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Differential effects of methamphetamine and cocaine on conditioned place preference and locomotor activity in adult and adolescent male rats

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Summary

Human and animal laboratory studies show that adolescents and adults respond differently to drugs and that drug administration during adolescence leads to different behavioral effects than during adulthood. Although there are a number of studies on the effects of cocaine, little is known about the effects of methamphetamine in adolescent vs adult rats. In the present study, sensitivity to the conditioned reward of multiple doses of methamphetamine or cocaine was evaluated in male adolescent (PND 34) and adult (PND 66) rats using a conditioned place preference (CPP) paradigm. In addition, the locomotor-activating effects of methamphetamine were determined across a five-day period of administration. After three days of training with cocaine, both adolescent and adult male rats developed CPP to cocaine, however, the dose-effect curve for cocaine CPP was shifted to the left in adolescent compared to adult rats. In contrast to the development of CPP to cocaine in both groups after three days of conditioning, methamphetamine CPP occurred only in adolescent, and not in adult rats. After five days of training, however, both adolescent and adult rats exhibited identical responses to multiple doses of methamphetamine and a significant CPP was observed in both groups. Daily administration of methamphetamine increased locomotor activity in both adolescent and adult rats, with a greater effect seen in the adults. In neither group, was there evidence of a significant sensitization to the locomotor-activating effects of methamphetamine. These data show that adolescents are more sensitive to psychostimulant reward and thus to the conditioned rewarding properties of cocaine or methamphetamine than adults. A better understanding of this difference may lead to age-specific preventions and treatments for psychostimulant abuse.

Keywords

methamphetamine; CPP; adolescent; development

Introduction

Most illicit drug use initiation begins between the ages of 12 and 20, with peak periods of initiation of drug use between ages 15 and 19 [18]. Clinical studies suggest that drug use during adolescence may lead to an increased likelihood of chronic drug use during adulthood [19]. There are reports of unique maturational changes occurring in neurotransmitter systems and

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behavioral repertoires during late childhood/young adulthood. It has been suggested that these changes during adolescence could lead to differential responses to drugs compared to that seen in juveniles or adults [36]. Thus, it is important to understand the effects of drugs during adolescence and to study further this developmental stage as a critical time period for drug use. The most recent National Survey on Drug Use and Health shows that although rates of methamphetamine use have decreased somewhat in the past year, the rates remain higher among youths aged 12–17 than among adults aged 26 or older [27].

In animals, levels of dopamine content and dopamine D₁ and D₂ receptors in the striatum exhibit a gradual increase until the time of puberty, when adult levels are reached [4;25]. It has been suggested that cocaine may have a greater addictive potential among adolescents than adults [19], perhaps because of the difference in neurochemical make-up throughout puberty. It has been suggested that the increased novelty-seeking and exploration behavior in animals, as well as elevated human sensation-seeking associated with adolescence [37], relate to an increased biological vulnerability to the effects of drugs of abuse [23]. It also has been shown that exploratory motivation is enhanced in 35 day old rats compared to younger and older animals [32]. Using the conditioned place preference paradigm, it has been found that while there was no reliable conditioned place preference to amphetamine in adolescent rats at postnatal day (PND) 30, conditioned place preference to amphetamine did develop in adult (PND >60) rats [3]. In contrast, it has been reported that adolescent rats (PND 35) responded to a lower dose of cocaine than adults [6]. In addition, adolescent rats (PND 35) were shown to acquire amphetamine self-administration faster than adults (PND 60) with a higher number of infusions [31]. Thus, the effects of psychostimulants in adults and adolescents may be different depending upon which drug is studied and it may be important to study multiple doses of a drug at both ages to determine whether there are fundamental differences in the rewarding effect of the drug or whether any differences may be dose-related. In none of the prior studies was methamphetamine studied. In 2006, there were 731,000 users of methamphetamine, of which 259,000 were new users [27]. The majority of users were adolescents or young adults and youths aged 12–17 who used methamphetamine for non-medical reasons and were much more likely to have used other illicit drugs than did non-methamphetamine users [30].

Because of the spread of methamphetamine use across the USA, and the high level of use in adolescents, the present study was done to determine whether methamphetamine conditioned reward and stimulation of activity are the same in adult and adolescent rats. In the present study, the effects of multiple doses of methamphetamine were examined on locomotor activity and conditioned place preference in adult and adolescent male rats. The adolescent rats in these studies were tested during the 10–12 day period immediately prior to puberty, which is during the periadolescent period [32]. As a comparison to the effects of methamphetamine, cocaine conditioned place preference also was examined in both groups.

Methods

Subjects

The animals used in this study were maintained and the studies were conducted in accordance to the guidelines of the Guide for Care and Use of Laboratory Animals, National Research Council, Department of Health, Education and Welfare, NIH Publication 85–23, revised 1996. Male Sprague-Dawley adolescent (tested during the periadolescent period, PAM) and adult (ADM) rats (Charles River, MA) were used in all studies. Rats were housed two per cage in a temperature and humidity-controlled environment under a 12 h light/dark cycle with lights on at 7 a.m. and off at 7 p.m. Both rats in each individual cage received the same dose of drug.

All behavioral tests were done during the light schedule between 9 a.m. and 4 p.m. with each rat tested/conditioned at the same hour on each day. Adult and adolescent rats receiving

different doses of drug were randomized across sessions. Food and water were available ad libitum.

Chemicals

Methamphetamine and cocaine HCl were obtained from the National Institute on Drug Abuse (Rockville, MD).

Locomotor activity

Locomotor activity sessions were conducted once daily for 5 days starting at PND 34 for the adolescent rats and at PND 66 for the adults. Each rat was placed in a locomotor activity chamber for a 15 minute habituation period followed by an i.p. injection of 0.125 or 0.5 mg/kg of methamphetamine or saline and activity was measured for 1 h. The chambers were clear acrylic boxes (40.64 × 40.64 cm) inside Digiscan activity monitors (Accuscan, Columbus, OH) that were equipped with infrared light sensitive detectors mounted 2.5 cm apart along two perpendicular walls. Mounted along the opposing walls were infrared light beams that were directed at the detectors. Total distance was recorded for a total of 60 min during which beam breaks were measured over 12 consecutive 5 min time periods. Each group consisted of 8 rats.

Conditioned place preference (CPP)

The apparatus consisted of an acrylic box (40.64 × 40.64 cm) with a removable center barrier. On one side, the walls and the lid were white and the floor was smooth. On the other side, the walls and the lid were black and white striped, and the bottom was covered with a mesh floor. CPP studies were done with either three or five training days. For the studies using three training days, a pretest was done on PND 34 (adolescents) or PND 66 (adults), followed by three days of training and a post-test on PND 38 or PND 70, respectively. During the pretest, the rats were placed into the CPP test chamber with the center barrier removed so that the rats were able to move freely to both sides. The amount of time spent in each side was recorded for 30 min. The preferred side was paired with saline and the non-preferred side was paired with the methamphetamine or cocaine for the training days. During the conditioning phase, the rats were trained in the morning with saline and in the afternoon with 0.06, 0.125, 0.5 or 1 mg/kg methamphetamine i.p. or 3, 5, 7.5, 10 or 20 mg/kg cocaine i.p. Different groups of rats were used for each tested dose and each training session lasted 30 min. This training schedule was used instead of training saline and drug on separate days because of the constraints involved in doing developmental studies. To ensure that the entire experiment could be completed within the adolescent period, it was important to keep the CPP training period as short as possible. The post-test was done in the middle of the day. During this test, rats were placed in the chamber with the center barrier removed and they were able to move freely to both sides, as during the pretest. The amount of time spent in each side was recorded for 30 min by observers blind as to which side had been paired with drug.

For the studies using five conditioning days, CPP began on PND 31 in the adolescent rats and PND 63 for the adult rats. On that day, a pretest was done to determine initial preference for the chambers. Conditioning occurred on each of the next five days (PND 34 – 38 in adolescents and PND 66–70 in adults) and the post-test was done on PND 41 and 73, respectively.

Although our prior studies showed that this apparatus did not produce a significant bias towards one side or the other across rats [1], the experiments were run in a biased manner with methamphetamine or cocaine paired with the non-preferred side for each rat, as determined by the pretest done prior to conditioning. The biased method was used because of a concern that there might be different levels of bias across groups and we wanted to ensure that this did not unknowingly confound our results.

Data analysis

Locomotor activity data were analyzed using a 3-way (age $\times$ dose $\times$ day) analysis of variance (ANOVA). Post hoc analysis using Fisher's Protected Least Significant Difference (PLSD) was used when warranted. P values less than 0.05 were considered significant for all tests.

CPP data for the dose-response curves for each drug were analyzed using a two-way ANOVA (training dose $\times$ age). Post hoc analysis using Fisher's PLSD was used when warranted. In addition, the data for each individual dose were analyzed using t-tests to compare the difference in time spent in the drug paired chamber (time in the methamphetamine- or cocaine-paired side during the post-test minus time spent in the methamphetamine- or cocaine-paired side during the pretest) to 0 to determine whether a significant change in behavior had occurred in each group. A value of 0 would mean that there was no change in preference, whereas a positive value would mean that more time was spent in the drug-paired side after training than during the pretest. P values less than 0.05 were considered significant for all tests.

Results

Locomotor Activity

Methamphetamine stimulated locomotor activity in both adult male (ADM) and adolescent male (PAM) rats compared to baseline (VEH) (Fig. 1). An overall 3-way ANOVA (age $\times$ dose $\times$ day) of the locomotor activity data showed that there was a significant effect of age ($F_{(1,210)} = 77.865$, $P \leq 0.0001$), of dose of methamphetamine ($F_{(2,210)} = 21.145$, $P \leq 0.0001$), and a significant age $\times$ dose interaction ($F_{(2,210)} = 4.987$, $P \leq 0.008$). Post hoc tests showed that there was not a significant difference in baseline activity levels in response to VEH between the adolescent and adult rats (Fig. 1). The data in Fig. 1 are expressed as mean $\pm$ SEM of distance traveled in 60 min test sessions across 5 days of treatment and testing, which is the same dosing regimen used in the CPP studies.

Neither adolescent nor adult rats exhibited activity that was significantly increased over baseline in response to repeated daily injections of 0.125 mg/kg methamphetamine. In both groups, however, 0.5 mg/kg methamphetamine produced significant increases in activity ($P \leq 0.05$, Fig. 1). The effect of the higher dose of methamphetamine was significantly greater in the adult rats compared to the adolescent rats ($P \leq 0.05$).

There was no significant effect of day such that activity levels across the 5-day period did not change in response to vehicle or to either dose of methamphetamine. A comparison of activity on days 3, 4, or 5 with day 1, showed that there were no significant differences in activity in response to the first injection of methamphetamine compared to the subsequent injections. Thus, even though there appears to be a trend toward an increase in activity in the adult rats across days during this treatment and testing period, there was not a significant sensitization or tolerance to the locomotor-stimulating effects of methamphetamine.

CPP

Methamphetamine—After three days of training, only the adolescent rats had developed a significant CPP to any tested dose of methamphetamine (Fig. 2A). There was a significant CPP to 0.5 mg/kg ($t_{(9)} = 3.04$, $P \leq 0.014$) and 1 mg/kg ($t_{(7)} = 2.59$, $P \leq 0.0355$) methamphetamine in the adolescent rats. A dose of 0.125 mg/kg methamphetamine did not lead to a significant change in time spent in the drug-paired chamber after three days of training. In contrast to the adolescent rats, none of the three doses tested produced a significant CPP to methamphetamine in the adult rats (Fig. 2A). A two-way ANOVA of age $\times$ dose in the adult and adolescent rats showed that there was a significant effect of age ($F_{(1,46)} = 3.95$, $P \leq 0.05$), but no significant effect of dose and no age $\times$ dose interaction.

After five days of training, CPP to methamphetamine was established in both adult and adolescent rats. A significant CPP developed in response to training with either 0.125 mg/kg ($t_{(9)} = 3.85$, $P \leq 0.0039$), 0.5 mg/kg ($t_{(9)} = 5.32$, $P \leq 0.0005$), or 1 mg/kg ($t_{(9)} = 2.85$, $P \leq 0.019$) methamphetamine in the adolescent rats (Fig 2B). Training with the lowest dose of 0.06 mg/kg methamphetamine did not lead to a significant CPP. The dose-effect curve for CPP in the adult rats was virtually identical to that of the adolescents with 0.125 mg/kg ($t_{(7)} = 2.64$, $P \leq 0.0337$), 0.5 mg/kg ($t_{(7)} = 7.56$, $P \leq 0.0001$), and 1 mg/kg ($t_{(7)} = 5.49$, $P \leq 0.0009$) each producing a significant CPP while 0.06 mg/kg methamphetamine did not.

One concern was that the difference in time points between the last training session and the post-test might account for the large difference in CPP in the adult rats after three compared to five days of training, since the post-test was done three days after the five-day training period and one day after the three-day training period. To determine whether the delay in testing could account for the different results in the adult rats, a separate study was done where 10 adult rats were trained for three days with saline and 0.5 mg/kg methamphetamine and the post-test was done three days later. This training and testing regimen did not lead to a significant CPP, and the data look similar to what was seen in the initial study with three days of training (Fig. 3). Thus, it appears that the extra time after training did not account for the difference in CPP observed after either three vs five days of training in the adult rats.

Cocaine

After three days of training, the adolescent rats exhibited a significant CPP to both 5.0 ($t_{(11)} = 5.27$, $P \leq 0.0003$) and 7.5 ($t_{(11)} = 2.34$, $P \leq 0.039$) mg/kg cocaine, as shown by a significant increase in the amount of time spent in the cocaine-paired chamber during the post-test compared to the pretest (Fig. 4). Neither 3 nor 10 mg/kg cocaine produced a significant CPP in the adolescent rats. In contrast to the adolescents, adult male rats did not develop a significant CPP to 5 or 7.5 mg/kg cocaine, but did spend significantly more time in the cocaine-paired chamber during the post-test after training with either 10 ($t_{(7)} = 3.50$, $P \leq 0.009$) or 20 ($t_{(9)} = 2.34$, $P \leq 0.044$) mg/kg cocaine. A two-way ANOVA of age $\times$ dose for the entire curves in both adolescent and adult rats showed that there were no significant main effects but that there was a significant age $\times$ dose interaction ($F_{(1,74)} = 6.51$, $P \leq 0.0025$). Post-hoc tests showed that there were significant differences in the responses of adult and adolescent rats in response to both the 5 and 10 mg/kg doses of cocaine ($P \leq 0.05$). It is interesting to note that although the dose-response curve for the adolescent rats is shifted to the left compared to the adult rats, the maximal level of CPP achieved in both groups is equal.

Discussion

The present study showed that there are differences between adolescent and adult rats in response to the conditioned reward of cocaine or methamphetamine such that the adolescents were more sensitive than the adults to these psychostimulants. In contrast, the adult rats appeared to be more sensitive than the adolescent rats to the locomotor-stimulant effects of methamphetamine. Although earlier studies have suggested that adolescent rats are more sensitive to cocaine reward, there were no prior studies showing that the same was true for methamphetamine.

Locomotor Activity

In the present study the adult rats showed a larger response to methamphetamine on locomotor activity than the adolescents. Similar to these findings with methamphetamine, it has been shown previously that adolescent rats exhibited lower levels of locomotor activity across days than adult rats, and that adolescent rats did not develop sensitization in response to repeated cocaine [15] or nicotine [14] administration. It also has been shown that there is a

hyporesponsivity to amphetamine [2,8] and other psychostimulants [2,8,32] although another study showed that in adolescent (PND45) and adult (PND69) male rats, single or repeated doses (0.5 or 1 mg/kg) of amphetamine produced an equal stimulation of locomotor activity [24]. Thus, most studies suggest that less stimulated activity may be a characteristic of multiple, but not necessarily all, psychostimulant drugs.

Although the adults were more sensitive than the adolescents to the locomotor stimulant effects of methamphetamine, sensitization to the five repeated injections of methamphetamine was not observed after treatment with either 0.125 or 0.5 mg/kg methamphetamine. Thus, although there appeared to be a slight trend upwards during the five days of methamphetamine administration in the adult rats, there was no significant sensitization. This is consistent with previous reports that show that while sensitization occurred after eight days of 0.5 mg/kg methamphetamine, this dose did not produce sensitization either on the fifth day of treatment [7] or three days later in response to a challenge injection of methamphetamine [20] in adult rats. Thus, while higher doses or longer treatments with this dose do lead to a sensitized response, the present data are consistent with the existing literature on the effects of methamphetamine in rats.

CPP

After only three training sessions with methamphetamine and saline, the adolescent rats developed a significant CPP, whereas there was no CPP in the adults at any of the doses used. In contrast, after five days of pairing the drug with the chamber, methamphetamine produced equal high levels of CPP in both adolescent and adult rats. Unlike what was seen with methamphetamine, cocaine CPP was established to the same magnitude in both adolescent and adult rats after only three days of conditioning. However, the curve for the adolescent rats was shifted to the left, with the maximal CPP observed in response to training with 5 mg/kg cocaine, compared to the adults who had a maximal CPP in response to 10 mg/kg cocaine.

Since the strength of conditioning relies on both the strength of the reward value and on the strength of the association between the stimuli (chamber cues) and the reward (methamphetamine), there are three possible explanations for the differences in CPP observed between adolescents and adult rats after three vs five pairings of methamphetamine with the CPP chamber. The first is that the reward value of methamphetamine is more salient in the adolescent rats than in the adult rats. The second is that there is a difference in the ability to learn the relationship between the cues and reward in adolescent vs adult rats. The third is that the stimuli (chamber cues) are more salient in the adolescent rats than in the adult rats.

The greatest likelihood is that the first reason is true – that the reward value of methamphetamine is greater in the adolescent rats. It is unlikely that the difference across age is due to the ability to learn the connection between the chamber and the drug after three sessions because cocaine CPP is evident after three days of training in both adult and adolescent rats, and the magnitude of the maximal CPP is not different across groups. Thus, if the cues and the drug are both salient, it is possible for the adults to develop a CPP. Since the test chambers used for both cocaine and methamphetamine CPP sessions were the same, and the cues were salient enough for cocaine CPP to develop after three days of training, it appears that the salience of the cues does not account for the difference in adult CPP after three or five days of training. Thus, it appears that the difference is in the value of methamphetamine as a reward in the adolescent vs the adult rats.

For cocaine CPP, the difference between groups is clearer in that the dose-response curve for cocaine-induced CPP is parallel and shifted to the left in the adolescents compared to adults, while maximal CPP is the same in both groups. This finding is consistent with a previous study showing that adolescent rats had a greater response to conditioning with 5 mg/kg cocaine than

did adult rats [6]. Recently, it was shown that adolescent rats take longer than adults to extinguish CPP to cocaine and that they exhibit a stronger reinstatement upon priming, suggesting that the cocaine cue may have greater salience in the adolescent rats [10]. In contrast to these studies and the present data, however, is a study showing that there are no differences between cocaine CPP in adolescent and adult rats in response to conditioning with either 5 or 10 mg/kg cocaine [11]. One factor that could possibly account for these differences is that in the latter study, data for male and female rats were collapsed into one. Thus, it is possible that the addition of females could alter the overall response to a given dose of cocaine. The present results show full dose-effect curves for cocaine and methamphetamine CPP in both adult and adolescent rats, and this has not been reported in earlier studies. The data show that both methamphetamine and cocaine are more rewarding in adolescent than in adult male rats, however, this difference is manifest in different ways for the two drugs.

One caveat is that there is an additional difference between the studies done with three days of training and the studies done with five days of training and that is the number of days between the last training session and the post-test. The rats were tested one day after being trained for three days and three days after being trained for 5 days. To determine whether this difference was responsible for the differential data, a separate study was done where adult rats were trained for three days with saline and 0.5 mg/kg methamphetamine (a dose that produced maximal CPP after five days of training but no CPP after three days of training) and the post-test was done three days later. In this case, the results were virtually identical to those seen after three day training with a one-day delay, where no CPP was observed. Thus, the delay prior to the post-test did not account for the vastly different results seen after the two different training sets in the adult rats. In fact, other studies have shown that cocaine CPP increases with the number of cocaine-paired sessions and decreases with time after the last training session [9,26], thus one might expect that if the timing played a role, the opposite effect would have been observed.

In a recent study, where the number of methamphetamine-paired sessions (1, 2 or 3) resulted in the same amount of CPP, it was hypothesized that methamphetamine CPP was more related to a preference for the novelty of the drug-paired compartment due to disruption of the sensorial processing by methamphetamine in mice [13]. That idea is not supported by the present data, where the magnitude of CPP increased with additional training sessions.

It is interesting to note that while both doses of methamphetamine, 0.125 and 0.5 mg/kg, were sufficient to establish CPP after 5 methamphetamine conditioning sessions in adolescent and adult rats, only the higher dose (0.5 mg/kg) significantly increased locomotor activity over 5 days of testing in both age groups. However, both of these doses failed to produce CPP in adult rats after 3 days of conditioning training. Thus, it does not appear that the locomotor-activating effects of methamphetamine influenced the development of CPP. In addition, the magnitude of the increased locomotor activity was not significantly changed across test days. Thus, it also does not appear that sensitization to the locomotor-activating effects played a role in the differential CPP observed after three or five days in the adult rats. These data suggest that the locomotor-stimulating and conditioned rewarding effects of methamphetamine are regulated through different mechanisms. This idea is supported by a prior study showing that after pretreatment with a neurotoxic dose of methamphetamine (3×5 mg/kg), adult mice developed sensitization to the locomotor-induced effects of a challenge dose of methamphetamine but were desensitized to its conditioned rewarding effects [21].

Whether there are differences in brain structure and function between adolescents and adults that underlie the discrepancies in the rewarding properties of psychostimulants is not clear. It has been shown that during development there are excessive amounts of D₁ and D₂ dopamine receptors, which reach a maximum at PND 40, after which they remain constant in the nucleus accumbens, or are decreased by pruning to adult levels thereafter in the striatum and prefrontal

cortex [5,33]. Lower dopamine levels in adolescent rats also have been reported [4]. It is not clear whether these differences can account for the increased reward in the adolescent rats, and further studies will be necessary to determine the mechanisms of the differences.

Other effects of methamphetamine differ across development. For example, it has been shown that treatment with four doses per day for 10 days between PND 11 and PND 20 impaired spatial learning and memory in the Morris water maze once the rats were adults, but had no effect after administration during PND 1 to PND 10 [35]. During PND 31–40, only a high dose of methamphetamine (4×6.25 mg/kg daily), which caused a significant elevation in mortality, produced any cognitive deficits when tested on PND 70 [34]. There was a discrepancy found in the neurotoxic effects of high doses of methamphetamine (e.g. 4×10 mg/kg) depending on the age of animals with PND 20 and 40 rats shown virtually no hyperthermia or methamphetamine-induced alterations in neostriatal dopamine- and serotonergic systems, as well as no methamphetamine-induced reactive gliosis when the drug was administered at standard room temperature (22°C) compared to the PND 60 rats [12]. Interestingly, methamphetamine pretreatment in adolescent rats prevented the dopamine deficits and attenuated the hyperthermia caused by a neurotoxic methamphetamine regimen later in adulthood [29]. It also was suggested that age-dependent pharmacokinetics of methamphetamine and differential hyperthermia responses could contribute into the lack of dopaminergic system deficits observed in PND 40, but not older animals [22]. It is unlikely that pharmacokinetics played a significant role in the lack of CPP in the adult rats after three days of training, since the effects of methamphetamine on locomotor activity were the opposite to that of the CPP (i.e. there was a larger effect in adults than adolescents). Thus, a lack of access of the methamphetamine into the brains of the adult animals is not likely.

Recently an age-related differential short- and long-term responses in vesicular dopamine uptake to methamphetamine has been reported [28]. This could affect the formation of reactive oxygen species from cytoplasmic dopamine - one of the mechanisms of methamphetamine neurotoxicity [16,17]. However, in those studies the doses of methamphetamine, which resulted in neurotoxicity and cognitive deficits, were much higher than in the present study. Thus it is very unlikely that neurotoxicity contributed to the differential effects in adult and adolescent rats.

These data show that CPP to both methamphetamine and cocaine can be achieved in adolescent rats, albeit at different doses than in adult rats. These data show that it is necessary to test multiple doses of a drug, and possibly different training regimens, before ruling out the likelihood that a CPP exists. For example, if only the 10 mg/kg dose of cocaine had been tested, the conclusion would have been that CPP occurs in adult, but not in adolescent rats in response to cocaine. After testing a range of doses, however, the data show that not only does cocaine CPP occur in adolescent rats, but that the adolescent rats are more sensitive than adults to the conditioned reward effects of cocaine.

The present data show that adolescent rats are hyporesponsive to methamphetamine-induced locomotor activity, while they are more sensitive to the conditioned rewarding effects of both methamphetamine and cocaine compared to adult rats. Thus it is important when doing studies of drug reward across development, to determine the parameters for each group and not assume that the same doses of drug are appropriate at different ages. Increased sensitivity to the reward associated with these psychostimulants may suggest an increased vulnerability to abuse of these drugs, and further study will be necessary to determine the long-term effects of cocaine and methamphetamine in adolescence compared to adults.

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Fig. 1.

Locomotor activity in (A) periadolescent male (PAM) and (B) adult male (ADM) rats in response to VEH, 0.125 mg/kg or 0.5 mg/kg methamphetamine. The data are expressed as mean $\pm$ SEM of distance traveled in 60 min test sessions across 5 days of treatment and testing. The dose of 0.5 mg/kg methamphetamine significantly increased activity over saline levels in both groups ($P \leq 0.05$), with a greater effect in adults, and the effect of this dose was not significantly altered across days. MA = methamphetamine

Fig. 2.

Methamphetamine CPP in response to training for (A) 3 days or (B) 5 days. Data are presented as the amount of time spent in the methamphetamine-paired chamber during the post-test minus time spent in the methamphetamine-paired chamber during the pretest. A value of 0 represents no change. A positive value represents an increase in preference for the methamphetamine-paired side and a negative value represents an increased preference for the saline-paired side. After 3 days of training (A), both 0.125 mg/kg and 0.5 mg/kg methamphetamine produced significant increases in the amount of time spent in the methamphetamine-paired side of the chamber during the post-test in adolescent rats, but none of the doses led to a significant CPP in the adult rats. After 5 days of training (B), either 0.125 mg/kg, 0.5 mg/kg or 1.0 mg/kg methamphetamine led to a significant CPP in both adolescent and adult rats. A dose of 0.06 mg/kg methamphetamine did not produce a significant CPP after either training paradigm. $N = 8-10$ per group. Doses in the x-axis are shown on a log scale. *significantly different from 0 ($P < 0.05$). MA = methamphetamine

Fig. 3.

Methamphetamine CPP in adult rats in response to training with 0.5 mg/kg. for: 3 days with a post-test conducted one day after the last training session (3D + 1, n=10), 3 days with a 3 day delay before testing (3D + 3, n=10), or 5 days with a 3 day delay before testing (5D + 3, n=8). Data are presented as the amount of time spent in the methamphetamine-paired chamber during the post-test minus time spent in the methamphetamine-paired chamber during the pretest.

Only the five-day training paradigm led to a significant change in preference over the pretest.

*significantly different from 0 ($P < 0.05$). MA = methamphetamine

Fig. 4.

Cocaine conditioned place preference. Adolescent and adult rats were trained with cocaine (3–20 mg/kg/day) and saline for three days. Data are presented as time spent in the cocaine-paired chamber during the post-test (day 5) minus time spent in cocaine-paired chamber during the pretest (day 1, prior to training) expressed as seconds. The 0 line represents no preference. A positive value represents an increase in preference for the cocaine-paired side and a negative value represents an increased preference for the saline-paired side. $N = 8–12$ animals per group. Doses in the x-axis are shown on a log scale. *significant difference from 0 ($P < 0.05$).