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Adolescent mice are more vulnerable than adults to single injection-induced behavioral sensitization to amphetamine

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ABSTRACT

Drug-induced behavioral sensitization in rodents has enhanced our understanding of why drugs acquire increasing motivational and incentive value. Compared to adults, human adolescents have accelerated dependence courses with shorter times from first exposure to dependence. We compared adolescent and adult mice in their ability to develop behavioral sensitization to amphetamine following a single injection. Adult (90-day-old) and adolescent (45-day-old) male Swiss mice received an acute intraperitoneal injection of saline or amphetamine (1.0, 2.0 or 4.0 mg/kg). Seven days later, half of the mice from the saline group received a second injection of saline. The remaining animals were challenged with 2.0 mg/kg amphetamine. Following all of the injections, mice were placed in activity chambers and locomotion was quantified for 45 min. The magnitude of both the acute and sensitized locomotor stimulatory effect of amphetamine was higher in the adolescent mice. Previous experience with the test environment inhibited the acute amphetamine stimulation in both adolescent and adult mice, but facilitated the detection of elevated spontaneous locomotion in adolescent animals. These results support the notion that the adolescent period is associated with an increased risk for development of drug abuse. Additionally, they indicate a complex interaction between the environmental novelty, adolescence and amphetamine.

1. Introduction

Behavioral sensitization has been characterized by a progressive increase in drug-elicited behavioral responses in rodents following repeated administration (Robinson and Becker, 1986). Sensitization to drug-induced hyperlocomotion in rodents has become dominant over other behavioral parameters in neuropsychopharmacological studies because it is useful for studying mechanisms of plasticity in the dopaminergic mesoaccumbens pathway (Henry and White, 1991; Wolf et al., 1994), which is linked to the development of drug cravings in humans. Indeed, the activity of the mesolimbic dopaminergic system is a key component in the chain of events that leads from the molecular action of drugs of abuse to the establishment of drug addiction (Robinson and Berridge, 1993, 2008; Vezina, 2004).

Importantly, it has been demonstrated that it is not necessary to repeatedly administer amphetamine for long periods of time to produce behavioral sensitization. Indeed, a single pre-treatment with amphetamine has been reported to enhance both stereotypy (Browne and Segal, 1977; Chinen et al., 2006) and locomotor stimulation (Alvarez et al., 2006; Calzavara et al., 2008; Chinen et al., 2006; Vanderschuren et al., 1999) produced by an injection of amphetamine given hours, days or weeks after the first injection. This suggests that a single injection of amphetamine is sufficient to elicit an immediate and long lasting sensitization of the neuronal dopaminergic mechanisms related to drug craving.

Adolescence is characterized by a heightened risk for the development of substance abuse (Laviola et al., 1999; Spear, 2000; Wahlstrom et al., 2010). In apparent contrast with these clinical data there is a large literature showing that adolescent rodents exhibit lower or lack of locomotor sensitization compared to adults in response to repeated psychostimulants, nicotine or ethanol (Collins and Izenwasser, 2002; Cruz et al., 2005; Faria et al., 2008; Frantz et al., 2007; Kolta et al., 1990; Laviola et al., 1999; McDougall et al., 1994; Tirelli et al., 2003; Ujike et al., 1995). However, in the only study performed to compare single injection-induced behavioral sensitization in adolescent and adult

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rodents, Caster et al. (2007) observed enhanced sensitization to cocaine in adolescent rats. From a clinical point of view, this finding is in accordance with reports that adolescent humans go from first drug exposure to dependence in a much shorter timeframe than adults (Clark et al., 1998; Estroff et al., 1989). From a basic point of view, it is in line with recent evidence highlighting molecular divergences between single injection-induced sensitization and the classical sensitization induced by repeated injections (Valjent et al., 2010). Thus, it is important to confirm the higher sensitivity of adolescent subjects to single injection-induced sensitization to other drugs of abuse and in a different rodent species.

The aim of the present study is to compare single injection-induced sensitization to the locomotor stimulatory effect of amphetamine in adolescent and adult mice.

2. Methods

2.1. Subjects

Adult (90-day-old) and adolescent (45-day-old) Swiss EPM-M1 male mice from a lab-operated breeding colony were housed 9–10 per cage in polypropylene cages (41 cm × 34 cm × 16 cm). Each cage contained animals from the same experimental group. The *vivarium* was maintained at 22–23 °C with a 12-h light/dark cycle (lights on at 06:45 h). Food and water were available *ad libitum* throughout the experiment.

The age for adolescent mice was chosen based on a review by Laviola et al. (2003), which reported three age-intervals for adolescence in rodents. Since the adolescent period is quite short in rodents, we chose to start behavioral testing during what is considered to be the middle-adolescence/periadolescent period (post-natal day—PND—34 to 46). Adolescent mice were tested at 45–51 days of age and adult mice were tested at 90–96 days of age.

The experimental protocol was approved by the Committee for the Use of Animal Subjects from our Institution (Universidade Federal de São Paulo—UNIFESP). The animals used in this study were maintained in accordance with the guidelines of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). All efforts were taken to minimize pain and discomfort of the animals throughout the course of the study.

2.2. Drugs

D-Amphetamine (SIGMA®) was diluted in saline. A saline injection was used as the control solution. The solutions were delivered intraperitoneally (ip) at a volume of 10 ml/kg body weight.

2.3. Behavioral testing

Activity was recorded in ten identical activity monitoring chambers consisting of transparent Plexiglas boxes (45 × 45 × 34.5 cm high) equipped with 16 infrared light emitters and detectors placed 4 cm above the floor (Insight Instruments, Brazil). These were connected to a microcomputer that counted the number of times the photo beams were broken. The total number of horizontal beam breaks was used as a measure of locomotion. Animals were placed in the activity chambers immediately after being injected with saline or amphetamine and their locomotion was monitored for 45 min. Animals of both ages were alternated when locomotor activity was recorded. All behavioral testing was done between 13:00 and 17:00.

2.4. Experimental procedure

Adult (90-day-old) and adolescent (45-day-old) mice received an ip injection of saline (Sal) or amphetamine at doses of 1.0 (Amph1), 2.0 (Amph2) or 4.0 (Amph4) mg/kg. Activity was measured for 45 min post-injection to evaluate the locomotor stimulant effect of amphetamine (session 1). For session 1, animals were divided into eight groups: Adult-Sal (N = 18), Adult-Amph1 (N = 9), Adult-Amph2 (N = 10), Adult-Amph4 (N = 10), Adolescent-Sal (N = 19), Adolescent-Amph1 (N = 10), Adolescent-Amph2 (N = 10) and Adolescent-Amph4 (N = 10).

Seven days after the initial injection, mice received a challenge injection of either saline (-Sal) or 2.0 mg/kg amphetamine (-Amph) to assess behavioral sensitization (session 2). Thus, the following groups were formed in session 2: Adult-Sal-Sal (N = 9), Adult-Sal-Amph (N = 9), Adult-Amph1-Amph (N = 9), Adult-Amph2-Amph (N = 10), Adult-Amph4-Amph (N = 10), Adolescent-Sal-Sal (N = 10), Adolescent-Sal-Amph (N = 9), Adolescent-Amph1-Amph (N = 10), Adolescent-Amph2-Amph (N = 10) and Adolescent-Amph4-Amph (N = 10). After the challenge injection, locomotor activity was monitored for 45 min.

2.5. Statistical analysis

Data from session 1 were analyzed by a 2 × 4 (age × treatment factors) two-way ANOVA and data from session 2 were analyzed by a 2 × 5 (age × treatment-challenge factors) two-way ANOVA. Multiple comparisons were performed using the Duncan's post-hoc test when necessary. Statistical significance was defined as $P<0.05$.

3. Results

Fig. 1 shows the session 1 locomotion frequencies of adult and adolescent mice after acute administration of saline or amphetamine (1.0, 2.0 or 4.0 mg/kg). A two-way ANOVA revealed significant effects of age (adult × adolescent) [$F(1,88)=15.7$, $P<0.05$] and acute treatment (Sal × Amph1 × Amph2 × Amph4) [$F(3,88)=143.8$, $P<0.05$]. There was also a significant interaction between age and acute treatment [$F(3,88)=6.1$, $P<0.05$]. A Duncan's test showed that acute administration of amphetamine produced a significant increase in locomotion in both adult and adolescent mice, however, this effect was only observed at the 2.0 and 4.0 mg/kg doses. The enhancement in locomotion was dose-dependent (Amph4>Amph2) regardless of age. Importantly, adolescent mice had significantly greater locomotor activity than adult mice given 1.0 or 2.0 mg/kg amphetamine.

Fig. 2 shows the locomotion frequencies of adult and adolescent mice after a saline or amphetamine (2.0 mg/kg) challenge injection (session 2) administered 7 days after session 1. A two-way ANOVA

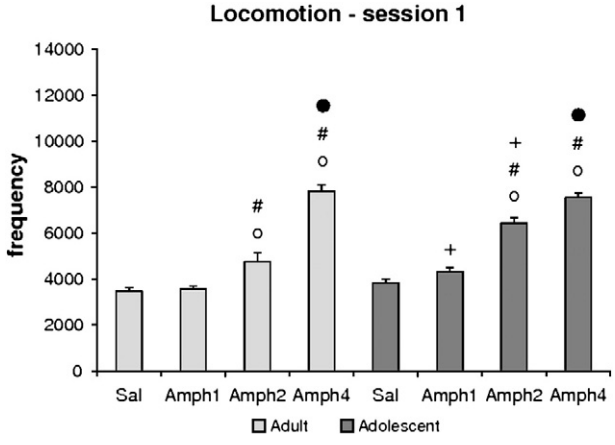

Fig. 1. Mean (±SEM) locomotion frequency (number of horizontal beam breaks/45 min) during pre-treatment with saline or 1.0, 2.0 or 4.0 mg/kg amphetamine in adult and adolescent mice (session 1). Data were analyzed by two-way ANOVA followed by Duncan's test. ○ $p<0.05$ compared to the group of the same age but acutely treated with saline (Sal). # $p<0.05$ compared to the group of the same age but acutely treated with 1.0 mg/kg amphetamine (Amph1). ● $p<0.05$ compared to the group of the same age but acutely treated with 2.0 mg/kg amphetamine (Amph2). + $p<0.05$ compared to adult mice with the same drug treatment.

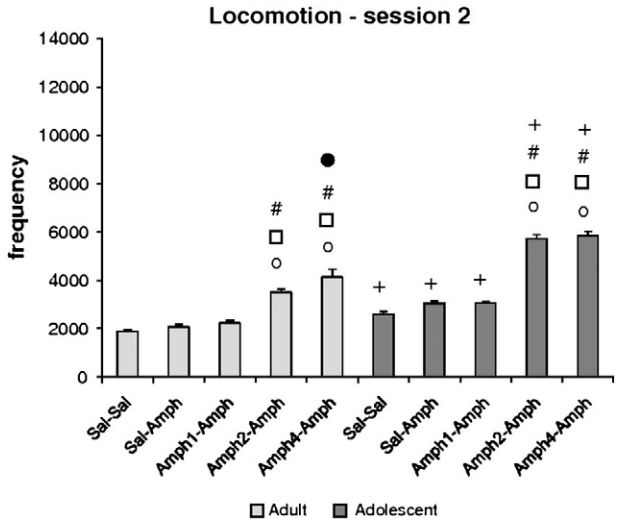

Fig. 2. Mean (±SEM) locomotion frequency (number of horizontal beam breaks/45 min) during amphetamine challenge (session 2) in adult and adolescent mice 7 days after pre-treatment with saline or one of the three different doses of amphetamine. ○ $p<0.05$ compared to the group of the same age but treated and challenged with saline (Sal-Sal). □ $p<0.05$ compared to the group of the same age but treated with saline and challenged with 2.0 mg/kg amphetamine (Sal-Amph). # $p<0.05$ compared to the group of the same age but treated with 1.0 mg/kg amphetamine and challenged with 2.0 mg/kg amphetamine (Amph1-Amph). ● $p<0.05$ compared to the group of the same age but treated and challenged with 2.0 mg/kg amphetamine (Amph2-Amph). + $p<0.05$ compared to adult mice with the same drug treatment and challenge.

revealed significant effects of age (adult × adolescent) [$F(1,86) = 164.1$, $P<0.05$] and treatment-challenge (Sal-Sal × Sal-Amph × Amph1-Amph × Amph2-Amph × Amph4-Amph) [$F(4,86) = 134$, $P<0.05$]. There was also a significant interaction between these two factors [$F(4,86) = 8.7$, $P<0.05$]. Unlike session 1, acute administration of 2.0 mg/kg amphetamine did not affect locomotion of adult or adolescent mice during session 2 (Sal-Sal = Sal-Amph). The Duncan's test showed that, in contrast to session 1, adolescent mice had a significantly higher frequency of spontaneous locomotion than adult controls in session 2 (Adolescent-Sal-Sal > Adult-Sal-Sal). In addition, only mice pre-treated with 2.0 or 4.0 mg/kg amphetamine developed behavioral sensitization regardless of age (Amph2-Amph and Amph4-Amph > Sal-Amph). Although the magnitude of behavioral sensitization did not vary across the amphetamine pre-treatment doses in adolescent mice, adults pre-treated with 4.0 mg/kg amphetamine displayed enhanced behavioral sensitization. Regardless of the amphetamine pre-treatment dose, the magnitude of behavioral sensitization was significantly greater in adolescent than in adult mice.

4. Discussion

The main findings of the present study are: 1) adolescent mice are more sensitive to the locomotor stimulatory effect induced by acute administration of moderate, but not high, doses of amphetamine; 2) both adolescent and adult mice exhibited locomotor sensitization to amphetamine after a single injection, but adolescent mice showed a higher magnitude of sensitization; 3) the acute locomotor stimulatory effect of a moderate (2.0 mg/kg) dose of amphetamine was abolished by previous experience with the test environment in both adolescent and adult mice; and 4) previous experience with the test environment facilitated the detection of increased spontaneous locomotor activity in adolescent mice as compared to adult mice.

Although acute administration of a high dose of amphetamine (4.0 mg/kg) resulted in a similar increase in locomotor activity regardless of age, adolescent mice were more sensitive than adults to the locomotor-stimulating effect of a moderate amphetamine dose (2.0 mg/kg). Additionally, while the 1.0 mg/kg dose of amphetamine did not produce locomotor stimulation in adolescent and adult mice, there was a trend in this direction in adolescent mice. This trend resulted in a significantly higher locomotor activity in amphetamine-treated adolescents when compared to amphetamine-treated adult mice. Thus, there was a leftward shift in the amphetamine dose–response curve in adolescent mice, indicating an increased sensitivity to the locomotor-stimulating effect during this age period.

There is controversy regarding the sensitivity of adolescent and adult rodents to the acute locomotor-stimulating effect of psychostimulants. For example, several investigations indicate that adolescent rodents are less responsive than older counterparts to the acute locomotor-activating effects of amphetamine or cocaine (Bolanos et al., 1998; Lanier and Isaacson, 1977; Laviola et al., 1995, 1999, 2003). In contrast, adolescent rodents have been reported to be more sensitive (Badanich et al., 2008; Maldonado and Kirstein, 2005a,b) or to show the same sensitivity (Camarini et al., 2008; Niculescu et al., 2005) to the acute locomotor-stimulating effect of psychostimulants. These contradictory findings can be explained by differences in behavioral analyses, such as handling (see Maldonado and Kirstein, 2005a,b), duration of the observation session or previous exposure to the test environment (Niculescu et al., 2005). Differences in the experimental design, such as stage of adolescence [i.e., early (PND 24 to 35), middle (PND 37 to 48) or late (PND 50 to 61) adolescence—see Adriani et al., 2002] and species chosen, may also explain the discrepancies found in the literature (Badanich et al., 2008). Differences among laboratory animal housing conditions should also be considered. Indeed, we have previously demonstrated that mice housed in groups of 15 exhibit greater ethanol-induced locomotor sensitization than mice housed in groups of 5 or in isolation (Araujo et al., 2005).

Interestingly, in terms of neurochemical effects, age-related differences in dopaminergic responses to acute amphetamine or cocaine administration have been reported and the literature is also inconsistent. For example, adolescent rodents have been reported to be less (Cao et al., 2007; Laviola et al., 2001) or more (Stansfield and Kirstein, 2006) sensitive to the ability of psychostimulants to elevate extracellular levels of dopamine in the *striatum/nucleus accumbens* as compared to adults. Additionally, Camarini et al. (2008) did not find significant differences in acute cocaine-induced increases in extracellular levels of dopamine in the *nucleus accumbens* of adolescent and adult mice.

In the present study, adolescent mice have higher sensitivity to the locomotor-activating effect of amphetamine. Following the acute administration of a high dose of amphetamine, Adriani and Laviola (2000) also verified a marked locomotor activity in periadolescent rats (PND 33–43) and enhanced stereotyped behaviors in adult counterparts. Increased sensitivity to the locomotor stimulatory effect of amphetamine in adolescent mice is in line with an increased risk of developing drug abuse behaviors and drug-related problems associated with the adolescent period in humans (Chambers et al., 2003; Compas et al., 1995; Spear, 2000; Wahlstrom et al., 2010). The body of evidence points to the importance of activation of the mesoaccumbens dopamine pathway in both drug-induced locomotor stimulation in rodents and reward in both rodents and humans (Di Chiara and Imperato, 1988; Dreher et al., 2009; Koob, 1992; Self and Nestler, 1995; Wheeler and Carelli, 2009). Supporting this notion, our study shows that adolescent mice have a higher magnitude of locomotor sensitization induced by a single injection of amphetamine when compared to adults. As mentioned previously, sensitization to the locomotor stimulatory effect of drugs of abuse in rodents is believed to be a useful model to study the mechanisms underlying drug craving in humans (Robinson and Berridge, 1993). Both behavioral phenomena seem to share plastic mechanisms in the mesolimbic dopamine system (Alcaro et al., 2007; Araujo et al., 2009; Costa et al., 2007; Henry et al., 1989; Nestler, 2004; Volkow et al., 2002; White and Wang, 1984).

Interestingly, as reviewed by Kuhn et al. (2010) (also see the Introduction), behavioral sensitization produced by repeated treatment with psychostimulants is greater in adults than in adolescent rodents. Following a single drug exposure, however, Caster et al. (2007) have observed enhanced locomotor sensitization to cocaine in adolescent rats when compared to adults. Similarly, we demonstrated herein that adolescent mice present increased locomotor sensitization to amphetamine treatment with a single injection protocol. Although the molecular mechanisms underlying sensitization are largely unknown, there is evidence to suggest that sensitization to repeated psychostimulant injections is less reliably dependent on the dopamine D_1 receptor than sensitization to a single injection of these drugs (see Valjent et al., 2010). Within this context, while the phosphoprotein DARPP-32 has been shown to play a role as an amplifier of the dopamine D_1 signaling pathway (Valjent et al., 2010), sensitization to repeated injections of cocaine was increased (Hiroi et al., 1999), whereas sensitization to a single injection of cocaine was reduced in DARPP-32 knockout mutant mice (Valjent et al., 2005). Importantly, the percentage of prefrontal cortex pyramidal cells that project to the *nucleus accumbens* containing dopamine D_1 receptors peaks at levels that are notably higher late in adolescence (>40%) than in younger or older animals (<4–5%) (see Doremus-Fitzwater et al., 2010 for a recent review). These findings are intriguing given the importance of prefrontal cortex projections to the *nucleus accumbens* in drug seeking (Kalivas et al., 2005). Also relevant to this issue is that D_1 receptors have been reported to be present at a higher density in the *striatum* area at PND 40 than at PND 80 in rats (Andersen and Teicher, 2000).

The aforementioned considerations of the molecular mechanisms by which adolescent rodents are more sensitive than adults to psychostimulant-induced locomotor sensitization after a single injection protocol but less sensitive (in the great majority of the studies) after repeated injections are speculative, and further work is clearly required to characterize the substrates involved. It should also be noted that some studies have reported increased locomotor sensitization to psychostimulants in adolescent rodents when compared to adults, even after the classical repeated injection protocol (Adriani et al., 1998; Camarini et al., 2008; Laviola et al., 1995). Importantly, Laviola et al. (1995) have reported that adolescent rats showed greater sensitization to the locomotor-activating effects of repeated administration of cocaine, whereas adults presented a consistent sensitization profile for stereotyped behaviors. This controversy notwithstanding, the findings that adolescent rodents show higher sensitization to the locomotor-activating effect after a single injection of cocaine (Caster et al., 2007) or amphetamine (present study) appear to be in accordance with reports that adolescent humans progress from the first drug exposure to dependence in a much shorter timeframe than adults (Clark et al., 1998). However, one must always be wary of extrapolating clinical relevance from animal data.

Two additional interesting findings involve the influence of previous experience with the test environment on both amphetamine and adolescence effects on mouse locomotor activity. First, in both adult and adolescent mice, the locomotor-activating effect of a moderate dose (2.0 mg/kg) of amphetamine was detected only in the first session, when the test environment was completely novel. These results are consistent with studies using other psychostimulant drugs, such as cocaine (Carey et al., 2005) and apomorphine (Montanaro et al., 1983). Carey et al. (2005) stated that the dose of cocaine required to evoke locomotor stimulation in a novel environment elicits substantially less locomotor stimulation after familiarization with the test environment. Within this context, environmental novelty provokes dopamine release in the *nucleus accumbens* (Rebec et al., 1997) and can potentiate the motivational effects of addictive drugs (Alvarez et al., 2006; Fukushiro et al., 2010; Fukushiro and Frussa-Filho, 2010). Notably, familiarization with the test environment did not decrease the response to a second administration of 2.0 mg/kg amphetamine when mice had been pre-treated with the psychostimulant at the doses of 2.0 and 4.0 mg/kg. Because these priming doses of amphetamine had the ability to promote sensitization (as demonstrated by the significantly higher locomotor activity of the Amph2-Amph and Amph4-Amph groups when compared to the Sal-Amph group in session 2—see Fig. 2) one might suggest that the sensitization phenomenon avoided the expression of the familiarization effects.

On the other hand, by using *t*-tests to analyze the paired samples, we found a significant decrease in the locomotion frequency of the Sal-Sal and Amph2-Amph groups in session 2 as compared to session 1. Thus, another possibility is that familiarization with the test environment attenuated the expression of amphetamine-induced behavioral sensitization in the Amph2-Amph groups. We should also highlight the importance of environmental context in the development of behavioral sensitization. In this regard, Laviola et al. (1995) have demonstrated that behavioral sensitization to cocaine developed only when the drug was administered in the test environment; in addition, they have shown that the development of this sensitization was a function of age-specific alterations in sensitivity of rats to psychostimulants. In the present study, the adult and adolescent mice received amphetamine injections always paired with the test environment. Therefore, the conditioning effects of the context-dependent amphetamine-induced behavioral sensitization may also account for the present data.

Second, previous experience with the test environment facilitated the detection of an increased spontaneous locomotor activity in adolescents. These results are in accordance with data from Adriani and Laviola (2000) who demonstrated that adolescent mice displayed higher activity levels than adults only near the end of a 120-min session in activity chambers. The authors concluded that adolescent mice exhibit a reduced habituation to the novel environment. This reduced habituation might justify the elevated basal levels of locomotion (i.e., in response to saline) presented by adolescent mice when compared to adults in session 2 of the present study.

The link between mesoaccumbens dopaminergic activity and motivational behavior is robust in both human and animal literature. Locomotor behavior serves as the primary indicator of a dopaminergic-related incentive state in rodents (Robinson and Berridge, 1993; Wahlstrom et al., 2010). Taken as a whole, our data suggest that adolescent mice are more sensitive than adults to both the acute and sensitized motivational behavioral effects induced by the dopaminergic agent amphetamine. Our findings also indicate a complex interaction between the effects of environmental novelty, adolescence and amphetamine.

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