Medical Xpress

Research shows how PCBs promote dendrite growth, may increase autism risk

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New research from UC Davis and Washington State University shows that PCBs, or polychlorinated biphenyls, launch a cellular chain of events that leads to an overabundance of dendrites — the filament-like projections that conduct electrochemical signals between neurons — and disrupts normal patterns of neuronal connections in the brain.

"Dendrite growth and branching during early development is a finely orchestrated process, and the presence of certain PCBs confuses the conductor of that process," said Pamela Lein, a developmental neurobiologist and professor of molecular biosciences in the UC Davis School of Veterinary Medicine. "Impaired neuronal connectivity is a common feature of a number of conditions, including autism spectrum disorders."

Reported today in two related studies in the journal *Environmental Health Perspectives*, the findings underscore the developing brain's vulnerability to environmental exposures and demonstrate how PCBs could add to autism risk.

"We don't think PCB exposure causes autism," Lein said, "but it may increase the likelihood of autism in children whose genetic makeup already compromises the processes by which neurons form connections."

The senior authors of the studies were Lein and Isaac Pessah, chair of molecular biosciences in the School of Veterinary Medicine and director of the Center for Children's Environmental Health at UC Davis. Both are

researchers with the UC Davis MIND Institute, which is dedicated to finding answers to autism and other neurodevelopmental disorders. The lead author was Gary Wayman of Washington State University's Program in Neuroscience, who first described the molecular pathway that controls the calcium signaling in the brain that guides normal dendrite growth.

Wayman found that key cellular players, called calcium and calmodulin kinases, are activated by increased calcium levels. Activated calmodulin kinase then turns on the protein known as CREB that regulates genes that produce Wnt2, a potent molecule and the final arbiter of whether and how dendrites grow. Wnt2 directs structural proteins to construct scaffolding that supports dendrite growth and branching.

"Orderly choreography of the calmodulin kinase-to-Wnt2 pathway translates normal increases in calcium levels into normal levels of dendrite production," said Wayman. "The wiring of billions of neurons is dependent on the health of this cellular process and is crucial to proper development of virtually all complex behaviors, learning, memories and language."

For the current studies, the team set out to determine if that pathway was altered by exposure to PCBs, focusing on neurons of the hippocampus — the brain region linked with learning and memory and known to suffer impaired connectivity in many neurodevelopmental disorders.

The scientists also focused on the effects of an understudied PCB subset known as non-dioxin-like PCBs, which have been shown to increase calcium levels in neurons. Both non-dioxin-like PCBs and the more familiar dioxin-like subset were widely used in electrical equipment in the 1950s and 1960s. Banned in the 1970s because of the potential for dioxin-like PCBs to cause cancer, all PCBs are stable compounds that persist throughout the environment today.

One of the current UC Davis studies examined dendrite growth in rat pups born to and nursed by PCB-exposed mothers. Another study analyzed how PCBs affect rat neurons in cell cultures at developmental stages similar to those in the third trimester of pregnancy in humans. In both studies, PCB exposure levels were similar to those found in the human diet and in human tissues, including the placenta and breast milk.

Evaluation of the brains of the rats exposed to PCBs early in life showed significant overproduction of dendrites. The cellular studies showed that PCBs triggered the calcium pathway that led to the aberrant brain architecture, and that dendrite production was normal when that cellular pathway was blocked.

"We are the first to show that non-dioxin-like PCBs alter how the developing brain gets wired by hijacking the calcium signaling pathway and greatly expanding dendrite growth," said Lein.

The experiments also helped identify for the first time the specific trigger for this cellular chain of events as the ryanodine receptor (RyR) calcium channel. Pessah, a recognized leader in calcium-channel dysfunction and neurodevelopment, previously showed that RyR is selectively activated by non-dioxin-like PCBs. The new studies prove that RyR is a necessary component in the pathway that controls dendritic growth.

"These same calcium pathways are implicated in some forms of autism and, while environmental exposures alone do not cause autism, these new findings provide good evidence that PCBs could add to autism risk in genetically predisposed children," said Pessah. "Understanding the fundamental mechanisms by which PCBs alter neural networks sets the stage for research on environmental contaminants that are structurally related to PCBs, including flame retardants, and their risks to susceptible populations."

More information: The studies —"PCB 95 Promotes Dendritic Growth via Ryanodine Receptor-Dependent Mechanisms" and "PCB 95 Modulates Calcium-Dependent Signaling Pathway Responsible for Activity-Dependent Dendritic Growth" — will be published in a future print issue of the journal with several other investigations focused on autism and the environment. Copies of the UC Davis-Washington State University studies are available online now at dx.doi.org/10.1289/ehp.1104832 and dx.doi.org/10.1289/ehp.1104833

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