Pharmacology, Biochemistry and Behavior 104 (2013) 169–176

Contents lists available at SciVerse ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Enhanced nicotine-seeking behavior following pre-exposure to repeated cocaine is accompanied by changes in BDNF in the nucleus accumbens of rats ☆

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ARTICLE INFO

Article history:
Received 13 August 2012
Received in revised form 26 December 2012
Accepted 10 January 2013
Available online 17 January 2013

Keywords:
BDNF
Cocaine
Gene expression
Locomotor activity
Nicotine
RT-PCR
Self-administration

ABSTRACT

We investigated the behavioral and molecular interactions between cocaine and nicotine, through evaluating locomotor activity, nicotine intravenous self-administration and gene expression. Locomotor sensitization was induced in male Wistar rats by repeated cocaine (20 mg/kg; i.p.) or saline injections once a day over 7 days. Three days after the last injection, rats were challenged with either saline or cocaine (15 mg/kg; i.p.) and the locomotor activity was measured. The very next day animals received either saline or nicotine (0.4 mg/kg; s.c.) and the locomotor cross-sensitization was tested. Animals were then prepared with intrajugular catheters for nicotine self-administration. Nicotine self-administration patterns were evaluated using fixed or progressive ratio schedules of reinforcement and a 24-h unlimited access binge. Immediately after the binge sessions animals were decapitated, the brains were removed and the nucleus accumbens was dissected. The dynorphin (DYN), μ-opioid receptor (mu opioid), neuropeptide Y (NPY), brain-derived neurotrophic factor (BDNF), tropomyosin-related tyrosine kinase B receptor (TrkB) and corticotropin-releasing factor receptor type 1 (CRF-R1) gene expression were measured by the reverse transcription-polymerase chain reaction (RT-PCR). Pretreatment with cocaine caused sensitization of cocaine motor response and locomotor cross-sensitization with nicotine. In the self-administration experiments repeated cocaine administration caused an increase in the nicotine break point and nicotine intake during a 24 h binge session.

1. Introduction

An important issue in the field of drug abuse research is the characterization of risk factors related to increased vulnerability to drug addiction (Anthony and Petronis, 1995). There is growing clinical evidence suggesting that previous exposure to cocaine increase the vulnerability to nicotine addiction. Controlled human studies have demonstrated that acute cocaine administration increases cigarette smoking (Roll et al., 1996). Moreover, cocaine-dependent smokers often report smoking more cigarettes during cocaine use (Budney et al., 1993; Higgins et al., 1994; Torchalla et al., 2011).

Pre-clinical studies also provide evidences for cocaine-induced increase in the vulnerability to nicotine abuse and addiction. For example, in rhesus monkeys, higher rates of combined nicotine and cocaine self-administration were observed, relative to isolated cocaine or nicotine self-administration (Freeman and Woolverton, 2009; Mello and Newman, 2011).

In rats, several studies have demonstrated the effects of nicotine exposure on cocaine self-administration (Horger et al., 1992; Anker and Carroll, 2011). For example, it has been reported that nicotine exposure increases the acquisition rates of cocaine self-administration (Horger et al., 1992) and its break point under a progressive-ratio (PR) schedule of reinforcement (Anker and Carroll, 2011). While, several studies have demonstrated the influence of nicotine exposure on cocaine self-administration, the effect of previous exposure to cocaine on nicotine self-administration has been poorly investigated.

Repeated nicotine administration may also lead to a sensitized locomotor response following psychostimulant challenge (Santos et al., 2009). This phenomenon is termed behavioral cross-sensitization. Behavioral sensitization is suggested to reflect neuroadaptive processes

☆ **Support**: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP — 2011/07469-9).

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http://dx.doi.org/10.1016/j.pbb.2013.01.007

associated to drug addiction (Robinson and Berridge, 1993). Recently, it was demonstrated that nicotine priming enhances cocaine-induced behavioral sensitization. However the effect of previous cocaine treatment on nicotine-induced locomotor sensitization has not demonstrated yet.

Many studies indicate that neuroadaptations of the mesocorticolimbic dopamine system are related to drug abuse and addiction (Wise, 2009; Pierce and Kumaresan, 2006; Nestler, 2001; Kalivas, 2007). In this way, it has been demonstrated that repeated cocaine or nicotine exposure produces many long-lasting alterations in the mesocorticolimbic system that contribute to addiction-like behaviors (Cao et al., 2011; Koya et al., 2009; Guez-Barber et al., 2011).

It has been proposed that cocaine and nicotine produce persistent alterations in the mesolimbic system due to changes in gene expression (Russo et al, 2010; Dreyer, 2010). Studies suggest that administration simultaneous of equipotent doses of nicotine and cocaine, produce additive effects on nucleus accumbens dopamine release (Sziraki et al., 1999; Gerasimov et al., 2000). However, change in gene expression, associated with the effect of cocaine on increased vulnerability to nicotine addiction is still poorly understood.

Cocaine and nicotine modulate the release of neurotransmitters, which activate their different receptors, leading to the activation of transcription factors. Transcriptional activation in the mesocorticolimbic system has been associated to neural plasticity related to the development of drug addiction (Chandrasekar and Dreyer, 2009).

Indeed, repeated cocaine or nicotine administration may change the expression of neurotransmitters (e.g. dynorphine (DYN), neuropeptide Y (NPY)), receptors (e.g. μ-opioid receptor, tropomyosin-related tyrosine kinase B receptor (TrkB) and corticotropin-releasing factor receptor type 1 (CRF-R1)), and transcription factors (e.g. brain-derived neurotrophic factor (BDNF)) (Ang et al., 2001; Ghitza et al., 2010; Hope et al., 1994; Houdi et al., 1998; Kivinummi et al., 2011; Nestler, 2005a, 2005b, 2008; Shippenberg and Rea, 1997). These changes may increase drug-seeking behavior.

Thus, the goal of the present study was to investigate the behavioral and molecular changes that result from the interactions between cocaine and nicotine. To this end we evaluated whether the pretreatment with cocaine could modify cocaine- or nicotine-induced locomotor activity, nicotine intravenous self-administration, and the expression of DYN, mu opioid, NPY, BDNF, TrkB and CRF-R1 genes.

2. Materials and methods

2.1. Subjects

Male Wistar rats, 225–250 g at arrival, obtained from the animal breeding facility of the Univ. Estadual Paulista — UNESP were individually housed in plastic cages 19 cm (width) × 30 cm (length) × 14 cm (height).

Rats were continuously maintained on a reversed light cycle (12-h:12-h, lights off at 08:00 a.m.) with controlled temperature (21 °C) and humidity (35–40%), with unrestricted access to food and water. During the experiment, rats received 18 g rat chow per day provided in their home cage after each daily experimental session. This feeding schedule results in the gradual weight gain of approximately 15 g/week (Donny et al., 1995). Unlimited access to water was available throughout all experiments. All experiments were performed during the dark phase.

The experimental protocol was approved by the Ethics Committee for Use of Human or Animal Subjects of the School of Pharmaceutical Science — UNESP (CEP-19/2008).

2.2. Locomotor response to cocaine and nicotine

2.2.1. Apparatus

Locomotor activity measures were conducted in commercially available (Columbus Instruments, Columbus, OH, USA) activity monitoring chambers, consisting of Plexiglas cages. The chambers, measuring 44 cm (width) × 44 cm (length) × 20 cm (height) cm included 10 pairs of photocells beams, which were used to measure the horizontal locomotor activity. The consecutive interruption of two beams was recorded as one locomotor count.

2.2.2. Locomotor measurement

Rats were pretreated with cocaine (20 mg/kg; i.p.) or saline for 7 days (Marin et al., 2008). Three days after the last cocaine (COC) or saline (SAL) administration, rats were challenged with saline (COC–SAL n = 10; SAL–SAL n = 10) or cocaine (15 mg/kg; i.p.) (COC–COC n = 10; SAL–COC n = 10). Immediately following the injections, animals were put in an activity chamber and their locomotor activity was recorded during a 30-minute testing session as described above. In the very next day the same animals received saline (COC–SAL n = 10; SAL–SAL n = 10) or nicotine (NIC) (0.4 mg/kg; s.c.) (COC–NIC n = 10; SAL–NIC n = 10). Immediately following the injections, animals were put in an activity chamber and their locomotor activity was recorded during a 15-minute testing session as described above. In both tests, animals were allowed a 20-minute habituation period to the photocell apparatus immediately prior to injections. Animals from different groups were tested randomly during the dark phase between 10:00 a.m. and 14:00 p.m.

2.3. Intravenous drug self-administration

Seven days after the locomotor test, animals were subjected to intravenous nicotine self-administration procedures. The general procedure was adapted from George et al. (2007).

2.3.1. Apparatus

For nicotine self-administration the animals were put individually in Plexiglas experimental chambers (30 × 30.5 × 24.5 cm), enclosed in light- and sound attenuating boxes. The floor of the chambers consisted of a Plexiglas tray covered with sawdust. A hole in the ceiling allowed the passage and free movement of the tethered catheter (Strategic Applications Inc., Libertyville, IL, USA) that was connected to a counterbalanced swivel and an infusion pump (Insight Equipments®, Ribeirão Preto, SP, Brazil). The front wall of the chamber contained one interchangeable panel. The panel was equipped with two levers, located 5 cm from the floor, two cue lights (red and green) above each lever and a session light in the middle of the panel (12 cm from the floor).

2.3.2. Drug

(−) — Nicotine 99% was obtained from Sigma-Aldrich (St Louis, MO, USA). The dose of nicotine was chosen based on previous experiments conducted in our laboratory (Leão et al., 2012).

2.3.3. Training

Training consisted of three 60-minute training sessions, in which each response on the active lever (alternated between left and right sides) was reinforced with the delivery of 0.2 ml sucrose (6%) (fixed ratio schedule of reinforcement; FR 1), followed by a 10-second time-out. Each rat was allowed continuous access to sucrose solution during the entire 60-minute. Responding on the inactive lever had no scheduled consequence.

2.3.4. Surgery

Twenty-four hours after the last training session, cocaine and saline pretreated rats were implanted with permanently indwelling catheters (Silastic™ silicon tubing, inner diameter = 0.63 mm, outer diameter = 1.17 mm) into the right jugular vein under a combination of ketamine (100.0 mg/kg) and xylazine (6.0 mg/kg) anesthesia. The catheter was passed subcutaneously to the rat's back where it exited through a small incision and was affixed to a plastic pedestal