

Long-Term Potentiation (LTP) in the Central Amygdala (CeA) Is Enhanced After Prolonged Withdrawal From Chronic Cocaine and Requires CRF₁ Receptors

Yu Fu, Sebastian Pollandt, Jie Liu, Balaji Krishnan, Kathy Genzer, Luis Orozco-Cabal, Joel P. Gallagher, and Patricia Shinnick-Gallagher

Department of Pharmacology and Toxicology, University of Texas, Medical Branch, Galveston, Texas

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Fu Y, Pollandt S, Liu J, Krishnan B, Genzer K, Orozco-Cabal L, Gallagher JP, Shinnick-Gallagher P. Long-term potentiation (LTP) in the central amygdala (CeA) is enhanced after prolonged withdrawal from chronic cocaine and requires CRF₁ receptors. *J Neurophysiol* 97: 937–941, 2007. First published November 1, 2006; doi:10.1152/jn.00349.2006. The amygdala is part of the brain reward circuitry that plays a role in cocaine-seeking and abstinence in animals and cocaine craving and relapse in humans. Cocaine-seeking is elicited by cocaine-associated cues, and the basolateral amygdala (BLA) and CeA are essential in forming and communicating drug-related associations that are thought to be critical in long-lasting relapse risk associated with drug addiction. Here we simulated a cue stimulus with high-frequency stimulation (HFS) of the BLA–CeA pathway to examine mechanisms that may contribute to drug-related associations. We found enhanced long-term potentiation (LTP) after 14-day but not 1-day withdrawal from 7-day cocaine treatment mediated through *N*-methyl-D-aspartate (NMDA) receptors (NRs), L-type voltage-gated calcium channels (L-VGCCs), and corticotropin-releasing factor (CRF)₁ receptors; this was accompanied by increased phosphorylated NR1 and CRF₁ protein not associated with changes in NMDA/AMPA ratios in amygdalae from cocaine-treated animals. We suggest that these signaling mechanisms may provide therapeutic targets for the treatment of cocaine cravings.

INTRODUCTION

The amygdala is essential in forming stimulus–reward associations and associational processing of conditioned cues (Aggleton 1992; Shinnick-Gallagher et al. 2003). Drug-associated cues can induce craving in cocaine users and alter neural activity in the amygdala (Childress et al. 1999), and electrical stimulation of the basolateral amygdala (BLA) can reinstate drug-seeking in animals (Hayes et al. 2003). Drug-cue associations are not well understood, but the mechanisms may be similar to forms of synaptic plasticity and the induction and expression of cocaine sensitization, a model for long-term neuroadaptations important in addiction (De Vries et al. 1999; Kalivas and Alesdatter 1993; Robinson and Berridge 1993). Antagonizing *N*-methyl-D-aspartate (NMDA) receptors (NRs) in the amygdala can prevent and block locomotor sensitizing effects of chronic cocaine (Kalivas and Alesdatter 1993), and amygdala NR1 protein levels are increased after acute and chronic cocaine (Turchan et al. 2003). Likewise, activation of L-type calcium channels mimics the induction (Lin et al. 2001) and antagonists block expression of cocaine sensitization

(Pierce et al. 1998). Furthermore, corticotropin-releasing factor (CRF) systems in the amygdala play a significant role in cocaine addiction (Sarnyai et al. 2001). In cocaine-treated animals, CRF release in the amygdala is enhanced during acute withdrawal (Richter and Weiss 1999) and in response to a cocaine challenge (Richter et al. 1995). Amygdala CRF immunolabeling decreases after short-term, but increases after long-term withdrawal from chronic cocaine (Zorrilla et al. 2001). Furthermore, cocaine-induced locomotor activity is blocked by intracerebroventricular injection of a CRF antagonist (Sarnyai et al. 1992). These data provide strong rationale for testing the role of CRF receptors in synaptic plasticity in the central amygdala (CeA). This study shows that specific cocaine treatment and withdrawal paradigms resulted in enhanced synaptic plasticity, that NR, L-type calcium channels, and CRF₁ were required for long-term potentiation (LTP) in the BLA–CeA pathway, and that phosphorylated-NR1 (P-NR1) and CRF₁ protein but not synaptic potentials were increased after withdrawal from chronic cocaine.

METHODS

Cocaine HCl was a gift from the National Institute of Drug Abuse. Male Sprague-Dawley albino rats (Harlan, 4–6 wk) were injected daily with cocaine (15 mg/kg, ip) or saline (0.1 ml/kg, ip), once or twice per day for 1 or 2 wk to assess how duration and frequency of cocaine treatment and withdrawal time influence synaptic plasticity. Behavioral sensitization measuring the progressive locomotor stimulant properties resulting from chronic cocaine treatment was analyzed with a photocell apparatus before and on the first and last days of cocaine or saline treatment (Fig. 1E) as a measure of cocaine's effectiveness. After 7 days, locomotor activity was increased significantly over 1-day activity in the cocaine-treated ($F_{1,120} = 260.07$, $P < 0.001$) but not in the saline-treated ($P > 0.05$) group. No significant differences were observed between animals injected once per day for 7 days or twice daily for 14 days. Coronal brain slices (500 μ m) were prepared and incubated at room temperature for 1 h with oxygenated, modified artificial cerebrospinal fluid (ACSF) solution (in mM): 119 NaCl, 3.0 KCl, 1.2 NaH₂PO₄, 1.2 MgSO₄, 2.5 CaCl₂, 25 NaHCO₃, and 11.5 glucose. They were then submerged in a chamber (1.0 ml, 2.5 ml/min) at $30 \pm 1^\circ\text{C}$ for another hour before recording. BLA fibers were stimulated with concentric electrodes (50 k Ω) using 150- μ s pulses of varying intensity (3–15 V) at 0.05 Hz, and field excitatory postsynaptic potentials (fEPSPs) were recorded in the capsula/medial CeA with tungsten electrodes (2–5 M Ω). fEPSP mag-

Address for reprint requests and other correspondence: P. Shinnick-Gallagher, 301 University Blvd., Galveston, TX 77555-1031 (E-mail: psgallagher@utmb.edu).

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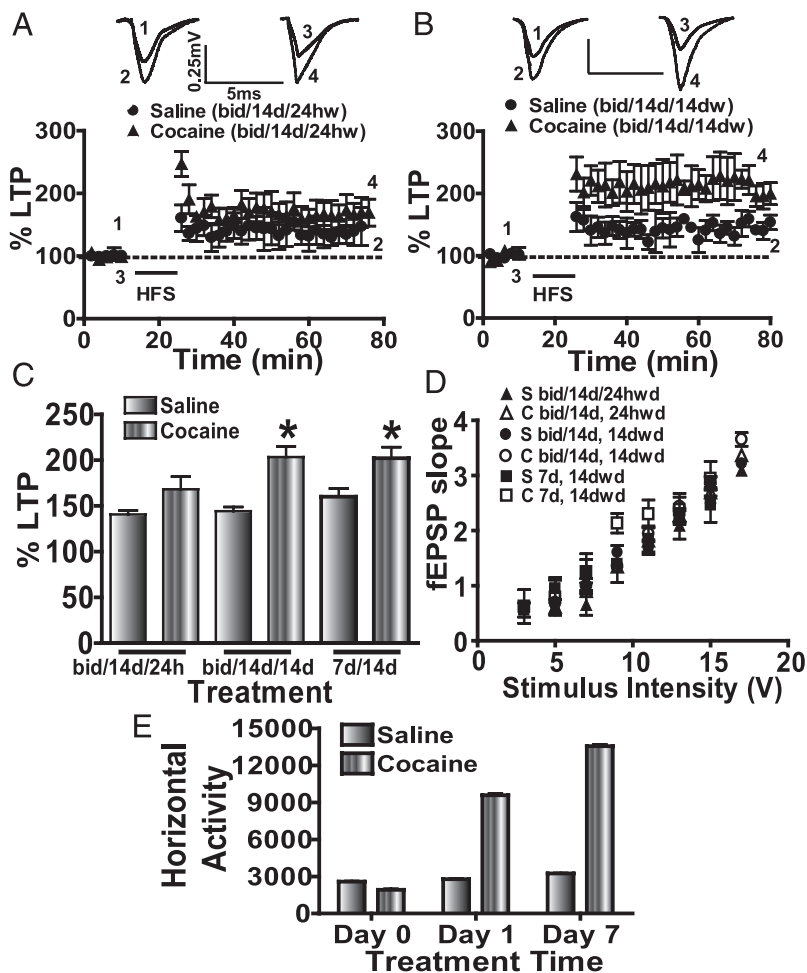


FIG. 1. Long-term potentiation (LTP) at the basolateral amygdala (BLA)-central amygdala (CeA) pathway was enhanced after 2-wk (B) but not 24-h (A) withdrawal from chronic cocaine without changes in single field excitatory postsynaptic potential (fEPSP) responsiveness (D). A and B: traces above indicated fEPSPs before and after high-frequency stimulation (HFS)-LTP at the times indicated in the bottom graphs, showing summary data of LTP time-course. C: plot of last 10 fEPSPs (mean \pm SE) 1 h after LTP induction showed enhanced LTP after 7- and 14-day cocaine treatment and 14-day withdrawal but not after 14-day treatment and 24-h withdrawal. Time-course of 7-day treatment and 14-day withdrawal is shown in Figs. 2 and 3. D: input-output relationships are not altered in any treatment paradigm. E: horizontal locomotor activity is enhanced after 7 days of cocaine treatment, suggesting behavior sensitization. Calibrations are the same in A and B.

nitude was adjusted to 30% of maximum response and baseline recorded, and LTP was induced using high-frequency stimulation (HFS) consisting of five trains of stimuli (100 Hz for 1 s, 3-min intervals). fEPSPs were recorded at 0.05 Hz for another hour, and their slopes were normalized to baseline values. A one- or two-tailed unpaired *t*-test or one-way ANOVA with appropriate post hoc tests were used for statistical analysis; *n* equals the number of slices. Methodologies for patch recording (Liu et al. 2004) and Western blot analysis (Zinebi et al. 2003) were similar to that reported previously.

RESULTS

Amygdala slices were prepared, and LTP was assessed in the BLA-CeA pathway (Fig. 1, A-D). We first tested the influence of varying cocaine administration paradigms and withdrawal time on LTP. Animals received cocaine or saline either once per day for 7 days or twice per day for 14 days, followed by either 1 or 14 days of withdrawal. Input-output relationships were similar in all treatment groups (Fig. 1D). In slices from animals treated with cocaine twice per day for 14 days and a 14-day withdrawal, fEPSP slopes after HFS ($203.5 \pm 11.7\%$, $n = 10$) were significantly enhanced compared with fEPSPs obtained from control animals ($144.2 \pm 4.7\%$, $n = 10$, $P < 0.001$). When treatment duration and frequency were reduced to 7 days of cocaine once per day, HFS-LTP ($202.1 \pm 12.1\%$, $n = 12$) remained significantly enhanced compared with saline-treated animals ($160.1 \pm$

9.0% , $n = 12$; $P < 0.05$) after 14 days of withdrawal. LTP was not significantly different between 7- and 14-day cocaine treatment groups. However, when withdrawal time was reduced to 1 day in animals receiving cocaine twice per day for 14 days, the resulting LTP ($168.3 \pm 13.7\%$, $n = 7$) was not significantly different from saline controls ($140.8 \pm 4.3\%$, $n = 9$, $P > 0.05$), indicating that withdrawal time was crucial in enhancing LTP, whereas treatment duration or frequency had no significant impact. Subsequent experiments used the 7-day treatment (once per day) and 14-day withdrawal paradigm.

Previously, we showed that HFS-LTP in the BLA-CeA pathway depends on NRs and L-VGCCs (Fu and Shinnick-Gallagher 2005). To examine whether induction mechanisms were altered in cocaine-enhanced LTP (Fig. 2), slices were superfused with the NMDA antagonist APV ($50 \mu\text{M}$) in ACSF or the L-VGCC antagonist nimodipine (NIM, $10 \mu\text{M}$) 15 min before HFS. APV blocked LTP both in cocaine (control: $202.1 \pm 12.1\%$, $n = 12$; APV: $110.4 \pm 2.4\%$, $n = 5$, $P < 0.001$) and saline (control: $160.1 \pm 9.0\%$, $n = 12$; APV: $107.7 \pm 7.4\%$, $n = 5$, $P < 0.005$) groups. Similarly, NIM blocked LTP in cocaine-treated (control: $202.1 \pm 12.1\%$, $n = 12$; NIM: $104.0 \pm 11.8\%$, $n = 5$, $P < 0.001$) and saline-treated (control: $160.1 \pm 9.0\%$, $n = 12$; NIM: $109.0 \pm 7.7\%$, $n = 5$, $P < 0.005$) groups. These data indicated that NMDA receptors and L-VGCCs are necessary for LTP induction by HFS in cocaine and saline treatment groups.

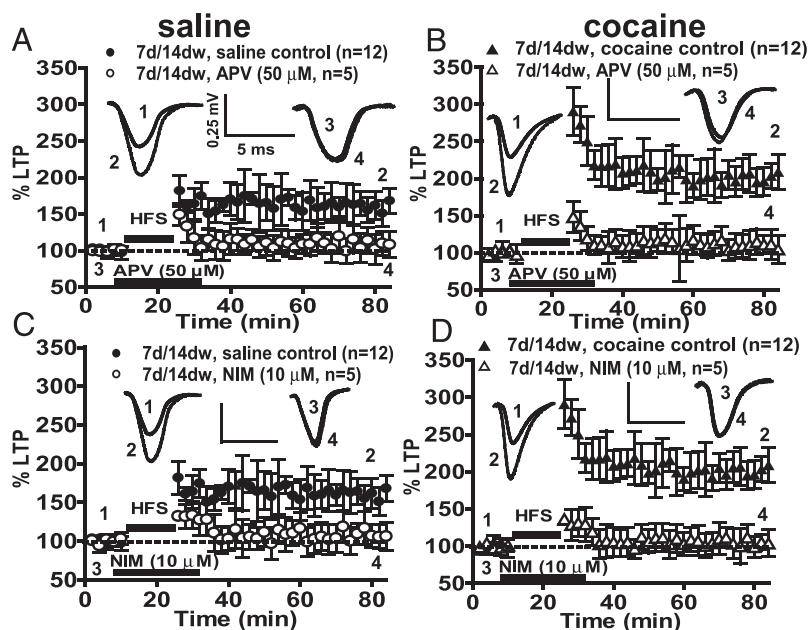


FIG. 2. LTP in the BLA pathway is dependent on *N*-methyl-D-aspartate (NMDA) receptors (A and B) and L-type voltage-gated calcium channels (L-VGCCs) (C and D) in slices 14 days after 7-day treatment with either saline (left) or cocaine (right). In each panel, numbered traces show responses before and after HFS at times indicated in graph in slices from saline (A and C)- and cocaine (B and D)-treated animals in presence and absence of APV (A and B) or nimodipine (NIM; C and D). Graphs below show summary data of LTP time-course in slices from saline (A and C)- and cocaine (B and D)-treated groups in the presence and absence of APV (A and B) or NIM (C and D). The same control data are plotted for saline (A, C, and Fig. 3C) and cocaine (B, D, and Fig. 3D). Calibrations in B–D are the same as in A.

Because CRF has been implicated in the pathophysiology of drug addiction (Sarnyai et al. 2001), we also examined whether CRF receptors modulate HFS-LTP (Fig. 3). The selective CRF₁ antagonist NBI27914 (250 nM) blocked HFS-LTP in cocaine (control: $202.1 \pm 12.1\%$, $n = 12$; NBI: $114.0 \pm 7.4\%$, $n = 5$, $P < 0.001$) and saline (control: $160.1 \pm 9.0\%$, $n = 12$; NBI: $119.9 \pm 2.8\%$, $n = 5$, $P < 0.05$) groups; astressin2-B, a selective CRF₂ antagonist, did not significantly affect HFS-LTP in either group (saline: $164 \pm 25.1\%$, $n = 6$, $P > 0.05$; cocaine: $191 \pm 26.3\%$, $n = 6$, $P > 0.05$). These data indicated an obligatory role for CRF₁ in synaptic plasticity in the BLA–CeA pathway.

To further study the mechanisms contributing to cocaine-enhanced LTP, we analyzed amygdala protein levels using Western blots (7 animals/group; Fig. 3C). NR1 protein was not quite significantly elevated ($P = 0.07$) and P-NR1 protein was significantly increased ($P < 0.03$) in cocaine withdrawn animals, whereas the L-VGCC $\alpha 1C$ subunit (Ca_v1.2, $P > 0.2$) was not altered, suggesting that signaling through NMDA may

be altered after cocaine treatment. However, NMDA/AMPA ratios measured at -20 mV were not changed in cocaine-treated animals (saline: 0.097 ± 0.015 , cocaine: 0.110 ± 0.019 , $n = 6$ /group), indicating that increased phosphorylated NR protein was not reflected in the ratio at this synapse. In agreement with our electrophysiological results, CRF₁ protein levels were significantly increased after cocaine treatment ($P < 0.04$), whereas CRF₂ remained unchanged ($P > 0.35$).

DISCUSSION

Our studies show for the first time that LTP in the BLA–CeA pathway was enhanced after long- but not short-term withdrawal from chronic cocaine, that HFS-induced LTP was modulated endogenously by CRF₁, and that elevated P-NR1 and CRF₁ protein may contribute to cocaine-enhanced LTP. The withdrawal-induced enhancement of LTP may be related to the neuroadaptive effects associated with behavioral sensitization that can persist for 2 wk (Kalivas et al. 1988) and that

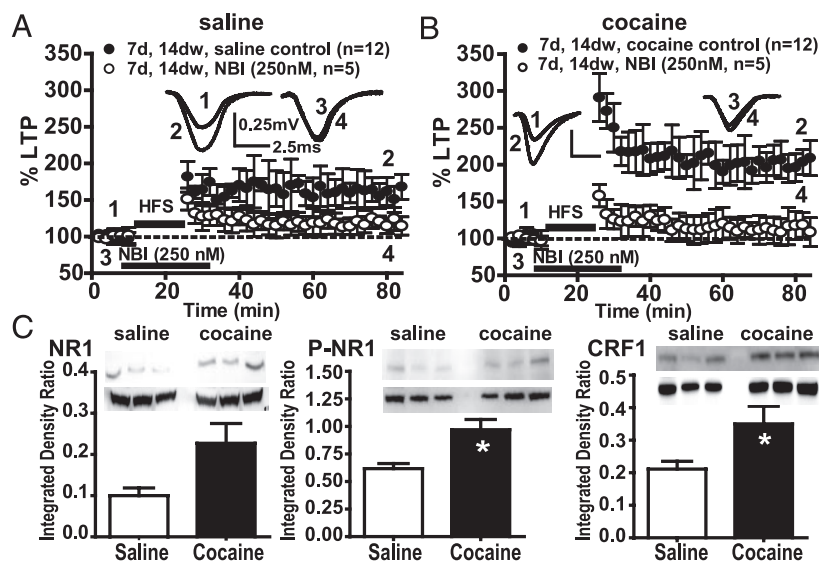


FIG. 3. LTP in BLA–CeA pathway is dependent on corticotropin-releasing factor (CRF)₁ receptors in saline- and cocaine-treated populations and P-NR1, and CRF₁ protein is increased in cocaine-treated populations. A and B: numbered top traces recorded in slices from saline (A)- and cocaine (B)-treated groups show fEPSPs before and after HFS-induced LTP at times indicated in the bottom graphs, which show summary data for LTP time-course. C: Western blots for NR1 (Santa Cruz), P-NR1 (Upstate), and CRF1 (Santa Cruz) protein (top blots) and corresponding actin (Santa Cruz) protein (bottom blots) are expressed as optical density ratios in the summary graphs below. The same control data are plotted for saline (C and Fig. 2, A and C) and cocaine (D and Fig. 2, B and D).

may have a component of associative contextual conditioning (Carey and Gui 1998). Markers for BLA neuronal activity increase in animals exposed to a cocaine environment (Brown et al. 1992; Neisewander et al. 2000; Thomas et al. 2003) even after 4-mo withdrawal (Ciccocioppo et al. 2001). Thus stimulating the BLA may simulate neuronal activity during cue exposure after the animal has been sensitized.

Cocaine-enhanced LTP in the BLA–CeA pathway was critically dependent on withdrawal, whereas baseline fEPSP responsiveness was unchanged. After 4- to 6-day withdrawal after 5-day cocaine treatment, hippocampal LTP was enhanced (Thompson et al. 2002), but after 100-day withdrawal and at higher self-administered cocaine doses, LTP was reduced (Thompson et al. 2004); these effects were also not correlated with an altered fEPSP amplitude. Conversely, at an intralateral amygdala (LA) synapse, an increased baseline response and reduced LTP were observed with cocaine treatment (15 mg/kg, 3 times per day, 1-h intervals for 7 days) and 1- to 3-day withdrawal, but the effect dissipated within 9 days; this reduction in LTP was interpreted as occlusion caused by the facilitated baseline EPSP response (Goussakov et al. 2006). Functionally, these data indicated that long-lasting effects of cocaine were consistently revealed with HFS. Although disparities in findings suggest that changes in synaptic facilitation and plasticity are dependent on brain area, synapse, and treatment paradigm, the studies provide insight into the relative persistence of the effects of cocaine treatment.

HFS-LTP at the BLA–CeA synapse is dependent on NMDA receptors and L-VGCCs. After 2-wk withdrawal from chronic cocaine, NR2B and NR1 subunits are upregulated in other brain areas (Loftis and Janowsky 2000). Here we report a similar increase in P-NR1 protein in the amygdala, which could contribute to the enhanced HFS-LTP after chronic cocaine. However, changes in NMDA/AMPA ratios were not detected, suggesting that the increased P-NR1 proteins may not be accessible to transmitter evoked with single stimuli at this synapse. Cocaine withdrawal also increases calcium entry through L-VGCCs (Nasif et al. 2005), and L-VGCC antagonists block establishment of conditioned locomotion by cocaine (Reimer and Martin-Iverson 1994), suggesting that greater L-VGCC activity in cocaine withdrawn animals could contribute to the cocaine-enhanced HFS-LTP. However, it is unlikely that increased L-VGCC activity contributed to the cocaine-enhanced LTP because $\alpha 1C$ subunit protein was unchanged in the cocaine group. CRF₂ receptor activation potentiated NMDA responses in ventral tegmental area neurons (Ungless et al. 2003) but CRF₂ was not involved in HFS-LTP in the BLA–CeA pathway, and amygdala CRF₂ protein was not increased with chronic cocaine. These data suggest that L-type VGCCs or CRF₂ receptors may not play a role in the cocaine-enhanced LTP, whereas increased P-NR1 protein may contribute to enhanced HFS-LTP but not to singly evoked EPSPs at the BLA–CeA synapse.

Although the CRF₁ antagonist did not affect baseline fEPSPs, subsequent HFS failed to induce LTP in slices from cocaine and saline groups, indicating that CRF₁ receptors are required for LTP induction. We previously showed that exogenous CRF directly enhanced mEPSC frequency in the CeA, suggesting a presynaptic increase in glutamate release (Liu et al. 2004). Repetitively stimulating cerebellar afferents is known to release CRF (Tian and Bishop 2003), and afferent stimulation

(foot-shock) can increase endogenous CRF release in the CeA and BLA (Roozendaal et al. 2002). These results suggested that HFS could enhance endogenous CRF release in the CeA. CRF priming enhances HFS-induced LTP (Blank et al. 2002), CRF itself can induce LTP in the hippocampus (Wang et al. 1998), and at LA–CeA (Pollandt et al. 2006) and BLA–CeA (Fu et al. 2004) synapses, and CRF-induced LTP is enhanced after chronic cocaine. Furthermore, both CRF₁ protein (Radulovic et al. 1998) and mRNA (Chalmers et al. 1995) are found in the BLA, and CRF₁ receptors are located on excitatory type terminals in the CeA (Chalmers et al. 1995), suggesting an anatomical basis for a CRF₁-mediated effect on glutamate release. The block of HFS-LTP by the CRF₁ antagonist, increase in CRF₁ protein, and enhanced responsiveness to CRF in the BLA–CeA pathway (Fu et al. 2004) after cocaine withdrawal suggests that endogenously released CRF acting through CRF₁ receptors contributes to the enhanced LTP in cocaine. CRF is known to enhance locally evoked GABA inhibition in the CeA through CRF₁ receptors (Nie et al. 2004). With GABA inhibition intact, we previously found that low CRF concentrations inhibited evoked excitatory postsynaptic currents (EPSCs) ~40%, whereas in the presence of GABA antagonists, CRF inhibited miniature EPSCs by only 20% (Liu et al. 2004), indicating that one half of CRF-induced inhibition of evoked EPSCs may be caused by CRF-induced GABA release. However, HFS-LTP in this pathway is not significantly altered by GABA antagonists (Fu and Shinnick-Gallagher 2005), and GABA antagonists did not affect NBI inhibition of HFS-LTP (data not shown). Altogether the results suggest that an HFS-induced increase in CRF release in the presence of GABA antagonists resulted in facilitated glutamate release, which prevailed over an inhibitory effect and induced LTP.

Furthermore, our data suggest that increases in P-NR1 and CRF₁ protein and/or their downstream signaling mechanisms may contribute to the cocaine-enhanced LTP at the BLA–CeA synapse.

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