Developmental neurotoxicity of brominated flame-retardants, polybrominated diphenyl ethers and tetrabromo-bis-phenol A

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Introduction

Polybrominated diphenyl ethers (PBDEs) are used in large quantities as flame-retardant additives in polymers, especially in the manufacture of a great variety of electrical appliances, including television and computer casing, building materials, and textiles (1). One of the earliest reports of PBDE in the environment came in 1981 (2). 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 (3). The PBDE congeners that dominate in environmental and human samples are 2,2',4,4'-tetrabromodiphenylether (PBDE 47) and 2,2',4,4',5-pentabromodiphenylether (PBDE 99). These agents together with tetrabromo-bis-phenol-A (TBBPA) have been also detected recently in human plasma samples. These compounds are known also to increase in mother's milk (personal communication Koidu Norén, KI, Sweden).

In several reports we have shown that low-dose exposure of environmental toxic agents such as PCB, DDT, pyrethroids, organophosphates, paraquat and nicotine, during the period of rapid brain growth, known as the "brain growth spurt" ("BGS"), in neonatal mice can lead to disruption of the adult brain function, and also to an increased susceptibility to toxic agents at adult ages (5). The studies have also shown that there is a critical phase in the neonatal development, when the maturational processes of the developing brain and CNS are at a stage of critical vulnerability, that these persistent effects are induced. This BGS does not take place at the same time point in all mammalian species (6). 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 the BGS is neonatal, spanning the first 3-4 weeks of life.

In view of an increasing amount of these PBDEs and TBBPA in the environment, and in mother's milk, the present study was undertaken to investigate possible behavioural effects of PBDEs and TBBPA when given during the rapid development of the brain.

Materials and Methods

The polybrominated diphenylethers 2,2',4,4'-tetrabromodiphenyl ether (PBDE 47), 2,2',4,4',5-pentabromodiphenylether (PBDE 99) were synthesized at the Wallenberg Laboratory (7), University of Stockholm, Sweden. Tetrabromo-bis-phenol-A (TBBPA), was purchased from Aldrich and was recrystallized from chloroform. The substances were orally administered to neonatal NMRI-mice as one single oral dose on postnatal day 10. The amounts of the different compounds given were as follows; 2,2',4,4'-tetrabromodiphenyl ether (PBDE 47), 0.7 mg (1.4 μmol), 10.5 mg (21.1 μmol)/kg b.wt.; 2,2',4,4',5-pentabromodiphenylether (PBDE 99), 0.8 mg (1.4 μmol), 12.0 mg (21.1 μmol)/kg b.wt.; tetrabromo-bis-phenol-A, 0.75 mg (1.4 μmol), 11.5 mg (21.1 μmol)/kg b.wt. Mice serving as controls received 10 ml/kg b.wt. of the 20% fat emulsion vehicle in the same manner.
Spontaneous behaviour: the test was performed in male mice at the age of 2 and 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.

Results and Discussion

The spontaneous motor behaviour data showed a dose-response related disruption of habituation in adult mice neonatally exposed to PBDE 47 and PBDE 99. Habituation, defined here as a decrease in 'locomotion', 'rearing', and 'total activity' variables in response to the diminishing novelty of the test chamber over 60 min, was demonstrated in the control animals and animals exposed to TBBPA, whereas mice given the higher dose of PBDE 47 and PBDE 99 were obviously hypoactive early in the 60-min test period, while toward the end they became hyperactive. This non-habituating behaviour profile has also been reported in adult mice neonatally exposed to certain ortho-substituted PCBs and some co-planar PCBs (8,9,10,11). The results from the spontaneous behaviour tests further indicate that the functional disorder worsens with increasing age, as the aberrations appeared to be more pronounced in 4-month-old than in 2-month-old mice. This change in spontaneous motor behaviour profile, both time dependent and dose related, indicates the advance of a brain dysfunction process induced at the time of rapid brain development in the neonatal mouse.

The ability of adult mice to learn and memorize a spatial navigation task was studied using a swim maze of Morris water-maze type. The swim maze allowed a 4-day acquisition period followed by reversal trials on the fifth day, when the platform was moved. In control mice and in mice given PBDE 47, PBDE 99 and TBBPA, latency to locate the platform decreased during the acquisition training, and all tested animals performed equally well at the end of the

acquisition period. In the reversal trials on the fifth day, however, mice exposed to the higher dose of PBDE 99 (12.0 mg/kg b.wt.) did not improve in finding the new location of the platform, as did control mice and mice exposed to the other compounds.

The present investigation shows that neonatal exposure to PBDE 47 and PBDE 99, can induce neurotoxic effects in the adult animal. Both PBDE 47 and PBDE 99 induced permanent abberations in spontaneous motor behaviour, a disruption that also worsens with age. Furthermore, neonatal exposure to PBDE 99 also affected learning and memory functions in the adult animal. The increasing concentration of PBDEs in mother's milk and the observed similarities in behavioural disturbances as earlier seen for PCBs call for further research of PBDEs as potential neurotoxicants.

Acknowledgements

Financial support by grants from the Swedish Environmental Protection Board.

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