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NEUROTROPHINS IN THE VENTRAL TEGMENTAL AREA: ROLE IN SOCIAL STRESS, MOOD DISORDERS AND DRUG ABUSE

E. M. NIKULINA, [a*] **C. E. JOHNSTON,** [a,b] **J. WANG** [b†] **AND R. P. HAMMER Jr.** [a,b,c]

[a] *Department of Basic Medical Sciences, University of Arizona College of Medicine, Phoenix, AZ, USA*

[b] *Interdisciplinary Neuroscience Program, Arizona State University, Tempe, AZ, USA*

[c] *Department of Pharmacology and Department of Psychiatry, University of Arizona College of Medicine, Tucson, AZ, USA*

Abstract—This review discusses the impact of neurotrophins and other trophic factors, including fibroblast growth factor and glial cell line-derived neurotrophic factor, on mood disorders, weight regulation and drug abuse, with an emphasis on stress- and drug-induced changes in the ventral tegmental area (VTA). Neurotrophins, comprising nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophins 3 and 4/5 play important roles in neuronal plasticity and the development of different psychopathologies. In the VTA, most research has focused on the role of BDNF, because other neurotrophins are not found there in significant quantities. BDNF originating in the VTA provides trophic support to dopamine neurons. The diverse intracellular signaling pathways activated by BDNF may underlie precise physiological functions specific to the VTA. In general, VTA BDNF expression increases after psychostimulant exposures, and enhanced BDNF level in the VTA facilitates psychostimulant effects. The impact of VTA BDNF on the behavioral effects of psychostimulants relies primarily on its action within the mesocorticolimbic circuit. In the case of opiates, VTA BDNF expression and effects seem to be dependent on whether an animal is drug-naïve or has a history of drug use, only the latter of which is related to dopamine mechanisms. Social defeat stress that is continuous in mice or intermittent in rats increases VTA BDNF expression, and is associated with depressive and social avoidance behaviors. Intermittent social defeat stress induces persistent VTA BDNF expression that triggers psychostimulant cross-sensitization. Understanding the cellular and molecular substrates of neurotrophin effects may lead to novel therapeutic approaches for the prevention and treatment of substance use and mood disorders.

Key words: BDNF, cross-sensitization, depression, drug abuse, social stress.

INTRODUCTION

Neurotrophins are closely related neuropeptides of the nerve growth factor (NGF) family that control many aspects of neuronal survival, development, growth, and functions such as synapse formation and synaptic plasticity (see review of Reichardt, 2006). Trophic support for midbrain dopaminergic neurons by local synthesis of brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) was initially described more than twenty years ago (Hyman et al., 1991; Gall et al., 1992). Prior to that, NGF was identified and characterized in the pivotal research of Levi-Montalcini (1987), and found to act specifically on cholinergic neurons (Thoenen, 1991). Due to their critical effects, neurotrophins have accumulated more than 10,000 publications with multiple reviews in recent years, mostly concerning their molecular mechanisms and functional significance (for recent reviews see ''BDNF special issue'' of Neuropharmacology, 2014).

During the synthesis of neurotrophins, pro-neurotrophins are cleaved to produce the mature neurotrophin proteins (Mowla et al., 2001; Lu et al., 2005). Immature neurotrophins preferentially bind to the p75 neurotrophin receptor, while mature neurotrophins have a lower affinity for the p75 receptor and show ligand specificity for the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases (Fig. 1; Segal, 2003; Longo and Massa, 2013). BDNF and neurotrophin-4 (NT-4) recognize the tropomyosin-regulated kinase B (TrkB) receptor, while NGF binds specifically with TrkA, and NT-3 activates TrkC (Chao, 2003; Reichardt, 2006). Trk receptor dimerization leads to trans-autophosphorylation and activation of intracellular signaling cascades that are activated by BDNF. Three well-characterized intracellular signaling pathways include the Ras/extracellular signal-regulated kinase (ERK), the phosphatidylinositol-3′-OH-kinase (PI3K)–AKT pathway, and the phospholipase C-γ (PLC-γ) pathway (Fig. 1; for more details see the recent review by Park and Poo, 2013). Many of the

*Corresponding author. Address: Department of Basic Medical Sciences, University of Arizona College of Medicine – Phoenix, 425N 5th Street, Phoenix, AZ 85004, USA. Tel: +1-602-827-2168; fax: +1-602-827-2130.

E-mail address: nikulina@email.arizona.edu (E. M. Nikulina).

† Present address: Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260, USA.

Abbreviations: BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; GDNF, glial cell line-derived neurotrophic factor; MAPK, mitogen-activated protein kinase; MOR, mu-opioid receptor; NAc, nucleus accumbens; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; NT, neurotrophin; PFC, prefrontal cortex; PLC-γ, phospholipase C-γ; TrkB, tropomyosin-regulated kinase B; tVTA, tail of ventral tegmental area; VTA, ventral tegmental area.

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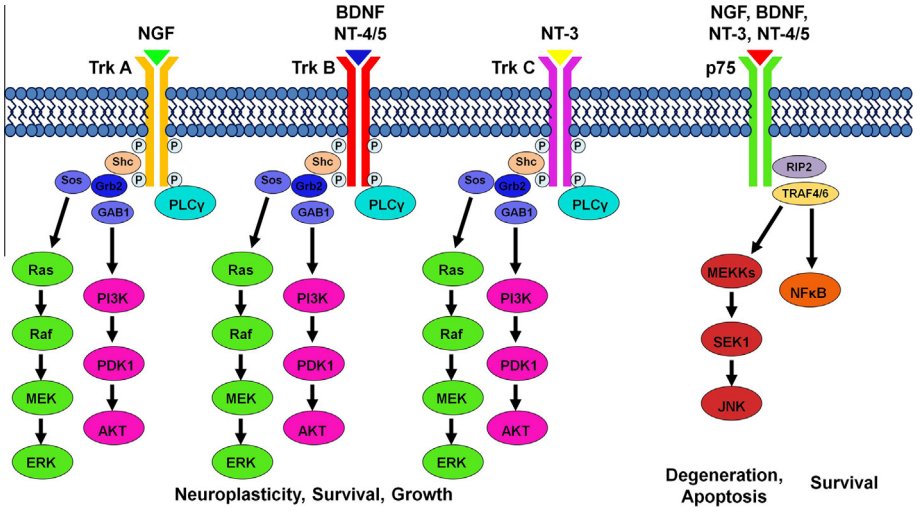

Fig. 1. Neurotrophin ligand-receptor specificity and intracellular signaling cascades. Neurotrophins show ligand specificity for Trk receptors, and activate intracellular signaling cascades, including Ras/ERK, PI3K/AKT, and PLCγ to alter neuronal survival, growth and neuroplasticity. Trk receptor activation results in the recruitment of Src homology domain-containing protein (Shc) and PLCγ to the intracellular domain. Localization of Shc to the receptor site recruits growth factor receptor-bound protein 2 (Grb 2), which recruits the intermediary proteins Sos and GAB1 to activate the Ras/ERK and PI3K/AKT pathways, respectively. Upon activation, the Ras/ERK, PI3K/AKT, and PLCγ signaling pathways can activate other signaling pathways, as well as nuclear factors. In addition, all neurotrophins can bind to p75 to activate the Jun N-terminal kinase (JNK) or nuclear factor kappa B (NFκB) intracellular signaling cascades responsible for neuronal fate and apoptosis. P75 receptor activation recruits receptor interacting protein 2 (RIP2) and tumor necrosis factor receptor associated factor 4/6 (TRAF4/6). Depending on context, neurotrophins binding to the p75 receptor can activate either the NFκB pathway to promote survival and augment Trk effects, or the JNK pathway to promote apoptosis and antagonize the effects of Trk receptors. For additional details on neurotrophin ligand–receptor signaling, see reviews by Segal (2003), Reichardt (2006), Longo and Massa (2013).

intracellular signaling components that mediate neurotrophin signaling, such as ERK, AKT, PLC, PKC, Ras, JNK, and NF-κB, are not unique to neurotrophins, and these common elements may serve as cross-talk tools between neurotrophins and other neurotransmitter systems.

Expression of BDNF, perhaps the most widely studied neurotrophin, is intimately regulated by neural activity. Detailed mapping of BDNF immunolabeling and mRNA expression have revealed that the VTA contains a medium-to-high density of BDNF expression. At the same time, mesolimbic projection areas such as the bed nucleus of the stria terminalis and nucleus accumbens (NAc) have distinctive BDNF immunoreactive fibers and intracellular protein in the absence of mRNA expression, suggesting anterograde axonal transport of BDNF protein via afferent systems (Conner et al., 1997). BDNF is further known to undergo both retrograde and anterograde transport (Altar et al., 1997). The prefrontal cortex (PFC) contains dense BDNF mRNA-expressing neurons (Conner et al., 1997), which supply BDNF to both the NAc and VTA, thereby modulating the functions of these brain regions (Seroogy et al., 1994; Guillin et al., 2001).

Populations of various neuronal types are differentially distributed throughout the rostrocaudal and mediolateral axes of the VTA (Nair-Roberts et al., 2008). The VTA as a whole contains mainly dopaminergic neurons (50–65%), with approximately 1/3 GABAergic neurons (30–35%; Swanson, 1982; Oades and Halliday, 1987; Yamaguchi et al., 2007; Nair-Roberts et al., 2008) and a few glutamatergic neurons (2–3%; Nair-Roberts et al., 2008). Glutamatergic neurons, as defined by their expression of vesicular glutamate transporter type 2, are mostly confined to the medial portion of the rostral VTA (Kawano et al., 2006; Nair-Roberts et al., 2008). Some VTA neurons that release glutamate also express tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (Tagliaferro and Morales, 2008; Yamaguchi et al., 2011).

In the VTA, approximately 50% of all neurons were found to co-label for both tyrosine hydroxylase and BDNF (Seroogy et al., 1994). The diverse intracellular signaling pathways activated by BDNF may represent precise physiological functions specific to the VTA, such as behavioral response to drug and natural reward, stress, and some mood disorders. These functions can be studied using viral-mediated gene transfer (Carlezon et al., 2000) to manipulate selectively the expression of a single gene in a specific brain region at a particular time.

This review will focus on recent work assessing the role of neurotrophin-activated intracellular signaling cascades in social stress, depression, and the behavioral effects associated with drugs of abuse.

VTA BDNF IN DEPRESSION AND SUSCEPTIBILITY TO STRESS

The involvement of mesolimbic dopamine in human and animal models of depression has been known since the early 1980s. Evidence for dysfunction of dopamine neurotransmission in major depression began with the observation that reduced dopamine metabolites are present during anhedonia-like behavior, and that antidepressant treatment increases mesolimbic dopamine transmission (Chiodo and Antelman, 1980;

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