NEUROTOXIC EFFECTS IN ADULT MICE NEONATALLY EXPOSED TO ORTHO-SUBSTITUTED POLYCHLORINATED BIPHENYLS.

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Introduction

Human epidemiological studies indicate that perinatal exposure to polychlorinated biphenyls (PCBs) might cause developmental neurotoxic effects, and animal studies have shown that exposure to PCBs during fetal and postnatal development can cause behavioural deviations and changes in brain transmitters[1]. Some of the animal studies, performed with commercial mixtures of PCBs, and in vitro studies suggest that ortho-substituted PCBs might be of importance for the neurotoxic effects[2]. In our previous studies we have shown that low dose exposure to environmental toxicants, such as DDT, pyrethroids and nicotine, when given during a defined period of the perinatal brain development can lead to permanent derangement of the cholinergic system and of the animals´ behaviour as adults[3,4].

The present study was undertaken to investigate the effects of neonatal exposure to ortho-substituted PCB congeners 2,4,4´-trichlorobiphenyl (IUPAC 28), 2,2´,5,5´-tetrachlorobiphenyl (IUPAC 52), 2,3´,4,4´,5-pentachlorobiphenyl (IUPAC 118) and 2,3,3´,4,4´,5-hexachlorobiphenyl (IUPAC 156) on: spontaneous motor behaviour, learning and memory function, cholinergic muscarinic and nicotinic receptors and biogenic amines in the CNS, of the adult animal.

Methods

The PCB congeners 2,4,4´-trichlorobiphenyl (PCB 28), 2,2´,5,5´-tetrachlorobiphenyl (PCB 52), 2,3´,4,4´,5-pentachlorobiphenyl (PCB 118) and 2,3,3´,4,4´,5-hexachlorobiphenyl (PCB 156) were generously donated by Dr. Å. Bergman (Wallenberg Laboratory, University of Stockholm, Sweden). The substances were orally administered to neonatal NMRI-mice as one single dose on postnatal day 10. The amounts of the different congeners given were as follows; 2,4,4´-trichlorobiphenyl, 0.18 mg (0.7 μmol), 0.36 mg (1.4 μmol), 3.6 mg (14 μmol)/kg body wt; 2,2´,5,5´-tetrachlorobiphenyl, 0.20 mg (0.7 μmol), 0.41 mg (1.4 μmol), 4.1 mg (14 μmol)/kg body wt; 2,3´,4,4´,5-pentachlorobiphenyl, 0.23 mg (0.7 μmol), 0.46 mg (1.4 μmol), 4.6 mg (14 μmol)/kg body wt; 2,3,3´,4,4´,5-hexachlorobiphenyl, 0.25 mg (0.7 μmol), 0.51 mg (1.4 μmol), 5.1 mg (14 μmol)/kg body wt. Mice serving as controls received 10 ml/kg body wt. of the 20% fat emulsion vehicle in the same manner.

Spontaneous behaviour: the test was performed in male mice at the age of 4 months. The test measures locomotion: horizontal movement, rearing: vertical movement, and total activity: all types of vibration within the test cage, i.e. those caused by mouse movements, shaking (tremors) and grooming.

Swim maze: the test was performed in male mice at an age of 5 months. The swim maze was of Morris water maze type. The mice ability to find a submerged platform was studied for 5 days. Performance in a swim maze of Morris maze type has been suggested to be correlated to cholinergic function in the CNS.

Radial-arm maze: the test was performed in male mice at an age of 5 months. The radial maze was constructed of 8 arms radiating from a circular platform. All arms were baited with a small food pellet and the latency to find all 8 pellets and the number of errors (errors made in acquiring all 8 pellets) were studied.

Receptor assays: Measurement of the nicotinic cholinergic receptors (NAChR), the proportions of high- and low affinity binding sites and their corresponding affinity constants, in the P2 fraction from cerebral cortex was performed in a competition binding assay by using the tritium-labeled nicotine (L-(-)-[N-methyl-^{3}H]-nicotine and different concentrations of unlabelled (-)nicotine. The muscarinic cholinergic receptor (MAChR) density in hippocampus was assayed by measuring tritium-labelled quinuclidinyl benzilate ([^{3}H]QNB) specifically bound in the P2 fraction.

The levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) in striatum were measured by high-performance liquid chromatography.

Results and Discussion

The spontaneous behaviour test revealed in the experiment with PCB 28 and PCB 52 significant group x period interactions for the 'locomotion', 'rearing' and 'total activity' variables, respectively. Pairwise testing between PCB 28, PCB 52 and control groups showed a significant dose-related change, in all three test-vaiables, locomotion, rearing and total activity. In the experiment with PCB 118 and PCB 156 there were no significant group x period interactions for the 'locomotion', 'rearing' and 'total activity' variables, respectively, nor were there any treatment effects.

The maze learning tests was performed in mice receiving the two highest doses of PCB 28 and PCB 52, mice that showed deviated spontaneous behaviour. Swim maze performance during the acquisition period of the spatial learning ability, measured from day 1 to day 4, showed that all mice significantly improved their ability to find the platform, and there were no significant group x period interactions for either PCB 28 or PCB 52 vs control. On day 5 the location of the platform was changed for relearning by reversal trials. Controls significantly improved their ability to find the new position but mice receiving PCB 52 (4.1 mg/kg bw) was significantly different from controls. Adult mice neonatally exposed to PCB 52 (4.1 mg/kg bw) showed also impairment in radial-arm maze learning. These mice displayed significantly longer latencies and made more errors than control mice.

Nicotinic receptors were analysed in adult mice (5 mon) neonatally exposed to the highest dose of PCB 28 and PCB 52. The competition binding assay revealed only one population of binding sites, high-affinity, in the cerebral cortex of adult mice neonatally treated with PCB 52 (4.1 mg/kg bw). Comparison between controls and PCB 28 treated mice showed no significant difference in either the proportion of high- and low-affinity binding sites or in the corresponding affinity constants. No significant changes were observed in the density of MAChR in the hippocampus or in the levels of DA, DOPAC, HVA, 5-HT and 5-HIAA in the striatum in adult mice neonatally exposed to PCB 28 or PCB 52.

The present investigation shows that neonatal exposure to low chlorinated ortho-substituted PCBs, 2,4,4´-tri- and 2,2´,5,5´-tetrachlorobiphenyls, can induce neurotoxic effects in the adult animal. Both PCB 28 and PCB 52 induced permanent abberations in spontaneous motor behaviour. Furthermore, neonatal exposure to PCB 52 also affected learning and memory functions in the adult animal. In the animals showing deficits in memory and learning function the cholinergic nicotinic receptors in the cerebral cortex was affected.

Acknowledgements

Financial support by grants from the Swedish Environmental Protection Board, the Swedish Work Environmental Foundation and the Bank of Sweden Tercentenary Foundation.

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