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Temporal and dose-dependent differences in simultaneously-induced cocaine hypervigilance and conditioned-place-preference in marmoset monkeys

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ABSTRACT

Background: Although repeated exposure to cocaine can induce hypervigilance and conditioned-place-preference (CPP) in nonhuman primates (NHPs), more detailed analyses are warranted since the outcome can be influenced by different factors.
Methods: We evaluated in marmoset monkeys (*Callithrix penicillata*): (1) the onset time-course and dose-dependent (3 or 7 mg/kg; i.p.) profile of their hypervigilance and CPP response to repeated cocaine exposure; (2) whether these behavioral measures are still detectable after a 15-day no-drug period; (3) the relationship between their hypervigilance and CPP responses; and (4) if these behavioral changes correlate with pre- and post-drug behaviors (i.e., vigilance, locomotion, exploration), and/or first response to cocaine.
Results: Hypervigilance had a slow-onset, was only effective with the 7 mg/kg dose of cocaine, lacked long-term conditioned effects and was not related to the initial cocaine response or pre-drug behaviors, regardless of the dose tested. CPP was promptly induced with the 3 and 7 mg/kg doses, and had a dose-dependent long-term effect and negative correlation with pre-drug locomotion and exploration. Hypervigilance and CPP were not significantly correlated.
Conclusions: Although hypervigilance and CPP were induced, they had distinct temporal and dose-dependent profiles, and were not equally co-expressed in the same marmoset. Also, in NHPs, pre-drug locomotion and exploration were predictive of the low-dose CPP response.

1. Introduction

In nonhuman primates (NHPs), several behavioral, hormonal and neurochemical changes, similar to those observed in humans, occur following repeated exposure to psychostimulants such as cocaine (reviewed in Bradberry, 2007; Mello and Mendelson, 2002). Among their most prominent and consistent behaviors are stereotyped psychotomimetic or hallucinatory-like responses, particularly those related to vigilance (Bradberry, 2007). This response becomes progressively enhanced in different NHP species after both repeated escalating or same-dose regimes (Cagni et al., 2012, 2014; Castner and Goldman-Rakic, 1999, 2003; Castner et al., 2000; Farfel et al., 1992; Kleven and Woolverton, 1990; Melamed et al., 2013; Post et al., 1976; Ridley et al., 1982; Saka et al., 2004), and may persist for weeks or even months after administrations are discontinued (Castner and Goldman-Rakic, 1999). In terms of cocaine, NHPs will also exhibit hypervigilance when subsequently challenged with this drug some time later, independently from the enhanced locomotion typically seen in rodents (Melamed et al., 2013), with both profiles corresponding to a behavioral sensitization (Vezina and Leyton, 2009). As a result, functional neuroadaptations take place within the brain's reward-circuit, which in NHPs may involve the co-participation of several neurochemical mechanisms besides the putative enhancement of the dopamine system (Bradberry, 2007; Melamed et al., 2013).

Repeated exposure to drugs of abuse, including cocaine, may also lead to environmentally-triggered conditioned responses, such as a conditioned-place-preference (CPP). This effect is based on an associatively-learned preference for certain locations that is acquired in response to having previously experienced a rewarding agent at that same place. In fact, it has become an increasingly prevalent procedure to evaluate aspects of addiction-like behaviors

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(Tzschentke, 2007). Although commonly reported in rodents, the CPP paradigm has only recently been demonstrated in NHPs using both drug- (Barros et al., 2013; Foltin and Evans, 2001; Wang et al., 2012) and food-related stimuli (Duarte et al., 2014; Foltin and Evans, 2002; Monclaro et al., 2014; Valentinuzzi et al., 2008). As the outcome in rodents can be significantly influenced by several factors, including drug dose, injection-conditioning interval, duration of the conditionings and number of drug-pairings (reviewed in Tzschentke, 2007), a more detailed evaluation in NHPs is warranted. Also, long-lasting cocaine CPP effects have yet to be determined in NHPs.

Cocaine-induced CPP and enhanced behavioral responding may actually interact at different levels. Both are mediated by overlapping neurosignaling pathways (Tzschentke, 2007; Steketee and Kalivas, 2011). Furthermore, the CPP response can be potentiated in previously sensitized individuals (Shippenberg and Heidbreder, 1995), while the expression of sensitized behaviors may be controlled by conditioned environmental stimuli (Mattson et al., 2008). However, the two aspects are rarely evaluated simultaneously in the same individual, with reports only for rodents (Orsini et al., 2005; Seymour and Wagner, 2008; Shimosato and Ohkuda, 2000). Their CPP behavior and locomotor sensitization were not co-expressed to the same extent in the same animal (Brabant et al., 2005; Orsini et al., 2005; Seymour and Wagner, 2008). Therefore, such an approach could help establish whether these two key behavioral measures interact positively or compete with each other at the individual level.

Here we evaluated in marmoset monkeys: (1) the onset time-course and dose-dependent (3 mg/kg or 7 mg/kg) profile of their hypervigilance and CPP response to repeated cocaine exposure; (2) whether these behavioral measures are still detectable after a 15-day no-drug period; (3) the relationship between their hypervigilance and CPP responses; and (4) if these behavioral changes correlate with pre- and post-drug behavioral repertoires (i.e., vigilance, locomotion, exploration), and/or first response to cocaine exposure.

2. Methods

2.1. Subjects and housing conditions

Ten adult male captive black tufted-ear marmosets (*Callithrix penicillata*) were used, weighing 360 ± 15 g (range: 305–465 g) at the beginning of the study. They were pair-housed in different home-cages (2 × 1 × 2 m each) of a same colony room at the Primate Center of the University of Brasilia. This room consisted of a semi-outdoor/indoor housing system with two parallel rows of 12 cages each, separated by a common wire-mesh enclosed central corridor. The animals were thus exposed to natural light, temperature and humidity conditions. Fresh food was provided daily at 07:00 h, consisting of a mixture of pieces of fruits and vegetables, and unconsumed items were removed 17:00 h. Boiled eggs, nuts and/or cooked chicken breast were given several times a week, also at 07:00 h. Water and chow were available ad libitum. Housing conditions complied with the regulations of the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA).

2.2. Apparatus and experimental set-up

Testing was conducted in a two-compartment CPP box, suspended 1 m from the floor. Each compartment (60 × 60 × 35 cm) had three walls and floor made of aluminum, whereas the fourth wall and the top were made of glass. However, each compartment had different visual and tactile cues: one was white with a smooth surface, whereas the other had black and white diagonal stripes with a rough surface. The aluminum wall common to both compartments consisted of a horizontally-sliding door. If retracted, it gave subjects direct access to both sides of the apparatus. Each compartment, however, had an independent entry/exit point consisting of a horizontally-sliding door located on the aluminum wall directly opposite the glass wall. Attached to the apparatus, and encompassing both access doors, was a common aluminum antechamber (15 × 10 × 35 cm). Subjects could only access the compartments' sliding doors and enter the respective compartment via this common antechamber, which in turn had a guillotine-type door as its access point.

The CPP box was set-up in a test-room 50 m away from the colony room. Subjects were transported to and from the test-room in an aluminum transportation box (35 × 20 × 23 cm) that attached directly to the antechamber's guillotine-type door. The CPP box was monitored remotely using two digital cameras (Fire-i, Unibrain, USA): one placed 1.5 m above the apparatus (top-view) and the other 1.5 m in front of its glass wall (side-view). The cameras were connected directly to a laptop, on which all tracking and behavioral recordings took place. The laptop was set-up in an observation-room adjacent to the test-room.

2.3. Drugs

Cocaine hydrochloride (3 and 7 mg/kg; Sigma-Aldrich, USA) was dissolved in phosphate buffered saline and injected intraperitoneally, in a volume of 1.0 mL/kg, 5-min prior to the behavioral testing. Saline was used as vehicle control on alternating days with cocaine injections (see Section 2.4). The doses used were based on previous reports in the same species (Barros et al., 2013; Cagni et al., 2012; Melamed et al., 2013). As subjects had been previously submitted to routine prophylactic clinical treatment injections for at least a 1-year period prior to the present study, a specific habituation protocol to the injection procedure was not currently adopted.

2.4. Procedure

Each marmoset was initially submitted to two 20-min habituation trials in the CPP box, held on consecutive days (days 1–2; H1–H2; Fig. 1). On these trials, the common sliding-wall was kept partially retracted giving marmosets a direct 20-cm passage between the two compartments. As a general innate preference for either context was not observed, an unbiased apparatus design was used. Marmosets were then randomly assigned to one of two groups: one received 3 mg/kg of cocaine ($n = 5$) and the other received the 7 mg/kg dose ($n = 5$). On days 3–8 and 10–15 (Fig. 1), they all underwent daily conditioning training in one of the compartments, with the common sliding-wall of the CPP box remaining shut at all times. On alternate days, subjects were given a cocaine (3 or 7 mg/kg) or saline injection and after 5-min they were confined for 20-min in their designated cocaine- or saline-paired compartment, respectively (i.e., days 3, 5, 7 and 10, 12, 14 with cocaine (C1–C6); and days 4, 6, 8 and 11, 13, 15 with saline (S1–S6)). Half of the subjects were arbitrarily cocaine-conditioned in the white context and saline-conditioned in the striped compartment, whereas the opposite was used for the other half. On days 9 and 16 all marmosets were tested for a CPP response (T1 and T2, respectively), as well as 15 days after the last conditioning on day 30 (T3; Fig. 1). During this 15-day period subjects were left undisturbed in their home-cages. On the three test days, they were re-exposed to the entire CPP box (i.e., sliding-wall was again retracted 20-cm), for 20-min and without any prior cocaine/saline injections.

On all trials, subjects were captured in their home-cages, given their pre-established cocaine/saline injection, placed in the transportation-box and taken to the test-room where they were released into the CPP box's antechamber. On habituation and test