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SBRP "Research Brief" - Number 49

Title: Exploring the Mechanisms of Neurotoxicity Caused by Exposure to Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are a group of widely distributed, persistent environmental contaminants that accumulate in the tissues of animals and magnify in concentration as they are transferred through food chains. Humans are as susceptible to these processes of bioaccumulation and biomagnification as wildlife; in fact, most of us have some measurable level of PCBs in our bodies, primarily through consumption of food and water contaminated with trace amounts of these compounds. Once in the body, PCBs have a half-life of about 10 years, which varies by congener or specific PCB compound. The ubiquity and persistence of PCBs both in the environment and in humans are a concern, as are their associated toxic effects.

One of the greatest public health concerns surrounding PCBs is evidence from epidemiological studies suggesting that prenatal exposures to these compounds may lead to subtle behavioral, neurological and intellectual deficits in infants and young children. Similar neurotoxic effects have been reported in animals, including non-human primates exposed to PCBs in utero. Understanding the biological basis of the neurological effects induced by PCBs in animal models is a key to resolving the issue of whether these compounds are developmental neurotoxins in humans.

Researchers at the University at Albany-SUNY are investigating how PCBs alter brain physiology, with a focus on how these compounds affect a process called long-term potentiation (LTP). LTP is a long-lasting increase in the efficacy of synaptic transmission that results in a strengthening of the connection between nerve cells. It occurs only at selected sites in the brain, in areas known to be involved in higher brain functions. But it is absent in very old animals, as well as in animals that perform poorly in learning new tasks. LTP is blocked by agents such as lead that are known to result in a reduction of IQ. Therefore, it is widely accepted as one of the best model systems for studies of learning and memory, and is also an obvious possible site of action for PCBs.

Recently published work by this group has shown that acute exposure of brain slices from control animals results in an almost total block of LTP. This action occurs not only with several different PCB mixtures (Aroclors), but also with a coplanar, dioxin-like congener (3,4,3',4'-tetrachlorobiphenyl), as well as with a non-coplanar, ortho-substituted congener (2,4,4'-trichlorobiphenyl). This observation was somewhat surprising because several laboratories, including this one, have demonstrated a selective neurocytotoxicity of ortho-substituted congeners, but not coplanar ones. Thus, the scientists conclude that both ortho-substituted and coplanar PCBs have an inhibitory effect on LTP, but that these actions are distinct from those involved in PCB-mediated neuronal cell death.

The above experiments demonstrate that the effects of PCBs on IQ could potentially arise from a direct interaction of the compounds with brain cells. However, unpublished results of another experiment support a pathway whereby PCBs affect LTP through the depression of thyroid activity, which is a documented adverse effect of PCB exposure. The researchers have shown that animals made hypothyroid during development with a known goiter-producing compound have reduced LTP and that this effect is additive with acutely applied 2,4,4'-trichlorobiphenyl. These results suggest the effects of PCBs on cognitive function may be secondary to the actions of

these compounds on thyroid function.

Subsequent experiments have investigated how gestational and lactational administration of the highly persistent congener 2,4,5,2',4',5'-hexachlorobiphenyl affects LTP. This congener is present in most animals, including humans, and was once thought to be biologically inactive. Pregnant rats were exposed at three dose levels (1.25, 5.0 and 20.0 mg/kg/day) through day 21. LTP was recorded at day 30. What the researchers found is that LTP was reduced by greater than 50% at all dose levels, indicating that even the lowest dose was too high to see a dose-response relationship. These findings suggest this very persistent congener is highly neurotoxic.

Based on these studies, the scientists conclude that several different PCB mixtures and congeners can suppress LTP, a process that is considered to be an important part of the biological mechanism underlying learning and memory formation in mammals. The results suggest that LTP may be a possible site of action for PCBs and may contribute to the developmental neurotoxicity associated with PCB compounds. In addition to shedding light on potential mechanisms of neurotoxicity, these studies are significant for improving our understanding of the health consequences of PCBs, which will ultimately lead to a more accurate risk assessment for these compounds.

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To learn more about this research please refer to the following sources:

Niemi W.D., J. Audi, B. Bush, D.O. Carpenter. 1998. PCBs reduce long-term potentiation in the CA1 region of rat hippocampus. Exp Neurol 151: (1) 26-34.

As always, your feedback is welcomed.

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