Pharmacology & Therapeutics 143 (2014) 74–86

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: J.S. Fedan

Brain-derived neurotrophic factor in the airways☆,☆☆

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ARTICLE INFO

Available online 19 February 2014

Keywords:
Neurotrophin
Lung
Asthma
Inflammation
Fibrosis
Development

ABSTRACT

In addition to their well-known roles in the nervous system, there is increasing recognition that neurotrophins such as brain derived neurotrophic factor (BDNF) as well as their receptors are expressed in peripheral tissues including the lung, and can thus potentially contribute to both normal physiology and pathophysiology of several diseases. The relevance of this family of growth factors lies in emerging clinical data indicating altered neurotrophin levels and function in a range of diseases including neonatal and adult asthma, sinusitis, influenza, and lung cancer. The current review focuses on 1) the importance of BDNF expression and signaling mechanisms in early airway and lung development, critical to both normal neonatal lung function and also its disruption in prematurity and insults such as inflammation and infection; 2) how BDNF, potentially derived from airway nerves modulate neurogenic control of airway tone, a key aspect of airway reflexes as well as dysfunctional responses to allergic inflammation; 3) the emerging idea that local BDNF production by resident airway cells such as epithelium and airway smooth muscle can contribute to normal airway structure and function, and to airway hyperreactivity and remodeling in diseases such as asthma. Furthermore, given its pleiotropic effects in the airway, BDNF may be a novel and appealing therapeutic target.

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Abbreviations: BDNF, Brain-derived neurotrophic factor; NGF, Nerve growth factor; NT-3, Neurotrophin 3; TrkB, Tropomyosin related kinase B; P75NTR, Pan-neurotrophin receptor; NT, Neurotrophin; COPD, Chronic obstructive pulmonary disease; CREB, cAMP response element binding protein; PKA, Protein kinase A; NFkB, Nuclear factor kappa B; ERK, Extracellular signal regulated kinase; PLC, Phospholipase C; ECM, Extracellular matrix; MMP, Matrix metalloproteinase.

☆ Funding acknowledgment: Supported by NIH grants HL088029 (Prakash) and HL056470 (Prakash, Martin).

☆☆ Financial and competing interests disclosure: The authors have nothing to declare in terms of financial or other conflicts of interest relevant to the subject matter of materials discussed in this review. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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1. Introduction

From the time of birth (indeed, even during fetal life) through childhood and adulthood, intrinsic and environmental factors determine the balance between continued lung health vs. the onset and progression of lung diseases. In this regard, development, growth and health of the airways are key towards maintenance of the respiratory function of the lung. Diseases of the airway can stem from factors such as fetal and neonatal developmental abnormalities, exposures to allergens and inflammatory mediators, pollutants, first and secondhand tobacco smoke, and other environmental insults. This results in a wide range of clinically

http://dx.doi.org/10.1016/j.pharmthera.2014.02.006
0163-7258/

important conditions such as asthma, bronchitis, chronic obstructive pulmonary disease (COPD), fibrosis and cancer, all of which collectively represent a substantial global healthcare and financial burden. Thus, from both clinical and research perspectives, it is important to understand the mechanisms that regulate normal airway development, growth and maintenance, as well as the pathways that contribute to airway disease pathogenesis. Here, unlike in cardiac or liver disease where a few intrinsic cell types are likely involved, the heterogeneity of cell types just in the airway such as the bronchial epithelium, airway smooth muscle, interstitial fibroblasts, resident immune cells, and airway nerves, makes it likely that a number of complex and interactive mechanisms are involved in the pathogenesis of airway disease. Nonetheless, it is possible to speculate that certain mechanisms that are common to different airway diseases do exist and would therefore be important to identify and understand. Recent studies indicate that the family of growth factors called neurotrophins (NTs) that have pleiotropic effects may play such a role in the lung (Braun et al., 2000; Hoyle, 2003; Lommatzsch et al., 2003; Piedimonte, 2003; Jacoby, 2004; Renz et al., 2004; Rochlitzer et al., 2006; Taylor-Clark & Undem, 2006; Yao et al., 2006; Prakash et al., 2010; Aven & Ai, 2013). While the NT family consists of different members, brain-derived neurotrophic factor (BDNF) is emerging as a particularly important player in the lung or airways (Lommatzsch et al., 2003; Yao et al., 2006; Prakash et al., 2010). Of course, data on BDNF expression, its signaling and its physiological or pathophysiological significance are still being explored. However, given the importance of NTs in the brain, the fortuitous increasing recognition that BDNF is a key player in neurological and psychiatric diseases (Allen et al., 2013; Dooley et al., 2014; He et al., 2013; Leal et al., 2013; Nowacka & Obuchowicz, 2013; Numakawa et al., 2013; Park & Poo, 2013; Suliman et al., 2013; Zagrebelsky & Korte, 2014) has led to substantial novel information on complex and elegant aspects of BDNF expression or signaling that may be relevant to airway structure and function. In this article, we review current understanding of the sources and targets of BDNF in the normal airway at different life stages, and the potential contribution of altered BDNF expression and signaling in diseases such as neonatal and adult asthma, COPD, pulmonary fibrosis and cancer. Here, given the limited but emerging information on BDNF in the airways per se, we draw upon information in other cell systems to identify pathways by which BDNF may influence airway structure and function in health and disease, and suggest novel avenues for exploration of BDNF in the airway. Our intent is to stress upon the reader the potential for BDNF as an important physiological and pathophysiological player, perhaps a biomarker and importantly a therapeutic target in airway diseases. (See Table 1.)

2. Basics of BDNF expression and signaling

It is inappropriate not to recognize that much of our knowledge regarding NT signaling comes from studies on the nervous system, beginning more than 60 years ago with the work of individuals such as Rita Levi-Montalcini and Viktor Hamburger on the regrowth of nerves in embryonic limb buds (Levi-Montalcini, 1998; Teng & Hempstead, 2004; Blum & Konnerth, 2005; Lu et al., 2005; Reichardt, 2006; Hennigan et al., 2007). Although a number of pleotropic signaling factors can affect neuronal structure and function and thus act as growth factors, the NT family is classically considered to consist of 4 polypeptides of comparable structure and function: nerve growth factor (NGF), the "original" and best-characterized NT, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3) and neurotrophin-4 (NT4) (Chao et al., 2006; Reichardt, 2006; Skaper, 2008). Consistent with the idea of a nutritive, target-derived factor that promotes growth and survival, NTs including BDNF have been found to regulate neurogenesis, neuronal differentiation, survival, plasticity, and even synaptic transmission and nerve conduction (Teng & Hempstead, 2004; Kalb, 2005; Chao et al., 2006; Lykissas et al., 2007; He et al., 2013; Leal et al., 2013; Park & Poo, 2013; Suliman et al., 2013; Zagrebelsky & Korte, 2014). There is now considerable evidence (and interest) in the idea that NTs, particularly BDNF, are important pathophysiological players in diseases such as depression, schizophrenia, Alzheimer's disease (Angelucci et al., 2004; Shoval & Weizman, 2005; Schulte-Herbruggen et al., 2008; Dwivedi, 2009; Saragovi et al., 2009; Numakawa et al., 2013), cerebral tumors (Nagatsu et al., 2000; Nagatsu & Sawada, 2005; Thiele et al., 2009), and spinal cord injury repair (Blesch & Tuszynski, 2002; Murray et al., 2002; Pezet & Malcangio, 2004; Sieck & Mantilla, 2009; Dale-Nagle et al., 2010; Ramer, 2012; Skaper et al., 2012; Weishaupt et al., 2012; Awad et al., 2013; He et al., 2013). Here, it is increasingly apparent that BDNF is not just a growth factor, but that BDNF expression and signaling are intricately enmeshed with a number of regulatory pathways including other NTs, sex steroids, glucocorticoids, and inflammation (Miranda et al., 1994; Simpkins et al., 1997; Schaaf et al., 2000; Kapfhammer, 2004; Tabakman et al., 2004; Nagatsu & Sawada, 2005; Babayan & Kramar, 2013; Numakawa et al., 2013; Pluchino et al., 2013). The relevance of many if not all of these pathways lies in their recognized roles in airway diseases such as asthma and COPD (Panettieri, 2004; Carey et al., 2007; Damera et al., 2009; Tam et al., 2011; Townsend et al., 2012; Prakash, 2013). Accordingly, understanding how BDNF expression and signaling occurs in the nervous system may provide insight into airway diseases as well: a theme highlighted in this review, and certainly a topic for future research.

2.1. Production of BDNF

The BDNF gene has at least 9 distinct promoters that allow for multiple mRNA transcripts with each containing the entire open reading frame for the BDNF protein (Aid et al., 2007; Boulle et al., 2012; Zheng et al., 2012). Via alternative promoters, splicing and polyA sites at least 22 transcripts can be generated, each for the same initial BDNF protein product. This level of complexity at the transcriptional level allows for multiple layers of regulation for BDNF generation and may be important in intracellular localization of BDNF mRNA or initial proteins. Furthermore, given multiple promoters, BDNF transcription can be regulated by several upstream intracellular cascades relevant to sex steroid, glucocorticoid or other factors. Agonist or electrical stimulation leading to increased $[Ca^{2+}]_i$ induces BDNF transcription highlighting activity-dependent BDNF regulation (Zheng et al., 2012). There are at least 3 Ca^{2+}-responsive elements in the regulatory region of one of the more important BDNF exons. Activation of these elements involves regulatory elements such as cAMP response element binding protein (CREB) and protein kinase A (PKA), calmodulin-dependent protein kinases I, II and IV, NFκB and NFAT (Fig. 1). The relevance of many of these elements lies in the fact that they are themselves activated by elevated $[Ca^{2+}]_i$ in cells (e.g. PKA, CREB, ERK 1/2, and importantly, these elements are known to regulate several processes in the airway, particularly in the context of inflammation. However, unlike in neurons, there is currently limited data on how BDNF transcription occurs in the airway.

In addition to transcriptional regulation, there is now evidence in non-airway cell types (particularly neurons) that epigenetic mechanisms such as chromatin remodeling (histone acetylation/methylation) and DNA methylation also regulate BDNF levels (Boulle et al., 2012; Zheng et al., 2012). Such regulation appears to be highly complex, coordinated, and context-dependent, with further complication introduced by different BDNF exons being influenced differentially. Given that the role of epigenetics in the airway is still being investigated (Yang & Schwartz, 2012; Clifford et al., 2013), examining regulation of BDNF by these mechanisms is likely premature.

BDNF is initially synthesized in the endoplasmic reticulum as a precursor protein (pre-pro-BDNF; ~27 kDa) (McDonald & Chao, 1995; Robinson et al., 1995; Butte et al., 1998; Lessmann et al., 2003; Lessmann & Brigadski, 2009) (Fig. 1). The signal peptide is then cleaved to produce pro-BDNF which is then transported to the Golgi where it is sorted into either constitutive or regulated secretory vesicles. Vesicular pro-BDNF can be converted intracellularly into mature BDNF by