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

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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 $\times$ 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.

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Keywords

ceftriaxone; β -lactam antibiotic; cocaine; glutamate transporter; GLT-1; sensitization; psychostimulant

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 [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.

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-hour 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 $\times$ 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.

Results

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).

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 between the latter group of animals (CTX-COC) and control mice (SAL-SAL) were detected at only two time points ($P < 0.05$ at 40 and 60 min post-injection). For cumulative locomotor activity over the entire 60 min following cocaine injection (Fig. 2A, box), a significant main effect [$F(3, 28) = 4.801$, $P < 0.01$] was detected. Locomotor activity in mice treated with cocaine (SAL-COC) was enhanced compared to cocaine-naïve mice (SAL-SAL) ($P < 0.05$) but was not significantly different from mice treated with CTX and cocaine (CTX-COC) ($P > 0.05$).

CTX effects against locomotor activity produced by 30 mg/kg of cocaine are shown in Fig. 2B. Two-way ANOVA conducted on the temporal data revealed significant treatment [$F(1, 14) = 70.12$, $P < 0.0001$] and time [$F(6, 98) = 2.835$, $P < 0.05$] effects and identified a significant interaction [$F(6, 98) = 2.919$, $P < 0.05$] (Fig. 2B). Post-hoc analysis revealed that 30 mg/kg of cocaine produced significantly less locomotor activity in CTX-treated mice than in CTX-naïve mice ($P < 0.05$ at 10 and 50 min post-injection; $P < 0.001$ at 20 and 30 min post-injection; and $P < 0.01$ at 40 min post-injection). For cumulative locomotor

activity over the entire 60-min period following cocaine injection (Fig. 2B, box), locomotor activity was significantly reduced in the CTX-COC group ($P < 0.01$, Student's t-test).

Discussion

CTX attenuated hypersensitivity to the locomotor-stimulant effects of cocaine in two dosing regimens, one in which it was co-administered with cocaine during development of locomotor sensitization and one in which it was administered only during the period of forced absence following discontinuation of repeated cocaine exposure. The mechanism by which CTX attenuated the locomotor-stimulant effects caused by repeated cocaine exposure is unclear, but a glutamate-based mechanism may have contributed. CTX enhances cellular glutamate uptake through GLT-1 transporter activation [3, 7, 21, 23, 27, 32-33 40, 43]. Furthermore, repeated cocaine administration produces GLT-1 transporter dysfunction in brain reward and motor substrates that contributes to its locomotor-activating properties [18-19, 28, 37, 40]. Extracellular glutamate in the nucleus accumbens, a limbic structure that mediates the locomotor response to cocaine [9, 42], follows a distinctive profile across different stages of cocaine exposure, with glutamate levels declining during cocaine absence and increasing following reintroduction to cocaine [1, 24, 39]. CTX, through activation of GLT-1 transporters, reduces extracellular glutamate levels in the nucleus accumbens of otherwise drug-naïve rats [29]. Taken together, the most parsimonious explanation for CTX efficacy observed here is that increased cellular glutamate uptake capacity following repeated CTX treatment normalizes part of the glutamate dysfunction that facilitates the sensitized locomotor response to cocaine, particularly the elevation in extracellular glutamate that is produced by cocaine challenge.

A caveat associated with this interpretation is that CTX treatment might be predicted to exacerbate the reduction in extracellular glutamate that occurs in the nucleus accumbens of cocaine-withdrawn rats [1], thereby enhancing, rather than suppressing, a triggering mechanism for the expression of behavioral sensitization. However, since CTX does attenuate the behavioral-sensitizing effects of cocaine in our paradigm, and in a different paradigm and species [37], it is more likely that cocaine-withdrawn rats display a near-maximal reduction in basal extracellular glutamate that is not further reduced through GLT-1 transporter activation by CTX. Cross-talk between glutamate uptake and antiport systems may be one reason for this; for example, enhancement of glutamate reuptake by GLT-1 activation is offset to a degree by compensatory upregulation of glutamate efflux into the extrasynaptic space through activation of cystine-glutamate exchange, thereby preventing more extensive reductions in basal glutamate levels of cocaine-withdrawn rats [40]. Analysis of the time course data also reveal that sensitization to cocaine was modest and brief, occurring over the first 10 min following cocaine challenge, and that it was this initial component which was attenuated by prior CTX exposure. Prior work indicates that CTX-induced deficits in extracellular glutamate levels are persistent, lasting for several weeks following discontinuation of exposure, suggesting that non-glutamate mechanisms may have contributed to the effects of CTX observed here.

Consistent with prior work showing that CTX attenuates acute locomotor activation produced by cocaine and amphetamine in rats [28, 37], CTX reduced the acute locomotor-

stimulant effect of cocaine in mice. It is unclear whether the mechanism of action of CTX involves modulation of glutamate or non-glutamatergic systems, or both systems. Hyperlocomotion elicited by acute cocaine exposure is primarily dependent on enhancement of extracellular dopamine and activation of striatal dopamine D₁ receptors [5-6], but the response is also sensitive to changes in glutamate homeostasis. Initial cocaine exposure increases extracellular glutamate in the nucleus accumbens [30, 36] and produces hyperlocomotion that is attenuated to varying degrees by NMDA, AMPA and mGluR5 receptor antagonists [15, 22, 41, 45]. One explanation is that a glutamate uptake block by CTX causes a reduction in extracellular glutamate that leads to downstream inhibition of striatal glutamate and dopamine signaling, such as reduction of glutamate transmission at post-synaptic glutamate receptors and disruption of dopamine D₁ receptor transmission. The possibility that CTX efficacy against acute cocaine is dependent on disruptions in dopamine signaling is supported by evidence that CTX attenuates the acute locomotor-stimulant effects of caffeine [37]. Caffeine and cocaine both require increased dopamine signaling to produce acute hyperlocomotion; however, only cocaine requires increased glutamate signaling for the said effect [10, 12, 26]. It should also be noted that a broad-spectrum glutamate transporter inhibitor (l-trans-pyrrolidine-2,4-dicarboxylic acid) increases extracellular glutamate as well as dopamine levels in the striatum [11], suggesting that glutamate transporters may regulate dopamine release from the striatal dopaminergic nerve terminals. Even a direct inhibition by CTX of calcium-dependent dopamine release cannot be excluded because antibiotics with a central β -lactam core exhibit a strong metal chelating ability [13].

It is interesting to note that in our experiments CTX efficacy against acute locomotor activity was dependent on the dose of cocaine against which it was tested. CTX attenuated locomotor activity produced by acute exposure to a high dose (30 mg/kg) of cocaine but not to a lower dose (15 mg/kg). The locomotor response to 30 mg/kg of cocaine may have involved recruitment and activation of multiple neurotransmitter systems and pathways downstream of an initial enhancement of dopamine signaling. If so, preferential effects of CTX on the higher dose may reflect stronger impacts on non-dopaminergic versus dopaminergic systems. Future work is planned to further investigate CTX effects on dopamine signaling in reward and motor pathways to better delineate the neurochemical mechanisms underlying the behavioral effects of CTX.

In conclusion, the present data provide additional evidence for the significance of a GLT-1 transporter activator in modulating acute and chronic behavioral effects of psychostimulants [19, 35, 37, 44]. The distinguishing feature of our results is that CTX maintains its efficacy when administered only during forced cocaine absence. Taken with contingent self-administration results [18, 34], these data point toward studying pharmacological upregulation of GLT-1 transporters as a strategy for reversing deficits associated with prior cocaine exposure.

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References

1. Baker DA, Xi ZX, Shen H, Swanson CJ, Kalivas PW. The origin and neuronal function of in vivo nonsynaptic glutamate. *J Neurosci*. 2002; 22:9134–9141. [PubMed: 12388621]
2. Bell K, Kalivas PW. Context-specific cross-sensitization between systemic cocaine and intra-accumbens AMPA infusion in the rat. *Psychopharmacology (Berl)*. 1996; 127:377–383. [PubMed: 8923575]
3. Bellesi M, Melone M, Gubbini A, Battistacci S, Conti F. GLT-1 upregulation impairs prepulse inhibition of the startle reflex in adult rats. *Glia*. 2009; 57:703–713. [PubMed: 18985735]
4. Bradberry CW. Cocaine sensitization and dopamine mediation of cue effects in rodents, monkeys, and humans: areas of agreement, disagreement, and implications for addiction. *Psychopharmacology (Berl)*. 2007; 191:705–717. [PubMed: 17031707]
5. Broderick PA. Cocaine: on-line analysis of an accumbens amine neural basis for psychomotor behavior. *Pharmacol Biochem Behav*. 1991; 40:959–968. [PubMed: 1816582]
6. Cabib S, Castellano C, Cestari V, Filibeck U, Puglisi-Allegra S. D1 and D2 receptor antagonists differently affect cocaine-induced locomotor hyperactivity in the mouse. *Psychopharmacology (Berl)*. 1991; 105:335–339. [PubMed: 1839178]
7. Chu K, Lee ST, Sinn DI, Ko SY, Kim EH, Kim JM, Kim SJ, Park DK, Jung KH, Song EC, Lee SK, Kim M, Roh JK. Pharmacological Induction of Ischemic Tolerance by Glutamate Transporter-1 (EAAT2) Upregulation. *Stroke*. 2007; 38:177–182. [PubMed: 17122424]
8. Craig CP, Unterwald EM. Serotonin (2C) receptor regulation of cocaine-induced conditioned place preference and locomotor sensitization. *Behav Brain Res*. 2013; 238:206–210. [PubMed: 23103406]
9. Creese I, Iversen SD. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res*. 1975; 83:419–436. [PubMed: 234270]
10. Dalia A, Uretsky NJ, Wallace LJ. Dopaminergic agonists administered into the nucleus accumbens: effects on extracellular glutamate and on locomotor activity. *Brain Res*. 1998; 788:111–117. [PubMed: 9554973]
11. Del Arco A, Mora F. Effects of endogenous glutamate on extracellular concentrations of GABA, dopamine, and dopamine metabolites in the prefrontal cortex of the freely moving rat: involvement of NMDA and AMPA/KA receptors. *Neurochem Res*. 1999; 24:1027–1035. [PubMed: 10478942]
12. Garrett BE, Holtzman SG. D1 and D2 dopamine receptor antagonists block caffeine-induced stimulation of locomotor activity in rats. *Pharmacol Biochem Behav*. 1994; 47:89–94. [PubMed: 7906891]
13. Ji HF, Shen L, Zhang HY. Beta-lactam antibiotics are multipotent agents to combat neurological diseases. *Biochem Biophys Res Commun*. 2005; 333:661–663. [PubMed: 15907788]
14. Kalivas PW, Duffy P. Time course of extracellular dopamine and behavioral sensitization to cocaine. I. Dopamine axon terminals. *J Neurosci*. 1993; 13:266–275. [PubMed: 8423473]
15. Karler R, Calder LD. Excitatory amino acids and the actions of cocaine. *Brain Res*. 1992; 582:143–146. [PubMed: 1498676]
16. Karler R, Calder LD, Bedingfield JB. Cocaine behavioral sensitization and the excitatory amino acids. *Psychopharmacology (Berl)*. 1994; 115:305–310. [PubMed: 7871069]
17. Karler R, Calder LD, Chaudhry IA, Turkanis SA. Blockade of “reverse tolerance” to cocaine and amphetamine by MK-801. *Life Sci*. 1989; 45:599–606. [PubMed: 2671566]
18. Knackstedt LA, Melendez RI, Kalivas PW. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. *Biol Psychiatry*. 2010; 67:81–84. [PubMed: 19717140]
19. Kovalevich J, Corley G, Yen W, Rawls SM, Langford D. Cocaine-Induced Loss of White Matter Proteins in the Adult Mouse Nucleus Accumbens Is Attenuated by Administration of a β -Lactam Antibiotic during Cocaine Withdrawal. *Am J Pathol*. 2012; 181:1921–1927. [PubMed: 23031254]
20. Li Y, Vartanian AJ, White FJ, Xue CJ, Wolf ME. Effects of the AMPA receptor antagonist NBQX on the development and expression of behavioral sensitization to cocaine and amphetamine. *Psychopharmacology (Berl)*. 1997; 134:266–276. [PubMed: 9438676]
21. Lipski J, Wan CK, Bai JZ, Pi R, Li D, Donnelly D. Neuroprotective potential of ceftriaxone in in vitro models of stroke. *Neuroscience*. 2007; 146:617–629. [PubMed: 17363173]

22. Mcgeehan AJ, Janak PH, Olive MF. Effect of the mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine (MPEP) on the acute locomotor stimulant properties of cocaine, D-amphetamine, and the dopamine reuptake inhibitor GBR12909 in mice. *Psychopharmacology (Berl)*. 2004; 174:266–273. [PubMed: 14726993]
23. Omrani A, Melone M, Bellesi M, Safiulina V, Aida T, Tanaka K, Cherubini E, Conti F. Up-regulation of GLT-1 severely impairs LTD at mossy fibre--CA3 synapses. *J Physiol*. 2009; 587:4575–4588. [PubMed: 19651762]
24. Pierce RC, Bell K, Duffy P, Kalivas PW. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J Neurosci*. 1996; 16:1550–1560. [PubMed: 8778304]
25. Pudiak CM, Bozarth MA. L-NAME and MK-801 attenuate sensitization to the locomotor-stimulating effect of cocaine. *Life Sci*. 1993; 53:1517–1524. [PubMed: 8412518]
26. Pulvirenti L, Swerdlow NR, Koob GF. Microinjection of a glutamate antagonist into the nucleus accumbens reduces psychostimulant locomotion in rats. *Neurosci Lett*. 1989; 103:213–218. [PubMed: 2771183]
27. Ramos KM, Lewis MT, Morgan KN, Crysdale NY, Kroll JL, Taylor FR, Harrison JA, Sloane EM, Maier SF, Watkins LR. Spinal upregulation of glutamate transporter GLT-1 by ceftriaxone: therapeutic efficacy in a range of experimental nervous system disorders. *Neuroscience*. 2010; 169:1888–1900. [PubMed: 20547213]
28. Rasmussen B, Unterwald EM, Rawls SM. Glutamate transporter subtype 1 (GLT-1) activator ceftriaxone attenuates amphetamine-induced hyperactivity and behavioral sensitization in rats. *Drug Alcohol Depend*. 2011; 118:484–488. [PubMed: 21524862]
29. Rasmussen BA, Baron DA, Kim JK, Unterwald EM, Rawls SM. β -Lactam antibiotic produces a sustained reduction in extracellular glutamate in the nucleus accumbens of rats. *Amino Acids*. 2011; 40:761–764. [PubMed: 20383795]
30. Reid MS, Hsu K, Berger SP. Cocaine and amphetamine preferentially stimulate glutamate release in the limbic system: studies on the involvement of dopamine. *Synapse*. 1997; 27:95–105. [PubMed: 9266771]
31. Robinson TE, Berridge KC. Review. The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc Lond B Biol Sci*. 2008; 363:3137–3146. [PubMed: 18640920]
32. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl RW, Kanai Y, Hediger MA, Wang Y, Schielke JP, Welty DF. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron*. 1996; 16:675–686. [PubMed: 8785064]
33. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su ZZ, Gupta P, Fisher PB. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature*. 2005; 433:73–77. [PubMed: 15635412]
34. Sari Y, Smith KD, Ali PK, Rebec GV. Upregulation of GLT1 attenuates cue-induced reinstatement of cocaine-seeking behavior in rats. *J Neurosci*. 2009; 29:9239–9243. [PubMed: 19625514]
35. Schmidt HD, Pierce RC. Cocaine-induced neuroadaptations in glutamate transmission: potential therapeutic targets for craving and addiction. *Ann N Y Acad Sci*. 2010; 1187:35–75. [PubMed: 20201846]
36. Smith JA, Mo Q, Guo H, Kunko PM, Robinson SE. Cocaine increases extraneuronal levels of aspartate and glutamate in the nucleus accumbens. *Brain Res*. 1995; 683:264–269. [PubMed: 7552364]
37. Sondheim I, Knackstedt LA. Ceftriaxone prevents the induction of cocaine sensitization and produces enduring attenuation of cue- and cocaine-primed reinstatement of cocaine-seeking. *Behav Brain Res*. 2011; 225:252–258. [PubMed: 21824497]
38. Steketee JD, Kalivas PW. Drug wanting: behavioral sensitization and relapse to drug-seeking behavior. *Pharmacol Rev*. 2011; 63:348–365. [PubMed: 21490129]
39. Torregrossa MM, Kalivas PW. Microdialysis and the neurochemistry of addiction. *Pharmacol Biochem Behav*. 2008; 90:261–272. [PubMed: 17928041]

40. Trantham-Davidson H, LaLumiere RT, Reissner KJ, Kalivas PW, Knackstedt LA. Ceftriaxone normalizes nucleus accumbens synaptic transmission, glutamate transport, and export following cocaine self-administration and extinction training. *J Neurosci.* 2012; 32:12406–12410. [PubMed: 22956831]
41. Uzbay IT, Wallis CJ, Lal H, Forster MJ. Effects of NMDA receptor blockers on cocaine-stimulated locomotor activity in mice. *Behav Brain Res.* 2000; 108:57–61. [PubMed: 10680757]
42. Vanderschuren LJ, Kalivas PW. Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl).* 2000; 151:99–120. [PubMed: 10972458]
43. Verma R, Mishra V, Sasmal D, Raghubir R. Pharmacological evaluation of glutamate transporter 1 (GLT-1) mediated neuroprotection following cerebral ischemia/reperfusion injury. *Eur J Pharmacol.* 2010; 638:65–71. [PubMed: 20423712]
44. Ward SJ, Rasmussen BA, Corley G, Henry C, Kim JK, Walker EA, Rawls SM. Beta-lactam antibiotic decreases acquisition of and motivation to respond for cocaine, but not sweet food, in C57Bl/6 mice. *Behav Pharmacol.* 2011; 22:370–373. [PubMed: 21543969]
45. Witkin JM. Blockade of the locomotor stimulant effects of cocaine and methamphetamine by glutamate antagonists. *Life Sci.* 1993; 53:L405–410.
46. Wolf ME, Jeziorski M. Coadministration of MK-801 with amphetamine, cocaine or morphine prevents rather than transiently masks the development of behavioral sensitization. *Brain Res.* 1993; 613:291–294. [PubMed: 8186979]

Research 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.

Fig. 1. Effects of CTX treatment on sensitization of cocaine-induced locomotor activity

Mice were challenged with cocaine (COC) (15 mg/kg) following pretreatment with SAL-SAL, SAL-COC, CTX-COC, or COC-CTX. Time-course data are expressed as locomotor activity counts (mean + S.E.M.) in 10-min intervals. N=6-8 mice per group. *** $P < 0.001$ compared to SAL-SAL + COC and +++ $P < 0.001$ compared to SAL-COC + COC. (**Box**) Data are expressed as cumulative locomotor activity counts (mean + S.E.M.) over the 20-min following cocaine challenge. * $P < 0.05$ compared to SAL-SAL + COC; + $P < 0.05$ compared to SAL-COC + COC.

Fig. 2. Effects of CTX treatment on locomotor activity produced by acute cocaine exposure

(2A) Mice pretreated with CTX or saline for 10 days were injected with cocaine (COC) (15 mg/kg) or saline on the following day and locomotor activity was recorded. Time-course data are expressed as locomotor activity counts (mean + S.E.M.) in 10-min intervals. N=8 mice per group. *** $P < 0.001$ or * $P < 0.05$ compared to SAL-SAL. **(Box)** Treatment effects on cumulative locomotor activity (mean + S.E.M.) over the entire 60 min following SAL or COC injection are presented. * $P < 0.05$ compared

to SAL-SAL group. **(2B)** Experiments were repeated with a higher dose (30 mg/kg) of COC and time-course and cumulative data are presented. N=8 mice per group. *** $P < 0.001$, * $P < 0.01$, or * $P < 0.05$ compared to SAL-COC group.