Brief Communications

Upregulation of Glt1 Attenuates Cue-Induced Reinstatement of Cocaine-Seeking Behavior in Rats

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Relapse to cocaine-seeking behavior depends on increased glutamate transmission in key regions of the mesocorticolimbic motive circuit, including prefrontal cortex (PFC) and nucleus accumbens (NAcc). Because GLT1 is responsible for the uptake of ≥90% of extracellular glutamate, we tested the hypothesis that increased GLT1 expression attenuates cocaine relapse. Rats were trained to self-administer cocaine (0.125 mg per intravenous infusion) in a lever-pressing task in a daily 2 h session for 10–14 d followed by 5 d of extinction training. Immediately after each extinction session, rats received ceftriaxone (intraperitoneally), a β-lactam antibiotic believed to increase GLT1 expression, or vehicle. On the following day, presentation of the cue (light and tone) previously associated with cocaine self-administration reinstated lever pressing in rats treated with vehicle, whereas 100 or 200, but not 50 mg/kg ceftriaxone blocked this response. Immunoblotting confirmed that the ceftriaxone-induced blockade of cocaine relapse was associated with an increase in GLT1 expression in both PFC and NAcc. Separate groups of rats, 200 mg/kg ceftriaxone failed to block cue-induced food seeking, arguing against a ceftriaxone-induced effect unique to extinction training or lever pressing. Our results suggest that glutamate plays a key role in cue-induced relapse to cocaine-seeking behavior, implicating GLT1 as a potential therapeutic target for cocaine addiction.

Introduction

Relapse is a common feature of cocaine addiction even after long periods of abstinence (Shaham and Stewart, 1995; Erb et al., 1996; McFarland and Ettenberg, 1997; McFarland and Kalivas, 2001). Several types of stimuli are known to induce cocaine relapse, including the following: stress (Ahmed and Koob, 1997), reexposure to the previously self-administered drug (McFarland and Kalivas, 2001), and cues previously paired with the drug (Chidress et al., 1993). Although there is no effective treatment, the neural circuitry underlying relapse is rapidly coming into focus (Berridge and Robinson, 1998; Kalivas, 2004). Key components include prefrontal cortex (PFC), which processes the signals that trigger relapse (Goldstein and Volkow, 2002), and nucleus accumbens (NAcc), which has long been implicated in goal-directed behavior, including drug seeking (Childress et al., 1999). Both regions receive substantial input from midbrain dopamine (DA) neurons, and all major drugs of abuse, including cocaine, increase forebrain DA transmission (Berridge and Robinson, 1998; Kalivas, 2004). DA involvement in relapse, however, appears to require an increase in glutamate, an excitatory amino acid implicated in cocaine-induced neuroplasticity (Kalivas, 2004). In fact, glutamate is the primary driver of PFC neurons, and relapse to cocaine seeking requires the release of glutamate from the PFC projection to NAcc (McFarland et al., 2003).

Although glutamate accumulation in extracellular fluid is controlled by a family of transporter proteins (Geglashvili and Schousboe, 1997; Seal and Amara, 1999; Anderson and Swanson, 2000), GLT1, a sodium-dependent transporter found on astrocytes (Rothstein et al., 1994; Anderson and Swanson, 2000), is responsible for the removal of at least 90% of extracellular glutamate (Rothstein, 1995; Rothstein et al., 1995; Danbolt, 2001; Mitani and Tanaka, 2003). If an increase in glutamate transmission plays a critical role in cocaine relapse, then upregulation of GLT1 should attenuate this response. We tested this hypothesis in rats trained to press a lever for self-administration (SA) of cocaine and a compound cue (light and tone). After 5 d of extinction training, rats were tested for cue-induced reinstatement. Each extinction session was followed by an injection of ceftriaxone, a β-lactam antibiotic believed to increase GLT1 expression (Rothstein et al., 2005; Miller et al., 2008), or vehicle. Relative to vehicle, 100 or 200, but not 50 mg/kg ceftriaxone significantly attenuated the reinstatement response. Immunoblotting, moreover, revealed that the decline in reinstatement occurred with an increase in GLT1 expression in both PFC and NAcc. Separate groups of rats tested for cue-induced reinstatement of food seeking were unaffected by ceftriaxone. Collectively, these results implicate GLT1 as a potential therapeutic target for cocaine relapse.

Materials and Methods

Animals. Data were obtained from 38 male Sprague Dawley rats (350–400 g at the start of experimentation) and were bred from animals supplied by Harlan Industries. Animals were single-housed in a temperature- and humidity-controlled vivarium. Food and water were
available ad libitum, and lights operated on a 12 h cycle (on at 7:00 A.M.). All housing and experimental procedures were approved by the Institutional Animal Care and Use Committee.

Behavioral chambers. Rats were tested in eight standard operant chambers (27 cm (length) × 22.5 cm (width) × 23.5 cm (height)) supplied by MED Associates. One wall of each chamber was equipped with two levers (active and inactive; spaced 13 cm apart and 10 cm above the grid floor) and 1 W cue light (located 3.5 cm above each lever). The number of inactive lever presses was <5% of that of active lever presses throughout the entire study. A food hopper, located between the two levers, was connected to a food dispenser installed outside each chamber. A programmable speaker, used to deliver a tone (54 dB), was installed on the opposite wall along with a 5 W house light. Each chamber was housed in a light- and sound-attenuating cubic. A fluid pump, positioned outside each cubic, was used to deliver cocaine.

Operant training. Rats, food-restricted for 1 week to reduce their weight to 85%, were trained to press the active lever for food (rodent food pellet, formula A/I) on a fixed-ratio 1 (FR1) schedule of reinforcement. When the rats obtained 60 reinforcements within 30 min, the reinforcement schedule increased to FR5. After responding for food stabilized (~5 d), the rats returned to ad libitum feeding for 1 week in preparation for subsequent surgery.

Animal surgery. Each rat was anesthetized with xylazine (10 mg/kg, i.p.) and ketamine (80 mg/kg, i.p.) for surgical implantation of a jugular vein catheter as previously described (Sun and Rebec, 2003). After the incision site was sutured, the animals were closely monitored for 1 week, during which the catheters were flushed twice daily with heparinized physiological saline (30 U/ml heparin). To assess catheter patency during the period of cocaine SA, 0.1 ml of Brevital (1%) was injected as necessary. Loss of muscle tone within 5 s after injection indicated a patent catheter.

Cocaine SA. Food deprivation was resumed, and rats were retested on a FR5 schedule for food. Animals that matched their presurgery responding were allowed to begin cocaine SA training on the following day. Pressing the active lever was reinforced by an infusion of cocaine on a modified FR5 schedule of reinforcement, in which the first response was reinforced by an infusion of 0.125 mg of cocaine in a volume of 0.05 ml over 1 s. Subsequent reinforcements, consisting of the same volume and concentration of cocaine, continued on a FR5 schedule. Each cocaine infusion was paired with a cue (light and tone) that lasted 4 s and was followed by a 16 s time-out signaled by illumination of the house light.

Responses on the inactive lever were recorded but did not have any programmed consequences. Training sessions lasted for 2 h or until the rats reached 60 infusions of cocaine. A food group with identical handling and food training was run on the same schedule, but was reinforced with food pellets. Rats continued on a cocaine SA schedule until they displayed stable responding (~10–14 d), which was defined as <10% variation in the number of active lever presses for 4 consecutive days. Extinction training began on the following day.

Extinction and drug treatment. Rats underwent 5 d of extinction training in which lever pressing was recorded, but no cue or drug was delivered. Shortly after each extinction session, which lasted 60 min, rats with cocaine SA training received (intraperitoneally) either 50, 100, or 200 mg/kg ceftriaxone or vehicle (an equal volume of 0.9% saline). Rats in the food group received (intraperitoneally) either 200 mg/kg ceftriaxone or vehicle. By the fifth day, all rats reached a level of responding on the active lever that was <20% of the level during cocaine or food SA.

Reinstatement. The reinstatement session began on the sixth day with presentation of the cue for 4 s followed by a 16 s time-out as in the cocaine SA sessions. Responding was reinforced by the cue alone, contingent on a modified FR5 schedule in which the first presentation of the cue occurred either noncontingently or in response to the first lever press. Each reinstatement session lasted 60 min.

Western blot for GLT1 expression. Immediately after the reinstatement session, rats were killed by decapitation, brains were removed, and the PFC and NAcc from both hemispheres were dissected and frozen for subsequent immunoblotting. Western blot for GLT1 was performed as described previously (Miller et al., 2008). Extracted proteins were separated in 4–20% glycine gel (Invitrogen) and then transferred onto a nitrocellulose membrane electrophoretically at 30 V for 1 h. Unbound sites on the membrane were blocked by incubating with 3% milk in TBST (0.5 mM Tris–HCl; 1.5 mM NaCl, pH 7.4; 10 ml of 10% Tween 20) for 30 min at room temperature. The guinea pig anti-GLT1 antibody (Millipore Bioscience Research Reagents) diluted 1:5000 in 3% milk in TBST was incubated overnight at 4°C. Horseradish peroxidase (HRP) secondary antibody was used at a 1:10,000 dilution. Films were developed on a SRX-101A machine. Digitized images of immunoblots were quantified using an image analysis system.

Protein extractions and Western blots were performed at different times for the saline and 50 mg/kg ceftriaxone comparison, the saline and 200 mg/kg ceftriaxone comparison, and the comparison between the food and cocaine groups. Any differences in GLT1 levels were resolved by loading a similar quantity of total protein (~10 μg) in each case. Film exposure times were carefully monitored to rule out saturation effects.

Drugs. Cocaine hydrochloride was provided by the National Institute on Drug Abuse (Bethesda, MD). Ceftriaxone was purchased from Sigma.
Aldrich. Both drugs were dissolved in physiological (0.9%) saline solution.

Statistical analyses. ANOVA was used to analyze behavioral and body weight data. Bonferroni’s post hoc pairwise comparisons were made between individual treatment groups. Some behavioral data were analyzed by independent-samples t test. Western blot data were analyzed by t tests for comparisons between groups. All statistical tests were based on \( p < 0.05 \) level of significance.

Results

Ceftriaxone blocks cue-induced reinstatement of cocaine-seeking behavior

All rats exhibited stable responding on the active lever during the last 4 d of cocaine SA training (within-subject variability of <10% in daily cocaine intake). Collapsed across groups, the mean (±SEM) number of daily active lever presses during this period was 256.99 ± 6.87. As shown in Figure 1, this number decreased significantly during extinction training in all groups \((F_{(6,208)} = 89.55; p < 0.001)\) and never exceeded 10 presses on the final extinction day in any treatment group. No significant differences in extinction rates or the last 4 d of cocaine SA were found between the saline- and ceftriaxone-treated groups. These groups also did not differ in body weight; all rats were within 15 g of each other. As shown in Figure 2, testing for cue-induced reinstatement revealed a significantly lower response rate in rats treated with either 100 or 200 mg/kg ceftriaxone relative to the 50 mg/kg or saline groups \((F_{(3,27)} = 9.79; p < 0.001)\). In fact, extinction and reinstatement responding were not significantly different in the 100 and 200 mg/kg groups, whereas rats treated with the lowest dose or saline showed a clear reinstatement response \((F_{(1,52)} = 35.14; p < 0.01)\). In contrast, cue-induced reinstatement of food seeking occurred in rats treated with either 200 mg/kg ceftriaxone or saline (Fig. 2, inset); both treatment groups showed food reinstatement relative to extinction \((F_{(1,12)} = 24.99; p < 0.001)\).

The ceftriaxone effect correlates with GLT1 expression

Group differences in GLT1 expression paralleled the cue-induced relapse response (Fig. 3). An independent t test revealed that neither vehicle nor 50 mg/kg ceftriaxone altered GLT1 expression in PFC and NAcc, but there was a significant GLT1 increase in both PFC \((t_{(6)} = 3.17; p < 0.05)\) and NAcc \((t_{(6)} = 3.1; p < 0.05)\) in rats treated with 200 mg/kg ceftriaxone. GAPDH, used as a loading control, did not show any expression differences among the treatment groups.

To determine whether cocaine itself upregulates GLT1, we compared the food and cocaine groups treated with saline. Figure 4 shows no significant difference between these groups in either PFC or NAcc.

Discussion

We report here that ceftriaxone attenuates cue-induced cocaine relapse in a dose-dependent manner. This effect, moreover, correlates with increases in GLT1 expression in PFC and NAcc, two forebrain regions in which elevated glutamate transmission appears to drive drug craving. Cue-induced food relapse, in contrast, was unaltered by ceftriaxone. Our results implicate GLT1 as a key factor in the modulation of cue-induced cocaine-seeking behavior.

Ample evidence suggests that glutamate transmission in key neural circuits plays a critical role in the initiation and expression of addiction-related behaviors, including motor sensitization and drug seeking (Kalivas et al., 2009). Glutamate input to the ventral tegmental area (VTA), for example, is necessary for the development of the sensitized motor response to repeated, intermittent injections of cocaine and other psychostimulants (Kalivas and Weber, 1988; Wolf, 1998). Activation of VTA neurons by glutamate, moreover, appears to be an essential requirement for cocaine SA as well as cocaine-primed reinstatement (Sun and Rebec, 2005). Glutamate input to the basolateral amygdala (BLA) also is important in the addiction response (Kalivas, 2004). In fact, cue-induced relapse to cocaine seeking depends on BLA activation (Kantak et al., 2002). The major source of glutamate in both these regions is the PFC, which integrates most, if not all, addiction-related information and routes it to the NAcc for subsequent motor output (McFarland and Kalivas, 2001). Thus, glutamate in PFC and NAcc is likely to drive addictive behavior. Consistent with this view, rats withdrawn from repeated exposure to cocaine respond to a cocaine challenge with an increase in extracellular glutamate in PFC (Williams and Steketee, 2004) and NAcc (Pierce et al., 1996). In addition, presentation of cues or context previously associated with cocaine elevates NAcc extracellular glutamate.
cellular glutamate (Bell et al., 2000; Hotsenpiller et al., 2001). Furthermore, reinstatement can be blocked by PFC inactivation (McFarland et al., 2003) or by intra-PFC infusion of brain-derived neurotrophic factor, which prevents the increase in extracellular glutamate in NAcc (Berglind et al., 2009). Interestingly, cocaine-induced reinstatement is inhibited by N-acetyl cysteine, which activates the glutamate/cysteine exchanger causing an immediate increase in extracellular glutamate (Baker et al., 2003). Although this finding suggests that glutamate blocks rather than promotes relapse, the opposite may be true because the increase in glutamate induced by N-acetyl cysteine also activates mGlu2/3 receptors, which appear to inhibit glutamate release (Hu et al., 1999; Xi et al., 2002). Repeated sessions of cocaine SA, moreover, enhance burst activation of PFC neurons as they process cocaine-related information (Sun and Rebec, 2006). Thus, elevated extracellular glutamate in PFC and its downstream target in NAcc is a likely mechanism underlying drug craving.

The EC$_{50}$ for a ceftriaxone-induced increase in GLT1 expression is 3.5 $\mu$M (Rothstein et al., 2005), which is similar to brain levels in humans treated for meningitis (Nau et al., 1993). An antibiotic action, however, is an unlikely explanation for our results in that our animals showed no signs of sepsis, and ceftriaxone had no effect on body weight. Rather, like other $\beta$-lactam antibiotics, ceftriaxone elevates GLT1 expression via nuclear factor-κB (NF-κB), a transcription factor that regulates genes involved in immune responses as well as cell growth and survival (Karin, 2006; Massa et al., 2006). A binding site for NF-κB on GLT1 promotes its upregulation (Lee et al., 2008). Furthermore, single daily injections of 200 mg/kg ceftriaxone for 5 d, which parallels our treatment conditions, increases glutamate uptake in striatum, a primary target of cortical glutamate input (Miller et al., 2008). Thus, the ceftriaxone-induced increase in GLT1 expression has a direct effect on glutamate function. Consistent with this view, activation of GLT1 by MS-153 [(R)-(−)-5-methyl-1-nicotinoyl-2-pyrazoline], a neuroprotective drug also known to increase glutamate uptake (Shimada et al., 1999), has been shown to attenuate the conditioned place preference response of mice treated with cocaine (Nakagawa et al., 2005). Another interesting observation is that treatment with ceftriaxone attenuates abstinence-induced withdrawal from cocaine in plac-naria (Rawls et al., 2008). It is unlikely that cocaine itself elevated GLT1 because GLT1 expression was identical in both the food and cocaine groups treated with saline. In addition, glutamate transporters are not significantly elevated after 5 d of extinction training in rats trained on cocaine SA (Miguéns et al., 2008). Thus, accelerated removal of extracellular glutamate appears to underlie the ability of ceftriaxone to dampen cocaine craving.

This hypothesis supports evidence that blockade of the AMPA subtype of glutamate receptor in NAcc blocks cue-induced reinstatement (Di Ciano and Everitt, 2001), whereas activation of these receptors triggers this response (Cornish et al., 1999). Unlike AMPA receptor antagonists, however, ceftriaxone can be administered systemically without widespread behavioral effects or global disruption of ionotropic glutamate receptors. In fact, behavioral testing indicates that at 200 mg/kg ceftriaxone did not alter spontaneous locomotion or other measures of behavioral activity in rodents (Rothstein et al., 2005; Miller et al., 2008). This dose of ceftriaxone also failed to prevent responding for cue-induced food reinstatement, further arguing against a motor impairment. Our food group also rules out an effect of ceftriaxone on extinction training, a conclusion supported by the comparable rates of extinction in all treatment groups, including saline, and on subsequent cue-induced lever pressing.

The effect of ceftriaxone on glutamate transmission appears to be limited to GLT1 in that other glutamate transporters are unaffected by this drug (Rothstein et al., 2005). Thus, although it is possible that GLT1 expression is elevated throughout the motive circuit, including the VTA and BLA, our results suggest that GLT1 activation in PFC and NAcc is a potential mechanism for countering the glutamate increase in these sites known to promote drug craving. Our results implicate GLT1 as a likely target in the search for an effective therapeutic strategy against cocaine relapse.

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