Published in final edited form as:

Dev Psychobiol. 2008 March ; 50(2): 127–133. doi:10.1002/dev.20252.

Early Adolescents Show Enhanced Acute Cocaine-Induced Locomotor Activity in Comparison to Late Adolescent and Adult Rats

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Abstract

Initiation of drug use during adolescence is associated with an increased probability to develop a drug addiction. The present study examined dose–response effects of cocaine (0, 5, 10, or 20 mg/kg, i.p.) on locomotor activity in early adolescent (postnatal day (PND) 35), late adolescent (PND 45), and young adults (PND 60) by measuring total distance moved (TDM) and frequency of start–stops. In response to 20 mg/kg cocaine, early adolescents showed the greatest cocaine-induced increase in TDM in comparison to late adolescent and adult rats. At this same dose, early adolescents showed the greatest cocaine-induced attenuation of start–stops relative to older rats. Results suggest that early adolescents engage in more cocaine-induced locomotor activity and less stationary behavior indicating that early adolescents are more sensitive to locomotor activating effects of high dose cocaine than older rats.

Keywords

Sprague–Dawley; adolescent rat; dopamine; limbic system; drug abuse

INTRODUCTION

To assess whether there are age-related behavioral differences in sensitivity to drugs of abuse, adult animal models of acute drug administration have recently been extended to investigate the impact of drugs on adolescent behavior by measuring locomotor activity in an open field (Adriani & Laviola, 2000; Bolanos, Glatt, & Jackson, 1998; Catlow & Kirstein, 2005; Laviola, Wood, Kuhn, Francis, & Spear, 1995; Maldonado & Kirstein, 2005a,b; Niculescu, Ehrlich, & Unterwald, 2005). In adult rodents, acute amphetamine (0.5–2 mg/kg; Adriani & Laviola, 2000; Bolanos et al., 1998) and acute cocaine (5–40 mg/kg; Bhattacharyya & Pradhan, 1979; Catlow & Kirstein, 2005; Elliott, Rosen, & Nemeroff,

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NOTES

The present study was completed in partial fulfillment of Kristopher J. Adler's undergraduate honor's thesis.

1987; Laviola et al., 1995; Maldonado & Kirstein, 2005a,b; Niculescu et al., 2005; Ushijima, Carino, & Horita, 1995; Yeh & Haertzen, 1991) have been shown to increase locomotor activity. Interestingly, locomotor activity in response to psycho-stimulants is age-dependent with adolescents differing from younger and older rodents (Adriani & Laviola, 2000; Bolanos et al., 1998; Catlow & Kirstein, 2005; Laviola et al., 1995; Laviola, Adriani, Terranova, & Gerra, 1999; Maldonado & Kirstein, 2005a,b; Niculescu et al., 2005; Spear & Brake 1983). Naïve adolescent mice show less locomotor activity than adults (Adriani & Laviola, 2000). Furthermore, adolescents show attenuated locomotor activity in response to psychostimulants relative to younger and older rodents (Bolanos et al., 1998; Laviola et al., 1995; Spear & Brake, 1983). Acute amphetamine administration differentially affected locomotor activity in adolescent and adult rodents with adolescents displaying lower levels of activity than adults at low doses (0.5–2 mg/kg; Adriani & Laviola, 2000; Laviola et al., 1999). However, adolescent and adult rodents showed similar locomotor activity to 5 mg/kg amphetamine and an adolescent hypersensitivity in comparison to adults at the highest dose (10 mg/kg amphetamine), suggesting that age differences in acute psychostimulant-induced locomotor activity is dependent on drug dose.

Age-related differences in locomotor activity have been found in response to acute cocaine as well, however, the findings have been inconsistent. Adolescents displayed less locomotor activity than adults after acute cocaine administration (Laviola et al., 1995) while others have shown adolescents to have greater cocaine-induced locomotor activity than preadolescent and adults (Catlow & Kirstein, 2005; Maldonado & Kirstein, 2005a,b; Niculescu et al., 2005). Due to the fact that findings on the behavioral profile of adolescents in response to cocaine are inconsistent, the purpose of the current study was to examine dose–response effects of acute cocaine on locomotor activity in adolescent and adult male rats. It was hypothesized that examining the dose–response relationship between acute cocaine administration and locomotor activity may reveal subtle differences in cocaine’s effects on behavior during early adolescence, late adolescence, and young adulthood.

MATERIALS AND METHODS

Subjects

One hundred nineteen male Sprague–Dawley rats derived from established breeding pairs at the University of South Florida, Tampa (Harlan Laboratories, IN), were used in the present study. Litters were sexed and culled to 10 pups per litter on postnatal day (PND) 1, with the date of birth designated as PND 0. Pups were housed with their respective dams until PND 21 when they were weaned and housed in groups of two or three with same sex littermates. The colony room was maintained in a humidity- and temperature-controlled vivarium on a 12:12 hr light/dark cycle, with lights on from 0700 to 1900 hr. Rats were allowed ad libitum access to food and water in the home cage. Adolescence in rodents occurs at approximately PND 28 to PND 46 and is marked by several developmental events including the onset of puberty and changes in neuroendocrine systems in addition to increased socialization and exploratory behaviors (Spear, 2000; Tirelli, Laviola, & Adriani, 2003). For purposes of the present study, rats were divided into three age groups: PND 35 (early adolescent), PND 45 (late adolescent), and PND 60 (young adults). In order to control for litter effects, a total of

47 litters were used for the entire project ($N=119$ rats). Additionally, pups from the same litter were assigned to separate treatment conditions. No more than one male pup per litter was used in any given condition. Remaining pups from each litter were used for other concurrently running lab experiments. In all respects, maintenance and treatment of the rats were within the guidelines for animal care by the National Institutes of Health.

Apparatus

The apparatus consisted of an open field with a smooth black plastic floor ($D=96.5$ cm) and a smooth white plastic circular barrier ($H=45.7$ cm) in which rats were allowed free access to move about. A camera was suspended above the open field and movement of the animal was digitally recorded. This signal was tracked, quantified, and analyzed using an Ethovision video tracking system (Noldus Information Technology, Utrecht, Netherlands). Two separate locomotor activity measures were used: (1) total distance moved (TDM) in cm and (2) start–stops. Each start was defined as movement for 3 s and each stop was defined as nonmovement for 3 s.

Procedure

Each rat was handled for 5 min, 3 days prior to the day of the experiment (PND 32–34, PND 42–44, PND 57–59) in order to acclimate rats to experimental manipulation. On the day of behavioral testing, PND 35, PND 45, or PND 60, rats were removed from the colony room, weighed, and placed on the novel circular open field for 20 min and behavior recorded. After 20 min, rats were administered an acute injection of either cocaine (5, 10, or 20 mg/kg, i.p.) or saline (0.9% NaCl), and immediately placed back on the novel circular open field for 30 min and behavior recorded.

Design and Analyses

TDM and start–stops for the 20-min baseline session were both analyzed using a two-way mixed model design analyses of variance (ANOVA) with age (3; PND 35, PND 45, PND 60) as the between-subjects factor and time as the repeated measure (four 5 min intervals). In order to investigate age- and dose-related time-course differences in acute cocaine responsivity, TDM and start–stop data were both analyzed using a three-factor mixed-model design ANOVA with age (3; PND 35, PND 45, PND 60) and dose (4; saline, 5, 10, and 20 mg/kg cocaine) as the between-subjects factors and time (six 5-min intervals) as the repeated measure. Significant effects were isolated with the appropriate statistical analyses (simple effects, Fisher's least significant difference).

RESULTS

Total Distance Moved

Baseline TDM levels are shown collapsed across treatment groups for each age tested (Fig. 1). There was a significant Age $\times$ Time interaction ($F(6, 348)=3.83$, $p<0.05$), during the 20 min baseline. All ages showed similar baseline locomotor activity levels during the first 5 min (Fig. 1). Interestingly, baseline locomotor activity decreased more rapidly for early and late adolescents (PND 35, PND 45) relative to adults (PND 60) during the 15 min preceding the cocaine injection (Fig. 1; $F(2, 116)=5.07$, $p<0.05$).

Time course effects of cocaine-induced TDM for PND 35, PND 45, and PND 60 rats can be seen in Figure 2. However, because there were baseline differences in TDM across age, all TDM scores were normalized and expressed as a percent change from their respective saline control group. These data revealed a significant three-way interaction of Age $\times$ Dose $\times$ Time ($F(30, 530) = 3.66, p < 0.05$).

In order to illustrate subsequent post hoc analyses of Age, data were plotted by Dose in each panel (Fig. 2A–C; Note the different scales in panels). Following 20 mg/kg cocaine (Fig. 2C), TDM was greater in PND 35 than in PND 60 from 10 to 30 min and PND 45 from 15 to 30 min post cocaine injection (10 min: $F(2, 26) = 6.06, p < 0.05$; 15 min: $F(2, 26) = 15.27, p < 0.05$; 20 min: $F(2, 26) = 19.87, p < 0.05$; 25 min: $F(2, 26) = 23.91, p < 0.05$; 30 min: $F(2, 26) = 20.42, p < 0.05$). There were no significant Age effects following 10 mg/kg cocaine (Fig. 2B). Following 5 mg/kg cocaine (Fig. 3A), TDM was greater in PND 35 than in PND 45 and 60 rats from time points 25–30 min (25 min: $F(2, 28) = 7.49, p < 0.05$; 30 min: $F(2, 28) = 4.28, p < 0.05$).

Subsequent post hoc analyses of Dose revealed that for PND 35 rats (Fig. 2C), 20 mg/kg cocaine increased TDM to 816%. Specifically, TDM following 20 mg/kg cocaine injection was significantly greater than saline (100%) from 5 to 30 min post cocaine injection (5 min: $F(3, 33) = 5.09, p < 0.05$; 10 min: $F(3, 33) = 23.37, p < 0.05$; 15 min: $F(3, 33) = 29.22, p < 0.05$; 20 min: $F(3, 33) = 28.70, p < 0.05$; 25 min: $F(3, 33) = 30.99, p < 0.05$; 30 min: $F(3, 33) = 28.58, p < 0.05$). Additionally, there was a trend for PND 35 rats treated with 10 mg/kg (Fig. 2B) to demonstrate increased TDM relative to saline controls from 25 to 30 min post cocaine injection (25 min: $p = 0.09$; 30 min: $p = 0.08$). For PND 45 rats (Fig. 2B), 20 mg/kg cocaine increased TDM to 462%. Following 20 mg/kg cocaine, TDM was significantly greater than saline at 5–30 min post cocaine injection (5 min: $F(3, 36) = 3.60, p < 0.05$; 10 min: $F(3, 36) = 10.59, p < 0.05$; 15 min: $F(3, 36) = 5.42, p < 0.05$; 20 min: $F(3, 36) = 5.96, p < 0.05$; 25 min: $F(3, 36) = 9.58, p < 0.05$; 30 min: $F(3, 33) = 7.30, p < 0.05$). Additionally, PND 45 rats treated with 10 mg/kg (Fig. 2B) cocaine showed significantly greater TDM than saline controls at 20 min post cocaine injection (20 min: $F(3, 36) = 5.96, p < 0.05$). For PND 60 rats, 20 mg/kg cocaine increased TDM to 264% relative to saline as indicated by a main effect of Dose ($F(3, 37) = 8.57, p < 0.05$). This would suggest that cocaine-induced TDM was increased similarly at all time points in PND 60 rats treated with 20 mg/kg cocaine.

Start–Stops

The same animals from the TDM dataset were also analyzed for frequency of start–stops to address whether cocaine elicited an increase in the number of nonmovement bouts and whether this nonmovement could differentially inhibit cocaine-induced TDM at each age. Baseline start–stop levels are shown collapsed across treatment groups for each age tested (Fig. 3). There was a main effect of Age ($F(2, 348) = 11.05, p < 0.05$) and a main effect of Time ($F(3, 348) = 450.68, p < 0.05$), during the 20 min baseline. In general, PND 35 and PND 45 rats had greater frequency of start–stops than PND 60 rats during the 15 min preceding the cocaine injection.

Time course effects of cocaine-induced start–stops for PND 35, PND 45, and PND 60 rats can be seen in Figure 4A–C. However, because there were baseline differences in start–stops

across age, baseline start–stops were normalized and expressed as a percent change from their respective saline control group. These data revealed a significant three-way interaction of Age $\times$ Dose $\times$ Time ($F(30, 530) = 1.69, p < 0.05$).

In order to illustrate subsequent post hoc analyses of Age, data were plotted by Dose in each panel (Fig. 4A–C). Following 20 mg/kg cocaine (Fig. 4C), start–stops were lower in PND 35 than in PND 45 and PND 60 rats from 10 to 30 min post cocaine injection (10 min: $F(2, 26) = 4.05, p < 0.05$; 15 min: $F(2, 26) = 5.86, p < 0.05$; 20 min: $F(2, 26) = 5.35, p < 0.05$; 25 min: $F(2, 26) = 7.14, p < 0.05$; 30 min: $F(2, 26) = 9.08, p < 0.05$). There was a significant main effect of Age following 10 mg/kg cocaine, indicating that PND 60 rats displayed significantly lower levels of start–stops relative to PND 35 and PND 45 rats ($F(2, 27) = 4.92, p < 0.05$; Fig. 4B). Following 5 mg/kg cocaine (Fig. 4A), start–stops were lower in PND 45 and PND 60 than in PND 35 rats at 20 min post cocaine injection (20 min: $F(2, 28) = 5.12, p < 0.05$).

Subsequent post hoc analyses of Dose revealed that for PND 35 rats (Fig. 4C), 20 mg/kg cocaine attenuated start–stops to 23%. Specifically, start–stops following 20 mg/kg cocaine injection was significantly lower than saline-injected controls from 10 to 30 min post cocaine injection (10 min: $F(3, 33) = 26.37, p < 0.05$; 15 min: $F(3, 33) = 23.31, p < 0.05$; 20 min: $F(3, 33) = 11.60, p < 0.05$; 25 min: $F(3, 33) = 8.36, p < 0.05$; 30 min: $F(3, 33) = 17.35, p < 0.05$). There were no significant dose effects for start–stops in PND 45 rats. For PND 60, 20 mg/kg cocaine attenuated start–stops to only 73%, as indicated by a significant main effect of Dose ($F(3, 37) = 4.68, p < 0.05$). Together, start–stop and TDM data suggest that cocaine-induced locomotor activity varies with Age and Dose.

DISCUSSION

The dose–response relationship of cocaine’s effects on locomotor activity differed as a function of age. All ages showed increases in TDM following 20 mg/kg cocaine relative to lower cocaine doses and saline; however, early adolescent rats exhibited greater TDM relative to late adolescents and adults (Fig. 2C). One plausible explanation for a hyper-responsiveness to an acute cocaine injection in early adolescent rats is that a lack of competing behaviors may potentiate cocaine’s excitatory effects in early adolescent rats. PND 35 rats showed a substantial increase in TDM following 20 mg/kg cocaine in addition to a substantial attenuation in start–stop behavior (Fig. 4c) suggesting that cocaine-induced excitation of TDM in PND 35 rats is no longer inhibited by start–stop behavior and therefore potentiates resulting cocaine-induced TDM as illustrated in Figure 2C. On the other hand, late adolescent and adult rats had significant increases in TDM following 20 mg/kg cocaine (Fig. 2c) in addition to showing relatively high levels of start–stop behavior that were similar to age-matched saline controls. These data suggest that cocaine-induced excitation of TDM following 20 mg/kg cocaine in PND 45 and PND 60 rats may be inhibited by concurrent start–stop behavior. Although stereotypy was not measured in the current study, it is also possible that PND 60 rats showed the least cocaine-induced excitation of TDM due to substantial induction of stereotypy following 20 mg/kg cocaine. Due to the fact that stereotypy can be expressed as repetitive behaviors, an induction of stereotypical behaviors following 20 mg/kg cocaine would most certainly negatively impact the amount of distance

traveled. Although the above suggested impact of stereotypy on TDM is plausible, it is not likely as a single dose of cocaine does not produce robust stereotypy in adults and we have recently found no age differences in stereotypy between early adolescent and adult rats following a single injection of 20 mg/kg cocaine (Catlow & Kirstein, 2007).

PND 45 rats were the only age to show a trend for cocaine-induced TDM following 10 mg/kg (Fig. 2B) cocaine and none of the three ages tested showed cocaine-induced TDM following 5 mg/kg cocaine relative to saline-injected controls (Fig. 2A). The general lack of responsiveness to lower doses of cocaine, in adult rats at least, was unexpected. Others have shown low cocaine doses (5–10 mg/kg) to increase locomotor activity relative to saline controls (Fletcher, Grottick, & Higgins, 2002; Gambarana et al., 1999; Laviola et al., 1995; Sahakian, Robbins, Morgan, Iversen, 1975). One possible explanation for the lack of responsiveness to lower cocaine doses may very likely be the use of a relatively short habituation period. Saline controls, regardless of age, show TDM levels still dropping below baseline levels 5–10 min post saline injection (data not shown). Extending the habituation period out until baseline activity stabilized may have increased cocaine-induced TDM at lower doses and potentiated cocaine-induced TDM at the high dose. Injecting rats after baseline TDM levels have stabilized would clearly control for the inhibitory effects of environmental habituation competing with cocaine's excitatory effects on TDM.

The present study found that early and late adolescent rats had lower baseline TDM than adults (Fig. 1) and a greater baseline frequency of start–stop behavior (Fig. 3) during the 15 min preceding the saline injection suggesting that early and late adolescent rats are hypoactive relative to adults in a novel environment. Various findings have been reported for locomotor activity in drug-naïve adolescent and adult rats. Lower (Adriani & Laviola, 2000; Schramm-Sapota, Pratt, & Winder, 2004) and higher (Spear & Brake, 1983; Stansfield & Kirstein, 2006) levels of locomotor activity were reported for naïve adolescent relative to naïve adult rodents. Differences in novel environment-induced locomotor activity between adolescent and adults have been previously attributed to adolescents perceiving a novel environment as less stressful than adults and were supported by the fact that adolescents have greater basal corticosterone levels and a hyposensitive neuroendocrine and stress response system at this relatively young developmental stage (Adriani & Laviola). Therefore, lower baseline levels of locomotor activity for adolescent rats in the present study may be explained by the potential for adolescents to experience less stress and engage in less stress-induced hyperactivity, exploration, and escape responses than is typically characteristic of adults when placed in a novel environment. Age differences in novelty preference and reactions to stressful stimuli indicate that habituating rats to the test environment is especially crucial when comparing adolescent and adult rats. Additionally, stressful experiences, such as first time exposure to an open field, may likely contribute to the lack of responsiveness following low cocaine doses in the present study.

Various findings have also been reported for psychostimulant-induced locomotor activity in adolescent and adult rats. Lower (Bolanos et al., 1998; Laviola et al., 1995; Spear & Brake, 1983) and higher (Caster, Walker, & Kuhn, 2005; Catlow & Kirstein, 2005; Maldonado & Kirstein, 2005a,b; Niculescu et al., 2005) rates of psychostimulant-induced locomotor activity have been reported for adolescent relative to preadolescent and adult rodents.

Various findings may be due to methodological differences such as pre-exposure handling used to reduce the stress of experimenter manipulation, habituation to a novel environment prior to drug challenge, specific adolescent age (early, mid, late adolescence), rodent strain, differences in dosing regimens utilized and drug site of action (amphetamine/dopamine (DA) release, cocaine/DA reuptake). Future experiments need to investigate the impact of different methodologies (i.e., adolescent age, size of apparatus, alternative activity measures) on locomotor activity in adolescent and adult rats.

Given that cocaine inhibits reuptake of DA by blocking DA transporters, age-related differences in cocaine's effects may likely be due to the ongoing development of nigrostriatal and mesolimbic DA pathways. In male rats, DA receptors peak in density at PND 40 followed by receptor pruning into young adulthood (PND 60; Teicher, Andersen, Hostetter, 1995). It is possible that enhanced TDM following 20 mg/kg cocaine in early adolescents may be due to a greater density of mesolimbic and nigrostriatal D1 receptors while lower TDM following 20 mg/kg cocaine in adults may be due to complete maturation of D2 receptors (Anderson, Dumont, & Teicher, 1997). A rapid increase in DA transporter density in the nucleus accumbens during preadolescence (Tarazi, Tomasini, & Baldessarini, 1998) and an upregulation of DA transporters in the adult striatum after repeated cocaine treatment, an effect absent in adolescent rats (Collins & Izenwasser, 2002), may also be contributing factors to age-related differences in cocaine-induced locomotor activity. Further, age dependent differences in extracellular DA concentrations in the nucleus accumbens may impact cocaine-induced locomotor activity (Badanich, Adler, & Kirstein, 2006).

Taken together, findings from the present study demonstrate that differences between adolescents and adults in cocaine-induced locomotor activity depend on the cocaine dose tested and also suggest that some of the discrepancies in the behavioral literature concerning adolescence may be due, at least in part, to differences in dosing regimens utilized. Robust differences between adolescent and adult rats found in the present study at a high dose of cocaine have implications for further research on how early use affects subsequent responsivity to drugs during adulthood. Future research should examine the dose-response relationship of cocaine administered throughout adolescence and subsequent behavioral responding during adulthood.

Acknowledgments

Contract grant sponsor: National Institute of Drug Abuse

Contract grant number: RO1DA14024

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FIGURE 1. Total distance moved in a novel environment

Baseline total distance moved (TDM) data are shown collapsed across treatment groups and represent all animals tested at each age: PND 35, $n=37$; PND 45, $n=40$; PND 60, $n=42$. Baseline TDM decreased more rapidly for PND 35 and PND 45 relative to PND 60 rats. *PND 45 less than PND 60; **PND 35 and PND 45 less than PND 60. All data points represent mean and SEM.

FIGURE 2. Age effects in cocaine-induced total distance moved

Each panel represents 1/3 the total number of rats run in the present study. Rats per group were as follows: PND 35 (saline, $n=9$; 5 mg/kg cocaine, $n=10$; 10 mg/kg cocaine, $n=9$; 20 mg/kg cocaine, $n=9$). PND 45 (saline, $n=10$; 5 mg/kg cocaine, $n=10$; 10 mg/kg cocaine, $n=10$; 20 mg/kg cocaine, $n=10$). PND 60 (saline, 10; 5 mg/kg cocaine, 11; 10 mg/kg cocaine, 11; 20 mg/kg cocaine, 10). (A) PND 35 rats had greater TDM than PND 45 and PND 60 rats following 5 mg/kg cocaine at the 25 and 30 min time points. *PND 35 significantly differs from PND 45 and PND 60. (B) There were no significant age differences in TDM following 10 mg/kg cocaine. #Significantly differs from saline (100%). (C) PND 35 rats had greater TDM than PND 45 and PND 60 rats following 20 mg/kg cocaine. *35 significantly differs from PND 45 and 60; **35 significantly differs from PND 60. ##PND 35, PND 45 and PND 60 significantly differs from saline (100%). All data points represent mean and SEM.

FIGURE 3. Start-stops in a novel environment

Baseline start-stop data are shown collapsed across treatment groups and represent all animals tested at each age: PND 35, $n=37$; PND 45, $n=40$; PND 60, $n=42$. In general, baseline start-stops were greater for early adolescents and late adolescents relative to adults. Each data point represents mean and SEM.

FIGURE 4. Age effects in cocaine-induced start-stops

Each panel represents 1/3 the total number of rats run in the present study. Rats per group were as follows: PND 35 (saline, $n=9$; 5 mg/kg cocaine, $n=10$; 10 mg/kg cocaine, $n=9$; 20 mg/kg cocaine, $n=9$). PND 45 (saline, $n=10$; 5 mg/kg cocaine, $n=10$; 10 mg/kg cocaine, $n=10$; 20 mg/kg cocaine, $n=10$). PND 60 (saline, $n=10$; 5 mg/kg cocaine, $n=11$; 10 mg/kg cocaine, $n=11$; 20 mg/kg cocaine, $n=10$). (A) PND 35 rats had more start-stops than PND 45 and PND 60 rats following 5 mg/kg cocaine at the 20 min time point. *35 significantly differs from PND 45 and PND 60. (B) There were no significant age differences in start-stops following 10 mg/kg cocaine. (C) PND 35 rats had less start-stops than PND 45 and PND 60 rats following 20 mg/kg cocaine. *35 significantly differs from PND 45 and PND 60. #Significantly differs from saline (100%). All data points represent mean and SEM.