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Brain-Derived Neurotrophic Factor in the Airways

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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.

Keywords

Neurotrophin; Lung; Tropomyosin related kinase; p75; Asthma; Rhinitis; Inflammation; Fibrosis; Bronchopulmonary Dysplasia; Development

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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 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(Aven and Ai, 2013; Braun et al., 2000; Hoyle, 2003; Jacoby, 2004; Lommatzsch et al., 2003; Piedimonte, 2003; Prakash et al., 2010; Renz et al., 2004; Rochlitzer et al., 2006; Taylor-Clark and Undem, 2006; Yao et al., 2006). 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; Prakash et al., 2010; Yao et al., 2006). 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., 2013; He et al., 2013; Leal et al., 2013; Nowacka and Obuchowicz, 2013; Numakawa et al., 2013; Park and Poo, 2013; Suliman et al., 2013; Zagrebelsky and Korte, 2013) 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.

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 (Blum and Konnerth, 2005; Hennigan et al., 2007; Levi-Montalcini, 1998; Lu et al., 2005; Reichardt, 2006; Teng and Hempstead, 2004). 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 (Chao et al., 2006; He et al., 2013; Kalb, 2005; Leal et al., 2013; Lykissas et al., 2007; Park and Poo, 2013; Suliman et al., 2013; Teng and Hempstead, 2004; Zagrebelsky and Korte, 2013). 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; Dwivedi, 2009; Numakawa et al., 2013; Saragovi et al., 2009; Schulte-Herbruggen et al., 2008; Shoval and Weizman, 2005), cerebral tumors (Nagatsu et al., 2000; Nagatsu and Sawada, 2005; Thiele et al., 2009), and spinal cord injury repair (Awad et al., 2013; Blesch and Tuszynski, 2002; Dale-Nagle et al., 2010; He et al., 2013; Murray et al., 2002; Pezet and Malcangio, 2004; Ramer, 2012; Sieck and Mantilla, 2009; Skaper et al., 2012; Weishaupt et al., 2012). 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 (Babayan and Kramar, 2013; Kapfhammer, 2004; Miranda et al., 1994; Nagatsu and Sawada, 2005; Numakawa et al., 2013; Pluchino et al., 2013; Schaaf et al., 2000; Simpkins et al., 1997; Tabakman et al., 2004). The relevance of many if not all of these pathways lies in their recognized roles in airway diseases such as asthma and COPD (Carey et al., 2007; Damera et al., 2009; Panettieri, 2004; Prakash, 2013; Tam et al., 2011; Townsend et al., 2012). 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 (Figure 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 (Clifford et al., 2013; Yang and Schwartz, 2012), 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) (Butte et al., 1998; Lessmann and Brigadski, 2009; Lessmann et al., 2003; McDonald and Chao, 1995; Robinson et al., 1995) (Figure 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 endoproteases such as furin or within secretory granules by pro-protein convertases (Mowla et al., 2001) allowing for one more level of regulation of BDNF expression within cells. In this regard, vesicular secretion can involve both pro-BDNF and mature BDNF, with the amount of secreted mature BDNF depending on the type and activity of the convertases. Pro-BDNF is then extracellularly cleaved by factors such as plasmin (through tPA conversion of plasminogen) and importantly matrix metalloproteinases (MMPs) into the mature form. Since mature BDNF is highly homologous across species, examination of its biology is facilitated using animal models, particularly transgenics that lack or overexpress specific aspects of BDNF signaling, and exogenous recombinant BDNF.

2.2. BDNF Signaling

Although pro-BDNF was initially thought to be biologically inactive, there is now evidence that both pro- and mature BDNF can bind to and signal through two distinct, principal receptor types: the low-affinity “pan-neurotrophin” receptor p75NTR, and the high-affinity tropomyosin related kinase (Trk) receptor (~140KDa), with BDNF (and NT4) binding to the TrkB isoform (Barker, 2004; Blochl and Blochl, 2007; Chen et al., 2009). Nerve growth factor (NGF) binds specifically to TrkA, while NT3 binds to TrkC (Lu et al., 2005; Reichardt, 2006; Teng and Hempstead, 2004) (Figure 2). In addition, there is some heterologous binding, with NT3 and NT4 also activating TrkA, and NT3 activating TrkB.

The present review obviously focuses on TrkB and p75NTR, however, it is important to recognize that the other receptor systems may also be relevant in the airways (see below).

P75NTR is a member of the TNF receptor superfamily and lacks intrinsic enzymatic activity, but can recruit signaling adaptors and modulate Trk signaling as well as a number of intracellular processes (Blochl and Blochl, 2007; Chen et al., 2009; Ibanez and Simi, 2012; Lu et al., 2005; Skaper, 2008; Underwood and Coulson, 2008; Yamashita et al., 2005). p75NTR can modulate a number of intracellular pathways including PI3/Akt, NFκB, MAPKs, JNK, RhoA, PKA, and HIF, all of which are familiar in the context of airway contractility, proliferation, growth, and responsiveness to factors such as inflammation (Chiba and Misawa, 2004; Damera et al., 2009; Gosens et al., 2006; Halayko and Amrani, 2003; Halayko and Solway, 2001; Hirota et al., 2005; James, 2005; Panettieri, 2004). Mature BDNF binding to p75NTR, depending on the context, can enhance TrkB receptor signaling through MAPK or Akt, and promote cell survival through NFκB. Alternatively, p75NTR can inhibit Trk effects through JNK and RhoA. Pro-BDNF can bind to sortilin and forms a ternary complex with p75NTR, which then activates cell death pathways (Figure 3). Accordingly p75NTR-induced effects can be diverse and context-specific, and seemingly contradictory: cell survival vs. cell death, proliferation vs. inhibition of cellular outgrowth etc. making for a diverse range of BDNF effects just through the low-affinity receptor.

The TrkB gene is on chromosome 9q22 and contains 24 exons (Barbacid, 1994; Ohira and Hayashi, 2009; Thiele et al., 2009). Four major protein isoforms are formed, but alternatively splicing can lead to 36 different isoforms being formed. Although BDNF is unlikely to function via all of these isoforms, the full-length version of the transmembrane TrkB receptor (TrkB-FL) is particularly important. TrkB-FL contains an intracellular tyrosine kinase domain that is essential for BDNF signaling (Figure 3). TrkB-FL undergoes autophosphorylation to induce conformational changes, and substrate binding sites for Shc, GRB2, ATP, and PLCγ are exposed. Trk signaling in general occurs through three tyrosine kinase mediated pathways (Barbacid, 1995; Chao and Hempstead, 1995; Ohira and Hayashi, 2009; Pitts et al., 2006; Thiele et al., 2009): the PLCγ1/PKC pathway relevant to IP_3 and thus $[Ca^{2+}]_i$ signaling, the MAPK-ERK pathway and the PI3/Akt pathway, both of which can modulate cell survival and differentiation. In addition to TrkB-FL, the most important truncated isoform lacking the tyrosine kinase domain (among the different alternatively spliced constructs) is TrkB-T1 (Cheng et al., 2007; Fenner, 2012; Li et al., 1998; Rose et al., 2003). Truncated isoforms are thought to have dominant negative effects, or in sequestering BDNF to prevent signaling, or activating alternative pathways. For example, TrkB-T1 binds to and internalizes BDNF but does not undergo autophosphorylation (unlike the full-length receptor). TrkB-T1 also dimerizes with TrkB-FL to indirectly inhibit BDNF functionality (Fenner, 2012). In addition, TrkB-T1 can regulate cytoskeletal remodeling via a TrkB-T1 homodimer that functions independently of BDNF. Non-neuronal cells use plasma membrane TrkB-T1 expression to regulate extracellular BDNF levels by binding to the ligand, internalization and sequestration of the BDNF into transport vesicles that can then by exocytosed when necessary. TrkB-T1 can also mediate BDNF-induced proliferation, but the underlying mechanisms are not known. Overall, the high-affinity receptors for BDNF can have complex effects on cells as well as BDNF regulation itself.

The above discussion highlights the fact that the actual biological efficacy of BDNF is dependent not only on ligand concentrations, but also the balance between full-length vs. truncated TrkB receptor expression, along with a modulating role for p75NTR. In this regard, data from knockout mice on neuronal survival suggest that Trk receptors are key to biological activity of NTs (Conover and Yancopoulos, 1997), and can influence survival (e.g., transgenic animals lacking TrkB show early mortality). As discussed above, p75NTR also appears to be involved in neuronal survival, but it can conversely influence cell death as well. Nonetheless, differences in expression of TrkB isoforms vs. p75NTR and biological availability of BDNF all allow for considerable heterogeneity in BDNF signaling across different cell types.

Following receptor activation, a number of downstream signaling cascades can be activated by BDNF, with cell-specific transcription factors that contribute to the many effects of BDNF such as differentiation, survival, apoptosis, and growth: events that are genomic in nature. Here, some of the identified transcription factors such as NFκB, AP-1 and CREB (Figure 3) are highly relevant to airway inflammation (Damera et al., 2009; Gosens et al., 2006; Halayko and Amrani, 2003; Halayko and Solway, 2001). In addition, there is increasing recognition that BDNF can have relatively rapid, likely “non-genomic” effects on much shorter timeframes (seconds to minutes), and most likely involve high-affinity TrkB receptors (Blum and Konnerth, 2005; Carvalho et al., 2008; Kovalchuk et al., 2004; Rose et al., 2004). Much of this data comes from neurons where BDNF, which is released in a Ca^{2+}-dependent fashion akin to neurotransmitters, can modulate the efficacy of synaptic transmission (Blum and Konnerth, 2005). In neurons, BDNF can also non-genomically modulate plasma membrane receptors, Ca^{2+} influx channels and voltage-gated Na^{+} channels (Blum and Konnerth, 2005; Carvalho et al., 2008; Kovalchuk et al., 2004; Rose et al., 2004). While the repertoire of receptors, ion channels and signaling cascades differs between neurons and non-neuronal cells of the airways, the relevance of these genomic and non-genomic BDNF effects in neurons lies in the potential that any common mechanisms and cascades may be targets for BDNF effects in the airways.

3. BDNF in the Lung

As nutritive factors, the target organs of the central and peripheral nervous systems such as skin, skeletal muscles, epithelia and smooth muscles of different types can be expected to express NTs (Nockher and Renz, 2005; Sariola, 2001), thus modulating their own innervation. Here, the concept of local production of NTs such as BDNF vs. their “targets” is important in that it is entirely possible for a cell type or tissue to only be the recipient of BDNF which is actually derived from a remote source (e.g. neurons or even circulating BDNF) vs. autocrine/paracrine effects of locally produced BDNF. In this regard, it is now clear that both a range of Trk receptors are widely distributed in non-neuronal tissues (Hoyle, 2003; Lommatzsch et al., 2003; Nassenstein et al., 2004; Prakash et al., 2010), and accordingly local release and autocrine/paracrine functions of NTs have to be considered. Relevant to this discussion, all of the NTs (particularly BDNF) and their receptors have now been shown to be expressed, albeit to different extents, in different lung compartments: nerves, immune cells, bronchial and alveolar epithelium, smooth muscle, fibroblasts and vascular endothelium (Prakash et al., 2010; Ricci et al., 2004; Ricci et al., 2007). What is

less known is what roles these NTs play in lung structure or function. The relevance of BDNF effects in the airways lies in recent recognition that circulating BDNF levels as well as local receptor expression are both increased in asthma and that there is clinical evidence for increased BDNF levels in both sputum and bronchoalveolar lavages of patients with chronic inflammatory airway diseases following smoking or cigarette smoke exposure, viral infections, allergens and other insults (Andiappan et al., 2011; Dagnell et al., 2010; Ricci et al., 2005; Rochlitzer et al., 2006; Tortorolo et al., 2005). While these studies obviously associate airway disease with elevated BDNF, the question is regarding the source of BDNF and the functional relevance of elevated BDNF. Here, emerging data from several groups including our own suggest important roles for BDNF expression and signaling in airway smooth muscle, innervation and epithelium are potentially important.

3.1. BDNF in Airway Smooth Muscle

There is now increasing evidence that airway smooth muscle (ASM) is a significant source of NTs including BDNF. For example, immunocytochemical staining of human lung sections show constitutive expression of NGF, BDNF and NT3 by ASM (Ricci et al., 2004). Substantial expression of BDNF has also been noted in isolated human ASM cells from non-asthmatic humans by both immunocytochemistry (Prakash et al., 2006) as well as Western analysis (Prakash et al., 2009). The importance of this complementary evidence lies in establishing that while “traditional” sources such as airway nerves (discussed below) can serve as sources and targets for BDNF, the sheer mass of ASM (or other cell types) within the airways would be a much larger source of BDNF for local signaling in the airways. Furthermore, we have previously demonstrated TrkB expression in human ASM cells and tissues (Abcejo et al., 2012; Meuchel et al., 2011; Prakash et al., 2006; Prakash et al., 2009; Vohra et al., 2013) and have also found p75NTR expression (Prakash et al., 2006).

In addition to constitutive expression, emerging data suggest that factors relevant to airway diseases can enhance ASM BDNF and receptor expression (Braun et al., 1999; Kemi et al., 2006; Meuchel et al., 2011; Prakash et al., 2009; Sathish et al., 2013; Vohra et al., 2013), thus raising the possibility that BDNF is a “player” in mediating or modulating the effects of these factors. For example, Kemi et al. (Kemi et al., 2006) reported that IL-1β produces sustained increases in BDNF (but only transient increase in NGF) in human ASM cells, an effect mediated through COX. In contrast IFNγ decreases BDNF expression while IL-4 had no effect. Interestingly, neurokinins such as Substance P (that can be released by airway nerves) can also enhance BDNF/TrkB expression, as we reported in rat ASM (Meuchel et al., 2011). Oxidant stress, e.g. induced by cigarette smoke increases BDNF and TrkB-FL (with relative decrease in TrkB-T1) in human ASM (Sathish et al., 2013). Indirect evidence of TNFα effects can further be derived from the blunting of siRNAs against BDNF or TrkB-FL on cell proliferation (Aravamudan et al., 2012) or $[Ca^{2+}]_i$ (Prakash et al., 2009).

Overall, the limited but exciting data point to baseline, endogenous production of BDNF. The question then is how is BDNF production or secretion regulated in ASM. As discussed above, in neurons elevation in $[Ca^{2+}]_i$ (e.g. following electrical stimulation) leads to vesicular release (Sadakata and Furuichi, 2009). While it is unlikely that ASM requires rapid secretion of BDNF as in neurons, vesicular secretion pathways do exist in airway cells

(Proskocil et al., 2004). Here, $[Ca^{2+}]_i$ is known to modulate secretion in general (with a well-recognized role for cAMP (Furman et al., 2010; Hofer, 2012; Schmidt et al., 2013; Seino et al., 2009)), and elevated $[Ca^{2+}]_i$ does increase BDNF secretion in neurons and vasculature (Lessmann and Brigadski, 2009; Nakahashi et al., 2000). Thus mechanisms that regulate $[Ca^{2+}]_i$ in ASM may also play a role in modulating BDNF secretion. The mechanisms involved in $[Ca^{2+}]_i$ regulation in ASM are manifold and have been reviewed elsewhere (Amrani and Panettieri, 2002; Gerthoffer, 1991; Hall, 2000; Janssen, 1998). In non-ASM cells, canonical transient receptor potential (TRPC) channels are involved in fluid secretion and exocytosis of other intracellular proteins (Bollimuntha et al., 2011). ASM cells express a variety of TRPC channels, with TRPC3 being particularly important for modulating Ca^{2+} entry and in airway responses to inflammation (Amrani, 2007; Sweeney et al., 2002; Vohra et al., 2013; White et al., 2006). In non-neuronal cells, TRPC3 regulates secretion (Kim et al., 2011; Lavender et al., 2008). In a recent study, using DNA constructs to produce GFP-tagged BDNF, and real-time fluorescence imaging, we showed that vesicular BDNF release occurs in human ASM cells, and is regulated by TRPC3 (Vohra et al., 2013). Furthermore, inflammation induced by TNFα or mixed allergens relevant to asthma enhances TRPC3 expression and its effects on BDNF release. $[Ca^{2+}]_i$ does play a part, as suggested by reduced BDNF secretion when $[Ca^{2+}]_i$ levels are chelated with a substance like BAPTA, vs. increased BDNF secretion when a bronchoconstrictor agonist such as ACh is applied. The latter effect is particularly interesting since it is possible that activated ASM, e.g. during bronchoconstriction, can enhance BDNF secretion in the airway. The next question then is what effects BDNF has on ASM or other cell types.

In previous studies, we reported that exogenous BDNF acutely (within 30 min) enhances $[Ca^{2+}]_i$ and force responses of human ASM to agonists such as ACh (Prakash et al., 2006). Such effects are further enhanced in the presence of inflammatory cytokines such as TNFα (Prakash et al., 2009). These data indicate that regardless of the source of BDNF, this NT can directly enhance ASM contractility via non-genomic mechanisms. BDNF exerts its effects on ASM $[Ca^{2+}]_i$ by enhancing Ca^{2+} influx across the plasma membrane (Prakash et al., 2006), particularly via store-operated Ca^{2+} entry (SOCE) that involves TRPC3 and the regulatory proteins STIM1 and Orai1 (Abcejo et al., 2012). BDNF can also enhance intracellular Ca^{2+} release via the IP_3 pathway (important in ASM), consistent with TrkB activation of PLCγ. Here, it is important to note that the non-genomic effects of BDNF appear to be mediated almost exclusively by TrkB, and not p75NTR (Prakash et al., 2009).

From a genomic standpoint, BDNF can enhance expression and function of $[Ca^{2+}]_i$ regulatory proteins (Abcejo et al., 2012), leading to increased Ca^{2+} responses and contractility in response to bronchoconstrictor stimuli. In this regard, our recently demonstrated involvement of TRPC3 in BDNF secretion is relevant, since it is possible that enhanced secretion of BDNF could then act in an autocrine fashion to promote BDNF expression. Furthermore, in other cell types such as HEK293 and dorsal root ganglion, the neurotrophin NGF can enhance trafficking of TRPV1 channels to the plasma membrane (Stein et al., 2006). Whether BDNF can promote trafficking of TRPC channels is not known, but could present a novel positive feedback mechanism for BDNF to maintain its release and signaling. The relevance of such novel BDNF effects further lies in the potential for BDNF enhancement of plasma membrane mechanisms such as caveolae (invaginations

that harbor receptors, channels and signaling proteins) (Suzuki et al., 2007; Suzuki et al., 2004), thus promoting integration and amplification of signaling at the cell surface.

Separately, BDNF can also increase ASM proliferation (Aravamudan et al., 2012). Indeed, chelation of extracellular BDNF in unstimulated human ASM cells using the chimeric TrkB-Fc protein blunts baseline proliferation (Aravamudan et al., 2012). Importantly, TNFα or IL-13 enhancement of cell proliferation is substantially blunted by TrkB-Fc, TrkB siRNA or BDNF siRNA highlighting the importance of ASM-derived BDNF and its autocrine effects on ASM proliferation. Here, it appears that BDNF effects are largely via TrkB (p75NTR siRNA had only small effect). In terms of signaling, BDNF activates p42/p44 MAP kinase and NFκB to enhance ASM proliferation (Aravamudan et al., 2012).

In vascular smooth muscle, NGF (which activates TrkA) induces migration but not proliferation (Kraemer et al., 1999), while p75NTR activation induces apoptosis (Wang et al., 2000). Whether BDNF enhance ASM migration has been examined only to a limited extent. The importance of ASM migration lies in airway remodeling that occurs in diseases such as asthma and perhaps COPD, especially in the setting of altered extracellular matrix (ECM) production and composition (Bai, 2010; Halayko and Amrani, 2003; Holgate, 2002; Joubert and Hamid, 2005; Lagente and Boichot, 2009). Here, the link to BDNF is particularly interesting and relevant since MMPs, particularly the gelatinases MMP-2 and MMP-9 extracellularly cleave pro-BDNF (Ethell and Ethell, 2007; Lee et al., 2001; Soleman et al., 2013), while these MMPs are also key to breakdown and recomposition of ECM proteins such as collagens and fibronectin. Accordingly, BDNF effects on MMPs in the airway could be particularly important in the context of remodeling. There is currently only one study that has examined this issue in human ASM cells, and reported that BDNF increases MMP-9 but not MMP-2 secretion (Dagnell et al., 2007). Furthermore, the study also reported that BDNF enhances ASM cell migration. In ongoing studies, we have found that physiologically-relevant concentrations of BDNF enhance MMP-9 mRNA, protein and extracellular levels (Thompson, Prakash, Britt, unpublished observations). Furthermore, the inflammatory cytokines TNFα, and to a lesser extent IL-13 enhance MMP-9 expression and activity via BDNF (chelation of extracellular BDNF blunts cytokine effects).

Overall, these emerging data show that BDNF has both non-genomic and genomic effects on ASM Ca^{2+}, cell proliferation, migration and ECM formation and deposition, aspects very relevant to normal airway structure and function, and airway hyperresponsiveness and remodeling in diseases such as asthma. What is not known is whether these longer-term effects of BDNF occur through TrkB only or via p75NTR. For example, our previous proliferation data suggest TrkB-FL (Aravamudan et al., 2012), but the effects on cell migration could involve cytoskeletal remodeling (as occurs in neurons) which could occur through homodimerization of TrkB-T1, a potentially novel regulatory pathway. Here, the lack of information on TrkB-T1 is unfortunate, given that in spite of TrkB-FL expression in ASM (or other cell types in the airway), the eventual functional efficacy of BDNF will be dictated by the relative levels of TrkB-FL v. TrkB-T1, especially if the latter serves a negative dominant role. In addition to TrkB, whether nuanced effects of p75NTR via signaling pathways such as NFκB or RhoA are also involved in ASM remains to be determined.

3.2. BDNF and Airway Innervation

Neural control of the airway is extensive and exquisite (see (Canning, 2006; Kc and Martin, 2010; Racke and Matthiesen, 2004; Undem and Nassenstein, 2009; Undem and Potenzieri, 2012; Verhein et al., 2009) for review). CNS control involves integrated networks, particularly medullary vagal preganglionic neurons which send signals to intrinsic tracheobronchial ganglia in close proximity to effector systems of the postganglionic axons that are diffusely distributed within the airways. In addition to cholinergic pathways, intrinsic airway neurons release a number of neuromodulators including vasoactive intestinal peptide and nitric oxide (the so called non-adrenergic, non-cholinergic system) that promote bronchodilation (although an excitatory component can also exist). Vagal afferents of sensory ganglia are present throughout the bronchopulmonary tree and sense chemical, mechanical, or thermal stimuli. There is considerable heterogeneity here, in that some receptors contain the pro-inflammatory bronchoconstricting neuropeptides substance P and neurokinin A (Groneberg et al., 2006), while other mechanosensitive reflex systems control breathing and parasympathetic outflow to regulate airway tone. The relevance of complex neural pathways lies in the fact that increased airway hyperresponsiveness in diseases such as asthma or bronchitis can be modulated by increased cholinergic outflow from the parasympathetic nervous system (neurogenic asthma) (Butler and Heaney, 2007; Nassini et al., 2010; Nockher and Renz, 2006; Pisi et al., 2009) and that commonly used drugs such as ipratropium bromide target cholinergic innervation. Accordingly, by virtue of being a growth factor for neurons, BDNF could potentially affect several neural mechanisms relevant to airway tone and thus influence airway diseases.

Initial immunohistochemical studies of human lung showed obvious presence of NGF and BDNF in neurons and to a lesser extent satellite cells of parasympathetic ganglia (Ricci et al., 2004). While one would expect such ganglia to respond to BDNF, immunoreactivity for Trks was not observed, but p75NTR was present. On the other hand, in lung sections, nerve fibers that may form the sympathetic component showed moderate immunoreactivity for both TrkB and p75NTR. The functional role of such NT receptors in airway innervation has been examined to some extent, but mostly for NGF (reviewed in (Freund-Michel and Frossard, 2008; Frossard et al., 2004)) which may or may not be representative of BDNF effects. In mouse airway, NGF increases Substance P content of sensory nerves (Freund-Michel and Frossard, 2008). Inflammation due to allergens or respiratory syncytial virus can induce *de novo* neuropeptide production in vagal afferents that are important for cough and reflex airway responses. In mice overexpressing airway NGF, increased sensory innervation has been reported (Hoyle et al., 1998) suggesting neural outgrowth. These neurons express p75NTR and may therefore respond to BDNF (although this remains to be shown).

The relevance of expanded airway innervation or increased neurogenic stimulation by NTs lies in increased sensitivity of the airway to a variety of stimuli in diseases such as asthma or with environmental exposures (allergens, cigarette smoke, pollutants). Here, NTs may actually mimic inflammation or other such stimuli. For example, in mice, exogenous NGF enhances airway hyperresponsiveness even in the absence of allergen sensitization and challenge) (Freund-Michel and Frossard, 2008), although this effect does not appear to occur in guinea pigs treated with NGF (Pan et al., 2010). On the other hand, in guinea pigs,

BDNF can mimic allergen sensitization by enhancing expression of TRPV1 channels in vagal tracheal cough-causing mechanosensitive neurons of the nodose ganglia, thus enhancing cough reflexes (Lieu et al., 2012). Sensory neurons of mice overexpressing NGF show enhanced responses to capsaicin and hyperinnervation of SP-containing nerves (Hoyle et al., 1998). In addition to NGF, lesser numbers of studies have shown that BDNF may also play a role in airway innervation. For example, mice treated with functional antibodies targeting BDNF show reduced airway responsiveness to capsaicin (Braun et al., 2004). In ferrets, in situ hybridization, immunohistochemistry and ELISA of BDNF levels showed that parasympathetic premotor neurons innervating the extrathoracic trachea (airway-related vagal preganglionic neurons) produce BDNF and express TrkB receptors, suggesting they are both source and target for BDNF (Zaidi et al., 2005). Here, BDNF may increase cholinergic outflow from these neurons to postganglionic parasympathetic nerves, indirectly leading to enhanced bronchoconstriction and bronchopulmonary reflexes.

Overall, these data, although exclusively in animals, underline a central role for NTs such as NGF and BDNF in neural control of the airways. What has been examined to a lesser extent are the mechanisms by which the function of airway innervation can be modulated. As a growth factor, BDNF (potentially derived from local tissues or nerves themselves) could enhance survival or expansion of receptive fields of sensory nerve endings. Certainly, increased BDNF expression and secretion by ASM in the inflamed airway may act on postganglionic parasympathetic airway nerves. Furthermore, given that neuronal activity itself can enhance BDNF expression and release, a positive feedback cycle may be set up in the setting of disease which would exaggerate nerve expansion. Separately, BDNF can enhance expression of other receptors or enhance synaptic transmission, again enhancing bronchoconstriction. For example, upregulated neurokinin receptor expression can occur as demonstrated with NGF (Piedimonte, 2003) as well as with BDNF (Meuchel et al., 2011). However, beyond this rudimentary understanding, there is much not known about how BDNF or other NTs can influence airway innervation and neuronal function, especially given that there is currently no clear cut information on the distribution of receptors (TrkB, p75NTR) in airway nerve endings.

3.3. BDNF in Bronchial Epithelium

The airway epithelium serves as a barrier to allergens and infectious agents, but also as a modulator of airway responses to insults, and a source for bronchoconstrictive and bronchodilatory factors (Crystal et al., 2008; Dekkers et al., 2009; Gras et al., 2013; Hirota and Martin, 2013; Holgate, 2013). Accordingly BDNF expression or function in this important cell type is relevant to basic airway function and its modulation in disease. However, there are very few studies on NTs in airway epithelium in general, and are mostly focused on NGF (Hahn et al., 2006; Othumpangat et al., 2009; Ricci et al., 2004). Immunocytochemistry shows that airway epithelium constitutively expresses NGF, BDNF and NT3. Increased expression of epithelial BDNF has been reported in mouse models of allergic airway hyperresponsiveness (Hahn et al., 2006; Lommatzsch et al., 2003). While these data show epithelial production of BDNF, its function in epithelium is less clear. In situ hybridization of mouse lung epithelium as well as immunohistochemistry of surgical human lung samples do not show receptor expression (Ricci et al., 2004), raising the

question of whether airway epithelia are only a source, but not a target (unlike ASM). However, in a recent study using isolated human bronchial epithelial cells, we detected TrkB protein expression by Western blot (Meuchel et al., 2010). Separately, the NGF receptor TrkA is expressed by human bronchial epithelial cells (Hahn et al., 2006), and infection induced epithelial cell death is worsened in the absence of NGF (Othumpangat et al., 2009). Given some cross-activation of TrkA by BDNF, its function on epithelium cannot be entirely ruled out.

Assuming that TrkB is present in epithelium, as with ASM, BDNF may also have rapid (i.e. non-genomic) effects on airway epithelium. For example in isolated human bronchial epithelial cells, we found that BDNF, acting via TrkB, can elevate $[Ca^{2+}]_I$, phosphorylate eNOS and induce nitric oxide production within minutes (Meuchel et al., 2010). Furthermore, in ongoing studies using human bronchial epithelial cells, we have found that BDNF enhances expression of arginase 1 and 2 via a TrkB and NFκB mediated mechanism (Thompson, Prakash, unpublished observations). The relevance of this novel data lies in the fact that arginase can limit availability of L-arginine for production of NO, and furthermore enhance production of proline, a precursor to collagen formation. Thus, these preliminary and limited data at least suggest that BDNF (regardless of source) can potentially influence epithelial structure and function. Certainly much more study is needed to determine the contribution of BDNF signaling and of its receptors in normal epithelium and role in airway diseases.

4. BDNF in the Developing Lung

4.1 Normal Lung Development

NTs such as BDNF are critical for embryonic development of the central and peripheral nervous systems (Reichardt, 2006). Accordingly, detailed studies on BDNF in development of any organ including lung are severely limited by early mortality of transgenic animals lacking BDNF receptors, especially TrkB. In the developing mouse, a dynamic pattern of increasing vs. decreasing levels of NGF vs. BDNF has been observed in whole lung lysates (Lommatzsch et al., 2005). However, the relevance of these patterns are not clear, given that different cell type sin the lung likely express various NTs or their receptors to different levels, further leading to cell-dependent effects.. Nonetheless, in ongoing studies in whole embryonic lung, we found that BDNF mRNA levels rise at ~E12 and TrkB mRNA at ~E13, a period of initiation of lung development, and are maintained until birth (Hartman, Prakash, unpublished observations). A single published study examined TrkB during lung development in the mouse, comparing wild-type animals to those carrying a *trkB* gene mutation leading to a non-functional protein (resulting in postnatal survival of a few weeks) (Garcia-Suarez et al., 2009). They reported higher TrkB mRNA in early postnatal development, lasting until 15 days postnatal, with progressive decline after that age.

The function(s) of BDNF/TrkB in the developing lung are not entirely clear. The single study using transgenic TrkB mice (Garcia-Suarez et al., 2009) reported that neuroepithelial bodies and lung innervation have high TrkB expression. Interestingly, transgenic animals showed thinner bronchial epithelium, larger airway luminal diameter and larger alveolar spaces compared to wildtype animals. These data suggest that BDNF/TrkB is important for

cell proliferation and/or migration and thus proper formation of functioning airways with adequate amounts of epithelium and ASM. On the other hand, another study found that that absence of BDNF does not significantly affect lung development (Lommatzsch et al., 1999). Separately, given its role as a neurotrophic factor, BDNF effects on airway innervation need to be considered. During embryogenesis, axon outgrowth into the distal lung is tied to formation of ASM, with progressive growth and expansion of ASM layers leading to elongation and spreading of adjacent neural branches (Sparrow et al., 1999; Tollet et al., 2001). These data would suggest an ASM-derived neurotrophic factor. Again, a single study in mice reported BDNF is expressed by embryonic ASM and that the BDNF knockout embryos display reduced axonal branching in targeting the ASM (Radzikinas et al., 2011). Here, BDNF expression in the embryonic lung appears to be post-transcriptionally coordinated with ASM development (via a sonic hedgehog pathway where a microRNA 206 inhibits BDNF expression until the appropriate time). What is less clear is the source(s) of BDNF in the developing airway. Certainly, consistent with its presence in adult ASM, fetal or neonatal ASM could be a source, as could bronchial epithelium. However, there is currently no published data on this topic, but represents an important topic for future research.

Overall, these limited data suggest that BDNF is involved in lung and airway development, potentially by affecting neuronal regulation of growth and proliferation of lung elements. However, the actual physiology is likely more complex and remains to be unexplored. Here, a potentially elegant technique to examine the role of BDNF/TrkB signaling in lung development may be the TrkB “knock-in” mouse model developed by Ginty and colleagues (Chen et al., 2005) where small molecule inhibitors of mutated TrkB tyrosine kinase domains allow for normal receptor expression and function until the kinase activity is transiently and reversibly inhibited by a small peptide inhibitor without affecting expression. The appeal of this model lies in the fact that TrkB expression and function are normal throughout critical periods in lung development and in the postnatal period, and can be interrupted at specific time points to examine the role of BDNF/TrkB signaling in the context of ASM growth in the fetal/perinatal period vs. that which occurs during postnatal lung growth, thus setting the stage to examine the importance of BDNF in different aspects of perinatal airway disease.

4.2. Neonatal Airway Disease

Prematurity and associated neonatal lung injury, characterized by bronchopulmonary dysplasia (BPD) can result in high incidence of childhood asthma (Hack et al., 2005). Neonatal hyperoxic exposure, e.g. as occurs in the intensive care unit, can be particularly contributory. The role of hyperoxia has been examined in animal models such as rat pups, and is associated with increased cholinergically-mediated airway contractile responses *in vitro* and *in vivo* (reviewed in (Yao et al., 2006)). However, the mechanisms by which cholinergic effects are upregulated are not clear. We have evaluated hyperoxia effects on lung expression of BDNF and TrkB (Yao et al., 2005; Yao et al., 2006) and found that hyperoxia (95% O2) starting at birth (thus mimicking the ICU experience) increases BDNF and TrkB mRNA and protein in the airways, particularly in the peribronchial smooth muscle. Here, BDNF may be the NT of interest in that hyperoxia does not appear to increase

NGF (as opposed to elevated NGF when neonates are exposed to infection (Tortorolo et al., 2005)). These findings raise the possibility that upregulation of BDNF and its autocrine signaling may result in enhanced airway reactivity in neonates, thus contributing to neonatal/pediatric asthma, and other inflammatory airway disease in infants and children (Yao et al., 2006). This scenario is also consistent with the finding that BDNF is expressed in airway preganglionic neurons (Zaidi et al., 2005), and additionally that hyperoxia substantially increases ACh content in the lung: an effect inhibited by tyrosine kinase inhibitors. These findings, albeit in animals, suggest that BDNF/TrkB signaling increases neuronal ACh production and resultant cholinergic outflow to the airways under conditions of hyperoxia (Sopi et al., 2008). Accordingly, hyperoxia increases contraction, and tyrosine kinase inhibition reduces it (Sopi et al., 2008).

Overall, these limited but interesting data show that factors such as hyperoxia increase BDNF/TrkB signaling in the airways in early life. However, the mechanisms underlying enhanced BDNF, or downstream pathways activated by BDNF in the context of airway disease are not known. As discussed above, in adult ASM, BDNF can enhance $[Ca^{2+}]_I$, cell proliferation, migration and airway remodeling in general. These processes are equally important in the developing airway, perhaps more so given that a stiffer, thicker airway can lead to severe respiratory decompensation in children. Here, it is possible that many of the signaling cascades such as MAPK, NFκB etc. are activated by BDNF in developing ASM, but remain to be demonstrated. The significance of such studies lies in the potential for pharmacological modulation of BDNF/TrkB signaling to counter airway hyperreactivity and remodeling.

5. BDNF and Asthma

Asthma involves inflammation-driven changes in airway structure and function, represented by hyperresponsiveness to bronchoconstrictors, impaired bronchodilation and a largely irreversible remodeling of the airway leading to obstruction. With evidence for BDNF expression and signaling in airway innervation, epithelium and smooth muscle there is obviously significant interest in the potential role for targeting NTs such as BDNF in asthma (Abram et al., 2009; Bennedich Kahn et al., 2008; Dagnell et al., 2007; Freund-Michel and Frossard, 2008; Frossard et al., 2004; Nassenstein et al., 2006; Nockher and Renz, 2006; Prakash et al., 2009; Renz et al., 2004; Rochlitzer et al., 2006). In this regard, there is some evidence for an association between BDNF and asthma, particularly in children as well as increased asthma association with a variant of the BDNF gene (Andiappan et al., 2011; Koskela et al., 2010; Szczepankiewicz et al., 2007; Szczepankiewicz et al., 2010; Szczepankiewicz et al., 2009; Yinli et al., 2013; Zeilinger et al., 2009). Furthermore, in humans as well as in mouse models of asthma, allergen challenge increases NGF and BDNF levels in bronchoalveolar lavage fluid (Braun et al., 1999; Virchow et al., 1998). Certainly such increases may be a result of enhanced BDNF secretion by resident airway cells, as well as by immune cells that also happen to expression BDNF and its receptors (reviewed in (Prakash et al., 2010)). Increased BDNF may then promote airway irritability via the nerves, modulate epithelium-derived bronchodilator responses, or increase ASM $[Ca^{2+}]_i$ and contractility, especially in the presence of inflammatory cytokines (Prakash et al., 2009). Finally, BDNF may modulate airway remodeling. via proliferation, migration and secretion

of inflammatory mediators and modulators such as MMPs (Bai, 2010; Dekkers et al., 2009; Lagente and Boichot, 2009). Indeed, BDNF does increase MMP9 (but not MMP2), and enhances smooth muscle migration (Dagnell et al., 2007). We have shown increased human ASM cell proliferation by BDNF in the presence of cytokines such as TNFα and IL-13 that are relevant to asthma pathophysiology (Aravamudan et al., 2012). Whether BDNF expression is intrinsically higher in ASM of asthmatics, or altered to a different level in the presence of inflammation is not known. Similarly, the effect of BDNF in asthmatic ASM may be enhanced or may differ in the contribution of downstream signaling pathways. There is currently no information on these important issues. Nonetheless, based on the diverse data to date, it is very likely that BDNF plays a role in asthma pathophysiology. Given that BDNF can be targeted via TrkB-Fc, it may therefore represent a potential therapeutic avenue in asthma.

6. BDNF and Environmental Exposures

Air pollutants are risk factors in development of allergic diseases and for respiratory infections. For example, active smoking as well as secondhand smoke can potentiate effects of other allergens. The role of BDNF expression and/or signaling in this context has been examined to a limited extent. In patients with atopic keratoconjuctivitis (where BDNF levels are elevated in tears), smoking elevates BDNF levels (Kimata, 2004). In rats, nicotine exposure increases expression of p75NTR (but not Trk receptors) (Urrego et al., 2009). In a recent study using human ASM, we found that exposure to cigarette smoke substantially increases both TrkB and p75NTR expression, and that BDNF potentiates cigarette smoke enhancement of ASM $[Ca^{2+}]_i$ responses and thus contractility (Sathish et al., 2013). While the mechanisms by which cigarette smoke enhances TrkB or p75NTR expression are not known, factors such as nicotine and oxidant stress are possibilities that remains to be explored. Here, it is interesting to note that nicotine by itself does not increase the NGF receptor TrkA in rat lung (Urrego et al., 2009). More complex mechanisms may involve nicotine-induced increase in BDNF (as occurs in neuroblastoma cells (Serres and Carney, 2006)) with autocrine effects on enhancing TrkB. While there is much more information needed in this area, these limited data point to participation of BDNF in enhanced airway inflammation and reactivity following environmental exposures. In response, BDNF may potential neuronal or immune effects in the airway as well as directly influence airway remodeling, increase airway irritability or hyperresponsiveness. Again, as with asthma, targeting of BDNF may be an attractive therapeutic avenue.

7. BDNF and Fibrosis

One aspect of airway remodeling in diseases such as asthma or COPD is increased fibrosis. Here, altered MMPs and ECM components are obviously contributory, and BDNF may play a role in this regard. A single study reported that fibroblast-rich areas in lungs of patients with pulmonary fibrosis (Ricci et al., 2007) stained for BDNF and TrkB. In fibroblasts from these patients, BDNF increased cell proliferation, compared to control patients. A more recent study (Avcuoglu et al., 2011) reported higher expression of TrkB in patients with idiopathic pulmonary fibrosis and in mice with bleomycin-induced fibrosis. Importantly, the pro-fibrotic cytokine TGFβ1 was found to enhance TrkB expression. Furthermore, the

enhanced TrkB was found to have functional effects in enhancing proliferation that would only further promote the cycle of fibrosis. Separately, in pulmonary sarcoidosis, epithelioid cells and multinucleated giant cells within granulomas have been found to show immunoreactivity for BDNF and TrkB (Dagnell et al., 2010). Overall these limited but interesting data suggest that BDNF expression or signaling is altered in lung fibrosis, although the actual mechanisms and end effects of BDNF in the fibrotic lung remain to be determined. Nonetheless, the potential for targeting BDNF in fibroblasts or other associated cell types offers a novel target for this disease.

8. BDNF and TrkB as Therapeutic Targets

From the perspective of understanding normal airway structure/function as well as exploring novel therapeutic options for airway diseases, BDNF and its receptors represent attractive targets. However, the very pleiotropic effects of BDNF on different airway components which would be attractive in terms of therapy would also make it a challenge to specifically target particular cell types, especially if they are not as easy to access. A prime example is targeting ASM via inhalational routes without disrupting the epithelium. Simple nebulization or intratracheal administration of BDNF has been performed in animal studies (Braun et al., 2004; Lommatzsch et al., 2003), but it is not clear that the extent of penetration into the lung, local vs. systemic levels, or degradation vs. elimination has actually been studied. Here, approaches such as nanoparticle carriers and cell-specific markers to facilitate preferential uptake by cells of interest, viral vectors, or cellular scaffolds may be appealing as we move forward. Small molecule activators (or inhibitors) of Trks vs. p75NTR are potential options as well (Longo and Massa, 2008; 2013; Skaper, 2008; Thiele et al., 2009; Webster and Pirrung, 2008). Molecules such as TrkB-Fc that bind extracellular BDNF and prevent its action could be helpful, but again access to specific cell types may be limiting. However, even these novel approaches are limited by the complexity of NT receptors and signaling. For example, depending on the relative expression of TrkB-FL vs. TrkB-T1 vs. p75NTR, small molecules that act on TrkB may have differential effects on cell survival vs. cell death. On the other hand, small, synthetic peptides have been generated that can selectively activate specific aspects of TrkB or p75NTR and thus mimic BNDF (Longo and Massa, 2013). However, due to limitations of peptides for drug development including stability, bioavailability and barrier penetration, small peptides may not be ideal options. Ligands for TrkB have also been developed (Longo and Massa, 2013), in particular the specific agonists 7,8-dihydroxyflavone (Jang et al., 2010b) or deoxygedunin (Jang et al., 2010a)

While these exciting developments in approaches to modulating BDNF/TrkB are very interesting, their applicability to airway diseases is less clear for the simple reason that in the airways, BDNF appears to be pro-inflammatory, pro-contractility and pro-remodeling, and therefore inhibition of BDNF expression and signaling is needed. However, much of the focus on BDNF-based therapies are geared towards enhancing BDNF/TrkB effects in the context of neurological diseases where loss of trophic influences is the problem. Accordingly, there is much need for identifying novel approaches to inhibiting BDNF/TrkB in the context of airway diseases.

9. Summary and Conclusions

While signaling via BDNF in different airway components has now been recognized (Figure 4), a complete, integrated physiological model for BDNF function in the airway needs to be developed. Here, a number of questions can be put forth: A) What are the normal, major sources of BDNF in the airway? Here ASM appears to be particularly important; B) What are the primary target cell types for BDNF? As discussed in this review, it appears that epithelium, ASM, fibroblasts and nerves are all potential targets. What is less clear is whether BDNF acts on each of these cells under normal circumstances, i.e. If BDNF is widely expressed in the airway, from an evolutionary standpoint, what is its intended function: modulation of neurogenic airway tone vs. airway structure (remodeling) vs. immune function? C) If BDNF is important in neuronal development, is there a role in lung development as well? D) Under disease conditions, is altered BDNF expression and function secondary or due to initiating insults such as inflammation or infection, or is BDNF itself a trigger of disease? Ongoing research integrating *in vitro* and *in vivo* approaches should help address many of these issues. Given substantial homology of BDNF, TrkB and p75NTR across species, corroboration of animal experiments with human samples, especially patients with specific, well-defined airway diseases will be particularly helpful.

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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

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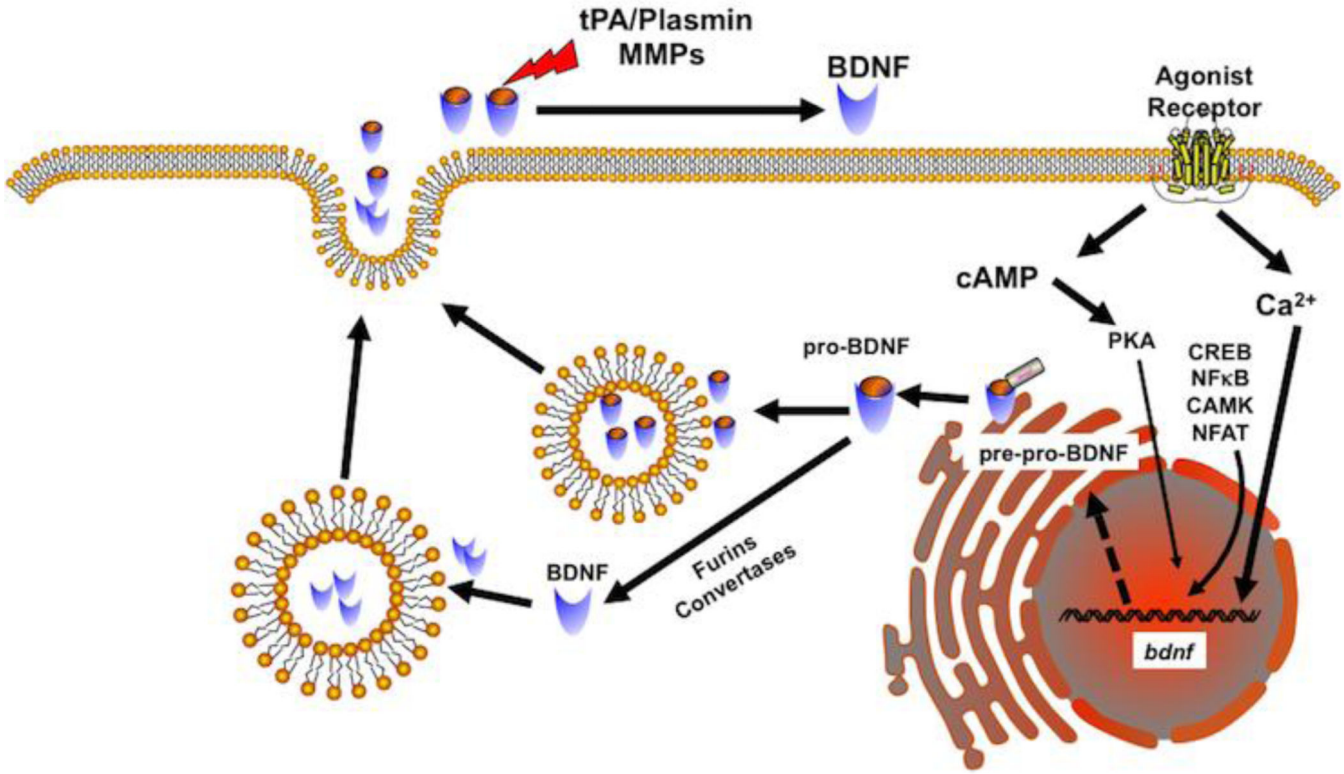

Figure 1. Production of brain-derived neurotrophic factor (BDNF)

Stimulation by agonists or other molecules leading to elevated Ca^{2+} is a common mechanism for inducing BDNF in cells. Other processes that enhance cAMP, or activate signaling intermediates such as CREB, NFkB, CaM kinases or NFAT may also activate the BDNF gene. BDNF is first produced as a pre-pro-peptide that is then cleaved in the Golgi to produce pro-BDNF that is then packaged into vesicles. Pro-BDNF can also be cleaved intracellularly by furins and vesicular convertases to produce mature BDNF that is also packaged. Vesicular release of pro-BDNF or mature BDNF can then act on neurotrophin receptors to produce effects. Extracellularly, pro-BDNF is cleaved by factors such as matrix metalloproteinases or tissue plasminogens.

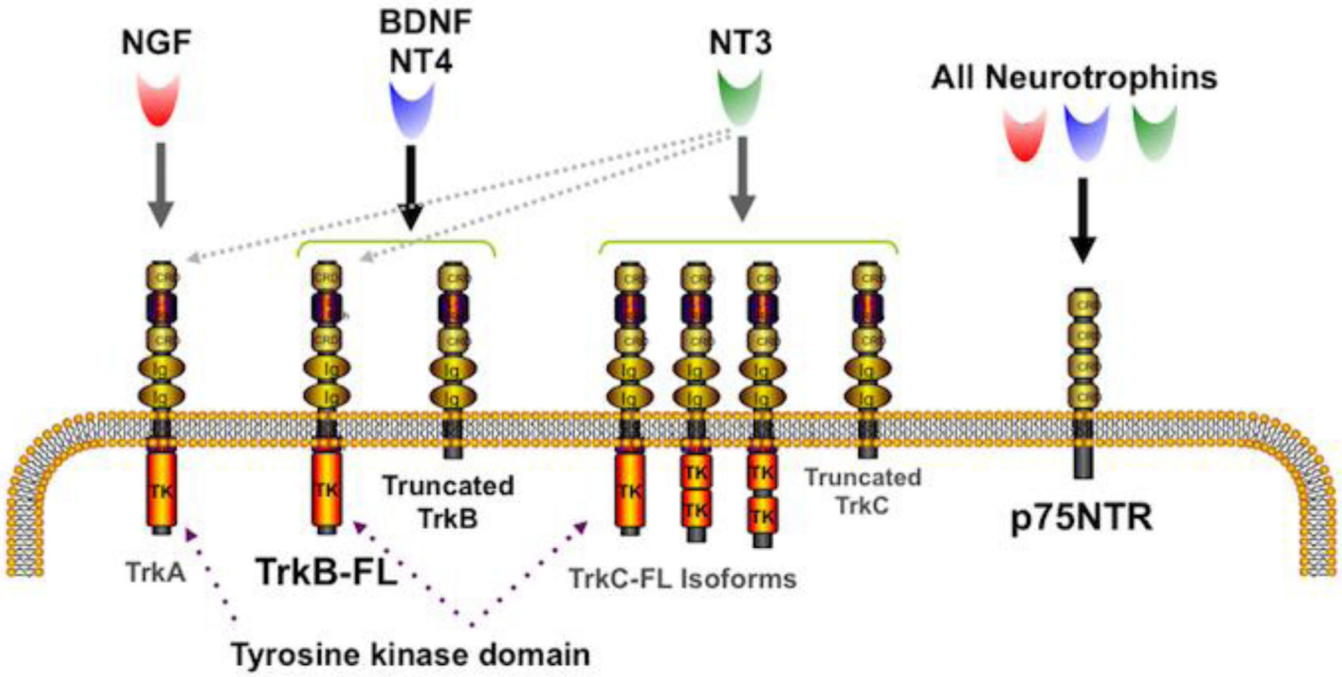

Figure 2. Neurotrophins and their receptors

The neurotrophin family consists of four polypeptide proteins that activate two classes of receptors. All of the neurotrophins (NGF, BDNF, NT4 and NT3) bind to the low-affinity p75NTR receptor that lacks a tyrosine kinase domain but can use adaptor proteins. P75NTR is a member of the tumor necrosis factor receptor family. The high-affinity receptors are the tropomyosin related kinases (Trks) that in their full-length (FL) form have an intracellular tyrosine kinase domain via which they function. In addition, 'truncated" Trks also exist that do not have the tyrosine kinase domain but can act via other mechanisms. NGF preferentially binds to TrkA, while TrkB is the preferred receptor for BDNF and NT4, and TrkC preferentially binds to NT3. In addition, NT3 can bind to the other Trks with lower affinity.

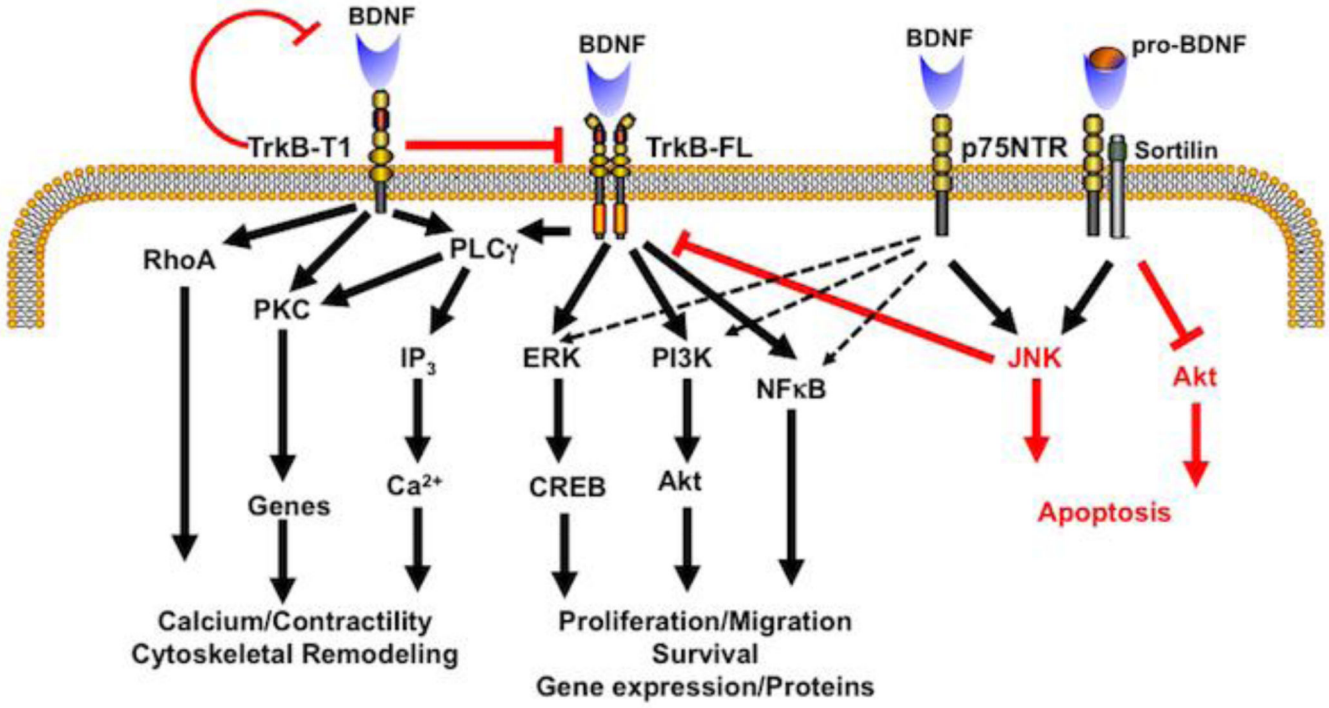

Figure 3. BDNF signaling

As discussed in the main text, BDNF signaling via TrkB vs. p75NTR is complex but elegant, allowing for a diversity of signaling mechanisms and cellular effects that are cell type- and context-dependent. Activation of the full-length TrkB by mature BDNF classically results in activation of PLCγ with downstream effects on $[Ca^{2+}]_i$ via the IP3 pathway that can enhance contractility, the ERK pathway and the PI3K/Akt pathway that can both promote cell proliferation and survival. In addition TrkB can work through the NFκB pathway. In contrast to TrkB-FL, the truncated TrkB-T1 can be both inhibitory (red; by dimerizing with TrkB-FL or chelating BDNF) and activating via RhoA and PKC, leading to cytoskeletal remodeling, gene regulation and other effects. The low-affinity p75NTR, when activated by mature BDNF is typically activating to pathways that TrkB-FL works through, but importantly can be inhibitory via the JNK or Akt pathways. This is particularly the case when p75NTR is activated by pro-BDNF and forms a ternary complex with the adaptor protein sortilin.

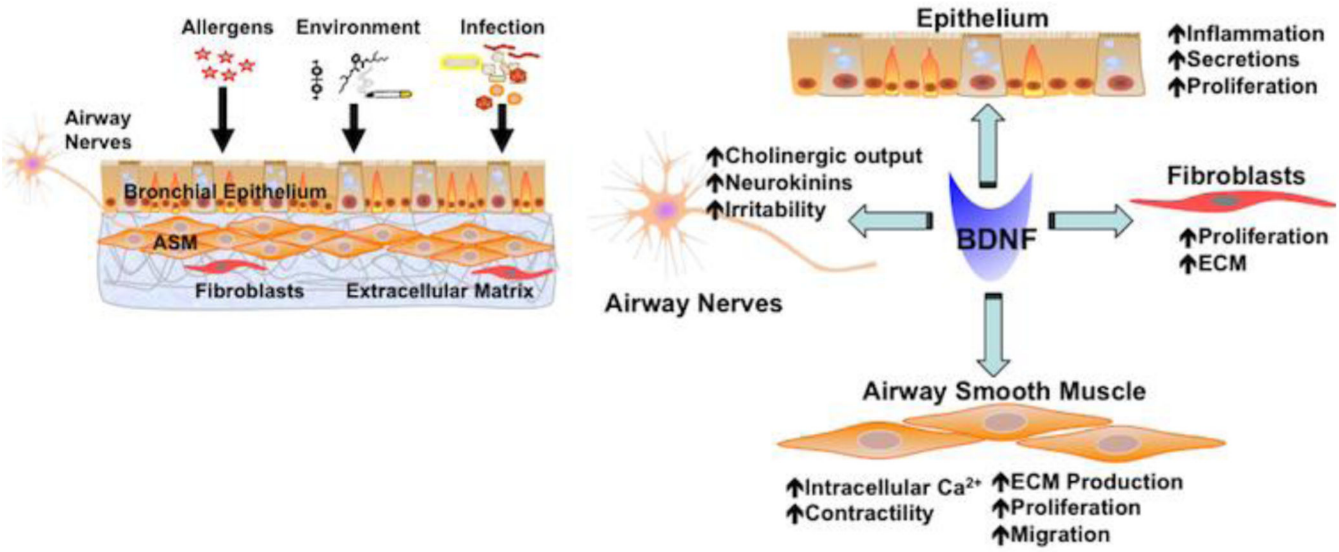

Figure 4. BDNF and the airway

There is increasing evidence that BDNF can be produced by cells of the airway such as epithelium, airway smooth muscle (ASM), airway nerves, and even fibroblasts. Furthermore, each of these cell types can be a target of BDNF. In the context of airway diseases, BDNF can enhance airway irritability and responsiveness to agonist via the nerves or ASM itself (where $[Ca^{2+}]_i$ is increased) or enhance airway remodeling in diseases such as asthma or COPD by increasing cell proliferation, migration, fibrosis and formation of extracellular matrix.

Table 1

BDNF in the Airways

Cell/Tissue Component	Receptors	Reported Effects	Reported Role in Diseases
Bronchial Epithelium	TrkB p75NTR	Essential for airway and lung development Cell survival (decreased apoptosis) NO release Airway remodeling	↑ BDNF in asthma ↑ BDNF and TrkB, ↓ p75NTR with infection ↑ Airway thickening in asthma or inflammation ↑ TrkB, p75NTR with cigarette smoke
Airway Smooth Muscle	TrkB p75NTR	Airway development Enhanced airway contractility with exogenous and endogenous BDNF Increased cell proliferation Airway remodeling	↑ BDNF, TrkB with hyperoxia in fetal or neonatal ASM ↑ Endogenous BDNF production and secretion with airway inflammation ↑ TrkB, p75NTR with allergic airway inflammation ↑ ASM contractility in inflammation Mediates and enhances ASM cell proliferation in the presence of cytokines ↑ Extracellular matrix deposition ↑ TrkB, p75NTR with cigarette smoke ↑ ASM contractility with smoke exposure
Nerves	TrkB p75NTR	↑ SP and ACh content of sensory nerves, vagal afferents ↑ NK1 receptor expression ↑ neurotransmitter release	↑ Cholinergic outflow ↑ BDNF in asthma ↑ Neurally-mediated airway hyperresponsiveness ↑ neuronal plasticity
Fibroblasts	TrkB p75NTR	Proliferation Migration Myofibroblast differentiation	↑ BDNF and TrkB in inflammation ↑ Proliferation
Blood			↑ BDNF in asthma ↑ p75NTR with nicotine exposure Association between BDNF gene variants and asthma
BAL			↑ BDNF in asthma

Information gleaned from multiple studies in human or animals, all included in bibliography.