Behavioural Brain Research 262 (2014) 42–46

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Short Communication

Time-dependent changes in nicotine behavioral responsivity during early withdrawal from chronic cocaine administration and attenuation of cocaine sensitization by mecamylamine

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HIGHLIGHTS

- Changes in nicotinic neurotransmission may play a role in cocaine behavioral sensitization.
- Locomotor stimulation by nicotine increases during early cocaine withdrawal in a time-dependent manner.
- Daily mecamylamine during this period prevents subsequent maintenance of cocaine sensitization.
- Nicotine receptors may be an effective target for treatment of chronic cocaine abuse.

ARTICLE INFO

Article history:
Received 13 August 2013
Received in revised form
24 December 2013
Accepted 26 December 2013
Available online 7 January 2014

Keywords:
Cocaine abuse
Cocaine sensitization
Cocaine withdrawal period
Mecamylamine
Nicotinic antagonist

ABSTRACT

Cocaine abuse is associated with a high prevalence of nicotine dependence. In animals, nicotinic antagonists have been reported to block the development of cocaine behavioral sensitization and to attenuate cocaine place preference or self-administration. In the present study, we have determined: (1) changes in the locomotor responses to nicotine challenge during the first week of withdrawal from daily cocaine pretreatment; and (2) effects of the non-selective nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine given during the first 5 days of cocaine withdrawal on the maintenance of cocaine behavioral sensitization. Male Sprague-Dawley rats were pretreated with daily saline (SI) or cocaine (CI) injections for 14 days. In Experiment 1, separate animals in the SI and CI groups received a single nicotine challenge on day 1, 3, or 7 of withdrawal from their respective pretreatments. The CI group displayed enhanced locomotor responses to nicotine as compared to SI controls on days 3 and 7 of withdrawal, but not day 1. In Experiment 2, SI and CI animals were treated once a day with either saline or mecamylamine during the first 5 days of withdrawal, and were subsequently challenged with single cocaine injections on both withdrawal days 7 and 14. Mecamylamine treatment significantly attenuated expression of cocaine behavioral sensitization on both withdrawal days 7 and 14. Time-dependent changes in nicotinic responses occur during the first week of cocaine withdrawal, and intact nAChR neurotransmission during this period may be necessary for maintenance of cocaine behavioral sensitization.

1. Introduction

Epidemiological studies have consistently reported high rates of comorbidity between cocaine abuse and nicotine dependence [1–3]. Cocaine abusers smoke tobacco more often than non-abusers [4,5] and the magnitude of nicotine dependence predicts time to cocaine relapse among abstinent addicts who smoke [6]. It has been also hypothesized that nicotine replacement therapy in cocaine abusers, who are trying to quit smoking, may be detrimental to the achievement of cocaine abstinence [2]. Given these considerations, a greater understanding of the role of nicotinic acetylcholinergic receptors (nAChRs) in cocaine abuse is warranted.

Mecamylamine (Inversine®) is the first orally available antihypertensive agent and a nAChR antagonist, which has been shown to clinically reduce smoking [7], subjective effects of cocaine and nicotine [8,9], and cue-induced cocaine craving in humans [10]. In animals, mecamylamine can decrease cocaine place preference and disrupt development of cocaine sensitization when given with daily cocaine injections; in contrast, responses to acute cocaine administration in naive animals are not altered [11]. In addition to cocaine place preference and behavioral sensitization,

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http://dx.doi.org/10.1016/j.bbr.2013.12.051

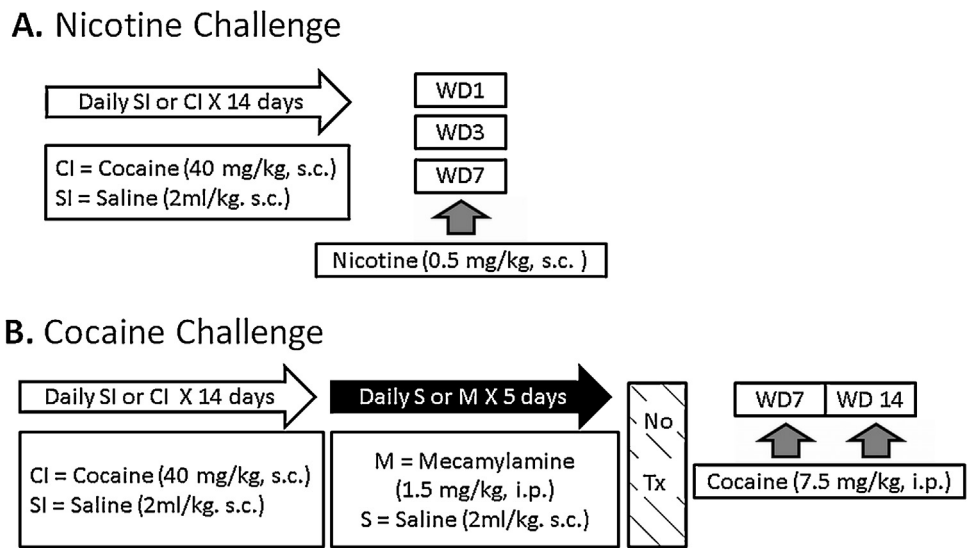

Fig. 1. Schematic representation of experimental designs for Experiment 1 (A) and Experiment 2 (B). For both experiments, animals were injected once a day with cocaine (CI) or saline (SI) for 14 days (open arrow). (A) On day 1 (WD1), day 3 (WD3), and day 7 (WD7) of withdrawal from SI or CI treatment, separate groups of rats were injected with nicotine (gray arrows), and locomotor activity was recorded for 60 min. (B) Animals were treated with daily mecamylamine (M) or saline injection (S) during the first 5 days of cocaine withdrawal (black arrow). These rats were challenged with cocaine (gray arrow) on WD7 and again on WD14. Locomotor activity was counted using an automated monitoring system and behavioral rating scores were simultaneously recorded using the Ellinwood/Balster scale [13]. See Davidson et al. [25] for additional descriptions of cocaine sensitization regimen and behavioral assessment.

mecamylamine treatment has been shown to attenuate cocaine self-administration in rats [12].

The above considerations indicate that nAChR-dependent processes may partly underlie development and maintenance of cocaine sensitization in animals and cocaine abuse in humans. In the present study we sought to assess: (1) changes in behavioral sensitivity to nicotine during the first week of *withdrawal* from chronic intermittent cocaine pretreatment; and (2) effect of mecamylamine on the maintenance of cocaine behavioral sensitization when administered once a day between cocaine withdrawal days (WD) 1 and 5.

2. Methods and materials

2.1. Animals

Male Sprague Dawley rats, initially weighing 175–200 g (Charles River Laboratories, Raleigh, NC), were acclimated to the vivarium on a 12 h light/dark cycle (light 7 AM–7 PM) for 1 week prior to the experiments. Rats were housed in pairs in plastic cages and cared for in accordance with NIH and Duke IACUC guidelines. Food and water were available ad libitum. This study was approved by Duke University Institutional Animal Care and Use Committee.

2.2. Drug treatments and behavioral measurements

All animals were injected once a day for 14 days with either 40 mg/kg, s.c. cocaine (CI) or equivalent volume (2 ml/kg) of saline (SI). In Experiment 1, separate groups of rats were challenged with nicotine (0.5 mg/kg, s.c.) on day 1, 3 or 7 of saline or cocaine withdrawal (WD1, WD3 or WD7) to determine time-dependent alterations in nicotine-induced stimulation of locomotor activity (see Fig. 1 for illustration of procedural time lines and experimental group designations). In Experiment 2, both the SI and CI groups were treated with daily injections of saline or mecamylamine (1.5 mg/kg, i.p.) during the first 5 days of withdrawal. On WD7, all animals were challenged with cocaine (7.5 mg/kg, i.p.), and locomotor activity and behavioral rating scores were determined (Fig. 1). These rats were again challenged with cocaine on WD14 to determine whether or not the earlier mecamylamine treatment had sustained effects on cocaine sensitization.

Locomotor responses to either nicotine or cocaine challenge were measured using an automated activity monitor. Activity counting was accomplished in individual cages (28 cm × 18 cm × 12 cm) placed inside Opto-Varimex photobeam monitors (8 × 8 beams, Columbus Instruments, OH, U.S.A.). Since nicotine-induced locomotor stimulation depends on the animals being well acclimatized, rats were transferred to the testing facility 18 h prior to testing and were left undisturbed until nicotine challenge assessment in their home cages.

Following a 15 min stable baseline activity measurement, animals were injected with nicotine (0.5 mg/kg, s.c.; Experiment 1) or cocaine (7.5 mg/kg, i.p.; Experiment 2) and activity over 60 min were measured. Each animal was challenged with nicotine only once on WD1, WD3 or WD7 (i.e., between-subject design), while animals in Experiment 2 underwent testing on both WD7 and WD14 (i.e., within-subject design). In addition to locomotor responses, behavioral responses to cocaine (Experiment 2) were simultaneously rated by a blind observer using the modified Ellinwood and Balster behavioral rating scale [13] (see Table 1). Exposure to high doses of psychostimulant can lead to restriction of the behavioral repertoire of animals in the open field, such that locomotor activity is replaced by in-place stereotypy [13]. Therefore, the rating scale was used to determine whether a decrease in locomotion counts following a cocaine challenge was not due to emergence of stereotypy (indicating increased cocaine sensitization).

2.3. Data analysis

All experimental data were normally distributed. Data from Experiment 1 were analyzed using between-subject, one-way analysis of variance (ANOVA). Since the three SI groups (SI-WD1, SI-WD3 and SI-WD7) were not statistically different from one another, they were combined into a single SI control group for ANOVA and determination of individual group differences (Dunnett's test with SI as the control). In Experiment 2, where animals were challenged with cocaine on both days 7 and 14, locomotor