CO-EXPOSURE TO AN ORTHO-SUBSTITUTED PCB (PCB 153) AND METHYLMERCURY ENHANCES DEVELOPMENTAL NEUROTOXIC EFFECTS

Celia Fischer[1], Anders Fredriksson[1], Per Eriksson[1]

[1]Dept Environment. Toxicol., Uppsala University, Uppsala

Introduction

In our environment there are innumerable hazardous contaminants. Many of these compounds are the well-known persistent organic pollutants (POPs) like PCB and DDT. Another persistent agent in our environment is methylmercury (MeHg). These agents are known to be neurotoxic in laboratory animals and humans. Fetuses and neonates are known to be high-risk groups for exposure to these agents. A naturally occurring circumstance is the exposure to a combination of different persistent compounds. The knowledge of interaction between different toxic agents during development is sparse.

In mammals, the main elimination route of highly lipophilic chemicals, which have been sequestered in adipose tissue, is lactation[1]. In many mammalian species the lactation period coincides with a rapid growth and development of the brain. Mammalian development includes periods, which can be critical for normal maturation. As the CNS develops, every region of and structure in the brain follows an intricately planned and precisely timed developmental sequence, for example neurogenesis, differentiation and synaptogenesis. In many mammalian species a rapid growth of the brain occurs during perinatal development, the so-called "brain growth spurt"[2]. In the human, this period begins during the third trimester of pregnancy 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 which the brain undergoes several fundamental phases, such as axonal and dendritic outgrowth and the establishment neural connections. This stage of development is associated with numerous biochemical changes that transform the feto-neonatal brain into that of the mature adult. This is also the period when animals acquire many new motor and sensory abilities and when spontaneous motor behaviour peaks.

In several studies we have shown that low-dose exposure of environmental toxic agents such as PCBs, DDT, BFRs (brominated flame retardants) 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 "BGS", in neonatal mice can lead to disruption of the adult brain function, and to an increased susceptibility to toxic agents as adults[3,4,5,6,7]. 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[8]. Just recently we have seen that neonatal co-exposure to an ortho-substituted PCB, 2,2',5,5'-tetrachlorobiphenyl (PCB 52), together with a brominated flame retardant, 2,2',4,4',5-pentabromodiphenylether (PBDE 99), can enhance developmental neurotoxic effects when the exposure occurs during a critical stage of neonatal brain development.

The present study was carried out in order to see whether PCB and MeHg could interact to cause enhanced developmental neurotoxic effects on spontaneous behaviour and habituation capability when given to neonatal mice.

Materials and methods

The polychlorinated biphenyl, 2,2',4,4',5,5' -hexachlorobiphenyl (PCB 153) was synthesized at the Wallenberg Laboratory, University of Stockholm, Sweden. Methylmercury (methylmercuric chloride, Merck) was purchased from KEBO, 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; PCB153, 0.5 mg/kg body weight; MeHg, 0.08 mg, 0.4 mg, 4.0 mg/kg body weight; PCB 153 +MeHg, 0.5 mg + 0.08mg, 0.5 mg + 0.4 mg, 0.5 mg + 4.0 mg/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 2 and 4 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[8])

Results and discussion

The present study shows that PCB and MeHg, 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 153 (0.5 mg)+ MeHg (0.4 mg)/kg body weight or PCB 153 (0.5 mg)+ MeHg (4.0 mg)/kg body weight showed significantly impaired spontaneous motor behaviour at the age of 2 months and 4 months. This deranged spontaneous behaviour was also seen in mice exposed to the highest dose of MeHg (4.0 mg/kg body weight). In mice neonatally exposed to just PCB 153 (0.5 mg), MeHg (0.08 mg), MeHg (0.4 mg) or PCB 153 (0.5 mg)+ MeHg (0.08 mg)/kg body weight no significant changes were observed on the spontaneous behaviour.

Of special interest is the effect on spontaneous behaviour in mice exposed to the combined low dose of PCB 153 (0.5 mg)+ MeHg (0.4 mg)/kg body weight compared to mice receiving just the highest dose of MeHg (4.0 mg/kg bw). Neither PCB 153 (0.5 mg) nor MeHg (0.4 mg) alone affected the adult spontaneous behaviour, but the combination caused an effect as high as 10 times the single high dose of MeHg (0.4 mg), namely MeHg (4.0 mg/kg body weight). Recently we have observed this type of interaction between environmental agents given to neonatal mice. Neonatal exposure to both PCB 52 and PBDE 99 showed interaction between PBDE 99 and PCB 52, with an effect significantly more pronounced than the 5 times higher dose of just PCB 52[9].

The present study supports a recently published developmental neurotoxicity study in rats by Roegge et al[10]. Their study indicated an interaction between PCB (Aroclor 1254) and MeHg. Offspring's to dams exposed during pregnancy and lactation period showed reduced performance on motor tasks involving cerebellar functions. Furthermore, an in vitro study by Bemis and Seegal[11] also show that PCBs and MeHg can interact in striatum to affect the DA-system. Taken together these studies indicate that different mechanisms of action can be involved and/or that different brain regions are affected, to enhance developmental neurotoxic effects.

The present study shows that PCBs and MeHg can interact during a critical stage of neonatal brain development to enhance developmental neurotoxic effects. Exposure to low doses of environmental toxicants, that can interact to enhance developmental neurotoxic effects, are of special concern and calls for further studies.

Acknowledgements
Financial support by grants from Formas and EU-project FOOD-CT-2003-506143

References

1. Gallenberg LA, and Vodicnik MJ., Drug Metab Rev, 1987, 21, 277.
2. Davison A.N. and Dobbing J. (1968) Applied Neurochemistry; Blackwell, Oxford, pp. 178, 253.
3. Eriksson P. (1997) *Neurotoxicology,* 18, 719
4. Eriksson P. and Talts U. (2000) *Neurotoxicology,* 21, 37.
5. Eriksson P., Jakobsson E., and Fredriksson A., *Environ Health Perspect*, 2001, 109, 903.
6. Viberg H, Fredriksson A, and Eriksson P., *Toxicology and Applied Pharmacology*, 2003, 192, 95.
7. Viberg H, Fredriksson A, Jakobsson E, Örn U, and Eriksson P., (2003). *Toxicological Sciences*, 2003, 76 , 112.
8. Eriksson P. Perinatal developmental neurotoxicity of PCBs. Report 4897, Stockholm, Swedish Environmental Protection Agency, 1998.
9. Eriksson P, Fischer C, and Fredriksson A.,*Organohalogen Compounds*, 2003,61, 81.
10. Roegge CS., Wang VC., Powers BE., Klintsova AY, Villareal S., Greenough WT., Schantz SL., *Toxicological Sciences*, 2004, 77 , 315.
11. Bemis JC., and Seegal RF., *Environ Helath Perspect*, 1999, 107, 879.