Interaction between PCBs and between PCBs and other environmental agents

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Introduction

Our environment is exposed to innumerable hazardous contaminants and mental health is constantly affected by a variety of environmental pollutants, whether singly or in various combinations. Many of the chlorinated hydrocarbons used in various industrial processes, e.g. PCBs (polychlorinated hydrocarbons) and as pesticides, e.g. DDT, have become known as persistent contaminants of the environment. Other potential environmental hazards can be the short-acting substances which, although they do not become bioconcentrated in biological systems, may nevertheless induce irreversible disorders in organisms.

Several epidemiological studies indicate that exposure to environmental pollutants during early human development can have deleterious effects on cognitive development in childhood. Such exposure may also be involved in the slow, implacable induction of neurodegenerative disorders and /or to interfere with the normal aging process.

During perinatal development of the mammalian brain, there is a period of rapid brain growth, known as the 'brain growth spurt' (1). In Man, this period begins during the third trimester of gestation and continues throughout the first 2 years of life. In mouse and rat, this period is neonatal, spanning the first 3-4 weeks of life. During this period of rapid growth, the brain undergoes several fundamental developmental phases, viz. maturation of axonal and dendritic outgrowth, establishment of neural connections, synaptogenesis, multiplication of glia cells with accompanying myelinization, and cell, axonal and dendritic death. The 'brain growth spurt' is associated with numerous biochemical changes that transform the feto-neonatal brain into that of the mature adult. One of the major signal substances in the CNS is acetylcholine (ACh), which acts as the transmitter in the cholinergic pathways. In rodents, this transmitter system in the CNS undergoes rapid development during the first 3-4 weeks after birth (2) when gradually increasing numbers of muscarinic and nicotinic receptors are found in the cerebral cortex and hippocampus (2,3). The cholinergic transmitter system is involved in many behavioural phenomena (4) and correlates closely with cognitive functions.

In a series of studies we have shown that low-dose exposure to environmental agents such as DDT, pyrethroids, organophosphates, paraquat, PCBs, and nicotine, during the rapid development of the neonatal mouse brain, can lead to irreversible changes in adult brain function (5). The induction of these disturbances occurs at doses that apparently have no permanent effects when administered to the adult animal. We have also seen that there can be a critical period during neonatal development of the mouse brain when these permanent effects are induced (5,6,7,). Furthermore, an increased susceptibility to toxic agents can be observed in adult animals exposed during neonatal life, indicating that neonatal exposure to toxic agents can potentiate and/or modify the reaction to adult exposure to xenobiotics (8,9).

Experiments

Neonatal exposure to different single PCB congeners have been shown to induce neurotoxic effects that become functionally evident in the adult animal. Induction of permanent aberrations in spontaneous behaviour have been seen after neonatal exposure to ortho-substituted PCBs such as 2,4,4'-tri- (PCB 28), 2,2',5,5'-tetra- (PCB 52) and 2,2',4,4',5,5'-hexachlorobiphenyls (PCB 153) (5,11), and after neonatal exposure to co-planar PCBs such as 3,3',4,4'-tetra- (PCB 77), 3,3',4,4',5-penta- (PCB 126) and 3,3',4,4',5,5'-hexachlorobiphenyl (PCB 169) (5,12). This effect seems also to worsen with age, as seen after neonatal exposure to PCB 153, PCB 126 and PCB 169. Furthermore, neonatal exposure to the di-ortho substituted PCBs, PCB 52 and PCB 153, and the co-planar PCBs, PCB 126 and PCB 169, also affected learning and memory functions in the adult animal. In the animals showing deficits in learning and memory function after neonatal exposure to PCB 52, the cholinergic nicotinic receptors in the cerebral cortex were affected, and after neonatal exposure to PCB 126, the cholinergic nicotinic receptors in the hippocampus were affected.

These PCB studies have also indicated region specific effects from neonatal exposure to PCBs where the di-ortho-substituted PCB 52 affects nicotinic receptors in the cerebral cortex while the co-planar PCB 126 affects nicotinic receptors in the hippocampus. This might implicate interactive neurotoxic effects between di-ortho substituted and co-planar PCBs. Recent studies have also shown an increased functional disorder to occur in spontaneous behaviour when neonatal mice are co-exposed to both PCB 52 and PCB 126 (Fig. 1). Furthermore, it appears that both brain regions have to be affected before this interactive functional disorder is seen, indicating a threshold-value for induction of interactive effects.

In our investigations we have seen that two of the most widely spread environmental toxicants, PCB and nicotine, can affect the same type of cholinergic receptor in the cerebral cortex, namely the nicotinic receptors (5,11,13).

Nicotine is an agent known to affect the cholinergic transmitter function. Nicotine, which can be found in certain pesticides, makes its impact on human health as a component in tobacco products. Nicotine is also known as one of the most commonly used dependence producing substances. Nicotine is an agonist for nicotinic receptors, but may also mediate the release of neurotransmitters such as ACh, dopamine, norepinephrine and serotonin. Neonatal exposure to low doses of nicotine on spontaneous behaviour and nicotine-induced behaviour in 4-month-old mice and on the development of nicotinic receptors in the brain indicated that nicotine can prevent the development of LA nicotinic binding sites (assayed with (-)-[N-methyl-^{3}H]nicotine)

in the cerebral cortex and that this exposure induces a different behavioural response to nicotine in adult animals (5,13). This effect is similar to that observed after neonatal exposure to PCB 52 (5,11). In a recent study we have observed that co-exposure to both nicotine and PCB 52 affects the development of nicotinic receptors, measured by binding of alfa-bungarotoxin. Alfa-bungarotoxin is an antagonist to ACh and is suggested to bind to nicotinic receptor subtype made up by alfa$_7$ subunits, showing similarities to the LA nicotine binding sites. The binding of alfa-bungarotoxin was significantly lower in mice neonatally exposed to both nicotine and PCB 52, compared when the agents were administerd one by one. This interactive effect was also seen on the spontaneous behaviour response to nicotine at adult age, where an increased response were seen in the neonatally co-exposed mice.

Polybrominated diphenyl ethers (PBDEs) are used in large quantities as flame-retardant additives in polymers, especially in electric apparatuses, TV sets, computers, building materials and textiles (14). One of the earliest reports of PBDE in our environment came in 1981 (15). PBDEs are persistent compounds that appear to have an environmental dispersion similar to that of PCB and DDT. PBDE has been found in various wildlife species and in human adipose tissue. These compounds are known also to increase in mother's milk (personal communication Koidu Norén, KI, Sweden). In ongoing experiments we have seen that neonatal exposure to PBDE 99 can cause disturbances in spontaneous behaviour in a similar manner as observed for the above reported PCBs. Learning and memory in a swim maze of Morris water maze type was also found to be affected in the same manner as observed after neonatal exposure to PCB 52 and PCB 126, namely re-learning was significantly reduced. Another striking feature was that the effects on spontaneous behaviour worsen with age, as seen for PCB 153, PCB 126 and PCB 169.

Concluding remarks

Our investigations have shown that low-dose exposure to certain ortho-substituted and some co-planar PCBs during the period of rapid development of the neonatal brain (so-called brain growth spurt) and cholinergic system, in the mouse, can give rise to irreversible changes in adult brain function. Furthermore, PCB 52 and PCB 126 can cause interactive effects on spontaneous behaviour.

PCB and nicotine can cause interactive effcts as observed with PCB 52 and nicotine on cholinergic nicotinic receptors and behaviour.

The recent findings that developmental exposure PBDE can cause similarities in behavioural disturbances as seen for PCBs is of special interest, not only for PDBE as a single agent but of possible interactive effects between these persistent environmental agents and the present background levels of PCBs.

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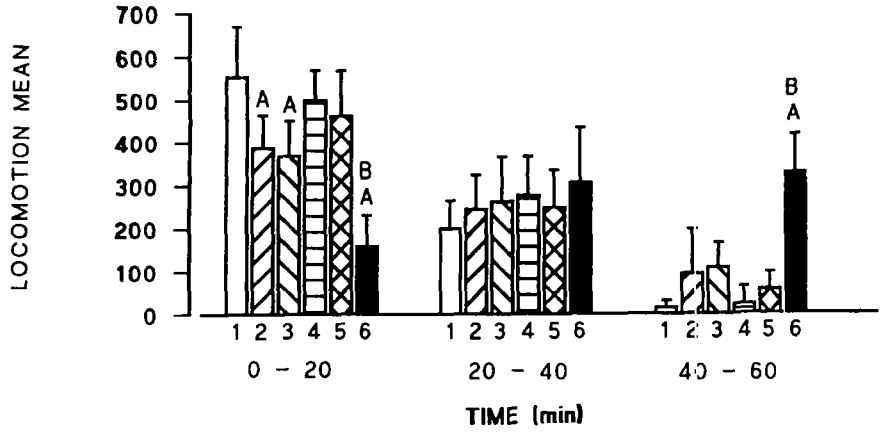

Figure 1. Spontaneous behaviour in 4-month-old NMRI male mice exposed to a single oral dose of PCB 52 (2,2´,5,5´-tetrachlorobiphenyl), PCB 126 (3,3´,4,4´,5-pentachlorobiphenyl), co-exposure to PCB 52 and PCB 126, or the 20% fat emulsion vehicle at an neonatal age of 10 days. Each treatment group contained 8 mice from three different litters Spontaneous behaviour, observed as locomotion, rearing, and total activity, was measured as described elsewhere (5,11). The statistical evaluation was by ANOVA with a split-plot design, and pairwise testing with the Tukey HSD test.There were significant group x period interactions [$\underline{F}(10,84)=22.21$ $\underline{F}(10,84)=35.00$, $\underline{F}(10,84)=20.64$], for the 'locomotion', 'rearing' and 'total activity' variables, respectively. Pairwise testing between PCB exposed and control groups was performed with the Tukey HSD tests. The treatment groups are indicated by: 1) control, 10 ml 20% fat emulsion vehicle/kg body wt; 2) PCB 52, 4.1 mg (14 μmol)/kg body wt; 3) PCB 126, 0.46 mg (1.4 μmol)/kg body wt; 4) PCB 52 + PCB 126, 0.2 mg + 0.023 mg/kg body wt; 5) PCB 52 + PCB 126, 0.4 mg + 0.046 mg/kg body wt; 6) PCB 52 + PCB 126, 4.1 mg + 0.46 mg/kg body wt. The heights of the bars represents mean ± SD. Significant difference ($\underline{P}<0.01$) from the control is indicated by A, and from PCB 52 (2) or PCB 126 (3) is indicated by B.

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