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CO-EXPOSURE TO A POLYBROMINATED DIPHENYL ETHER (PBBE 99) AND AN ORTHO-SUBSTITUTED PCB (PCB 52) ENHANCES DEVELOPMENTAL NEUROTOXIC EFFECTS

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Introduction

In our environment there are innumerable hazardous contaminants. Many of these compounds are well known persistent organic pollutants (POPs) like PCB and DDT that still are present in our environment. A naturally occurring exposure circumstance is the exposure to these older POPs and to new ones, like certain brominated flame-retardants, which are seen to increase in the environment. A challenging question is whether these new agents can interact with old ones to enhance toxic effects.

Brominated flame-retardants (BFR) are a novel group of global environmental contaminants[1,2,3]. Within this group the polybrominated diphenyl ethers (PBDE) constitute a class that are found in electrical appliances, building materials, and textiles. PBDEs are persistent compounds that appear to have an environmental dispersion similar to that of polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT)[2]. While we observe a decrease for PCBs and DDT the PBDEs have been found to increase in the environment and in human mother's milk[4,5,6].

In several studies we have shown that low-dose exposure of environmental toxic agents such as PCBs, DDT, as well as well-known neurotoxic agents such as nicotine, organophosphorous compounds and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), during the period of rapid brain growth, known as the "brain growth spurt" ("BGS")[7], in neonatal mice can lead to disruption of the adult brain function, and to an increased susceptibility to toxic agents as adults[8,9]. Our studies concerning developmental neurotoxic effects after neonatal exposure to single PCB congeners have shown that some ortho-substituted PCBs (such as PCB 28, PCB 52, PCB 153) and some co-planar PCBs (such as PCB 77, PCB 126, PCB 169) cause derangement of adult behaviour that can worsen with age. Furthermore, the cholinergic receptors in the brain were also found to be affected[10].

In recent studies we have seen that certain PBDEs, such as PBDE 47, PBDE 99, PBDE 153 and PBDE 209 can cause developmental neurotoxic effects, like those observed for certain PCBs. Neonatal exposure to those PBDEs have been shown to cause deranged spontaneous behaviour, e.g. hyperactivity, reduced habituation capability and learning and memory. Neonatal exposure to PBDE 99 or PBDE 153 have also been shown to affect the cholinergic system, manifested as altered behavioural response to the cholinergic agent nicotine and also reduced amount of nicotinic receptors in hippocampus[11,12,13,14].

All these studies have shown that there is a critical phase in the neonatal development, when the maturational processes of the developing CNS are at a stage of critical vulnerability, during which these persistent effects are induced[7,10]. In humans, this period begins during the third trimester of

pregnancy and continues throughout the first 2 years of life; in mice and rats this period is neonatal, spanning the first 3-4 weeks of life.

With regard to the similarities in developmental neurotoxic effects between PCBs and PBDEs the present study was carried out in order to see whether PBDE and PCB can interact to cause enhanced developmental neurotoxic effects on spontaneous behaviour and habituation capability when given to neonatal mice.

Materials and methods

The polybrominated diphenylether 2,2',4,4',5-pentabromodiphenylether (PBDE 99) and 2,2′,5,5′-tetrachlorobiphenyl (PCB 52) were synthesized at the Wallenberg Laboratory, University of Stockholm, Sweden. The substances were administered orally as one single oral dose to neonatal NMRI- mice on postnatal day 10. The amounts of the different compounds given were as follows; PCB 52, 0.4 mg (1.4 µmol), 4.0 mg (14 µmol)/kg body weight; PBDE 99, 0.8 mg (1.4 µmol), 8.0 mg (14 µmol)/kg body weight; PCB 52 + PBDE 99, 0.4 mg + 0.4 mg (1.4 µmol +1.4 µmol)/kg body weight. Mice serving as controls received 10 ml/kg body weight of the 20% fat emulsion vehicle in the same manner. Each treatment group comprised mice from 3-4 different litters.

Spontaneous behaviour was tested in the male mice at the ages of 4 and 6 months. Motor activity was measured over 3x20 min in an automated device consisting of cages (40x25x15 cm) placed within two series of infrared beams (low level and high level. The test measures locomotion: horizontal movement, rearing: vertical movement, and total activity: all types of vibrations within the test cage, i.e. those caused by mouse movements, shaking (tremors) and grooming (see[7,10,11]

Results and discussion

The present study shows that PBDEs and PCBs, at low doses, can interact and enhance developmental neurotoxic effects when the exposure occurs during a critical stage of neonatal brain development.

Animals neonatally exposed to the combined low dose of PCB 52 (1.4 µmol/kg bw) + PBDE 99 (1.4 µmol/kg bw) showed significantly impaired spontaneous motor behaviour at the age of 4 months and 6 months. This deranged spontaneous behaviour were also seen in mice exposed to the high dose of PCB 52 (14 µmol/kg bw) and the high dose of PBDE 99 (14 µmol/kg bw), but not at the low dose (1.4 µmol/kg bw). The effect on spontaneous behaviour were even more pronounced in mice receiving the combined dose of PCB 52(1.4 µmol/kg bw) + PBDE 99 (1.4 µmol/kg bw) compared to mice neonatally exposed to just the high dose of PCB 52(14 µmol/kg bw). Furthermore, in animals exposed to the combined dose of PCB 52(1.4 µmol/kg bw) + PBDE 99 (1.4 µmol/kg bw), and the high dose of PCB 52, the defects worsen with age as the habituation capability was significantly worse in 6-month-old mice compared to 4-month-old mice.

The spontaneous behaviour results in mice exposed to either PCB 52 or PBDE 99 were the same as earlier reported[10,11,12,14,15,16]. In those studies it was found that neonatal exposure to PCB 52 (0.7-14 µmol/kg bw) induced persistent aberrations in spontaneous behaviour, and reduced re-learning in learning and memory tests of Morris water maze type. In these animals the cholinergic nicotinic receptors in the cerebral cortex were reduced, and it was also found that adult mice showed an altered spontaneous behaviour response to nicotine. The same has been observed in mice neonatally exposed to PBDE 99 (1.4- 21.1 µmol/kg bw), namely induction of persistent

aberrations in spontaneous behaviour, reduced re-learning in learning and memory tests of Morris water maze type and altered spontaneous behaviour response to nicotine. These behavioural aberrations after neonatal exposure to PBDE 99 or PCB 52 have also been induced during the defined critical period of "BGS", occuring around postnatal day 10. Moreover, the effects have been induced at doses, on molar level, that are the same between the two agents[10,12].

The effects on developmental neurotoxic behavioural and cholinergic variables are similar between PCB and PBDE suggests similar mechanisms of action between PBDEs and PCBs. However, the present observed interaction between PBDE 99 and PCB 52, with an effect significantly more pronounced than the 5 times higher dose of just PCB 52, indicate that additional mechanisms can be involved and/or that different brain regions are affected.

Taken together, the interaction between PBDEs and PCBs, and the fact that PBDEs are increasing in the environment and eventually reaching levels of those of PCBs, in mother's milk and in the environment, calls for further investigations whether certain PBDEs and PCBs can interact to cause enhanced development neurotoxic effects. Their role as possible environmental toxicants involved in the processes of neurodegeneration and aging also calls for further studies.

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References

1. de Boer J., Wester P. G., Klamer H. J., Lewis W. E., and Boon J. P., *Nature*, 1998, 394, 28.
2. de Wit C. A., *Chemosphere*, 2002, 46, 583.
3. Andersson Ö. and Blomkvist G., *Chemosphere*, 1981, 10, 1051.
4. Manchester-Neesvig J.B., Valters K, Sonzogni W.C., *Environ Sci Technol*, 2001, 35, 1072
5. Meironyté D. and Norén K., *Journal of Toxicology and Environmental Health Part A*, 1999, 58, 329.
6. Norén K. and Meironyté D., *Chemosphere*, 2000, 40, 1111.
7. Davison A.N. and Dobbing J. (1968) Applied Neurochemistry*;* Blackwell, Oxford, pp. 178, 253.
8. Eriksson P. (1997) *Neurotoxicology*, 18, 719
9. Eriksson P. and Talts U. (2000) *Neurotoxicology*, 21, 37.
10. Eriksson P. Perinatal developmental neurotoxicity of PCBs. Report 4897, Stockholm, Swedish Environmental Protection Agency, 1998.
11. Eriksson P., Jakobsson E., and Fredriksson A., *Environ Health Perspect*, 2001, 109, 903.
12. Eriksson P., Viberg H., Jakobsson E., Örn U., and Fredriksson A., *Toxicological Sciences*, 2002, 67, 98.
13. Viberg H., Fredriksson A., and Eriksson P., *Toxicol Appl Pharmacol*, 2002, In press.
14. Viberg H., Fredriksson A., and Eriksson P., *Toxicological Sciences*, 2002, 67.
15. Eriksson P., and Fredriksson A., *Environ. Toxicol Pharmcol*, 1996, 1, 155.
16. Eriksson P., and Fredriksson A., *Environ. Toxicol Pharmacol***,** 1996, 1, 217.