

Novel Pathway Involved in Neurodevelopmental Toxicity of PCBs

Non-dioxin-like (NDL) polychlorinated biphenyls (PCBs) are widespread environmental contaminants previously associated with neurological disorders in children. In a new study funded in part by the University of California (UC), Davis Superfund Research Program, UC Davis investigators working in collaboration with colleagues at Washington State University demonstrated a novel mechanism of PCB developmental neurotoxicity. Despite extensive research documenting that PCBs interfere with normal neurodevelopment, only recently have adverse outcome pathways of PCB developmental neurotoxicity been described. In this study, researchers extend on observations to explain one way NDL PCBs may be potential environmental risk factors for impaired brain development.

PCBs are a class of synthetic compounds grouped according to their molecular structure as dioxin-like or non-dioxin like. Although commercial production of PCBs was banned in most countries, including the United States in 1979, NDL PCBs persist in the environment and human tissues.

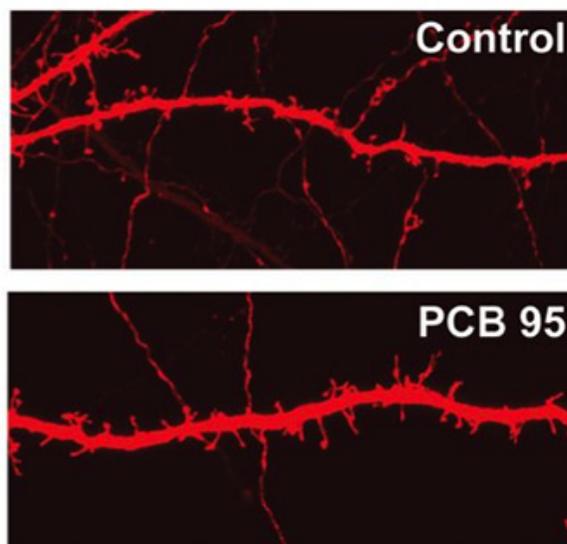
Understanding the pathway

A neuron, also known as a nerve cell, processes and transmits information through electrical and chemical signals. Chemical synapses are the structure that allows neurons to signal to each other and to non-neuronal cells such as those in muscles or glands. These synapses allow the nervous system to connect to and control other systems of the body.

A branched projection from a neuron, called a dendrite, conducts signals received from other cells through synapses to the cell body of the neuron. NDL PCBs have been shown to increase the growth of dendrites by stabilizing ryanodine receptor (RyR) calcium channels when they are in their open state, increasing calcium in the cell. RyRs are critically involved in regulating calcium release, which can activate a number of proteins that control dendrite growth in the body.

In this new study, authors extended previous findings of NDL PCB effects on dendrites to dendritic spines, small extensions from a neuron's dendrite. Dendritic spines are critical to normal neural function because they are the primary site to receive input from synapses. Dendritic spines are responsive to external cues moderated primarily by signaling pathways dependent on calcium, especially during development. Abnormalities in the density or shape of dendritic spines are associated with many neurodevelopmental disorders, including mental retardation, autism spectrum disorders, and schizophrenia.

The growth of dendrites by RyR calcium channels is dependent on the cyclic adenosine monophosphate response element binding protein, known as CREB, a factor capable of binding DNA and regulating gene expression. Researchers addressed the question of whether activation of CREB by NDL PCBs also affects the density or shape of dendritic spines.



PCB 95 induces dendritic spine formation in mouse hippocampal slice cultures, indicated by the additional outgrowths on the dendritic spine in the PCB 95-treated cells. (Image source: Lesiak et al., 2014, *J Neurosci* 34(3): 717-25)

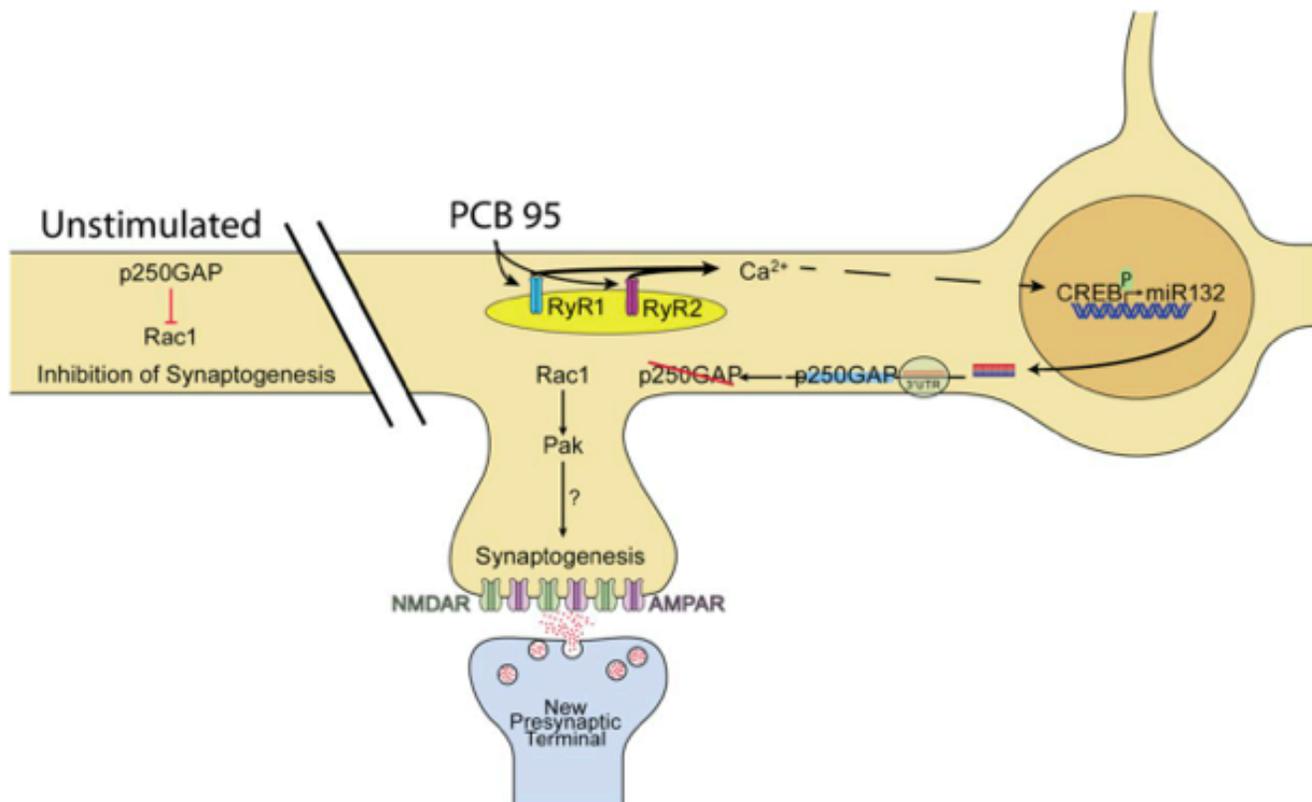
Pinpointing the mechanism of toxicity

PCB 95, a form of NDL PCBs, was administered to neuronal cell cultures from the hippocampus of the rat brain to identify the density of dendritic spines and potential for PCB 95 to modulate the signaling pathways that normally control dendritic spine formation.

Study authors found that PCB 95 significantly increased the number of dendritic spines and synapses, indicating abnormal growth and signaling. This also coincided with an increase in the production of a specific short non-coding RNA molecule, miR132, which functions to regulate protein expression via inhibition of mRNA. Specifically, miR132 suppresses the creation of the protein p250GAP that regulates the formation of synapses between neurons, or synaptogenesis.

Although synaptogenesis occurs throughout a human's life, synapse formation peaks during early brain development, making this an important period for normal neurodevelopment and a potentially critical window of susceptibility for PCB exposure.

These results demonstrate a novel mechanism of PCB developmental neurotoxicity where RyR sensitization modulates spine formation and synaptogenesis by increasing the production of miR132. Because miR132 interacts with several proteins involved in cognitive impairment and autism spectrum disorders, the authors speculate that PCB 95 exposure may contribute to increased risk for similar neurodevelopmental disorders.



Model of PCB 95-induced synaptogenesis. PCB 95 exposure sensitizes RyR1 and RyR2 to increase release of internal calcium stores. Increased cytoplasmic calcium triggers CREB, turning the protein on, stimulating CREB-dependent transcription. CREB activation increases creation of miR132 that then suppresses p250GAP translation. The decreased translation of p250GAP effectively releases inhibition of the Rac1 protein, which increases synaptogenesis. (Figure source: Lesiak et al., 2014, *J Neurosci* 34(3): 717-25)

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For more information, please refer to the following source:

Lesiak A, Zhu M, Chen H, Appleyard SM, Impey S, Lein PJ, Wayman GA. 2014. The Environmental Neurotoxicant PCB 95 Promotes Synaptogenesis via Ryanodine Receptor-Dependent miR132 Upregulation. *J Neurosci* 34(3): 717-25. doi: [10.1523/JNEUROSCI.2884-13.2014](https://doi.org/10.1523/JNEUROSCI.2884-13.2014)

