Published in final edited form as:

Drug Alcohol Depend. 2011 November 1; 118(2-3): 484–488. doi:10.1016/j.drugalcdep.2011.03.022.

Glutamate transporter subtype 1 (GLT-1) activator ceftriaxone attenuates amphetamine-induced hyperactivity and behavioral sensitization in rats

Bruce Rasmussen^a, Ellen M. Unterwald^{b,c}, and Scott M. Rawls^{a,b}

^a Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA 19140, United States

^b Center for Substance Abuse Research, Temple University Health Sciences Center, Philadelphia, PA 19140, United States

^c Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA 19140, United States

Abstract

BACKGROUND—The β -lactam antibiotic and glutamate transporter subtype 1 (GLT-1) activator ceftriaxone prevents relapse to cocaine-seeking and inhibits morphine-induced physical dependence and tolerance in rats, but its efficacy against amphetamine-induced behaviors is unknown.

METHODS—Here, we tested the hypothesis that ceftriaxone (200 mg/kg, i.p.) inhibits hyperactivity produced by acute amphetamine administration (2 mg/kg, i.p.) and sensitization of hyperactivity induced by repeated amphetamine exposure (2 mg/kg, i.p.). For acute experiments, rats treated with ceftriaxone for 5 days were injected with amphetamine or saline on day 6.

RESULTS—Amphetamine elicited less ambulatory and stereotypical activity in ceftriaxone-treated rats than in ceftriaxone-naïve rats. For chronic experiments, rats injected with ceftriaxone or saline for 8 days were also injected with amphetamine or saline on days 6–8 and then challenged with amphetamine 5 days later. Amphetamine produced greater ambulatory and stereotypical activity in amphetamine-pretreated rats than in rats previously naïve to amphetamine. Amphetamine challenge produced less ambulatory and stereotypical activity in rats pretreated with a combination of ceftriaxone (200 mg/kg) and amphetamine than in rats pretreated with only amphetamine.

CONCLUSION—The present demonstration that ceftriaxone attenuates amphetamine-induced hyperactivity and behavioral sensitization suggests its documented efficacy against adverse cocaine and morphine effects extends to amphetamine.

Keywords

amphetamine; β -lactam antibiotic; GLT-1; ceftriaxone; glutamate; sensitization; addiction

© 2011 Elsevier Ireland Ltd. All rights reserved.

Corresponding Author: Scott M. Rawls, Associate Professor of Pharmacology, Department of Pharmaceutical Sciences, Temple University Health Sciences Center, 3307 North Broad Street, Philadelphia PA, 19140, United States, Tel: (215) 707-4942; Fax: (215) 707-3678; scott.rawls@temple.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

No FDA-approved medication is available to treat cocaine or amphetamine addiction, but evidence that psychostimulant exposure produces deficits in mesocorticolimbic glutamate function that contribute to relapse and craving indicate glutamate-based approaches may be effective (Schmidt and Pierce, 2010; Gass and Olive, 2008). *In vivo* microdialysis data reveal that acute amphetamine or cocaine injection can increase extracellular glutamate in the nucleus accumbens and that withdrawal from repeated psychostimulant exposure causes a reduction in accumbal glutamate levels (Smith et al., 1995; Xue et al., 1996; Baker et al., 2003; Xi et al., 2003). Rats expressing behavioral sensitization to cocaine display an increase in extracellular glutamate in the nucleus accumbens and prefrontal cortex following cocaine challenge (Reid and Berger, 1996; Pierce et al., 1996; Williams and Steketee, 2004). Pharmacological studies indicate that a number of glutamate-directed compounds, including mGluR2/3 receptor agonists, glutamate carboxypeptidase II inhibitors, and cystine-glutamate antiporters, display efficacy in rat models of cocaine self-administration and conditioned place preference (Peng et al., 2010; Li et al., 2010; Moran et al. 2005).

Another promising, but understudied, approach is glutamate transporter subtype 1 (GLT-1) activation. GLT-1 is a predominantly astrocytic transporter that mediates about 90% of cellular glutamate uptake in the mammalian forebrain (Rothstein, 1996). The only practical class of pharmaceuticals known to directly increase GLT-1 transporter activity is β -lactam antibiotics (Rothstein et al., 2005; Lipski et al., 2007; Miller et al., 2008). Repeated administration of the representative β -lactam antibiotic ceftriaxone, through GLT-1 activation, elicits an enduring reduction in extracellular glutamate in the nucleus accumbens (Rasmussen et al., 2011). A link between the level of GLT-1 activity and efficacy of addictive drugs is provided by data showing that repeated ceftriaxone administration inhibits development of morphine analgesic tolerance and physical dependence and prevents relapse to cocaine-seeking in rats (Rawls et al., 2010a, b; Knackstedt et al., 2010; Sari et al., 2009). Ceftriaxone also inhibits abstinence-induced withdrawal from amphetamine in an invertebrate assay (Rawls et al., 2010c), but its effects against amphetamine-induced behaviors in mammals have not been reported. Two preclinical measures of amphetamine effects that are sensitive to changes in glutamate transmission at ionotropic (NMDA, AMPA, kainate) and group II metabotropic receptors are acute hyperactivity and behavioral sensitization of hyperactivity (Karler et al., 1989, 1990, 1991; Wolf and Khansa, 1991; Li et al., 1997; Kim and Vezina, 1998). Thus, we tested the hypothesis that repeated administration of a GLT-1 activator (ceftriaxone) would reduce hyperactivity elicited by acute amphetamine exposure and behavioral sensitization induced by repeated amphetamine exposure.

2. Methods

Male Sprague-Dawley rats (225–250 g at the start of experiments) housed 2–3 per cage were maintained on a 12-hour light-dark cycle and provided food and water *ad libitum*. Animal use procedures were conducted in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee. Ceftriaxone hydrochloride (Baxter Healthcare Corporation) and amphetamine (NIDA) were dissolved in normal saline and administered intraperitoneally (i.p.). Activity was detected with the Digiscan Dmicro System and analyzed with Micropro version 1.3 software. Eight adjacent plexiglass chambers were placed in frames equipped with 16 infrared beams. Ambulatory behavior was registered when consecutive light beams were interrupted. Stereotypy was detected when the same light beam was repeatedly broken. For acute amphetamine experiments, rats pretreated with ceftriaxone (200 mg/kg) or saline for 5

days were placed into the test chambers on day 6. Following a 20-min acclimation interval, all rats were injected with saline to control for injection itself. Twenty minutes later, rats were injected with either amphetamine (2 mg/kg) or saline and activity (ambulatory and stereotypy) was quantified for 80 min. Experiments were then repeated with lower doses (50, 100 mg/kg) of ceftriaxone. For chronic amphetamine experiments, rats injected for 8 days with ceftriaxone (200 mg/kg, afternoon) or saline were also injected with amphetamine (2 mg/kg, morning) or saline on days 6–8. All rats were challenged with amphetamine (2 mg/kg) on day 13 (20 min after a control injection of saline), and activity was recorded as described above. The dosing paradigm selected for ceftriaxone was based on extensive literature indicating that the repeated administration of ceftriaxone is necessary to increase GLT-1 activity in the brain (Rothstein et al., 2005; Knackstedt et al., 2010; Rawls et al., 2010a, b). Control experiments were conducted to test the effect of a single acute ceftriaxone (200 mg/kg) injection (20-min pretreatment), on acute ambulatory and stereotypical activity induced by amphetamine (2 mg/kg). In all experiments, beam breaks were collected in 10-min bins and presented as mean $\pm$ S.E.M. of ambulatory and stereotypical activity over an 80-min time course. Significance testing on time-course data was determined with two-way (treatment $\times$ time) repeated-measures ANOVA (RMANOVA). *Post-hoc* comparisons were done with Bonferroni's multiple comparisons test. Criterion for significance was $p < 0.05$.

3. Results

3.1. Effects of repeated ceftriaxone on acute hyperactivity induced by amphetamine

Fig. 1 shows the effect of repeated ceftriaxone exposure (50, 100, 200 mg/kg) against the stereotypical and ambulatory activity induced by acute amphetamine (2 mg/kg) exposure. For stereotypy (Panel A), there were significant main effects for treatment [$F(5, 49)=14.29$; $p < 0.0001$]; time [$F(11, 539)=27.52$; $p < 0.0001$]; and interaction [$F(55, 539)=7.17$; $p < 0.0001$]. In rats pretreated with saline, amphetamine injection on day 6 produced significantly greater stereotypical activity at each time point than did an injection of saline ($p < 0.05$, 10 min; $p < 0.01$, 20 min; $p < 0.001$, 30–80 min). Rats pretreated with the highest dose of ceftriaxone (200 mg/kg) and then injected with amphetamine on day 6 displayed significantly less stereotypical activity 50 and 60 min post-amphetamine injection compared to ceftriaxone-naïve rats injected with amphetamine ($p < 0.05$). Ceftriaxone pretreatment (200 mg/kg) did not affect basal stereotypical activity as stereotypy induced by a saline injection on day 6 was not significantly different in saline- and ceftriaxone-pretreated rats ($p > 0.05$). Pretreatment with lower ceftriaxone doses (50, 100 mg/kg) did not significantly affect amphetamine-induced stereotypical activity ($p > 0.05$).

For ambulatory activity (Panel B), there were significant main effects for treatment [$F(5, 49)=20.40$; $p < 0.0001$]; time [$F(11, 539)=46.05$; $p < 0.0001$]; and interaction [$F(55, 539)=9.03$; $p < 0.0001$]. In ceftriaxone-naïve rats, amphetamine elicited significantly greater ambulatory activity at each time point than did saline ($p < 0.001$, 10–80 min). Rats pretreated with ceftriaxone (200 mg/kg) and injected with amphetamine on day 6 displayed significantly less ambulatory activity 50 min post-amphetamine injection compared to ceftriaxone-naïve rats injected with amphetamine ($p < 0.05$). Basal ambulatory activity was not significantly different following an injection of saline in ceftriaxone- and saline-pretreated rats ($p > 0.05$). Pretreatment with lower ceftriaxone doses (50, 100 mg/kg) did not significantly affect amphetamine-induced ambulatory activity ($p > 0.05$).

3.2. Effects of repeated ceftriaxone on amphetamine-induced behavioral sensitization

Fig. 2 displays the effect of ceftriaxone (200 mg/kg) on the development of sensitized stereotypical and ambulatory responses to repeated amphetamine exposure (2 mg/kg). For

stereotypical activity (Panel A), main effects were as follows: treatment [$F(3, 28)=2.90$; $p = 0.0524$]; time [$F(11, 308)=39.21$; $p < 0.0001$]; and interaction [$F(33, 308)=2.48$; $p < 0.0001$]. Post-hoc analysis indicated that stereotypical activity elicited by amphetamine on day 13 was significantly greater in rats pretreated with amphetamine than in rats previously naïve to amphetamine ($p < 0.01$, 10 and 30 min; $p < 0.05$, 20 and 40 min). Amphetamine challenge on day 13 elicited significantly less stereotypy 30 min post-injection in rats pretreated with a combination of amphetamine and ceftriaxone than in ceftriaxone-naïve rats pretreated with amphetamine ($p < 0.05$). For ambulatory activity (Panel B), main effects were as follows: treatment [$F(3, 28)=2.74$; $p = 0.0619$]; time [$F(11, 308)=46.23$; $p < 0.0001$]; and interaction [$F(33, 308)=2.03$; $p = 0.0011$]. Post-hoc analysis revealed that amphetamine injection on day 13 produced greater ambulatory activity 10 min post-injection in rats pretreated with amphetamine than in previously amphetamine-naïve rats ($p < 0.001$). Ambulation elicited by amphetamine challenge was not significantly different in rats pretreated with a combination of amphetamine and ceftriaxone compared to ceftriaxone-naïve rats pretreated with amphetamine ($p > 0.05$).

3.3. Effect of a single ceftriaxone injection on acute hyperactivity induced by amphetamine

Fig. 3 shows the effect of a single injection of ceftriaxone (200 mg/kg) on stereotypical and ambulatory activity induced by acute amphetamine (2 mg/kg) exposure. Ceftriaxone-naïve rats injected with amphetamine displayed stereotypical (Panel A) and ambulatory (Panel B) activity that was not significantly different from rats pretreated with ceftriaxone ($p > 0.05$).

4. Discussion

These data reveal that a member of the world's most widely prescribed class of antibiotics displays anti-amphetamine properties in rats. Ceftriaxone, a β -lactam antibiotic and GLT-1 transporter activator, attenuated amphetamine-induced hyperactivity and behavioral sensitization in rats. The most plausible mechanism underlying the observed ceftriaxone efficacy is GLT-1 transporter activation, either through upregulation of the GLT-1 transporter protein or independent modulation of transporter activity (Rothstein et al., 2005; Chu et al., 2007; Rasmussen et al., 2011). In the current model, rats simultaneously exposed to ceftriaxone and amphetamine display reduced locomotor responses that are presumably explainable by enhanced glutamate uptake that prevents normal increases in glutamate transmission at NMDA and AMPA receptors that facilitate amphetamine-induced hyperactivity (Schmidt and Pierce, 2010). Support for this hypothesis comes from previous work indicating that anti-glutamate agents attenuate behaviors elicited by amphetamine. For example, NMDA antagonists inhibit the development, but not expression, of amphetamine-evoked behavioral sensitization in rats and mice (Karler et al., 1989, 1990, 1991; Wolf and Khansa, 1991). AMPA antagonists also inhibit development of amphetamine-induced stereotypical sensitization in mice and prevent sensitization of amphetamine-evoked ambulation, but not stereotypy, in rats (Karler et al., 1991; Li et al., 1997). It is worth mentioning that MS-153, a pharmacologically diverse agent that enhances glutamate uptake in COS-7 cells, reduces the conditioned rewarding effects of cocaine and methamphetamine in mice (Nakagawa et al., 2005). However, the specificity of the effect was unclear because MS-153 interacts with voltage-gated channels and glutamate-releasing mechanisms that also impact amphetamine behaviors (Uenishi et al., 1999).

The identification of anatomical sites of ceftriaxone action is challenging because amphetamine-induced ambulatory and stereotypical activation is a multifactorial process involving multiple brain regions, but the nucleus accumbens and striatum are likely candidates. Both substrates mediate psychostimulant-induced behaviors and contain a rich supply of glutamate receptors and transporters (Creese and Iversen, 1975; Vanderschuren and Kalivas, 2000). Furthermore, ceftriaxone, through GLT-1 activation, reduces

extracellular glutamate in the accumbens for at least three weeks following discontinuation of antibiotic exposure (Rasmussen et al., 2011). This persistent anti-glutamate effect of ceftriaxone may be capable of inhibiting the elevation in accumbal glutamate levels known to occur in rats that are reintroduced to psychostimulants following a period of abstinence, thereby providing an explanation for the capacity of ceftriaxone to attenuate sensitized responses produced by amphetamine challenge (Torregrossa and Kalivas, 2008). Future studies will investigate the ceftriaxone-amphetamine interaction at the neurochemical and molecular levels and determine if β -lactam compounds also alter non-glutamatergic systems, such as dopamine and GABA, to regulate amphetamine-induced behaviors (Jayaram and Steketee, 2004).

The present data suggest that ceftriaxone efficacy against acute amphetamine effects may be dependent on either the time interval between discontinuation of ceftriaxone treatment and initial amphetamine exposure or the frequency of ceftriaxone exposure. We observed a significant inhibition of amphetamine-evoked hyperactivity when amphetamine was administered one day following discontinuation of a 5-day ceftriaxone exposure. However, in the case in which amphetamine was administered five days after cessation of an 8-day ceftriaxone treatment, we did not observe a reduction in amphetamine-evoked hyperactivity. One explanation for the loss of ceftriaxone efficacy is that compensatory mechanisms, activated in response to ceftriaxone-induced increases in GLT-1 activity, manifest to a greater degree in animals that undergo an extended period of ceftriaxone abstinence. Another possibility is that ceftriaxone efficacy is sensitive to the number of exposures. To our knowledge, only one paper has investigated time-course effects of ceftriaxone on GLT-1 expression (Chu et al., 2007). In that study, Chu and colleagues (2007) detected increases in GLT-1 expression as early as day three of repeated ceftriaxone exposure. GLT-1 expression levels peaked on the fifth day of ceftriaxone administration but decreased thereafter. In fact, GLT-1 expression was actually lower on the seventh day of ceftriaxone exposure than on the third day (Chu et al., 2007). Thus, in the present experiments, it is conceivable that the combination of a 5-day ceftriaxone dosing schedule and shorter ceftriaxone abstinence period produced an enhancement of GLT-1 activity that was responsible for ceftriaxone efficacy.

In summary, we provide evidence that a GLT-1 activator displays anti-amphetamine effects in mammals. Our findings extend prior work demonstrating that ceftriaxone inhibits abstinence-induced withdrawal from amphetamine in an invertebrate assay (Rawls et al., 2008) and suggest ceftriaxone efficacy against cocaine and morphine extends to amphetamine (Sari et al., 2009; Knackstedt et al., 2010; Rawls et al., 2010a, b). Future work will investigate ceftriaxone action against additional behavioral and neurochemical effects of cocaine and amphetamine.

References

- Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, Kalivas PW. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci.* 2003; 6:743–749. [PubMed: 12778052]
- 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]
- Creese I, Iversen SD. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res.* 1975; 83:419–436. [PubMed: 234270]
- Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. *Biochem Pharmacol.* 2008; 75:218–265. [PubMed: 17706608]

- Jayaram P, Steketee JD. Effects of repeated cocaine on medial prefrontal cortical GABAB receptor modulation of neurotransmission in the mesocorticolimbic dopamine system. *J Neurochem*. 2004; 90:839–847. [PubMed: 15287889]
- 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]
- Karler R, Chaudhry IA, Calder LD, Turkanis SA. Amphetamine behavioral sensitization and the excitatory amino acids. *Brain Res*. 1990; 537:76–82. [PubMed: 1964842]
- Karler R, Calder LD, Turkanis SA. DNQX blockade of amphetamine behavioral sensitization. *Brain Res*. 1991; 552:295–300. [PubMed: 1913191]
- Kim JH, Vezina P. Metabotropic glutamate receptors are necessary for sensitization by amphetamine. *Neuroreport*. 1998; 9:403–406. [PubMed: 9512379]
- Knackstedt LA, Melendez RI, Kalivas PW. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. *Biol Psychiatry*. 2010; 67:81–84. [PubMed: 19717140]
- 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*. 1997; 134:266–276. [PubMed: 9438676]
- Li X, Li J, Gardner EL, Xi ZX. Activation of mGluR7s inhibits cocaine-induced reinstatement of drug-seeking behavior by a nucleus accumbens glutamate-mGluR2/3 mechanism in rats. *J Neurochem*. 2010; 114:1368–1380. [PubMed: 20534005]
- 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]
- Miller BR, Dorner JL, Shou M, Sari Y, Barton SJ, Sengelaub DR, Kennedy RT, Rebec GV. Up-regulation of GLT1 expression increases glutamate uptake and attenuates the Huntington’s disease phenotype in the R6/2 mouse. *Neuroscience*. 2008; 153:329–337. [PubMed: 18353560]
- Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *J Neurosci*. 2005; 25:6389–6393. [PubMed: 16000629]
- Nakagawa T, Fujio M, Ozawa T, Minami M, Satoh M. Effect of MS-153, a glutamate transporter activator, on the conditioned rewarding effects of morphine, methamphetamine and cocaine in mice. *Behav Brain Res*. 2005; 156:233–239. [PubMed: 15582109]
- Peng XQ, Li J, Gardner EL, Ashby CR Jr, Thomas A, Wozniak K, Slusher BS, Xi ZX. Oral administration of the NAALADase inhibitor GPI-5693 attenuates cocaine-induced reinstatement of drug-seeking behavior in rats. *Eur J Pharmacol*. 2010; 627:156–161. [PubMed: 19887067]
- 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]
- 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]
- Rawls SM, Cavallo F, Capasso A, Ding Z, Raffa RB. The beta-lactam antibiotic ceftriaxone inhibits physical dependence and abstinence-induced withdrawal from cocaine, amphetamine, methamphetamine, and clorazepate in planarians. *Eur J Pharmacol*. 2008; 584:278–284. [PubMed: 18342307]
- Rawls SM, Zielinski M, Patel H, Sacavage S, Baron DA, Patel D. β -lactam antibiotic reduces morphine analgesic tolerance in rats through GLT-1 transporter activation. *Drug Alcohol Depend*. 2010a; 107:261–263. [PubMed: 20004063]
- Rawls SM, Baron DA, Kim JK. β -lactam antibiotic inhibits development of morphine physical dependence in rats. *Behav Pharmacol*. 2010b; 21:161–164. [PubMed: 20215965]
- Reid MS, Berger SP. Evidence for sensitization of cocaine-induced nucleus accumbens glutamate release. *Neuroreport*. 1996; 7:1325–1329. [PubMed: 8817559]
- 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]

- 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]
- Schmidt HD, Pierce RC. Cocaine-induced neuroadaptations in glutamate transmission: potential therapeutic targets for craving and addiction. *Ann NY Acad Sci*. 2010; 1187:35–75. [PubMed: 20201846]
- 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]
- Torregrossa MM, Kalivas PW. Microdialysis and the neurochemistry of addiction. *Pharmacol Biochem Behav*. 2008; 90:261–272. [PubMed: 17928041]
- Uenishi H, Huang CS, Song JH, Marszalec W, Narahashi T. Ion channel modulation as the basis for neuroprotective action of MS-153. *Ann NY Acad Sci*. 1999; 890:385–399. [PubMed: 10668444]
- 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*. 2000; 151:99–120. [PubMed: 10972458]
- Xi ZX, Shen H, Baker DA, Kalivas PW. Inhibition of non-vesicular glutamate release by group III metabotropic glutamate receptors in the nucleus accumbens. *J Neurochem*. 2003; 87:1204–1212. [PubMed: 14622100]
- Xue CJ, Ng JP, Li Y, Wolf ME. Acute and repeated systemic amphetamine administration: effects on extracellular glutamate, aspartate, and serine levels in rat ventral tegmental area and nucleus accumbens. *J Neurochem*. 1996; 67:352–363. [PubMed: 8667013]
- Williams JM, Steketee JD. Cocaine increases medial prefrontal cortical glutamate overflow in cocaine-sensitized rats: a time course study. *Eur J Neurosci*. 2004; 20:1639–1646. [PubMed: 15355331]
- Wolf ME, Khansa MR. Repeated administration of MK-801 produces sensitization to its own ambulatory stimulant effects but blocks sensitization to amphetamine. *Brain Res*. 1991; 562:164–168. [PubMed: 1839240]

Fig. 1.

Effect of repeated ceftriaxone (CTX) (50, 100, 200 mg/kg) or saline (SAL) injections on the stereotypical (Panel A) or ambulatory (Panel B) response to an acute injection of amphetamine (AMPH) (2 mg/kg) or SAL. Data are expressed as mean stereotypical or ambulatory counts + S.E.M. quantified in 10-min bins. N = 8 rats/group except for the SAL + AMPH group (N=15). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to respective SAL + SAL group and + $p < 0.05$ compared to respective SAL + AMPH group.

Fig. 2.

Effect of repeated ceftriaxone (CTX) (200 mg/kg) or saline (SAL) injections on sensitization of stereotypical (Panel A) or ambulatory (Panel B) activity produced by repeated amphetamine (AMPH) (2 mg/kg) exposure. All rats were injected with AMPH on day 13 following pretreatment with SAL + SAL, CTX + SAL, SAL + AMPH, or CTX + AMPH. Data are expressed as mean stereotypical or ambulatory counts + S.E.M. quantified in 10-min bins. N = 8 rats/group. *p < 0.05, **p < 0.01, ***p < 0.001 compared to respective SAL + SAL pretreated group and +p < 0.05 compared to respective SAL + AMPH pretreated group.

Fig. 3.

Effect of an acute injection of ceftriaxone (CTX) (200 mg/kg) on the stereotypical (Panel A) or ambulatory (Panel B) response to an acute injection of amphetamine (AMPH) (2 mg/kg) or saline (SAL). Data are expressed as mean stereotypical or ambulatory counts + S.E.M. quantified in 10-min bins. N = 8 rats/group.