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REVIEW

BDNF: NO GAIN WITHOUT PAIN?

PETER A. SMITH *

Centre for Neuroscience and Department of Pharmacology, 9.75 Medical Sciences Building, University of Alberta, Edmonton, AB T6G 2H7, Canada

Abstract—Injury to the adult nervous system promotes the expression and secretion of brain-derived neurotrophic factor (BDNF). Because it promotes neuronal growth, survival and neurogenesis, BDNF may initiate compensatory processes that mitigate the deleterious effects of injury, disease or stress. Despite this, BDNF has been implicated in several injury-induced maladaptive processes including pain, spasticity and convulsive activity. This review will concentrate on the predominant role of BDNF in the initiation and maintenance of chronic and/or neuropathic pain at the spinal, peripheral and central levels. Within the spinal dorsal horn, the pattern of BDNF-induced changes in synaptic transmission across five different, identified neuronal phenotypes bears a striking resemblance to that produced by chronic constriction injury (CCI) of peripheral nerves. The appearance of this ''pain footprint'' thus reflects multiple sensitizing actions of microglial-derived BDNF. These include changes in the chloride equilibrium potential, decreased excitatory synaptic drive to inhibitory neurons, complex changes in inhibitory (GABA/glycinergic) synaptic transmission, increases in excitatory synaptic drive to excitatory neurons and the appearance of oscillatory activity. BDNF effects are confined to changes in synaptic transmission as there is little change in the passive or active properties of neurons in the superficial dorsal horn. Actions of BDNF in the brain stem and periphery also contribute to the onset and persistence of chronic pain. In spite of its role in compensatory processes that facilitate the recovery of the nervous system from injury, the widespread maladaptive actions of BDNF mean that there is literally ''no gain without pain''.

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Key words: neuropathic pain, dorsal horn, neurotrophin, electrophysiology, organotypic culture, Central sensitization.

*Tel: + 1-780-492-2643; fax: +1-780-492-4325.
E-mail address: peter.a.smith@ualberta.ca

Abbreviations: ASIC1a, acid-sensing ion channels; BDNF, brain-derived neurotrophic factor; CCI, chronic constriction injury; DRG, dorsal root ganglia; ERK, extracellular signal-related kinase; KCC2, K^+-Cl^- cotransporter; MOR, mu-opioid receptor; p75NTR, p75 neurotrophin receptor; PI3K, phosphatidylinositol 3-kinase; ras-MAPK, ras mitogen-activated protein kinase; TrkB, tropomyosin-related kinase B.

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INTRODUCTION

Various forms of stress and/or injury to peripheral nerves, spinal cord or brain increase the expression of brain-derived neurotrophic factor (BDNF) in the affected regions (Meyer et al., 1992; Cho et al., 1998; Michael et al., 1999; Zochodne and Cheng, 2000; Fukuoka et al., 2001; Hicks et al., 1997; Lipska et al., 2001; Wong et al., 1997; Yang et al., 1996; Dougherty et al., 2000; Frisen et al., 1992). Because it promotes neuronal growth, development, synaptogenesis, differentiation, survival and neurogenesis, this led to the idea that BDNF initiates compensatory mechanisms which seek to counter the deleterious effects of injury or stress (Barde et al., 1982; Leibrock et al., 1989; Pencea et al., 2001; Scharfman et al., 2005; Yoshii and Constantine-Paton, 2010; Park and Poo, 2013; Parkhurst et al., 2013). BDNF thus has the potential to facilitate recovery from traumatic nerve injury (Menei et al., 1998; Gordon et al., 2003; Weishaupt et al., 2012; Huang et al., 2013) and to mitigate neurodegenerative disease (Lynch et al., 2007; Zuccato and Cattaneo, 2009). The obvious implication

of these findings is that BDNF itself, or agents that mimic or potentiate its action, would hold considerable therapeutic potential (O'Leary and Hughes, 2003; Binder and Scharfman, 2004; Massa et al., 2010; Nagahara and Tuszynski, 2011; Weishaupt et al., 2012; Longo and Massa, 2013). Such potential may extend to the management of psychiatric disorders as BDNF levels are reduced in both depression and bipolar disorder (Autry and Monteggia, 2012).

Unfortunately, this potential is limited by several undesirable actions of BDNF. For example, it can enhance nociceptive processes and may be a major factor in the development of chronic inflammatory and neuropathic pain (Kerr et al., 1999; Thompson et al., 1999; Garraway et al., 2003; Coull et al., 2005; Pezet and McMahon, 2006; Herradon et al., 2007; Merighi et al., 2008b; Bardoni and Merighi, 2009; Lu et al., 2009a; Biggs et al., 2010; Trang et al., 2011; Beggs and Salter, 2013). BDNF can also promote spasticity (Boulenguez et al., 2010; Fouad et al., 2013) and convulsive activity (Hughes et al., 1999; Gill et al., 2013). It may contribute to opioid dependence (Vargas-Perez et al., 2009) and to "paradoxical" opioid hyperalgesia (Ferrini et al., 2013).

On the other hand, attempts to treat chronic and/or neuropathic pain by preventing BDNF action may be precluded by the development of depression (Autry and Monteggia, 2012) and/or disturbance of neuroplastic processes such as long-term potentiation (Montalbano et al., 2013) and memory (Malcangio and Lessmann, 2003).

In view of the theme of this special issue of *Neuroscience* on "Compensation following injury to the adult brain: always for good?" this review will concentrate on the undesirable actions of BDNF, with particular emphasis on its role in the onset and persistence of neuropathic pain.

SYNTHESIS AND SECRETION OF BDNF

The *Bdnf* gene has unique structural features. The human gene spans >70 kb and is composed of nine exons controlled by nine promoters. The observation that promoter IV is highly responsive to neuronal activity has provided a molecular underpinning to studies of the role of BDNF in the mature nervous system (Park and Poo, 2013). It is made and secreted by neurons, microglia and astrocytes (Lindholm et al., 1992; Rudge et al., 1992; Coull et al., 2005; Lu et al., 2009a; Trang et al., 2011). But BDNF is also found in several tissues outside the nervous system such as kidney (Huber et al., 1996), prostate gland (Dalal and Djakiew, 1997) blood platelets (Yamamoto and Gurney, 1990) and retina (Herzog et al., 1994).

Prepro-BDNF is synthesized in the endoplasmic reticulum. This is cleaved into the smaller 35-kDa precursor, pro-BDNF. There is disagreement as to whether pro-BDNF is secreted intact (Matsumoto et al., 2008; Barker, 2009; Yang et al., 2009; Waterhouse and Xu, 2009; Park and Poo, 2013) or whether it is first converted to mature 14-kDa BDNF which is secreted from dense core vesicles in an activity and Ca^{2+}-dependent manner (Lessmann et al., 2003; Trang et al., 2009). Pro-BDNF nevertheless has effects in the nervous system that are independent of mature BDNF and are mediated via the p75 neurotrophin receptor (p75NTR) (Lessmann et al., 2003; Matsumoto et al., 2008; Barker, 2009).

In humans, a common single nucleotide polymorphism (SNP) of BDNF has been identified in which valine at position 66 is replaced by methionine (Val66Met BDNF). This polymorphism has been associated with a plethora of effects including molecular, cellular and brain structural modifications that are associated with deficits in social and cognitive functions (Baj et al., 2013). It remains to be determined whether individuals expressing Val66Met BDNF are more or less prone to exhibit maladaptive BDNF responses. This is important in terms of individuals' responses to nerve injury as the occurrence of neuropathic pain is highly variable and depends on a variety of environmental and genetic factors. Interestingly, it was recently reported that the expression of the Val66Met BDNF genotype impacts spinal plasticity in humans (Lamy and Boakye, 2013). Persons expressing this polymorphism may thus display increased susceptibility to developing chronic pain in response to nerve injury.

TRK B SIGNALING

Mature BDNF signals both through p75NTR and through the tropomyosin-related kinase B (TrkB) receptor (Reichardt, 2006). Binding of BDNF to TrkB induces receptor dimerization and autophosphorylation. Dimerized receptors recruit the adapter protein Shc to Tyr515 as well as phospholipase Cγ1(PLCγ1) to Tyr785. This leads to the activation of at least three intracellular signaling cascades:

1) the phospholipase Cγ1 (PLCγ1) pathway, which leads to activation of protein kinase C (PKC) by diacylglycerol and the release of intracellular Ca^{2+} by inositol trisphosphate ($InsP_3$).
2) the ras mitogen-activated protein kinase (ras-MAPK) pathway. MAPK is also known as extracellular signal-related kinase (ERK). Shc interacts with another protein, Grb2 that recruits and activates the guanine exchange factor, SOS. This promotes removal of GDP from the monomeric G-protein, ras. GDP-GTP exchange is facilitated and ras is activated. This triggers the Raf, MEK, ERK phosphorylation cascade (Reichardt, 2006).
3) the Grb2, SOS, ras cascade also leads to activation of phosphatidylinositol 3-kinase (PI3K). This further phosphorylates the membrane phospholipid, phosphatidylinositol biphosphate (PIP2) to the corresponding triphosphate (PIP3), which in turn activates the serine/threonine kinase, Akt.

As well as promoting relatively slow neurotrophic actions which take hours or days to develop, BDNF can promote rapid changes in synaptic transmission and ion

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