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Cocaine self-administration causes signaling deficits in corticostriatal circuitry that are reversed by BDNF in early withdrawal

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Abstract

Cocaine self-administration disturbs intracellular signaling in prefrontal cortical neurons that regulate neurotransmission in the nucleus accumbens. The deficits in dorsomedial prefrontal cortex (dmPFC) signaling change over time, resulting in different neuroadaptations during early withdrawal from cocaine self-administration than after one or more weeks of abstinence. Within the first few hours of withdrawal, there is a marked decrease in tyrosine phosphorylation of critical intracellular and membrane-bound proteins in the dmPFC that include ERK/MAP kinase and the NMDA receptor subunits, GluN1 and GluN2B. These changes are accompanied by a marked increase in STEP tyrosine phosphatase activation. Simultaneously, ERK and PKA-dependent synapsin phosphorylation in presynaptic terminals of the nucleus accumbens is increased that may have a destabilizing impact on glutamatergic transmission. Infusion of brain-derived neurotrophic factor (BDNF) into the dmPFC immediately following a final session of cocaine self-administration blocks the cocaine-induced changes in phosphorylation and attenuates relapse to cocaine seeking for as long as three weeks. The intra-dmPFC BDNF infusion also prevents cocaine-induced deficits in prefronto-accumbens glutamatergic transmission that are implicated in cocaine seeking. Thus, intervention with BDNF in the dmPFC during early withdrawal has local and distal effects in target areas that are critical to mediating cocaine-induced neuroadaptations that lead to cocaine seeking.

Keywords

BDNF; ERK MAP kinase; glutamate; nucleus accumbens; prefrontal cortex; reinstatement

1. Therapeutic intervention during early withdrawal for cocaine addiction

Development of pharmacotherapies for substance use disorders (SUDs) targets all phases of the addictive process: intoxication, withdrawal preceding abstinence initiation, use reduction, and maintenance of relapse prevention (Ross and Peselow, 2009). However, there

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is no FDA-approved pharmacological agent that effectively prevents any phase of the addiction process (Skolnick and Volkow, 2012; Volkow and Skolnick, 2012). Preclinical evidence indicates that early withdrawal is a critical period in which to intervene with BDNF to prevent persistent relapse to cocaine-seeking (Berglind et al., 2007; Whitfield et al., 2011). However, despite BDNF's enduring effects on cocaine-seeking when infused into the dorsomedial prefrontal cortex (dmPFC), it is not a good candidate for therapy because it is expensive and does not cross the blood-brain barrier effectively. In contrast, there are systemically-active SUD medication candidates that target cocaine-induced disturbances in glutamate transmission with the aim of strengthening fronto-striatal inhibitory control over relapse to cocaine-seeking. These include *N*-acetyl-cysteine (Baker et al., 2003; Kupchik et al., 2011), ceftriaxone (Knackstedt et al., 2010; Sondheim and Knackstedt, 2011; Ward et al., 2011), and modulators of metabotropic glutamate receptors (Gass and Olive, 2008; Hao et al., 2010). However, all of these glutamate-related ligands have been administered immediately before a drug-seeking or -taking test in animals after different periods of abstinence. In contrast to intervention after neuroadaptations have emerged during abstinence from cocaine self-administration (SA) (Kalivas, 2009), early intervention has the potential advantage of preventing the emergence of long-term drug-induced neuroadaptations that promote persistent relapse to drug-seeking. Moreover, early intervention underscores the dynamic nature of cocaine-induced changes over time and suggests that treatment based on strengthening prefrontal inhibitory control over drug-seeking may be most effective when the intervention occurs before impulsive drug-seeking becomes compulsive. Thus, identification of treatments that prevent cocaine-induced neuroadaptations early in withdrawal represents a novel approach that may prevent escalation of drug use and reduce the suffering and burden of SUDs in human cocaine abusers.

2. The significance of altered PFC functioning during early withdrawal from cocaine

The PFC is a major brain executor of goal-directed behaviors and impulse control, with several subdivisions that selectively mediate responses to different environmental stimuli relevant to cocaine abuse (Capriles et al., 2003; Goldstein and Volkow, 2002; Jentsch and Taylor, 1999; McFarland and Kalivas, 2001; Peters et al., 2008; Volkow and Fowler, 2000). Chronic human cocaine users are vulnerable to persistent drug-seeking that is linked to reduced metabolic activity in the PFC during abstinence (Baler and Volkow, 2006; Goldstein and Volkow, 2002; Hester and Garavan, 2004) and increased metabolic activity in response to cues associated with cocaine (Childress et al., 1999). Animals with a cocaine SA history also have reduced activity in the PFC during cocaine withdrawal (Porrino and Lyons, 2000; McGinty et al., 2010) and increased immediate early gene expression elicited by relapse to cocaine-seeking (Hearing et al., 2008; Zavala et al., 2008; Cruz et al., 2014).

Cocaine-induced deficits in the structure and/or function of the PFC have been demonstrated after both short and long access preclinical models (Briand et al., 2008; George et al., 2008; Kalivas 2009; Whitfield et al., 2011; Sun et al., 2013). A common feature arising out of these reports is that PFC deficits become greater and last longer as the duration of cocaine

intake escalates. In fact, it has been proposed that intervention to strengthen prefrontal inhibitory control when goal-directed behavior is still intact and escalation to compulsive drug-seeking and negative affective states have not yet solidified may be the most effective time to begin treatment and prevent the transition to addiction (Koob and Volkow, 2009; George and Koob, 2010). The ability to strengthen PFC inhibitory control depends on a better understanding of how cocaine triggers dysfunction of glutamatergic neurons that project from PFC to NAc, a dysfunction that emerges after short access to cocaine in animal models. Reinstatement of drug-seeking induced by conditioned cues or a drug prime in rats with a cocaine SA history is driven in large part by a suppression of basal extracellular glutamate levels that is associated with an excessive cocaine prime-induced extracellular overflow of glutamate in the NAc core (McFarland et al., 2003). Basal glutamate levels in the NAc are suppressed as early as 24 hr after a short access cocaine SA regimen and the suppression persists for weeks (Lutgen et al., 2012).

Few other studies have investigated changes in the PFC and NAc during cocaine SA or early withdrawal in rodents. However, two stand out because they provide important clues about the effects of repeated cocaine SA on glutamatergic transmission. First, Sun and Rebec (2006) demonstrated that repeated short access (2 hr daily) cocaine SA decreased baseline firing (from day 1) but increased the duration of bursting (from session 10–21) by pyramidal neurons in the PFC, suggesting that alterations in PFC excitability and sensitivity to repeated short access cocaine emerge early during exposure and persist. Second, Miguens and colleagues (2008) demonstrated that, once cocaine SA is established, but not after acute i.v. cocaine administration, extracellular glutamate levels in the NAc increase markedly toward the end of a daily 2-hr session and remain elevated for at least 40 min after the end of SA (the maximum duration of the measurements). These data suggest that glutamate uptake mechanisms are overwhelmed by repeated cocaine infusions so that glutamate overflows into the extrasynaptic space and the effects endure beyond the last cocaine infusion (Kalivas, 2009).

3. Cocaine SA dephosphorylates ERK and GluN2B in the PFC

ERK phosphorylation is a reliable biomarker associated with combined dopamine and glutamate receptor activation that causes a transient, NMDA receptor-mediated spike in Ca^{2+} influx (Fiore et al., 1993). Intermittent cocaine exposure causes this type of ERK phosphorylation in the striatum that is associated with the rewarding and memory consolidating properties of cocaine (Miller et al., 2007; Valjent et al., 2000, 2005). However, prolonged exposure to glutamate causes ERK dephosphorylation by causing a further rise in Ca^{2+} that activates protein phosphatase 2B (PP2B) (Mulholland et al., 2008; Paul and Connor, 2010). PP2B dephosphorylates and activates PP1 that dephosphorylates and thereby activates the protein tyrosine phosphatase, STEP (striatal-enriched tyrosine phosphatase), which then dephosphorylates ERK in cortical cultures (Paul and Connor, 2010). This cascade is blocked by NMDA receptor GluN2B subtype-selective antagonists. Interestingly, the NMDA-induced ERK shut-off in cortical cultures is over-ridden by BDNF, the effects of which are linked to synaptic strengthening (Mulholland et al., 2008). We have found that within 2 hr of the end of cocaine SA, ERK and CREB in the dmPFC are profoundly dephosphorylated and a single BDNF infusion into dmPFC immediately after the

end of SA prevents this deactivation (Whitfield et al., 2011). Thus, it is possible that prolonged extracellular glutamate causes overstimulation of NMDA receptors, triggering the critical shut-off of ERK phosphorylation in the dmPFC that contributes to relapse, a process that is reversed by intra-dmPFC infusion of BDNF immediately after the last cocaine SA session (Figure 1). This hypothesis is consistent with our more recent data demonstrating that 2 hr after the end of cocaine SA, not only are ERK and CREB dephosphorylated but STEP is activated and GluN2B, also a substrate of STEP, is dephosphorylated at Y1472 (Sun et al., 2013). The total amount of GluN2B is also decreased in dmPFC, suggesting that during early withdrawal from repeated cocaine exposure, there is a compensatory reduction in the total number of GluN2B-containing receptors as well as fewer GluN2B receptors on the cell surface of dmPFC neurons because phosphorylation of the Y1472 site is critical for surface expression of NMDA receptors (Lau and Huganir, 1995; Goebel-Goody et al., 2008). Alternatively GluN2A may be dephosphorylated by STEP at Y1325 as selective inhibition of GluN2A receptors also attenuates cocaine-seeking (Go et al., in prep). The link between TrkB receptors and NMDA receptors is most likely via activation of Src family kinases (SFKs) known to phosphorylate Y1472 in GluN2B and Y1325 in GluN2A (Salter and Kalia, 2004) as a SFK inhibitor, PP2, also attenuates cocaine-seeking (Barry et al., in prep).

Whereas ERK is activated almost exclusively by the MAPK, MEK1/2, it is a substrate for at least three different phosphatase families: (1) the protein tyrosine phosphatases (PTP-Tonks, 2006), (2) the serine/threonine protein phosphatase 2A (PP2A-Alessi et al., 1995), and (3) the dual-specificity map kinase phosphatases (MKP-Owens and Keyes 2007). Based on extensive research by Lombroso and colleagues, calcineurin-activated STEP appears to be the most likely mediator of the NMDA receptor-mediated ERK shut-off (Braithwaite et al., 2006b; Paul et al., 2003; Paul and Connor, 2010) because it is blocked by GluN2B antagonists and the calcineurin inhibitor, cyclosporin A. Further, STEP⁶¹ (an isoform of STEP with MW 61kDa) is well-expressed in PFC pyramidal neurons (Boulanger et al., 1995) and STEP activation can be detected by a decrease in its phosphorylated (resting) state. When activated STEP binds to and selectively dephosphorylates the Y1472 site in the GluN2B receptor subunit and dephosphorylates the Src family kinase, fyn, that phosphorylates GluN2B at that site, endocytosis and LTD are facilitated (Braithwaite et al., 2006a,b). Therefore, an attractive hypothesis is that GluN2B/PP2B/PP1-activated STEP mediates the cocaine SA-induced ERK shutoff in the dmPFC. In support of this hypothesis, phospho-STEP⁶¹-immunoreactivity is decreased in the dmPFC 2 hr after the end of cocaine SA, suggesting that STEP is activated and is a likely mediator of the cocaine SA-induced ERK shutoff in the dmPFC during early withdrawal (Sun et al., 2013). In contrast, phospho-Y307-PP2A is elevated 2 hr after the end of cocaine SA (Sun et al., 2013), suggesting that PP2A is inactivated (Mao et al., 2005) and does not mediate the cocaine SA-induced ERK shutoff.

4. Cocaine SA increases synapsin I phosphorylation in nucleus accumbens

We have previously demonstrated that one intra-dmPFC BDNF infusion immediately following the last cocaine SA session normalized the cocaine-induced disturbance of glutamate transmission in the NAc after extinction and a cocaine prime that is associated

with cocaine-seeking (Berglind et al., 2009). However, the molecular mechanism mediating the BDNF effect on cocaine-induced alterations in extracellular glutamate levels is unknown. Because BDNF activates ERK phosphorylation, we searched for ERK targets that regulate glutamate release and chose to investigate the phosphorylation state of synapsins, presynaptic proteins that mediate synaptic vesicle mobilization, that are phosphorylated at several sites by different kinases. Two hr after SA ended, phospho-synapsin Ser9 (PKA/CAMKI) and phospho-synapsin Ser62/67 (ERK), but not phospho-synapsin Ser603 (CAMKII), were increased in the NAc of cocaine SA rats and at 22 hr, only phospho-synapsin Ser9 was still elevated (Sun et al., in press). The elevated phospho-synapsin at both timepoints was attenuated by an intra-dmPFC BDNF infusion immediately after the end of cocaine SA. BDNF also reduced cocaine SA withdrawal-induced phosphorylation of the protein phosphatase 2A C-subunit (PP2Ac) at both time points, suggesting that BDNF disinhibits PP2Ac, consistent with p-synapsin Ser9 dephosphorylation. Further, co-immunoprecipitation demonstrated that PP2Ac and synapsin are associated in a protein-protein associated complex that was reduced after 2 hr of withdrawal from cocaine SA and reversed by BDNF. Taken together, these findings demonstrate that BDNF normalizes the cocaine SA-induced elevation of phospho-synapsin in NAc that may underlie a disturbance in the probability of neurotransmitter release or represent a compensatory neuroadaptation in response to the hypofunction within the PFC-NAc pathway during cocaine withdrawal.

6. PKA-dependent CREB and GluA1 Ser845 phosphorylation is upregulated in dmPFC after one week of abstinence and reversed by relapse

Abstinence from cocaine SA is associated with neuroadaptations in the dmPFC and NAc that are implicated in cocaine-induced neuronal plasticity and relapse to drug-seeking. Alterations in PKA signaling are prominent in medium spiny neurons in the NAc after repeated cocaine exposure but little is known about similar changes in the PFC. Because cocaine SA induces disturbances in glutamatergic transmission in the PFC-NAc pathway, we examined whether dysregulation of PKA-mediated molecular targets in PFC-NAc neurons occurs during abstinence and, if so, whether it contributes to cocaine seeking. We measured the phosphorylation of CREB (Ser133) and GluA1 (Ser845) in the dmPFC and synapsin I (Ser9, Ser62/67, Ser603), in the NAc after 7 days of abstinence from cocaine SA with or without cue-induced cocaine-seeking. We also evaluated whether infusion of the PKA inhibitor, 8-bromo-Rp-cyclic adenosine 3', 5'-monophosphorothioate (Rp-cAMPs), into the dmPFC after abstinence would affect cue-induced cocaine-seeking and PKA-regulated phosphoprotein levels. Seven days of forced abstinence increased the phosphorylation of CREB and GluA1 in the dmPFC and synapsin I (Ser9 but not Ser 62/67 or Ser603) in the NAc. Induction of these phosphoproteins was reversed by a cue-induced relapse test of cocaine-seeking (Sun et al., 2014). Bilateral intra-dmPFC Rp-cAMPs rescued abstinence-elevated PKA-mediated phosphoprotein levels in the dmPFC and NAc and suppressed cue-induced relapse. Thus, by inhibiting abstinence-induced PKA molecular targets, relapse reverses neuroadaptations in the dmPFC after one week of abstinence.

7. Conclusions

Cocaine-induced disturbances in dmPFC signaling during early withdrawal from cocaine self-administration differ from those that emerge after one or more weeks of abstinence. Within the first few hours of withdrawal, there is a marked decrease in tyrosine phosphorylation of critical intracellular and membrane-bound proteins in the dmPFC that include ERK MAP kinase and the NMDA receptor subunits, GluN1 and GluN2B that are likely mediated by STEP tyrosine phosphatase. Further destabilization of dmPFC-NAc transmission may be indicated by ERK- and PKA-dependent synapsin phosphorylation in presynaptic terminals of the NAc. Infusion of BDNF into the dmPFC immediately following a final session of cocaine self-administration blocks the cocaine-induced changes in phosphorylation and attenuates relapse to cocaine seeking. The intra-dmPFC BDNF infusion also prevents cocaine-induced deficits in dmPFC-NAc glutamatergic transmission that are implicated in cocaine seeking. However, cocaine-induced neuroadaptations in PKA-dependent signaling occur after one week of abstinence, when BDNF infusions are no longer effective (Berglind et al., 2007), that are normalized by a PKA inhibitor and relapse. Thus, restoring synaptic activity in the dmPFC requires different types of intervention at different intervals during abstinence in order to decrease susceptibility to relapse in animals with a history of cocaine exposure.

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Abbreviations

BDNF	brain-derived neurotrophic factor
CREB	cAMP response element binding protein
ERK	extracellular-regulated kinase
MAPK	mitogen activated protein kinase
MEK	mitogen activated extracellular-regulated protein kinase
NAc	nucleus accumbens
dmPFC	dorsomedial prefrontal cortex
PKA	protein kinase A
SA	self-administration
STEP	striatal-enriched protein tyrosine phosphatase
SUD	substance use disorder

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Highlights

1. Cocaine induces signaling deficits in corticostriatal circuitry during early withdrawal
2. STEP is implicated in cocaine-induced dephosphorylation in the prefrontal cortex
3. BDNF restores phosphorylation in the prefrontal cortex and nucleus accumbens
4. Cocaine induces PKA-dependent signaling in corticostriatal circuitry that is reversed by relapse after one week of abstinence

Figure 1A

Figure 1B

Figure 1.

Possible substrates underlying dephosphorylation of ERK and CREB in PFC during early withdrawal from cocaine self-administration (A) and restoration of phosphorylation by intra-dmPFC BDNF infusion (B). A. Prolonged extra-synaptic NMDA receptor activation causes a sharp rise in Ca^{2+} that activates PP2B, and, likely via DARPP-32 dephosphorylation, disinhibits PP1 that dephosphorylates and thereby activates the protein tyrosine phosphatase, STEP, that then dephosphorylates ERK. B. An intra-dmPFC BDNF infusion immediately after the last cocaine SA session enhances ERK and CREB phosphorylation in a synaptic NMDA receptor-dependent manner likely mediated by a Src family kinase. AC=adenylyl cyclase, B=BDNF, DA=dopamine, D1R=dopamine 1 receptor, D32=DARPP32, Glu=glutamate, P=phosphate, PP1=protein phosphatase 1, PP2B=protein phosphatase 2B, SFK= Src family kinase, STEP=striatal-enriched phosphatase. Fuzzy postsynaptic membrane=postsynaptic density.