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Cross-sensitization between testosterone and cocaine in adolescent and adult rats

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ABSTRACT

Cocaine and anabolic–androgenic steroids are substances commonly co-abused. The use of anabolic steroids and cocaine has increased among adolescents. However, few studies investigated the consequences of the interaction between anabolic–androgenic steroids in animals' model of adolescence. We examined the effects of acute and repeated testosterone administration on cocaine-induced locomotor activity in adult and adolescent rats. Rats received ten once-daily subcutaneous (s.c.) injections of testosterone (10 mg/kg) or vehicle. Three days after the last testosterone or vehicle injections rats received an intraperitoneal (i.p.) challenge injection of either saline or cocaine (10 mg/kg). A different subset of rats was treated with a single injection of testosterone (10 mg/kg) or vehicle and three days later was challenged with cocaine (10 mg/kg, i.p.) or saline. Immediately after cocaine or saline injections the locomotor activity was recorded during forty minutes. Our results demonstrated that repeated testosterone induced locomotor sensitization to cocaine in adolescent but not adult rats.

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1. Introduction

Anabolic–androgenic steroids (AAS) are a class of hormones that includes testosterone and its several synthetic variants (Kanayama et al., 2009). The abuse of AAS among athletes, bodybuilders, and others with the purpose of enhancing performance and improving their physical appearance has increased substantially over the past three decades (Kanayama et al., 2009). It is relevant to note that AAS use seems to be higher among male adolescents (Kanayama et al., 2009). Moreover, DuRant et al. (1993) reported a significant association between the use of anabolic steroids and the abuse of cocaine during adolescence. However, few studies have investigated the interaction between androgens and psychostimulants in adolescent animals.

In humans AAS can cause a dependence syndrome that shares many features with the classical dependence to psychoactive substances, such as cocaine and opioids (Kanayama et al., 2009). Pre-clinical evidences also indicate the dependence potential of AAS. For instance, it has been demonstrated that AAS induces conditioned place preference (Alexander et al., 1994) and self-administration (Wood et al., 2004).

There are evidences that nuclear and membrane steroid receptors are present in areas of the mesocorticolimbic system such as the ventral tegmental area (VTA) and the nucleus accumbens (NAc) (Wood and Newman, 1995). Moreover, it has been shown that dopaminergic activity is enhanced by testosterone administration (de Souza Silva et al., 2009). The dopamine system has a key role in mediating several effects related to cocaine abuse (Di Chiara and Imperato, 1988). In addition, enduring neuroplaticities in this system have been associated with cocaine addiction (Thomas et al., 2008).

It has been found that androgens can modulate behavioral effects of psychostimulants, however the results are controversial. Overall, different effects of acute AAS pretreatment on cocaine-induced locomotor responses were observed. While some studies showed that acute pretreatment with AAS increased cocaine-induced locomotor response (Martinez-Sanchis et al., 2002) others found a decrease in this response (Beatty et al., 1982; Long et al., 1994).

Although the effects of acute testosterone administration on cocaine-induced locomotor activity have already been examined, the consequences of repeated testosterone on cocaine-induced behavioral changes have received little attention. Nevertheless, Kailanto et al. (2011) showed that subchronic treatment with nan-

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drolone attenuated stereotyped behavior and locomotor activity evoked by cocaine in adult rats.

Repeated administration of cocaine or other drugs of abuse can induce a progressive and enduring enhancement of the motor stimulant effect of these drugs, termed behavioral sensitization. This phenomenon has been implicated in the development of psychostimulant-induced craving and psychosis (Robinson and Becker, 1986; Robinson and Berridge, 1993). In adult rats, the enhanced motor stimulant effect of cocaine can persist for several weeks as a result of neuroadaptations in the mesocorticolimbic dopamine pathway engendered by intermittent drug administration (Vanderschuren and Kalivas, 2000; Hope et al., 2006). Moreover, it has been shown that repeated treatment with an addictive drug produces sensitization to that drug and cross-sensitization to other drugs of abuse (Akimoto et al., 1990; Cunningham and Kelley, 1992; Dafny and Yang, 2006). Although behavioral sensitization is mostly investigated following repeated drug administration it has been shown that even a single administration of some drugs of abuse is sufficient to induce long-lasting behavioral sensitization (Vanderschuren and Kalivas, 2000; Vanderschuren et al., 2001; Jing et al., 2014).

In the present study, we evaluated whether acute or repeated exposure to testosterone sensitizes cocaine-induced locomotion in adolescent and adult rats. To this end, adult or adolescent rats were acutely or repeatedly pretreated with testosterone for 10 days and tested for cocaine effects on locomotor activity three days after the cessation of the pretreatment. The time interval used to examine the sensitizing effects of testosterone was based on previous studies showing that an incubation period is necessary from the development to the full expression of sensitization (Vanderschuren and Kalivas, 2000; Vanderschuren et al., 2001; Jing et al., 2014).

2. Materials and methods

2.1. Subjects

Subjects were male Wistar rats on postnatal day (PND) 21 or 45, obtained from the animal breeding facility of the São Paulo State University—UNESP. Groups of 4–5 animals were housed in plastic cages 32 (width) × 40 (length) × 16 (height) cm in a room maintained at 23 ± 2 °C. Rats were kept in a 12:12 hour light/dark cycle (lights on at 07:00 a.m.) and allowed free access to food and water. Each animal was used only in one experimental procedure. All experiments were performed during the light phase. Each experimental group consisted of 6–9 animals. In rats, the period of adolescence occurs approximately from postnatal day (PND) 21–42 (Spear and Brake, 1983).

The experimental protocol was approved by the Ethics Committee for Use of Animal Subjects of the School of Pharmaceutical Science—UNESP (CEP-15/2010).

2.2. Drug

1. Testosterone (Pharma Nostra) (10 mg/kg).
2. Cocaine (Merk) (10 mg/kg).

Testosterone was dissolved in almond oil (vehicle) and cocaine in 0.9% sterile saline. The dose of cocaine used in these experiments is known to induce locomotor activity in the absence of focused stereotypy (Marin et al., 2008; Ushijima et al., 1995). The dose of testosterone was previously shown to change cocaine-induced locomotor activity and is consistent with the abuse dosage used for humans (Martinez-Sanchis et al., 2002; Minerly et al., 2010).

2.3. Behavior apparatus

Behavioral testing was conducted in commercially available (Columbus Instruments, CA) activity monitoring chambers, consisting of Plexiglas cages. The chambers, measuring 45.1 (width) × 44.1 (length) × 8 (height) cm, have included 10 pairs of infrared photocells, which were used to measure the horizontal locomotor activity. The consecutive interruption of two beams was recorded as one unit of locomotion count.

2.4. Effects of acute testosterone administration on cocaine-induced locomotor activity in adolescent and adult rats

Adolescent (PND 37, $N = 30$) and adult (PND 61, $N = 25$) rats were weighed and given a subcutaneous injection of testosterone (10 mg/kg) or vehicle. Immediately after the injections, the animals returned to their home cages. Seventy-two hours after the acute testosterone (TEST) or vehicle (VEH) injections, animals were given an intraperitoneal challenge injection of saline (1 mL/Kg) (SAL) [(VEH-SAL, adolescent $N = 8$; adult $N = 6$) and TEST-SAL, adolescent $N = 8$; adult $N = 6$)] or cocaine (10 mg/kg) (COC) [(VEH-COC, adolescent $N = 7$; adult $N = 6$) and TEST-COC, adolescent $N = 7$; adult $N = 7$)]. Immediately following the challenge injections, locomotion counts accumulated in 5-min intervals were recorded during a 40-min session. The animals were allowed a 20-min adaptation period to the photocell apparatus immediately prior the challenge injections. On the test day adolescent and adult rats were on PND 40 and 64, respectively.

2.5. Effects of repeated testosterone administration on cocaine-induced locomotor activity in adolescent and adult rats

The procedure started on adolescence (PND 28, $N = 36$) or adulthood (PND 52, $N = 28$) and the whole protocol took 13 days. From day 1 to 10, rats were weighed and given a subcutaneous injection of testosterone (10 mg/kg) or vehicle (1 mL/Kg), once a day. Immediately after the injections, the animals were returned to their home cages. On days 11 and 12 animals did not receive any treatment. On day 13 (test day) the animals from testosterone (TEST) or vehicle (VEH) pretreated groups were given intraperitoneal challenge injections of saline (1 mL/Kg) (SAL) [(VEH-SAL, adolescent $N = 9$; adult $N = 7$) and (TEST-SAL, adolescent $N = 9$; adult $N = 7$)] or cocaine (10 mg/kg) (COC) [(VEH-COC, adolescent $N = 9$; adult $N = 7$) and (TEST-COC, adolescent $N = 9$; adult $N = 7$)]. Locomotor activity was recorded as described above (item 2.4.). At the test day adolescent and adult rats were, respectively, on PND 40 and PND 64.

2.4. Statistical analyses

Locomotor activity was analyzed using a two-way ANOVA for repeated measures, considering group (VEH-SAL, VEH-COC, TEST-SAL, TEST-COC) and time factors (from 5 to 40 min). When a significant main effect was observed for ANOVA Bonferoni's test was employed for post-hoc comparisons. Significant differences are reported for $p < 0.05$.

3. Results

3.1. Effects of acute testosterone administration on cocaine-induced locomotor activity in adolescent and adult rats

The locomotor response to cocaine in adolescent and adult rats pretreated with a single injection of testosterone 3 days before the test is shown in Fig. 1.

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