Published in final edited form as:
Neurotoxicol Teratol. 2008 ; 30(3): 202–212. doi:10.1016/j.ntt.2008.01.003.

Behavioral responses during the initial exposures to a low dose of cocaine in late preweanling and adult rats

Kiersten S. Smith* and **Joan I. Morrell**
Center for Molecular and Behavioral Neuroscience, Rutgers University, United States

Abstract

Human drug experimentation begins during late childhood and early adolescence, a critical time in physical and CNS development, when the immature CNS is vulnerable to the long-term effects of psychoactive drugs. Few preclinical animal studies have investigated responses to such drugs in a developmental stage equivalent to late childhood of humans. We used a rodent model to examine behavioral responses of female Sprague–Dawley late preweanling and adult rats during acute and repeated exposures to a low dose of cocaine. Results show that after cocaine injection, preweanling rats (18–21 days old) have locomotor responses that differ from adults, but after postnatal day 22, the responses are indistinguishable from adults even though rats are still not weaned. Before day 22, locomotor effects of cocaine differ from those in adults in three ways: preweanlings are active for a longer time after cocaine injection at day 18; preweanling activity peaks more rapidly after subcutaneous administration; and after only three injections of cocaine, a tolerance-like pattern is seen in preweanlings whereas an emerging pattern of sensitization to cocaine is seen in adults. The behavioral patterns of this age group offer a preclinical model of the early effects of drugs of abuse.

Keywords

Preweanling; Adult; Cocaine; Behavior; Postnatal; Development

1. Introduction

Experimentation with psychoactive substances such as alcohol, nicotine, and psychostimulants often begins surprisingly early during late childhood and early adolescence [10,33,61,71]. According to the 2005 Monitoring the Future survey [33], approximately 21% of 8th graders, an age considered to be late childhood–early adolescence [61], had already sampled such substances, with up to 7% reporting regular use of stimulants [33]. Young girls have higher rates of drug use, including cocaine, than boys [16,34]. The onset of drug abuse can occur when casual experimentation is replaced by more regular drug use [56]; those who begin experimenting early and progress to regular drug use are more likely to develop addictions than individuals who initiate drug use as an adult [22,28,76,78]. Furthermore, early onset of

* Corresponding author. Laboratory of Genetic Neuropharmacology, McLean Hospital and Harvard Medical School, 115 Mill Street, Belmont, MA 02478, United States. Tel.: +1 617 855 2010; fax: +1 617 855 2012. E-mail address: ksmith@mclean.harvard.edu (K.S. Smith).

drug use is highly correlated with and predictive of psychiatric disorders during adulthood [9].

Specific characteristics of drug taking in human youth are different than in adults. Initial patterns of use are different; for example, in children and early adolescents the first exposure to alcohol typically involves a few episodes of sampling small amounts of it [29,75]. The progression from use to abuse in youth is much faster than in adults, and consumption by adolescents is predominantly characterized by bingeing episodes perhaps reflecting the fact that adolescents have decreased sensitivity to various substances of abuse than adults [61].

We examined behavioral responses to cocaine in the preweanling rat, a developmental stage chosen as a model of late childhood, which specifically precedes the onset of complex developmental changes during adolescence driven by pubertal hormones. We used this period as a preclinical rodent model for females who are at a particularly vulnerable age when earliest drug sampling begins. Considering the trends in human drug use patterns, it is important to use preclinical models to understand how drugs affect children in this target age group relative to older adolescents and adults. Furthermore, late childhood is when the use of psychoactive drugs, which can exert long-term consequences on the developing organism [4,15,61], frequently begins.

In the rat, hallmarks of neural development during the late preweanling period (the third and fourth postnatal weeks) correspond to those expressed during the period of late childhood and early adolescence in the human [61], a period clearly prior to puberty. Based on Spear's definition of adolescence in humans which spans ages 12–18 [61], we consider late childhood as the ages immediately preceding this age range, approximately 9–12 years. During the preweanling period, young rats are increasingly able to maintain physiological processes such as thermoregulation and elimination and even forage for food and water [5,54]. They have full use of all major senses, a remarkable adult-like capacity for locomotor activity, and high levels of response to specific stimuli in their environment [58,59]. This is a period just before weaning (days 18–22), when they still require some nursing and protection by their mother but are first allowed out of an otherwise mother-controlled nest area [5,26,27,45,54].

Most studies of the behavioral effects of stimulants in young rodents used i.p. injections [18, 40,72,82,83]. In additional studies, multiple doses of stimulants were administered to preweanling or adolescent animals, but those studies examined the effects of the long-term expression of sensitization either later in adolescence [58,68,72] or in adulthood [72]. To date, only one study has examined infant, late preweanling and adolescent responses to s.c. injections of cocaine [62] and characterized the immediate effects of the drug. All of those studies documented locomotor behavior during the first 30–60 min after cocaine injection, which is the rising phase of the blood levels of cocaine.

Although differences in behavioral choices among human youth concerning favored routes of administration are known, less is known about consequent blood levels of substances in the young. For example, intranasal snorting of cocaine is the commonly preferred method of administration over intravenous (i.v.) injection for young adolescents compared with older teens and adults [16]. In adult humans, the intranasal route produces cocaine absorption rates similar to those seen following subcutaneous (s.c.) administration in adult rats while cocaine absorption patterns following i.v. administration more closely resembles absorption rates following smoking in humans and intraperitoneal (i.p.) administration in rats [30–32].

Plasma levels of cocaine after s.c. or i.p. injections and drug-induced changes in locomotor activity are well-characterized in adult rats. In adult rats, the profile of blood levels of cocaine after i.p. injection is fairly similar to that reported for i.v. administration in humans. The plasma level profile in adult rats after s.c. injections is most similar to that reported for humans via the

intranasal route [24,30–32,74], and of course differs substantially from the i.p. route profile. In adult rats, blood levels peak about 30 min after i.p. injection and return to baseline within 60–90 min [24], whereas the s.c. route yields peak levels after 60 min and return to baseline in 3–5 h [74,77]. Because the total experience of cocaine extends well beyond the initial rising phase which is most rewarding, we examined the behavioral responses over a time sufficient to characterize the rising and falling phases of the blood levels of cocaine after either s.c. or i.p. administration.

In marked contrast to our knowledge about plasma levels in adults after cocaine administration, very little is known about blood levels of this drug or its pharmacokinetics in either human or rodent young, regardless of route of administration. To our knowledge, only one study has examined the blood plasma and brain concentrations of cocaine and its metabolites in developing versus adult rodents. This study shows that p35 periadolescent mice have lower levels of cocaine and higher levels of benzoylecognine than adults following acute i.p. administration of cocaine suggesting that younger animals may metabolize the drug faster than adults [44]. There are no studies on cocaine metabolism in infant or preweanling rodents.

We examined the responsiveness to a relatively modest dose (10 mg/kg) because this dose is sufficient to stimulate locomotor activity in both preweanlings and adults [15,41,43,74] but avoids stereotypy and physiological pathologies [70,74]. This dose is reported to be the lowest effective dose with hedonic properties in both adult and postnatal day 35 (p35) adolescent rats [12]. Plasma levels of cocaine and its metabolites in adult virgin male and female rats as well as in postpartum females after a 10 mg/kg dose of cocaine are within the range achieved in human use [8,30,31,63,74,77]. They are also similar to levels in children after cutaneous administration of an anesthetic containing 11.76% cocaine [25]. A recent study in young rats reported that cocaine levels after perioral administration were within the range of adult rats after s.c. administration [53,74].

The purpose of our behavioral study was to provide a detailed characterization of preweanling versus adult animal responses to acute and a short course of repeated exposures of cocaine. Characterization of age-related behavioral differences will additionally inform us as to which ages should be targeted in subsequent studies to cocaine absorption and pharmacokinetics during the infant and preweanling period.

In particular, this study examined whether the initial responses of a late preweanling–early adolescent rat to cocaine differ from the responses of an adult. We measured locomotor activity for three hours after injection of a relatively low dose (10 mg/kg) of cocaine via one of the two most commonly used routes (i.p. or s.c.) in late preweanling female rats compared with adult females. This work is part of our series of studies of the effects of cocaine on female rats of various endocrine states [43,74,77]. Although there are gender differences in cocaine response in adults [23,42], none are found in preweanling rats [62]. We examined behavioral responses during the first few exposures to cocaine because our working hypothesis is that such a preclinical model using low doses in this manner mimics the pattern of initial sampling of drugs of abuse by young humans prior to the onset of bingeing behavior [7,14,19]. By discerning such differences in cocaine's effect on behavior, we may better understand how cocaine affects the brain and behavior of young versus adult drug users.

2. Methods

2.1. Subjects

Subjects were p18–p22 preweanling (35–50 g), p28–p29 early adolescent (60–75 g), and p60 adult (190–225 g) female Sprague–Dawley rats from our animal colony maintained in the Laboratory Animal Facility (LAF) at Rutgers University (Newark, NJ), an American

Association of Accreditation of Laboratory Animal Care (AAALAC)-accredited institution. Our animals were originally obtained from Charles River Laboratories (Wilmington, MA) with additional males and females purchased periodically from the same vendor to keep the colony genetically consistent with the original breeding stock from Charles River. All litters were culled to 12 pups (half each gender) during the first neonatal week and weaned on p28.

Although there are reports that drug responsivity is affected by early weaning (before p22) [21,52], to our knowledge, there are no reports demonstrating that weaning after p22, specifically during early adolescence, impacts the behavioral response to cocaine. We wanted to avoid the variable of weaning as we examined subjects from p18–p28; in the natural setting and in certain laboratory paradigms, weaning occurs from p21 to as late as p35. Therefore, preweanlings and early adolescents were housed with their dam and siblings prior to testing. Adults were housed in pairs with a same-sex sibling. Subjects were randomly divided into the following groups: experimental groups received either 1 cocaine injection or 1 cocaine injection per day for 3 days, and control groups received parallel saline injections.

Subject groups were composed of randomly selected same-sex littermates, with a maximum of two pups used from any given litter to reduce the probability that litter effects influenced the experimental results [20,46,79]. Subjects were housed in standard shoebox cages with wood chip bedding (Beta Chip, Northeastern Products, Warrensburg, NY) and maintained under a 12-hour (h) light–dark cycle (lights on at 0700 h) and a stable, environmental temperature of 22 °C with *ad libitum* access to food (Formulab Diet 5008, PMI, Nutrition International, Brentwood, MO) and water. All procedures used in this study followed the standards approved by the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and the Rutgers University Animal Care and Facilities Committee.

2.2. Drug administration

Cocaine hydrochloride in highly (>90%) purified powdered form was provided by the National Institute of Drug Abuse, Research Triangle Park, NC, USA. Animals received either i.p. or s.c. injections of 10 mg/kg of cocaine freshly dissolved in sterile 0.9% buffered saline to obtain a concentration of 4.5 mg/ml. Control animals received saline injections of equivalent volume. Subcutaneous injections were placed in alternating dorsal and caudal flank regions, and injection sites were massaged briefly to avoid skin ischemia [55]. To ensure that s.c. injection sites remained in the subcutaneous compartment, a 25-gauge, 5/8 inch (in.) needle was used for preweanlings and adolescents (Becton Dickson and Co., Franklin Lakes, NJ), and a 23-gauge, 1 in needle was used for s.c. injections to adults and for i.p. injections at all ages. All subjects were hand held during the injections so that the injection would not be associated with the testing apparatus.

2.3. Measures of general physiology and health

Subjects were physically examined by the investigators and the LAF staff; all animals were healthy throughout the experiments and the weight gain of all subjects was within normal parameters. Alerted by published accounts of skin lesions caused by s.c. injections in laboratory rats [11,63,73], we checked the injection areas daily in animals that received repeated s.c. drug administration; no skin lesions were found.

2.4. Apparatus and activity measures

Subjects were tested in clear Plexiglas open-field boxes (42 × 42 × 31 cm) (no bedding, food, or water) inserted into an automated locomotor activity apparatus (VersaMax Animal Activity Monitor, Model VMMAW, AccuScan Instruments Inc., Columbus, OH). Activity boxes were not proportionally scaled to subject size since rodents in the natural setting emerge from the maternal nest and must interact with world in its full-scaled form; we wanted our testing

environments to most closely mimic the natural condition. The boxes were illuminated by the overhead lighting in the testing room with an average luminance of 34 lm s/m^2; the illumination difference between the center and the perimeter of each box was <1% and not statistically significant (p=0.82).

Measures of activity consisted of the total distance (cm) traveled in the entire apparatus and time (s) spent in the center. We examined subject activity in the margins and center of the open field. Although the apparatuses were not proportionally scaled to subject size, we used the ZoneMap software provided by AccuScan to change the margin width to calculate and scale the center area for subjects in each age group. The margin width was changed so that it was proportional to the shoulder width of animals in each age group (shoulder width: preweanlings, 3 cm; adolescents, 4 cm; adults, 5 cm); the margin for preweanlings and adolescents was set to 5.25 cm and for adults, 6.5 cm.

2.5. Procedure

Subjects were removed from their home cage, weighed, and placed into a clean shoebox holding cage lined with bedding but without food and water, for 5 min before the start of the test session. Subjects were injected with cocaine or saline and immediately placed into the activity testing boxes described above for a 3-h test session. Subjects that received daily injections as part of our longer 5-day testing protocol (details below) were returned to their home cages immediately after the end of the test session. Testing was conducted during the light phase of the daily cycle primarily between 0900 h and 1200 h when preweanlings and adults are equally active (1st quartile) [59]. After each experiment, subjects were euthanized using CO_2 gas according to the Rutgers University IRB-approved protocol.

2.5.1. Single exposure of cocaine or saline—Animals were examined for locomotor activity levels at different postnatal ages after subjects received a single exposure to cocaine during a 3-hour test session, in three comparisons, all of which were separate subject groups. The first comparison was between preweanlings (p18–p19) and adults (p60) that received a single i.p. injection of cocaine (preweanling, n=12; adults, n=16) or saline (preweanlings, n=12; adults, n=12). The second comparison was between preweanlings and adults that received a single s.c. injection of drug (preweanlings, n=11; adults, n=12) or saline (preweanlings, n=12; adults, n=12). The third comparison examined the effect of a single s.c. injection of cocaine either during the preweanling period (p18, n=7; p19–22, n=4 per age group), or early adolescence (p28–29, n=4 per age group), or adulthood (p60, n=12). Based on the bimodal distribution of behavior, subjects were grouped into young (n=19) and adult-like (n=24) groups. Immediately after the injection, subjects were individually placed into the clear Plexiglas box inserts of the Accuscan monitoring system, which was a completely novel open field for these subjects, and activity was recorded for 3 h. For some subjects (p19, p20, p21), activity was recorded for 2.5 h due to the availability of the apparatuses but it was unlikely that the absence of data in the last 30 min affected our data analysis.

Our examination of adult locomotor activity following acute administration of cocaine showed that 3 females in the s.c. group and 7 in the i.p. group were in estrous [23, prior unpublished observations]. However, adult hormonal status had no impact on the essential preweanling-adult differences observed in this study since preweanling activity responses were of significantly greater magnitude than those of adults, which have a much smaller magnitude of difference in locomotor activity levels across the estrous cycle.

2.5.2. Three consecutive exposures to cocaine—At the start of the 5-day injection protocol, subjects were p18 preweanling (n=24) and p60 adult (n=24) females; half of each age group received s.c. injections and half i.p. injections. On the first day of testing, when the

environment was completely novel to the subjects, we evaluated baseline activity (day 1 of treatment, preweanlings, p18; adults, p60). On that day, subjects received a single 10 mg/kg injection of 0.9% buffered saline. On testing days 2–4 (preweanlings, p19–21; adults, p61–63), each subject received a single 10 mg/kg injection of cocaine daily. On day 5 of testing, subjects' (preweanlings, p22; adults, p64) second baseline locomotor activity responses were evaluated after a single injection of saline.

2.6. Data analysis

Subject locomotor activity is reported as an overall mean across the entire test session or summed at 30-min intervals to examine with more detail the time course of activity across the test session. All data met the requirements for use of parametric statistical tests, i.e., normal distribution and homogeneity of variance. Overall mean data from the single-injection experiments were analyzed using a two-way analysis of variance (ANOVA; subject age × drug condition) followed by Tukey's post-hoc test. Analysis of the time course activity in 30-min intervals across the entire 3-hour test session was carried out with a two-way ANOVA (subject age × time interval) with time as the repeated measure. Some i.p. single-injection data for only p18 preweanlings and p60 adults were summed so that the subject activity was examined in the first versus the second half of the test period (1st half, 0–90 min; 2nd half, 90–180 min); all of these subjects had complete data from the entire 3-h test session. This analysis provided another means to highlight preweanling-adult differences to acute administration of cocaine. These data were analyzed using an independent *t*-test.

Data from the repeated-injections experiment were first analyzed between the two age groups using a two-way ANOVA (subject age × time) with a repeated measure of time and then examined within each age group using a one-way repeated measures ANOVA. The General Linear Model procedure (GLM) was used to implement the ANOVA comparisons for all analyses. The significance level was set at $p<0.05$ for all tests. The data were analyzed using SAS statistical software version 8.2 for personal computers (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Baseline responses to saline

Preweanlings and adults had subtle but statistically significant differences in their baseline locomotor responses to saline injection and placement in a novel environment. Preweanlings were two to three times more active than adults during a 3-hour test ($p<0.05$) (Fig. 1a and c; Fig. 3, here note saline components only). Second baseline responses after the series of injections and chamber exposures were not different between adults and p22 preweanlings (Fig. 3), and first and second adult baseline responses were identical (Fig. 3b and d).

3.2. Behavioral responses to a single dose of cocaine: p18 vs. p60

Cocaine substantially increased the locomotor activity of all subjects over their age-matched controls. Overall, preweanlings were 3 times more active after i.p. cocaine than at baseline whereas adults were 7 times more active than at baseline [significant main effect of drug condition, $F(1, 48)=21.23$, $p<0.0001$] although the activity in the entire three hours after cocaine was not different between the two age groups (Fig. 1a). However, examination of the time course of activity in greater detail revealed subtle differences in the rate of activity at particular time points within the three hour test period between the two age groups [significant subject age × time interaction, $F(5, 130)=2.66$, $p<0.05$] (Fig. 1b). Adults returned to baseline activity levels by 120 min after cocaine while preweanlings maintained an elevated level of activity across the entire test period, including being significantly more active than adults in the last 90 min of the test [preweanlings, 3545 ± 1186 cm; adults, 831 ± 286 cm; $t(12.3)=-1.48$, $p<0.05$].

Preweanlings and adults had more notable differences in locomotor activity responses after s.c. cocaine that were observed in both the analysis of the overall means and in the activity time courses. When the total locomotor activity was summed across the three hour test period, both preweanlings and adults were 5 times more active overall after s.c. cocaine compared to their own age-matched saline controls [significant subject age × drug condition interaction, $F(1, 43)=4.41$, $p<0.05$] (Fig. 1c). Further, preweanlings were approximately 3 times more active than adults after cocaine when total locomotor activity was summed across the three hours [Tukey's post-hoc, $p<0.05$].

Examination of the locomotor effects of s.c. cocaine with greater temporal detail across the test period revealed further differences. First, preweanlings were consistently more active than adults across the entire test session (significant subject age × time interaction, $F(5, 105)=3.49$, $p<0.01$] (Fig. 1d) with significant differences in activity levels at specific time points (Fig. 1d). Secondly, activity levels in adults increased gradually after drug, reached their peak by 90 min, and returned to baseline by 3 h (Fig. 1d). In contrast, preweanlings were immediately 6 times more active than adults, a difference that was seen within the first 10 min (data not shown). Further, preweanlings maintained an elevated activity level throughout the remainder of the test session.

3.2.1. Center time—After saline injection, preweanlings spent significantly more time than adults in the center of the apparatus throughout the entire test session, even when the locomotor activity of the two groups was similar. After cocaine injection, irrespective of route of administration, both preweanlings and adults spent substantially more time in the center compared with age-matched controls. Although preweanlings still spent more time in the center compared with adults (data not shown), this difference was derivative of their cocaine-induced increase in locomotor activity.

3.3. Behavioral responses to a single dose of s.c. cocaine: preweanling period into early adolescence and adulthood

Preweanlings aged 18 to 21 days had similar levels of activity, but beginning on day 22, preweanlings had a diminished locomotor activity response to cocaine (Fig. 2a and b); this response was the same as that in p28–29 early adolescents and p60 adults. Based on this empirically uncovered bimodal distribution, the data were operationally grouped into the categories of Young and Adult-Like activity for statistical analysis (Fig. 2c and d).

Subjects in the Young group (p18–p21) were more active overall than subjects in the Adult-Like group (p22 or older) when the data were examined as overall averages [$t(23)=3.24$, $p<0.01$] (Fig. 2c) and were consistently active across most of the 3 h test session [$F(5, 30)=3.90$, $p<0.01$] (Fig. 2d). Young animals were initially more active, but their activity level declined modestly by 120 min, whereas animals in the Adult-Like group were comparatively less active at all time points and maintained a consistent activity level throughout (Fig. 2d).

3.4. Behavioral responses to three doses of cocaine during the preweanling period vs. adulthood

With each subsequent dose of cocaine, preweanlings and adults in this study were progressively more active during the first 30 min after injection (data not shown). Across the entire 3-h test session, however, preweanlings and adults had very different activity profiles. Adults were progressively more active after each daily dose of i.p. or s.c. cocaine, whereas preweanlings were less active by their third cocaine exposure (Fig. 3; details below).

Preweanlings were more active than adults after the first and second i.p. exposures to cocaine (p19 and p20 vs. p61 and p62) (10% and 105% respectively), but were slightly less active than

adults during the third drug exposure [significant subject age × time interaction, $F(2, 21)=3.82$, $p<0.05$] (Fig. 3a and b). Both preweanlings [$F(4, 44)=11.17$, $p<0.0001$; Tukey's post-hoc, $p<0.05$] (Fig. 3a) and adults [$F(4, 44)=13.01$, $p<0.0001$; Tukey's post-hoc, $p<0.05$] (Fig. 3b) were significantly more active during all three i.p. cocaine exposures compared with baseline. Adults were progressively more active with each subsequent injection of cocaine, having the greatest locomotor response after their third drug exposure on p63 (Fig. 3b).

Preweanlings were 3 times more active than adults during the first and second s.c. exposures to cocaine [significant subject age × time interaction, $F(2, 21)=6.72$, $p<0.01$] (Fig. 3c and d) but were slightly less active than adults during the third exposure (Fig. 3c and d). After each s.c. cocaine exposure, preweanlings [$F(4, 44)=12.13$, $p<0.0001$; Tukey's post-hoc, $p<0.05$] (Fig. 3c) and adults [$F(4, 44)=7.56$, $p<0.0001$; Tukey's post-hoc, $p<0.05$] (Fig. 3d) were significantly more active compared with the first baseline measurement. Pre-weanlings were most active after the first and second cocaine exposures and were least active after their third s.c. drug exposure on p21 (Fig. 3c).

4. Discussion

The data show that from postnatal days 18–21 the initial patterns of locomotor response after cocaine injection in preweanlings are distinguishable from adult patterns. However, as early as postnatal day 22, the initial responses are indistinguishable from adult patterns even though subjects have not yet been weaned suggesting that the dramatic shift in responding between p21 and p22 is a function of subject age and not weaning. Prior to day 22, locomotor effects of cocaine are distinguishable from those of adults in three ways: (1) at day 18, preweanlings are active for a longer time after cocaine injection; (2) preweanling activity peaks more rapidly after s.c. administration; and (3) a tolerance-like pattern is seen in preweanlings after only three injections of cocaine, whereas an emerging pattern of sensitization to cocaine is seen in adults after three injections of cocaine. The differences between adult and preweanling responses to i.p. injection of cocaine were smaller; by using a s.c. route of administration, which provides drug over a longer time course, greater differences are revealed.

Such differences in behavioral response are mostly likely due to either differences in the peripheral or central drug metabolism or differences in the structural or neurotransmitter components of catecholaminergic and/or serotonergic systems that underlie sensitization processes. It is also possible that both contribute to the adult-preweanling differences we found since it seems likely that both the pharmacokinetics of cocaine, and a sculpting and reorganization in the neural substrate responsive to this drug, are in development and hence different in the preweanling than the adult state. Our data indicate that the time point between p21 and p22 may have particular significance in these maturation processes, and future experiments examining changes in both pharmacokinetics and CNS systems could be targeted systematically in the days, and possibly hours, earlier and later than this period. Pharmacokinetic analysis would also verify that injections of similar doses actually yield similar blood levels in these age groups as it is formally possible that differences in the peripheral tissues that receive the injections are also involved.

Although the degree to which each which mechanism may underlie the age-related behavioral differences is unknown, our detailed characterization of responses to cocaine revealed key developmental differences not previously reported in the literature. Our data further suggest that examination of cocaine metabolism should be targeted to animals in the preweanling period especially during the third and fourth postnatal weeks, ages generally younger than that found in the literature where there is a surprising gap in our current knowledge on the topic. Future studies examining the pharmacokinetics of cocaine in preweanling, early adolescent, and adult animals are being planned in our laboratory.

The data from the first 30–90 min of the test session accord well with data from other studies that examined preweanlings (p21) [62,72,82,83] and data from our lab and others that examined virgin adults over longer test sessions (2.5 h and 5 h) [49,74]. Our data also accord well with those of Spear and Brick [62] who showed that p21 rats were significantly more active than both the older subjects (p35 adolescents) in that study and the older subjects in our study (p22–p29) after s.c. cocaine injection. Together these data suggest that an adult-like response to cocaine is achieved during the preweanling period before the onset of early adolescence and is maintained throughout adolescence. We had anticipated that all of our preweanling subjects (p18–p22) would respond similarly to cocaine, but that was not the case.

When we restricted our data analysis to the first 30 min of the test session, the locomotor activity data for both preweanlings and adults revealed that subjects in both age groups became progressively more active with each subsequent exposure to the drug suggesting that both preweanlings and adults were developing a sensitization response to cocaine. Our preweanling data, when examined only in the first 30 min, is consistent with a report by Wood et al. [69] showing that for the 30 min after cocaine injection (15 mg/kg), p14–p20 rodents are more active during each subsequent exposure to cocaine. Sensitization is traditionally assessed by administering a drug challenge after a period of drug absence. With short test session data collection, preweanling rats, including neonatal rat pups, have a sensitization-like pattern to cocaine after either an acute or chronic administration of the drug [6,40,60,69,70,72,82,83]. Although we did not use a traditional challenge-dose after drug vacation paradigm to assess this behavioral response, as it uses developmental days during the period of drug vacation, the progressive increase in locomotor activity during the first 30 min of the test session is consistent with a sensitization-like outcome of others using the challenge paradigm [36,50,64,69,81].

We found a different pattern, however, in preweanling responses to successive drug exposures when we examined locomotor activity across the entire 3-h test session; this pattern would have been masked with examination of only the 30 min period immediately after the drug was injected. As expected, adults were more active with each successive exposure to cocaine throughout the entire three hours after drug administration, a finding consistent with prior work [35,40,57,64]. In contrast, during the first two exposures, preweanling rats showed an increased locomotor response (like sensitization) over the entire three hour test period but by the third exposure activity over the three hours was decreasing compared to prior days (tolerance-like response). This was similar to findings in periadolescent rats showing no increased locomotor response in the sequence of 7 daily exposures (a higher dose than we used), and no evidence of sensitized response with challenge after drug vacation [17]. Together, these data [17] and our data suggest that drug-induced locomotor responses in the young have a pattern that differs from the adult when both the rising and falling phases of the plasma levels are considered.

The data on successive exposures to the environment after the two saline exposures, one prior to the sequence of drug injections and one the day after the last drug injection, show that adults were equally and modestly active during both saline exposures indicating neither habituation nor sensitization to the environment. In contrast, the preweanlings were more active during their first exposure to the novel testing apparatus together with a novel saline injection on p18 than during the second saline exposure on p22. Our preweanling baseline activity after a saline injection was consistent with results from another study showing that p21 preweanlings were more than twice as active as p56 adults when placed in a novel environment after an i.p. injection of saline [72]. We believe, however, that differences in activity levels in preweanlings versus adults are due to the response to a novel environment and not to the novel injection process since this was also found in our prior study on p18 versus p60 activity levels during exposure to a novel environment with no injection process [59].

There are several reasonable interpretations of the differences between adult and preweanling responses to repeated exposures to the same environment after saline injection. Possibly the preweanlings simply habituated to the environment. An alternative interpretation is that the locomotor activity differences observed between p18 and p22 preweanlings reflect the ongoing neural and physical maturational processes that are sculpting the young animal's capacity for locomotor activity during this window of time. Thus the younger, less-matured preweanling may have responded with higher levels of activity while by day 22 they are more adult-like in their locomotor pattern.

The results in this study were also identical to our previous finding showing that preweanlings spend more time in the center of an open field than adults without an injection component to the paradigm [59]. One interpretation is that preweanlings are not processing risky and/or anxiogenic stimuli at an adult-like level, a response that emerges during adolescence at the onset of puberty [47,48]. When exposed to cocaine, subjects of all ages spent significantly more time in the center of the open field, a known anxiety-provoking location, than saline controls but this was a direct function of the locomotor-stimulating effects of the drug and so cannot be attributed to the drug interfering with inhibitory processes that serve to prevent exploration of a potentially harmful location. Since the open and exposed area represented by the center of the open field nonetheless places rodents at increased risk, we conclude that one of the direct and possibly harmful effects of the stimulating properties of cocaine is increased time spent in potentially dangerous locations with the caveat that preweanlings are at an even greater risk than adults.

The behavioral characterization reflected in these data provides further insight into how young rats respond to stimulant drugs with the potential for abuse during early postnatal development when the CNS is particularly sensitive to the long-term effects of drugs. The data suggest that early sampling of small amounts of cocaine, particularly during the very first exposures may result in fundamentally different behavioral responses to the drug compared to adults. For example, in preclinical studies, adults exhibit sensitization after repeated daily exposures to cocaine and one interpretation relevant for the clinical situation is that the expression of sensitization represents the shift from recreational drug use to addiction [51]. In contrast, we posit that preweanlings exhibit tolerance to the drug, a finding relevant for the clinical situation in that human youth are more likely to use greater quantities of drugs and hence engage in bingeing considerably more than adults. This behavior might be elicited because the initial sampling of modest doses quickly becomes ineffective at eliciting salient hedonic effects in youth [29,61]. The present preadolescent, preclinical rodent model provides key information about a relatively understudied yet critical period of postnatal development that should be importantly targeted for future studies examining how cocaine is metabolized compared to adults, and examination of the neural substrate likely to mediate these effects.

Although many differences between the preweanling and adult CNS have been documented, those in the mesolimbic dopamine system are particularly relevant because this system is a known focus for the action of stimulants [37,80]. Such differences between preweanlings and adults exist from earliest infancy; for example, dopamine release in the striatum of p5–p10 pups is less than that in adults [2,38,39]. During the preweanling period major sculpting of the CNS begins, and it continues throughout adolescence, including further specific changes in the mesolimbic dopamine system [3,61,66,67]. For example, p14 and p21 preweanling rats have fewer D1 and D2 receptors in the dorsal and ventral striatum than adults [65–67]. Adult levels of these receptors are attained by mid-adolescence (p35) [3,61,3,65–67]. The longer time-frame effects of stimulant drug exposure in infancy and the preweanling period versus adolescence and adulthood may be due in part to the developmental state of the dopaminergic systems during the preweanling period and early adolescence [1,13,70].

The differences in responses before postnatal day 22 may be due to developmental differences in the CNS and may be important in the long time-course effects of drugs that are administered during the preweanling period in rats or late childhood in humans. Alternatively the behavioral differences may be attributed to developmental differences in the pharmacokinetics of cocaine metabolism. Possibly both forces are at work in this period. These two issues are topics for currently planned preclinical studies in our laboratory. Such CNS and/or pharmacokinetic differences, if present in humans, might support key differences in youth versus adult drug-seeking patterns after initial exposure. The data also suggest that in humans the length of efficacy afforded by various routes of administration may be a variable worth examining in the context of youth drug use.

Acknowledgements

The research presented in this study was supported by a training grant from the National Institute of General Medicine and Science MBRS S 5 R25 GM 060826-06, A. Cali, P.I., J.I. Morrell, Associate P.I., for training support for K.S. Smith; and grants from the National Institutes of Health DA014025 and March of Dimes 12-FY05-134 to J.I. Morrell.

References

1. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci Biobehav Rev 2003;27:3–18. [PubMed: 12732219]
2. Andersen SL, Gazzarra RA. The ontogeny of apomorphine-induced alterations of neostriatal dopamine release: effects on spontaneous release. J Neurochem 1993;61:2247–2255. [PubMed: 8245975]
3. Andersen SL, Rutstein M, Benzo JM, Hotstetter TC, Teicher MH. Sex differences in dopamine receptor overproduction and elimination. Neuroreport 1997;8:1495–1498. [PubMed: 9172161]
4. Andersen SL, Arvanitogiannis A, Pliakas AM, LeBlanc C, Carlezon WA Jr. Altered responsiveness to cocaine in rats exposed to methylphenidate during development. Nat Neurosci 2002;5:13–14. [PubMed: 11731802]
5. Barnett, SA. The Rat: A Study in Behavior, Revised Edition. University of Chicago; Chicago, IL: 1975.
6. Barr GA, Wang S. Behavioral effects of chronic cocaine treatment in the week-old rat pup. Eur J Pharmacol 1993;233:143–149. [PubMed: 8472743]
7. Black YD, Maclaren FR, Naydenov AV, Carlezon WA Jr, Baxter MG, Konradi C. Altered attention and prefrontal cortex gene expression in rats after binge-like exposure to cocaine during adolescence. J Neurosci 2006;26:9656–9665. [PubMed: 16988036]
8. Bowman BP, Vaughan SR, Walker QD, Davis SL, Little PJ, Scheffler NM, Thomas BF, Kuhn CM. Effects of sex and gonadectomy on cocaine metabolism in the rat. J Pharmacol Exp Ther 1999;290:1316–1323. [PubMed: 10454509]
9. Brook DW, Brook JS, Zhang C, Cohen P, Whiteman M. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. Arch Gen Psychiatry 2002;59:1039–1044. [PubMed: 12418937]
10. Brown SA, Tapert SF. Adolescence and the trajectory of alcohol use: basic to clinical studies. Ann NY Acad Sci 2004;1021:234–244. [PubMed: 15251893]
11. Bruckner JV, Jiang WD, Ho BT, Levy BM. Histopathalogical evaluation of cocaine-induced skin lesions in the rat. J Cutan Pathol 1982;9:83–95. [PubMed: 6212605]
12. Campbell JO, Wood RD, Spear LP. Cocaine and morphine-induced place conditioning in adolescent and adult rats. Physiol Behav 2000;68:487–493. [PubMed: 10713288]
13. Carlezon WA Jr, Konradi C. Understanding the neurobiological consequences of early exposure to psychotropic drugs: linking behavior with molecules. Neuropharmacology 2004;47:7–60.
14. Caster JM, Walker QD, Kuhn CM. Enhanced behavioral response to repeated-dose cocaine in adolescent rats. Psychopharmacology 2005;183:218–225. [PubMed: 16175404]
15. Chausmer AL, Katz JL. Comparison of interactions of D1-like agonists, SKF 81297, SKF 82958 and A-77636, with cocaine: locomotor activity and drug discrimination studies in rodents. Psychopharmacology 2002;159:145–153. [PubMed: 11862342]

16. Chen K, Kandel D. Relationship between extent of cocaine use and dependence among adolescents and adults in the United States. Drug Alcohol Depend 2002;68:65–85. [PubMed: 12167553]
17. Collins SL, Izenwasser S. Cocaine differentially alters behavior and neurochemistry in periadolescent versus adults rats. Dev Brain Res 2002;138:27–34. [PubMed: 12234655]
18. Crawford CA, Zavala AR, Karper PE, Collins RL, Loring-Meier T, Watson JB, McDougall SA. Amphetamine treatment during the preweanling period produces enduring changes in striatal protein kinase A activity. Pharmacol Biochem Behav 2000;66:835–840. [PubMed: 10973523]
19. Crews FT, Braun CJ, Hoplight B, Switzer RC 3rd, Knapp DJ. Binge ethanol consumption causes differential brain damage in young adolescent rats compared with adult rats. Alcohol Clin Exp Res 2000;24:1712–1723. [PubMed: 11104119]
20. Elsner J, Suter KE, Ulbrich B, Schreiner G. Testing strategies in behavioral teratology: IV. Review and general conclusions. Neurobehav Toxicol Teratol 1986;8:585–590. [PubMed: 3785521]
21. Falhke C, Hard E, Eriksson CJ. Effects of early weaning and social isolation on subsequent alcohol intake in rats. Alcohol 1997;14:175–180. [PubMed: 9085719]
22. Fergusson DM, Lynskey MT, Horwood LJ. Childhood exposure to alcohol and adolescent drinking patterns. Addiction 1994;89:1007–1016. [PubMed: 7950847]
23. Festa ED, Quinones-Jenab V. Gonadal hormones provide the biological basis for sex differences in behavioral responses to cocaine. Horm Behav 2004;46:509–519. [PubMed: 15555492]
24. Festa ED, Russo SJ, Gazi FM, Niyomchai T, Kemen LM, Lin SN, Foltz R, Jenab S, Quinones-Jenab V. Sex differences in cocaine-induced behavioral responses, pharmacokinetics, and monoamine levels. Neuropharmacology 2004;46:672–687. [PubMed: 14996545]
25. Fitzmaurice LS, Wasserman GS, Knapp JF, Roberts DK, Waeckerle JF, Fox M. TAC use and absorption of cocaine in a pediatric emergency department. Ann Emerg Med 1990;19:515–518. [PubMed: 2331095]
26. Galef BG. Weaning from mother's milk to solid foods. Ann NY Acad Sci 1992;662:37–52. [PubMed: 1456638]
27. Galef BG, Kennett DJ. Different mechanisms for social transmission of diet preference in rat pups of different ages. Dev Psychobiol 1987;20:209–215. [PubMed: 3582781]
28. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. J Subst Abuse 1997;9:103–110. [PubMed: 9494942]
29. Guilamo-Reyes V, Turrisi R, Jaccard J, Wood E, Gonzalez B. Progressing from light experimentation to heavy episodic drinking in early and middle adolescence. J Stud Alcohol 2004;65:494–500. [PubMed: 15376824]
30. Isenschmid DS, Fischman MW, Foltin RW, Caplan YH. Concentration of cocaine and metabolites in plasma of humans following intravenous administration and smoking of cocaine. J Anal Toxicol 1992;16:311–314. [PubMed: 1294836]
31. Javaid JI, Fischman MW, Schuster CR, Dekirmenjian H, Davis JM. Cocaine plasma concentration: relation to physiological and subjective effects in humans. Science 1978;202:227–228. [PubMed: 694530]
32. Javaid JI, Musa MH, Fischman M, Schuster CR, Davis JM. Kinetics of cocaine in humans after intravenous and intranasal administration. Biopharm Drug Dispos 1983;4:9–18. [PubMed: 6839006]
33. Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. NIH Publication No. 05–5726. National Institute on Drug Abuse; Bethesda, MD: 2005. Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings.
34. Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. NIH Publication No. 06–5883. National Institute on Drug Abuse; Bethesda, MD: 2006. Monitoring the Future National Survey Results on Drug Use, 1975–2005: Volume I, Secondary School Students.
35. Kalivas PW, Duffy P, DuMars LA, Skinner C. Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J Pharmacol Exp Ther 1988;245:485–492. [PubMed: 3130474]
36. Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev 1991;16:223–244. [PubMed: 1665095]

37. Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science 1988;242:715–723. [PubMed: 2903550]
38. Kosten TA, Zhang XY, Kehoe P. Chronic neonatal isolation stress enhances cocaine-induced increases in ventral striatal dopamine levels in rat pups. Brain Res Dev Brain Res 2003;141:109–116.
39. Kosten TA, Zhang XY, Kehoe P. Neurochemical and behavioral responses to cocaine in adult male rats with neonatal isolation. J Pharmacol Exp Ther 2005;314:661–667. [PubMed: 15845857]
40. Laviola G, Wood RD, Kuhn C, Francis R, Spear LP. Cocaine sensitization in periadolescent and adult rats. J Pharmacol Exp Ther 1995;275:345–357. [PubMed: 7562570]
41. Leri F, Flores J, Rajabi H, Stewart J. Effects of cocaine in rats exposed to heroin. Neuropsychopharmacology 2003;28:2102–2116. [PubMed: 12955094]
42. Lynch WJ, Carroll ME. Reinstatement of cocaine self-administration in rats: sex differences. Psychopharmacology 2000;148:196–200. [PubMed: 10663435]
43. Mattson BJ, Williams S, Rosenblatt JS, Morrell JI. Comparison of two positive reinforcing stimuli: pups and cocaine throughout the postpartum period. Behav Neurosci 2001;115:683–694. [PubMed: 11439457]
44. McCarthy LE, Mannelli P, Niculescu M, Gingrich K, Unterwald EM, Ehrlich ME. The distribution of cocaine in mice differs by age and strain. Neurotoxicol Teratol 2004;26:839–848. [PubMed: 15451047]
45. Numan, M.; Insel, TR. The Neurobiology of Parental Behavior. Springer-Verlag; New York, NY: 2003.
46. Olazabal DE, Kalinichev M, Morrell JI, Rosenblatt JS. MPOA cytotoxic lesions and maternal behavior in the rat: effects of midpubertal lesions on maternal behavior and the role of ovarian hormones in maturation of MPOA control of maternal behavior. Horm Behav 2002;41:126–138. [PubMed: 11855898]
47. Primus RJ, Kellogg CK. Pubertal-related changes influence the development of environment-related social interaction in the male rat. Dev Psychobiol 1989;22:633–643. [PubMed: 2792573]
48. Primus RJ, Kellogg CK. Gonadal status and pubertal age influence the responsiveness of the benzodiazepine/GABA receptor complex to environmental challenge in male rats. Brain Res 1991;561:299–306. [PubMed: 1666328]
49. Quinones-Jenab V, Ho A, Schlussman SD, Franck J, Kreek MJ. Estrous cycle differences in cocaine-induced stereotypic and locomotor behaviors in Fischer rats. Behav Brain Res 1999;101:15–20. [PubMed: 10342395]
50. Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res Brain Res Rev 1986;11:157–198.
51. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 1993;18:247–291. [PubMed: 8401595]
52. Rockman GE, Hall A, Markert L, Glavin GB. Early weaning effects on voluntary ethanol consumption and stress responsivity in rats. Physiol Behav 1987;40:673–676. [PubMed: 3671534]
53. Rofael HZ, Turkall RM, Abdel-Rahman MS. Immunomodulation by cocaine and ketamine in postnatal rats. Toxicology 2003;188:101–114. [PubMed: 12748044]
54. Rosenblatt, JS.; Mayer, AD.; Siegel, HI. Maternal behavior among the nonprimate mammals. In: Adler, N.; Pfaff, D.; Goy, RW., editors. Handbook of Behavioral Neurobiology. Plenum Press; New York: 1985. p. 229-298.
55. Scott DW, Morrell JI, Vernotica EM. Focal necrotizing panniculitis and vascular necrosis in rats given subcutaneous injection of cocaine hydrochloride. J Cutan Pathol 1997;24:25–29. [PubMed: 9027629]
56. Shedler J, Block J. Adolescent drug use and psychological health: a longitudinal inquiry. Am Psychol 1990;45:612–630. [PubMed: 2350080]
57. Shimosato K, Ohkuma S. Simultaneous monitoring of conditioned place preference and locomotor sensitization following repeated administration of cocaine and methamphetamine. Pharmacol Biochem Behav 2000;66:285–292. [PubMed: 10880680]

58. Smith, KS.; Morrell, JI. 2003 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience; 2003. Distinct adult-juvenile responses to novelty correlate to postnatal changes in glutamatergic innervation. Online. Society for Neuroscience: Washington, DC
59. Smith KS, Morrell JI. Comparison of infant and adult rats in exploratory activity, diurnal patterns, and responses to novel and anxiety-provoking environments. Behav Neurosci 2007;121:449–461. [PubMed: 17592936]
60. Snyder KJ, Katovic NM, Spear LP. Longevity of the expression of behavioral sensitization to cocaine in preweanling rats. Pharmacol Biochem Behav 1989;60:909–914. [PubMed: 9700975]
61. Spear LP. The adolescent brain and age-related manifestations. Neurosci Biobehav Rev 2000;24:417–463. [PubMed: 10817843]
62. Spear LP, Brick J. Cocaine-induced behavior in the developing rat. Behav Neural Biol 1979;26:401–415. [PubMed: 574000]
63. Spear LP, Frambes NA, Kirstein CL. Fetal and maternal brain plasma levels of cocaine and benzoylecgonine following chronic subcutaneous administration of cocaine during gestation in rats. Psychopharmacology 1989;97:427–431. [PubMed: 2498938]
64. Stewart J, Badiani A. Tolerance and sensitization to behavioral effects of drugs. Behav Pharmacol 1993;4:289–312. [PubMed: 11224198]
65. Tarazi FI, Baldessarini RJ. Comparative postnatal development of D1, D2 and D4 receptors in rat forebrain. Int J Dev Neurosci 2000;18:29–37. [PubMed: 10708903]
66. Tarazi FI, Tomasini EC, Baldessarini RJ. Postnatal development of dopamine D4-like receptors in rat forebrain regions: comparison with D2-like receptors. Brain Res Dev Brain Res 1998;110:227–233.
67. Tarazi FI, Tomasini EC, Baldessarini RJ. Postnatal development of dopamine and serotonin transporters in rat caudate-putamen and nucleus accumbens septi. Neurosci Lett 1998;254:21–24. [PubMed: 9780082]
68. Tirelli E. Short-term contextual sensitization and conditioned hyperkinesia produced by cocaine in suckling rats aged 4–10 days and 14–20 days. Psychopharmacology 2001;156:42–52. [PubMed: 11465632]
69. Tirelli E, Ferrara M. Neonatal and preweanling rats are able to express short-term behavioral sensitization to cocaine. Eur J Pharmacol 1997;328:103–114. [PubMed: 9218691]
70. Tirelli E, Laviola G, Adriani W. Ontogenesis of behavioral sensitization and conditioned place preference induced by psychostimulants in laboratory rats. Neurosci Biobehav Rev 2003;27:163–178. [PubMed: 12732232]
71. Turner L, Mermelstein R, Flay B. Individual and contextual influences on adolescent smoking. Ann NY Acad Sci 2004;1021:175–197. [PubMed: 15251888]
72. Ujike H, Tsuchida K, Akiyama Y, Fujiwara Y, Kuroda S. Ontogeny of behavioral sensitization to cocaine. Pharmacol Biochem Behav 1995;50:613–617. [PubMed: 7617709]
73. Vernotica EM, Lisciotto CA, Rosenblatt JS, Morrell JI. Cocaine transiently impairs maternal behavior in the rat. Behav Neurosci 1996;110:315–323. [PubMed: 8731058]
74. Vernotica EM, Morrell JI. Plasma cocaine levels and locomotor activity after systemic injection in virgin and in lactating maternal females. Physiol Behav 1998;64:399–407. [PubMed: 9748111]
75. Vives R, Nebot M, Ballestin M, Diez E, Villalbi JR. Changes in the alcohol consumption pattern among schoolchildren in Barcelona. Eur J Epidemiol 2000;16:27–32. [PubMed: 10780339]
76. Wagner FA, Anthony JC. From first drug use to drug dependence: developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. Neuropsychopharmacology 2002;26:479–488. [PubMed: 11927172]
77. Wansaw MP, Lin SN, Morrell JI. Plasma cocaine levels, metabolites, and locomotor activity after subcutaneous cocaine injection are stable across the postpartum period in rats. Pharmacol Biochem Behav 2005;82:55–66. [PubMed: 16115667]
78. Warner LA, White HR. Longitudinal effects of age at onset and first drinking situations on problem drinking. Subst Use Misuse 2003;38:1983–2016. [PubMed: 14677779]
79. Williams MT, Vorhees CV, Boon F, Saber AJ, Cain DP. Methamphetamine exposure from postnatal day 11 to 20 causes impairments in both behavioral strategies and spatial learning in adult rats. Brain Res 2002;958:312–321. [PubMed: 12470867]

80. Wise RA. Psychomotor stimulant properties of addictive drugs. Ann NY Acad Sci 1988;537:228–234. [PubMed: 3059926]

81. Wise RA, Leeb K. Psychomotor-stimulant sensitization: a unitary phenomenon? Behav Pharmacol 1993;4:339–349. [PubMed: 11224202]

82. Wood RD, Tirelli E, Snyder KJ, Heyser CH, LaRocca TM, Spear LP. Evidence for behavioral sensitization to cocaine in preweanling rat pups. Psychopharmacology 1998;138:114–123. [PubMed: 9718280]

83. Zavala AR, Nazarian A, Crawford CA, McDougall SA. Cocaine-induced behavioral sensitization in the young rat. Psychopharmacology 2000;151:291–298. [PubMed: 10972476]

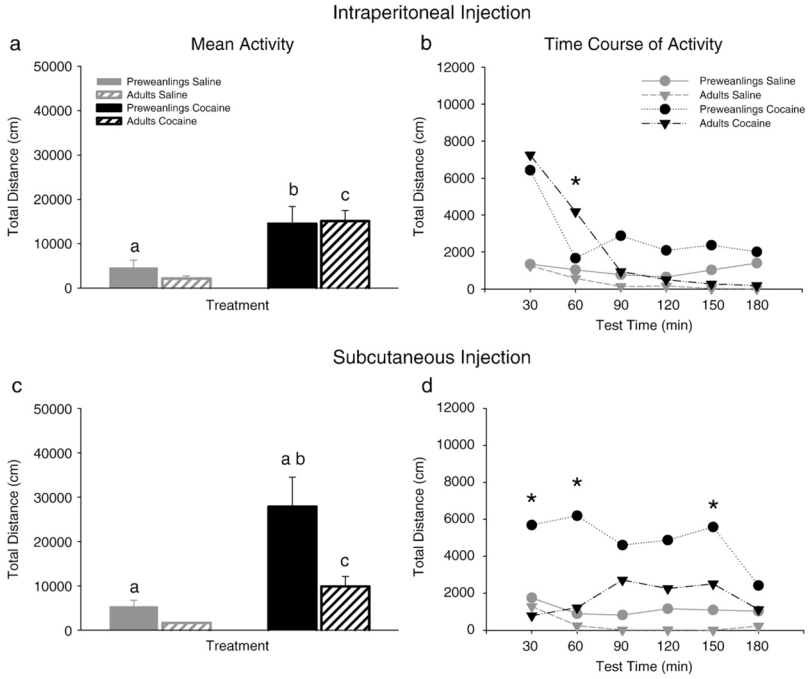

Fig. 1.

Overall total distance traveled (mean ± SEM) and time courses of locomotor activity (mean) exhibited by subjects across a 3-hour test session following either a single i.p. (a and b) or s.c. (c and d) injection of cocaine or saline. a = significantly different from adults. b=preweanlings significantly different from saline controls. c=adults significantly different from saline controls. *=significant preweanling-adult difference in response to cocaine at selected time points.

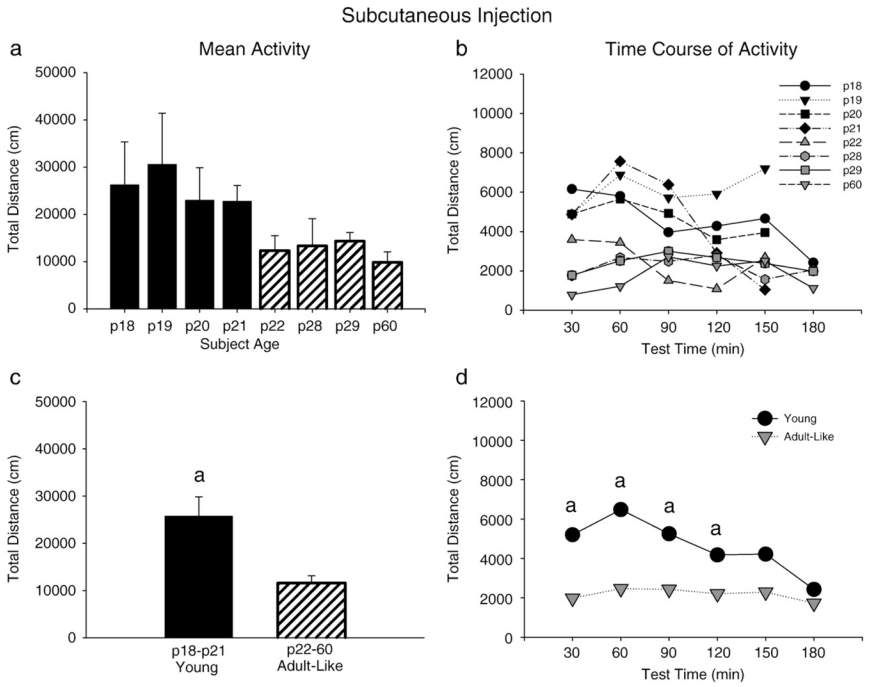

Fig. 2.

(a) Locomotor activity (mean ± SEM) of subjects at different postnatal ages after a single s.c. exposure to cocaine and (b) the activity profiles for each age group throughout a 3-hour test session. These same data were grouped into Young and Adult-Like groups and reflect (c) the overall group averages and (d) patterns of activity across the test session. a=significantly different from the Adult-Like group.

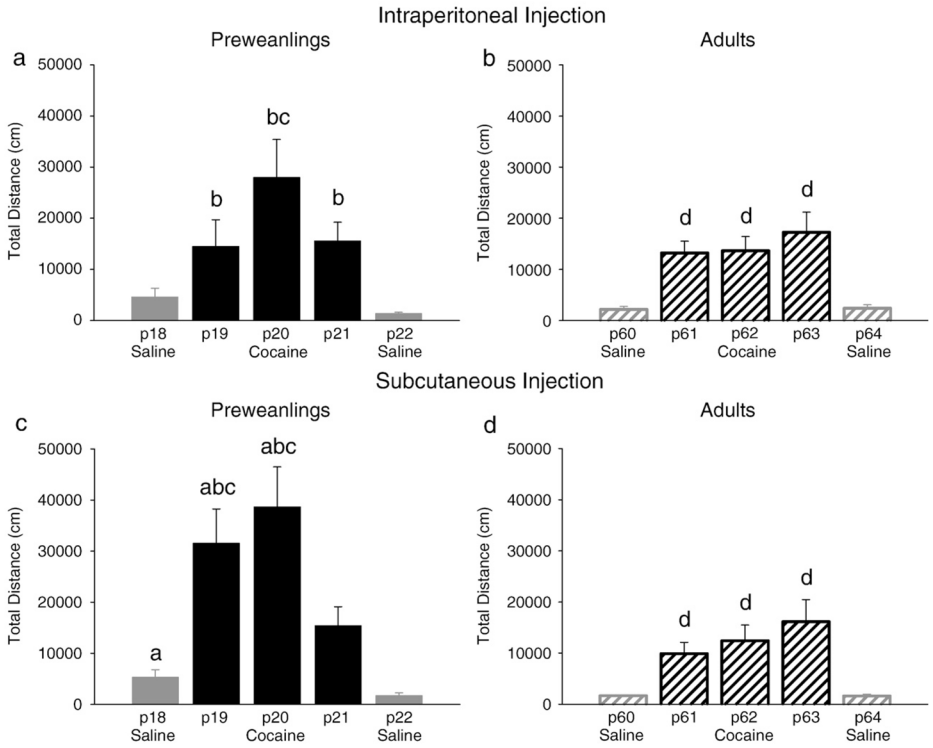

Fig. 3.

(a) Preweanling and (b) adult daily activity averages (mean ± SEM) following repeated exposures of saline and a low-dose of cocaine after i.p. administration. (c) Preweanling and (d) adult daily activity averages were also examined after repeated s.c. injections of saline and cocaine. a=significantly different from adults on the same day. b=preweanling activity after cocaine significantly different from activity after first saline injection on p18. c=preweanling activity during first and/or second exposures to cocaine significantly greater than activity during the third exposure. d=adult activity after cocaine significantly different from activity after first saline injection on p60.