Neuroscience Letters 556 (2013) 155–159

Contents lists available at ScienceDirect

Neuroscience Letters

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

Ceftriaxone attenuates locomotor activity induced by acute and repeated cocaine exposure in mice

Christopher S. Tallarida[a,b], Gladys Corley[a,b], Jane Kovalevich[c], William Yen[c], Dianne Langford[c], Scott M. Rawls[a,b,*]

[a] Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA
[b] Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
[c] Department of Neurosciences, Temple University School of Medicine, Philadelphia, PA, USA

HIGHLIGHTS

- β-Lactam antibiotic ceftriaxone attenuates development of cocaine-induced behavioral sensitization.
- β-Lactam antibiotic ceftriaxone counteracts pre-existing cocaine-induced behavioral sensitization.
- β-Lactam antibiotic ceftriaxone attenuates acute locomotor-activating effect of cocaine.
- β-Lactam compounds may be CNS-active therapeutics to treat cocaine abuse.

ARTICLE INFO

Article history:
Received 5 June 2013
Received in revised form
21 September 2013
Accepted 28 September 2013

Keywords:
Ceftriaxone
β-Lactam antibiotic
Cocaine
Glutamate transporter
GLT-1
Sensitization
Psychostimulant

ABSTRACT

Ceftriaxone (CTX) decreases locomotor activation produced by initial cocaine exposure and attenuates development of behavioral sensitization produced by repeated cocaine exposure. An important question that has not yet been answered is whether or not CTX reduces behavioral sensitization to cocaine in cases in which the antibiotic is administered only during the period of cocaine absence that follows repeated cocaine exposure and precedes reintroduction to cocaine. We investigated this question using C57BL/6 mice. Mice pretreated with cocaine (15 mg/kg × 14 days) and then challenged with cocaine (15 mg/kg) after 30 days of cocaine absence displayed sensitization of locomotor activity. For combination experiments, CTX injected during the 30 days of cocaine absence attenuated behavioral sensitization produced by cocaine challenge. In the case in which CTX was injected together with cocaine for 14 days, development of behavioral sensitization to cocaine challenge was also reduced. CTX attenuated the increase in locomotor activity produced by acute cocaine exposure; however, its efficacy was dependent on the dose of cocaine as inhibition was detected against 30 mg/kg, but not 15 mg/kg, of cocaine. These results from mice indicate that CTX attenuates locomotor activity produced by acute and repeated cocaine exposure and counters cocaine's locomotor activating properties in a paradigm in which the antibiotic is injected during the period of forced cocaine absence that follows repeated cocaine exposure.

1. Introduction

The β-lactam antibiotic ceftriaxone (CTX) displays efficacy in animal models of CNS diseases (e.g. amyotrophic lateral sclerosis, Huntington's disease, stroke, epilepsy, depression) through a mechanism involving activation of glutamate transporter subtype 1 (GLT-1) [3,7,21,23,27,32,33,40,43]. Preclinical studies indicate that CTX is also efficacious against adverse effects of drugs of abuse; for example, CTX reduces the reinforcing and drug-seeking properties of cocaine, inhibits the rewarding and locomotor-activating effects of amphetamine, reduces the analgesic tolerance and physical dependence produced by morphine, and attenuates the analgesic tolerance that develops during repeated nicotine exposure [28,34,37,44]. A well-documented neuropharmacological effect of psychostimulants is behavioral sensitization, which is present in cases in which repeated drug exposure produces enhanced locomotor activity compared to that produced by initial exposure [2,4,16,17,20,24,25,31,38,42,46]. In studies involving cocaine, repeated CTX administration attenuates locomotor activation produced by acute cocaine exposure and inhibits development of locomotor sensitization produced by repeated cocaine administration [37]. CTX displays comparable efficacy against amphetamine

* Corresponding author at: Department of Pharmacology, Center for Substance Abuse Research, Temple University School of Medicine, 3500 North Broad Street, Philadelphia, PA 19140, USA. Tel.: +1 215 707 4942; fax: +1 215 707 6661.
E-mail address: scott.rawls@temple.edu (S.M. Rawls).

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http://dx.doi.org/10.1016/j.neulet.2013.09.072

[28]. In both studies, the effects of CTX were tested in two separate experimental paradigms: (1) an acute design in which rats were pretreated with repeated CTX and then injected with a single dose of stimulant and (2) a chronic paradigm in which rats were treated repeatedly with a combination of CTX and stimulant and then challenged with cocaine following an interval of drug absence. Here, using a different species (mice) and modified paradigm, we tested the hypothesis that CTX disrupts sensitization of cocaine-induced locomotor activity in the case in which the antibiotic is administered only during the interval of forced cocaine absence that follows discontinuation of repeated cocaine exposure and precedes reintroduction to cocaine.

2. Materials and methods

The study used 10-week-old male C57BL/6 mice (Charles River Laboratories, Wilmington, MA). Procedures were conducted in accordance with Institutional Animal Care and Use Committee guidelines. Mice were supplied with food and water ad libitum and housed under conditions of constant airflow, controlled temperature (21–23 °C), and a 12-h light/dark cycle. Cocaine hydrochloride was generously provided by the National Institute on Drug Abuse (NIDA), and ceftriaxone sodium (CTX) was purchased from Baxter Healthcare Corporation (Chicago, IL, USA). Drugs were dissolved in saline and injected intraperitoneally (i.p.). Doses of CTX (200 mg/kg) and cocaine (15, 30 mg/kg) were selected on the basis of previous in vivo studies [4,8,28–30,33].

Locomotor activity was detected with the Digiscan Dmicro System as previously described [8,28]. Ambulatory counts were registered when consecutive light beams were interrupted, and stereotypical counts were detected when the same light beam was repeatedly broken. Mice were placed into activity chambers on the morning of behavioral experimentation. Following a 60-min acclimation period, baseline activity was recorded for 30 min followed by cocaine or saline administration and recording of activity for 60 min.

For chronic cocaine (15 mg/kg) experiments, 27 mice were tested in a dosing regimen spanning 45 days (14 days of repeated cocaine exposure, 30 days of no cocaine exposure, and then cocaine challenge). The 30-day absence interval was selected because extended intervals produce robust sensitization accompanied by glutamate dysregulation [1,14,24]. Four treatment groups were used: Group 1 (acute cocaine, or SAL-SAL + COC) – saline + saline for 14 days, saline for 30 days, cocaine challenge; Group 2 (repeated cocaine, or SAL-COC + COC) – saline + cocaine for 14 days, saline for 30 days, cocaine challenge; Group 3 (repeated cocaine and CTX, or CTX-COC + COC) – CTX + cocaine for 14 days, saline for 30 days, cocaine challenge; Group 4 (repeated cocaine then CTX, or COC-CTX + COC) – saline + cocaine for 14 days, CTX for 30 days, cocaine challenge. We used a context-independent design in which injections were conducted in home cages with the exception of challenge day. Locomotor activity was recorded on the day of cocaine challenge. The magnitude and frequency of CTX dosing were based on evidence that its repeated administration (e.g. 7–10 days) at a dose of 200 mg/kg is required for CNS efficacy and glutamate transporter activation [19,21,28,33,37]. Effects of an acute CTX injection were not tested because repeated exposure is required for CNS efficacy [18,28,29,33,34].

Separate experiments controlled for the effects of repeated CTX on locomotor activity produced by acute cocaine exposure. A total of 48 mice were used in a dosing regimen spanning 11 days. Mice were pretreated with CTX or saline for 10 days and injected with cocaine (15 mg/kg) or saline on the following day. Experiments were repeated with a higher dose (30 mg/kg) of cocaine. Locomotor activity was recorded on the day of cocaine administration.

Locomotor results were presented both as a time-course and as cumulative activity over a specific interval. Time-course data were presented in 10-min intervals and analyzed by two-way (treatment × time) ANOVA followed by a Bonferroni's test. Cumulative locomotor data were analyzed by one-way ANOVA followed by a Tukey's test or a Student's *t*-test. $P < 0.05$ was considered statistically significant in all cases.

3. Results

3.1. CTX attenuates sensitization of cocaine-induced locomotor activity

Effects of CTX (200 mg/kg) against sensitization of locomotor activity induced by repeated cocaine (15 mg/kg) exposure is presented in Fig. 1. Two-way ANOVA conducted on the time-course data revealed significant treatment [F (3, 23) = 6.043, $P = 0.0006$] and time [F (6, 161) = 9.049, $P < 0.0001$] effects and identified a significant interaction [F (18, 161) = 2.182, $P < 0.01$]. Post hoc analysis revealed that cocaine challenge produced greater locomotor activity in mice pretreated with cocaine (SAL-COC + COC) than in mice that were previously naïve to cocaine (SAL-SAL + COC) ($P < 0.001$: 10 min post-injection). In mice that were pretreated with cocaine and then injected with CTX only during the absence interval (COC-CTX + COC), cocaine challenge produced less locomotor activity compared to CTX-naïve mice that were pretreated only with cocaine (SAL-COC + COC) ($P < 0.001$: 10 min post-injection). Similarly, cocaine challenge produced less locomotor activity in mice that were pretreated concurrently with cocaine and CTX (CTX-COC + COC) than in mice pretreated with only cocaine (SAL-COC + COC) ($P < 0.001$: 10 min post-injection). For clarity, cumulative locomotor activity counts across the first 20 min following cocaine administration is presented (Fig. 1 box). One-way ANOVA revealed a significant main effect [$F(3, 23) = 4.068$, $P < 0.05$]. Similar to time-course results, cocaine challenge produced greater locomotor activity in mice previously exposed to cocaine [SAL-COC + COC] than in previously cocaine-naïve mice [SAL-SAL + COC], thus indicating sensitization ($P < 0.05$) (Fig. 1, box). Further, in mice previously treated with cocaine, cocaine challenge produced less locomotor activity in those mice that were also exposed to CTX, either concurrently with repeated cocaine treatment [CTX-COC + COC] or following repeated cocaine treatment [COC-CTX + COC], than in previously CTX-naïve mice [SAL-COC + COC] ($P < 0.05$) (Fig. 1, box). For cumulative locomotor counts over the entire 60 min (rather than 20 min) following cocaine challenge, one-way ANOVA did not reveal a significant main effect [F (3, 23) = 1.761, $P > 0.05$] (data not shown).

3.2. CTX attenuates acute locomotor stimulant effect of 30 mg/kg cocaine

Fig. 2 presents the effects of CTX against locomotor activity induced by acute exposure to 15 mg/kg (2A) or 30 mg/kg (2B) of cocaine. For experiments with 15 mg/kg of cocaine, two-way ANOVA conducted on the time-course data revealed significant treatment [$F(3, 28) = 25.72$, $P < 0.0001$] and time [$F(6, 196) = 2.806$, $P < 0.05$] effects and identified a significant interaction [F (18, 196) = 2.861, $P = 0.0002$] (Fig. 2A). Post hoc analysis revealed differences in locomotor activity between the SAL-SAL and SAL-COC groups ($P < 0.001$ at 30, 40, and 50 min post-injection and $P < 0.05$ at 60 min post injection). Significant differences in locomotor activity were not detected between the SAL-COC and CTX-COC groups at any of the time points ($P > 0.05$). However, cocaine's locomotor effect was somewhat stronger in CTX-naïve mice than in CTX-pretreated mice, as significant differences in activity counts