The articles highlighted in this issue are three reports by Kevin Crofton and colleagues dealing with neuromodulatory effects of PCB (Gilbert, Mundy, and Crofton, pp. 102–111; Roegge et al., pp. 121–130; and Crofton et al., pp. 131–140).

Although the use of polychlorinated biphenyls (PCBs) has been banned in the United States since 1977, there is considerable evidence that humans continue to be exposed to PCBs, due primarily to consumption of contaminated foods. The consequences of these exposures have been investigated in a series of epidemiological studies that have demonstrated an association between consumption of contaminated fish and deficits in development and neuropsychological performance of infants and children whose mothers consumed these fish (Jacobson and Jacobson, 1996; Stewart et al., 2000), or following developmental exposure to environmental levels of PCBs and/or dioxins (Patandin et al., 1999).

The readers of this issue of Toxicological Sciences will have the opportunity to read three research articles describing the neurotoxicological consequences of developmental exposure of rats to PCBs. Although these articles deal with such seemingly diverse areas as behavior (Roegge et al.), electrophysiology (Gilbert et al.), and PCB-induced changes in thyroid hormone-mediated hearing loss (Crofton et al.), they provide an introduction to the complex nature of PCB neurotoxicology.

The article by Roegge et al. demonstrates that perinatal exposure of rats to 6 mg/kg/day of a commercial mixture of PCBs (Aroclor 1254) results in deficits in performance on a spatially mediated task (i.e., a twelve-arm, radial-arm maze task) in only male offspring. Because male rats perform better on spatial tasks than females, the authors suggest that PCBs may de-masculinize male offspring by altering endocrine function during development, resulting in similar performance of the treated male and the untreated female offspring. Although not mentioned by the authors, PCBs (or more likely their hydroxylated metabolites) also interfere with thyroid hormone function by binding to the T4 transporter, inducing metabolism and reducing circulating concentrations of thyroid hormone. Thus, PCBs may affect various endocrine systems, including thyroid and gonadal hormones, during critical periods of brain development that may have profound, but differential effects, on learning and memory in male and female rats.

The article by Gilbert et al. describes changes in hippocampal long-term potentiation (LTP), a fundamental plasticity process that reflects the neurophysiological and biochemical changes that support learning at the synaptic level. Decrements in the magnitude of dentate gyrus LTP in vivo, and increases in the threshold necessary to induce it, were found in adult males following developmental exposure to the same commercial mixture used in the previous studies. These findings are significant because they identify a brain region affected by developmental exposure to PCBs and provide an experimental model system that may aid in understanding the mechanisms by which PCBs induce neurotoxicity. Although decrements in LTP were observed, PCB-exposed animals performed similarly to controls on a hippocampally-mediated spatial task, the Morris Water Maze. This lack of concordance between LTP and one measure of spatial learning demonstrates not only the complexity of the neuronal changes induced by perinatal exposure to PCBs, but also the difficulties in selecting behavioral tasks that reflect underlying neuronal processes altered by PCBs. However, deficits in performance on a twelve-arm, radial-arm maze task were noted by Roegge et al., perhaps suggesting an association between deficits in induction of LTP and performance on a more demanding spatial task.

The article by Crofton et al. employs cross-fostering techniques to determine whether their previously reported thyroid-mediated otoxic effects were due primarily to prenatal versus postnatal exposure to PCBs. These authors demonstrated that perinatal (i.e., pre- and postnatal exposure), as well as postnatal exposure only, resulted in significant decreases in circulating concentrations of T₄, and an approximately 20-dB increase in
hearing thresholds with no changes observed in animals exposed only during gestation. These findings are significant because they clearly illustrate the different critical windows of susceptibility of the peripheral auditory system (i.e., the cochlea) compared to the central nervous system (CNS), following PCB-induced hypothyroidism (i.e., the critical period for PCB effects on the rat auditory system is entirely postnatal, while the critical periods for CNS development include both the prenatal and postnatal period). In addition, the research from Crofton et al. clearly links PCB-induced changes in thyroid hormone during a specific period of development with structural (i.e., cochlear hair cells) and functional (i.e., hearing loss) changes.

These three articles are briefly reviewed, rather than highlighting a single article, in order to emphasize the complex changes in CNS function that occur following exposure to PCBs. Thus, despite these well-planned and -executed studies (as well as the numerous other articles that have been published on the same topic), there is still little consensus concerning which underlying mechanisms are responsible for the reported changes in complex behaviors (i.e., learning and memory) that occur following developmental exposure of both humans and experimental animals to PCBs. For example, PCBs induce changes in several neurotransmitter systems, including biogenic amines and the cholinergic system (Eriksson and Fredriksson, 1996; Seegal, 1995), that mediate many of the behaviors altered by PCBs. Nevertheless, there are few if any studies that have either successfully correlated change in neurotransmitter function in behaviorally “relevant” brain areas with PCB-induced behavioral deficits or perturbed neurotransmitter systems, using pharmacological agents to investigate neurotransmitter changes following developmental exposure to PCBs. Thus, Roegge et al. challenged animals with scopolamine (a cholinergic agent) but were unable to detect any drug-induced differences in behavior between PCB-exposed and control animals again demonstrating the complex processes that affect cognitive performance.

Considerable attention has been devoted to understanding the endocrine consequences of developmental exposure of both wildlife and experimental animals. However, the majority of these studies are limited to examination of the effects of PCBs on thyroid hormone and estrogen. PCBs and/or their metabolites bind with high affinity to the T₄ transporter (i.e., transthyretin) and induce metabolism of T₄ due to upregulation of UDPGT (Brouwer et al., 1998). However, due to increased activity of the enzyme that converts T₄ to T₃ (i.e., Type II deiodinase), brain concentrations of the biologically more relevant T₃ are not altered in offspring of PCB-treated dams. However, unlike the brain, PCB-induced decreases in circulating levels of T₄ and T₃ have profound consequences on cochlear development that are reversible following T₃ supplementation, perhaps suggesting that the cochlear deiodinase is not upregulated to the same extent as that in the brain.

Some PCB congeners (or more likely their hydroxylated metabolites) act as weak estrogen agonists, bind to the estrogen receptor, induce cellular proliferation in MCF-7 cells (a human breast cancer cell line), and increase uterine wet weight in prepubertal rats. These effects may, in part, be mediated by hydroxylated PCB metabolites that inhibit estradiol sulfotransferase activity (Kester et al., 2000), thus increasing the likelihood that the fetus may be exposed to elevated levels of estrogen. The consequences of such exposure, particularly during critical periods of brain development, have not been fully elucidated. However, they may play a role in the gender-specific effects of PCBs on maze learning reported by Roegge et al., as well as in the elevation of brain dopamine seen following developmental exposure to certain coplanar PCB congeners (Seegal et al., 1997).

So far, only the neurotoxicological consequences of developmental exposure to PCBs have been discussed. In addition, the most relevant vectors for exposure of humans to anthropogenic contaminants are via food products, including freshwater fish that contain many known and suspected toxicants in addition to PCBs. Thus, a daunting but highly relevant and important task, investigation of the neurotoxicological consequences of simultaneous exposure to several toxicants, needs to be addressed if environmental neurotoxicologists and risk assessors are to better understand the risks and mechanisms of action by which the complex mixtures of toxicants found in the environment alter CNS function and behavior.

In summary, some of the complexities and opportunities for further research in the sub-discipline of PCB neurotoxicology have been mentioned. Unlike other environmental neurotoxicants such as lead and mercury, PCBs consist of several different classes of congeners that differ in structure and in the potential mechanisms by which they alter nervous and endocrine systems, differences that ultimately may influence behavior. Due to these complexities, it is likely that a full understanding of their neurotoxic potential can only be realized by collaborative, multi-disciplinary studies similar to those presented in this issue.

REFERENCES


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