin isoform 2 (JP2), the major form in cardiac muscle functionally uncouples $Ca_V1.2$ and RyR2 and is embryonic lethal due to contractile failure, whereas 5 missense mutations are associated with hypertrophic cardiomyopathy in humans (Landstrom et al., 2007; Matsushita et al., 2007).

Mice lacking neural junctophilins (JP3 and JP4) exhibit impaired exploratory behavior in the open-field task, and impaired performance in the Y-maze and multiple-trial passive avoidance tests indicating impaired short- and long-term memory (Moriguchi et al., 2006). Ablation of JP3 and JP4 uncouples functional interactions among NMDA receptors, ryanodine receptors, and small-conductance Ca^{2+}-activated K^+ channels activation. These results reveal that activation of small-conductance Ca^{2+}-activated K^+ channels, which is necessary for afterhyperpolarization in hippocampal neurons, requires Ca^{2+} release through RyRs, and is triggered by NMDA receptor-mediated Ca^{2+} influx. Junctophilins stabilize close apposition of "junctional" postsynaptic membranes that permit crosstalk between RyRs and their signaling partners in the plasma membrane. These observations reveal the essential role of RyRs in mediating changes in synaptic plasticity (Kakizawa et al., 2008). These newly discovered mechanisms might be directly relevant to how PCBs mediate neurotoxicity.

2.3. Structure-activity of PCBs toward RyR1 and RyR2

Non-coplanar PCBs were shown to potently and selectively sensitize both RyR1 and RyR2 channel activities in studies with SR membranes isolated from mammalian skeletal and cardiac muscle, respectively, using radioligand binding studies with [^{3}H]ryanodine ([^{3}H]Ry) and macroscopic Ca^{2+} flux measurements across isolated SR membrane vesicles (P. W. Wong & Pessah, 1996). [^{3}H]Ry binds to RyR1 with high selectivity and specificity only to an activated conformation of RyRs, thereby providing a rapid and quantitative method for screening chemicals that enhance or inhibit channel activity (Pessah, Stambuk, & Casida, 1987; Pessah, Waterhouse, & Casida, 1985). Figure 10 (left panel) highlights two important aspects of the PCB structure-activity relationship towards RyR1: (1) chlorine substitutions at the *ortho*-positions which restrict the biphenyl rings to non-coplanarity; and (2) the contribution of *para*-substituents which can reduce or eliminate activity. For example PCB 126, one of the most potent PCB congeners toward the arylhydrocarbon hydroxylase (Ah) receptor, lacks activity toward RyR1 at its solubility limits. In general, PCBs lacking at least one *ortho*-substitution are inactive toward RyR1 and RyR2, regardless of the degree of chlorination. A similar structure-activity profile applies for activation of RyR2 channels isolated from cardiac muscle (P. W. Wong & Pessah, 1996),

ER preparations isolated from adult cerebellum, hippocampus or cortex contain all three RyR isoforms, although RyR1 and RyR2 predominate (P. W. Wong, Brackney, & Pessah, 1997). Of the congeners assayed on ER preparations from brain, noncoplanar PCB 95 exhibited the highest potency toward activating high affinity [^{3}H]Ry binding, whereas mono-*ortho* PCB 66 (2,3,4,4′-tetrachlorobiphenyl) and PCB 126 were inactive. Ca^{2+} transport measurements made with cortical ER vesicles revealed that PCB 95 discriminates between inositol 1,4,5-trisphosphate- and ryanodine-sensitive stores, and PCB 95 induced Ca^{2+} was dose-dependent and completely inhibited by ryanodine receptor blockers (P. W. Wong, Brackney et al., 1997).

A more detailed structure-activity analysis was completed with RyR1. Figure 2 shows a ranking of the 28 most active congeners of 35 tested based on the concentration required to double [^{3}H]Ry binding activity to RyR1 (Pessah et al., 2006). Many of these are found in environmental and human samples and collectively they can comprise up to 50% of the total PCB burden. PCB 95 and PCB 136 and (2,2′,3,3′,6,6′-hexachlorobiphenyl) share asymmetric chlorine substitutions on the phenyl rings (2,3,6 and 2′,3′,6′ for PCB 136 *vs.* 2,3,6 and 2′,5′ for PCB95) and both are racemic mixtures of two atropisomers (see below). The 2′,5′-Cl configuration of PCB 95 is equivalent to a 3′6′-Cl configuration of PCB 136 (i.e. 2,3,6,2′,5′ *vs.* 2,3,6,3′,6′) assuming a calculated dihedral angle of ~90° based on the crystal solution of PCB 84 (Lehmler, Robertson, & Parkin, 2005). The 2,3,6-Cl configuration on one ring with *ortho*, *meta* on the other is optimal for recognizing a binding site within the RyR1 complex and for sensitizing channel activation. *Para*-chloro substitution lowers the maximum efficacy towards RyR1 regardless of the presence of one or more *ortho*-substitutions. Comparing the relative activities of PCB 30 and PCB 75 (2,4,6,4′-tetrachlorobiphenyl), the additional *para*-Cl-substitution completely eliminates activity towards RyR1. Thus complete lack of activity observed here with PCB 75 is likely due to the di-*para*-chloro substitution. In general, PCB structures possessing 4,4′-Cl exhibit lower activity towards RyR1, regardless of the presence of one or more *ortho*-substitutions (Pessah et al., 2006). Hydroxylated PCBs are appearing in human tissues and there is currently great interest in determining whether these metabolites are more biologically active than the corresponding parent structures (Fernandez et al., 2008;Y. Liu et al., 2009; . J. S Park et al., 2008;Park, Petreas, Cohn, Cirillo, & Factor-Litvak, 2009). The 4-OH derivative of PCB 30 (4′OH-PCB 30) was found to be significantly more active toward RyR1 than the parent PCB 30 (2,4,6-Cl) (Fig 10, right panel). Thus a *para*-OH group on the phenyl ring that carries no other deactivating substitution confers potency and

efficacy towards activating RyR1. Two possible mechanisms could be responsible. First, the acidic property of the lone phenyl-OH substituent is likely to contribute hydrogen-bonding potential to stabilize interactions with the receptor site. Alternatively, if the hydroxyl group is partially or wholly ionized, then electrostatic interactions would be expected to stabilize the PCB-RyR1 complex. In support of this interpretation, the di-OH derivative of PCB30, 3′,4′-di-OH,2,4,6-PCB, was found to possess lower potency but similar efficacy to PCB 30. The presence of two adjacent –OH moieties would be expected to promote intramolecular hydrogen bonding and could preclude stabilizing interactions with RyR1 that impact the apparent affinity and efficacy for channel activation (Pessah et al., 2006). There is an excellent correlation (r^2 =0.87) between the initial rate of PCB-induced Ca^{2+} efflux and the concentration needed to increase [^{3}H]Ry binding by two fold, a measure of potency (Fig 11), and PCB-induced Ca^{2+} release from ER/SR membrane without inhibiting the SR/ER Ca^{2+}-ATPase (SERCA pump). Moreover, the release can be completely inhibited by prior block of RyR channels with ryanodine or ruthenium red, suggesting a selective receptor mediated mechanism is responsible.

2.3.1. Enatioselectivity of Chiral PCBs toward RyRs—Nineteen of the possible 209 polychlorinated biphenyl (PCB) structures exist as pairs of atropisomers (also referred to as enantiomers) that are sufficiently stable to permit separation by gas or liquid chromatography using chiral column matrices (Haglund, 1996). Stable enantiomeric PCB structures have unsymmetrical chlorine substitutions in their respective phenyl rings and possess ≥3 chlorine atoms in the *ortho*-positions that restrict the degree of rotation about the biphenyl bond. Evidence of enantioselective enrichment of PCB atropisomers in environmental samples (Asher et al., 2007; Pessah, 2001; Jamshidi, Hunter, Hazrati, & Harrad, 2007; Robson & Harrad, 2004; C. S. Wong, Garrison, Smith, & Foreman, 2001; C. S. Wong et al., 2004; C. S. Wong et al., 2007), food (Bordajandi & Gonzalez, 2008; Bordajandi, Ramos, Sanz, Gonzalez, & Ramos, 2008; Bordajandi, Ramos, & Gonzalez, 2005), as well as biological tissues from animals (Chu, Covaci, Van de Vijver et al., 2003; Kania-Korwel, Hornbuckle, Robertson, & Lehmler, 2008a, 2008b; Kania-Korwel, Shaikh, Hornbuckle, Robertson, & Lehmler, 2007) and humans (Chu, Covaci, & Schepens, 2003; Harrad et al., 2006) are being widely reported. Recently (−) PCB 136 was shown to directly sensitize activation of RyR1 and RyR2, whereas (+) PCB 136 did not when assayed at either 25 or 37°C (Pessah et al., 2009) (Fig 12). (−) PCB 136 rapidly mobilized SR Ca^{2+} stores by activating RyR1 in the presence of low (resting) levels of cytoplasmic Ca^{2+}, and (+) PCB 136 failed to competitively inhibit the actions of (−) PCB 136. The mechanism by which (−) PCB 136 promotes RyR activity is to coordinately stabilize the open, while destabilizing the closed, states of the RyR1 channel.

The enantiospecificity of (−) PCB 136 indicates that the spatial configuration of the chlorine substitutions about the biphenyl is significantly more important than the overall physicochemical properties of the PCB for optimizing interactions with RyRs and implies a highly ordered binding interaction between active PCBs and their site(s) of interaction within RyR complexes. It is interesting to note that the four most active PCBs toward RyR thus far tested are chiral (Figs 2 & 11) although the degree of enantiospecificity toward sensitizing RyR activity may vary (Lehmler, Robertson, Garrison, & Kodavanti, 2005;Pessah et al., 2009).

2.4. RyRs in smooth muscle

All three RyR isoforms are expressed in smooth muscle myocytes (McGeown, 2004). The patterns of RyR isoform expression and their contribution to smooth muscle contractility differ among specific organs in which they are found including vascular, urinary bladder, ureter, airway and the gastrointestinal track (Cheng & Lederer, 2008; McGeown, 2004). RyRs also localize to regions of SR that are in close proximity (≤ 100 nm) to the plasma membrane of a variety of smooth muscle myocytes where they are responsible for generating spontaneous and

depolarization evoked CICR (Gollasch et al., 1998; Lesh et al., 1998). The patterns of expression of RyR isoforms is highly dependent on the type of smooth muscle and multiple isoforms can be expressed within a smooth muscle cell (Chalmers, Olson, MacMillan, Rainbow, & McCarron, 2007). For example, recent RT-PCR results have indicated that RyR2 and RyR3 are expressed in cultured myocytes from rat mesenteric artery (Berra-Romani, Mazzocco-Spezzia, Pulina, & Golovina, 2008) or vas deferens (Ohno, Ohya, Yamamura, & Imaizumi, 2009), although the ratio of the two isoforms can change with proliferation. In contrast, uterine smooth muscle expresses two splice variants of RyR3 that are differentially expressed in nonpregnant and pregnant myometrium, although their functional significance has been recently questioned (Noble, Matthew, Burdyga, & Wray, 2009). It appears that expression of a functional long form of RyR3 is responsive to caffeine and cADP ribose, whereas expression of a non-functional short form can inhibit the function of the long-form when they are concomitantly expressed (Dabertrand, Fritz, Mironneau, Macrez, & Morel, 2007). At the end of pregnancy, the relative expression of RyR3 long form appears to increase suggesting physiological regulation of RyR3 alternative splicing may be important in regulating uterine contractility at the end of pregnancy.

In smooth muscle that undergoes action potential driven phasic contraction (e.g., smooth muscle of the uterer, the periodicity of Ca^{2+} sparks appear to be functionally coupled to pacemaker ionic currents that, collectively, set the rhythm of the firing of action potentials (Burdyga & Wray, 2005; S. Q. Wang et al., 2002; Wray, Burdyga, & Noble, 2005). By contrast, RyRs expressed in arterial and urinary bladder smooth muscles are co-localized with and tightly coupled to large conductance Ca^{2+}-activated potassium channels (BK_{Ca}) that mediate spontaneous outward currents (STOCs) (Herrera & Nelson, 2002; Jaggar et al., 1998; Nelson et al., 1995; Perez, Bonev, Patlak, & Nelson, 1999). Voltage-activated Ca^{2+} entry into arterial smooth muscle is primarily responsible for enhancing tone. However, an important consequence of the co-localization and tight functional coupling between RyRs and BK_{Ca} is that activation of sub-plasmalemmal RyR-mediated Ca^{2+}-induced Ca^{2+} release efficiently enhances STOCs thereby hyperpolarizing the surface membrane and shutting off voltage-dependent Ca^{2+} entry (Nelson et al., 1995). Therefore, activation of RyRs play a pivotal physiological role in arterial smooth muscle relaxation and the abnormal RyR-BK_{Ca} coupling have been shown to cause hypertension and left ventricular hypertrophy (Amberg, Bonev, Rossow, Nelson, & Santana, 2003; Brenner et al., 2000; Pluger et al., 2000).

2.4.1. Cellular toxicity of PCBs to smooth muscle—Exposure of uterine smooth muscle cells isolated from gestation day 10–pregnant rats to non-coplanar PCB 4 (2,2′-dichlorobiphenyl) was shown to inhibit contractility and synchronization (Chung & Loch Caruso, 2005). These effects on contractility were initially attributed to MAPK-mediated phosphorylation of connexin 43 that resulted in inhibition of myometrial gap junctions. However, additional studies revealed that antioxidants could reverse the inhibitory influence of PCB on contraction and synchronicity without restoring gap junction function (Chung & Caruso, 2006), suggesting other mechanisms are involved. Paradoxically, complex PCB mixtures significantly stimulated uterine contraction frequency with the least chlorinated mixture, Aroclor 1242, being most potent. The actions of micromolar Aroclor 1242 on uterine smooth muscle contractility seem at least in part mediated by enhanced Ca^{2+} entry through a nifedipine-sensitive pathway (Bae, Stuenkel, & Loch-Caruso, 1999; Wrobel, Kaminski, & Kotwica, 2005). Aroclor 1260 did not exhibit significant effects on rat uterine strips *in vitro* (Bae, Mousa, Quensen, Boyd, & Loch-Caruso, 2001; Tsuneta et al., 2008). However subsequent to microbial metabolism, a partially dechlorinated mixture dominated by ortho-substituted PCBs with ≤4 chlorines substituents increased uterine contraction frequency over 7-fold. Exposure of bovine myometrial cells to A1248 initially increased the spontaneous force of contractions but with longer exposures (≥24hr) was inhibitory (Wrobel et al., 2005). Non-coplanar PCB-153 (2,2′,4,4′,5,5′-hexachlorobiphenyl) increased the spontaneous and

oxytocin-evoked frequency of myometrial contractions, and these effects were greater in cells isolated before than after ovulation. On the other hand, PCB 153 delayed or inhibited oxytocin-stimulated rise in intracellular Ca^{2+} concentration without altering cell viability (Wrobel et al., 2005; Wrobel & Kotwica, 2005). *Ortho*-substituted PCBs and their metabolites were found to reduce proliferation of myometrial cells originating from pregnant women exposed *in vitro* (Bredhult, Backlin, & Olovsson, 2007).

The mechanisms responsible for the seemingly paradoxical effects of PCBs on uterine smooth muscle contractility (decreased contractility produced by PCB 4 *vs.* enhanced contractility induced by an *ortho*-rich mixtures and PCB153) are currently not understood. Collectively these results suggest that non-coplanar PCBs, especially lightly chlorinated congeners, are most active toward altering myometrial contractility through a mechanism involving altered Ca^{2+} signaling.

2.5. PCB Developmental Neurotoxicity

2.5.1 RyRs in the Nervous System—Neurons have an extensive ER membrane system that extends deep into the soma to envelope the nucleus and out into proximal regions of the dendrites and axon. Specialized regions of the ER closely appose the plasma membrane and are present in more distal aspects of the neuron such as growth cones, axon terminals and dendritic spines. As in non-neuronal cells, Ca^{2+} release from neuronal ER stores can be evoked by stimulation of RyRs or IP_3Rs, and both receptor types can couple to the activation of neurotransmitter-gated receptors and voltage-gated Ca^{2+} channels on the plasma membrane. This organization enables the ER to function not only as a buffer and source of Ca^{2+} in axonal and somatodendritic compartments but to also discriminate between different types of neuronal activity and integrate Ca^{2+}-dependent signaling between the plasma membrane, cytosol and nucleus (Bardo, Cavazzini, & Emptage, 2006; Berridge, 2006). Ca^{2+} spark-like events arising from both RyRs and IP_3Rs in nerve growth factor-differentiated PC12 cells and cultured hippocampal neurons exhibit different kinetic properties than their counterparts found in cardiac muscle, with greater spatial width and significantly longer duration (Koizumi, Bootman et al., 1999; Koizumi, Lipp, Berridge, & Bootman, 1999). Long lasting local Ca^{2+} signals spreading several microns, called “syntillas” have been measured within presynaptic terminals of basket cells of the cerebellum (Collin, Marty, & Llano, 2005), and in peptidergic terminals of murine hypothalamic neurons and neuroendocrine (chromaffin) cells (De Crescenzo et al., 2006; De Crescenzo et al., 2004; ZhuGe et al., 2006). Syntillas observed in hypothalamic neuronal terminals are triggered by membrane depolarization and are restricted near the inner leaflet of the plasma membrane. RyR1s anchored to the ER in very close proximity to plasmalemmal L-type voltage dependent Ca^{2+} channels engage in a form of voltage-induced Ca^{2+} release (VICaR) that is similar to muscle EC coupling (De Crescenzo et al., 2006).

High-affinity [^{3}H]ryanodine-binding sites are expressed in rat brain microsomal fractions from cerebral cortex, cerebellum, hippocampus and brainstem (Zimanyi & Pessah, 1991) and form caffeine sensitive Ca^{2+} channels (McPherson et al.,1991). All three RyR isoforms are expressed in the central nervous system (CNS) but are differentially distributed between specific brain regions, cell types and subcellular localizations, reflecting their participation in specialized functions. In situ hybridization studies of mouse brain (Mori, Fukaya, Abe, Wakabayashi, & Watanabe, 2000) indicate that during embryogenesis, RyR1 is predominantly expressed in the rostral cortical plate whereas RyR3 is prominent in the caudal cortical plate and hippocampus. However, from postnatal day 7 into adulthood, RyR2 expression is upregulated and RyR3 expression downregulated so that RyR1 and RyR2 are more highly and broadly expressed than RyR3. In the postnatal brain, RyR1 expression is most prominent in the dentate gyrus and Purkinje cell layer but this isoform has also been detected in the caudate/putamen nuclei, olfactory tubercle, olfactory bulb, and cortex. RyR2 is the major isoform expressed in many

brain regions and RyR2 transcripts have been observed in the hippocampus, cerebellum, medial habitual nuclei, amygdala, cortex and more anterior brain regions including granular cell layer of the olfactory bulb. In the cerebellum, RyR2 mRNA specifically localized to the granular cell layer. RyR3, which accounts for about 2% of the total RyR protein in the brain (Murayama & Ogawa, 1996), shows distinctive patterns of expression in several structures of mouse brain. RyR3-specific antibodies appeared to preferentially stain the granular layer in the cerebellum even though the signal intensity was less than RyR2. Immunocytochemical studies have also detected RyR3 in the hippocampus and sporadic patterns of RyR3 staining have been reported in the thalamus and the caudate/putamen nuclei.

Detailed *in situ* hybridization (Furuichi et al., 1994; Giannini, Conti, Mammarella, Scrobogna, & Sorrentino, 1995; Mori et al., 2000) and immunocytochemical (Hertle & Yeckel, 2007) studies of the distribution of RyR isoforms in the hippocampus of rodent brains indicate that RyR1 is enriched in the stratum oriens, stratum pyramidale and stratum radiatum of CA1 and CA3 subfields of hippocampus. The densest RyR1 immunolabeling localized to the somata of pyramidal cells within the stratum pyramidale and portions of their apical dendrites in the stratum radiatum (Hertle & Yeckel, 2007). By contrast, RyR1 has relatively lower expression in dentate gyrus. RyR2 is primarily expressed in the cells of the dentate gyrus and in the stratum lucidum of CA3 with weaker staining in pyramidal cells in stratum pyramidale and within stratum radiatum of CA1 (Hertle & Yeckel, 2007; Lai et al., 1992). RyR2 is localized in axons to a greater degree than in dendrites, and is most densely distributed in the hippocampal mossy fiber pathway and in axon bundles traversing the cortical laminae (Hertle & Yeckel, 2007; Seymour-Laurent & Barish, 1995). RyR3 immunoreactivity was detected in all hippocampal subfields but was stronger in CA1 than CA3. Intense RyR3 immunoreactivity was detected along the dentate gyrus/hilus border and within the hilus.

RyR expression has also been documented in non-neuronal cells of the CNS. Diffuse staining of the hippocampal neuropil indicates that RyR3 is expressed in astrocytic processes (Matyash, Matyash, Nolte, Sorrentino, & Kettenmann, 2002), and separate studies of cultured glial cells derived from rodent brain confirmed RyR expression in not only astrocytes (Matyash et al., 2002; Straub & Nelson, 2007) but also oligodendrocytes (Haak et al., 2001; Weerth, Holtzclaw, & Russell, 2007). These studies further indicated that astrocytes (Matyash et al., 2002) and oligodendrocyte progenitors (Haak et al., 2001) express RyR3 but not RyR1 or RyR2. In oligodendrocyte progenitor, RyR3 and IP3R type 2 were shown to have a differential distribution within their processes that might explain differences in local and global Ca^{2+} signals mediated by these two channel types, and their functional interactions appear to determine the spatial and temporal characteristics of Ca^{2+} signaling in these cells. In contrast, human microglia cultured from both fetal and adult brain samples express mRNA for RyR1 and RyR2, whereas RyR3 mRNA can be detected only in fetal microglial cells. RyR expression has also been examined in peripheral nervous system (PNS) neurons. Transcripts encoding RyR2 and RyR3 but not RyR1 have been detected in sympathetic ganglia isolated from adult rats and ganglionic levels of RyR3 but not RyR2 mRNA decline with advanced age (Vanterpool, Vanterpool, Pearce, & Buchholz, 2006). Immunohistochemical studies of dorsal root ganglia (DRG) revealed immunoreactivity for RyR3 but not RyR1 or RyR2 (Lokuta, Komai, McDowell, & Valdivia, 2002; Ouyang et al., 2005) in these sensory neurons.

2.5.2. RyR-Mediated Mechanisms in Neurodevelopment—Given that RyRs are expressed in both presynaptic and postsynaptic sites in virtually all brain areas (Hidalgo, 2005; Nozaki et al., 1999; Ogawa & Murayama, 1995) as well as in CNS glial cells and PNS neurons, it is perhaps not unexpected that experimental evidence indicates that RyRs contribute to fundamentally important aspects of neuronal excitability and use-dependent synaptic plasticity (Berridge, 1998; Kennedy, 2000; Korkotian & Segal, 1999; Matus, 2000; Segal, 2001). In axon terminals, RyRs mediate spontaneous, evoked and facilitated neurotransmission

(Collin et al., 2005; De Crescenzo et al., 2006; T. W. Dunn & Syed, 2006; Q. Liu et al., 2005; Shimizu et al., 2008) and regulate the mobilization and recycling of synaptic vesicles (Levitan, 2008; Shakiryanova et al., 2007). RyRs localized to the somatodendritic domain influence the intracellular encoding of neural activity and are implicated in modulating both neurochemical (Bardo et al., 2006; Berridge, 2006) and structural (Segal, Korkotian, & Murphy, 2000) aspects of synaptic plasticity. Diverse neurochemical changes associated with dendritic synaptic plasticity have been shown to rely on RyR function, including: 1) activity-dependent postsynaptic translation (Jourdi et al., 2009) and secretion (Kolarow, Brigadski, & Lessmann, 2007) of neurotrophins, 2) modulation of Gq-coupled receptor function by stress peptides and hormones (Riegel & Williams, 2008); 3) activity-dependent enhancement of glutamate responses and the associated increase of GluR1 within spines mediated by synaptopodin, an actin-binding protein that co-localizes with RyRs within the spine apparatus of hippocampal neurons (Vlachos et al., 2009); and 4) sequential activation of CaM kinases, CREB and transcription of genes encoding Ca^{2+}-regulated proteins triggered by repetitive or prolonged depolarization of hippocampal neurons (Deisseroth, Heist, & Tsien, 1998). RyRs similarly function in peripheral neurons to regulate the release of (Cong, Takeuchi, Tokuno, & Kuba, 2004; W. Huang, Wang, Galligan, & Wang, 2008; Ouyang et al., 2005) and response to (Brain, Trout, Jackson, Dass, & Cunnane, 2001; Locknar, Barstow, Tompkins, Merriam, & Parsons, 2004) neurotransmitters and neuropeptides, and their function underlies the exocytotic release of glutamate from astrocytes (reviewed in Reyes & Parpura, 2009). Changes in postsynaptic efficacy are also associated with morphological changes in dendritic spines. Pulse application of caffeine, a RyR agonist, has been reported to cause a rapid and significant increase in the size of existing dendritic spines in mature cultures of hippocampal neurons and this effect is blocked by antagonizing concentrations of ryanodine (Korkotian & Segal, 1999), supporting the involvement of RyR in mediating activity-dependent changes in dendritic spine morphology.

Consistent with the demonstrated role of RyRs in neurotransmission and synaptic plasticity at the cellular level, ligands that directly modulate RyR, such as ryanodine, alter functional aspects of neuroplasticity including long term potentiation (LTP) (Y. Wang, Wu, Rowan, & Anwyl, 1996) and long term depression (LTD) (Y. Wang, Rowan, & Anwyl, 1997) in the hippocampus. FK506 and rapamycin, which deregulate RyR2 by dissociating the RyR2/FKBP12/12.6 complexes also inhibit LTD (Li, Kato, & Mikoshiba, 1998). Thus, RyRs appear to play a critical role in use-dependent plasticity that underlies the early stages of associative memory. Earlier evidence suggested that RyR2 through its interaction with calexcitin might also alter Ca^{2+} signaling over a longer time frame, implying a critical role for RyRs in the consolidation phase of associative memory (Alkon, Nelson, Zhao, & Cavallaro, 1998). Most intriguing is work showing a tight correlation between acquisition of spatial learning and selective up-regulation of RyR2 in the dentate gyrus and CA3 (Cavallaro et al., 1997), implicating RyR2 in storage phases of associative memory (Alkon et al., 1998). Additional studies demonstrate that mice with targeted deletion of RyR3 have deficits in contextual fear conditioning but improved spatial learning in the Morris water maze task (Futatsugi et al., 1999; Kouzu et al., 2000). Interestingly, comprehensive behavioral phenotyping of RyR3 knockout mice revealed decreased social interaction, hyperactivity and mildly impaired prepulse inhibition, whereas no measurable impairments in motor function and working and reference memory tests were detected (Matsuo et al., 2009).

A recent discovery is that RyRs also function as a key element of the output pathway from the molecular circadian clock in neurons of the suprachiasmatic nucleus (SCN). Electrophysiological and calcium mobilization experiments indicate that RyR activation by administration of caffeine or 100 nM ryanodine increased the firing frequency of SCN neurons, whereas inhibition of RyRs by dantrolene or 80 μM ryanodine decreased firing rate, suggesting that RyRs are involved in the circadian rhythmicity of SCN neurons (Aguilar-Roblero,

Mercado, Alamilla, Laville, & Diaz-Munoz, 2007). Subsequent behavioral studies demonstrated that RyR activation induced a significant shortening of the endogenous period, whereas RyR inhibition disrupted circadian rhythmicity. In both experiments, the period of rhythmicity returned to basal levels upon cessation of pharmacological treatment (Mercado et al., 2009). In light of these studies, it is interesting to note that it had been reported some 25 years earlier that PCBs interfered with rhythmic pituitary-adrenal function in rats (J. D. Dunn, Carter, & Henderson, 1983).

Dynamic changes in intracellular Ca^{2+} concentrations play a crucial role in not only neuronal excitability and synaptic plasticity but also in cell proliferation and differentiation, cell movement, and cell death (Cline, 2001; Moody & Bosma, 2005; Spitzer, Root, & Borodinsky, 2004; Zheng & Poo, 2007). Thus, it might be predicted that RyRs function to regulate diverse aspects of neurodevelopment, and emerging evidence supports that prediction. Early reports that RyRs are upregulated during NGF-induced differentiation of adrenal chromaffin cells (Jimenez & Hernandez-Cruz, 2001) suggested the possibility that RyRs mediate the CICR necessary for neurogenesis and neuronal differentiation. In support of this hypothesis, it was recently shown that activation of L-type Ca^{2+} channels, $GABA_A$ receptors or RyRs promoted neuronal differentiation, while inhibition of these channels/receptors had the opposite effect on mouse embryonic stem (ES) cells (Yu et al., 2008). Moreover, the activity of intracellular Ca^{2+} signaling, expression of the neuronal transcription factor NeuroD and the rate of neurogenesis was significantly inhibited in neuronal cells derived from embryonic stem cells obtained from RyR2 deficient mice relative to wild-type controls even in the presence of L-type Ca^{2+} channel and $GABA_A$ receptor activation. Apoptosis is another neurodevelopmental process that is essential to normal brain development (Dikranian et al., 2001; Martin, 2001), occurring in proliferative zones and in postmitotic cells in both the fetal and postnatal brain (White & Barone, 2001). The spatiotemporal pattern of apoptosis in the developing CNS is tightly regulated and disruption of either the timing or the magnitude of apoptosis in a given brain region can alter cell number and thus connectivity, causing deficits in higher order function even in the absence of obvious pathology (Barone, Das, Lassiter, & White, 2000; Martin, 2001; Sastry & Rao, 2000). Increased Ca^{2+} and ROS are significant triggers of apoptosis, and RyR activation a critical component of apoptotic signaling pathways (Berridge, Lipp, & Bootman, 2000; Carmody & Cotter, 2001; Ermak & Davies, 2002; Ravagnan, Roumier, & Kroemer, 2002; Robertson, Chandra, Gogvadze, & Orrenius, 2001).

RyRs have also been implicated in regulating morphogenetic processes in the developing nervous system. Specifically, RyR3 has been shown to be necessary for astrocyte migration (Matyash et al., 2002), and for axonal growth cone responses to nitric oxide (Welshhans & Rehder, 2007) or activation of cell adhesion molecules (Ooashi, Futatsugi, Yoshihara, Mikoshiba, & Kamiguchi, 2005). With respect to the latter, in the presence of RyR3-mediated CICR, growth cones exhibited attractive turning, but in the absence of RyR3-mediated CICR, $Ca2^{+}$ signaling elicited growth cone repulsion. The authors suggest on the basis of these observations that the source of Ca^{2+} influx, rather than its amplitude or the baseline Ca^{2+} level, is the primary determinant of the direction of axonal growth cone turning. Based on pharmacological inhibition studies, RyRs have also been implicated in regulating Ca^{2+}-dependent neurite outgrowth (Arie et al., 2009) in DRG neurons, a cell type that extends only axons, as well as activity-dependent dendritic growth and retraction in retinal ganglia neurons (Lohmann, Finski, & Bonhoeffer, 2005; Lohmann, Myhr, & Wong, 2002). A generalization emerging from studies of activity-dependent dendritic growth is that Ca^{2+} exerts bimodal effects on dendritic structure. Thus, increased intracellular Ca^{2+} has been linked to both dendritic growth and to dendritic retraction (reviewed in Lohmann & Wong, 2005; Redmond, Kashani, & Ghosh, 2002; Segal et al., 2000). Two possibilities have been proposed to explain why Ca^{2+} signaling stimulates dendritic growth in some cases while inhibiting dendritic plasticity in others. First, Segal et al. (2000) suggest that moderate and/or transient increases

in intracellular Ca^{2+} cause growth of dendritic branches and spines, whereas large Ca^{2+} increases cause destabilization and retraction of these dendritic structures (Fig 13). Consistent with this possibility, relatively sustained increases in intracellular Ca^{2+} *versus* transient changes in Ca^{2+} influx activate different Ca^{2+}-dependent signaling pathways with distinct effects on dendrites (Redmond et al., 2002; Wilson, Kisaalita, & Keith, 2000). The second possibility is that dendritic responses to Ca^{2+} differ with neuronal maturation such that early in development, increased Ca^{2+} promotes dendritic growth, while later in development, increased Ca^{2+} functions to stabilize dendritic structure (Lohmann & Wong, 2005). While pharmacological manipulation of RyRs has been shown to influence activity-dependent dendritic morphogenesis, the specific isoforms associated with any specific effect have yet to be determined.

In addition to regulating neurodevelopment and physiological processes in the central and peripheral nervous system, RyRs are also implicated in Ca^{2+} dysregulation associated with cell toxicity, aging and neurodegeneration (reviewed in Thibault, Gant, & Landfield, 2007). The model that has been proposed is that aging and/or pathological changes occur in both L-type Ca^{2+} channels and RyRs and these interact to abnormally amplify Ca^{2+} transients. In turn, the increased transients result in dysregulation of multiple Ca^{2+}-dependent processes ultimately accelerating functional decline. Diverse pathogenic stimuli, including HIV-1 Tat (Norman et al., 2008), amyloid-beta and prion peptides (Ferreiro, Oliveira, & Pereira, 2008) as well as mutations associated with neurodegeneration such as the presenilin (PS2) mutation (S. Y. Lee et al., 2006) activate apoptotic or excitotoxic pathways via RyR-dependent mechanisms that increase intracellular Ca^{2+} levels in neurons. Consistent with this model, two recent reports confirm a role for interactions between presenilins and RyRs in regulating release of calcium from both pre-synaptic and post-synaptic ER (C. Zhang et al., 2009; S. Chakroborty, Goussakov, Miller & Stutzmann, 2009). This interaction is perturbed in 3xTg-AD mice such that RyR-evoked Ca^{2+} release in CA1 pyramidal neurons is markedly increased resulting in altered synaptic homeostasis of these neurons relative to wildtype mice (Chakroborty et al., 2009). Interestingly, the RyR2 isoform was found to be selectively increased more than fivefold in the hippocmpaus of 3xTg-AD mice relative to controls and the authors propose this as the mechanism to explain the deviant, yet functional calcium signaling evident in presymptomatic 3xTg-AD mice long before the onset of AD histopathology. RyR-dependent Ca^{2+} release from presynaptic internal stores is also required for ethanol to increase spontaneous γ-aminobutryic acid release onto cerebellum Purkinje neurons (Kelm, Criswell, & Breese, 2007), and the imbalance between excitatory and inhibitory circuits that underlies NMDA receptor-mediated epileptiform persistent activity is blocked by inhibition of the ryanodine receptor (W.-J. Gao & Goldman-Rakic, 2006). These observations support the hypothesis that factors that alter RyR expression and/or function have the potential to interfere with normal neurodevelopment and neuronal function.

2.5.3. Experimental evidence of RyR-mediated mechanisms of PCB neurotoxicity—Of the various adverse effects associated with PCBs, developmental neurotoxicity has emerged as a particularly vulnerable endpoint (Carpenter, 2006; NIEHS, 1999; Schantz et al., 2003). Population-based studies have consistently demonstrated that PCBs negatively impact neuropsychological function in exposed children (Carpenter, 2006; Korrick & Sagiv, 2008; Schantz et al., 2003). PCB exposure has been positively correlated with decreased IQ scores, impaired learning and memory, lower reading comprehension, attentional deficits and psychomotor dysfunction (Y. C. Chen et al., 1992; Grandjean & Landrigan, 2006; Jacobson et al., 1992; Koopman-Esseboom et al., 1996; Roegge & Schantz, 2006; Rogan & Ragan, 2007; Schantz et al., 2003; P. W. Stewart et al., 2008). Comparable cognitive and psychomotor behavioral deficits are observed in primate and rodent models following developmental PCB exposures (Rice, 1998; Schantz, 1996; Schantz, Levin, Bowman, Heironimus, & Laughlin, 1989; Schantz, Moshtaghian, & Ness, 1995; Tilson, Jacobson, &

Rogan, 1990; Tilson & Kodavanti, 1998). More recently, it has been postulated that exposure of the developing brain to PCBs may also influence the susceptibility of the adult brain to acute stressors and neurodegeneration (Lein, Kim, Berman, & Pessah, In press). This hypothesis is derived in part from a mortality study of 17,000 workers occupationally exposed to PCBs that revealed an increased incidence of PD in female subjects (Steenland et al., 2006) and findings of a positive correlation between PCB exposure and depression and impaired memory and learning among adults 49–86 years of age living in Michigan and exposed to PCBs via consumption of Great Lakes fish (Schantz et al., 2001) and adults 55–74 years of age living along regions of the Hudson River in New York that have been heavily contaminated with PCBs (Fitzgerald et al., 2008). In the latter study, the PCB body burdens of affected individuals were similar to those of the general population, suggesting persistent neuropsychological effects from prior exposures. Whether early-life exposures to PCBs increase susceptibility to neurodegenerative processes that contribute to dementia and motor deficits is difficult to determine from these studies because the critical exposure period could not be identified. However, several recent studies using experimental animal models support this possibility. The first set of studies utilized a well-established model of focal cerebral ischemia, middle cerebral artery occlusion (MCAO) in rats, to demonstrate that exposure to Aroclor 1254 in the maternal diet throughout gestation and lactation confers neuroprotection against focal ischemic stress in the adult brain (Dziennis et al., 2008). Congener-specific analyses of tissues harvested from adult animals immediately following MCAO indicated no difference in PCB levels between control and PCB-exposed brains, suggesting that PCB effects on stroke outcome may reflect PCB interactions with developmental processes. In the second set of studies, developmental PCB exposure was shown to influence seizure susceptibility in the weanling and young adult rat. Seizure susceptibility was assessed by quantifying the threshold for seizures induced by flurothyl (bis-2,2,2-triflurothyl ether), a convulsive drug used to investigate seizure susceptibility in rodents (Ferland & Applegate, 1998; Szot et al., 2001) and the response to pentylenetetrazole (PTZ), which kindles seizures within 15–20 injections of initially subconvulsive doses in rats (Corda et al., 1991). Exposure to PCB 95 in the maternal diet from gestational day 5 through weaning on postnatal day 21 significantly decreased seizure thresholds in animals challenged with flurothyl on postnatal day 35 and caused faster kindling with PTZ on postnatal day 60–83 (Lein et al., In press). Considered collectively, these studies support the possibility that exposure of the developing brain to PCBs may elicit persistent changes in the brain that influence the susceptibility of the adult brain to subsequent stressors.

How developmental PCB exposure causes persistent neuropsychological impairment in either children or adults has yet to be resolved. Several lines of evidence suggest mechanisms independent of the AhR. First, congener-specific analyses of brain tissues from human subjects (Corrigan, Murray, Wyatt, & Shore, 1998) and experimental animals (Dziennis et al., 2008; D. Yang et al., 2009) exhibiting neuropsychological impairment associated with exposure to complex PCB mixtures indicate enrichment of non-coplanar ortho-rich congeners. Second, studies utilizing purified congeners have consistently demonstrated developmental neurotoxicity associated with non-coplanar ortho-rich congeners (Fonnum et al., 2006; P. R. S. Kodavanti, 2005; Mariussen & Fonnum, 2006; Schantz et al., 2003; Tilson & Kodavanti, 1998). For example, perinatal exposure to PCB 95 has been shown to persistently alter cognitive and psychomotor activity in rodent models (Schantz, Seo, Wong, & Pessah, 1997) as well as LTP in hippocampal slice cultures (P. W. Wong, Joy, Albertson, Schantz, & Pessah, 1997), and to alter the ratio of excitatory to inhibitory neurotransmission in the developing auditory cortex (Kenet et al., 2007) and hippocampal slice cultures (Kim, Inan, Berman, & Pessah, 2009).

The mechanisms underlying the neurotoxic effects of non-coplanar PCBs are only partially understood. Biological activities associated with ortho-rich and hydroxyl metabolites of ortho-poor PCBs include: 1) endocrine disruption, specifically weak estrogenicity (Safe, 2004),

enhanced insulin (Fischer et al., 1999) and arachidonic acid secretion (Bae, Peters-Golden et al., 1999), and disruption of the hypothalamic-pituitary-thyroid axis (Knerr & Schrenk, 2006; Zoeller, 2005; Zoeller et al., 2000); 2) reduced levels of dopamine and other biogenic amines in the brain and in cultured neurons (Mariussen & Fonnum, 2006; Seegal, 1996); and 3) increased levels of reactive oxygen species (ROS) and intracellular Ca^{2+} in neurons (P. R. S. Kodavanti, 2005; Mariussen & Fonnum, 2006). There is evidence that non-coplanar PCBs may induce increases in intracellular Ca^{2+} by several mechanisms, including influx of extracellular Ca^{2+} through L-type voltage-sensitive Ca^{2+} channels or the NMDA receptor (Inglefield & Shafer, 2000; Mundy, Shafer, Tilson, & Kodavanti, 1999) or via release of intracellular Ca^{2+} stores subsequent to activation of IP_3Rs (Inglefield et al., 2001) or RyR (P. W. Wong, Brackney et al., 1997); however, RyR activation is the most sensitive of these mechanisms (P. W. Wong, Brackney et al., 1997; P. W. Wong, Joy et al., 1997; P. W. Wong & Pessah, 1996). It is interesting to note that these mechanisms may not be mutually exclusive since RyR activation is known to interact with IP_3R and with both L-type voltage-sensitive Ca^{2+} channels and the NMDA receptor (see section 2.5.4.), and low μM concentrations of non-coplanar PCBs have been shown to enhance significantly the sensitivity of primary cultured neurons to NMDA- and AMPA-elicited Ca^{2+} signals (Gafni et al., 2004), revealing a functional link between PCB amplification of RyR signaling and sensitivity to excitatory amino acids.

The causal relationship between these biological activities of non-coplanar PCBs and the neuropsychological deficits associated with PCB developmental neurotoxicity remains a pressing question in the field. It has been postulated that these biological activities contribute to the developmental neurotoxicity associated with non-coplanar PCBs by interfering with the patterning of neuronal connectivity in the developing brain (Gilbert, 2000; Seegal, 1996). Critical determinants of neuronal connectivity include neuronal apoptosis (Barone et al., 2000; Martin, 2001; Sastry & Rao, 2000) and dendritic morphogenesis (Kennedy, 2000; Matus, 2000). Altered patterns of neuronal apoptosis not only impact neuronal connectivity in the developing brain, but also influence the susceptibility of the adult brain to subsequent environmental insults or aging (Barlow, Cory-Slechta, Richfield, & Thiruchelvam, 2007; Langston et al., 1999). The shape of the dendritic arbor determines the total synaptic input a neuron can receive (Purpura, 1967; Purves, 1975, 1988), and influences the types and distribution of these inputs (Miller & Jacobs, 1984; Schuman, 1997; Sejnowski, 1997). Altered patterns of dendritic growth and plasticity are associated with impaired neuropsychological function in experimental models (Berger-Sweeney & Hohmann, 1997) and are thought to contribute to diverse disorders of neurodevelopmental origin (Connors et al., 2008; Pardo & Eberhart, 2007; Zoghbi, 2003) as well as neurodegenerative diseases (de Ruiter & Uylings, 1987; Flood & Coleman, 1990; Jagadha & Becker, 1989). Each of the biological activities associated with non-coplanar PCBs have been shown to influence neuronal apoptosis and to contribute to the dynamic control of dendritic growth; however, to date, experimental evidence linking these activities to PCB-induced alterations in neuronal connectivity has been reported only for RyR-dependent mechanisms.

PCBs have been shown to induce caspase-dependent apoptosis in primary cultures of hippocampal neurons (Howard et al., 2003). Neuronal apoptosis was induced by A1254 and non-coplanar PCB 47 but not by coplanar PCB 77. Aroclor 1254 contains predominantly ortho-rich PCBs with significant activity at the RyR (P. W. Wong, Brackney et al., 1997; P. W. Wong & Pessah, 1996), and SAR studies identified PCB 47 as a RyR-active congener and the coplanar PCB 77 as a congener with negligible activity at the RyR (Pessah et al., 2006). Further evidence that RyR activation mediated the pro-apoptotic activity of PCBs includes the inhibition of PCB-induced apoptosis by FLA 365, a selective RyR antagonist (Chiesi, Schwaller, & Calviello, 1988; Mack, Zimanyi, & Pessah, 1992) but not by antagonists previously shown to block PCB-mediated Ca^{2+} flux through L-type voltage-sensitive channels, NMDA receptors, and IP_3Rs in cultured neurons.

Recent evidence suggests that PCBs may also interfere with neuronal connectivity *in vivo*. Developmental exposure to A1254 was observed to enhance basal levels of dendritic growth but block experience-dependent dendritic growth in the cortex and cerebellum of weanling rats (P. J. Lein et al., 2007; D. Yang et al., 2009) (Fig 14), and developmental exposure to PCB 95 was reported to disrupt the balance of neuronal inhibition to excitation in the developing rat auditory cortex (Kenet et al., 2007). Several lines of evidence suggest that PCB sensitization of RyRs contributes to the effects of these compounds on neuronal connectivity. First, these changes in neuronal connectivity are associated with exposure to non-coplanar PCB congeners with high affinity for the RyR. Second, PCB-induced changes in dendritic growth and plasticity are coincident with increased [^{3}H]ryanodine binding sites and RyR expression in the brains of untrained animals and inhibition of training-induced RyR upregulation. Moreover, the dose-response relationship for PCB effects on dendritic growth and plasticity were similar to that of PCB effects on RyR expression but not to that of PCB effects on thyroid hormone levels or sex-steroid-dependent developmental endpoints (D. Yang et al., 2009). Increased RyR expression in brain tissues has also been associated with PCB-induced changes in gene expression (Royland & Kodavanti, 2008; Royland, Wu, Zawia, & Kodavanti, 2008) and locomotor activity (Roegge et al., 2006). In vitro studies confirmed a link between PCB sensitization of RyR and effects on dendritic arborization. PCB 95, a congener with potent RyR activity, but not PCB 66, a congener with negligible RyR activity, promoted dendritic growth in primary cortical neuron cultures and this effect was blocked by pharmacological antagonism of RyR activity (D. Yang et al., 2009). The downstream mechanisms by which PCB sensitization of the RyR influences dendritic arborization have yet to be established, but it is postulated these involve modulation of Ca^{2+}-dependent signaling pathways linked to activity-dependent dendritic growth and plasticity. Activation of a CaMK-CREB-Wnt signaling pathway has recently been demonstrated to link neuronal activity to transcription of gene products that regulate dendritic growth (Wayman et al., 2006) (Fig 15); and activity-dependent translation is mediated by the serine-threonine protein kinase mammalian target of rapamycin (mTOR) (Gong, Park, Abbassi, & Tang, 2006; Jaworski, Spangler, Seeburg, Hoogenraad, & Sheng, 2005; Kumar, Zhang, Swank, Kunz, & Wu, 2005; Takei et al., 2004). RyR activation has been shown to cause sequential activation of CaM kinases, CREB and transcription of genes encoding Ca^{2+}-regulated proteins (Deisseroth et al., 1998); translation mechanisms of activity-dependent growth are Ca^{2+}-dependent; and PCB effects on RyR-mediated Ca^{2+} signaling require interactions with FKBP12 (Gafni et al., 2004; P. W. Wong et al., 2001; P. W. Wong & Pessah, 1997), which regulates mTOR activity (reviewed in (J. Chen & Fang, 2002)).

These data linking a direct molecular effect of PCBs (RyR activation) to disruption of specific neurodevelopmental events (neuronal apoptosis and dendritic growth and plasticity) provide the first evidence of a receptor-based mechanism for PCB developmental neurotoxicity. This not only provides a powerful means for predicting which of the 209 possible congeners within the PCB family present the greatest risks to neurodevelopment, but also supports the development of mechanism-based tools for screening other chemical classes of environmental health concern, such as PBDEs. Human polymorphisms in *RYR* genes are linked to environmentally triggered disorders including malignant hyperthermia (MH) (Gronert, Pessah, Muldoon, & Tautz, 2004), cardiac arrhythmias (Wehrens, Lehnart, & Marks, 2005), and sudden death (Laitinen et al., 2004), suggesting the testable hypothesis that individuals with mutation(s) in one or more CRU proteins exhibit increased susceptibility to developmental neurotoxicity resulting from low-level environmental exposures to non-coplanar PCBs. In support of this hypothesis, we recently showed that non-coplanar PCB 95 is significantly more potent and efficacious in disrupting cation regulation of MH mutation R615C-RyR1 compared to wild type RyR1 (Ta & Pessah, 2007). Considered together, these observations identify non-coplanar PCBs with high RyR activity as candidate environmental risk factors in neurodevelopmental disorders and provide insight regarding potential gene-environment

interactions that influence susceptibility to environmentally triggered neurodevelopmental deficits.

2.5.4. RyRs as a point of convergence in PCB neurotoxicity—While emerging evidence clearly identifies RyRs as critical molecular targets in PCB developmental neurotoxicity, other biological activities have been ascribed to non-coplanar PCBs, including increased intracellular levels of ROS (Fonnum et al., 2006; Mariussen & Fonnum, 2006), disruption of thyroid hormone signaling (Crofton, 2008; Zoeller, 2007) and decreased levels of dopamine (Mariussen & Fonnum, 2006). Are these biological activities causally related to PCB developmental neurotoxicity, and if so, do they represent divergent or convergent mechanisms of PCB developmental neurotoxicity?

In the case of PCB disruption of thyroid hormone signaling, animal studies have shown that reductions in circulating TH levels with developmental exposure to PCBs are associated with low frequency hearing loss and damage to cochlear hair cells, especially outer hair cells (Goldey, Kehn, Lau, Rehnberg, & Crofton, 1995; Lasky, Widholm, Crofton, & Schantz, 2002). Since TH is necessary for normal cochlear development (Uziel, 1986), the loss of hair cells has been considered the indirect consequence of TH deficiency during critical periods of development. However, the profile of cochlear damage following PCB exposure is not entirely consistent with models of hypothyroidism, and TH replacement in PCB-exposed rats only partially reversed hearing deficits (Crofton, Ding, Padich, Taylor, & Henderson, 2000; Crofton & Zoeller, 2005; Goldey & Crofton, 1998; Sharlin, Bansal, & Zoeller, 2006). Additional evidence that an alternative, TH independent, mechanism contributes to PCB ototoxicity was recently presented (Powers BE, 2009). Interestingly, these effects on cochlear development are produced primarily by non-coplanar PCBs (Kostyniak et al., 2005; Powers, Widholm, Lasky, & Schantz, 2006), and all three RyR isoforms are differentially expressed throughout the organ of Corti, including inner and outer hair cells, and within spiral ganglion neurons (Grant, Slapnick, Kennedy, & Hackney, 2006; Morton-Jones, Cannell, Jeyakumar, Fleischer, & Housley, 2006). RyR1 is the major isoform expressed in the outer hair cells where it is co-localized with nicotinic cholinergic receptors at “synaptic cisterns” resembling triadic junctions that are essential for engaging excitation-contraction coupling in skeletal muscle (Lioudyno et al., 2004). RyR1 channels tightly couple Ca^{2+} release from ER stores in response to cholinergic input to the outer hair cell thereby regulating Ca^{2+}-activated potassium currents that are necessary for long-term survival of olivocochlear fibers and synapses (Murthy et al., 2009). RyRs expressed in inner hair cells functionally couple to Ca^{2+}-activated potassium channels (Beurg et al., 2005), whereas in spiral ganglion neurons, RyRs are functionally coupled to somatic AMPA-type glutamate receptors (Morton-Jones, Cannell, & Housley, 2008). These observations suggest the possibility that the cochlea represents a direct target of RyR-active PCBs, and that RyR-dependent mechanisms work in parallel or in series with TH-dependent mechanisms to cause ototoxicity.

Emerging evidence from diverse areas of research raises the intriguing possibility that RyR sensitization contributes to other known biological activities of PCBs. For example, it has been demonstrated that PCBs activate the RyR causing release of Ca^{2+} from the ER (P. W. Wong & Pessah, 1997), which in turn can increase production of ROS (Ermak & Davies, 2002; Ravagnan et al., 2002) (Fig 16). This might be a reciprocal interaction in that ROS can directly modulate the channel activity of the RyR (Feng, Liu, Allen, & Pessah, 2000; I. N. Pessah, 2001). An interesting speculation is that RyR-dependent mechanisms also contribute to the decreased levels of circulating thyroid hormone associated with PCB exposure. The thyroid gland is a major target organ of the sympathetic nervous system, and sympathetic neurons express RyRs (Vanterpool et al., 2006) and neurotransmitter release from sympathetic neurons is regulated by RyR activity (Cong et al., 2004). Conversely, since thyroid hormone regulates RyR expression in at least the heart (Dillmann, 2002; Hudecova, Vadaszova, Soukup, &

Krizanova, 2004; Jiang, Xu, Tokmakejian, & Narayanan, 2000), perhaps PCB effects on thyroid hormone signaling are mediated in part by changes in RyR expression.

Similarly, emerging evidence regarding a role for RyRs in regulating dopamine homeostasis suggests the possibility that PCB sensitization of RyR contributes to the effects of PCBs on dopamine. Several mechanisms are currently postulated to contribute to dopamine reductions seen following PCB exposure, including inhibition of tyrosine hydroxylase and L-aromatic acid decarboxylase (Angus & Contreras, 1996; Angus et al., 1997), two of the enzymes involved in the synthesis of dopamine, decreased striatal levels of the dopamine transport (DAT) (Caudle et al., 2006) and selective activation of oxidative stress-related pathways in dopaminergic neurons (D. W. Lee & Opanashuk, 2004). Ryanodine induces dopamine release from striatal dopaminergic neurons and this effect is significantly attenuated in striatal slices isolated from RyR3 null mice (Wan, Moriya, Akiyama, Takeshima, & Shibata, 1999). More recently, it has been demonstrated that pharmacological manipulations of RyR activity alter somatodendritic dopamine release (Patel, Witkovsky, Avshalumov, & Rice, 2009) as well as action potential- and NMDA receptor - evoked Ca2+ signaling (Cui, Bernier, Harnett, & Morikawa, 2007; Harnett, Bernier, Ahn, & Morikawa, 2009) in midbrain dopaminergic neurons, and that internal Ca^{2+}stores are necessary for the abnormal release of dopamine via reverse transport through the dopamine transporter caused by amphetamine and methamphetamine (Goodwin et al., 2009). Collectively these observations provide biological plausibility to the intriguing speculation that RyR sensitization may be a convergent mechanism of PCB developmental neurotoxicity.

2.6. Convergent mechanism for non-coplanar POPs: Toward an alternative TEF

The observation that RyRs play a critical role in diverse tissue types and in numerous cellular processes raises an interesting challenge in light of emerging data identifying RyRs as a direct molecular target in PCB neurodevelopmental toxicity. What factor(s) determine the specificity of PCB toxicity? Why do PCBs seem to preferentially target the developing nervous system? Certainly the timing of exposure will influence the biological outcomes of PCB exposures, as will pharmacokinetic parameters such as dosage, the metabolites produced, and distribution of PCBs within the body. But other factors that could be equally important include expression patterns of RyRs and the complement of accessory proteins that comprise the calcium release unit as well as the antioxidant capacity of the cell. Alternatively, perhaps the developing nervous system is not the only preferential target, and we have simply missed toxic effects of PCBs on peripheral target organs (muscle, cochlea, pancreatic beta cells, etc) because little attention has been paid to these endpoints. Given the role of the RyR in a number of peripheral tissues where PCBs have been shown to have effects, at least *in vitro*, understanding how PCBs impact these peripheral targets and their implications for human and animal health and risk assessment seem warranted.

Another interesting hypothesis that emerges from consideration of the structure-activity relationship of PCB interactions with the RyR is whether the RyR functions as a target for other toxicants that possess non-coplanar structures. Obvious candidates are the polybrominated diphenyl ethers (PBDEs) (Fig. 17). Recently Dingemans and coworkers reported that the 6-hydroxyl metabolite of BDE-47 (20–120 μM) rapidly influences intracellular Ca^{2+} homeostasis in PC12 cells, which can be at least partially accounted for by release from the ER store (Dingemans et al., 2008). Preliminary evidence that certain PBDE congeners and their metabolites directly alter RyR function has emerged (K. Kim, Marsh, Bergman, LaSalle & Pessah, 2009). Careful consideration of the 3-dimensional structure of these and related environmental contaminants concerning human health may reveal other RyR ligands. One such candidate, triclosan (Fig 17), has been shown in pilot studies to alter Ca^{2+} signals in a RyR-dependent manner (Anh et al, 2008). Another candidate, bisphenol A (Fig.

17), remains untested. Whether the effects of non-coplanar compounds that are capable of altering subtle aspects of RyR function are additive remains to be established. However, based on results obtained with non-dioxin-like PCBs, the potential for toxicological significance is clear. The SAR data available for PCB interactions with RyRs, and the identification of a RyR-based mechanism of neurodevelopmental toxicity, suggest the utility of developing an alternative TEF strategy for non-dioxin-like PCBs based on their relative RyR activity. This strategy has great appeal for assessing the risk of neurodevelopmental toxicity associated with exposure to mixtures of PCBs and has the flexibility to adjust to emerging data about exposures to existing and new non-coplanar compounds and their metabolites based on RyR activity.

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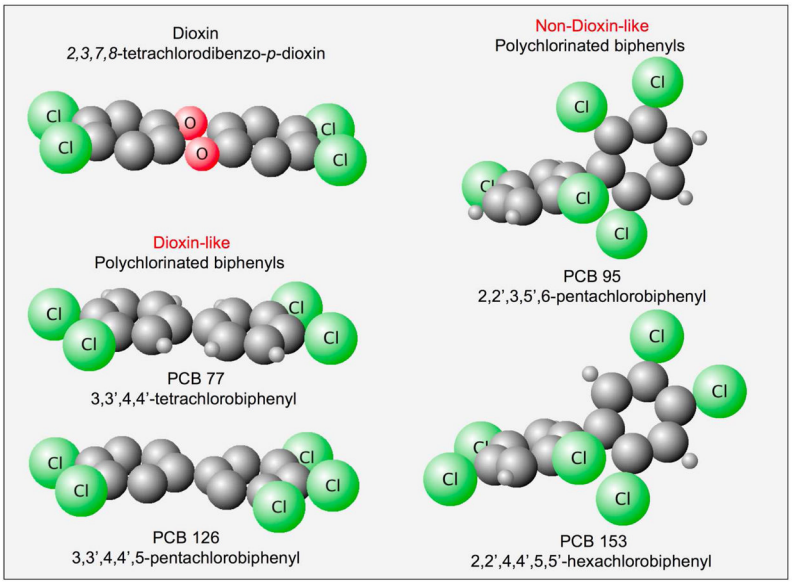

Fig 1.

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.).

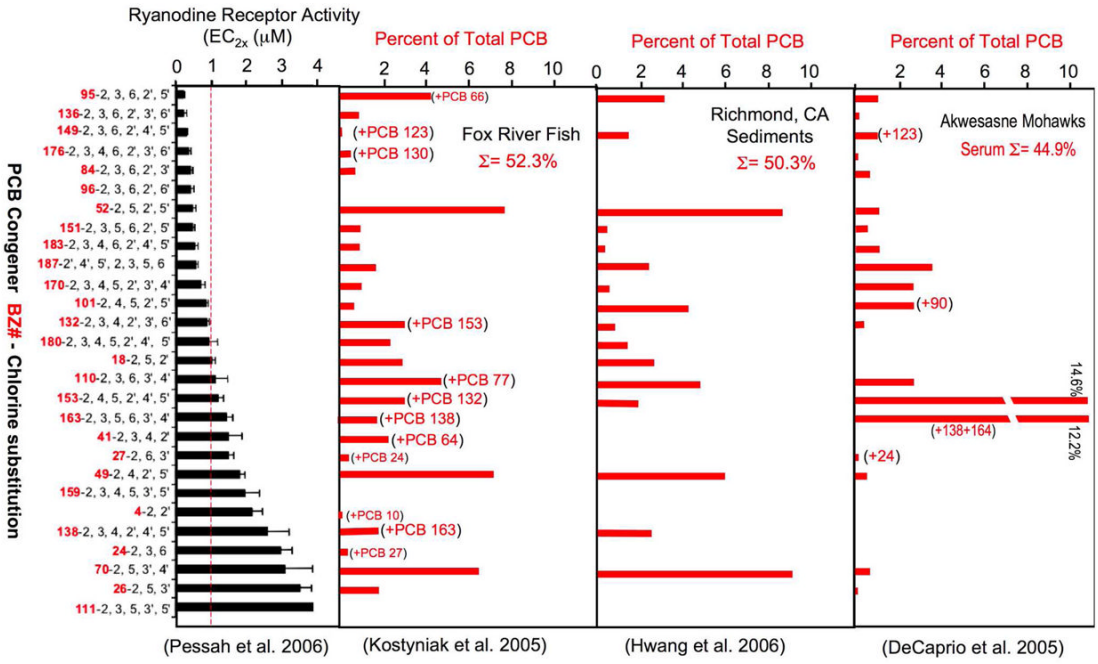

Fig 2.

Relative concentration of 28 non-coplanar PCBs needed to double [^{3}H]ryanodine binding to ryanodine receptor type 1 (RyR1; black bars) and their corresponding occurrence in Fox River fish, marsh sediments, and human serum (red bars). PCBs in parentheses are co-eluting congeners.

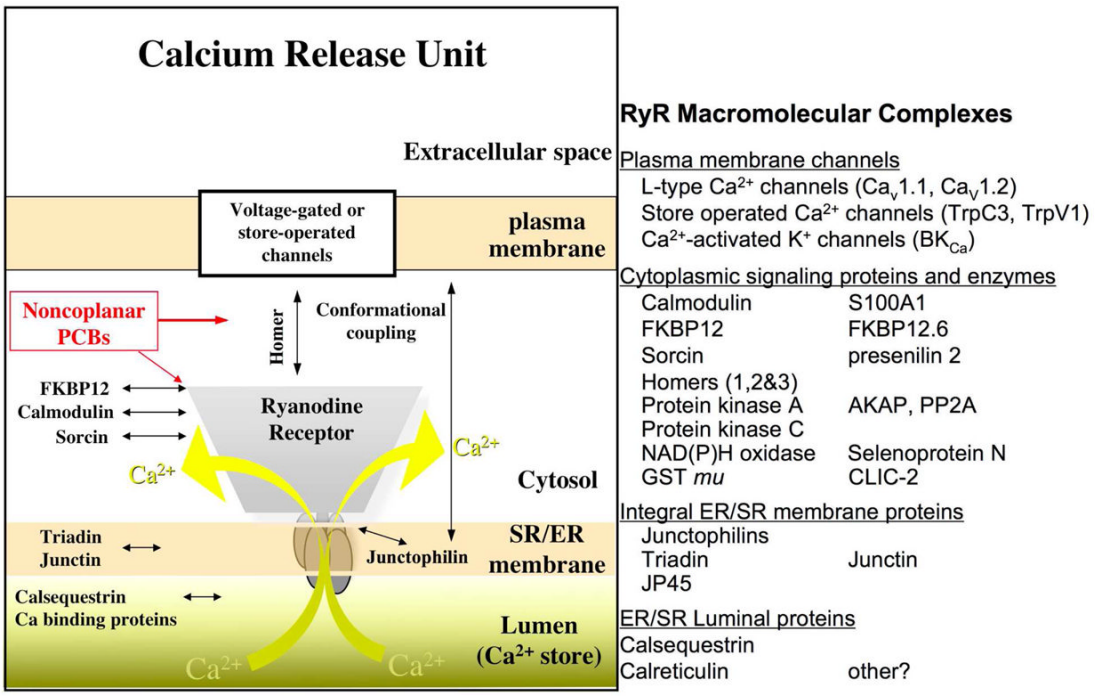

Fig 3.

Several proteins interact with RyRs to regulate their function as high conductance Ca^{2+} channels in striated muscle. The large cytoplasmic assembly ("junctional foot") interacts with ion channels in the plasma membrane, cytoplasmic signaling proteins, and cytoplasmic enzymes that regulate phosphorylation and redox sensing. The transmembrane assembly that anchors RyRs to the ER/SR interacts with proteins that fine tune communication with the Ca^{2+} stores within the SR/ER lumen. For clarity, interactions have been left out of the schematic.

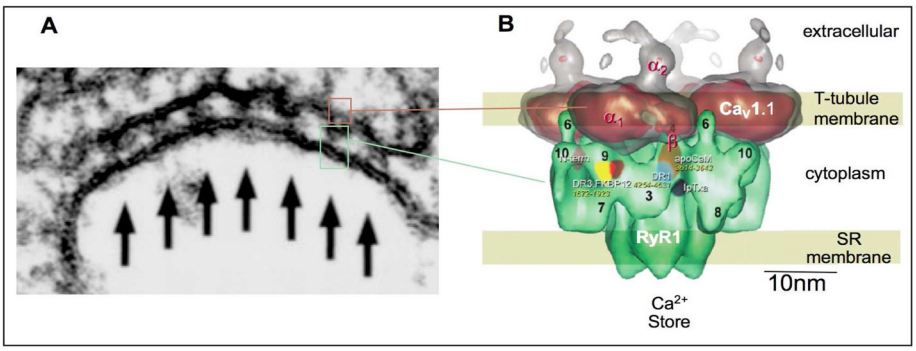

Fig 4.

(A) Electron micrograph of the T-tubule/SR junction of negatively stained skeletal myotubes. Arrows indicate the position of densely staining "junctional feet" that are the large cytoplasmic domain of a row of RyR1s that span the junctional space between the two membranes (adapted from (Protasi, Franzini-Armstrong, & Allen, 1998)). (B) 3-D model of the relative orientation of four $Ca_V1.1$ (i.e., α1s) L-type Ca^{2+} channel subunits (brown) and RyR1 (green) based on cyroEM reconstruction studies (adapted from (Wolf, Eberhart, Glossmann, Striessnig, & Grigorieff, 2003).

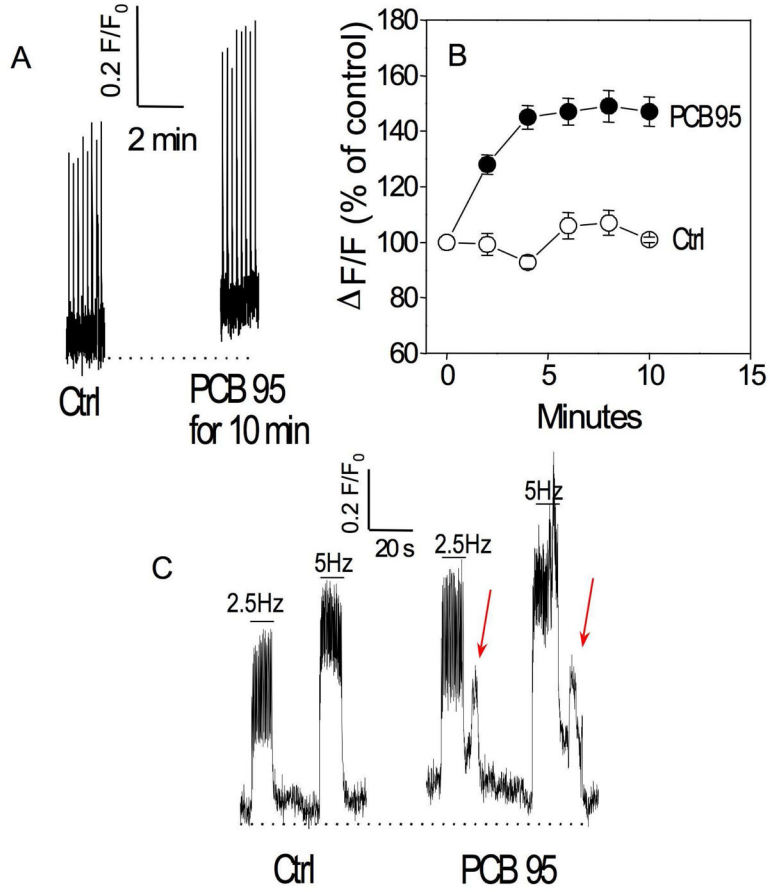

Fig 5.

Skeletal myotubes acutely exposed to 5μM PCB 95 exhibited significantly higher Ca^{2+} transient amplitudes evoked by low frequency (0.1Hz) electrical pulse trains (**A&B;** $p<0.05$) and a failure to recover their original baseline (i.e., resting Ca^{2+} level) compared to the corresponding control period when solvent (DMSO) alone was perfused (Ctrl). **(C)** Responses to 10 s electrical pulse trains of 2.5 or 5Hz resulted in significantly higher transient amplitudes compared to the corresponding control (Ctrl) period. Ectopic Ca^{2+} transients (red arrows) are frequently observed soon after electrical stimuli ceased in the PCB exposed myotubes and were not observed in control. Adapted from (Cherednichenko, 2009).

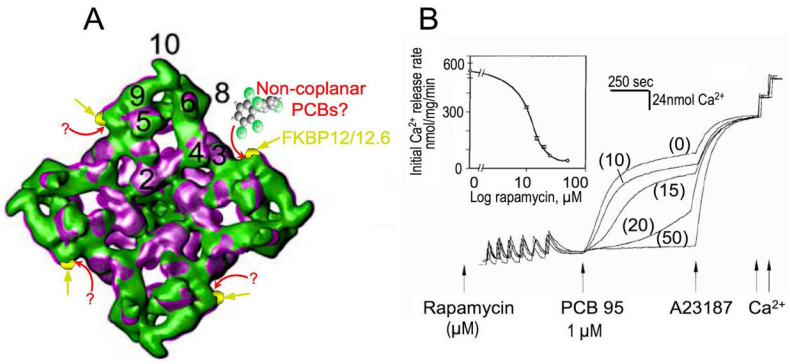

Fig 6.

(A) 3-D structure of RyR1 in the closed state at 10Å resolution showing the location of the FKBP12 docking site near domain 9 (adapted from (Samso, Feng, Pessah, & Allen, 2009). **(B)** PCB 95 triggered Ca^{2+} release from skeletal junctional SR is inhibited by pre-incubating with rapamycin that disrupts the FKBP12/RyR1 complex (adapted from (Wong & Pessah, 1997)

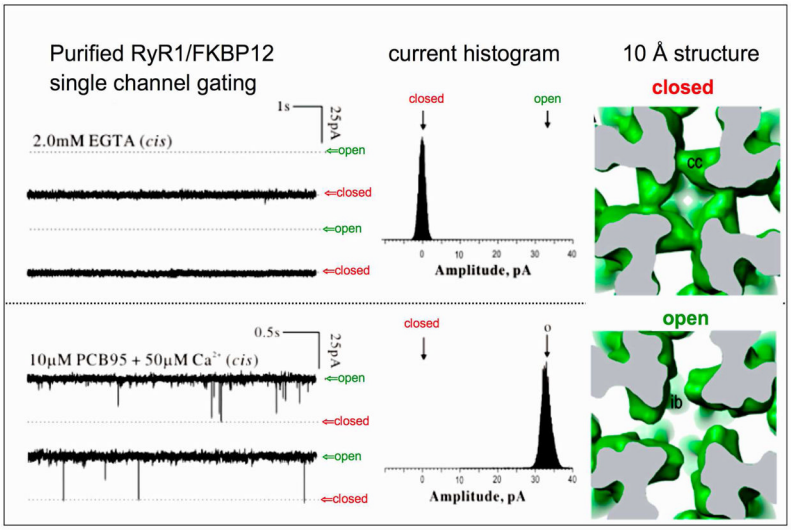

Fig 7.

PCB 95 directly stabilizes the fully open (conducting) conformation of the RyR1/FKBP12 channel complex reconstituted in the bilayer lipid membrane preparation, whereas EGTA fully closes the channel (left and middle panels). Right panels show the corresponding structural shifts calculated from cryoEM reconstruction of single hydrated particles showing the main constrictions along the ion pathway in the closed and open states. The cytosolic constriction (cc) relaxes and the inner branches (ib) become more separated in the open state. Adapted from (Samso et al., 2009)

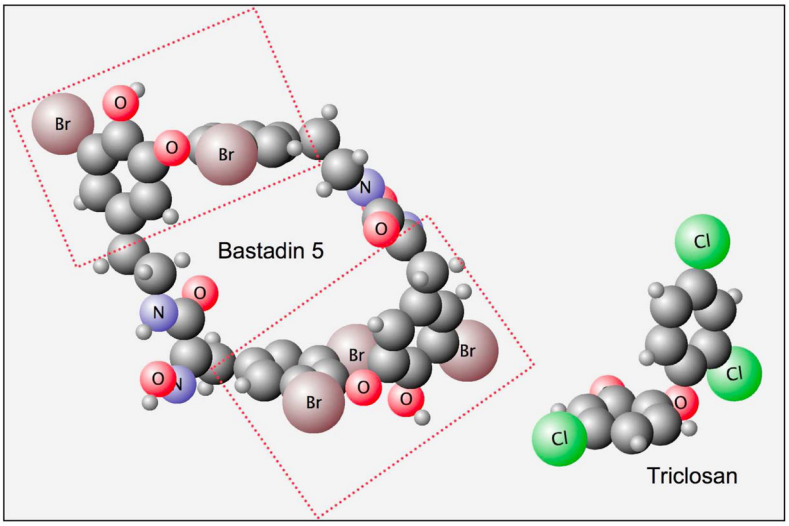

Fig 8.

Bastadin 5 showing “eastern: and “western” dibromocatechol ethers (red boxes) that are the putative pharmacophores for RyR1. The structure of the antibacterial triclosan is shown in the lower right.

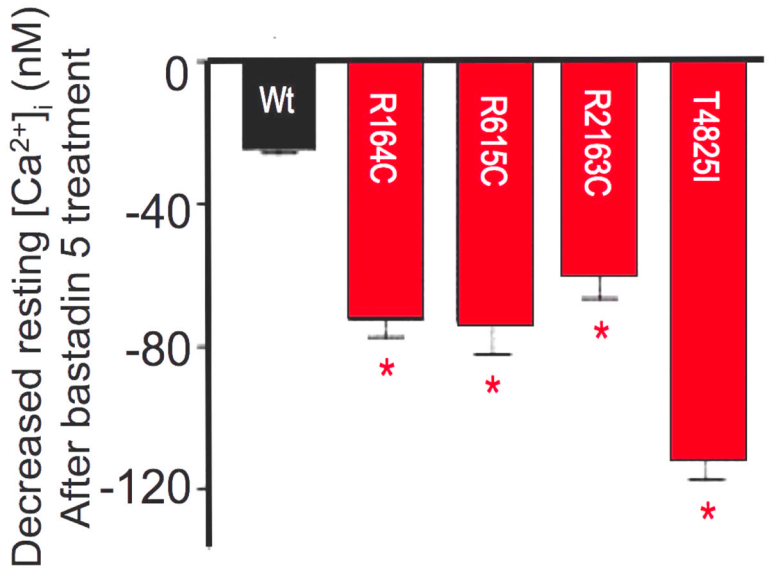

Fig 9.

Bastadin 5 in the presence of a ryanodine concentration that blocks RyR1 channels reduces resting Ca^{2+} to a greater extent in cells expressing missense mutations that confer MH susceptibility to humans than in cell expressing wild type RyR1 (Wt). *$p<0.05$ adapted from (T. Yang et al., 2007)

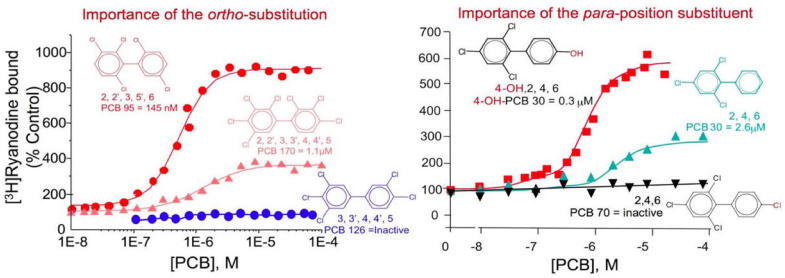

Fig 10.

Dose response relationship of selected PCBs towards enhancing the binding of [^{3}H]Ry to RyR1 showing the importance of ortho-substitutions (non-coplanarity (left panel) and substitutions at the *para* position.

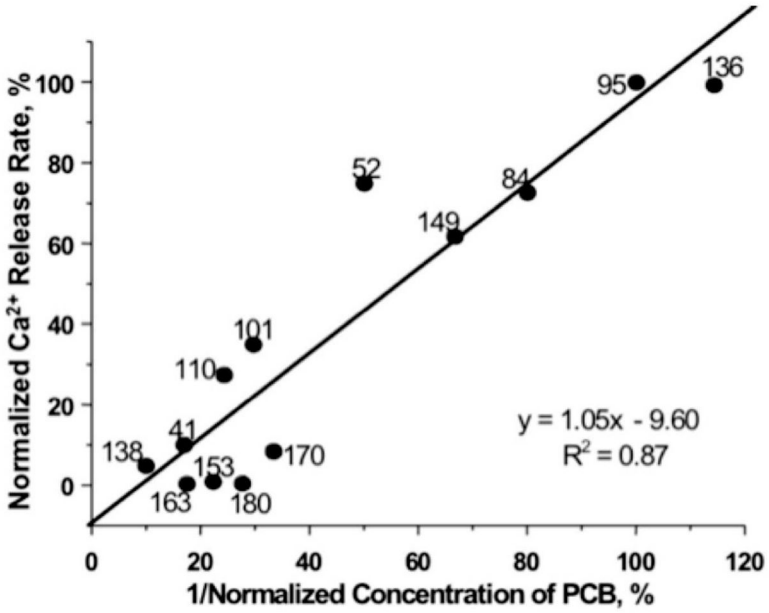

Fig 11.

Correlation between the PCB concentration needed to double [^{3}H]Ry binding to RyR1 and the initial rate of PCB-induced Ca^{2+} efflux from SR vesicles (data for each congener were normalized to respective parameters obtained with PCB 95). BZ numbers are given, Adapted from (Pessah et al., 2006).

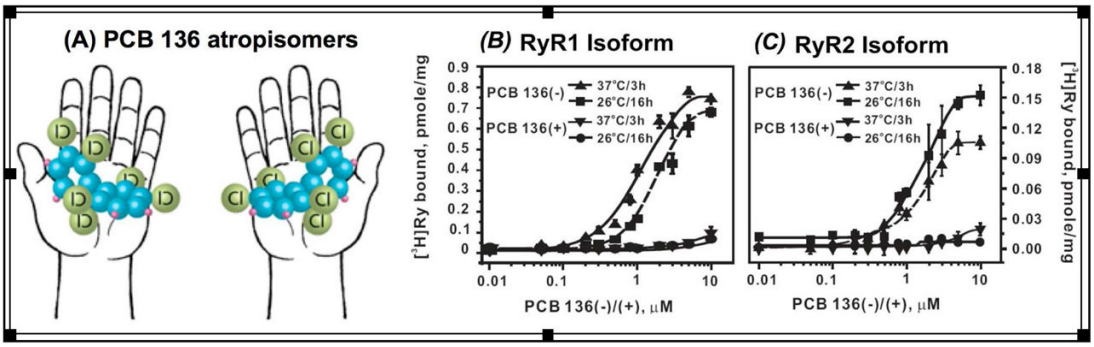

Fig 12.

(A) PCB 136 is chiral because the asymmetric distribution of chlorines prevents interconversion of its (+) and (−) atropisomers. Upon separation, (−) PCB 136 was found to be active towards enhancing the activity of RyR1 **(B)** and RyR2 **(C)**, whereas (+) PCB 136 was not active. Adapted from (Pessah et al., 2009)

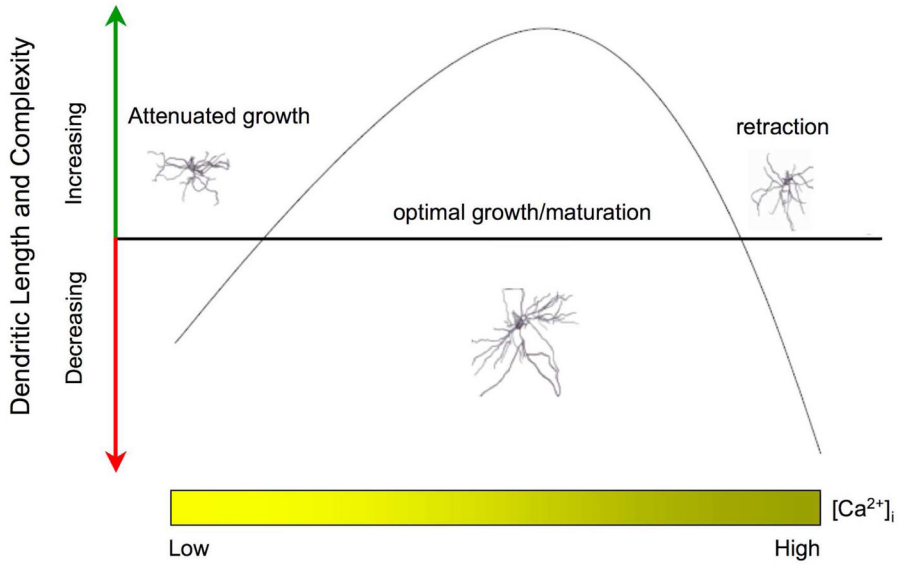

Fig 13.

Proposed relationship between intracellular Ca2+ concentration and dendritic growth. Adapted from (Segal, Korkotian, & Murphy, 2000).

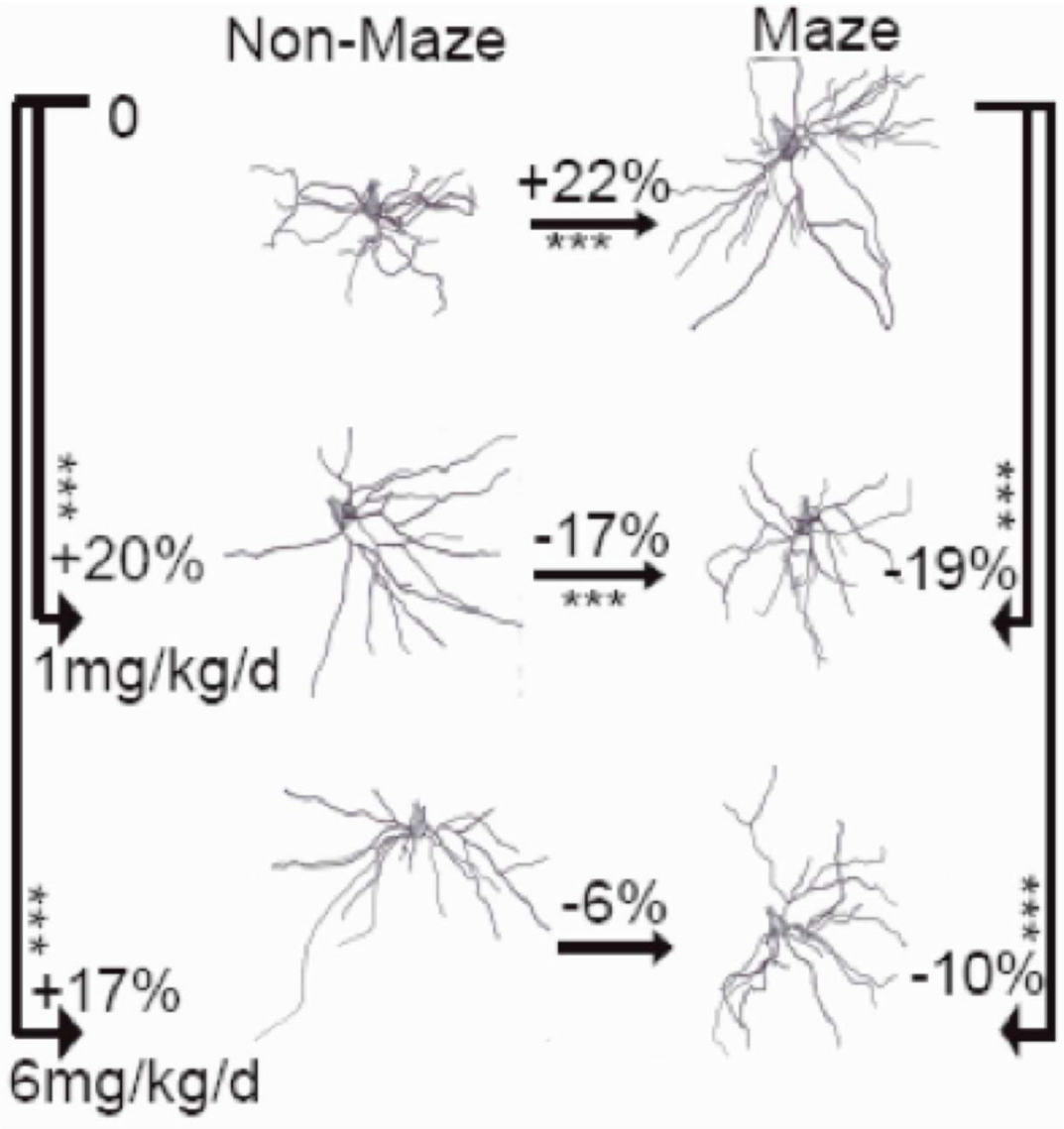

Fig 14. Developmental A1254 exposure interferes with normal dendritic growth and experience-dependent dendritic plasticity

Dendritic morphology was analyzed among P31 rats trained in the Morris water maze (Maze) and among littermates identically housed and exposed but not trained (Non-Maze). As seen in representative camera lucida drawings of the basilar dendritic arbor of cortical neurons, developmental exposure to A1254 at 1 or 6 mg/kg/d in the dam's diet throughout gestation and lactation significantly increased dendritic arborization relative to vehicle controls (0 mg/kg/d A1254). Maze training significantly increased dendritic complexity among animals in the control group but this experience-dependent plasticity was blocked among animals in the A1254 treatment groups with a more pronounced effect observed in the lower treatment group. Data are presented as the mean±SEM (N=17–21 neurons per group). The percent changes in dendritic length were calculated using data obtained from 17–21 neurons per treatment group. The percent change in dendritic length as a function of maze training was calculated as the difference in dendritic length of neurons in maze-trained animals versus non-maze-trained animals divided by the dendritic length of neurons in maze-trained animals multiplied by 100. *p<0.05; **p<0.01; ***p<0.001. From (D. Yang et al., 2009)

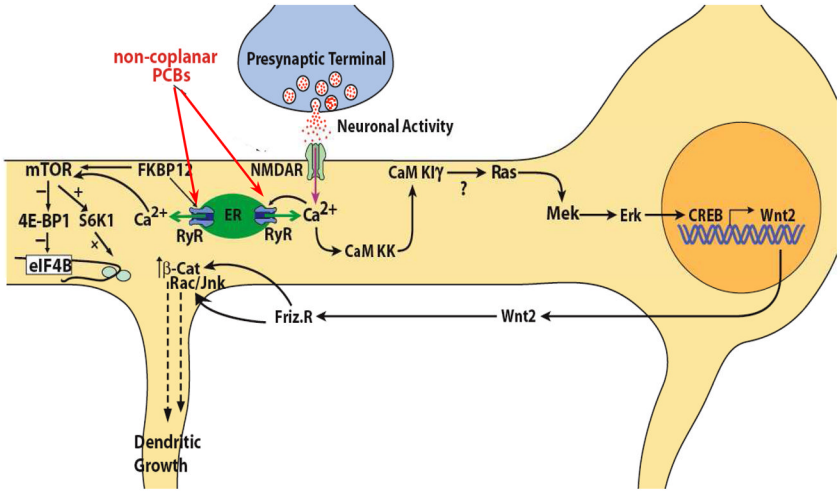

Figure 15.

Activity increases intracellular Ca2+ via NMDA receptor activation and calcium-induced calcium release, which alters dendritic growth via transcriptional or translational mechanisms. The former involves CaMK I activation and enhanced CREB-dependent Wnt transcription; Wnt binds the Frizzled receptor to activate downstream effector molecules β-catenin, JNK and Rac. The latter involves Ca2+-dependent activation of mTOR, which relieves repression of initiation factor-4E by 4EBP1. mTOR is regulated by FKBP12, which is targeted by non-coplanar PCBs.

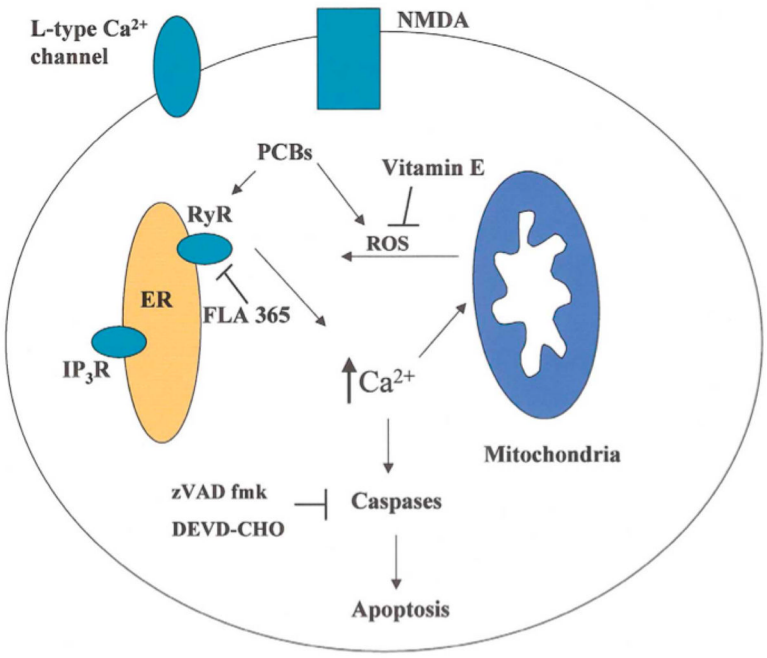

Fig 16. Mechanisms by which non-coplanar PCBs might induce apoptotic DNA fragmentation

Specific noncoplanar PCBs may directly activate the ryanodine receptor (RyR) causing release of Ca^{2+} from endoplasmic reticular (ER) stores. Increased cytoplasmic Ca^{2+} activates caspases resulting in apoptosis. Increased cytoplasmic Ca^{2+} may also cause increased mitochondrial Ca^{2+} influx, which increases generation of reactive oxygen species (ROS) thereby promoting caspase-dependent apoptosis. Alternatively, or in addition, PCBs may generate ROS directly, which then increase cytoplasmic levels of Ca^{2+} via activation of RyRs. Blocking the L-type voltage-sensitive Ca^{2+} channel with verapamil or the NMDA receptor with APV does not have any effect on PCB-induced DNA fragmentation, suggesting that, in this model system, extracellular calcium is not involved in the apoptotic signaling pathway.

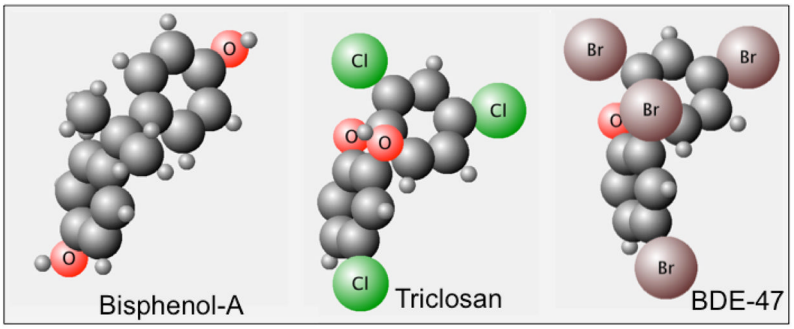

Figure 17.
3-D projections of Bisphenol A, triclosan, and 2,2′,4,4′-tetrabromodiphenylether (BDE-47). 3-D projections were calculated with the Molecular Dynamics Tool of ChemIDplus Advanced (Nat. Lib. Med.).