NON-AH RECEPTOR MECHANISMS UNDERLYING IMMUNOTOXICITY AND NEUROTOXICITY

ETIOLOGY OF PCB NEUROTOXICITY: FROM MOLECULAR TO CELLULAR DYSFUNCTION

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HUMAN DISEASE AND TISSUE PCB LEVELS: EPIDEMIOLOGICAL ASSOCIATIONS

Polychlorinated biphenyls (PCBs) are a group of synthetic halogenated aromatic hydrocarbons (HAHs) which have been widely dispersed in the environment. The unique chemical properties and low cost of producing PCBs have contributed to their extensive industrial use (1). The high lipophilicity and chemical stability of PCBs have resulted in widespread environmental contamination, and accumulation in biota. PCBs are found in extracts of virtually all environmental samples and human tissues (2, 3). Currently it is unclear if the presence of PCBs in biological tissues is causally or coincidentally related with human health problems (3). Among the 209 possible PCB congeners, those that lack chlorine substitutions at the *ortho*-position tend to be coplanar structures and are good ligands for the arylhydrocarbon (Ah) receptor. By contrast, PCB congeners with two or more *ortho*-chlorine substitutions favor noncoplanarity of the biphenyl, and exhibit little to no affinity for binding Ah receptor. Because of their very low Ah receptor activity, noncoplanar PCBs score very low on the standardized toxicity (TEQ) scale that is based on dioxin-like criteria. Thus the perception that PCBs with low TEQ have low biological activity and toxicity may be in large part responsible for why noncoplanar PCBs have received less scientific attention than their dioxin-like cousins. However, the seminal report of Seegal and co-workers in 1990 sparked attention of academic and government researchers to understand the nature and mechanisms by which noncoplanar PCBs elicit their rather unique biological activity. There is increasing evidence that ortho-substituted PCBs, and there metabolites, exhibit a unique spectrum of molecular and cellular effects compared to coplanar PCBs, especially their ability to alter Ca^{2+} signaling in lymphocytes, neurons and muscle cells (discussed below). Although noncoplanar PCBs have emerged as invaluable tools to probe the role of Ca^{2+} stores in neuronal cell growth and development, it must be emphasized that they collectively represent a significant component of PCB mixtures found in environmental samples and biological tissue (3). In this regard, it may be necessary to re-evaluate the TEQ as the only standardized measure of human health risk. Perhaps the most challenging goal in the field is to understand how molecular and cellular mechanism influence higher-ordered functions of the immune and nervous systems and they're relationship to disease.

In this respect, epidemiological studies suggest that in utero and lactational exposure to PCBs are correlated with overall decreased IQ scores, impaired learning and memory, neuromuscular function, and reading comprehension in children (4-7). More recently, Corrigan and coworkers identified a significantly higher level of PCBs having *ortho*-chlorine substitutions within the caudate nucleus of patients with Parkinson's disease (8). In a retrospective study, whole serum PCB levels were found to be highly correlated with the incidence of non-Hodgkin's lymphoma, whereas no such relationship was found with several other classes of xenobiotics (9).

Interestingly the risk of non-Hodgkin's lymphoma and PCB concentration and was poteniated by the presence of Epstein-Barr virus early antigen, suggesting a causal relationship involving specific mechanisms. Although epidemiological data fall short of proving causality, they do indicate that noncoplanar PCBs, once thought to lack biological activity, may mediate subtle changes in nervous and immune system function. Epidemiological data therefore provide compelling reasons to understand the molecular mechanisms by which noncoplanar PCBs (and related structures) alter aspects of signal transduction and processing not only in neurons, but also in immunocompetent cells (glia and lympocytes) which can indirectly alter nervous system function.

NON-COPLANAR PCBS ARE BIOLOGICALLY ACTIVE

The pioneering work of Seegal and co-workers (10-11) revealed that *ortho*-substituted PCB congeners, *i.e.*, those predicted to have low biological activity based on TEQ, in fact possess biological activity. In nonhuman primates, *ortho*-substituted PCB congeners decrease catecholamine levels in certain brain regions and reduced in rat pheochromocytoma cells (PC12 cells). Subsequent work substantiated this biological activity in primary cultures of cerebellar granule cells and implicated a mechanism involving general disruption of Ca^{2+} homeostasis and altered activity of protein kinase C (12, 13). How *ortho*-substituted PCB congeners alter Ca^{2+} regulation in neurons remains very controversial, although it is generally agreed that coplanar PCBs lack this type of activity. Whether *ortho*-substituted PCBs target multiple Ca^{2+} regulatory proteins and cellular membranes in a nonselective manner (11-14), or through a more selective receptor-mediated mechanism (15-19) is currently a central issue. Furthermore, the direct consequence of localized perturbation (as opposed to global) changes in Ca^{2+} signaling must be addressed considering our emerging understanding that cells rely on spatially distinct and temporally coded Ca^{2+} signals to control different aspect of function, growth, and neuroplasticity.

The goal of this presentation is to integrate current knowledge of how neurons and muscle cells generate meaningful Ca^{2+} signals, and to address what is known about how *ortho*-substituted PCB disrupt these signals. Clearly there are several gaps in our knowledge, especially about how PCB-modified Ca^{2+} signals relate to altered nerve cell growth, plasticity and higher order function. In this respect, we may seem to present a skewed perspective favoring a highly selective mechanism that involves "receptor" mediated interaction between ortho-substituted PCBs and the immunophilin FKBP12/ryanodine receptor complexes (FKBP12/RyR). Considering (1) new evidence demonstrating a central role of FKBP12/RyR in several important aspects of neuronal Ca^{2+} signaling, growth and plasticity and (2) the stringent structure-activity relationship for RyR activity, we feel this perspective is warranted.

Noncoplanar PCB elicit a unique array of biological activities. Allosteric modulation of microsomal Ca^{2+} channels can explain most of the biochemical and physiologic effects thus far reported with noncoplanar PCBs. The nature of the neurological effects induced by PCBs will depend on the congener present in a particular brain region and the time during development it is modifying localized Ca^{2+} signaling. Based on our current knowledge of localized signaling events, it is likely that noncoplanar will influence subtle aspects of development and aging of the nervous system by altering synaptic plasticity rather producing over pathophysiological lesions. In this

regard, the presence of other xenobiotics which alter Ca^{2+} signaling or Ca^{2+} dependent enzymes are likely to synergized the actions of PCBs. Considering the important role of immunophilins in regulating neuronal and immune cell function, it is likely that PCBs could synergize interactions between these two organs.

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