PCBs (PCB 153 and PCB 126) AND PBDE (PBDE 99) CAN INTERACT WITH METHYLMERCURY IN ENHANCING DEVELOPMENTAL NEUROTOXIC EFFECTS

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Introduction

Studies have shown a discrepancy between children in the Faroese Islands and children in the Seychelles Islands in relation to neuropsychological defects during early development. Both populations have a high consumption of MeHg contaminated fish with the exception that in the Faroese Islands the children were exposed to PCBs via the mother's dietary consumption of whale meat and blubber in adjunction to MeHg[1, 2, 3] In vivo experiments on rats exposed to PCBs and MeHg have shown that co-exposure did impair the rats ability to transverse a rotating rod compared to control rats[4]. Also in vitro studies have shown significantly altered dopamine concentrations to co-exposure to PCB and MeHg compared to both the individual compounds[5]. A primary route for contaminate exposure of highly lipophilic chemicals to children is through mother's milk[6]. Another group of contaminants with rising levels both in milk and in our environment are polybrominated biphenyl ethers (PBDEs)[7,8,9].

We have shown in previous studies that certain environmental contaminants, e.g. DDT, PCBs, PBDEs and mercury can induce and enhance developmental neurotoxic effects in animals, when these agents are present during a critical period of the neonatal brain development[10,11,12,13,14,15]. In many mammalian species a rapid growth of the brain occurs during perinatal development, the so-called "brain growth spurt" BGS[16]. In humans, this period takes place during the third trimester of pregnancy throughout the first two years of life. In mice and rats this period is neonatal taking place the first 3-4weeks of life. During the BGS the brain undergoes several fundamental phases, such as axonal and dendritic outgrowth, establishment of neural connections and numerous biochemical changes that transform the feto-neonatal brain into that of a mature adult. This time is also associated with when animals acquire many new motor and sensory abilities and when spontaneous motor behavior peaks. In several mammals, e.g. humans, the lactation period coincides with the BGS.

The present study was undertaken to explore developmental neurobehavioral effects on spontaneous behavior, habituation capability, learning and memory abilities from neonatal co-exposure to, 1: ortho-substituted PCB, (PCB 153) together with MeHg, 2: co-planer PCB (PCB 126) together with MeHg, and 3: PBDE (PBDE 99) together with MeHg.

Materials and Methods

The polychlorinated biphenyl, 2,2`,4,4`,5,5`-hexachlorobiphenyl (PCB 153), 3,3`, 4,4`,5-pentachlorobiphenyl (PCB 126) and 2,2`,4,4`,5-pentabromodiphenyl ether (PBDE 99) were synthesized at the Department of Environmental Chemistry, University of Stockholm, Sweden. Methyl mercury (methyl mercuric chloride, Merck) was purchased from KEBO, Sweden. Neonatal NMRI male mice, 10 days of age, were exposed to a single oral dose PCB153, PCB 126 or PBDE 99 (0.14 -1.4 µmol/kg body weight), MeHg 0.08, 0.40, or 4.0mg/kg body weight, co-exposure to PCB and MeHg, PBDE 99 and MeHg or a vehicle (20% fat emulsion). Each treatment group comprised mice from 3-4 different litters.

Spontaneous behavior was tested in male mice at ages 2 and 4 months. Motor activity was measured over 3x20min in an automated device consisting of cages (40x25x15cm) 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.

Morris swim maze[16] was preformed in four month old male mice. The swim maze shows spatial learning and re-learning abilities. The maze was conformed by a grey circular tube with a diameter of 102cm. It was filled with water at a 23 degree temperature to a depth of 13cm from the brim. In the center of one quadrant (north-west) of the pool a metal mesh platform was submerged one centimeter beneath the water surface. The test lasted for five days and each day consisted of five trials. The object of the test was for the mouse to locate the submerged platform. The first four days (trials 1-20) tested the animals spatial learning, on the fifth day (trials 21-25) the submerged platform was relocated and re-learning abilities were tested.

Results and Discussion

This study shows that co-exposure to PCB 153 and MeHg at low doses can interact enhancing developmental neurotoxic effects when exposure occurs during a critical stage of neonatal brain development. Mice neonatally co-exposed to low dose of PCB 153 (0.5mg) + MeHg (0.4mg)/kg body weight or PCB 153 (0.5mg) + MeHg (4.0mg)/kg body weight showed a significantly impaired spontaneous behavior both at 2 and 4 months of age. Neither the single dose of PCB153 nor the single dose of MeHg (0.4mg/kg body weight) affected the spontaneous behavior, but the co-exposure of these two agents caused an affect as high as the ten times higher dose of MeHg (4.0mg/kg body weight).

Co-exposure to PCB 126 and MeHg at low doses can interact, enhancing developmental neurotoxic effects. Mice neonatally co-exposed to PCB 126(0.46mg) + MeHg (4.0mg)/kg body weight had a significantly greater impact on the spontaneous behavior than the sole components by themselves both at 2 and 4 months of age. This data shows a deranged spontaneous behavior and habituation. The Morris swim maze behavioral data, day 1-4 showed a treatment effect where all treatments groups were significantly different from the control group. Re-learning on day 5 showed a treatment effect where all groups were significantly from the control group and that the co-exposed group (PCB 126 0.46mg + MeHg 4.0mg/kg body weight) was significantly different from the PCB 126 (0.46mg/kg body weight) and MeHg (4.0mg/kg body weight), indicating a decreased learning and memory abilities.

Co-exposure to PBDE 99 and MeHg at low doses can interact, enhancing developmental effects. Mice neonatally co-exposed to low dose of PBDE 99 (0.8mg) + MeHg (0.4mg)/kg body weight or PBDE 99 (0.8mg) + MeHg (4.0mg)/kg body weight showed a significantly impaired spontaneous behavior both at 2 and 4 months of age. Neither the single dose of PBDE 99 nor the single dose of MeHg (0.4mg/kg body weight) affected the spontaneous behavior, but the co-exposure of these two agents caused an affect as high as the ten times higher dose of MeHg (4.0mg/kg body weight). The Morris maze swim test data for days 1-4 showed a treatment x time effect, control<PBDE 99 (0.8 mg), MeHg (0.4mg) <MeHg (4.0), PBDE 99 (0.8mg) + MeHg (0.4mg), PBDE 99 (0.8mg) + MeHg (4.0mg)/kg bodyweight. Relearning on day 5 showed a treatment x trail effect, control, PBDE 99(0.8mg), MeHg (0.4mg) <PBDE 99 (0.8mg) + MeHg (0.4mg), PBDE 99 (0.8mg) + MeHg (4.0mg)/kg body weight. The spontaneous behavioral data shows deranged spontaneous behavior and habituation, the swim maze data indicates decreased learning and memory abilities.

Taken together, these results show that neonatal co-exposure to PCBs or PBDE in addition to MeHg at low doses can interact in enhancing developmental neurotoxic effects. The observed discrepancy between children in the Faroese Islands and children in the Seychelles Islands in relation to neuropsychological defects during early development might be attributed to the presence of both PCB and MeHg during a critical phase of brain development.

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