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Cocaine Sensitization in Adult Long-Evans Rats Perinatally Exposed to Polychlorinated Biphenyls

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Abstract

Polychlorinated biphenyls (PCBs) are ubiquitous environmental toxicants known to adversely affect the nervous system and more specifically the dopamine system. Developmental PCB exposure in rats has been shown to produce alterations in dopaminergic signaling that persist into adulthood. The reinforcing properties of psychostimulants are typically modulated via the dopaminergic system, so this project used a behavioral sensitization paradigm to evaluate whether perinatal PCB exposure altered sensitization to the psychostimulant cocaine. Long-Evans rats were perinatally exposed to 0, 3 or 6 mg/kg/day of PCBs throughout gestation and lactation. One male and female pup from each litter was retained for behavioral testing. Both horizontal and vertical activity were used to measure cocaine sensitization following repeated injections of 10 mg/kg cocaine (IP) on post-natal day (PND) 91–96 and again after a week in the home cage on PND 103. A final locomotor activity session following a challenge injection of 20 mg/kg was given on PND 110 to further evaluate the availability of presynaptic dopamine stores. The PCB-exposed rats appeared to be pre-sensitized to cocaine as they exhibited a greater degree of cocaine-induced locomotor activation to the initial injections of cocaine and therefore demonstrated a more rapid onset of cocaine behavioral sensitization compared to non-exposed controls. These results add to the literature detailing how perinatal exposure to dopamine-disrupting contaminants can change the developing brain, thereby producing permanent changes in the neurobehavioral response to psychostimulants later in life.

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Conflict of Interest Statement

Nothing to declare.

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1. Introduction

Polychlorinated Biphenyls (PCBs) are ubiquitous environmental toxicants that were widely used in industry until they were banned in the late 1970s. PCBs are very persistent in the environment and disperse into air, water, and soil where they bioaccumulate in the ecosystem (Gdaniec-Pietryka, Mechlinska, Wolska, Galuszka, & Namiesnik, 2013). This has led to their biomagnification up the food chain which results in one of the primary routes of human exposure (ATSDR, 2001). PCBs are very lipophilic and accumulate in brain and mammary tissues. PCBs readily cross the placenta, and are present in breast milk and thus released during lactation; thereby, leading to developmental exposure in the fetus/infant (Schantz, 1996). Of the PCB classes, *ortho*-PCBs have been implicated in adversely affecting the central nervous system (CNS) and in particular, the dopaminergic system as a major selective target (Faroon, Jones, & de Rosa, 2000).

PCBs affect dopamine synthesis, dopamine reuptake and storage, and dopamine release (Angus et al., 1997; Bemis & Seegal, 2004; Mariussen & Fonnum, 2001; Seegal, Brosch, Bush, Ritz, & Shain, 1989; Seegal, Brosch, & Okoniewski, 1997; Seegal, Bush, & Shain, 1990; Seegal, Okoniewski, Brosch, & Bemis, 2002). Previous research has established that perinatal PCBs alter the concentration of dopamine in specific brain regions such as the striatum (Seegal, 1994) and frontal cortex (Seegal et al., 1997) in laboratory animals. Adult exposure to commercial Aroclor mixtures consisting of mostly non-coplanar PCB congeners has been shown to decrease dopamine concentrations in the striatum of rats (Seegal et al., 2002), mice (Richardson & Miller, 2004), and non-human primates (Seegal, 1996; Seegal, Bush, & Brosch, 1991, 1994; Seegal et al., 1990). Similar effects have been established in these brain regions with *in vitro* studies (Lee & Opanashuk, 2004; Lyng & Seegal, 2008). PCBs may be altering the uptake of dopamine by inhibiting the dopamine transporter (DAT) and/or inhibiting the vesicular monoamine transporter (VMAT2) (Jones & Miller, 2008). Studies suggest that PCB-induced VMAT2 inhibition is responsible for decreased extracellular dopamine concentrations (Bemis & Seegal, 2004) while other studies suggest that DAT inhibition is what contributes to the changes observed in extracellular dopamine concentrations as a consequence of PCB exposure (Richardson & Miller, 2004; Seegal, 1994, 1996; Seegal et al., 1997; Seegal et al., 1991, 1994; Seegal et al., 1990; Seegal et al., 2002; Wigstrand, Stenberg, Walaas, Fonnum, & Andersson, 2013).

Adult rats perinatally exposed to PCBs have revealed alterations in behavior following administration of psychostimulants in several different behavioral paradigms. First, alterations in the discriminative stimulus effects of cocaine and amphetamine were observed in adult rats perinatally exposed to PCBs (Sable, Monaikul, Poon, Eubig, & Schantz, 2011). Also, research demonstrated that the locomotor activating effects following a single intraperitoneal amphetamine injection, as well as behavioral sensitization to repeated intraperitoneal injections of amphetamine, were affected by perinatal PCB exposure (Poon, Monaikul, Kostyniak, Chi, Schantz, & Sable, 2013). Lastly, adult rats perinatally exposed to PCBs exhibited differences in stimulated dopamine release following single and repeated cocaine injections in comparison to non-exposed controls, as measured by *in vivo* fixed potential amperometry (Fielding et al., 2013). The mechanism for these differences in

psychostimulant behavioral responses of adult rats perinatally exposed to PCBs appears to be tied to alterations in dopamine signaling.

This study looked at the effects of PCB exposure during gestation and lactation on behavioral sensitization to cocaine in Long-Evans rats. Specifically, this study examined the effects of perinatal PCB exposure on adult behavioral sensitization to cocaine. We expected to demonstrate differences in the locomotor-activating effects of experimenter-administered cocaine in PCB-exposed animals. We hypothesized that locomotor activation following the first injection of cocaine would be higher in rats developmentally exposed to PCBs but that behavioral sensitization following repeated injections of cocaine would be attenuated in these rats relative to controls. This hypothesis parallels the results of Fielding *et al.* (2013) who demonstrated stimulated DA release to the first injection of cocaine was enhanced in rats exposed to PCBs but later attenuated (compared to control rats not exposed to PCBs) following repeated cocaine injections.

2. Methods

2.1. Subjects

Thirty-seven nulliparous female Long-Evans rats (Harlan Barrier 202A; Indianapolis, IN) were used. All rats were maintained in a temperature- and humidity-controlled room (22° C, 40–55% humidity) on a 12-hr light/dark cycle (lights on 0800) and were housed in standard rat shoebox cages containing Harlan Teklad Laboratory Grade Sani-Chip bedding. All rats were given water *ad libitum* and fed a diet of Harlan Teklad 2020X. This was a high-protein, low phytoestrogen diet which helped maintain overall rodent health and ensured that pregnant females were able to support their litters. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Memphis (see protocol in Appendix) and were in accordance with the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (NIH, 2002) and the *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* (National Research Council, 2003).

2.1.1. PCB exposure—Upon arrival, each female was weighed and given an undosed vanilla wafer cookie to acclimate it to eating this novel food item. The female rats were divided into one of the three PCB dose groups which were counterbalanced for body weight. Dosing procedures were identical to those used by Sable *et al.* (2011) and Poon *et al.* (2013). The PCB mixture consisted of: 35% Aroclor 1242 (Monsanto Lot KB 05–415); 35% Aroclor 1248 (AccuStandard Lot F-110); 15% Aroclor 1254 (Monsanto Lot KB 05–612); and 15% Aroclor 1260 AccuStandard Lot 021-020). The stock solution of the Fox River PCB mixture (Kostyniak *et al.*, 2005) was diluted with corn oil to make three dosing solutions: 0 mg/ml PCBs (corn oil only; n = 14 litters), 7.5 mg/ml PCBs (n = 12 litters), and 15.0 mg/ml PCBs (n = 11 litters) which were confirmed using analytical methods (GC-MS). The stock solution was pipetted onto a vanilla wafer cookie at a volume of 0.4 mL/kg according to dam weight to yield final doses of 0, 3, and 6 mg/kg/day, thereby establishing the three dosing groups. It is known that the highest PCB dose (6 mg/kg/day) results in reduction in postnatal body weight gain, and that these effects mirror those found in

postnatal weight gain in children perinatally exposed to PCBs (Govarts et al., 2012; Kostyniak et al., 2005). Consumption of the cookie was visually confirmed each day.

2.1.2. Breeding—After a PCB body-burden of each respective PCB dosage had been established for 28 days in the females, they were paired with an unexposed Long-Evans male rat (Harlan barrier 202A). Breeding pairs remained together for eight days, with the female being removed for PCB dosing daily as previously described. Pregnancy was confirmed by an increase in body weight and the breeding pair was separated. The pregnant females continued to be dosed throughout gestation (roughly twenty-one days) and lactation (twenty-one days).

2.1.3. Weaning—At weaning, on postnatal day (PND) 21, one male/female pair from each litter was sacrificed to determine physiological and histological measures of toxicity. Physiological measures including the dam liver-weight, number of embryo implantation sites in the dam, and brain:body-weight, liver:body-weight and thymus:body-weight ratios in the pups were determined, as was the percent of gestational and lactational weight-gain in the dams and postnatal body weights of the pups on PND 0, 7, 14, and 21. These measures were very similar to what has previously been reported (Sable et al., 2011). In each litter, one additional female and male were tested for behavioral sensitization to cocaine as described below. The weaned pups were transferred to a different room with a light cycle of 14-hr light and 10-hr dark cycle (on at 0800, off at 2200). There the pups were paired or triple-housed according to cohort, exposure group, and gender until PND 90.

2.2. Apparatus and program

Behavioral sensitization was conducted in eight sex-specific automated activity box chambers (Med Associates; St. Albans, VT). These chambers were both sound attenuated and ventilated with a fan. The chambers consisted of a square plastic arena (46.5 x 46.5 x 46.5 cm) bisected with an array of photobeams and equipped with a tracking system (Med Associates). All activity chambers were controlled by a PC equipped with Med-PC IV software (Med Associates).

2.3. Drugs

Cocaine hydrochloride (Sigma, St. Louis, MO) was dissolved in pharmaceutical-grade 0.9% saline to yield 10 and 20 mg/ml concentrations. These concentrations were delivered via intraperitoneal (IP) injections in a volume of 1 ml/kg body weight to yield doses of 10 and 20 mg/kg. These doses have been used successfully in previous studies examining locomotor activation and behavioral sensitization to cocaine (Carey & Gui, 1997; Henry & White, 1995; Todtenkopf & Carlezon, 2006). The 10 mg/kg dose of cocaine was chosen after a pilot study of 20 mg/kg resulted in a locomotor ceiling effect after the first dose. The 10 mg/kg and 20 mg/kg cocaine doses have been shown to result in different levels of locomotor behavior (Gulley, Hoover, Larson, & Zahniser, 2003). The final challenge dose of 20 mg/kg was chosen to determine if perinatal PCB-exposure would attenuate cocaine-induced locomotor activity only after sensitization had been established to the 10 mg/kg cocaine dose. Also, the 20 mg/kg dose was examined in order to afford some degree of comparison

to Fielding *et al.* (2011) which measured stimulated dopamine release to single and repeated injections of 20 mg/kg cocaine, but in anesthetized animals.

2.4. Procedure

Fig. 1 is an overview of the timeline for perinatal exposure to PCB, weaning, and behavioral testing with subsequent post-mortem collection. When the rats reached PND 90, they were placed on an IACUC-approved food deprivation schedule of 90% of their free-feeding weight in order to maintain a relatively consistent body weight of the animal throughout the study (Spindler, 2012). All animals were weighed and fed at approximately the same time each day, during the lights-on phase of the cycle.

2.4.1. Behavioral sensitization to cocaine—On PND 90, the rats began behavioral testing in the activity boxes in a designated testing room. Each daily session consisted of a pre-injection habituation period and a post-injection test period. Each pre-injection (i.e., habituation) session was 30 min (consisting of 3-, 10-min blocks) and began by placing the rat into the chamber where activities of distance traveled (horizontal counts) and rearing (vertical counts) were measured. After this pre-injection period, the rat was given an intraperitoneal (IP) injection of saline exclusively on PND 90, and an IP 10 mg/kg cocaine injection every day for 6 days on PND 91–96, and for a single day on PND 103. After IP injection of either saline or cocaine the rat was immediately placed back into the activity box for the post-injection testing period which lasted for 60 min (consisting of 6-, 10-min blocks). Lastly, on PND 110, a final challenge injection of 20 mg/kg cocaine was administered via IP injection after the pre-injection habituation period. On PNDs 97–102 and 104–109 the rats remained in the colony room and did not undergo behavioral testing and were not administered cocaine. The testing chambers were thoroughly cleaned at the conclusion of each post-injection run.

2.5. Data Analysis

All statistical analyses were conducted using SPSS for MS Windows (version 23.0, SPSS Inc.; Chicago, IL) with statistical significance set at $p < 0.05$. The dependent variables for behavioral testing included distance traveled (in cm) and the total number of vertical photobeam breaks. Each dependent variable was analyzed with a 3 (PCB exposure) $\times$ 2 (sex) $\times$ 3 or 6 (10-min block) mixed ANOVA with PCB exposure group as the between-subjects factor, and sex (nested within litter) and 10-min block of activity both as the repeated-measures factors. The data from days 2–7 and 14 (10 mg/kg IP cocaine) also including testing day as an additional repeated-measures factor. This was not done for the analysis of data from day 1 (saline) and 21 (20 mg/kg IP cocaine). Data from these two days were each analyzed separately in accordance to the compound (saline or 20mg/kg cocaine) that was administered.

In the interest of brevity only significant PCB exposure and sex-related effects are presented. When significant PCB exposure-related effects were observed in the ANOVA, then additional analyses were conducted using Dunnett post hoc *t*-tests to determine the nature of each significant effect. To reveal the true nature of potential sex differences, if the main

effect of sex or the exposure x sex interaction was significant in the omnibus ANOVA, follow-up analyses were conducted separately for each sex.

3. Results

3.1. Day 1 Pre-injection Habituation

3.1.1. Distance traveled—The analysis of distance traveled during the habituation period on the first day of testing revealed a significant main effect of sex [$F(1, 34) = 5.238, p = .028$]. The males exhibited a greater distance traveled with a mean of 14448.66 cm (± 661.09) than females who had a mean of 13054.56 cm (± 575.69) during this first pre-injection habituation period. There were no significant PCB exposure-related differences (see Supplemental Fig. 1, day 1).

3.1.2. Vertical counts—Analysis of the number of vertical counts during the habituation period on day 1 also revealed a significant main effect of sex [$F(1, 34) = 19.452, p < .001$]. Males accrued more vertical photobeam breaks 177.89 (± 7.74) overall than females 138.65 (± 5.59). In addition to this main effect, there was a significant sex x block interaction [$F(2, 68) = 4.708, p = .012$]. As previously indicated, males displayed more vertical activity, but this was particularly evident in the second testing block. There were no significant PCB exposure-related differences (see Supplemental Fig. 2, day 1).

3.2. Day 1 Post-Saline Injection

3.2.1. Distance traveled—Statistical analysis of distance traveled after the injection of saline on day 1 revealed a significant PCB exposure x block interaction [$F(10, 170) = 1.992, p = .037$]. Within the first 10-min block only, rats exposed to 3 mg/kg/day PCBs displayed a greater distance traveled than non-exposed controls ($p = .015$). The main effect of PCB exposure was not significant. These data are presented in Fig. 2, day 1.

3.2.2. Vertical counts—Analysis of the number of accumulated vertical counts during the post-saline injection period revealed a significant main effect of sex [$F(1, 34) = 14.689, p < .001$] and a significant sex x block interaction [$F(5, 170) = 3.770, p = .003$]. Males accrued a greater number of vertical photobeam breaks 112.46 (± 10.79) overall than the females 65.08 (± 4.72) did, and this was especially evident in later testing blocks. There were no significant PCB exposure-related differences. These data are presented in Fig. 3, day 1.

3.3. Days 2–7, 14 Pre-injection Habituation

3.3.1. Distance traveled—Statistical analysis of distance traveled during the pre-injection habituation period on days 2–7 and 14 revealed a significant sex x testing day interaction [$F(6, 204) = 3.253, p = .004$]. Males exhibited greater locomotor activity than females, especially on later testing days. There was also a significant exposure x testing day x block interaction [$F(24, 408) = 2.406, p < .001$] and a significant exposure x sex x testing day x block interaction [$F(24, 408) = 1.607, p = .036$]. These significant interactions were driven by a significantly lower distance traveled by the 3 mg/kg/day females on day 6. There were no other significant PCB-related differences (see Supplemental Fig. 1, days 2–7 and 14).

3.3.2. Vertical counts—Analysis of vertical counts during the habituation period on days 2–7 and 14 revealed a significant main effect of sex [$F(1, 34) = 12.131, p = .001$] and a significant sex x block interaction [$F(2, 68) = 5.867, p = .004$]. Males displayed more vertical activity 128.22 (+/- 8.160) overall than females 95.629 (+/- 5.03), especially within later testing blocks. Lastly, there were also significant PCB exposure x testing day x block [$F(24, 408) = 1.802, p = .012$] and PCB exposure x sex x testing day x block [$F(24, 408) = 1.747, p = .017$] interactions. However, post hoc Dunnett analyses revealed no differences between PCB exposure groups versus same-sex non-exposed control groups on any testing day. There were no other significant PCB-related differences (see Supplemental Fig. 2, days 2–7 and 14).

3.4. Days 2–7, 14 Post-Cocaine Injections (10 mg/kg IP)

3.4.1. Distance traveled—Statistical analysis of distance traveled during the post-cocaine injection periods on days 2–7 and 14 revealed a significant main effect of sex [$F(1, 34) = 7.521, p = .010$] and a significant sex x block interaction [$F(5, 170) = 2.773, p = .020$]. Overall, females 42639.67 cm (+/- 2910.07) displayed a greater distance traveled than males 34344.95 cm (+/- 2910.07) following administration of 10 mg/kg cocaine (IP), especially in later blocks. Most notably, however, there was a significant PCB exposure x sex x testing day x block interaction [$F(60, 1020) = 1.443, p = .017$] (See Fig. 2, days 2–7 and 14). Within-group post hoc simple contrasts across testing days revealed that males exposed to 6 mg/kg/day PCBs exhibited behavioral sensitization by day 3 (i.e., second injection of cocaine), while 0 mg/kg/day PCB males (i.e., control males) and 3 mg/kg/day PCB males did not exhibit sensitization until day 6. Post hoc Dunnett *t*-tests revealed locomotor activation following the second cocaine injection on day 3 was significantly higher in 6 mg/kg/day PCB males compared to 0 mg/kg/day PCB males. Within-group post hoc simple contrasts across testing days revealed that females exposed to 6 mg/kg/day PCBs exhibited sensitization by day 3. Females exposed to 0 mg/kg/day PCBs did not exhibit sensitization until day 5 and females exposed to 3 mg/kg/day PCBs did not show sensitization until day 6. Post hoc Dunnett *t*-tests revealed locomotor activation following the third cocaine injection on day 4 was significantly higher in 6 mg/kg/day PCB females compared to 0 mg/kg/day PCB females.

Differences within testing blocks for days 3–6 are presented in Fig. 4. As previously indicated, males exposed to 6 mg/kg/day PCBs expressed sensitization by day 3 which is likely due to the consistent increase in ambulatory activity across the six 10-min blocks relative to 0 mg/kg/day PCB exposed males on that testing day. With increasing testing day, the distance traveled for the males exposed to 0 and 3 mg/kg/day PCBs gradually increased, approaching that of 6 mg/kg/day PCB-exposed males. By day 6, behavioral sensitization to cocaine was present in all three male exposure groups. A similar pattern across blocks was seen in the females as 6 mg/kg/day PCB-exposed females attained sensitization by day 3. While the increase in ambulatory activity across the six 10-min blocks relative to 0 mg/kg/day PCB exposed females on day 3 was not as profound as in the males, it became more apparent on day 4. Likewise (similar to the male data), by day 6 the control and 3 mg/kg/day PCB exposed females showed levels of ambulatory activity comparable to that of

6 mg/kg/day exposed females. All three female exposure groups exhibited cocaine sensitization by day 6.

3.4.2. Vertical counts—Analysis of vertical counts during the post-cocaine injection period on days 2–7 and 14 revealed a significant sex x block interaction [$F(5, 170) = 7.104$, $p < .001$] whereas the males had more vertical counts in the first 2 blocks (first 20 min) females exhibited more vertical counts during blocks 2–6 (20–60 min). There were no significant PCB-related effects. These data are presented in Fig. 3, days 2–7 and 14.

3.5. Day 21 Pre-injection Habituation

3.5.1. Distance traveled—The analysis of distance traveled during the habituation period on day 21 did not reveal any significant sex or PCB-exposure related differences (see Supplemental Fig. 1, day 21).

3.5.2. Vertical counts—Analysis of vertical counts during the post-cocaine injection period on day 21 revealed a significant main effect of sex [$F(1, 34) = 5.957$, $p = .020$] wherein males 48.42 (± 3.20) had more vertical counts overall than females 40.00 (± 3.01). There were no significant PCB-related effects (see Supplemental Fig. 2, day 21).

3.6. Day 21 Post-Cocaine Injection (20 mg/kg IP)

3.6.1. Distance traveled—Analysis of distance traveled during the post-cocaine injection period on day 21 revealed only a significant main effect of sex [$F(1, 34) = 5.026$, $p = .032$] wherein the females 62890.80 (± 4949.94) had a greater distance traveled overall compared to the males 50031.47 (± 4048.02). Pairwise analyses comparing distance traveled on day 21 versus day 2 was significant for each exposure group ($p < .05$ in all cases). However, the difference in distance traveled on day 21 versus day 14 was only significant for the 3 mg/kg/day PCB females ($p = .028$). These data are presented in Fig. 2, day 21. Although a difference among PCB exposure groups across all testing blocks for both the males and females appears evident (see Fig. 4, day 21), the analysis did not reveal any PCB-related effects.

3.6.2. Vertical counts—Analysis of vertical counts during the post-cocaine injection period on day 21 revealed a significant sex x block interaction [$F(5, 30) = 3.187$, $p = .020$]. However, pairwise comparisons for sex within each 10-min block did not reveal any significant differences. The omnibus analysis also revealed a significant PCB exposure x block interaction [$F(10, 62) = 2.747$, $p = .007$] as well as a significant PCB exposure x sex x block interaction [$F(10, 62) = 2.475$, $p = .015$]. However, additional post hoc Dunnett analyses did not reveal any significant differences between the non-exposed control group and the 3 or 6 mg/kg/day PCB groups within any block for either sex. These data are presented in Fig. 3, day 21.

4. Discussion

4.1. Summary of Findings

The present study demonstrated that perinatal PCB exposure in adult Long-Evans rats resulted in a greater degree of cocaine induced locomotor activation to the initial injections of cocaine and a more rapid onset of behavioral sensitization to cocaine in comparison to controls. The degree of psychomotor activation elicited by cocaine was substantially higher in the 6 mg/kg/day PCB males and females relative to their same-sex controls after only the 2nd and 3rd injection of 10 mg/kg cocaine, respectively. This ultimately resulted in a different time course for the onset of cocaine sensitization. While the 6 mg/kg/day PCB males and females showed enhanced locomotor activity after just the second IP injection of 10 mg/kg cocaine, the control males and females did not exhibit sensitization to this dose of cocaine until day 6 and 5, respectively. These findings suggest that the 6 mg/kg/day PCB rats were pre-sensitized to cocaine compared to the non-exposed controls.

4.2. Horizontal versus Vertical Locomotor Activity: Regional Specificity

Several researchers have postulated that ambulatory activity (i.e., distance traveled in the horizontal plane) is mediated by the mesoaccumbens dopamine system which ascends from the midbrain ventral tegmental area to the nucleus accumbens (Sharp, Zetterstrom, Ljungberg, & Ungerstedt, 1987; Wolf & Xue, 1998). As such, the early differences in distance traveled observed in the rats developmentally exposed to 6 mg/kg/day PCBs in the current study could represent an alteration in mesoaccumbens dopamine function – an outcome supported by the results of Fielding *et al.* (2013) discussed earlier. Disruption of dopamine function in mPFC, specifically hypofunctionality of mPFC dopamine, has also been linked to the expression of behavioral sensitization to psychostimulant drugs (Steketee, 2003). Developmental PCB exposure has been shown to result in decreased levels of dopamine in the prefrontal cortex (Seegal et al., 1997).

Interestingly, there were minimal PCB-related differences in vertical activity. Vertical activity can include rearing behavior and/or head and forepaw movements associated with stereotypy. Spontaneous hind leg rearing is believed to represent a novelty response, a brain related behavior associated with projections to and from the hippocampus (Lever, Burton, & O'Keefe, 2006). On the other hand, repetitive stereotyped behaviors are commonly observed following repeated administration of psychostimulants, and are believed to be mediated by nigrostriatal dopamine projections from the substantia nigra to the striatum (Sharp et al., 1987; Wolf & Xue, 1998). For the subjects used in this study, it is reasonable to infer PCB exposure did not differentially alter the effect of cocaine within the nigrostriatal dopamine system. This outcome is somewhat surprising since previous research has demonstrated developmental PCB exposure increased dopamine levels in several brain regions including the substantia nigra and caudate nucleus (Seegal et al., 1994).

4.3. Relevance to Previous Research

We found that with repeated cocaine injections, the degree of locomotor activation in non-exposed controls also increased, and with subsequent daily cocaine injections it became successively more difficult to distinguish between the controls and those perinatally exposed

to PCBs. Poon *et al.* (2013) had similar findings in adult male rats (but not females) perinatally exposed to PCBs that were administered repeated IP injections of amphetamine. However, with repeated amphetamine injections, PCB-exposed males exhibited a reduction in motor-activating effects in comparison to controls (Poon et al., 2013). Interestingly, this attenuation was not observed in PCB-exposed animals following repeated administration of 10 mg/kg cocaine. Conversely, a trend showing a decrease in distance traveled for the PCB-exposed males following the 20 mg/kg dose of cocaine, suggests this may be a function of cocaine dose. Recall that Fielding *et al.* (2013) demonstrated that stimulated dopamine release (measured in the nucleus accumbens) following a single injection of 20 mg/kg IP cocaine was significantly elevated compared to non-exposed controls in fixed potential amperometry. However, with repeated injections of 20 mg/kg IP cocaine, dopamine efflux was reduced in PCB-exposed rats relative to controls. These results are similar to the behavioral profile Poon *et al.* (2013) observed for amphetamine behavioral sensitization and suggest a replication of this study using a higher dose of cocaine throughout, might result in the same attenuated locomotor response after repeated injections. But as previously mentioned, a pilot study revealed that administration of 20 mg/kg IP cocaine from the start resulted in an immediate locomotor ceiling effect such that sensitization could not be easily demonstrated. As such, if a higher dose is to be examined to look for attenuated locomotor response following repeated injections, it appears that the dose would need to be higher than 10, but lower than 20 mg/kg IP.

Another consideration is that the interoceptive effects of cocaine and amphetamine may have been differentially affected by perinatal PCB exposure. Indeed, previous research using a drug discrimination paradigm found that PCB-exposed animals were more sensitive to the interoceptive effects of cocaine but less sensitive to the interoceptive effects of amphetamine in comparison to non-exposed controls (Sable et al., 2011). Thus, it is also possible that the blunted amphetamine sensitization response observed by Poon et al. (2013) occurred because with repeated injections, the rats became less sensitive to the interoceptive effects of amphetamine – an effect that did not happen in this study with repeated injections of cocaine.

4.4. A Consideration of Other Mechanisms

Another possibility is that PCB exposure may have altered cocaine metabolism, thereby decreasing the active dose of cocaine that reached the brain. We previously examined whether PCB exposure (using the same dosing paradigm used in this study) altered psychostimulant metabolism by measuring amphetamine content in both serum and whole brain and no differences associated with PCB exposure were found (Poon et al., 2013). Thus, we do not believe PCB exposure altered the metabolism of cocaine. On the other hand, altered dopamine metabolism resulting from perinatal PCB exposure may have occurred. Perinatal PCB exposure alters dopamine metabolism by increasing Catechol-O-methyltransferase (COMT) gene expression (DasBanerjee et al., 2008; Sazonova et al., 2011). Likewise, research has also demonstrated an increase in homovanillic acid (HVA) in rats and mice perinatally exposed to PCBs (Dervola et al., 2015). COMT is one of the enzymes involved in the breakdown of dopamine into one of its metabolites – HVA. Increased dopamine metabolism or decreased dopamine levels associated with PCB

exposure may contribute to the differences observed in behavioral sensitization to cocaine, perhaps due to compensatory changes in dopamine synthesis, release, reuptake, storage, and/or receptor activation (Jones & Miller, 2008).

Lastly, it has been previously reported that the same PCB dosing paradigm and PCB doses used in this study decreased serum T4 concentration at weaning (Poon, Powers, McAlonan, Ferguson, & Schantz, 2011). However, we believe that changes in dopamine levels that occur following PCB exposure occur independently of changes in thyroid hormones. Other research has shown that gestational exposure to a dose of the thyrostatic compound propylthiouracil (PTU) that reduced serum and thyroid T4 (relative to non-PTU-exposed controls) had no effect on the concentrations of dopamine and the dopamine metabolite DOPAC in the mPFC, thereby indicating dopamine and DOPAC levels were not dependent upon thyroid hormone concentrations (Roth-Harer et al., 2001).

4.5. Environmental Exposures Alter the Response to Psychostimulants

Numerous studies have examined the neurobiological and behavioral toxicity of PCBs, but only a handful of these have examined how perinatal PCB exposure alters the pharmacological effects of response to psychostimulants later in life. Although small in number, these studies have reliably shown (using several different paradigms) that perinatal PCB exposure alters the neurobiological response to experimenter-administered psychostimulants (Fielding et al., 2013; Poon et al., 2013; Sable et al., 2011). Of particular significance is the fact that studies using other dopamine-disrupting environmental contaminants have shown similar effects. For example, developmental lead (Clifford et al., 2011; Miller, Nation, & Bratton, 2001; Nation, Smith, & Bratton, 2004; Rocha, Valles, Bratton, & Nation, 2008; Rocha, Valles, Hart, Bratton, & Nation, 2008), cadmium (Nation & Miller, 1999), manganese (Guilarte et al., 2008; McDougall et al., 2008; Reichel et al., 2006), and methylmercury (Eccles & Annau, 1982; Rasmussen & Newland, 2001; Reed, Banna, Donlin, & Newland, 2008; Wagner, Reuhl, Ming, & Halladay, 2007) exposure have all been shown to alter the behavioral pharmacology of psychostimulants. The current study adds to this literature detailing how perinatal exposure to dopamine-disrupting contaminants can change the developing brain, thereby producing permanent changes in the neurobehavioral response to psychostimulants later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Long Evans rats were perinatally exposed to 0, 3, or 6 mg/kg/day PCBs.
- The locomotor-activating effects of cocaine were evaluated during separate daily sessions in one adult male and female per litter.
- 6 mg/kg/day PCB rats exhibited behavioral sensitization to 10 mg/kg cocaine (IP) earlier than non-PCB-exposed rats.

Developmental PCB Exposure & Cocaine Sensitization in a Rat Model

Fig. 1.

PCBs were dissolved in corn oil and pipetted onto half of a vanilla wafer (volume based on body weight) and fed to Long-Evans dams at doses of 0, 3, or 6 mg/kg. On PND 117 (after behavioral testing), brains were removed and striatum and mPFC sectioned out and rapidly frozen for later analysis ($n = 9-10$ animals/PCB exposure group). Behavioral sensitization testing began on PND 90 and commenced on PND 110 ($n = 11-14$ animals/PCB exposure group). GD=gestational day, PND=postnatal day

Fig. 2.

The effects of developmental PCB exposure on distance traveled in centimeters (cm) during the 60 minute post-injection period for the male and female offspring across all testing days. Cocaine sensitization occurred in the 6 mg/kg/day PCB males and females on day 3 while control males and females did not exhibit cocaine behavioral sensitization until days 6 and 5, respectively. Error bars represent standard error of the mean.

Fig. 3.

The effects of developmental PCB exposure on vertical counts as indicated by the number of vertical photobeam breaks during the 60 minute post-injection period for the male and female offspring across all testing days. There were no notable PCB-exposure related effects. Error bars represent standard error of the mean.

Post-injection Period

Fig. 4.

A more detailed look at the distance traveled within each testing block for all exposure groups on days 3–6 (10 mg/kg IP) and day 21 (20 mg/kg IP) of cocaine behavioral sensitization testing. At day 3, 6 mg/kg/day PCB males appeared fully sensitized while controls exhibited lower levels of locomotor activity. The 6 mg/kg/day PCB females exhibited increased activity on day 3 as well, but appeared to be fully sensitized by day 4. By day 6, female and male controls exhibited comparable levels of locomotor activity to the 6 mg/kg/day PCB groups. When a final challenge injection was given with a higher dose of cocaine (20 mg/kg), the 6 mg/kg/day PCB males appeared less activated by this cocaine dose, but the difference from the control males was not statistically significant. Likewise, the 3 mg/kg PCB females appeared to exhibit attenuated cocaine sensitization compared to controls following 10 mg/kg IP cocaine, but enhanced locomotor activation after the 20 mg/kg IP dose (day 21), but these differences did not reach the criterion for significance. Error bars represent standard error of the mean.