HHS Public Access

Author manuscript

Addict Neurosci. Author manuscript; available in PMC 2023 May 18.

Published in final edited form as:

Addict Neurosci. 2022 June ; 2: . doi:10.1016/j.addicn.2022.100006.

BDNF as a therapeutic candidate for cocaine use disorders

Jacqueline F. McGinty

Department of Neuroscience, Medical University of South Carolina, 173 Ashley Ave MSC 510, Charleston, SC 29425, USA

Abstract

Cocaine self-administration disturbs intracellular signaling in multiple reward circuitry neurons that underlie relapse to drug seeking. Cocaine-induced deficits in prelimbic (PL) prefrontal cortex change during abstinence, resulting in different neuroadaptations during early withdrawal from cocaine self-administration than after one or more weeks of abstinence. Infusion of brain-derived neurotrophic factor (BDNF) into the PL cortex immediately following a final session of cocaine self-administration attenuates relapse to cocaine seeking for an extended period. BDNF affects local (PL) and distal subcortical target areas that mediate cocaine-induced neuroadaptations that lead to cocaine seeking. Blocking synaptic activity selectively in the PL projection to the nucleus accumbens during early withdrawal prevents BDNF from decreasing subsequent relapse. In contrast, blocking synaptic activity selectively in the PL projection to the paraventricular thalamic nucleus by itself decreases subsequent relapse and prior intra-PL BDNF infusion prevents the decrease. Infusion of BDNF into other brain structures at different timepoints after cocaine self administration differentially alters cocaine seeking. Thus, the effects of BDNF on drug seeking are different depending on the brain region, the timepoint of intervention, and the specific pathway that is affected.

Keywords

BDNF; Cocaine; Heroin; Nucleus accumbens; Paraventricular thalamus; Prelimbic cortex

1. Intervention during early withdrawal for cocaine addiction

Development of pharmacotherapies for substance use disorders (SUDs) Development is needed to target all phases of the addictive process: intoxication, withdrawal preceding abstinence initiation, use reduction, and maintenance of relapse prevention [1]. However, there is no FDA-approved pharmacological agent that effectively prevents any phase of the addiction process [2,3]. Preclinical evidence indicates that withdrawal preceding abstinence is a critical period in which altering BDNF expression in the prefrontal prelimbic (PL) cortex decreases persistent relapse to cocaine-seeking [4,5]. The intra-

mcginty@musc.edu .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

PL BDNF infusion also prevents cocaine-induced deficits in PL->NAc glutamatergic transmission that are implicated in cocaine seeking [6]. In contrast to intervention after neuroadaptations have emerged during more prolonged abstinence from cocaine exposure [7], 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. However, despite BDNF's enduring effects on cocaine-seeking when infused into the PL cortex during early withdrawal, because it is a peptide, it is not a good candidate for therapeutic development because peptides (1) are expensive to manufacture [8], (2) have unsuitable pharmacokinetic profiles (short half life, poor blood-brain barrier penetrability, low bioavailability [9], and (3) have different effects in different brain regions at different timepoints during abstinence. This review will focus on the last point, covering studies in which exogenous BDNF or BDNF ligands are administered during or after cocaine self administration because it is the main body of literature in which BDNF has been studied outside the alcohol research field. The effect of BDNF manipulations in alcohol use disorder was reviewed comprehensively in 2020 [10].

2. BDNF is a neurotrophic peptide that mediates synaptic plasticity including drug-induced neuroadaptations

BDNF, a member of the neurotrophin polypeptide family that includes nerve growth factor, neurotrophin-3, and neurotrophin 4/5, is the most widely and abundantly expressed neurotrophin in the nervous system [11]. Like other neuropeptides, BDNF is synthesized as a pro-peptide (32 kDa) that is proteolytically processed into a smaller (14 kDa), mature form [12]. BDNF triggers changes in tropomyosin receptor kinase B (TrkB)-mediated intracellular signaling and transcription factor activity [13]. TrkB has two isoforms, the full length sequence (TrkB.FL) that contains tyrosine kinase activity and the truncated form (TrkB.T1) that does not [14]. TrkB.FL is primarily expressed in neurons whereas TrkB.T1 is predominantly expressed by astrocytes [15]. Through these mechanisms, BDNF enhances neuronal activity and synaptic plasticity related to cognitive function [16]. BDNF promotes both early- and late-phase long-term potentiation (LTP), promotes dendritic protein synthesis, and increases dendritic spine formation [17–19]. BDNF also regulates drug-induced long-term neuroadaptations that encompass alterations in molecular components at synapses, changes in gene expression, and modifications of learning and memory that affect behavioral output [20]. BDNF regulates the integration of dopaminergic and glutamatergic input to medium spiny neurons in the striatum that generates molecular changes in dendritic spines and activation of a variety of intracellular cascades important for associative learning [21]. Repeated alterations in calcium influx, phosphorylation–dephosphorylation events, and the activation of immediate early genes and transcription factors culminate in changes in neuronal structure and synaptic composition that ultimately modify behavior.

Cocaine effects on BDNF in key regions of reward circuitry has been extensively reviewed, most recently by Li and Wolf [22]. Briefly, repeated non-contingent or contingent cocaine exposure tends to increase *Bdnf* mRNA and/or BDNF protein levels in the PFC and NAc with considerable temporal variation during abstinence [23,24]. An exception was reported within 24 h of the end of cocaine exposure when *Bdnf* mRNA was decreased in the prelimbic cortex [4]. A decrease in *Bdnf*/BDNF levels during acute withdrawal may contribute to PFC hypoactivity and the ability of TrkB stimulation at that time to normalize PFC function and oppose subsequent cocaine seeking.

3. BDNF reverses PFC deficits 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 [25–29]. Chronic human cocaine users are vulnerable to persistent drug seeking that is linked to reduced metabolic activity in the PFC during abstinence [30–32]. Animals with a cocaine self-administration history also have reduced activity in the PFC during cocaine withdrawal [33–35].

The medial PFC in rodents is a heterogeneous region comprised of (from dorsal to ventral) the anterior cingulate, prelimbic (PL), and infralimbic (IL) cortices. A preponderance of evidence indicates that the PL region that projects to the NAc core drives cocaine seeking whereas the IL region that projects to the NAc shell decreases cocaine seeking after extinction [27,28]. Cocaine-induced deficits in the function of the PL PFC have been demonstrated after both short and long access cocaine self administration [5,36–38]. A common feature arising out of these reports is that PL PFC deficits, particularly in protein phosphorylation, morphological and synaptic plasticity, as well as cognitive function, 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 [39–40]. Accordingly, BDNF reverses the dysfunction of PL->NAc glutamatergic neurons that emerges during early withdrawal from cocaine and subsequently triggers relapse to cocaine seeking in animal models.

4. BDNF promotes synaptic strengthening through the regulation of kinase and phosphatase activity

In contrast to ERK MAP kinase phosphorylation (activation) induced by acute cocaine [41–43], prolonged exposure to cocaine causes ERK dephosphorylation by activating NMDA-mediated striatal-enriched tyrosine phosphatase, STEP [44]. Thus, a prolonged increase in extracellular glutamate levels causes overstimulation of NMDA receptors, triggering STEP activation and ERK MAP kinase dephosphorylation. Interestingly, the NMDA-induced ERK dephosphorylation in cortical cultures is overridden by BDNF, the effects of which are linked to synaptic strengthening [45]. We have found that within 2 h of the end of cocaine SA, ERK and the transcription factor, CREB (cAMP-dependent response element binding protein), in the PL cortex are profoundly dephosphorylated and a single BDNF infusion

into PL cortex immediately after the end of SA prevents this deactivation [5]. Further, our data demonstrate that STEP is activated and the AMPA receptor subunits, GluN2B and GluN2A, which are STEP substrates, are dephosphorylated in PL cortex [38]. Inhibition of STEP or selective blockade of GluN2A or GluN2B receptors in PL cortex attenuates cocaine-seeking [46–47]. Src family kinases (SFKs) have been shown to link TrkB receptors and NMDA receptors [48] and the SFK inhibitor, PP2, also attenuates cocaine-seeking [49]. When activated, STEP not only binds to and dephosphorylates the Y1472 site in the GluN2B receptor subunit but it also dephosphorylates the SFK, fyn, that phosphorylates GluN2B at that site, facilitating endocytosis and long term depression [50]. Finally, BDNF decreases STEP action through proteasomal degradation [51]. Fig. 1 illustrates BDNF-TrkB signaling in control rats and during early withdrawal from cocaine self administration.

5. BDNF has different effects in different brain regions at different timepoints during abstinence

Infusion of BDNF into subcortical structures, like the VTA and NAc, during early withdrawal or repeatedly during self administration, respectively, enhances cocaine seeking [52,53]. Conversely, repeated administration of BDNF antiserum into the NAc during cocaine self administration attenuates cocaine-induced reinstatement [53]. These findings have led some investigators to speculate that BDNF activity promotes vulnerability to drug addiction and that therapeutic approaches that inhibit BDNF signaling may decrease individuals' motivation to seek cocaine [22,53]. However, this conclusion is based only on effects in subcortical brain regions during or immediately after self administration and does not take into consideration that the effects of BDNF on drug seeking are site- and time-dependent [34,35]. In contrast, for example, when BDNF was infused into NAc 15 min before a cue-induced reinstatement test, it decreased cocaine seeking in rats with a cocaine history whereas blocking TrkB receptors or inactivating endogenous BDNF potentiated cocaine seeking [54]. Further, knocking down BDNF using a shRNA during cocaine self administration increased the cocaine break-point in a progressive ratio schedule of reinforcement [23]. Thus, BDNF has a diverse and complex role in relapse to cocaine-seeking based on its site-specific effects and timing of administration. Furthermore, these data underscore the complexity of endogenous BDNF activity and serve to caution the promotion of theories about BDNF's possible therapeutic value in the treatment of cocaine addiction.

In contrast to the ability of intra-PL BDNF to decrease cocaine seeking when infused during early abstinence, intra-PL BDNF administration after one week of abstinence, when pERK levels are normal, does not affect relapse to cocaine seeking [4]. In fact, after one week of abstinence, protein kinase A-dependent phosphorylation of pCREB and pGluA1 is elevated and a PKA inhibitor normalizes this hyperphosphorylation and decreases relapse [55]. Thus, plasticity-related protein activation in PFC that drives cocaine seeking undergoes biphasic changes during the first week of abstinence, altering its susceptibility to therapeutic interventions.

6. Divergent prelimbic cortical pathways interact with BDNF to regulate cocaine seeking

The ability of intra-PL BDNF administration during early withdrawal to decrease relapse is blocked by NMDA receptor antagonists in PL cortex [46]. However, NMDA receptors and TrkB, the cognate receptor for BDNF, are expressed by both interneurons and pyramidal projection neurons in the PFC [56], obscuring the cellular site of action of BDNF. To determine whether synaptic activity in excitatory neurons in PL cortex is sufficient for BDNF's effect on relapse, we utilized a viral vector chemogenetic approach to inhibit only the CAMKII-expressing glutamatergic projection neurons in the PL cortex [57]. The PL cortex of rats was infused with an inhibitory Designer Receptor Exclusively Activated by Designer Drugs (DREADD-hM4Di) viral vector driven by a CAMKII promoter. Immediately after the last of 14 cocaine self-administration sessions, rats were injected i.p. with clozapine-N-oxide (CNO) 30 min before an intra-PL BDNF microinfusion. DREADD-mediated inhibition of the PL cortex blocked the BDNF-induced decrease in cocaine seeking after abstinence and cue-induced reinstatement after extinction. Unexpectedly, DREADD inhibition of PL neurons in intra-PL PBS-infused rats also reduced cocaine-seeking, suggesting that multiple PL pathways affect relapse. We then used an intersectional viral vector DREADD approach to inhibit selective projection pathways originating in the PL cortex. We tested whether DREADD inhibition of PL projections to the NAc core altered cocaine-seeking in intra-PL BDNF- or PBS-infused rats. Selective inhibition of the PL->NAc pathway at the end of cocaine self-administration blocked the BDNF-induced decrease in cocaine seeking but had no effect in PBS-infused rats [57], confirming our hypothesis that the PL->NAc pathway is hypoactive during early cocaine withdrawal.

In order to determine what PL pathway mediates the ability of αCaMKII-driven hM4Di to decrease relapse independently of BDNF, we focused on the paraventricular thalamic nucleus (PVT) for several reasons. First PVT plays a crucial role in modulating motivational behaviors including relapse to drug seeking [58–62]. Second, layer VI neurons within the PL cortex provide a major source of innervation to the PVT [61,63]. Third, distinct neuronal ensembles within the PL cortex projecting to either NAc core or PVT show opposite neuronal activity in response to reward-associated conditioned cues [64]. In contrast to inhibiting the PL->NAc pathway, selective inhibition of the PL->PVT pathway in intra-PL PBS-infused rats decreased relapse to cocaine-seeking and this effect was prevented in BDNF-infused rats, restoring relapse. Thus, BDNF appears to strengthen synaptic transmission in both pathways, reversing the hypoactivity imposed by cocaine on the PL->NAc pathway to decrease relapse and reversing the chemogenic-induced inhibition of the PL->PVT pathway to restore relapse. Interestingly, *Bdnf* mRNA and BDNF protein are highly expressed in the PVT [65] but future experiments are necessary to discover the genetic profile of these neurons and where they project.

7. Conclusions

Cocaine-induced disturbances in PL 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 PL cortex that include ERK MAP kinase and the NMDA receptor subunits, GluN2A and GluN2B, that are mediated by STEP tyrosine phosphatase. Infusion of BDNF into the PL cortex immediately following a final session of cocaine self administration blocks the cocaine-induced changes in phosphorylation and attenuates relapse to cocaine seeking. The intra-PL BDNF infusion also prevents cocaine-induced deficits in PL->NAc glutamatergic transmission that are implicated in cocaine seeking [6]. However, BDNF infusions are no longer effective after one week of abstinence [4] when cocaine-induced neuroadaptations in PKA-dependent signaling occur. These neuroadaptations are normalized by local PL infusion of a PKA inhibitor that prevents relapse [55]. Thus, restoring synaptic activity in the PL cortex requires different types of interventions at different intervals during abstinence in order to decrease susceptibility to relapse in animals with a history of cocaine exposure. Further, activity in the PL->NAc pathway is responsible for the therapeutic effect of BDNF on cocaine seeking whereas inhibition of activity in the PL-pPVT pathway elicits a similar therapeutic effect in the absence of BDNF, suggesting that these two PL projection pathways exert opposing actions that trigger relapse. Fig. 2 illustrates the distribution of BDNF-TrkB signaling in this circuitry.

8. Future directions

BDNF is an outstanding research tool to probe the circuitry underlying substance use disorders in preclinical models because (a) its expression is highly affected in many areas of the reward system by several paradigms of drug administration, particularly well established for cocaine self-administration models in rodents and (b) direct brain manipulations or administration of BDNF profoundly affect drug seeking. However, beyond its expense and poor bioavailability, the effects of BDNF are site- and time-dependent which limits its value as a candidate for clinical therapeutic development. Future directions should focus on BDNF as a critical neurobiological research tool, discovering the cell- and projection-specific expression of BDNF and TrkB and manipulations within those cell populations. In addition, further development of small molecules that promote or antagonize BDNF function is a promising endeavor. However, a hurdle to overcome is that small molecules have difficulty binding to and activating the TrkB dimer in contrast to BDNF [9]. Despte this drawback, TrkB antagonists, such as ANA-12 and cyclotraxin-B, have anxiolytic effects [66,67] and a tat-cyclotraxin-B fusion protein that crosses the blood brain barrier decreases cocaine self administration and reinstatement after extinction [68]. In contrast, systemic injection of the small molecule TrkB agonist, 7,8-dihydroxyflavone (DHF), has been reported to activate TrkB receptors in the amygdala and to enhance the acquisition of fear and its extinction [69] but no studies have been reported that DHF is effective in decreasing cocaine seeking. Lastly, characterization of the function of truncated TrkB in astrocytes and its non-tyrosine kinase-dependent activation by BDNF [15] in preclinical substance use disorder research promise to propel the field forward.

Acknowledgments

This work was funded by National Institutes of Health grants [R01 DA033479 and R01 DA049711].

Abbreviations:

BDNF	brain-derived neurotrophic factor
CREB	cAMP response element binding protein
ERK	extracellular-regulated kinase
MAPK	mitogen activated protein kinase
NAc	nucleus accumbens
NMDA	N-methyl-D-aspartate
PL	prelimbic cortex
PKA	protein kinase A
PVT	paraventricular thalamic nucleus
STEP	striatal-enriched protein tyrosine phosphatase
SUD	substance use disorder

References

[1]. Ross SR, Peselow E, Pharmacotherapy of addictive disorders, Clin. Neuropharmacol 32 (2009) 277–289. [PubMed: 19834993]

[2]. Skolnick P, Volkow N, Addiction therapeutics: obstacles and opportunities, Biol. Psychiatry 72 (2012) 890–891. [PubMed: 23121867]

[3]. Volkow ND, Skolnick P, New medications for substance use disorders: challenges and opportunities, Neuropsychopharm. Rev 37 (2012) 290–292.

[4]. Berglind WJ, See RE, Fuchs RA, Ghee SM, Whitfield TW, Miller SW, McGinty JF, A BDNF infusion into the medial prefrontal cortex suppresses cocaine-seeking in rats, Eur. J. Neurosci 26 (2007) 757–766. [PubMed: 17651427]

[5]. Whitfield TW, Gomez AM, McGinty JF, The suppressive effect of an intra-prefrontal cortical infusion of BDNF on cocaine relapse is Trk receptor and extracellular signal-regulated protein kinase mitogen activated protein kinase dependent, J. Neurosci 31 (2011) 834–842. [PubMed: 21248106]

[6]. Berglind WJ, Whitfield TW, LaLumiere RT, Kalivas PW, McGinty JF, A single intra-PFC infusion of BDNF prevents cocaine-induced alterations in extracellular glutamate within the nucleus accumbens, J. Neurosci 29 (2009) 3715–3719. [PubMed: 19321768]

[7]. Kalivas PW, Glutamate homeostasis hypothesis of addiction, Nat. Rev. Neurosci 10 (2009) 561–572. [PubMed: 19571793]

[8]. Hamman JH, Enslin GM, Kotze AF, Oral delivery of peptide drugs, BioDrugs 19 (2005) 165–177. [PubMed: 15984901]

[9]. Price RD, Milne SA, Sharkey J, Matsuoka N, Advances in small molecules promoting neurotrophic function, Pharmacol. Ther 115 (2007) 292–306. [PubMed: 17599430]

[10]. Liran M, Rahamin N, Ron D, Barak S, Growth factors and alcohol use disorder, Cold Spring Harb. Perspect. Med 10 (2020) a039271. [PubMed: 31964648]

[11]. Thoenen H, Neurotrophins and neuronal plasticity, Science 270 (1995) 593–598. [PubMed: 7570017]

[12]. Kolbeck R, Jungbluth S, Barde YA, Characterization of neurotrophic dimers and monomers, Eur. J. Biochem 325 (1994) 995–1003.

[13]. Patapoutian A, Reichardt LF, Trk receptors: mediators of neurotrophin action, Curr. Opin. Neurbiol 11 (2001) 272–280.

[14]. Huang EJ, Reichardt LF, Trk receptors: roles in neuronal signal transduction, Annu. Rev. Biochem 72 (2003) 609–642. [PubMed: 12676795]

[15]. Holt LM, Hernandez RD, Pacheco NL, Torres Ceja B, Hossain M, L Olsen M, Astrocyte morphogenesis is dependent on BDNF signaling via astrocytic TrkB.T1, eLife 8 (2019) e44667. [PubMed: 31433295]

[16]. Lu B, Nagappan G, Lu Y, BDNF and synaptic plasticity, cognitive function, and dysfunction, Handb. Exp. Pharmacol (2014) 220–223.

[17]. Kang H, Welcher AA, Shelton D, Schuman EM, Neurotrophins and time: different role for TrkB signaling in hippocampal long term potentiation, Neuron 19 (1997) 653–666. [PubMed: 9331355]

[18]. Leal G, Bramham CR, Duarte CB, BDNF and hippocampal synaptic plasticity, Vitam. Horm 104 (2017) 153–195. [PubMed: 28215294]

[19]. Verpelli C, Piccoli G, Zibetti C, Zanchi A, Gardoni F, Huang KK, Brambilla D, Di Luca M, Battaglioli E, Sala C, Synaptic activity controls dendritic spine morphology by modulating eEF2-dependent BDNF synthesis, J. Neurosci 40 (2010) 5830–5842.

[20]. Pitts EG, Taylor JR, Gourley SL, Prefrontal cortical BDNF: a regulatory key in cocaine- and food-reinforced behaviors, Neurobiol. Dis 91 (2016) 326–335. [PubMed: 26923993]

[21]. Lu H, Cheng PL, Lim BK, Khoshnevisrad N, Poo MM, Elevated BDNF after cocaine withdrawal facilitates LTP in medial prefrontal cortex by suppressing GABA inhibition, Neuron 67 (2010) 821–833. [PubMed: 20826313]

[22]. Li X, Wolf ME, Multiple faces of BDNF in cocaine addiction, Behav. Brain Res 15 (2015) 240–254.

[23]. Sadri-Vakili G, Kumaresan V, Schmidt HD, Famous KR, Chawla P, Vassoler FM, Overland RP, Xia E, Bass CE, Terwiliger EF, Pierce RC, Cha JH, Cocaine-induced chromatin remodeling increases brain-derived neurotrophic factor transcription in the rat medial prefrontal cortex, which alters the reinforcing efficacy of cocaine, J. Neurosci 30 (2010) 11735–11744. [PubMed: 20810894]

[24]. Fumagalli F, Moro F, Caffino L, Cassina A, Giannotti G, et al. , Region-specific effects on BDNF expression after contingent or non-contingent cocaine i.v. self-administration in rats, Int. J. Neuropharmacol 16 (2013) 913–918.

[25]. Capriles N, Rodaras D, Sorge RE, Stewart J, A role for the prefrontal cortex in stress-and cocaine-induced reinstatement of cocaine seeking in rats, Psychopharmacology 168 (2003) 66–74 (Berl). [PubMed: 12442201]

[26]. Jentsch JD, Taylor JR, Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli, Psychopharmacology 146 (1999) 373–390 (Berl). [PubMed: 10550488]

[27]. Muller Ewald VA, De Corte BJ, Gupta SC, Lillis KV, Narayanan NS, Wemmie JA, LaLumiere RT, Atttenuation of cocaine seeking in rats via enhancement of infralimbic cortical activity using step-function opsins, Psychopharmacology 236 (2019) 479–490. [PubMed: 30003306]

[28]. Peters J, LaLumiere RT, Kalivas PW, Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats, J. Neurosci 28 (2008) 6046–6053. [PubMed: 18524910]

[29]. Volkow ND, Fowler JS, Addiction, a disease of compulsion and drive: involvement of orbitofrontal cortex, Cereb. Cortex 10 (2000) 318–325. [PubMed: 10731226]

[30]. Baler RD, Volkow ND, Drug addiction; the neurobiology of disrupted self control, Trends Mol. Med 12 (2006) 559–566. [PubMed: 17070107]

[31]. Goldstein RZ, Volkow ND, Drug addiction and its underlying neurobiological basis. Neuroimaging evidence for the involvement of the frontal cortex, Am. J. Psychiatry 159 (2002) 642–1652.

[32]. Hester R, Garavan H, Executive dysfunction in cocaine addiction: evidence from discordant frontal, cingulate, and cerebellar activity, J. Neurosci 24 (2004) 11017–11022. [PubMed: 15590917]

[33]. Porrino LJ, Lyons D, Orbital and medial prefrontal cortex and psychostimulant abuse: studies in animal models, Cereb. Cortex 10 (2000) 326–336. [PubMed: 10731227]

[34]. McGinty JF, Berglind WJ, Whitfield TW, Brain-derived neurotrophic factor and cocaine addiction, Brain Res 1314 (2010) 183–193. [PubMed: 19732758]

[35]. McGinty JF, Zelek-Molik A, Sun WL, Cocaine self-administration causes signaling deficits in corticostriatal circuitry that are reversed by BDNF in early withdrawal, Brain Res 1628 (Pt A) (2015) 82–87. [PubMed: 25268928]

[36]. Briand LA, Flagel SB, Garcia-Fuster MJ, Watson SJ, Akil H, Sarter M, Robinson TE, Persistent alterations in cognitive function and prefrontal dopamine D2 receptors following extended, but not limited, access to self-administered cocaine, Neuropsychopharmacology 33 (2008) 2969–2980. [PubMed: 18305460]

[37]. George O, Mandyam CD, Wise S, Koob GF, Extended access to cocaine self-administration produces long-lasting prefrontal cortex-dependent working memory impairments, Neuropsychopharmacology 33 (2008) 2472–2482.

[38]. Sun WL, Zelek-Molik A, McGinty JF, Short and long access to cocaine self-administration attenuates the tyrosine phosphatase STEP and GluN2B phosphorylation but differentially regulates AMPA subunit expression in the prefrontal cortex, Psychopharmacology 229 (2013) 603–613. [PubMed: 23624776]

[39]. Koob GK, Volkow ND, Neurocircuitry of addiction, Neuropsychopharmacology 35 (2009) 217–238.

[40]. George O, Koob GF, Individual differences in prefrontal cortex function and the transition from drug use to drug dependence, Neurosci. Biobehav. Rev 35 (2010) 232–247. [PubMed: 20493211]

[41]. Miller CA, Marshall JF, Molecular substrates of retrieval and reconsolidation of cocaine-associated contextual memory, Neuron 47 (2005) 1–12. [PubMed: 15996541]

[42]. Valjent E, Corvol JC, Pages C, Besson MJ, Maldonado R, Caboche J, Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties, J. Neurosci 20 (2000) 8701–8709. [PubMed: 11102476]

[43]. Valjent E, Pascoli V, Svenningsson P, Paul S, Enslen H, Corvol JC, Stipanovich A, Caboche J, Lombroso PJ, Nairn AC, Greengard P, Herve D, Girault JA, Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum, Proc. Natl. Acad. Sci. U. S. A 102 (2005) 491–496. [PubMed: 15608059]

[44]. Paul S, Connor JA, NR2B-NMDA receptor-mediated increases in intracellular Ca2+ concentration regulate the tyrosine phosphatase, STEP, and ERK MAP kinase signaling, J. Neurochem 114 (2010) 1107–1118. [PubMed: 20524968]

[45]. Mulholland PJ, Luong NT, Woodward JJ, Chandler LJ, BDNF activation of ERK is autonomous from the dominant extrasynaptic NMDA receptor ERK shut-off pathway, Neuroscience 151 (2008) 419–427. [PubMed: 18055129]

[46]. Go BS, Barry SM, McGinty JF, Glutamatergic neurotransmission in the prefrontal cortex mediates the suppressive effect of intra-prelimbic cortical infusion of BDNF on cocaine-seeking, Eur. Neuropsychopharmacol 26 (2016) 1989–1999. [PubMed: 27765467]

[47]. Siemsen BM, Lombroso PJ, McGinty JF, Intra-prelimbic cortical inhibition of striatal-enriched tyrosine phosphatase suppresses cocaine-seeking in rats, Addict. Biol 23 (2018) 219–229. [PubMed: 28349660]

[48]. Huang YZ, McNamara JO, Mutual regulation of Src family kinases and the neurotrophin receptor TrkB, J. Biol. Chem 285 (2010) 8207–8217. [PubMed: 20064930]

[49]. Barry SM, McGinty JF, SFK Involvement in BDNF-mediated suppression of cocaine-seeking and prevention of cocaine-Induced ERK, GluN2A, and GluN2B dephosphorylation, Neuropsychopharmacology 42 (2017) 1972–1980. [PubMed: 28585567]

[50]. Braithwaite SP, Adkisson M, Leung J, Nava A, Masterson B, Urfer R, Oksenberg D, Nikolich K, Regulation of NMDA receptor trafficking and function by striatal-enriched tyrosine phosphatase (STEP), Eur. J. Neurosci 23 (2006) 2847–2856. [PubMed: 16819973]

[51]. Saveedra A, Puigdellivol M, Tyebji S, Kurup P, Xu J, Gines S, Alberch J, Lombroso PJ, Perez-Navarro E, BDNF induces striatal-enriched protein tyrosine phosphatase 61 degradation through the proteasome, Mol. Neurobiol 53 (2015) 4261–4273. [PubMed: 26223799]

[52]. Lu L, Dempsey J, Liu SY, Bossert JM, Shaham Y, A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal, J. Neurosci 24 (2004) 1604–1611. [PubMed: 14973246]

[53]. Graham DL, Edwards S, Bachtell RK, DiLeone RJ, Rios M, Self DW, Dynamic BDNF activity in nucleus accumbens with cocaine use increases self-administration and relapse, Nat. Neurosci 10 (2007) 1029–1037. [PubMed: 17618281]

[54]. Bobadilla AC, Garcia-Keller C, Chareunsouk VJ, Hyde J, Medina Camacho D, Heinsbroek JA, Kalivas PW, Accumbens brain-derived neurotrophic factor (BDNF) transmission inhibits cocaine seeking, Addict. Biol 24 (2018) 860–873. [PubMed: 29890020]

[55]. Sun WL, Coleman NT, Zelek-Molik A, Barry SM, Whitfield TW, McGinty JF, Relapse to cocaine-seeking after abstinence Is regulated by cAMP-dependent protein kinase A in the prefrontal cortex, Addict. Biol 19 (2014) 77–86. [PubMed: 23461423]

[56]. Povysheva NV, Johnson JW, Tonic NMDA receptor-mediated current in prefrontal cortical pyramidal cells and fast-spiking interneurons, J. Neurophysiol 107 (2012) 2232–2243. [PubMed: 22236713]

[57]. Giannotti G, Barry SM, Siemsen BM, Peters J, McGinty JF, Divergent prelimbic cortical pathways control BDNF-dependent vs. independent suppression of cocaine seekin, J. Neurosci 38 (2018) 8956–8966. [PubMed: 30185459]

[58]. James MH, Dayas CV, What about me…? The PVT: a role for the paraventricular thalamus (PVT) in drug-seeking behavior, Front. Behav. Neurosci 7 (2013) 18. [PubMed: 23509439]

[59]. Kirouac GJ, Placing the paraventricular nucleus of the thalamus within the brain circuits that control behavior, Neurosci. Biobehav. Rev 56 (2015) 315–329. [PubMed: 26255593]

[60]. Matzeu A, Weiss F, Martin-Fardon R, Transient inactivation of the posterior paraventricular nucleus of the thalamus blocks cocaine-seeking behavior, Neurosci. Lett 608 (2015) 34–39. [PubMed: 26455867]

[61]. Millan EZ, Ong Z, McNally GP, Paraventricular thalamus: gateway to feeding, appetitive motivation, and drug addiction, Prog. Brain Res 235 (2017) 113–137. [PubMed: 29054285]

[62]. Kuhn BN, Klumpner MS, Covelo IR, Campus P, Flagel SB, Transient inactivation of the paraventricular nucleus of the thalamus enhances cue-induced reinstatement in goal-trackers, but not sign-trackers, Psychopharmacology 235 (2018) 999–1014 (Berl). [PubMed: 29285634]

[63]. Li S, Kirouac GJ, Sources of inputs to the anterior and posterior aspects of the paraventricular nucleus of the thalamus, Brain Struct. Funct 217 (2012) 257–273. [PubMed: 22086160]

[64]. Otis JM, Namboodiri VM, Matan AM, Voets ES, Mohorn EP, Kosyk O, McHenry JA, Robinson JE, Resendez SL, Rossi MA, Stuber GD, Prefrontal cortex output circuits guide reward seeking through divergent cue encoding, Nature 543 (2017) 103–107. [PubMed: 28225752]

[65]. Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S, Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport, J. Neurosci 17 (1997) 2295–2313. [PubMed: 9065491]

[66]. Cazorla M, Jouvenceau A, Rose C, Guilloux JP, Pilon C, Dranovsky A, Premont J, Cyclotraxin-B, the first highly potent and selective TrkB inhibitor, has anxiolytic properties in mice, PLoS One 5 (2010) e9777. [PubMed: 20333308]

[67]. Cazorla M, Premont J, Mann A, Girard N, Kellendonk C, Rognan D, Identification of a low-molecular weight TrkB antagonist with anxiolytic and antidepressant activity in mice, J. Clin. Invest 121 (2011) 1846–1857. [PubMed: 21505263]

[68]. Verheij MMM, Vendruscolo LF, Caffino L, Giannotti G, Cazorla M, Fumagalli F, Riva MA, Homberg JR, Koob GF, Contet C, Systemic delivery of a brain-penetrant TrkB antagonist reduces cocaine self-administration and normalizes TrkB signaling in the nucleus accumbens and prefrontal cortex, J. Neurosci 36 (2016) 8149–8159. [PubMed: 27488635]

[69]. Andero R, Heldt SA, Ye K, Liu X, Armario A, Ressler KJ, Effect of 7,8-dihydroxyflavone, a small molecule TrkB agonist, on emotional learning, Am. J. Psychiatry 168 (2011) 163–172. [PubMed: 21123312]

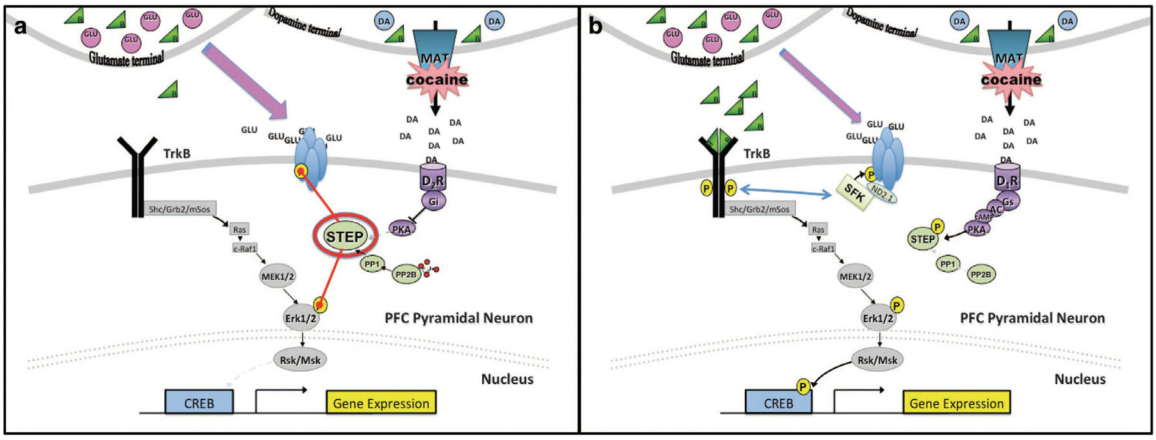

Fig. 1.

Proposed model of the crosstalk between TrkB and NMDARs in pyramidal neurons of the PL cortex after cocaine self-administration. (a) In rats infused with intra-PL PBS during early withdrawal from cocaine, the tyrosine phosphatase, STEP, is activated by dephosphorylation. STEP dephosphorylates and inactivates ERK MAP kinase and GluN2A/B. (b) In rats treated with intra-PL BDNF, BDNF binding to TrkB induces autophosphorylation of TrkB at Y705/Y706 and Y515, stimulating the ERK MAP kinase cascade. Autophosphorylated and activated TrkB phosphorylates and activates src family kinases (SFK) and active SFK promotes further phosphorylation of TrkB. Activated SFKs phosphorylate GluN2A and GluN2B via binding to a scaffolding protein (ND 2.1 in the case of Src) that results in the upregulation of GluN2A- and GluN2B-containing NMDAR function at the synapse.

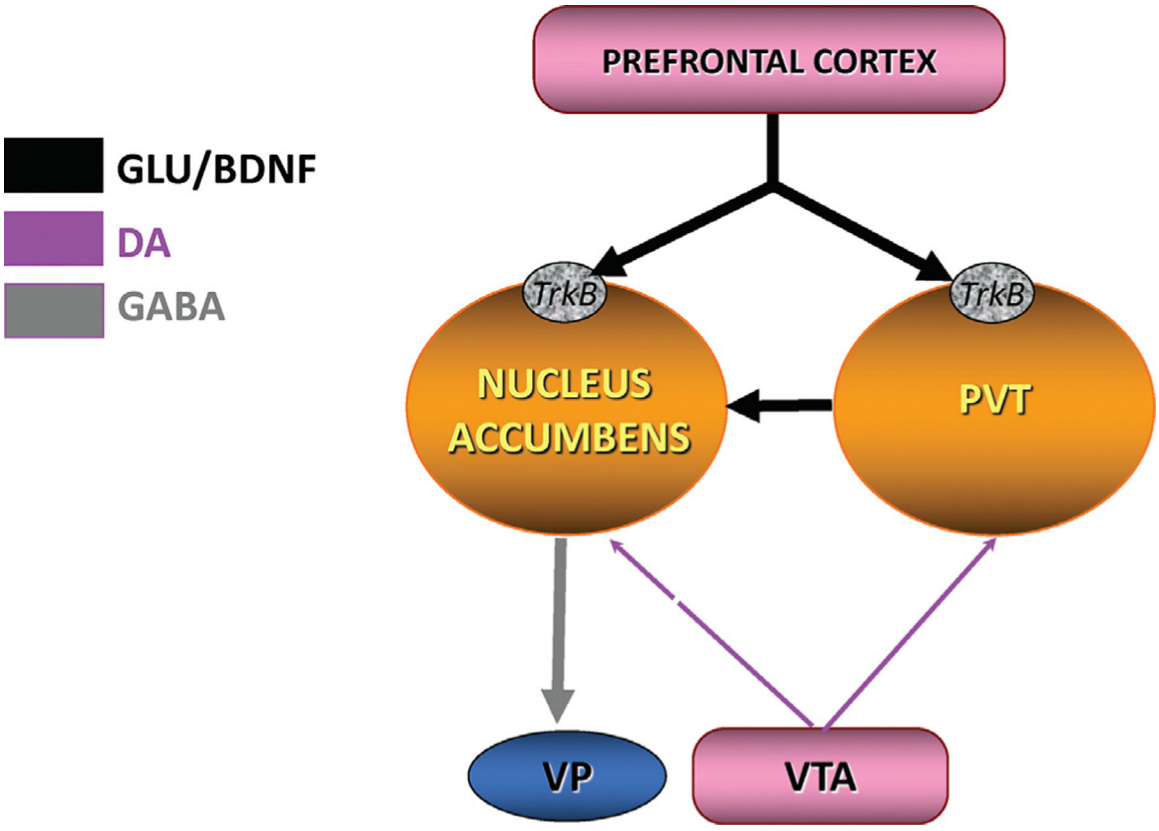

Fig. 2.

BDNF regulates activity in the corticostriatal and corticothalamic pathways. Prelimbic prefrontal projection neurons express BDNF that is transported anterogradely to multiple subcortical targets including NAc, particularly NAc core, and PVT. TrkB receptors are expressed on medium spiny NAc neurons and on PVT projection neurons. PVT projects to NAc, particularly targeting NAc shell. It is not yet known whether BDNF is expressed in the PVT->NAc shell pathway.