PCBs INDUCE LONG-TERM CHANGES IN DOPAMINERGIC FUNCTION IN THE NON-HUMAN PRIMATE

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The persistence of neurochemical change after cessation of exposure to PCBs was examined in the adult non-human primate. Male *Macaca nemestrina* were exposed to either Aroclor 1016 or 1260 for 20 weeks and then followed for an additional 24 weeks post-exposure. Initial exposure reduced regional brain dopamine (DA) concentrations in both Aroclor exposure groups. In spite of significant (50-60%) decreases in brain PCB concentrations in the post-exposure animals, brain DA concentrations continued to be depressed compared to control animals. We suggest that these persistent effects are due to the initial insult rather than the continued action of the remaining PCBs found in the brains of post-exposure animals.

INTRODUCTION

Perinatal exposure to PCBs yields long-lasting changes in behavior in humans[1] and behavior and neurochemistry in experimental animals.[2-4] These changes in neuronal function are thought to be due to toxicant effects on neuronal growth and synaptogenesis[5]. However, these potential actions cannot be the only mechanisms by which PCBs alter neurochemical function since exposure of the adult non-human primate and rodent also yields changes in neuronal function.[6,7] Information on the duration of neurochemical change in the adult and the mechanisms by which adult exposure to PCBs alters neuronal function will aid in elucidating potential mechanisms by which perinatal exposure to PCBs alters neuronal function.

METHODS

Subjects consisted of adult male non-human primates, *Macaca nemestrina*, three to five years of age. All animals were singly housed in stainless steel primate cages and given *ad libitum* access to water and NIH primate chow supplemented with fruit. All animal procedures were approved by the Institutional Animal Care and Use Committee.

Animals were orally-exposed to 3.2 mg/(kg·day) of either Aroclor 1016 or Aroclor 1260, on a daily basis, for twenty weeks. We measured daily food consumption, collected measures of animal well-being and determined, on a biweekly or monthly basis, serum concentrations of PCBs. Following the 20 week exposure to PCBs the animals were removed

from PCBs and followed for an additional 24 weeks post-exposure. In both the initial 20 week exposure and in the 24 week post-exposure groups there were 3-5 animals/group.

At the end of the post-exposure interval the animals were sacrificed, their brains rapidly removed, sliced along the mid-line, frozen in powdered dry-ice and stored in a -80°C freezer.

2-mm thick coronal sections were cut and 2-mm diameter punches were taken from the different brain regions, rapidly weighed and homogenized in forty volumes of ice-cold 0.2 N perchloric acid containing 100 mg/l of EGTA. Each sample was centrifuged and concentrations of biogenic amines and metabolites were determined in the supernatant by high-performance liquid chromatography with electrochemical detection.[8] PCB concentrations in the tissue pellet were determined by high-resolution glass capillary gas chromatography.[9]

RESULTS

Brain PCB Concentrations

Brain PCB concentrations, measured 24 weeks post-exposure, were lower than values obtained from similarly dosed animals sacrificed immediately following 20 weeks exposure (Table I). The highest PCB concentrations were observed in the Aroclor 1260 exposed animals.

PCB-Induced Changes in Brain Biogenic Amine Concentrations

Exposure to either Aroclor 1016 or Aroclor 1260 for 20 weeks significantly decreased DA concentrations in all brain regions except for the substantia nigra (Table II). DA concentrations in brain regions from both Aroclor exposure groups, except for the substantia nigra, continued to be depressed 24 weeks following removal from PCBs.

TABLE I. REGIONAL PCB CONCENTRATIONS IN NON-HUMAN PRIMATE BRAIN AFTER 20 WEEKS EXPOSURE OR 24-WEEKS POST-EXPOSURE

Region	Concentration (ppm)	
	20 Weeks Exposure	24 Weeks Post-Exposure
Aroclor 1016		
Caudate	4.1±0.4	1.3±0.3
Putamen	5.0±0.8	1.2±0.3
Substantia Nigra	4.1±2.0	2.2±0.3
Hypothalamus	3.4±0.7	1.0±0.2
Aroclor 1260		
Caudate	19.3±0.4	3.8±1.0
Putamen	21.9±0.6	5.0±2.0
Substantia Nigra	16.9±2.1	9.5±0.4
Hypothalamus	19.3±10.2	0.6±0.1

TABLE II. REGIONAL DOPAMINE CONCENTRATIONS IN NON-HUMAN PRIMATE BRAIN AFTER 20 WEEKS EXPOSURE OR 24 WEEKS POST-EXPOSURE

Region	Concentration (ppm)		
	Control (N=5)	20 Weeks Exposure (N=4)	24 Weeks Post-Exposure (N=4)
Aroclor 1016			
Caudate	18.3±1.2	15.2±0.3*	14.2±0.6*
Putamen	19.0±0.7	16.3±0.3**	15.1±0.6**
Substantia Nigra	3.6±0.9	1.2±0.5	3.4±0.6
Hypothalamus	0.9±0.1	0.4±0.1**	0.3±0.1**
Aroclor 1260			
Caudate	18.3±1.2	14.7±0.4*	14.1±0.8*
Putamen	19.0±0.7	15.8±0.6**	14.6±0.4**
Substantia Nigra	3.6±0.9	2.4±0.6	2.0±0.5
Hypothalamus	0.8±0.1	0.5±0.1**	0.4±0.0**

*=$p \leq 0.05$, **=$p \leq 0.01$, with respect to the control group using the Student-Newman-Keuls test.

DISCUSSION

The major finding of this study is that DA concentrations in the majority of the brain regions examined in animals sacrificed immediately after exposure continue to be depressed 24 weeks after removal from PCBs.

These findings are important because they demonstrate a weakening of the relationship between brain PCB concentrations and alterations in neurochemical function. In previous studies, where we examined the effects of continuous exposure to PCBs,[6,7] we demonstrated a strong relationship between applied dose, brain PCB concentrations and decreases in brain neurochemical function. However, in this study we find evidence of continued depression in brain DA concentrations in animals with brain PCB concentrations similar to those seen in lower-dosed animals sacrificed immediately after exposure who did not show evidence of decreases in brain DA concentrations[6]. Thus, the neurochemical changes induced by the initial 20-week exposure to the Aroclor mixtures persist 24 weeks post-exposure, in spite of reduced brain PCB concentrations that had not previously been associated with neurochemical change. These results suggest that the initial insult or injury, rather than the continued action of the lower concentrations of PCBs found in the brains of the post-exposure animals, is responsible for the continued depression in neurochemical function.

In summary, these results suggest that the long term dysfunctions in behavior and/or neurochemistry following perinatal exposure of both animals and humans to PCBs might be due not only to the neuroteratogenic action of PCBs but also to persistent alterations in dopaminergic function induced by the initial exposure and insult.

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