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Early Developmental Exposure to BDE 99 or Aroclor 1254 Affects Neurobehavioural Profile: Interference from the Administration Route

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Abstract

Among the most persistent and bio-accumulative environmental pollutants are the polybrominated diphenyl ethers (PBDEs), a class of chemicals widely used as flame retardants in plastics and textile coating, and the polychlorinated biphenyls (PCBs), previously used as coolants and lubricants in electrical equipment. Monitoring programs revealed high levels of both these classes of compounds in human breast milk, raising concerns for their potential noxious effects on infants. The aim of the present study was to investigate the neurotoxic effects of 2,2′,4,4′,5-penta BDE (BDE 99: 18 mg/kg/day) or Aroclor 1254 (A1254, a PCB mixture: 10 mg/kg/day) administration, from gestational day (GD) 6 to postnatal day (PND) 21, on neurobehavioral development in the CD-1 Swiss mouse. In addition, we investigated whether the administration route affects the emergence or the magnitude of the toxic effects of BDE 99 or A1254. In particular, we compared self-administration, consisting in letting the mouse drink spontaneously the compound dissolved in oil from a syringe, with gavage, consisting in force-feeding a substance by a tube inserted in the mouth and then into the stomach, a procedure reported to be stress-inducing. Both compounds induced hyperactivity, though BDE 99 affected activity profile only during adolescence and A1254 mainly at adulthood. Levels of total circulating thyroxine were decreased by both BDE 99 and A1254 administration, though only in the latter group the decrease was statistically significant. These findings suggest a different neurotoxic action exerted by PBDEs and PCBs. An effect of the administration route, independent from the compound administered, was found on thigmotactic behavior and gavage administration affected pup body weight gain only in the A1254 group, suggesting that the stress induced by gavage procedure may either affect results per se or modulate the detrimental action of selected compounds.

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Keywords: PBDE; PCB; Neurobehavioral development; Developmental exposure; Gavage; Self-administration

INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) are among the most persistent and bio-accumulative environmental pollutants. PBDEs, now being banned in several European countries, but still massively produced world-wide, are

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used as flame retardant in construction materials, coatings, textiles and polymers such as those employed in electronic equipment (e.g., computers, TV sets) (Birnbaum and Staskal, 2004; Darnerud et al., 2001; de Wit, 2002; Hale et al., 2001; Schmidt, 2003; Sjodin et al., 2003; WHO, 1994). PCBs were widely used as coolants and lubricants in electrical equipment and, though banned starting from the 1980s, they are still present in both wild-life species and in human tissues at levels endangering human health (Giesy and Kannan, 1998; Seegal, 1996).

Monitoring programs have revealed that both classes of compounds are present in human breast milk at concentrations rising concerns for potential noxious effects on the developing infant (Guvenius et al., 2003; Meironyte and Noren, 2001; Meironyte et al., 1999; Schecter et al., 2003; Ulbrich and Stahlmann, 2004). In Europe, on the basis of data on human milk collected in Sweden in 1999 and assuming that a 2–3-month-old infant weighing about 5 kg consumes 700 ml breast milk/day, the average daily intake of PBDEs via milk can be estimated at 50–100 ng/day (Meironyte et al., 1999). With regard to PCBs, breast milk concentrations have been recently determined to be approximately 60 times higher than those of PBDEs (Guvenius et al., 2003). In U.S.A., PBDE levels in maternal milk are 10–100 times greater than those found in Sweden (Betts, 2002; Schecter et al., 2003).

A number of experimental studies have been conducted in mice and rats, in order to evaluate the potential noxious effects of developmental exposure to PBDEs (Branchi et al., 2002, 2003; Eriksson et al., 2001; Viberg et al., 2003) or PCBs (Eriksson, 1997; Faroon et al., 2001; Storm et al., 1981; Tilson et al., 1990; Tilson and Kodavanti, 1998) on the developing and adult organism. PCB neurotoxicity data are available also in humans (Jacobson and Jacobson, 2003; Schantz et al., 2003). The results indicate that PBDEs and PCBs exert disrupting effects on neurobehavioural development, which show similarities but also important differences, suggesting that their actions do not always overlap. For example, both PBDEs and PCBs exert a disrupting effect on thyroid function (Crofton et al., 2000; Morse et al., 1996; Zhou et al., 2002), induce a hyperactivity profile (Branchi et al., 2002; Eriksson, 1997; Eriksson et al., 2001), and affect the cholinergic system (Eriksson, 1997; Viberg et al., 2002, 2003). However, PCBs seem to exert a stronger effect than PBDEs, though only a selected number of mixtures or single compounds has been compared to each other (Branchi et al., 2002, 2003; Hallgren et al., 2001). Furthermore, developmental exposure to PCBs, but not PBDEs, has been shown to produce in rats a decrement in the magnitude of evoked LTP and an increase in the train intensity required to induce LTP (Gilbert and Crofton, 2002; Gilbert et al., 2000).

Selected experimental procedures can induce or affect the emergence of noxious effects. In particular, gavage, a procedure routinely used in neurotoxicology studies to orally administrate compounds to laboratory animals and consisting in force-feeding a substance with a tube inserted in the mouth and then into the stomach, can exert a noxious effect by its-self, independently from that exerted by the compound administered (Roberts et al., 1995). This effect could be due to the stress induced by this administration procedure. Indeed, it has been shown that gavage, in particular when oil is used as vehicle, activates the stress response, as indicated by increased adrenal output of corticosterone (Brown et al., 2000). The combined exposure to stressful conditions and neurotoxicants, such as caffeine, aspirin and aluminum (Albina et al., 2002; Colomina et al., 2001, 1999; Murata et al., 1993; Rasco and Hood, 1994) has been reported to exacerbate the effects of exposure.

Aim of the present study was to investigate in mice the short- and long-term neurobehavioral effects of developmental exposure (from gestational day (GD) 6 to postnatal day (PND) 21) to 2-2′-4-4′-5 pentabromodiphenylether (BDE 99; Fig. 1), which is among the BDE congeners found more often and at highest levels in sentinel species and human tissues (Darnerud et al., 2001; de Boer et al., 1998; Guvenius et al., 2003; Hale et al., 2001; Meironyte and Noren, 2001; Schecter et al., 2003) or to Aroclor 1254 (A1254), a PCB mixture containing approximately 21% $C_{12}H_6Cl_4$, 48% $C_{12}H_5Cl_5$, 23% $C_{12}H_4Cl_6$, and 6% $C_{12}H_3Cl_7$ with an average chlorine content of 54%. Furthermore, in order to assess the possible effects due to a stressful experimental procedure, such as gavage, we compared the effects of both A1254 and BDE 99 provided to animals either by gavage or self-administration, consisting in letting the mouse drinks spontaneously the compound dissolved in oil from a syringe. The beha-

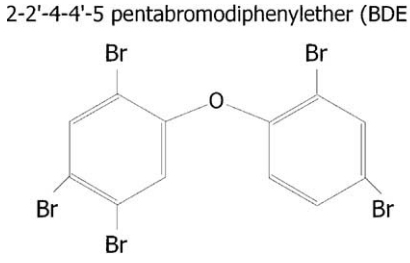

Fig. 1. Structural formula of BDE 99.

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