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Strategy set-shifting and response inhibition in adult rats exposed to an environmental polychlorinated biphenyl mixture during adolescence☆,☆☆

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ABSTRACT

Converging evidence from studies with animal models and humans suggests that early developmental exposure to polychlorinated biphenyls (PCBs) leads to deficits in cognitive flexibility and inhibitory control. These processes are mediated to a large extent by the prefrontal cortex, thus we examined the effects of PCB exposure during adolescence—a period of robust prefrontal cortical development—on both processes. Specifically, we used operant set-shifting and differential reinforcement of low rates of responding (DRL) tasks to assess cognitive flexibility and response inhibition, respectively. One male and one female pup from each of 14 litters were assigned to each of three treatment groups: 0, 3 or 6 mg PCB/kg/day. Rats were dosed orally from postnatal day (PND) 27–50 to capture the whole period of adolescence in rats. At approximately PND 90, they began testing in the set-shifting task which included an initial visual cue discrimination, an extra-dimensional shift to a position discrimination and a reversal of the position discrimination. There were no statistically significant group differences in errors to criterion on visual cue discrimination or on the shift from visual to position discrimination in either males or females. During the position reversal, the 6 mg/kg PCB males made significantly fewer errors to reach criterion than control males. The 3 mg/kg PCB males showed a trend in the same direction, but this did not reach statistical significance. Interestingly, error analysis revealed that PCB-exposed males made significantly fewer *perseverative* errors than controls in this phase. No group differences were observed in females. These results suggest a male-specific effect of adolescent PCB-exposure on the reversal phase of the set-shifting task. Following set-shifting, rats progressed to the DRL task in which they were required to withhold responding for a specified period of time (15 s) in order to receive a reinforcer. There were no exposure-related group differences in total presses or efficiency ratio in males or in females. In summary, there were subtle sex-specific effects of adolescent PCB exposure on the reversal phase of a set-shifting task, but no effects of exposure on performance on a DRL15 task, suggesting an effect on cognitive flexibility but not response inhibition.

1. Introduction

Polychlorinated biphenyls (PCBs) are widespread environmental contaminants formerly used as lubricants and dielectric fluids in capacitors and transformers as well as in the production of carbonless copy paper, caulking material and fluorescent light ballasts (Ross, 2004). PCBs are also inadvertently produced as a byproduct of the manufacture of paint pigments (Grossman, 2013). In this way, PCBs can contaminate, and have recently been detected in, indoor and outdoor air and sediment to which humans can be exposed (Koh et al., 2015). Furthermore, older buildings still containing PCBs in caulking and fluorescent light ballasts will continue to contribute PCBs to ecosystems as they are remediated or demolished (Hornbuckle and Robertson, 2010). Thus, PCBs are likely to remain persistent in our environment for the foreseeable future.

PCBs can cross the placenta and are released into breast milk during lactation (Jacobson et al., 1984). Because of this, the potential health effects of perinatal exposure to PCBs have been the topic of much research over the last four decades. Developmental PCB exposure has been associated with impairments of executive function in humans and animals (reviewed in Eubig et al., 2010). In particular, deficits in cognitive flexibility have been seen in rats and monkeys perinatally

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exposed to PCBs (reviewed in Sable and Schantz, 2006). Response inhibition is also disrupted in rats (Sable et al., 2009), monkeys (Rice and Hayward, 1997; Rice, 1998) and children (Stewart et al., 2006) developmentally exposed to PCBs.

Although extensive research has been carried out evaluating the effects of perinatal PCB exposure on cognitive functioning in humans and animals, very little research has assessed the effects of PCB exposure during adolescence. During this period, the frontal lobes are undergoing marked plasticity and maturation. Specifically, there is marked synaptic remodeling occurring in this region (reviewed in Lenroot et al., 2007; Selemon, 2013). These changes likely underlie the cognitive improvements that emerge during or after adolescence (Brenhouse and Andersen, 2011). For instance, adult rats perform better than adolescent rats on tasks engaging the prefrontal cortex, including tests of response inhibition (Andrzejewski et al., 2011) and behavioral set-shifting, a task of cognitive flexibility (Newman and McGaughy, 2011). Similarly, studies in humans have shown age-related improvements in executive functioning. One study in children aged 9 to 18 years found that increasing age from preadolescence (ages 9–12) through early adolescence (ages 13–15) to late adolescence (ages 16–19) was significantly associated with better performance on measures of strategy set-shifting and response inhibition (Rosso et al., 2004). Another study found that performance on tasks of response inhibition was poor in childhood but steadily improved with age, reaching adult levels of performance in mid to late adolescence (Luna et al., 2010). Thus, given the previous research indicating that perinatal PCB exposure results in deficits in response inhibition and cognitive flexibility (reviewed in Eubig et al., 2010) and that these cognitive abilities are further developing during adolescence, it was hypothesized that adolescence would be a critical period when PCB exposure could result in deficits in these aspects of executive function. To address this question, operant tests of set-shifting and response inhibition (differential reinforcement of low rates of responding, DRL) were administered to adult rats exposed to an environmentally-relevant PCB mixture throughout adolescence.

Most previous PCB studies have used individual PCB congeners or commercial PCB mixtures, but these approaches do not accurately represent what is in the environment and what human populations are exposed to. In this study, we used an experimental PCB mixture formulated to mimic the PCB congener profile found in walleye (a popular sport-caught fish) in the Fox River in northeastern Wisconsin (Kostyniak et al., 2005), a body of water from which the human cohort we have also studied consumed sport-caught fish (Monaikul et al., in preparation). Thus, this study was designed to address not only the paucity of research on the effects of adolescent PCB exposure on cognitive functioning in adulthood but also to use an environmentally relevant mixture that more accurately models the mixture of PCBs to which human populations are exposed.

2. Methods

2.1. Animals

Twenty-one nulliparous female and 21 male Long-Evans rats, approximately 70 days of age, were purchased from Harlan (Indianapolis, IN). Animals used in this study were maintained in facilities fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC). Rats were individually housed in standard plastic shoebox cages with beta-chip (virgin hardwood) bedding, in a temperature- and humidity-controlled room (22 °C, 40–55% humidity) and were maintained on a 12-hour reverse light-dark cycle (lights off at 0830 h). Standard rat chow and water were available ad libitum. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Illinois at Urbana-Champaign and were in accordance with the guidelines of the Public Health Service Policy on Humane Care and Use of Laboratory Animals (2015) and the National Research Council (US) Committee on Guidelines for the Use of Animals in Neuroscience and Behavioral Research (2003).

2.2. Exposure

Male and female rats were individually paired for breeding for 8 days. Only litters with 7 pups or greater were kept, and larger litters were culled to 8–10 pups per litter on postnatal day (PND) 2. At weaning (PND 21), 3 male and 3 female pups from each litter were retained for cognitive testing. One male and 1 female pup from each litter were randomly assigned to each of 3 treatment groups: 0, 3 and 6 mg/kg/day PCBs (n = 14, n = 13, and n = 14 male-female littermate pairs, respectively). The PCB mixture used in this study was formulated to mimic the congener profile found in walleye taken from the Fox River in northeast Wisconsin, thereby closely mimicking human PCB exposure from fish consumption. The mixture consisted of 35% Aroclor 1242 (Monsanto Lot KB 05-415), 35% Aroclor 1248 (AccuStandards Lot F-110), 15% Aroclor 1254 (Monsanto Lot KB 05-612), and 15% Aroclor 1260 (AccuStandards Lot 021-020). The mixture was found to have relatively low aryl hydrocarbon receptor (AhR) activity, but high ryanodine receptor (RyR) activity (Kostyniak et al., 2005). The chemicals were dissolved in corn oil to yield the dosing solutions.

At the time this study was designed, few studies existed in the literature regarding adolescent PCB exposure, especially not using a mixture comparable to the PCB mixture used here. As such, doses were chosen based on previous perinatal studies conducted in our lab using 0, 3 and 6 mg/kg/day of the Fox River PCB mixture that were shown to affect cognitive and behavioral function. These doses used in previous perinatal exposure studies were physiologically relevant because offspring born to dams given these doses appear phenotypically similar to children born to mothers with moderate to high PCB body burdens (Fein et al., 1984; Stewart et al., 2006). In particular, at these doses offspring have been shown to weigh less than control pups at birth and at weaning (Kostyniak et al., 2005) and have shown deficits in inhibitory control (Sable et al., 2009). Thus, as this study was the first to use this mixture in adolescent rats, we chose these dose levels that have had effects on cognition and behavior after perinatal exposure as a starting point to explore our hypotheses.

Dosing began at PND 27 and continued daily through PND 50. This age range was chosen initially based on reviews by Spear (2000, 2007) that describe age-specific behavioral “discontinuities” that are evident between younger and older animals. Overall, however, the literature is inconclusive in characterizing a definitive time frame for adolescence; thus, we chose a time frame (P27–P50) that captured a broad window of adolescence in both male and female rats. Pups were weighed daily through the dosing period, doses were adjusted daily to account for weight gain, and the appropriate amount of dosing solution was pipetted directly into the mouth of the pup. Beginning on PND 90, rats were weighed daily and access to food was restricted to 85% of the rats' free-feeding weight in order to keep the animals motivated to work for food rewards in the operant chambers. Prior to food restriction, mean female weight (± SEM) was 226.8 ± 2.1 g. On the first day of operant testing, mean female weight was 191.1 ± 1.9 g. At the end of operant testing, mean female weight was 225.5 ± 1.9 g. For males, mean weight (± SEM) was 360.8 ± 4.2 g prior to food restriction. On the first day of operant testing, mean male weight was 319.1 ± 4.5 g. At the end of operant testing, mean male weight was 328.9 ± 3.4 g. Food restriction has been routinely used in our lab, and there is no evidence that it confounds PCB-mediated effects.

2.3. Apparatus

Behavioral testing was conducted in 24 automated operant conditioning chambers (Med Associates; St. Albans, VT) housed in sound