Published in final edited form as:

Behav Pharmacol. 2012 August ; 23(4): 367–379. doi:10.1097/FBP.0b013e32835651c9.

Ontogeny of Methamphetamine- and Cocaine-Induced One-Trial Behavioral Sensitization in Prewanling and Adolescent Rats

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Abstract

The ontogenetic profile of psychostimulant-induced one-trial behavioral sensitization has not been determined. The purpose of this study was to systematically assess the ontogeny of methamphetamine- and cocaine-induced behavioral sensitization across the preweanling and adolescent periods. To this end, rats were injected with methamphetamine, cocaine, or saline in either an activity chamber or home cage during the preweanling (PD 12, PD 16, or PD 20), preadolescent (PD 24), or adolescent (PD 34) periods. One day later, rats were challenged with the same psychostimulant and locomotion was measured in an activity chamber. Results showed that methamphetamine produced one-trial locomotor sensitization on PD 13 and PD 17; whereas, cocaine-induced behavioral sensitization was only evident on PD 21. The sensitized responding of preweanling rats was not influenced by environmental context. Interestingly, preadolescent and adolescent rats did not exhibit locomotor sensitization. The latter result is generally consistent with past studies showing that rats from the middle and late adolescent periods do not exhibit cocaine-induced one-trial behavioral sensitization. The present results show that methamphetamine, as well as cocaine, can produce one-trial context-independent behavioral sensitization during early ontogeny, but sensitized responding is only apparent within a narrow developmental window.

Keywords

behavioral sensitization; ontogeny; methamphetamine; cocaine

Introduction

Various psychoactive compounds (e.g., alcohol, nicotine, morphine, methamphetamine, and cocaine) can induce behavioral sensitization, which is manifested as an augmented behavioral response that occurs after repeated drug exposure (Robinson and Becker, 1986; Vanderschuren and Kalivas, 2000; Meyer and Phillips, 2007; Vezina *et al.*, 2007). Sensitized responding is most typically assessed after multiple daily treatments with a psychostimulant drug (Kalivas and Stewart, 1991; Tirelli *et al.*, 2003), although young and adult rats are capable of exhibiting locomotor sensitization after a single pretreatment administration of cocaine (Weiss *et al.*, 1989; McDougall *et al.*, 2007). In adult rats and mice, this 'one-trial' behavioral sensitization is dependent on context, because adults only show a sensitized

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Disclosures: The National Institutes for Health (NIH) funded this project; the authors have no conflicts of interest or additional funding sources to disclose.

response when drug pretreatment and testing occur in the same previously novel environment (Drew and Glick, 1989; Weiss *et al.*, 1989; Battisti *et al.*, 1999; McDougall *et al.*, 2009b). In contrast, the one-trial sensitized responding of young rats does not appear to be under contextual control. Specifically, the strength and persistence of one-trial context-specific and context-independent behavioral sensitization is not readily dissociable in preweanling rats (McDougall *et al.*, 2009b, 2011b; Herbert *et al.*, 2010).

In adult rats and mice, various psychostimulants are known to produce one-trial behavioral sensitization (Weiss *et al.*, 1989; Jackson and Nutt, 1993; Battisti *et al.*, 1999; McDougall *et al.*, 2007; Kameda *et al.*, 2011). In contrast, we recently reported that only cocaine, but not methamphetamine, amphetamine, or methylphenidate, causes one-trial behavioral sensitization on postnatal day (PD) 21 (McDougall *et al.*, 2011a). The inability of other psychostimulants to support one-trial sensitized responding was surprising, because all four compounds (cocaine, methamphetamine, amphetamine, and methylphenidate) induce multi-trial behavioral sensitization during the preweanling period (Duke *et al.*, 1997; Wood *et al.*, 1998; McDougall *et al.*, 1999, 2011a; Tirelli, 2001). Various explanations can account for this psychostimulant-dependent effect. For example, the neural circuitry mediating behavioral sensitization may differ according to psychostimulant (for reviews, see White *et al.*, 1998; Vanderschuren and Kalivas, 2000), hence it is possible that only cocaine was able to induce the necessary neural modifications after a single drug exposure. Second, among the various psychostimulants used, cocaine may be especially effective at promoting the formation of environment-drug (CS-US) associations. The latter explanation assumes, probably incorrectly, that contextual conditioning strengthens the one-trial sensitized responding of preweanling rats. Finally, drug affinity and/or pharmacokinetic factors (e.g., a short half-life) may endow cocaine with a unique ability to induce one-trial behavioral sensitization in preweanling rats. Whichever explanation is correct, it would have to be specific to young animals because adult rats and mice exhibit one-trial sensitization to both amphetamine and cocaine (Drew and Glick, 1989; Weiss *et al.*, 1989; Battisti *et al.*, 2000; McDougall *et al.*, 2009a).

An important limitation of previous research examining the early ontogeny of one-trial behavioral sensitization is that only a single age group (e.g., PD 19–21) was typically tested. Using one age to represent early ontogeny can result in an overly simplistic understanding of the developmental process, because acute and repeated treatment with dopamine agonists often produces different behavioral effects as the animal matures (Moody and Spear, 1992; Frantz *et al.*, 1996; for reviews, see Spear, 1979; Andersen, 2005). In some cases, age-dependent behavior changes are due to the maturation of underlying neural mechanisms (e.g., alterations in DAT levels, dopamine receptor functioning, etc.; Sobrian *et al.*, 2003), while other ontogenetic effects are a consequence of programmed changes in the rats' behavioral repertoire (Moody and Spear, 1992). In terms of this study, it was previously reported that methamphetamine does not induce one-trial behavioral sensitization during the late preweanling period (i.e., PD 19–21), whereas cocaine causes robust context-independent behavioral sensitization at the same age (McDougall *et al.*, 2011a). Whether these two sets of findings are unique to the late preweanling period is unknown. Therefore, the purpose of the present study was twofold: First, to determine whether the inability of methamphetamine to induce one-trial behavioral sensitization is restricted to a specific developmental period (PD 19–21) or is a more general phenomenon characteristic of early ontogeny; Second, to determine whether cocaine-induced context-independent sensitization is only evident during the late preweanling period or will occur at younger or older ages. To examine this issue, rats were pretreated and tested with methamphetamine or cocaine across a range of developmental stages, including the early (PD 12–13), middle (PD 16–17), and late (PD 20–21) preweanling periods, as well as preadolescence (PD 24–25) and adolescence (PD 34–35). Context-specific and context-independent procedures were used at

each age (i.e., the psychostimulant was administered in either the activity chamber or the home cage on the pretreatment day). Age-dependent changes in the acute locomotor activating effects of methamphetamine and cocaine were also determined. It was hypothesized that cocaine would produce one-trial context-independent behavioral sensitization in all preweanling age groups, whereas methamphetamine would not support one-trial behavioral sensitization during the preweanling or adolescent periods. Experimental results did not fully support either of these hypotheses.

Methods

Subjects

Subjects were 288 male and female preweanling, preadolescent, and adolescent rats of Sprague-Dawley descent (Charles River, Hollister, California, USA) that were born and raised at California State University, San Bernardino (CSUSB). Litters were culled to 10 pups on PD 4 and weaned on PD 25. Except during testing, preweanling and preadolescent rats were kept with the dam and littermates, whereas adolescent rats were group housed with same sex littermates. All rats were housed on racks in large polycarbonate maternity cages (56 × 34 × 22 cm) with wire lids and Tek-Fresh® bedding (Harlan, Indianapolis, Indiana, USA). Food and water were freely available. The colony room was maintained at 22–23°C and kept under a 12 L:12 D cycle. Testing was done in separate experimental rooms, maintained at 24–25°C, and was conducted during the light phase of the cycle. Subjects were cared for according to the “Guide for the Care and Use of Laboratory Animals” (National Research Council, 2010) under a research protocol approved by the Institutional Animal Care and Use Committee of CSUSB.

Apparatus

Behavioral testing was done in activity monitoring chambers (Coulbourn Instruments, Allentown, Pennsylvania, USA), consisting of acrylic walls, a plastic floor, and an open top. Each chamber included an X–Y photobeam array, with 16 photocells and detectors, that was used to determine locomotor activity (distance traveled). To equate for differences in body size, rats tested on PD 12–25 were placed in smaller sized chambers (26 × 26 × 41 cm) than rats tested on PD 34–35 (41 × 41 × 41 cm). In all other regards, the different-sized chambers were identical to each other.

Drugs

(+)-Methamphetamine hydrochloride and (–)-cocaine hydrochloride were purchased from Sigma (St. Louis, Missouri, USA). All drugs were dissolved in saline and injected intraperitoneally (IP) at differing volumes depending on age (PD 12–25, 5 ml/kg; PD 34–35, 1 ml/kg).

Procedure

Experiment 1: Ontogeny of one-trial methamphetamine sensitization—Five different age groups were tested: PD 12–13, PD 16–17, and PD 20–21 (early, middle, and late preweanling periods, respectively), as well as PD 24–25 (preadolescence) and PD 34–35 (adolescence). On the pretreatment day (i.e., PD 12, PD 16, PD 20, PD 24, or PD 34), rats assigned to the Methamphetamine-Activity groups were taken to the testing room and injected with methamphetamine (4 mg/kg, IP) before being placed in the activity chambers. Locomotor activity was measured for 30 min. These rats were then returned to the home cage and injected with saline 30 min later. Rats in the Methamphetamine-Home groups were injected with saline before being placed in the activity chambers and injected with

methamphetamine (4 mg/kg, IP) 30 min after being returned to the home cage. The Acute Control groups were injected with saline in both the activity chamber and home cage.

On a single test day (i.e., PD 13, PD 17, PD 21, PD 25, or PD 35), all rats were given a challenge injection of methamphetamine (2 mg/kg) and immediately placed in activity chambers to determine the occurrence of locomotor sensitization. Locomotion was recorded for 180 min.

Experiment 2: Ontogeny of one-trial cocaine sensitization—The behavioral protocol was the same as described in Experiment 1, with the exception that saline or cocaine (30 mg/kg) was administered on the pretreatment day and cocaine (20 mg/kg) was administered on the test day. The same five age groups were used. Sensitized responding was apparent for a maximum of 120 min on the test day, so only those data are presented.

Statistics

Repeated measures (10-min time blocks) analyses of variance (ANOVAs) were used for statistical analysis of locomotor activity (distance traveled) data. When required, significant higher order interactions (e.g., Age $\times$ Group $\times$ Time block) were further analyzed using one- or two-way ANOVAs. When the assumption of sphericity was violated, as determined by Mauchly's test of sphericity, the Huynh-Feldt epsilon statistic was used to adjust degrees of freedom. Corrected degrees of freedom were rounded to the nearest whole number and are indicated by a superscripted "a". Post hoc analysis of locomotor activity data was done using Tukey tests ($P < 0.05$).

Litter effects were minimized by assigning one subject from each litter to a particular group (for a discussion of litter effects, see Zorrilla, 1997). In situations where this rule was violated (e.g., analyses of the pretreatment day), a single litter mean was calculated from multiple littermates assigned to the same group (Holson and Pearce, 1992; Zorrilla, 1997). Prepubescent rats do not typically exhibit drug-induced sex differences (Bowman et al. 1997; Snyder et al., 1998; McDougall et al., 2007), thus a combined total of eight male ($n = 4$) and female ($n = 4$) rats were assigned to each group on PD 24 and younger. Sensitized responding of older rats often differs according to sex (Becker et al., 2001), so twice as many male ($n = 8$) and female ($n = 8$) rats were assigned to each of the adolescent conditions. Preliminary analyses indicated that sex differences were not apparent at the younger ages (PD 13–PD 25), therefore those data are presented collapsed across the sex variable.

To assess the relative magnitude of cocaine-induced behavioral sensitization in the different age groups, a sensitization quotient was calculated within litter at each age [(locomotor activity scores of the Psychostimulant-Home or Psychostimulant-Activity group / locomotor activity scores of the Acute control group) $\times 100$]. A score of 100 would indicate the lack of a sensitized response and a progressively higher score would indicate a stronger sensitized response. Age-dependent differences in sensitization strength were analyzed with the Kruskal-Wallis (KW) nonparametric statistic, with Mann-Whitney U-tests being used for post comparisons (Siegel and Castellan, 1988).

Results

Experiment 1: Ontogeny of one-trial methamphetamine sensitization

Pretreatment day—Acute methamphetamine administration enhanced the expression of locomotor activity on the pretreatment day (Table 1) [Drug main effect, $F(1,86) = 164.08$, $P < 0.001$], with this effect being apparent at all ages tested [Drug $\times$ Age interaction, $F(4,86) =$

4.22, $P < 0.01$ and Tukey tests]. In general, the amount of locomotor activity exhibited increased with age [Age main effect, $F(4,86) = 14.03$, $P < 0.001$]. Among the saline groups, PD 34 rats locomoted more than all other age groups (with the exception of PD 20 rats); whereas, rats pretreated with methamphetamine on PD 24 or PD 34 exhibited more locomotor activity than PD 12 and PD 16 rats [Drug $\times$ Age interaction, $F(4,86) = 4.22$, $P < 0.01$ and Tukey tests].

Assessment of behavioral sensitization—Overall, an omnibus Age $\times$ Group $\times$ Time block ANOVA indicated that the age variable interacted with pretreatment condition to affect the locomotor activity of methamphetamine-challenged rats on the test day [Age $\times$ Group interaction, $F(8,129) = 9.79$, $P < 0.001$; ^aAge $\times$ Group $\times$ Time block interaction, $F(42,671) = 1.72$, $P < 0.01$]. To further assess this ontogenetic difference, separate Group $\times$ Time block ANOVAs were used to analyze the occurrence of sensitized responding at each age.

PD 13 test day—On the test day (i.e., PD 13), locomotor sensitization was apparent, because rats pretreated with methamphetamine in either the home cage (i.e., the Methamphetamine-Home group) or the activity chamber (i.e., the Methamphetamine-Activity group) exhibited more locomotor activity than the Acute Control group (upper left graph, Fig. 1) [Group main effect, $F(2,21) = 16.27$, $P < 0.001$ and Tukey tests]. The Methamphetamine-Activity group showed a sensitized locomotor response on time blocks 2–16, whereas the Methamphetamine-Home group exhibited a significantly elevated locomotor response on time blocks 2–14 [^aGroup $\times$ Time block interaction, $F(10,103) = 2.87$, $P < 0.01$ and Tukey tests].

PD 17 test day—On PD 17, rats in the context-independent and context-specific conditions exhibited significantly more locomotor activity than the Acute Control group (upper left graph, Fig. 1) [Group main effect, $F(2,21) = 19.34$, $P < 0.001$ and Tukey tests]. Differences between the Methamphetamine-Activity group and the Acute Controls were evident on time blocks 3–17, whereas the Methamphetamine-Home and Acute Control groups differed on time blocks 2–18 [^aGroup $\times$ Time block interaction, $F(8,59) = 2.84$, $P < 0.01$ and Tukey tests].

PD 21 test day—Locomotor sensitization was not evident on the test day (i.e., PD 21), since neither of the methamphetamine pretreatment groups differed significantly from the Acute Control group (lower left graph, Fig. 1). The only significant effect involved the time variable, with locomotor activity peaking on time block 3 and then showing a progressive decline until time block 14 [^aTime block main effect, $F(6,128) = 30.12$, $P < 0.001$ and Tukey tests].

PD 25 test day—When assessed on PD 25, there was no evidence of locomotor sensitization (lower right graph, Fig. 1). Instead, rats in the Methamphetamine-Home group exhibited more locomotion than the Methamphetamine-Activity group on time block 5 [^aGroup $\times$ Time block interaction, $F(9,97) = 2.40$, $P < 0.05$ and Tukey tests].

PD 35 test day—Locomotor sensitization was not observed on PD 35 (Fig. 2). Locomotor activity peaked on time block 4 and then declined across the testing session [^aTime block main effect, $F(4,169) = 47.46$, $P < 0.001$]. Overall, methamphetamine (2 mg/kg) stimulated significantly more locomotor activity in females than males [Sex main effect, $F(1,42) = 11.46$, $P < 0.01$].

Cross-age comparisons—Age comparisons of sensitization strength indicated that the PD 13 and PD 17 age groups had a sensitization quotient that was over 300% greater than the older age groups (Fig. 3). These age-dependent differences in sensitized responding were evident in both the context-specific [Age effect, $KW = 23.15$, $P < 0.001$ and Mann-Whitney U tests] and context-independent conditions [Age effect, $KW = 26.60$, $P < 0.001$ and Mann-Whitney U tests].

The ontogeny of methamphetamine-induced locomotor activity was assessed by comparing the locomotion of the Acute Control groups on the test day. Rats given an acute injection of methamphetamine (2 mg/kg) on PD 21, PD 25, or PD 35 exhibited significantly more locomotor activity than rats tested on PD 13 or PD 17 (right panel, Fig. 4) [Age main effect, $F(4,43) = 9.54$, $P < 0.001$ and Tukey tests]. Differences between the younger and older rats were especially prominent early in the testing session (left panel, Fig. 4). For example, rats tested on PD 21 and PD 25 had greater locomotion than PD 13 and PD 17 rats on time block 2 [^aAge $\times$ Time block interaction, $F(18,192) = 8.61$, $P < 0.001$ and Tukey tests]. On time blocks 3–9, all three of the older age groups exhibited more locomotor activity than PD 13 and PD 17 rats [Tukey tests]. PD 21 and PD 35 rats continued to locomote more than PD 13 and PD 17 rats on time blocks 10 and 11 [Tukey tests]. On time block 12, PD 21 rats had greater locomotor activity scores than the two younger age groups, while PD 35 rats locomoted more than PD 16 rats [Tukey tests]. On time block 13, only PD 21 rats exhibited more locomotor activity than PD 16 rats [Tukey tests]. The various age groups did not vary significantly on time blocks 14–18.

Experiment 2: Ontogeny of one-trial cocaine sensitization

Pretreatment day—On the pretreatment day, locomotor activity increased with age of the animal (Table 2) [Age main effect, $F(4,86) = 60.01$, $P < 0.001$] and cocaine (30 mg/kg) caused an overall enhancement in locomotion [Drug main effect, $F(1,86) = 163.04$, $P < 0.001$]. The significant Drug $\times$ Age interaction indicated that among the saline groups PD 34 rats locomoted more than all of the younger age groups, while saline-pretreated PD 24 rats were more active than PD 12 rats [Drug $\times$ Age interaction, $F(4,86) = 29.09$, $P < 0.001$ and Tukey tests]. A similar pattern of effects occurred among the cocaine groups, because (a) cocaine-pretreated PD 34 rats exhibited more locomotor activity than all other age groups; (b) cocaine-pretreated PD 24 and PD 20 rats locomoted more than PD 12 rats; and (c) cocaine produced more locomotor activity than saline at each age [Tukey tests].

Assessment of behavioral sensitization—Results of the Age $\times$ Group $\times$ Time block ANOVA indicated that age and pretreatment condition interacted to affect test day locomotor activity [Age $\times$ Group interaction, $F(8,129) = 3.72$, $P < 0.01$; ^aAge $\times$ Group $\times$ Time block interaction, $F(26,419) = 2.78$, $P < 0.001$]. As a consequence, separate Group $\times$ Time block ANOVAs were used to analyze sensitized responding at each age.

PD 13 test day—On the test day (i.e., PD 13), behavioral sensitization was not apparent because rats pretreated with cocaine in the activity chamber (i.e., the Cocaine-Activity group) or home cage (i.e., the Cocaine-Home group) did not exhibit greater locomotor activity than the Acute Control group (upper left graph, Fig. 5). Instead, rats in the Cocaine-Activity group showed significantly more test day locomotor activity than the Cocaine-Home group [Group main effect, $F(2,21) = 5.37$, $P < 0.05$ and Tukey tests].

PD 17 test day—There was no evidence of behavioral sensitization when locomotor activity data were collapsed across the testing session (upper right graph, Fig. 5) [Group main effect, $F(2,21) = 0.69$, $P > 0.05$]; however, analysis of the Group $\times$ Time block interaction indicated that some group differences were apparent on individual time blocks

[^aGroup $\times$ Time block interaction, $F(11,112) = 10.93$, $P < 0.001$]. More specifically, rats in the Cocaine-Activity and Cocaine-Home groups exhibited significantly more locomotor activity than rats in the Acute Control group on time blocks 1 and 10–12 [Tukey tests]. The reverse occurred on time blocks 2–4, with the Acute Control group showing elevated levels of locomotor activity when compared to the Cocaine-Activity and Cocaine-Home groups [Tukey tests].

PD 21 test day—Rats tested on PD 21 evidenced robust one-trial context-independent behavioral sensitization, because rats in the Cocaine-Home group, as well as the Cocaine-Activity group, exhibited significantly more locomotor activity than the Acute Control group (lower left graph, Fig. 5) [Group main effect, $F(2,21) = 12.74$, $P < 0.001$ and Tukey tests]. Differences between the cocaine-pretreated groups and the Acute Control group were statistically significant on time blocks 2–10 [^aGroup $\times$ Time block interaction, $F(5,54) = 3.06$, $P < 0.05$ and Tukey tests].

PD 25 test day—On the test day (i.e., PD 25), locomotor sensitization was not evident because the Cocaine-Activity and Cocaine-Home groups did not differ from the Acute Control group (lower right graph, Fig. 5). Although locomotor activity showed an initial increase across the first three time blocks and then a subsequent decline [^aTime block main effect, $F(3,69) = 84.90$, $P < 0.001$ and Tukey tests], there was no evidence that treatment condition interacted with time block to affect behavior [Group $\times$ Time block interaction, $P > 0.05$].

PD 35 test day—On PD 35, male and female adolescent rats did not exhibit behavioral sensitization, because the Cocaine-Activity and Cocaine-Home groups did not differ from the Acute Control group (Fig. 6). The only exception involved time block 1, when the Cocaine-Activity group showed significantly more locomotor activity than the Acute Controls [^aDrug $\times$ Time block interaction, $F(6,133) = 3.00$, $P < 0.01$ and Tukey tests]. A separate lower order ANOVA indicated that only female rats exhibited group differences on time block 1. No other sex differences were apparent. Overall, locomotor activity declined across the testing session [^aTime block main effect, $F(3,133) = 145.48$, $P < 0.001$].

Cross-age comparisons—The relative magnitude of sensitized responding in the context-specific condition varied according to age (upper graph, Fig. 7), with PD 21 rats showing a significantly greater sensitized response than all other age groups [Age effect, $KW = 13.76$, $P < 0.01$ and Mann-Whitney U tests]. Similarly, only PD 21 rats exhibited cocaine-induced behavioral sensitization in the context-independent condition (lower graph, Fig. 7) [Age effect, $KW = 21.38$, $P < 0.001$ and Mann-Whitney U tests].

In terms of the acute effects of cocaine, rats injected with 20 mg/kg of cocaine on PD 25 or PD 35 locomoted significantly more than rats tested on PD 13 or PD 17 (right panel, Fig. 8) [Age main effect, $F(4,43) = 27.36$, $P < 0.001$ and Tukey tests]. Cocaine also stimulated more locomotor activity on PD 21 than on PD 13 [Tukey tests]. The various aged rats exhibited different patterns of locomotor activity across the testing session (left panel, Fig. 8). On time blocks 2–6, PD 25 and PD 35 rats were more active than PD 13, PD 17, and PD 21 rats; whereas, the three older age groups (PD 21, PD 25, and PD 35) locomoted more than the two younger age groups on time blocks 1, 7, and 8 [^aAge $\times$ Time block interaction, $F(18,194) = 11.84$, $P < 0.001$ and Tukey tests]. Towards the end of the testing session, PD 21 rats exhibited more locomotor activity than PD 13 rats (time blocks 9 and 12) and PD 17 rats (time blocks 9–12) [Tukey tests].

Discussion

It was originally reported that methamphetamine would not support one-trial behavioral sensitization during the late preweanling period (i.e., on PD 21) (McDougall *et al.*, 2011a). The present study greatly extends these findings by showing that rats will exhibit robust one-trial context-independent behavioral sensitization when methamphetamine is administered to younger age groups (PD 12–13 or PD 16–17). Methamphetamine did not induce one-trial behavioral sensitization during the late preweanling period (PD 20–21), preadolescence (i.e., PD 24–25), or adolescence (PD 34–35). No sex differences in sensitized responding were observed during the preweanling period; however, female rats exhibited more methamphetamine-induced locomotor activity than male rats on PD 35 (see also Schindler *et al.*, 2002; Milesi-Hallé *et al.*, 2005, 2007). Cocaine caused a different pattern of effects, because cocaine-induced one-trial behavioral sensitization was only evident during the late preweanling period (i.e., PD 20–21), but not at younger or older ages. Similar to methamphetamine, the cocaine-induced locomotor sensitization exhibited by PD 21 rats was context-independent. These results are consistent with a separate series of studies showing that associative learning does not modulate the expression of one-trial behavioral sensitization during the preweanling period (McDougall *et al.*, 2009b, 2011b; Herbert *et al.*, 2010), even though contextual conditioning is necessary for the expression of one-trial behavioral sensitization in adult rats and mice (Weiss *et al.*, 1989; Fontana *et al.*, 1993; Jackson and Nutt, 1993; Battisti *et al.*, 1999; McDougall *et al.*, 2007).

One of the most surprising results of this study was that the two psychostimulants stimulated one-trial behavioral sensitization at different ages. More specifically, methamphetamine-induced locomotor sensitization was apparent on PD 13 and PD 17, while cocaine-induced sensitization was restricted to PD 21. Drug affinity differences, pharmacokinetic factors, and discrepancies in the dosing regimen are the most likely reasons for the disparate actions of the two psychostimulants. Although both cocaine and methamphetamine have an approximately equal affinity for dopamine and noradrenergic transporters, methamphetamine has a relatively lower affinity for the serotonin transporter than cocaine (Howell and Kimmel, 2008). Methamphetamine also primarily functions as a dopamine releaser, while cocaine is a transport inhibitor (McMillen, 1983). Pharmacokinetic factors may be relevant, because methamphetamine penetrates the brain more slowly and has a longer half-life than cocaine (Brien *et al.*, 1978; Benuck *et al.*, 1987; Lau *et al.*, 1991; Rivière *et al.*, 2000; Carmona *et al.*, 2005). Lastly, the current results are based on a single dose analysis, so it is possible that a different pattern of sensitization effects would be evident if doses were tailored to each age group. The cocaine doses used in our study were based on parametric experiments designed to maximize one-trial behavioral sensitization in preweanling rats (McDougall *et al.*, 2007; Herbert *et al.*, 2010). For this reason, the pretreatment (30 mg/kg) and test day (20 mg/kg) doses of cocaine are somewhat different than those typically used to induce one-trial behavioral sensitization in adult rats (pretreatment, 40 mg/kg; test day, 10 mg/kg; Weiss *et al.*, 1989; Fontana *et al.*, 1993; Jackson and Nutt, 1993). Even so, adult rats will exhibit one-trial locomotor sensitization using the same doses as in the present study (McDougall *et al.*, 2007, 2009a). The lack of methamphetamine-induced behavioral sensitization on PD 21 did not result from a similar dosing issue, because a sensitized locomotor response was not apparent on PD 21 even when various pretreatment (2, 4, 8 or 12 mg/kg) and test day (1, 4, or 8 mg/kg) doses of methamphetamine were used (McDougall *et al.*, 2011a).

It is interesting that neither cocaine nor methamphetamine produced one-trial behavioral sensitization during the preadolescent or adolescent periods. Using a multi-trial procedure, Collins and Izenwasser (2002) also reported that rats treated with cocaine during adolescence were incapable of exhibiting locomotor sensitization. They attributed the lack

of sensitized responding to age-dependent differences in psychostimulant-induced neuroadaptations (e.g., repeated cocaine treatment altered the densities of dopamine and serotonin transporters in adults but not adolescent rats). The absence of context-dependent behavioral sensitization has also been observed in adolescent rodents given repeated treatments with nicotine and ethanol (Collins and Izenwasser, 2004; Faria *et al.*, 2008). In contrast, Laviola *et al.* (1995) reported that adolescent rats given four daily cocaine administrations did not show a decrement in sensitized responding relative to adults, while the magnitude of amphetamine-induced one-trial behavioral sensitization was greater in adolescent mice than adults (Kameda *et al.*, 2011). In the study most similar to ours, rats tested on PD 42 or PD 65 did not exhibit one-trial locomotor sensitization, although a cocaine-induced sensitized response was evident on PD 28. These authors suggest that stress-induced alterations in hormone levels (e.g., corticosterone or testosterone) might have contributed to age-dependent differences in the occurrence of behavioral sensitization (Caster *et al.*, 2007).

In terms of the present study, ontogenetic changes in psychostimulant-induced neuroadaptations (Collins and Izenwasser, 2002) or stress-induced alterations in hormone levels (Caster *et al.*, 2007) could be fully or partially responsible for the absence of methamphetamine- and cocaine-induced behavioral sensitization in our preadolescent and adolescent rats. Of course, any explanation must account for the finding that rats transiently express robust locomotor sensitization during the preweanling period. Considering the age-dependent changes in responsiveness to methamphetamine and cocaine (see Figs. 4 and 8), it could be argued that the elevated levels of locomotor activity exhibited by preadolescent and adolescent rats, relative to the younger age groups, precluded the ability of PD 25 and PD 35 rats to express locomotor sensitization. This explanation is unlikely, however, because we previously showed that one-trial behavioral sensitization remained undetectable even when lower doses of methamphetamine were administered on the test day (i.e., locomotion declined with smaller doses, but sensitized responding was still not expressed) (McDougall *et al.*, 2011a). Moreover, PD 13 and PD 17 rats in the Acute Control group exhibited low levels of cocaine-induced locomotor activity on the test day, yet behavioral sensitization was not evident (Fig. 5).

This study also provides important information about how the acute locomotor activating effects of methamphetamine and cocaine vary across early ontogeny. Among those rats given methamphetamine (2 mg/kg) for the first time on the test day (i.e., the acute control groups), older rats (PD 21–PD 35) exhibited substantially more locomotor activity than rats tested on PD 13 or PD 17 (see Fig. 4). Similar age-dependent differences were apparent after rats were injected with 4 mg/kg of methamphetamine on the pretreatment day (see Table 1). Cocaine produced an analogous pattern of effects, with PD 21–PD 35 rats exhibiting more locomotor activity than younger rats. The latter results are not in agreement with an older study showing that adolescent rats given a systemic injection of cocaine (5, 10, or 25 mg/kg) on PD 28 or PD 35 exhibited fewer matrix crossings than rats tested during the preweanling period (i.e., on PD 14 or PD 21) (Spear and Brick, 1979). The reason for this discrepancy is uncertain although there are substantial procedural differences between the studies, including route of drug administration and behavioral assessment techniques. Ambient room temperature was similar in the two studies; however, we cannot exclude the possibility that the younger age groups experienced cold stress at the temperatures used. That being said, visual inspection of Figure 1 shows that PD 13 rats were capable of exhibiting substantial locomotor activity across the entire testing session, thus the occurrence of sensitized responding was not precluded by low ambient room temperature.

It is clear that the ontogeny of dopamine system functioning is more complex than was once envisioned. A simplistic view might suggest that dopamine-mediated behaviors should

progressively mature to their adult form as underlying neural mechanisms develop linearly from embryonic stages to adulthood. In fact, the behavioral repertoire of young rats changes dramatically across the preweanling period (Moody and Spear, 1992) and in many ways a rat at PD 20 is more similar to an “adolescent” rat than a “preweanling” rat at PD 12 (Spear, 2000). Not surprisingly, many dopaminergic elements do not show a monotonic pattern of development. For example, Teicher *et al.* (1995) have reported that D1 and D2 receptor sites in the dorsal striatum increase linearly in number until around the fourth postnatal week, at which time there is a dramatic overproduction of receptors and then a gradual decline of up to 35–50% until adult-like levels are reached (for reviews, see Tarazi and Baldessarini, 2000; Andersen, 2003). Andersen *et al.* (1997) suggest that perturbations in the overproduction of dopamine receptors, and their subsequent pruning, may be responsible for various psychopathologies in humans. This transient overabundance of D1 and D2 receptors during the adolescent period may also be responsible for ontogenetic changes in the acute effects of dopamine agonists. Complicating this analysis are discrepant results showing that the behavioral actions of psychostimulant drugs are either enhanced (Caster *et al.*, 2005; Parylak *et al.*, 2008; Walker *et al.*, 2010; Kameda *et al.*, 2011) or reduced (Lanier and Isaacson, 1977; Bolanos *et al.*, 1998; Collins and Izenwasser, 2002, 2004; Frantz *et al.*, 2006) during adolescence relative to adulthood. To some extent, these inconsistent findings may be explained by the psychostimulant used, because Walker *et al.* (2010) report that dopamine transport inhibitors (e.g., cocaine and methylphenidate) induce more locomotor activity in adolescent rats than adults, while dopamine releasers (e.g., amphetamine and methamphetamine) have similar behavioral actions in the two age groups.

In terms of repeated psychostimulant treatment, studies using multi-trial procedures typically report that behavioral sensitization is weaker and persists for a shorter period of time during the preweanling period than in adulthood (for a review, see Tirelli *et al.*, 2003). Smith and Morrell (2007) even propose that repeated subcutaneous cocaine administration causes tolerance, rather than sensitization, in preweanling rats. Our analysis of one-trial behavioral sensitization also suggests that the ontogeny of psychostimulant-induced behavioral sensitization is very complex. Specifically, methamphetamine- and cocaine-induced behavioral sensitization is expressed at restricted stages during the preweanling period, seemingly disappears during middle and late adolescence (see also Caster *et al.*, 2007), and again becomes prominent in adulthood (Weiss *et al.*, 1989; Fontana *et al.*, 1993; Jackson and Nutt, 1993; McDougall *et al.*, 2007, 2009a). The neural mechanisms underlying these dramatic age-dependent behavioral differences are not known, although various dopaminergic elements (e.g., dopamine transporters, dopamine content, tyrosine hydroxylase levels, adenylyl cyclase activity, as well as D1 and D2 receptor numbers) show pronounced changes across early ontogeny (Coyle and Campochiaro, 1976; Broaddus and Bennett, 1990; Tarazi *et al.*, 1998; Tarazi and Baldessarini, 2000; Kuperstein *et al.*, 2008). NMDA receptor functioning is also important for sensitized responding (for a review, see Wolf, 1998); hence, age-dependent changes in the glutamate system, which are very prominent (Insel *et al.*, 1990; Miller *et al.*, 1990; Nansen *et al.*, 2000), may underlie the complex ontogeny of behavioral sensitization. Lastly, associative processes, perhaps mediated by the striatum and amygdala (Badiani and Robinson, 2004), modulate the strength of the sensitized response (Carey and Gui, 1998; Anagnostaras *et al.*, 2002; Wang and Hsiao, 2003), thus it is possible that maturational changes in associative learning might contribute to ontogenetic differences in one-trial and multi-trial behavioral sensitization.

In sum, robust methamphetamine- and cocaine-induced behavioral sensitization was evident at various preweanling ages but completely disappeared during the preadolescent and adolescent periods. This ontogenetic shift in the expression of behavioral sensitization could be due to age-dependent changes in pharmacokinetic (e.g., alterations in stress or sex hormones) and/or pharmacodynamic factors (e.g., differences in psychopharmacological

responsiveness). Regardless of underlying cause, the present results show that both methamphetamine and cocaine can produce a strong sensitized locomotor response within a narrow developmental window during the preweanling period.

Acknowledgments

This research was supported by National Institute for Drug Abuse (NIDA) research grant DA027985 (SAM).

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Fig 1.

Mean ($\pm$ SEM) locomotor activity (cm) of rats given a challenge injection of methamphetamine (2 mg/kg, IP) before the 180-min testing session on PD 13, PD 17, PD 21, or PD 25 ($n = 8$ per group). The insets show mean distance traveled collapsed across the testing sessions. *Significant difference between the Meth-Activity and Acute Control groups ($P < 0.05$). †Significant difference between the Meth-Home and Acute Control groups ($P < 0.05$). ‡Significant difference between the Meth-Activity and Meth-Home groups ($P < 0.05$).

Fig 2.

Mean ($\pm$ SEM) locomotor activity (cm) of male and female rats given a challenge injection of methamphetamine (2 mg/kg, IP) before the 180-min testing session on PD 35 ($n = 8$ per group).. The insets show mean distance traveled collapsed across the testing sessions.

*Significantly different from male rats ($P < 0.05$).

Fig 3.

Sensitization quotients [(locomotor activity scores of the Meth-Home or Meth-Activity group / locomotor activity scores of the Acute Control group) $\times$ 100] for rats challenged with 2 mg/kg methamphetamine on PD 13, PD 17, PD 21, PD 25, or PD 35. A score of 100 indicates the lack of sensitized responding, while a progressively higher score indicates a stronger sensitized response. *Significantly different from PD 21, PD 25, and PD 35 rats ($P < 0.05$).

Fig 4.

Mean ($\pm$ SEM) locomotor activity (cm) of rats given an acute injection of methamphetamine (2 mg/kg, IP) before the 180-min testing session on PD 13, PD 17, PD 21, PD 25, or PD 35 (these rats are the Acute Control groups from Fig. 5). The right panel shows mean distance traveled collapsed across the testing session. *Significantly different from PD 13 and PD 17 rats ($P < 0.05$). †Significantly different from PD 17 rats ($P < 0.05$).

Fig 5. Mean ($\pm$ SEM) locomotor activity (cm) of rats given a challenge injection of cocaine (20 mg/kg, IP) before the 180-min testing session on PD 13, PD 17, PD 21, or PD 25 ($n = 8$ per group). The insets show mean distance traveled collapsed across the testing sessions.
 *Significant difference between the Cocaine-Activity and Acute Control groups ($P < 0.05$).
 †Significant difference between the Cocaine-Home and Acute Control groups ($P < 0.05$).
 ‡Significant difference between the Cocaine-Activity and Cocaine-Home groups ($P < 0.05$).

Fig 6.

Mean ($\pm$ SEM) locomotor activity (cm) of male and female rats given a challenge injection of cocaine (20 mg/kg, IP) before the 180-min testing session on PD 35 ($n = 8$ per group). The insets show mean distance traveled collapsed across the testing sessions. *Significant difference between the Cocaine-Activity and Acute Control groups ($P < 0.05$).

Fig 7.

Sensitization quotients [(locomotor activity scores of the Cocaine-Home or Cocaine-Activity group / locomotor activity scores of the Acute Control group) $\times$ 100] for rats challenged with 20 mg/kg cocaine on PD 13, PD 17, PD 21, PD 25, or PD 35. A score of 100 indicates the lack of sensitized responding, while a progressively higher score indicates a stronger sensitized response. *Significantly different from all other age groups ($P < 0.05$).

Fig 8.

Mean ($\pm$ SEM) locomotor activity (cm) of rats given an acute injection of cocaine (20 mg/kg, IP) before the 180-min testing session on PD 13, PD 17, PD 21, PD 25, or PD 35 (these rats are the Acute Control groups from Fig. 1). The right panel shows mean distance traveled collapsed across the testing session. *Significantly different from PD 13, PD 17, and PD 21 rats ($P < 0.05$). †Significantly different from PD 13 and PD 17 rats ($P < 0.05$). ‡Significantly different from PD 13 rats ($P < 0.05$). ^Significantly different from PD 17 rats ($P < 0.05$).

Table 1

Mean (+SEM) locomotor activity (cm) of rats injected with methamphetamine (4 mg/kg) or saline on the pretreatment day.

Postnatal Day (PD)	Pretreatment Group	
	Saline	Methamphetamine
PD 12	2,113 (+421)	7,081 (+789) *
PD 16	3,342 (+643)	7,474 (+1,234) *
PD 20	3,775 (+430)	11,031 (+1,343) *
PD 24	3,281 (+273)	12,546 (+933) * †
PD 34	5,275 (+344) ‡	14,430 (+1,136) * †

* Significantly different from saline-treated rats of the same age ($P < 0.05$).

† Significantly different from PD 12 and PD 16 rats from the same pretreatment group ($P < 0.05$).

‡ Significantly different from PD 12, PD 16, and PD 24 rats from the same pretreatment group ($P < 0.05$).

Table 2

Mean (+SEM) locomotor activity (cm) of rats injected with cocaine (30 mg/kg) or saline on the pretreatment day.

Postnatal Day (PD)	Pretreatment Group	
	Saline	Cocaine
PD 12	1,581 (+255)	3,522 (+462) *
PD 16	2,851 (+607)	6,616 (+464) *
PD 20	3,261 (+328)	10,186 (+576) * †
PD 24	3,436 (+536) †	11,921 (+1,416) * †
PD 34	5,485 (+233) ‡	23,507 (+1,310) * ‡

* Significantly different from saline-treated rats of the same age ($P < 0.05$).

† Significantly different from PD 12 rats from the same pretreatment group ($P < 0.05$).

‡ Significantly different from all other ages from the same pretreatment group ($P < 0.05$).