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Perinatal effects of exposure to PCBs on social preferences in young adult and middle-aged offspring mice

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ABSTRACT

In social species, social interactions between conspecifics constitute a fundamental component to establish relations, provide best chances to reproduce, and even improve survival rates. In this study, a three-chambered social approach test was used to estimate the level of sociability and level of preference for social novelty in both male and female young adult (postnatal day (PND) 50) and middle-aged (PND 330) offspring mice (n = 10 per group) that were perinatally exposed to a mixture of six polychlorinated biphenyls (PCBs), 28, 52, 101, 138, 153, and 180, at environmentally low doses (10 and 1000 ng/kg b.w. for dams during gestation and lactation), a profile that closely mimics human exposure to contaminated fish. Our results showed that PCBs bidirectionally modulated social preferences in offspring mice, and the effects were sex and age dependent. However, increased levels of social interactions were rather frequently detected in both assays of the three-chambered test. Reduced social interaction was only induced in 1000 ng/kg PCB-exposed middle-aged males, which exhibited similar preferences to social and non-social stimuli when compared to middle-aged controls. Furthermore, results showed that plasma levels of both corticosterone and acetylcholinesterase activity were higher in all PCB-exposed middle-aged males and females than in their control counterparts. In summary, although the effects of PCBs were only of moderate magnitude, our results suggest that a PCB mixture can act as an endocrine disruptor in offspring mice, disturbing the formation of normal social habits.

1. Introduction

Several lines of evidence indicate that early-life exposure to polychlorinated biphenyls (PCBs) alters behavior and cognitive function in later life (Boix et al., 2011; Cauli et al., 2012; Schantz et al., 1991; Soualeh et al., 2017; Tian et al., 2011). In addition, both behavioral and cognitive toxicity of PCBs has been shown on the offspring, in both human studies (Chen et al., 1994; Harada, 1976; Jacobson et al., 1985; Sagiv et al., 2012, 2010) and animal models (Eriksson and Fredriksson, 1996; Kuriyama and Chahoud, 2004; Schantz et al., 1991; Tian et al., 2011). Interestingly, effects on offspring through maternal exposure to PCBs can be both permanent (Dridi et al., 2017; Elnar et al., 2012) and transient (Cauli et al., 2012; Sugawara et al., 2006). Moreover, PCBs may act as endocrine disrupting chemicals, often having sexually dimorphic effects (Cauli et al., 2012; Dridi et al., 2017; Kavlock et al., 1996; Lesmana et al., 2014; Li et al., 2008; Soualeh et al., 2017).

However, less work has been focused on studying the effects of perinatal exposure to PCBs on social behavior. Investigations on humans have reported that prenatal exposure to PCBs modified gender-typical playing behavior expressed in school-age children recruited in both the Dutch and Duisburg cohorts (Vreugdenhil et al., 2002; Winneke et al., 2014). In rodent models, it has been stressed that early-life exposure to PCBs reduced socio-sexual interactions in rats including reduced lordosis behavior in females (Wang et al., 2002) and increased latency of sexual behavior in males (Colciago et al., 2009). Perinatal exposure to PCB 77 resulted in impaired partner preference in adult female rats (Cummings et al., 2008). Interestingly, alterations in these social behaviors could be related, at least to a lesser extent, to impairments in social memory and appetitive social investigation (Lee et al., 2008; Wang et al., 1999). In this regard, it has been shown that perinatal exposure to PCBs altered social behaviors in rats, including juvenile social recognition and adult social investigation (Jolous-Jamshidi et al., 2010). PCBs could further affect social interactions through their ability to cause sensory deficits in auditory, visual, and olfactory functions (Apfelbach et al., 1998; Bell, 2014), which are important in receiving and encoding social signals. In addition, social interactions could be affected by increased anxiety, which in turn leads to social avoidance, as demonstrated in rats prenatally exposed to PCB 126 displaying both anxiogenic behavior in an open field test and reduced interactive behavior in the social interaction test (Orito et al.,

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2007). In Inuit preschoolers, prenatal exposure to PCB 153 was correlated with anxiety and reduced positive affect (Plusquellec et al., 2010). Nevertheless, anxiolytic-like effects of developmental exposure to PCBs were also reported in animal models (Bell et al., 2016; Gillette et al., 2016), and thus, low levels of anxiety could facilitate social interactions in PCB-exposed animals. In this regard, sexually dimorphic effects on social and anxiety-like behavior were observed in rats following developmental exposure to PCBs (Aroclor 1221), as alterations have concerned only adolescent females, displaying an increase in pro-social and reduction in anxiety-related behavior (Bell et al., 2016). However, males have exhibited small but significant changes in socio-sexual preferences in adulthood (Bell et al., 2016). Discrepancies between findings from different studies could be related to several factors including differences in (i) the behavioral tests and/or the protocols employed, (ii) the study design, including the duration of exposure (e.g., gestational, lactational, or gestational plus lactational exposure), (iii) the type of PCB congeners or mixtures administered, (iv) PCB dosage, (v) the age of rodents at which the parameters were assessed, (vi) the sex of rodent studied, and (vii) the species (or the strain) of rodent used.

To the best of our knowledge, there is only one investigation that has evaluated the effect of gestational exposure to PCBs (Aroclor 1221 at 0.5 and 1 mg/kg) on sociability and preference for social novelty of male and female adult offspring rats, revealing a limited impact of prenatal PCB exposure on later adult social behavior in rats (Reilly et al., 2015). In the current study, the effects of gestational plus lactational exposure to PCBs at environmental low doses (10 and 1000 ng/kg) on social preferences in a three-chambered social approach test were evaluated in male and female young adult and middle-aged offspring mice. These two age populations were selected because in developmental studies assessing the neurotoxicity of chemicals, the life-stages of offspring (e.g., juvenile, adult, middle age, old age) at which the evaluation is performed may be critical, and some alterations may be manifested only later in life. Moreover, markers related to social aspects including concentrations of the stress marker corticosterone, inflammatory enzyme myeloperoxidase (MPO), acetylcholinesterase activity and serotonin levels, were assessed in the plasma of middle-aged mice. A mixture of six PCBs, 28, 52, 101, 138, 153, and 180, was used at environmentally low doses and with a profile that closely mimics human exposure to contaminated fish (for further details, see the next section, Materials and methods). We have chosen this mixture as these six PCB congeners are the most commonly found in food matrices, and they account for around 50% of all congeners present. The strength of this study is that the effects of the six PCBs on offspring social behavior are evaluated at both 10 and 1000 ng/kg to assess the estimated tolerable daily intake (TDI) and a more pronounced yet relevant environmental dose. A TDI of 10 ng/kg b.w./day was adopted for this group of six PCB congeners through a simple estimation from a reference dose of 20 ng/kg b.w./day for all 209 congeners (AFSSA, 2007).

2. Materials and methods

2.1. Animals

Thirty pregnant CD1 mice (Charles River, France), obtained after a mating session in our laboratory as detailed in our previous studies (Bouayed et al., 2009a; Dridi et al., 2014, 2017; Elnar et al., 2012), were used in this study. They were housed individually in standard cages with *ad libitum* access to water and food pellets free of phytoestrogens (SDS Dietex, St Gratien, France) and were maintained on standard 12-h light/dark cycles (lights "on" starting at 8:00 p.m.), temperature-controlled conditions (22 ± 2 °C), and a relative humidity of 55 ± 10%. The parturition day was considered to be postnatal day (PND) 1. All litters were randomly equalized to have n = 10 pups/litter, 5 pups/sex to prevent litter size bias. On PND 21 (i.e., at weaning), male and female offspring mice were separated from their mothers and housed in two different rooms (n = 5 per cage) to exclude the effects of sexual pheromones on behavior at adult age. Efforts were made to have a relevant number of females (> 150) in the same room in order to develop a prolonged estrous cycle, which is a phenomenon obtained by the effects of the all-female environment (crowded females) leading to the suppression of estrus due to a prolonged diestrum (Marsden and Bronson, 1965; Whitten, 1959). This method allowed us to obtain synchronized females, which removed the bias on their behavior originating from the different phases of estrous cycling. In addition to the three experimental offspring groups, we employed offspring (other than unexposed controls) originating from the breeding of unexposed mice to be used as the stranger conspecifics in the three-chambered test.

During the dark phase (1 h after lights "off") of the light/dark cycle, tests on animals were performed in a silent and isolated room under dim red lighting for a maximum of 4 h per day of experimentation (i.e., experiments were finished at 5 h after lights "off" to avoid circadian cycle bias). The test mice were socially isolated for 24 h prior to experiments to induce an increase in the amount of social interactions in the three-chamber test. All animal procedures were performed in accordance with the relevant European Union regulations (Directive 2010/63/EU) and were approved by the institutional ethics committee of the University of Lorraine (authorization number CELMEA-2013-0010).

2.2. Perinatal diet manipulation

2.2.1. Preparation of the six-PCB mixture

The six indicator NDL-PCBs (28, 52, 101, 138, 153, and 180) were purchased from Sigma–Aldrich Co. (St. Quentin Fallavier, France, purity > 99%). The profile of the PCBs in contaminated fish predominantly includes NDL-PCBs, in which the six NDL-PCB indicators constitute around 56%, whereas DL-PCBs represent only 9% (Bhavsar et al., 2007; Elnar et al., 2012). Of the six NDL-PCBs, PCBs 153 and 138 are the most abundant congeners, constituting approximately 37% and 32%, respectively, followed by PCB 101 (12%), PCB 180 (11%), PCB 52 (6%), and PCB 28 (2%) (Elnar et al., 2012; Karl et al., 2010; Naso et al., 2005; Szlinder-Richert et al., 2009).

A stock solution of the six NDL-PCBs (30 mg NDL-PCB mixture in 30 ml of rapeseed oil) was prepared depending on the occurrence of each congener in the contaminated fish matrices as mentioned above. To ensure perfect solubility and homogenization of the six PCBs in the rapeseed oil, we first dissolved PCBs (30 mg) in 2 ml of the ethyl acetate. Then, we added 30 ml of rapeseed oil to the mixture obtained. After magnetic agitation (1 h), the solvent was removed using a rotary evaporator at 40 °C.

2.2.2. PCB paste preparation

The contaminated food (paste consisting of PCBs and chow) was prepared daily for a group of mothers (n = 10) by mixing 10 g of powdered food pellets free of phytoestrogens with 10 ml of water, 0.5 ml of sweet syrup, and 1 ml of rapeseed oil diluted PCB solution (at 10 or 1000 ng/ml) with a household kitchen blender (Robot monofonction Seb Valentin 8553, France). Vigorous mixing was employed to ensure complete mixing, following protocols that were established in earlier investigations (Soualeh et al., 2017; Dridi et al., 2014). The obtained homogenous paste was heated at 37 °C for 24 h in an oven. On the following day, the paste was cut into smaller pieces depending on the weight of the pregnant and nursing females (40–70 g) in order to be delivered as 10 and 1000 ng of PCBs/kg-b.w./day to the mice. For example, a dam weighing 45 g received 0.9 g of low (10 ng/kg) or highly (1000 ng/kg) polluted paste with PCBs. For control pregnant and lactating mice (n = 10), the paste was prepared with the same ingredients mentioned above but without adding PCBs.