Behavioural Brain Research 279 (2015) 240–254

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Multiple faces of BDNF in cocaine addiction

Xuan Li[a,*], Marina E. Wolf[b]

[a] Behavioral Neuroscience Research Branch, Intramural Research Program, NIDA/NIH/DHHS, Baltimore, MD, USA
[b] Department of Neuroscience, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

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.

ARTICLE INFO

Article history:
Received 4 September 2014
Received in revised form 4 November 2014
Accepted 8 November 2014
Available online 15 November 2014

Keywords:
BDNF
TrkB
Cocaine addiction
AMPA receptor.

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.

Contents

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.

* Corresponding author at: Behavioral Neuroscience Research Branch, Intramural Research Program, NIDA, Suite 08A505.14, 251 Bayview Blvd, Baltimore, MD 21224, USA. Tel.: +1 443 740 2721.
E-mail address: anna.li@nih.gov (X. Li).

http://dx.doi.org/10.1016/j.bbr.2014.11.018
0166-4328/

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