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Multiple faces of BDNF in cocaine addiction

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Abstract

Brain-derived neurotrophic factor (BDNF) has been found to play roles in many types of plasticity including drug addiction. Here we focus on rodent studies over the past two decades that have demonstrated diverse roles of BDNF in models of cocaine addiction. First, we will provide an overview of studies showing that cocaine exposure alters (and generally increases) BDNF levels in reward-related regions including the ventral tegmental area, nucleus accumbens, prefrontal cortex, and amygdala. Then we will review evidence that BDNF contributes to behavioral changes in animal models of cocaine addiction, focusing on conditioned place preference, behavioral sensitization, maintenance and reinstatement of self-administration, and incubation of cocaine craving. Last, we will review the role of BDNF in synaptic plasticity, particularly as it relates to plasticity of AMPA receptor transmission after cocaine exposure. We conclude that BDNF regulates cocaine-induced behaviors in a highly complex manner that varies depending on the brain region (and even among different cell types within the same brain region), the nature of cocaine exposure, and the "addiction phase" examined (e.g., acquisition *vs* maintenance; early *vs* late withdrawal). These complexities make BDNF a daunting therapeutic target for treating cocaine addiction. However, recent clinical evidence suggests that the serum BDNF level may serve as a biomarker in cocaine addicts to predict future relapse, providing an alternative direction for exploring BDNF's potential relevance to treating cocaine addiction.

Keywords

BDNF; TrkB; cocaine addiction; AMPA receptor

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1. Introduction

Brain-derived neurotrophic factor (BDNF) belongs to a group of secreted homodimeric proteins termed neurotrophins, which are widely accepted as regulators of cell growth, survival and differentiation during nervous system development. Neurotrophins also play important roles in activity-dependent remodeling of neural function in adult nervous systems [1]. Such activity-dependent remodeling is increasingly recognized as critical for the transition from casual drug use to drug addiction, leading to investigation of BDNF's role in the actions of drugs of abuse. In particular, there has been considerable interest in the effect of BDNF on reward-related neuronal circuitry involving dopamine (DA) neurons of the ventral tegmental area (VTA) and their interconnected forebrain targets, such as the nucleus accumbens (NAc) and the prefrontal cortex (PFC). Here we will focus exclusively on cocaine addiction, and refer readers to other reviews for discussion of BDNF's role in the actions of other drugs of abuse [2, 3].

Over the past two decades, BDNF has been implicated in mediating synaptic plasticity associated with cocaine abuse, as well as cocaine-induced behaviors [3–5]. Building on these prior reviews, we will focus on how cocaine affects BDNF expression in addiction-related brain regions and how BDNF regulates cocaine-induced behaviors, namely conditioned place preference (CPP), behavioral sensitization, cocaine self-administration (including its maintenance, tests for reinstatement after extinction training, tests for cocaine seeking after forced abstinence/withdrawal, and the time-dependent intensification or incubation of cocaine seeking that occurs during withdrawal). As will be discussed, available information suggests that, instead of playing a universal role, BDNF plays multiple roles in cocaine addiction, depending on the brain region and addiction phase examined. We will also review findings on BDNF-induced synaptic plasticity that may be important for understanding its role in cocaine-induced behavioral effects.

BDNF is synthesized as precursor BDNF (32 kDa) in the endoplasmic reticulum (ER), sorted in the Golgi and cleaved either intracellularly or extracellularly into mature BDNF (14 kDa), which can be transported anterogradely to its target neurons [6]. BDNF can also be secreted from the target postsynaptic neurons and transported retrogradely after endocytosis by the axon terminal [7]. Due to multiple promoters and complex transcriptional control mechanisms, the *bdnf* gene has multiple transcripts, which might be differently involved in cocaine's actions (see Section 2.1). BDNF exerts its biological effects through binding to both high affinity tropomyosin receptor kinase B (TrkB) receptors and low affinity p75 neurotrophin receptors (p75NTR), although its major synaptic functions are mediated by TrkB receptors [8]. Binding of BDNF to the TrkB receptor results in receptor dimerization and autophosphorylation of tyrosine residues in the catalytic domain (Tyr706/707; a positionally equivalent autophosphorylation occurs for TrkA and TrKC), leading to receptor activation [9–11]. Activated receptors trigger a number of signal transduction cascades including the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3-K), and phospholipase C-γ (PLC-γ) pathways. These signals are transmitted into the nucleus and act on transcription factors to alter gene expression [12]. For example, activation of extracellular signal-regulated kinase 1/2 (ERK1/2), a component of MAPK pathways, can act on transcription factors such as cyclic AMP response element

binding protein (CREB), which subsequently regulates target gene expression [13]. However, some of these intracellular signals may also exert fast non-genomic effects [14]. For example, ERK regulates AMPA receptor (AMPAR) trafficking and related synaptic plasticity [15–19].

2. Effect of cocaine on BDNF levels in addiction-related brain regions

Under basal conditions, BDNF is highly expressed in VTA, amygdala, hippocampus and frontal cortex, but is less abundant in dorsal striatum and NAc [20]. Although *bdnf* mRNA is present in dorsal striatum and NAc [21–26], BDNF in these regions is predominantly supplied by anterograde axonal transport from cortical pyramidal neurons in frontal cortex, with a minor contribution from DA neurons in VTA [27]. In contrast, the TrkB receptor is more widely expressed throughout the brain than BDNF [28–30].

Cocaine exposure can influence BDNF levels in all of the brain regions listed above (Table 1). This has been observed after both non-contingent and contingent cocaine administration. In the former situation, the experimenter administers drug, so drug delivery is not contingent on the animal's behavior. In the latter situation, the animal performs an operant response to obtain the drug (i.e., drug self-administration) and drug delivery is therefore contingent on the animal's behavior. In the following sections, we review the effects of cocaine on BDNF levels in addiction-related brain regions after either non-contingent or contingent cocaine exposure.

2.1 Effect of non-contingent cocaine on BDNF levels

After a single non-contingent cocaine injection, multiple studies have found increased *bdnf* mRNA and protein levels in the NAc, dorsal striatum, and prefrontal cortex (PFC) (Table 1). In the NAc, there was a transient increase of *bdnf* mRNA levels 1 h after a single cocaine injection, followed by a delayed increase of BDNF protein levels 2 h post-injection [21, 22, 31]. In the PFC, a rapid and lasting elevation of *bdnf* mRNA levels was observed from 30 min to 24 h after a single cocaine injection, while elevation of BDNF protein was only detected at the 24-h time point [24, 32, 33]. These differences in temporal regulation of *bdnf* mRNA and protein levels suggest that increased BDNF protein levels induced by a single cocaine exposure may result from enhanced protein synthesis. In addition, BDNF transcript-specific studies have shown that cocaine regulates individual transcripts differently. For example, a single injection of a high dose of cocaine elevated *bdnf* exon IV expression in striatum (both dorsal and ventral striatum) and elevated exons I and IV in PFC 4 h later [24]. However, whether the non-contingent cocaine-induced elevation of these specific *bdnf* transcripts leads to changes in BDNF protein levels was not examined. BDNF transcript-specific studies in animals that self-administered cocaine [23, 24, 34–37] will be reviewed in detail in Section 2.2. Briefly, these studies found that, during withdrawal from cocaine self-administration, changes in specific *bdnf* transcripts were observed in the VTA (exon I; [37]) and the PFC (exon I and IV; [34–36]), but not in the dorsal striatum or NAc [23, 24, 34].

Repeated i.p. cocaine injections also produce increases in BDNF levels in multiple brain regions. In the NAc shell, *bdnf* mRNA levels were elevated on withdrawal day 5, regardless of whether a cocaine challenge was given, after a 5-day repeated injection regimen (10

mg/kg, i.p.) [21]. A different 5-day cocaine regimen (15 mg/kg, i.p.) produced a time-dependent increase in BDNF protein levels in the NAc shell, that is, trends during the first week of withdrawal that reached statistical significance on withdrawal day 14 and 28 [38]. Elevation of BDNF was proposed to mediate the impairment of mGluR-dependent LTD observed in the NAc shell at these withdrawal times, as no impairment was observed in BDNF knockout mice [38]. However, these two studies either measured *bdnf* mRNA levels only [21] or BDNF protein levels only [38] during withdrawal from repeated cocaine exposure. Therefore, it is difficult to speculate whether the time-dependent increase in BDNF protein observed by Huang et al. [38] was due to protein synthesis, anterograde transport from other brain regions (e.g., medial PFC and VTA; [6, 20, 27, 39]), or both.

Time-dependent increases in BDNF protein levels after repeated i.p. cocaine injections have also been observed in the VTA and PFC. In the VTA, BDNF protein was significantly elevated after 10–15 days of withdrawal from repeated cocaine injections but not on withdrawal day 1 [40]. In the PFC, significant increases in BDNF protein expression were observed on withdrawal days 8 and 14 but not withdrawal days 1 or 3 [41]. This delayed increase in BDNF levels was linked to suppression of GABAergic inhibition in the PFC [41]. However, another study found decreased BDNF protein levels in the PFC 2 h and 72 h after discontinuing repeated cocaine exposure, accompanied by a transient increase in *bdnf* mRNA levels at the 2-h time point [32]. The discrepancy between these two studies of PFC may be due to different cocaine regimens. Compared to Lu et al. [141], Fumagalli et al. [32] used a lower cocaine dose and fewer days of cocaine exposure. Nonetheless, these data provide evidence that cocaine can affect the level of BDNF protein in the PFC in both directions.

2.2 Effect of cocaine self-administration on BDNF levels

Similar to non-contingent cocaine exposure, cocaine self-administration has generally been found to increase BDNF levels in addiction-related brain regions. However, exactly where and when the increase in BDNF is detected depends on the self-administration regimen. One particularly important variable in drug self-administration studies is the duration of access to the drug. Therefore, self-administration procedures are often classified as limited access or extended access procedures. In limited access procedures, the drug is generally available for 1–2 h per session for a week or two. Extended access procedures utilize longer sessions (e.g. 6 h/day) or more days. Extended access regimens lead to different or enhanced behavioral changes that are believed to more closely model compulsive drug seeking and taking in addiction. These include escalation of drug intake during self-administration training, persistence of drug-taking even when it is paired with punishment, greater motivation for drug, and augmented cocaine, stress or cue induced reinstatement following a period of extinction training [42]. In addition, a time-dependent increase in cue-induced cocaine seeking (i.e., responses performed during a test in which responding results in delivery of a cue previously associated with cocaine, but no cocaine) occurs during the first months of withdrawal from extended access cocaine self-administration [43–45]. Cue-induced cocaine seeking provides a measure of cocaine craving. Thus, the time-dependent intensification of this response is termed “incubation of cocaine craving”. Incubation depends on the level of

cocaine intake during self-administration training and is accordingly less robust after limited access regimens [46].

Using limited access cocaine self-administration procedures, several studies have examined BDNF expression in different brain regions after 14 daily sessions of cocaine self-administration (2 h/day). In the VTA, *bdnf* mRNA expression was unchanged after 1 day of withdrawal from the 14-day regimen, but both *bdnf* exon I transcript and BDNF protein levels increased on withdrawal day 7 [37]. No study has yet measured BDNF protein expression in VTA at earlier withdrawal time points following limited access cocaine self-administration.

In the mPFC, *bdnf* mRNA was unchanged immediately after a single 2-h self-administration session [47]. *Bdnf* mRNA in mPFC was also unchanged 24 h after a 14-day regimen (2-h sessions), although increased *bdnf* exon I and decreased *bdnf* exon IV were observed [34]. In contrast, McGinty et al. [4] reported that *bdnf* mRNA in dorsomedial PFC decreased 22 h after 10 days of 2-h sessions. These discrepant results could be attributed to slightly different cocaine self-administration procedures or, more likely, to the brain region examined (McGinty et al. [4] focused on dorsomedial PFC instead of the whole mPFC). Morever, while *bdnf* exon IV increased in mPFC on withdrawal day 7 from the 14-day regimen [36], no change in *bdnf* mRNA was observed in dorsomedial PFC on withdrawal day 21 from 10 days of 2-h sessions [4]. In the absence of changes in *bdnf* mRNA, BDNF protein in a synaptosomal fraction of mPFC was increased 24 h after the 14-day regimen [34]. On withdrawal day 7 from 14 days of 2 h-sessions, while Sadri-Vakili et al. [36] reported an increase of BDNF protein in the mPFC, Fumagalli et al. [34] observed no increase in BDNF protein, possibly due to minor differences in cocaine self-administration procedures and/or tissue dissections. Consistent with Sadri-Vakili et al. [36], McGinty et al. [4] reported increased BDNF protein in dorsomedial PFC after 21 days withdrawal from 10 days of 2-h sessions. In this study, the cocaine rats received a priming injection of saline or cocaine 30 min prior to analysis; however, both groups exhibited increased BDNF, arguing against a significant effect of the priming injection. Together, these data suggest that withdrawal from self-administered cocaine, rather than cocaine self-administration itself, correlates with elevated BDNF expression in the mPFC. In addition, different regulation of *bdnf* transcripts (e.g., exon I, IV) suggests that divergent transcriptional mechanisms contribute to the increase in BDNF protein in the mPFC during early versus late withdrawal from the 14-day regimen.

Finally, BDNF levels in the NAc also increase in response to 2–4 h/day of cocaine self-administration, but in a faster and more transient way when compared to changes in BDNF expression in the mPFC. For example, BDNF protein levels in the NAc shell were elevated immediately after an 18-day cocaine self-administration regimen (4 h/day), but returned to basal levels 24 h later [22]. This result is consistent with the recent finding of a transient increase of BDNF protein levels in whole NAc immediately after a 14-day (2 h/day) regimen, with no change on withdrawal days 1 and 7 [34]. In summary, limited access cocaine self-administration leads to an increase in BDNF protein that occurs with different temporal patterns in different brain regions, with a transient increase immediately after the last session in the NAc, an increase in the mPFC reported on withdrawal days 1, 7 and 21,

and an increase in the VTA on withdrawal day 7. No study using limited access cocaine self-administration has yet examined BDNF expression beyond 21 days of withdrawal from the last session.

In studies using extended access cocaine self-administration, much of the focus has been on changes in BDNF levels that accompany the incubation of cue-induced cocaine seeking or craving. In the first of these studies, Grimm et al. [48] found time-dependent increases in BDNF protein levels in the NAc, VTA and amygdala (mRNA was not measured). In all cases, no significant change was found on withdrawal day 1, but significant changes were found at later times (withdrawal days 30 and 90) when cue-induced cocaine craving has "incubated". Recently, we further examined BDNF protein expression in core and shell of NAc during incubation of cocaine craving using a very similar cocaine regimen to that employed by Grimm and colleagues, and observed that BDNF was increased in NAc core on withdrawal day 45 and eventually elevated in both core and shell on withdrawal day 90 [23]. Temporal parallels between cocaine craving and BDNF levels suggested that BDNF might be contributing to incubation of cocaine craving, as discussed further in Section 3.4. Whether BDNF levels in VTA, NAc or amygdala increase at time-points between withdrawal days 1 and 30 is unknown, but this is an interesting question as incubation of craving can be detected as early as withdrawal day 7 [43]. It should be noted that withdrawal-dependent increases in BDNF protein levels do not occur in all brain regions, as our recent study failed to detect an increase in BDNF protein in the mPFC on withdrawal day 45 [23]. Furthermore, not all brain regions require prolonged withdrawal to show an effect of extended access cocaine self-administration on BDNF levels; in dorsal striatum, BDNF levels were significantly elevated 24 h after the last session of cocaine self-administration [49].

2.3 Differential effects of cocaine on BDNF levels in NAc core and shell

While previous portions of Section 2 have focused on the NAc as a whole, it is important to point out evidence that BDNF may be differently regulated within core and shell subregions of the NAc. These subregions are differentially involved in cocaine-induced behaviors. While the NAc core has been implicated in control of goal-directed behaviors such as drug seeking induced by drug-associated discrete cues, the NAc shell is involved in the primary reinforcing effects of drug of abuse as well as control of drug seeking induced by drug-associated contexts [50–55]. The earliest evidence for differential cocaine regulation of BDNF signaling in core versus shell came from a study showing increased TrkB protein levels in NAc core, but not shell, after 3 weeks of withdrawal from repeated non-contingent cocaine treatment [56]. Subsequent evidence has come largely from studies of cocaine self-administration. Thus, transient increases in BDNF and TrkB receptor levels were found in the NAc shell but not in the core immediately after a session of cocaine self-administration in cocaine-experienced animals [22, 57]. In studies of withdrawal from extended access cocaine self-administration, an extensive time course study performed in whole NAc (core plus shell) revealed increased BDNF levels on WD30 and WD90, as described above [48]. However, using the same regimen, we recently showed that the timing of the withdrawal-dependent BDNF increase differs significantly in core and shell [23]. Thus, on WD45, increased BDNF levels are detected in core but not shell. By WD90, levels in core are

further increased and an increase is now detectable in shell as well. Core-shell differences may help explain discrepancies in the literature regarding the role of BDNF in cocaine-induced behaviors (see Section 3.4).

2.4. Dissociation between *bdnf* mRNA and protein levels after cocaine exposure

Dissociation between cocaine's effects on *bdnf* mRNA and protein levels has been reported in several studies. For example, while *bdnf* mRNA levels in the mPFC increased 2 h after the last repeated non-contingent cocaine injection, BDNF protein levels decreased [32]. In addition, the time-dependent increase in BDNF protein in the NAc during incubation of cocaine craving was not accompanied by an increase in levels of either *bdnf* mRNA or exon IV [23], one of the *bdnf* transcripts that has been linked to epigenetic regulation of BDNF expression in the mPFC after cocaine self-administration [36]. These data suggest that fluctuations at the level of BDNF transcription after cocaine exposure may not necessarily affect overall BDNF protein expression, which can be influenced by several other factors, including regulation of translation, stability of existing *bdnf* mRNA, processing of pro-BDNF to mature BDNF, and anterograde transport from other brain regions [27, 58–60].

2.5 Summary

Overall, both non-contingent and contingent cocaine exposure generally lead to increases in BDNF levels in reward-related brain regions, but exceptions have also been observed. Moreover, the regional selectivity and timing of cocaine's effects can vary widely depending on experimental conditions. Lastly, exposure to cocaine does not always affect *bdnf* mRNA and protein expression in the same direction, possibly due to the complex regulation of BDNF synthesis or the potential for increasing BDNF protein in a particular region through anterograde transport rather than local synthesis.

3. Roles of BDNF in animal models of cocaine addiction

In the following sections, we review studies over the past two decades about how BDNF contributes to cocaine-induced behaviors, focusing on conditioned place preference, behavioral sensitization to cocaine, maintenance and reinstatement of cocaine self-administration, cocaine seeking, and incubation of cue-induced cocaine seeking. Studies discussed in this section are also summarized in Table 2.

3.1 Conditioned place preference

A simple animal model to study the rewarding effect of drugs, conditioned place preference (CPP) uses a classical Pavlovian conditioning procedure to pair an unconditioned stimulus (e.g., cocaine) with a designated area and measure the preference for the stimulus-paired area compared to the unpaired area [61]. The first evidence for a role of BDNF in CPP was that *bdnf* heterozygous knockout mice showed decreased cocaine CPP, as well as a decreased locomotor response to cocaine [62]. The decrease in cocaine CPP was recently replicated in *bdnf* heterozygous knockout rats; interestingly, this study also found that a median split of wild-type rats based on serum BDNF levels showed a correlation between higher BDNF levels and stronger cocaine CPP [63]. Although the use of constitutive knockouts leaves open the possible contribution of compensatory mechanisms during

development, decreased cocaine CPP was also observed in transgenic mice that expressed a dominant negative TrkB receptor in forebrain principal neurons from late embryonic life through adulthood [64]. Furthermore, over-expressing BDNF or TrkB in the rat NAc using lentivirus led to enhanced cocaine CPP, delayed CPP extinction, and increased cocaine-primed reinstatement [65]. Consistent with these results, knocking down BDNF or TrkB in mouse NAc using adenovirus had a suppressive effect on cocaine CPP [57]. In mouse VTA, adenovirus knockdown of BDNF but not TrkB decreased cocaine CPP [57]. Overall, currently available evidence supports an enhancing role of BDNF in cocaine reward measured using CPP. In addition, chronic infusion of BDNF into either the VTA or NAc increased responding for conditioned reward, both in the presence and absence of cocaine [66]. However, the relationship between BDNF transmission and CPP may be different in other brain regions. Otis et al. [67] showed that injection of either BDNF or a TrkB agonist into rat infralimbic cortex facilitated extinction of cocaine CPP through a mechanism involving activation of GluN2B-containing NMDA receptors. Additional complexity is introduced by evidence that BDNF can exert different effects on cocaine reward in different cell types within the same brain region. Lobo et al. [68] observed that while attenuating BDNF-TrkB signaling in D1-receptor positive neurons of the NAc enhanced cocaine CPP and cocaine-induced locomotor activity, opposite effects occurred when BDNF-TrkB signaling in D2-receptor positive neurons was suppressed.

3.2 Behavioral sensitization

Behavioral sensitization is defined as a progressive enhancement of drug-induced responses that develops during repeated drug treatment and then persists even after weeks of withdrawal. It can be produced by either contingent or non-contingent cocaine exposure (e.g., [69]). Behavioral sensitization is usually assessed as an increase in ability of cocaine or amphetamine to elicit locomotor activation and/or stereotyped behaviors. However, more obviously relevant to addiction, sensitization occurs to the incentive-motivational properties of drugs and cues paired with drugs [70]. For example, previous exposure to a sensitizing regimen will enhance both rate of acquisition and the motivation to work for drugs in subsequent self-administration paradigms [71, 72]. Therefore, neuroadapations during behavioral sensitization are able to model some aspects of addiction, such as initial development of increased motivation for drugs and persistence of drug-induced changes.

BDNF has long been known to have a role in the survival and function of midbrain DA neurons [73] and early work implicated BDNF-related signaling cascades in changes in the VTA associated with behavioral sensitization [74, 75]. Since then, several studies have examined the role of BDNF in the development of locomotor sensitization. Horger et al. [66] showed that *bdnf* heterozygous knockout mice exhibited a delayed development of locomotor sensitization to cocaine. A recent study [38] showed that conditional knockout of *bdnf* expression in mouse forebrain led to attenuated expression of locomotor sensitization in response to a challenge injection of cocaine administered 14 days after discontinuing repeated cocaine treatment. In addition to evidence from knockout animals, over-expression of a dominant-negative TrkB receptor in forebrain principal neurons from late embryonic life through adulthood blocked sensitization measured 28 days after a single injection of cocaine [64].

The results summarized above suggest that endogenous BDNF-TrkB signaling facilitates locomotor sensitization to cocaine. However, it is not clear in what brain region(s) BDNF is acting to produce this effect. The PFC was implicated by a study in which knocking down TrkB in PFC of young mice (P20) by lentivirus expressing TrkB shRNA led to a less robust expression of sensitization after a cocaine challenge on withdrawal day 8 from a 7 daily cocaine injection regimen, while knocking down TrkB in PFC of these young mice had no effect on the development of sensitization during the 7 daily cocaine injections [41]. In the NAc, endogenous TrkB signaling seems to facilitate acute locomotor effects of cocaine. Thus, when the function of the TrkB receptor in the NAc was abolished by either TrkT1 (a truncated form of TrkB that acts as a dominant-negative receptor; [76]) or TrkB specific siRNAs, animals showed less sensitivity to the locomotor activating effects of cocaine than control (GFP virus-treated) animals [65]. Curiously, the effect of long-term interruption of endogenous BDNF-TrkB signaling in the NAc on the development of sensitization has not been assessed. However, pretreatment with either intra-NAc or intra-VTA injections of a neutralizing antibody to BDNF prior to each of 4 daily cocaine injections did not affect the development of behavioral sensitization to cocaine [28]. This suggests that, if endogenous BDNF transmission in the NAc or VTA contributes to the development of sensitization, the requirement is probably for BDNF-initiated plasticity that extends beyond the period of each cocaine injection.

A distinct question is whether experimentally enhancing BDNF-TrkB signaling in a particular brain region can facilitate the development of sensitization. Several studies have shown that enhancing BDNF-TrkB signaling in the NAc facilitates the locomotor activating effects of acute cocaine [65, 66]. This was first demonstrated by Horger et al. [66], who used osmotic minipumps to deliver BDNF into the medial NAc shell for 2 weeks. A more recent study found the same effect after local over-expression of BDNF and/or TrkB in the NAc using lentiviral gene delivery [65]. Horger et al. [66] went on to demonstrate that chronic minipump delivery of BDNF into the NAc facilitated the development of behavioral sensitization, i.e., sensitization was observed with a low dose of cocaine that was subthreshold in control rats [66]. In the same study, osmotic minipump delivery of BDNF into the VTA enhanced the locomotor response to cocaine injection on both the first and the last test day, but no development of sensitization was observed over the test days, suggesting that enhancing BDNF signaling in the VTA possibly produces a ceiling effect on cocaine-induced locomotor activity; however, the effect of lower cocaine doses was not assessed [66]. Another study examined whether pre-exposure to BDNF (3 daily infusions into the VTA; no cocaine was administered) affected locomotor activity and responsiveness to subsequent cocaine exposure [77]. Compared to vehicle-infused rats, the BDNF group exhibited a progressive increase in locomotor activity on the three treatment days. However, this prior BDNF exposure did not alter the subsequent behavioral response to a cocaine injection administered 1 or 14 days later [77]. These results leave open the possibility that enhancing BDNF transmission in the VTA during the period of repeated cocaine exposure might facilitate sensitization. This possibility is indirectly supported by a study of synaptic plasticity discussed in the final paragraph of this section [40].

The studies reviewed above suggest that actions of BDNF in the NAc [66], the PFC [41], and possibly the VTA [77] facilitate the development of locomotor sensitization to cocaine.

Mechanisms in the NAc responsible for this effect are unknown. In the PFC, elevation of BDNF during withdrawal from repeated cocaine exposure was shown to facilitate the induction of LTP by suppressing GABA transmission. The resultant increase in excitability of PFC neurons was proposed to contribute to the maintenance of locomotor sensitization during withdrawal, explaining the ability of TrkB knockdown to diminish expression of sensitization [41]. A caveat is that these experiments were done in very young animals (P20 at the start of the study). Studies using adult rats have concluded that the cocaine-induced BDNF elevation in the PFC is a homeostatic response that opposes cocaine-seeking [36, 78, 79], as will be further discussed in Section 3.3.

More is known about potential mechanisms of BDNF action in the VTA. It is well established that cocaine exposure, ranging from a single injection to extended access cocaine self-administration, leads to LTP at excitatory synapses onto VTA dopamine neurons. However, available evidence indicates that this LTP does not initiate sensitization; instead, it is likely to be associated with or facilitate learning about the rewarding properties of drugs, and perhaps alter aspects of such learning that depend on subsequent synaptic plasticity in the VTA [80]. BDNF transmission in the VTA has been shown to be one of the variables influencing synaptic potentiation in VTA dopamine neurons [40]. Thus, a withdrawal-dependent elevation of endogenous BDNF levels in the VTA (P21-P40 rats), which was observed after 10–15 days but not 1 day of withdrawal from repeated cocaine injections, enhanced the ability of a weak presynaptic stimulus to produce synaptic potentiation. Furthermore, application of exogenous BDNF to VTA dopamine neurons of drug-naïve rats similarly facilitated synaptic potentiation. BDNF's effects required TrkB activation in the postsynaptic dopamine neuron, but were expressed presynaptically as an increase in glutamate release, suggesting involvement of a retrograde messenger [40]. This BDNF-induced facilitation is distinct from another mechanism for facilitation of electrically evoked synaptic potentiation in VTA dopamine neurons that is attributable to reduced GABA-mediated inhibition after cocaine exposure [81]. Two things should be kept in mind when integrating these studies with the report, discussed above, that intra-VTA injections of a neutralizing antibody to BDNF did not affect the development of behavioral sensitization to cocaine [28]. First, the neutralizing antibody was given along with each cocaine injection, while the BDNF-induced facilitation of synaptic potentiation was observed only after withdrawal [40]. Second, as noted above, there is a complex relationship between synaptic potentiation in the VTA and the development of behavioral sensitization [80].

3.3. Maintenance and reinstatement of cocaine self-administration

Cocaine self-administration refers to training rodents in an operant chamber to press a bar or poke their nose in a hole in order to receive an intravenous infusion of cocaine. Self-administration procedures can differ in many ways, including whether training to respond for food precedes drug self-administration, the dose of drug available, the number of responses required to obtain drug, and the duration of access to drug (see Section 2 for discussion of limited access and extended access cocaine self-administration procedures). This section will focus primarily on the role of BDNF in the maintenance of self-administration and in reinstatement of self-administration after extinction training, although some results of seeking tests following forced abstinence/withdrawal will also be discussed.

Incubation of cue-induced craving during forced abstinence/withdrawal will be considered in Section 3.4.

In agreement with results obtained in CPP and sensitization models, studies of cocaine self-administration have supported a role for BDNF in the rewarding effects of cocaine. Furthermore, they have indicated that BDNF has important effects in the NAc as well as in the VTA. In rats with cocaine self-administration experience (4 h/day for 18 days), Graham et al. [22] found that BDNF levels in the NAc shell, but not core, are increased immediately after a session of cocaine self-administration, but then return to normal within a day of withdrawal. They explored the functional significance of this by infusing either BDNF (to mimic the effect) or anti-BDNF antibody (to block the effect) into the shell immediately after self-administration training on 5 consecutive days. Three days after the last infusion, BDNF-treated rats showed an upward shift in the inverted U-shaped dose-response curve during self-administration compared to vehicle-treated animals, which has been suggested to indicate a more “addicted” state. Conversely, a downward shift in the cocaine self-administration dose response curve was observed in anti-BDNF antibody treated animals. Similarly, knocking down endogenous BDNF expression through delivery of an adeno-associated viral (AAV) vector into the mouse NAc also produced a downward shift in the dose-response curve. Furthermore, during both extinction training and subsequent reinstatement tests (by exposure to cue, cocaine, or foot-shock), intra-NAc BDNF injection potentiated lever responding, whereas anti-BDNF antibody injection led to effects in the opposite direction. Altogether, these results implicate NAc BDNF, transiently elevated in the shell subregion after cocaine self-administration, in maintaining higher cocaine intake during cocaine use and facilitating relapse to cocaine seeking [22]. Subsequently, the same group showed that TrkB protein levels were also elevated in the NAc shell after a similar cocaine self-administration regimen (4 h/day for 3–4 weeks). Moreover, TrkB knockdown in the whole NAc but not the VTA reduced cocaine reward in cocaine place conditioning experiments and produced a downward shift in the cocaine self-administration dose-response curve [57]. These data provide more evidence for facilitation of cocaine self-administration by BDNF-TrkB activation in the NAc shell.

In contrast, opposite effects on cocaine self-administration were observed after elevation of BDNF signaling in the mPFC, similar to opposite effects in NAc versus mPFC in CPP and sensitization models (see above). A single intra-mPFC injection of BDNF after the last self-administration session (2 h/day for 10 days) produced a suppressive effect on cocaine seeking behavior 22 h later, cue-induced seeking after 6 days of forced abstinence, and cue or cocaine primed reinstatement after 6 days of extinction training [78]. The suppressing effect of intra-mPFC BDNF injection was dependent on both TrkB receptor activation and ERK signaling in the dorsal medial PFC [79]. Additionally, decreasing BDNF expression in mPFC by short hairpin RNA increased the breakpoint for cocaine self-administration under a progressive ratio schedule [36]. All of these results are consistent in suggesting that elevation of BDNF signaling in the mPFC reduces cocaine self-administration and reinstatement.

However, the finding that an intra-PFC BDNF injection leading to decreased cocaine self-administration produced elevated BDNF protein levels not only in mPFC but also in the

NAc [78] (presumably due to its anterograde transport from mPFC to NAc) may seem surprising in light of evidence linking increased BDNF levels in the NAc shell to increased cocaine self-administration [22] (see above). These findings may be resolved by keeping in mind that intra-mPFC BDNF infusion will specifically increase presynaptic BDNF levels in terminals of the mPFC-NAc pathway (through anterograde transport) whereas intra-NAc BDNF infusion will lead to direct stimulation of postsynaptic TrkB receptors on all medium spiny neurons. Other differences between the two studies are also important to consider. First, the studies differed in the duration of daily cocaine access; this can be linked to different behavioral outcomes (see Section 2.2). Second, the different findings may be related to evidence for different roles of BDNF in NAc core and shell (see Section 3.4 for more discussion). Although Berglind et al. [78] did not distinguish NAc core and shell, the target region for BDNF injection in this study was the dorsomedial region of PFC, which projects primarily to the core [82]. In contrast to shell, BDNF transmission in the core can oppose cocaine seeking [23]. Thus, elevated BDNF levels in NAc (presumably core) may have contributed to the suppressive effect of intra-PFC BDNF injection on cocaine seeking in the study by Berglind et al. [78]. Finally, it is possible that the effect of elevating BDNF in the mPFC (reduction of cocaine self-administration) dominates over the effect of BDNF in other brain regions, explaining the reduction in self-administration observed by Berglind et al. [78].

3.4. Incubation of cocaine craving

This section will address BDNF's role in the incubation of cocaine craving. As introduced in Section 2.2, incubation refers to the time-dependent increase in cue-induced cocaine seeking that occurs during the first months of withdrawal from extended access cocaine self-administration [43–46, 83]. In studies of incubation, cue-induced cocaine seeking after withdrawal is measured under extinction conditions – that is, the operant response that was associated with cue presentation/cocaine infusion during training now results in delivery of the cue but no cocaine. However, extinction training (i.e., repeated extinction tests, conducted until the operant response is extinguished) is not performed prior to tests for cue-induced seeking. One benefit of this design is related to the fact that extinction training is itself a form of learning that is accompanied by its own neuroadaptations in the reward circuitry (e.g., [84]). By avoiding extinction training, one can focus on plasticity related to cocaine exposure and withdrawal rather than introducing additional variables related to the experience of extinction training.

Incubation is relevant to vulnerability to cue-induced relapse in human addicts who experience a period of forced abstinence due to hospitalization or incarceration and then encounter drug-related cues [85]. Three studies have now demonstrated incubation of craving in human addicts, although these studies have employed nicotine, alcohol and methamphetamine, not cocaine [86–88]. In rats, incubation of craving is not robust in procedures using limited access cocaine self-administration (2 h/day), indicating that it is closely related to the level or pattern of drug intake ([46]; see also [89]). Furthermore, the magnitude of cocaine-primed reinstatement does not undergo incubation during withdrawal, suggesting that it is the learned reward-cue association rather than the effect of drug that undergoes plasticity during incubation [83].

Accumulating evidence suggests that BDNF may mediate some of the long-term neuroplasticity associated with incubation of cocaine craving. First, BDNF levels were found to increase in mesolimbic regions (NAc, VTA and amygdala) during the first 90 days of withdrawal in parallel with the incubation of cue-induced cocaine craving [48]. In a second study, animals received a single intra-VTA infusion of BDNF 1–2 h after 10 days of extended access cocaine self-administration. Then, cue-induced cocaine seeking was assessed after 3, 10 or 30 days of withdrawal. Both vehicle and BDNF infused rats showed incubation of cue-induced cocaine seeking, but responses on all days were higher in the BDNF group, an effect reversed by infusion of a MEK (mitogen-activated protein/extracellular signal-regulated kinase kinase) inhibitor into the VTA [90]. Based on a comparison to incubation of sucrose seeking (which is not accompanied by increased mesolimbic BDNF levels and is less persistent than cocaine incubation; [48]), the authors speculated that, rather than mediating the basic process of incubation of cocaine craving, BDNF transmission in the VTA may trigger adaptations that enable the persistence of enhanced cocaine craving during withdrawal. Similarly, later studies showed that glial cell line-derived neurotrophic factor (GDNF) transmission in the VTA also plays a facilitating role in the incubation of cocaine craving [141].

Recently our group extended these findings by examining the functional significance of BDNF in the NAc core and shell during the incubation of cocaine craving [23]. In the NAc core, attenuating BDNF-TrkB signaling prior to extended access cocaine self-administration training, using lentiviral vectors that expressed either TrkB siRNA or a dominant-negative truncated form of TrkB (TrkB.T1), significantly enhanced cue-induced cocaine seeking on withdrawal day 1, but had no effect on withdrawal day 30 or withdrawal day 90 [23]. Because the cocaine-induced increase in endogenous BDNF does not occur until after withdrawal day 1 [48], these data suggest that basal levels of BDNF transmission in the NAc core normally exert a suppressive effect on cue-induced cocaine seeking in early withdrawal. It is interesting that intra-mPFC infusion of BDNF, which also elevated BDNF levels in the NAc, similarly suppressed cocaine seeking and cocaine-induced reinstatement [78], as described in Section 3.3. Furthermore, the suppressing effect of intra-mPFC BDNF infusion has been associated with normalizing cocaine-induced extracellular glutamate transmission in the NAc [91].

In contrast to our findings in the core, we found that attenuating BDNF-TrkB signaling in NAc shell did not disrupt cue-induced cocaine seeking on withdrawal day 1 and withdrawal day 45, but significantly suppressed cue-induced cocaine seeking on withdrawal day 90, when BDNF levels showed a late elevation in NAc shell [23]; also see Section 2.2). These results suggest that BDNF in the NAc shell does not play a role in the development of incubation of cocaine craving, but the late elevation of BDNF in the NAc shell contributes to the long-term maintenance of ‘incubated’ cocaine seeking during late withdrawal (withdrawal day 90). Studies of incubation of sucrose craving are consistent with a role of BDNF in long-term maintenance of incubated cocaine craving. Thus, as noted above, incubation of sucrose seeking is less persistent compared to cocaine, returning to basal levels by withdrawal day 90, and is not associated with increased BDNF levels in the NAc [46, 48].

In conclusion, elevation of BDNF in the NAc shell is associated with maintenance of incubation, whereas basal BDNF transmission in the NAc core may oppose incubation during early withdrawal. More generally, these studies demonstrate that BDNF's role in the incubation of cocaine craving is not only distinct in NAc core versus shell, but also in different time-frames during withdrawal. Adding to the complexity, BDNF levels also increase in dorsal striatum after extended access cocaine self-administration and over-expressing BDNF in the dorsal striatum using a lentiviral vector promoted escalation of cocaine self-administration [49].

3.5. Summary

In cocaine CPP and cocaine-induced behavioral sensitization, BDNF generally exerts a facilitating role, probably reflecting its actions in NAc and VTA. One exception is that BDNF in rat mPFC plays a suppressing role in cocaine CPP. Studies of cocaine self-administration indicate that BDNF transmission in NAc shell plays an enhancing role in cocaine seeking, although a suppressive role of BDNF has been observed after direct injection into mPFC. The role of BDNF in incubation of cocaine craving is even more complex. BDNF (and GDNF) transmission in VTA promotes incubation during the early withdrawal phase (up to WD13). In the NAc, however, the effect of BDNF depends not only on withdrawal time but also on the subregion analyzed. Thus, while basal levels of BDNF in NAc core suppressed cocaine seeking during early withdrawal (WD1), the late elevation of BDNF in NAc shell enhanced cocaine seeking during late withdrawal (WD90). Taken together, these data suggest that the way BDNF regulates cocaine craving greatly depends on the brain region and the phase of addiction being modeled (e.g., drug-taking; drug-seeking during abstinence; reinstatement after extinction training; early withdrawal *vs* late withdrawal).

Even when analysis is restricted to a specific region, understanding BDNF's effects is significantly complicated by the potential for cell-type specificity of BDNF action. For example, in cortical cultures, BDNF plays different roles in regulating synaptic strength in principal neurons versus interneurons [92] (see 4.1 for more details). Within the NAc, there is evidence for core-shell differences in the incubation model [23]; Section 3.4). Furthermore, altering BDNF-TrKB signaling had opposite effects on cocaine reward measured by cocaine CPP depending on whether signaling was manipulated in D1-receptor positive or D2-receptor positive medium spiny neurons [68].

4. BDNF and synaptic plasticity, with a focus on AMPA receptor (AMPAR) plasticity

BDNF and its signaling pathways have been well documented as modulators of synaptic plasticity. Over the past two decades, substantial evidence has established that BDNF plays a facilitating role in long-term potentiation (LTP), the most studied form of synaptic plasticity. Various mechanisms (e.g., facilitation of synaptic vesicle docking at presynaptic terminals, stimulation of postsynaptic transcription, and regulation of local dendritic protein synthesis) contribute to BDNF's role in LTP, but this greatly depends on the brain region and the type of stimulation used to elicit LTP. For a thorough review of the roles of BDNF

in LTP, we refer readers to other articles [76, 93–98]. Here we will focus on BDNF's roles in homeostatic synaptic scaling and AMPAR plasticity. We will also discuss the potential relationship between BDNF and cocaine-induced AMPAR plasticity in NAc.

4.1 BDNF and synaptic scaling

Synaptic scaling is a form of homeostatic plasticity in which long-term changes in the level of excitatory activity lead to compensatory changes in synaptic transmission. Thus, increasing excitatory activity in neuronal cultures for 1–2 days using bicuculline leads to a compensatory decrease in excitatory transmission that is often mediated by a decrease in synaptic AMPAR levels, while prolonged activity blockade (e.g., using TTX) produces the opposite effect [99]. As BDNF levels vary with the level of excitatory transmission, BDNF is a potential mediator of synaptic scaling. Indeed, in cultures prepared from rat visual cortex, the addition of exogenous BDNF opposed the increase in mEPSC amplitude produced by prolonged activity blockade with TTX, whereas scavenging BDNF with a TrkB-IgG fusion protein reproduced the effect of activity blockade in pyramidal neurons [92]. Consistent with these findings, application of a TrkB inhibitor to cultured hippocampal neurons increased mEPSC amplitude but produced no further increase in mEPSC amplitude when combined with TTX [100]. These findings suggested that reduced BDNF-TrkB signaling contributes to "scaling up" of excitatory transmission after activity blockade in both cortical and hippocampal pyramidal neurons. However, these studies did not find evidence that increased BDNF levels mediate the opposite direction of synaptic scaling, i.e., "scaling down" of excitatory transmission in response to prolonged increases in activity.

Our recent work suggests that the role of BDNF in synaptic scaling is different for NAc medium spiny neurons. We studied these neurons in a co-culture system that includes PFC neurons to restore excitatory inputs. In contrast to findings in pyramidal neurons that indicated a role for BDNF in "scaling up" (see previous paragraph), we found that, in NAc medum spiny neurons, BDNF is necessary for "scaling down" in response to a prolonged increase in neuronal activity produced by bicuculline (24 h). Thus, decreasing BDNF signaling with the extracellular BDNF scavenger TrkB-Fc prevented the scaling down of GluA1 and GluA2 surface levels in NAc neurons normally produced by bicuculline [17].

Overall, results in visual cortex and hippocampus, combined with our results in NAc neurons, suggest that the role of BDNF in synaptic scaling is cell-type specific. This idea is further supported by opposing roles of BDNF in homeostatic plasticity in principal neurons and inhibitory interneurons of the cortex, with BDNF exerting a negative influence on mEPSC amplitude in principal neurons but increasing mEPSC amplitude in interneurons [92]. Additionally, BDNF transmission is implicated in the regulation of GABA-mediated inhibition onto cortical and hippocampal pyramidal neurons during activity blockade [101, 102].

There are many potential reasons for differences in BDNF's role between regions and cell types. These include potentially different sources of BDNF and the possibility of fundamental differences in homeostatic plasticity mechanisms between principal neurons that are excitatory (e.g., visual cortex) versus inhibitory (NAc) (see [17] for more discussion).

4.2 BDNF and AMPAR plasticity

An important postsynaptic effect of BDNF is to regulate AMPAR trafficking. AMPARs are hetero-tetramers (dimers of dimers) made up of GluA1-GluA4 subunits. Their transport in and out of synapses has been shown to mediate activity-dependent changes in synaptic strength during different forms of plasticity [103–109]. While GluA2-containing AMPARs comprise the majority of AMPARs in most brain regions, there is also a population of AMPARs that do not contain the GluA2 subunit, called GluA2-lacking AMPARs (e.g., homomeric GluA1 or GluA1/3) or Ca^{2+} permeable AMPARs (CP-AMPARs). They have different properties than GluA2-containing receptors, including higher conductance, Ca^{2+} permeability of the receptor channel, and inward rectification due to voltage-dependent block by endogenous polyamines. Thus, their recruitment to synapses increases synaptic strength and adds another route for Ca^{2+} entry (which is independent of NMDA receptors and voltage-gated Ca^{2+} channels) [110–114], as well as altering the “rules” for subsequent induction of plasticity by enabling anti-Hebbian LTP (e.g., [115, 116].

Previous studies have established that BDNF can affect AMPAR subunit expression and AMPAR trafficking in different in vitro systems. Some studies have found that BDNF can modulate GluA2-containing AMPARs. In cultured hippocampal neurons, application of BDNF increased both mRNA and protein levels of GluA1 and GluA2, whereas for GluA3 only protein levels were increased [117]. In cultured cortical neurons, BDNF has been shown to increase surface GluA1 and GluA2/3 [118, 119], as well as total protein levels of these subunits [118–120]. In genetically modified non-neuronal cells, BDNF also induced a rapid translocation of GluA2-containing AMPAR to the cell surface [119]. In cultured NAc neurons, our recent studies demonstrated that incubation with BDNF for 30 min led to increases in surface GluA1 and GluA2 levels, as well as their colocalization [17]. Furthermore, adding back BDNF to brain slices from *bdnf* knockout mice turned silent synapses into AMPAR-containing synapses through a mechanism involving synaptic delivery of both GluA1 and GluA2 [121].

Considerable in vitro evidence also suggests that BDNF can specifically affect the expression and synaptic delivery of CP-AMPARs. Thus, in cultured hippocampal neurons, application of BDNF increased the amount of GluA1, but not GluA2, associated with the plasma membrane in a translation-dependent manner [117]. BDNF has been also shown to induce translocation of GluA1 to the postsynaptic membrane from a local pool in neocortical neurons [122], and stimulate the translation and synaptic insertion of GluA1-containing CP-AMPARs [123]. Furthermore, BDNF produced a rapamycin-sensitive increase in GluA1 translation in synaptoneurosomes prepared from the forebrain of P15 rat pups, suggesting enhanced translation of dendritically localized GluA1 mRNA [124]. In rat hippocampal organotypic slices that over-express GFP-GuA1 (leading to formation of homomeric GluA1 receptors), BDNF facilitated delivery of homomeric GluA1 receptors into synapses [117]. In pond turtle brainstem, bath application of BDNF for 80 min increased synaptic delivery of GluA1 and GluA4 through a TrkB and ERK-mediated mechanism, reproducing cellular changes associated with a classical conditioning model [15, 125] (for review, see [126]). Moreover, mutant mice with lower BDNF levels showed reduced hippocampal expression of GluA1, but not GluA2 or GluA3 [127].

4.3 BDNF and cocaine-induced AMPAR plasticity in the NAc

Section 4.2 reviewed information about BDNF-AMPAR interactions obtained primarily from in vitro studies. Far less is known about such interactions in the intact rodent. This section will focus on recent studies of BDNF and AMPAR plasticity in the NAc during the incubation of cocaine craving (see Section 3.4 for a description of this model). Changes in AMPAR levels and subunit composition have been found to play a critical role in animal models of cocaine addiction [80, 128]. An important neuroadaptation in the NAc during incubation of cocaine craving is the accumulation of CP-AMPARs (most likely homomeric GluA1) at excitatory synapses on medium spiny neurons. Normally present at relatively low levels in these synapses, an increase in CP-AMPAR levels is detected between 3 and 4 weeks of withdrawal; once present, their activation is required for the expression of incubated cue-induced cocaine craving [80, 129–131]. In light of in vitro evidence that BDNF can selectively promote the synaptic insertion of CP-AMPARs (Section 4.2), we hypothesized that the persistent elevation of BDNF protein found in the NAc during incubation [48] (see Section 2.2), might contribute to the observed accumulation of CP-AMPARs in the NAc.

An early study was supportive of this hypothesis. Thus, we demonstrated that BDNF injection into the NAc core of drug-naïve rats led to a rapid and transient increase in cell surface GluA1 that was dependent on protein synthesis and ERK activation; GluA2 and GluA3 were unaffected, suggesting that BDNF increased surface expression of homomeric GluA1 CP-AMPARs [132]. In a subsequent study, however, we found that chronically elevating BDNF in the NAc of drug naïve rats using lentiviral vectors, so as to mimic the withdrawal-dependent increase in BDNF levels in the NAc during incubation of cocaine craving, did not change cell surface or total expression of GluA1 or GluA2 [23]. These results suggest that elevation of BDNF signaling in the NAc is not sufficient to account for the accumulation of CP-AMPARs during incubation. Indeed, we obtained data suggesting that the reverse relationship may hold, that is, that enhanced AMPAR transmission after prolonged withdrawal (due to accumulation of high conductance CP-AMPARs) may be responsible for the time-dependent increase in BDNF levels in the NAc [23]. This novel hypothesis was based on studies using ampakines, positive allosteric modulators of AMPAR transmission that slow deactivation and desensitization of AMPARs [133]. Ampakines increase BDNF protein levels in cultured hippocampal neurons as well as rat hippocampus in vivo [134–137]. We showed that systemic administration of an ampakine to drug-naïve rats similarly increased BDNF levels in the NAc [23]. These results provide preliminary support for the hypothesis that enhanced AMPAR transmission in the NAc may contribute to elevation of BDNF levels during incubation of cocaine craving (for more discussion, see [23] and [130]).

4.4 Summary

In addition to a facilitating role in LTP, BDNF has been demonstrated to participate in many other forms of synaptic plasticity. In synaptic scaling, BDNF contributes to both “scaling up” and “scaling down” of synaptic strength in a cell-type specific manner. BDNF also can affect the expression and synaptic targeting of both GluA2-containing AMPAR and CP-AMPAR depending on the in vitro system studied. An important issue that has not been

resolved in the current literature is how BDNF-mediated synaptic plasticity is related to its involvement in cocaine action (reviewed in Section 3). Specifically, although BDNF has been implicated in regulating both AMPAR trafficking and the behavioral effects of cocaine, whether the effects of BDNF observed in animal models of cocaine addiction are attributable to alterations in AMPAR expression and distribution is still largely unknown.

5. Methodological considerations

There are several methodological issues to consider when interpreting the results reviewed here. Exogenous intracranial infusion of BDNF, a tool used in many studies, elevates BDNF levels many fold above its physiological levels (e.g., [132]), which may not mimic the temporal or spatial features of increases in endogenous BDNF after cocaine exposure. Similar concerns also apply to elevation of BDNF levels using viral vectors – this approach also fails to mimic physiological release of endogenous BDNF. Furthermore, BDNF can be transported either anterogradely or retrogradely to other brain regions after injection or over-expression by viral vectors and thus exert its effects by acting on brain regions other than the site of infusion [7].

For these reasons, studies interfering with endogenous BDNF levels (e.g., infusion of antibody to BDNF or TrkB, viral knockdown of BDNF or TrkB expression, and inhibition of TrkB signaling using dominant negative forms of TrkB) provide more direct evidence of the role of endogenous BDNF in cocaine seeking. The latter approaches also have the advantage of interfering with BDNF function at a specific time-point in adult animals, in contrast to studies using constitutive knockout animals, where caution is necessary due to possible compensatory mechanisms that might account for the effect of BDNF on cocaine-induced behaviors.

6. Conclusion

Taken together, preclinical studies reviewed here suggest that BDNF may play important modulatory roles in cocaine addiction. However, given that the nature of cocaine-BDNF interactions depends on cell type, brain region and phase of addiction, does systemic targeting of BDNF signaling represent a reasonable approach to the treatment of cocaine addiction? While this remains to be tested, the possibility cannot be ruled out, as blockade of BDNF action in some regions (e.g., NAc and VTA) might dominate over actions in other regions (e.g., PFC) and thus prove beneficial. On the other hand, emerging clinical evidence indicates that BDNF levels in serum may serve as a biomarker in cocaine addicts to predict future relapse. In D'Sa et al. [138], serum BDNF levels in cocaine-dependent patients, sampled after 3 weeks of abstinence, were positively correlated with propensity to relapse over the subsequent 90 days. Additionally, two recent studies showed that serum BDNF increased during early cocaine withdrawal [139, 140] and the extent of BDNF increase was inversely correlated with number of crack rocks used in the last 30 days [140]. These clinical findings may provide future directions for preclinical researchers to identify cocaine-BDNF interactions with translational significance.

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Abbreviations

AAV	adeno-associated virus
AMP	adenosine monophosphate
AMPAR	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF	brain-derived neurotrophic factor
CP-AMPAR	Ca^{2+} permeable AMPA receptor
CPP	conditioned place preference
CREB	cyclic AMP response element binding protein
DA	dopamine
ER	endoplasmic reticulum
ERK	extracellular signal regulated kinase
GABA	gamma-aminobutyric acid
Glu	glutamate
GluA1	glutamate receptor 1
GluA2	glutamate receptor 2
GluA3	glutamate receptor 3
GluA4	glutamate receptor 4
i.p.	intraperitoneal injection
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
MeCP2	Methyl-CpG-binding protein 2
mPFC	medial prefrontal cortex
NAc	nucleus accumbens
NMDA	N-methyl-D-aspartic acid
p75NTR	p75 neurotrophin receptor
pERK	phosphorylated extracellular signal-regulated kinase
PFC	prefrontal cortex
PI3-K	phosphoinositide 3-kinase
PLC-γ	phospholipase C-γ
TrkA	tropomyosin receptor kinase A

TrkB	tropomyosin receptor kinase B
TrkC	tropomyosin receptor kinase C
TTX	tetrodotoxin
VTA	ventral tegmental area

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Highlights

- Cocaine exposure generally increases BDNF in addiction-related brain regions.
- The roles of BDNF in animal models of cocaine addiction are diverse and complex.
- BDNF contributes to synaptic plasticity, sometimes by influencing AMPAR function.
- Many questions remain about how BDNF-related plasticity contributes to addiction.

Table 1

Summary of effects of cocaine on BDNF levels in addiction-related brain regions

Brain Region	Cocaine administration paradigm	Time points when tissue collected	Effect on *bdnf* mRNA	Effect on BDNF protein	Citations
Adult rat NAc	SA (6 h/day X 10 days; 1.0 mg/kg/infusion)	WD1 WD30, 90	ND ND	— ▲	[48]
	SA (6 h/day X 10 days; 0.5 mg/kg/infusion)	WD45	—	▲	[23]
	SA (2 h/day X 14 days; 0.25 mg/infusion)	No WD WD1, 7	ND ND	▲ —	[34]
Adult rat NAc core	SA (6 h/day X 10 days; 0.5 mg/kg/infusion)	WD45 WD90	— ND	▲ ▲	[23]
Adult rat NAc shell	SA (4 h/day X 18 days; 0.5 mg/kg/infusion)	No WD WD1	ND ND	▲ —	[22]
	Acute (20 mg/kg IP)	1 h 2 h	▲ —	— ▲	[22]
	SA (6 h/day X 10 days; 0.5 mg/kg/infusion)	WD45 WD90	— ND	— ▲	[23]
	Acute (10 mg/kg IP) Repeated (5 days X 10 mg/kg IP)	1 h WD5 WD5+Cocaine (10 mg/kg IP)	▲ ▲ ▲	ND ND ND	[21]
Adult mouse NAc	Acute (30 mg/kg IP)	2 h	ND	▲	[31]
P26-28 mouse NAc shell	Repeated (5 days X 15 mg/kg IP)	WD1, 3, 7 WD14, 28	ND ND	— ▲	[38]
Adult rat DS	Acute (40 mg/kg IP)	4 h	▲ (Exon IV)	ND	[24]
	SA (6 h/day X 7 days; 0.5 mg/kg/infusion)	WD1	ND	▲	[49]
	SA (6 h/day X 10 days; 1.0 mg/kg/infusion)	WD1	—	ND	[24]
Adult rat VS	Acute (40 mg/kg IP)	4 h	▲ (Exon IV)	ND	[24]
Adult rat FC	Acute (40 mg/kg IP)	4 h	▲ (Exon I, IV)	ND	[24]
	Acute (20 mg/kg IP)	2 h, 4 h	▲	ND	[33]
	SA (6 h/day X 10 days; 1.0 mg/kg/infusion)	WD1	—	ND	[24]
Adult rat PFC	Acute (5 mg/kg IP) Acute (10 mg/kg IP) Acute (20 mg/kg IP)	30 min, 2 h, 4 h, 6 h, 24 h 2 h 2 h	▲ ▲ ▲	▲ (24 h) ND ND	[32]

Brain Region	Cocaine administration paradigm	Time points when tissue collected	Effect on *bdnf* mRNA	Effect on BDNF protein	Citations
	Repeated (5 days X 5 mg/kg IP)	2 h 72 h	▲ —	▼ ▼	[32]
Adult rat mPFC	Acute (20 mg/kg IP)	2 h 4 h	▲ ▲	ND ND	[33]
	SA (2 h/day X 14 days; 0.25 mg/infusion)	WD7	▲ (Exon IV)	▲	[36]
	SA (2 h/day X 14 days; 0.25 mg/infusion)	No WD WD1 WD7	ND — ▲ (Exon I) ▼ (Exon IV) ND	— ▲ —	[34]
	SA (2 h session; 0.25 mg/infusion)	No WD	—	ND	[47]
	SA (24 h session X 10 days; 4 discrete trials/h; 1.5 mg/kg/infusion)	WD14 followed by 6-h extinction and 1-h reinstatement session	▲ (Exon IV)	ND	[35]
	SA (6 h/day X 10 days; 0.5 mg/kg/infusion)	WD45	—	—	[23]
Adult rat dorsomedial PFC	SA (2 h/day X 10 days; 0.2 mg/infusion)	22 h WD21 WD21+Saline (IP) WD21+Cocaine (10 mg/kg IP)	▼ — ND ND	ND ND ▲ ▲	[4]
P18-P24 rat mPFC	Repeated (7 days X 15 mg/kg IP)	WD1, 3 WD8, 14	ND ND	— ▲	[41]
Adult rat VTA	SA (6 h/day X 10 days; 1.0 mg/kg/infusion)	WD1 WD30, 90	ND ND	— ▲	[48]
	SA (2 h/day X 14 days; 0.25 mg/infusion)	WD1 WD7	— ▲ (Exon I)	ND ▲	[37]
P21-P40 rat VTA	Repeated (5–7 days X 15 mg/kg IP)	WD1 WD10-15	ND ND	— ▲	[40]

Abbreviations: NAc: nucleus accumbens; DS: dorsal striatum; VS: ventral striatum; FC: frontal cortex; PFC: prefrontal cortex; mPFC: medial prefrontal cortex; VTA: ventral tegmental area; SA: self-administration; IP: intraperitoneal injection; P: Postnatal day; WD: withdrawal day; ND: not determined. Symbols: (▲) increase; (▼) decrease; (—) no change.

Table 2

Summary of roles of BDNF in cocaine CPP, behavioral sensitization, and self-administration

Brain Region	BDNF/TrkB manipulations	Behavioral procedure	Withdrawal Day (WD)	Behavioral outcomes	Citations
Rat NAc	BDNF over-expression	CPP (5 or 20 mg/kg IP)	NA	Increased CPP Delayed CPP extinction Increased cocaine-primed reinstatement of CPP	[65]
	Chronic minipump infusion of BDNF	Behavioral sensitization (5–15 mg/kg IP X 7 days)	NA	Facilitated development of locomotor sensitization	[66]
	BDNF antibody injection	Behavioral sensitization (15 mg/kg IP X 4 days)	NA	No effect on development of locomotor sensitization	[28]
	BDNF and/or TrkB over-expression	Behavioral sensitization (15 mg/kg IP X 15 days)	NA	Potentiated cocaine-induced locomotor activity	[65]
	TrkB knockdown		NA	Decreased cocaine-induced locomotor activity	
Rat NAc Core	TrkB knockdown	SA (6 h/day X 10 days; 0.5 mg/kg/infusion)	WD1	Increased cue-induced extinction responding	[23]
			WD30, 90	No effect on cue-induced extinction responding	
Rat NAc Shell	TrkB knockdown		WD1, 45	No effect on cue-induced extinction responding	
			WD90	Decreased cue-induced extinction responding	
	BDNF injection	SA (4 h/day X 3–4 weeks; 0.5 mg/kg/infusion)	NA	Upward shift of dose response curve during SA	[22]
			NA	Increased responses under a progressive ratio schedule	
			WD11	Increased extinction responding	
			NA	Increased cocaine-primed reinstatement	
			NA	Increased cue-primed reinstatement	
			NA	Increased footshock-induced reinstatement	
	BDNF antibody injection		NA	Downward shift of dose response curve during SA	
			NA	Decreased responses under progressive ratio schedule	
			WD11	Decreased extinction responding	
			NA	Decreased cocaine-primed reinstatement	

Brain Region	BDNF/TrkB manipulations	Behavioral procedure	Withdrawal Day (WD)	Behavioral outcomes	Citations
			NA NA	No effect on cue-primed reinstatement Decreased food shock-induced reinstatement	
Mouse NAc	BDNF knockdown	CPP (10 mg/kg IP)	NA	Decreased CPP	[57]
	TrkB knockdown		NA	Decreased CPP	
	TrkB knockdown	SA (4 h/day X 3–4 weeks; 0.5 mg/kg/infusion)	NA	Decreased cocaine intake during SA No effect on acquisition of SA	[57]
	BDNF knockdown		NA	Decreased cocaine intake during SA	[22]
	TrkB knockout in D1+ neurons	CPP (7.5 mg/kg IP) Locomotor activity (10 mg/kg IP)	NA	Increased CPP Increased cocaine-induced locomotor activity	[68]
	TrkB knockout in D2+ neurons			Decreased CPP Decreased cocaine-induced locomotor activity	
Rat Dorsal Striatum	BDNF over-expression	SA (6 h/day X 19 days; 0.5 mg/kg/infusion)	NA	Increased cocaine intake during SA Upward shift of dose response curve during SA	[49]
	BDNF antibody injection	SA (6 h/day X 25 days; 0.5 mg/kg/infusion)	NA	Decreased cocaine intake during SA	
Rat VTA	BDNF antibody injection	Behavioral sensitization (15 mg/kg X 4 days IP)	NA	No effect on development of locomotor sensitization	[28]
	Chronic minipump infusion of BDNF	Behavioral sensitization (15–30 mg/kg IP X 7 days)	NA	Increased locomotor activity	[66]
	BDNF injection	SA (6 h/day X 10 days; 0.75 mg/kg/infusion)	WD3, 10	Increased cue-induced extinction responding	[91]
	BDNF injection	Behavioral sensitization (15 mg/kg IP X 3 days)	NA WD1, 14	Increased locomotor activity No effect on expression of sensitization in response to cocaine challenge	[77]
Mice VTA	BDNF knockdown	CPP (10 mg/kg IP)	NA	Decreased CPP	[57]
	TrkB knockdown	CPP (10 mg/kg IP)	NA	No effect on CPP	

Brain Region	BDNF/TrkB manipulations	Behavioral procedure	Withdrawal Day (WD)	Behavioral outcomes	Citations
Rat mPFC	TrkB knockdown	Behavioral sensitization (15 mg/kg IP X 7 days)	WD8	Suppressed expression of sensitization in response to cocaine challenge	[41]
	BDNF injection	SA (2 h/day X 10 days; 0.2 mg/infusion)	WD1, 7	Decreased cue-induced extinction responding Decreased cue-primed reinstatement Decreased cocaine-primed reinstatement	[78]
	BDNF knockdown	SA (2 h/day X 14 days; 0.25 mg/infusion)	NA	Increased breakpoint under a progressive ratio schedule	[36]
Rat infralimbic cortex	TrkB agonist Injection	CPP (10 mg/kg IP)	NA	Facilitated CPP extinction	[67]
Rat	BDNF heterozygous knockout	CPP (10 mg/kg IP)	NA	Abolished CPP	[63]
Mice	BDNF heterozygous knockout		NA	Decreased CPP	[62]
Mice	BDNF conditional knockout	Behavioral sensitization (15 mg/kg IP X 5 days)	WD14	Suppressed expression of sensitization in response to cocaine challenge	[38]
Mice	TrkB conditional knockdown	CPP (20 mg/kg IP) Behavioral sensitization (20 mg/kg IP X 1 day)	NA WD28	Abolished CPP Suppressed expression of sensitization in response to cocaine challenge	[64]
Mice	BDNF heterozygous knockout	Behavioral sensitization (10 mg/kg IP X 6 days)	NA	Delayed development of locomotor sensitization	[66]

Abbreviations: NAc: nucleus accumbens; mPFC: medial prefrontal cortex; VTA: ventral tegmental area; CPP: conditioned place preference; IP: intraperitoneal injection; SA: self-administration; NA: not applicable; WD: withdrawal day; ND: not determined.