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Review

Nerve growth factor and its receptors in asthma and inflammation

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Abstract

Nerve growth factor (NGF) is a high molecular weight peptide that belongs to the neurotrophin family. It is synthesized by various structural and inflammatory cells and activates two types of receptors, the TrkA (tropomyosin-receptor kinase A) receptor and the $p75^{NTR}$ receptor, in the death receptor family. NGF was first studied for its essential role in neuronal growth and survival. Recent reports indicate that it may also help mediate inflammation, especially in the airways. Several studies in animals have reported that NGF may induce bronchial hyperresponsiveness, an important feature of asthma, by increasing sensory innervation. It may also induce migration and activation of inflammatory cells, which infiltrate the bronchial mucosa, and of structural cells, including epithelial, smooth muscle cells and pulmonary fibroblasts. Increased NGF expression and release is observed in asthma patients after bronchial provocation with allergen. Taken together, the data from the literature suggest that NGF may play a role in inflammation, bronchial hyperresponsiveness and airway remodelling in asthma and may help us to understand the neuro-immune cross-talk involved in chronic inflammatory airway diseases.

Keywords: Airways; Asthma; Inflammation; Neurotrophin; NGF (nerve growth factor); Lung

Contents

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1. Introduction

Nerve growth factor (NGF), discovered by Rita Levi-Montalcini and co-workers more than 50 years ago (for reviews, see Levi-Montalcini and Angeletti, 1966; Levi-Montalcini, 1987; Levi Montalcini et al., 1995), belongs to the neurotrophin family (for review, see Dechant and Neumann, 2002), together with brain-derived neurotrophic factor (BDNF) (Barde et al., 1987) and neurotrophins (NT)-3 (Hohn et al., 1990, Maisonpierre et al., 1990), -4/5 (Hallbook et al., 1991, Ip et al., 1992, Berkemeier et al., 1991, 1992) and -6 (Gotz et al., 1994, Du et al., 2003). It was first known for its essential role in neuronal survival and development (Levi-Montalcini 1987). For example, mice without a functional NGF gene ($ngf^{-/-}$) lack small diameter sensory neurons and sympathetic postganglionic neurons and die shortly after birth (Crowley et al., 1994), while transgenic overexpression of NGF in these knockout mice, controlled by the K14 keratin promoter, rescues some elements of the peripheral nervous sympathetic and sensory system and thus restores normal growth and viability (Harrison et al., 2004). In addition, recent findings indicate that it may help play a role in inflammation. This review will present data about NGF expression and regulation in the airways and summarize information about its likely role in inflammatory diseases, especially asthma.

2. NGF and its receptors

2.1. NGF structure and synthesis

NGF is a high molecular weight peptide 7S-NGF which is a 130–140-kDa complex composed of α, β and γ subunits (Bax et al., 1993). The β subunit, responsible for its biological activity (Fahnestock, 1991), is a 26-kDa polypeptide dimer formed of two similar 118-amino acid subunits associated non-covalently (Ibanez, 1998; McDonald et al., 1991). The βNGF gene is located on the short arm of chromosome 1 in humans (Francke et al., 1983) and encodes a 34-kDa precursor, called pre-pro-NGF. This precursor is cleaved into pro-NGF, then into the mature biologically active βNGF after furin or pro-convertase action (for reviews, see Fahnestock, 1991; Chao, 2003). The βNGF structure is conserved in vertebrates (for review, see Gotz and Schartl, 1994); human and mouse proteins, for example, show 90% homology (Ullrich et al., 1983).

2.2. NGF receptors and transduction pathways

NGF forms covalent homodimers that activate two types of receptors: the TrkA receptor (tropomyosin-receptor kinase A), which has intrinsic tyrosine-kinase activity and binds NGF selectively (for review, see Patapoutian and Reichardt, 2001), and the $p75^{NTR}$ receptor for neurotrophins, which binds all neurotrophins and pro-neurotrophins, in particular pro-NGF (Lee et al., 2001; Beattie et al., 2002; for reviews, see Chao, 1994; Ibanez, 2002).

2.2.1. The TrkA receptor

The TrkA receptor is a 140-kDa transmembrane protein encoded by a proto-oncogene located on chromosome 1 (Martin-Zanca et al., 1986). This receptor comprises a tyrosine-kinase domain in its intra-cytoplasmic region and five extracellular domains, including two immunoglobulin-like domains involved in NGF binding and responsible for the specific selectivity of NGF for TrkA (Wiesmann et al., 1999). In humans, the TrkA receptor is expressed on cells throughout the nervous system (Muragaki et al., 1995) as well as on structural cells and other non-neuronal cells in the immune and neuroendocrine systems (for review, see Levi-Montalcini, 1987; Levi Montalcini et al., 1995; Aloe et al., 1997; Bonini et al., 2002).

When NGF binds to the TrkA receptor, it induces receptor homodimerisation, which initiates kinase activation and transphosphorylation (Kaplan et al., 1991). This kinase activation involves the small G proteins: G Ras, Rac, Rap-1, vav, the phospholipase C? (PLC?), protein kinases C (PKC) and phosphatidyl-inositol-3 kinase (PI3

kinase) in neural cells (Obermeier et al., 1993a,b; Melamed et al., 1999; York et al., 2000; Wu et al., 2001) (Fig. 1). The mitogen-activated protein kinase (MAPK) pathways are activated next: extracellular-regulated protein kinase (ERK) by the small G proteins; ERK, p38 and JUN-N-terminal kinase (JNK) MAPK by PKC; and p38 and JNK by PI3 kinase (for review, see Kaplan and Miller, 1997). PI3 k in turn induces activation of protein kinase B (PKB or Akt) and PKCξ (York et al., 2000).

NGF activation of the TrkA receptor induces cell proliferation, differentiation and survival; it inhibits apoptosis, increases neuronal excitability and induces mediator release from cells expressing TrkA (Levi-Montalcini, 1987; Levi Montalcini et al., 1995; Aloe et al., 1997; Bonini et al., 2002; Freund and Frossard, 2004).

2.2.2. The $p75^{NTR}$ receptor

The $p75^{NTR}$ receptor is encoded by a gene located on chromosome 17, which forms a 75-kDa glycoprotein (Huebner et al., 1986). It belongs to the family of death receptors and shows strong homology with the tumour necrosis factor-α (TNFα) p75 receptor (Chapman and Kuntz, 1995). Its extracellular domain comprises four repetitive sequences rich in Cys and basic amino acids (Arg, Lys, Asn); these sequences are responsible for its negative charge and for binding various neurotrophins to the receptor (Chapman and Kuntz, 1995). The transmembrane domain of the $p75^{NTR}$ receptor is unique and highly conserved among animal species (for review: Chao and Hempstead, 1995). Its intracellular domain comprises 155 amino acids (Johnson et al., 1986). The pro-neurotrophins have recently been shown to bind and activate the $p75^{NTR}$ receptor, preferentially inducing programmed cell death, or apoptosis (Lee et al., 2001, Beattie et al., 2002). The pro-NGF pro-domain masks the NGF binding domain to the TrkA receptor and thus increases selectivity for the $p75^{NTR}$ receptor (for review, see Ibanez, 2002). In addition, pro-NGF creates a signalling complex by simultaneously binding to $p75^{NTR}$ and sortilin, a 95-kDa

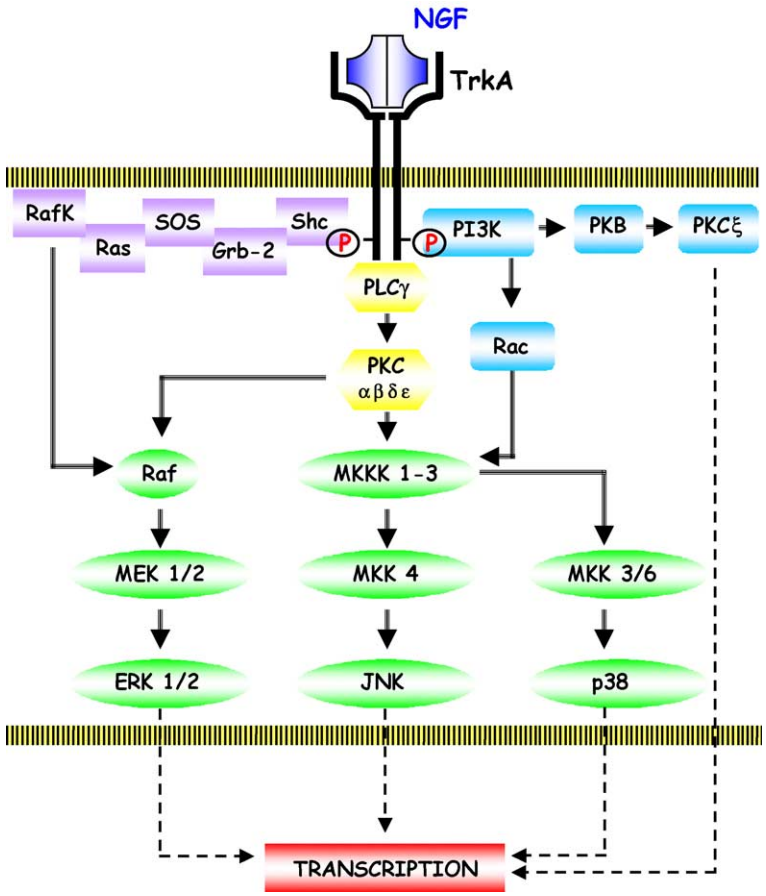

Fig. 1. Signal transduction pathways of the TrkA receptor. NGF binds the TrkA receptor, thus inducing its homodimerisation and autophosphorylation and the activation of different signalling pathways. Activation of phospholipase Cγ (PLCγ), of α, β, δ and ε protein kinases C and of protein G Ras induces activation of the different MAP-kinase pathways: ERK (extracellular-regulated kinase), p38 and JNK (JUN-N-terminal kinase). Activation of PI3-kinase induces protein kinase B (PKB, also named Akt) activation, leading to a MAP-kinase-independent, ξ protein kinase C (PKCξ)-dependent activation of transcription, or to a MAP-kinase-dependent pathway through activation of the small G protein Rac. Shc: Src homology 2-containing protein, Grb-2: growth factor receptor-bound protein, SOS: son of sevenless, RafK: Raf kinase, MKKK: MAP-kinase kinase kinase, MKK: MAP-kinase kinase, MEK: MAP ERK kinase. Based on Chao (2003), Kaplan et al. (1991), Obermeier et al. (1993a,b), York et al. (2000), Wu et al. (2001) and Kaplan and Miller (1997).

co-receptor, to induce apoptosis with higher affinity (Nykjaer et al., 2004). Regulation of the biological activity of the neurotrophin family therefore occurs through pro-neurotrophins, which preferentially induce apoptosis by activating the $p75^{NTR}$ receptor, or mature neurotrophins, which induce cell survival through selective activation of the Trk receptors (for review, see Chao, 2003), or both.

Stimulation of the $p75^{NTR}$ receptor by NGF first induces homodimerisation of the receptors, thereby initiating, activation of the adaptive proteins that bind to the extracellular domain (for review, see Roux and Barker, 2002), activation of an atypical PKC, the iota PKC (Ye et al., 1999; Mamidipudi et al., 2002; Mamidipudi et al., 2004), involvement of the transcription factor NF-κB (Carter et al., 1996), or synthesis of ceramides (Dobrowsky et al., 1994) and then activation of the JNK MAPK (Casaccia-Bonnefil et al., 1996) (Fig. 2). Signalling pathways activated by the $p75^{NTR}$ receptors appear to promote cell survival as well as apoptosis (for review, see Hempstead and Salzer, 2002); this advantage is reported both in the presence (Chao et al., 1998; Yano and Chao, 2000) and absence (Khursigara et al., 2001; DeFreitas et al., 2001) of TrkA receptor expression at the cell membrane. Beyond these previously reported receptor homodimerisations, recent findings have led to the proposal that co-expression of $p75^{NTR}$ and TrkA receptors may produce a high-affinity binding complex (Hempstead et al., 1991; Benedetti et al., 1993; Bibel et al., 1999; Esposito et al., 2001; Lad et al., 2003; for review: Chao, 2003).

3. NGF expression and regulation in the airways

3.1. Cell sources of NGF in the airways

The first sources of NGF identified were murine submaxillary glands and sarcomas, and snail venom (for review, see Levi-Montalcini, 1987). It is now well known that NGF

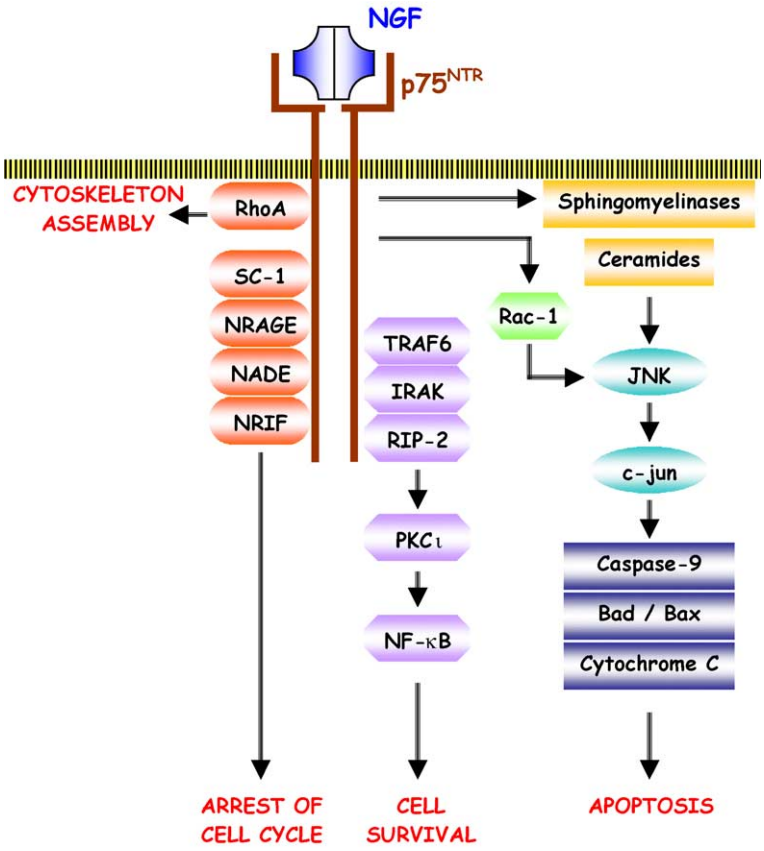

Fig. 2. Signal transduction pathways of the $p75^{NTR}$ receptor. NGF induces activation of the $p75^{NTR}$ receptor by inducing its homodimerisation, thus activating the transcription factor NF-κB through recruitment of adaptive proteins such as TRAF-6, IRAK and RIP2, activation of IRAK (IL-1 receptor-associated kinase) and of the atypical iota PKC (PKCι). NGF also induces activation of the JNK pathway, through activation of the small protein G Rac, or following sphingomyelinase activation and ceramide synthesis. NGF also activates the protein RhoA, involved in modifications of the cytoskeleton, and other adaptive proteins such as NRIF, NADE, NRAGE and SC-1, which may play a role in the cell cycle arrest. TRAF: TNF receptor-associated factor, NF-κB: nuclear factor-κB, NRIF: neurotrophin-receptor interacting factor, NADE: neurotrophin-associated cell death executor, NRAGE: neurotrophin-receptor-interacting MAGE homologue, SC-1: Schwann cell-1, RIP2: receptor-interacting protein-2. Based on Chao (2003), Roux and Barker (2002), Carter et al. (1996), Ye et al. (1999), Mamidipudi et al. (2002, 2004), Dobrowsky et al. (1994) Casaccia-Bonnefil et al. (1996), and Whitfield et al. (2001).

can be expressed and released by a variety of cell types in tissues. NGF is synthesised in the airways by various structural and inflammatory cells infiltrating the bronchial mucosa (Fig. 3).

3.1.1. In vitro studies

3.1.1.1. Inflammatory cells. Numerous studies have reported NGF synthesis by inflammatory cells. This involves T and B lymphocytes (Ehrhard et al., 1993; Santambrogio et al., 1994, Torcia et al., 1996; Lambiase et al., 1997), mast cells in rats (Leon et al., 1994) and humans (Nilsson et al., 1997), eosinophils (Solomon et al., 1998; Kobayashi et al., 2002) and monocytes/macrophages (Ehrhard et al., 1993; Ricci et al., 2000; Barouch et al., 2001); they all synthesise and release NGF. Thus, many of the inflammatory cells infiltrating the bronchial mucosa of asthma patients are immunoreactive for NGF, and may contribute to the increased levels of NGF found in the airways (Kassel et al., 2001; Olgart-Höglund et al., 2002; for review: Olgart-Höglund and Frossard, 2002).

3.1.1.2. Structural cells of the airways. NGF synthesis by airway structural cells has been demonstrated more recently. In vitro studies of human lung cells in culture show that bronchial epithelial cells (Fox et al., 2001; Pons et al., 2001), pulmonary fibroblasts (Olgart and Frossard, 2001) and bronchial smooth muscle cells (Freund et al., 2002) all express NGF. NGF messenger RNA has been measured with quantitative polymerase chain reaction (Q-PCR) (for example, 15 fg NGF cDNA (complementary DNA)/pg glyceraldehyde 3-phosphate dehydrogenase (GAPDH) cDNA in bronchial smooth muscle cells) and NGF protein by enzyme-linked immunosorbent assay (ELISA). The latter showed that NGF is synthesised by all three cell types, at levels of 12–22 pg NGF/ml of culture supernatant. These results are consistent with NGF expression by other cell types of other origins, including human cutaneous fibroblast cell lines (Murase et al., 1992), epithelial cells from the human intestine (Varilek et al., 1995) or retina (Ishida et al., 1997), and human vascular (Ueyama et al., 1993, Donovan et al., 1995, Nemoto et al., 1998) or vesical (Tanner et al., 2000) smooth muscle cells. NGF synthesis by airway structural cells is also concordant with reports of the synthesis and release of other neurotrophins by structural cells, including rat thoracic aortic smooth muscle cells, which express both BDNF and NT-3 (Nemoto et al., 1998), and human keratinocytes expressing NT-4/5 (Grewe et al., 2000).

3.1.2. In vivo studies

NGF immunolabelling (with anti-NGF antibodies) (Olgart-Höglund et al., 2002) of bronchial biopsy sections from patients who do not have asthma shows

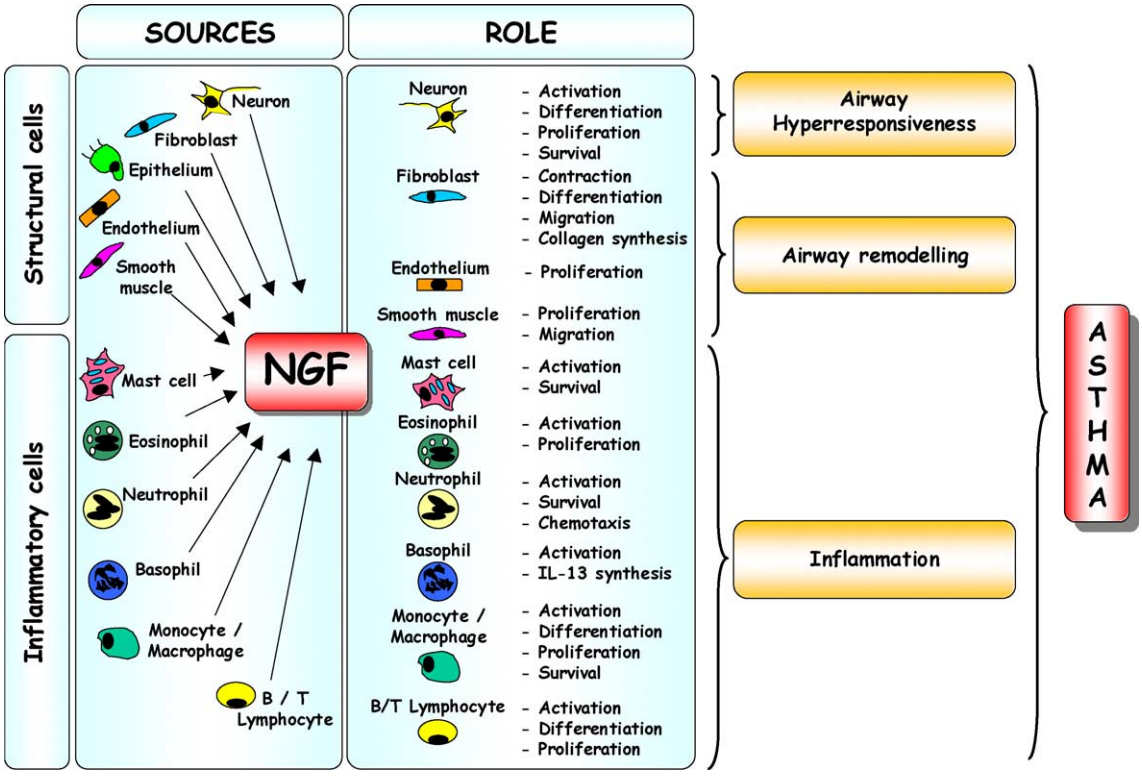

Fig. 3. Sources and role of NGF in the airways. NGF is expressed in the airways by structural cells as well as inflammatory cells infiltrated into the bronchial mucosa. Once released, NGF can stimulate different types of cells involved in the inflammation, bronchial hyperresponsiveness and airway remodelling that occur in asthma.

substantial staining of the epithelial cells, bronchial smooth muscle cells, and fibroblasts, consistent with our in vitro studies of airway cells in culture. Bronchial biopsy sections from asthma patients reveal additional immunolabelling of the infiltrated inflammatory cells (Olgart-Höglund et al., 2002, Kassel et al., 2001). In vivo studies in a murine model of asthma (Braun et al., 1998) and asthma patients (Kassel et al., 2001, Nassenstein et al., 2003) show that inflammatory cells of the bronchoalveolar lavage express NGF. These confirm the hypothesis suggested by the in vitro studies: inflammatory cells infiltrating the bronchial mucosa are a potential source of NGF in the airways.

3.2. Regulation of NGF synthesis in the airways

The regulatory mechanisms of NGF synthesis and secretion in vivo in the airways have not yet been adequately explored, but in vitro studies justify some hypotheses.

3.2.1. Regulation of NGF synthesis depends on cell density

Studies of human airway cells—either proliferating or quiescent—in culture show that regulation of NGF synthesis differs as a function of cell density. In both human pulmonary fibroblasts (Olgart and Frossard, 2001) and bronchial smooth muscle cells (Freund et al., unpublished data), the NGF level per cell is highest in the starting culture, when cells are sparse and cell contacts low; it progressively decreases as the number of cells increases. Similar observations in other cell types, including human keratinocytes (Di Marco et al., 1993) and skin fibroblasts (Murase et al., 1992), suggest that NGF is synthesised at higher rates in proliferative than in confluent cells. The observation of NGF receptors at the cell surface (Freund et al., unpublished data) suggests that newly synthesised NGF probably has an autocrine effect.

3.2.2. Increased NGF synthesis in inflammatory conditions

Cytokines such as the pro-inflammatory interleukin-1β (IL-1β) and TNFα or transforming growth factor-β (TGF-β), increase the synthesis of NGF by airway structural cells. This stimulation has been evidenced in vitro in human pulmonary fibroblasts (Olgart and Frossard, 2001; Micera et al., 2001), A549 epithelial cells (Pons et al., 2001) and bronchial smooth muscle cells (Freund et al., 2002). Studies also show that pro-inflammatory cytokines can act in concert to stimulate additional NGF secretion: TNFα, for example, increases the secretion of NGF induced by IL-1β and interferon γ (INFγ) in fibroblasts (Hattori et al., 1994) and by interleukin-4 (IL-4) in astrocytes (Brodie et al., 1998).

NGF synthesis in inflammatory conditions has also been demonstrated in vivo: elevated NGF concentrations are observed in cutaneous inflammation (Safieh-Garabedian et al., 1995) and in asthmatic airways (Olgart and Frossard, 2001; Kassel et al., 2001; Virchow et al., 1998). Taken together, these data suggest that pro-inflammatory cytokines, which are present at high levels in the airways of patients with asthma (Tillie-Leblond et al., 1999), might contribute to the elevated levels of NGF synthesis observed.

3.2.3. Decreased NGF synthesis by anti-inflammatory drugs

Corticosteroids are well known for their anti-inflammatory properties, in particular in asthmatic airways. Numerous studies report that the glucocorticoids dexamethasone and budesonide affect NGF expression. They cause a significant reduction in the increased NGF expression induced by pro-inflammatory cytokines; in one study, this action was shown to result from the repression of NGF gene transcription in endoneural fibroblasts from the rat sciatic nerve (Lindholm et al., 1990). Our team has reported that glucocorticoid treatment decreases the NGF secretion that the pro-inflammatory cytokines IL-1β and TNFα stimulate in cultures of human pulmonary fibroblasts (Olgart and Frossard, 2001) and in A549 epithelial cells (Pons et al., 2001). These results suggest that glucocorticoids inhibit NGF secretion in inflammatory conditions and that structural cells such as epithelial cells or fibroblasts may be a target for anti-inflammatory glucocorticoid action in the airways.

4. Effect of NGF in the airways

4.1. Effect of NGF on neuronal cells

Sensory hyperinnervation has been observed in the airways of a transgenic mouse specifically overexpressing NGF in airway tissue (Hoyle et al., 1998). This finding is consistent with the ability of NGF to stimulate the development, growth and survival of neurons, particularly of the sensory phenotype (for review, see Levi-Montalcini, 1987; Thoenen et al., 1987). These neurons express both TrkA and $p75^{NTR}$ NGF receptors (Muragaki et al., 1995; Verge et al., 1989; Lee et al., 1992; Schatteman et al., 1993; Smeyne et al., 1994). NGF also stimulates sensory neurons to secrete calcitonin gene-related peptide (CGRP) or tachykinins, such as substance P (Lindsay and Harmar, 1989; Donnerer et al., 1992; Vedder et al., 1993; Undem et al., 1999; Hunter et al., 2000). Injection of NGF into the tracheal wall of an anaesthetised guinea pig induces increased substance P expression by sensory neurons that are derived from the jugular ganglia and which innervate the airways. NGF injection also causes a neuronal phenotype switch: it induces expression of substance P in neurons derived from the nodose ganglia, which do not express it constitutively (Hunter et al., 2000). Together, these results show the primordial role of NGF in the nerve activity in the airways, in particular sensory innervation.

4.2. Effect of NGF on inflammatory cells

Most inflammatory cells in humans express TrkA and $p75^{NTR}$ NGF receptors. TrkA, for example, has been found on the extracellular membrane of mast cells (Nilsson et al., 1997; Tam et al., 1997), even infiltrated into the airway mucosa (Kassel et al., 2001), on T (Ehrhard et al., 1993; Lambiase et al., 1997), as well as on B (Torcia et al., 1996) lymphocytes, macrophages (Barouch et al., 2001) and basophils (Burgi et al., 1996).

An increased number of mast cells is observed in the tissue of new-born rats after NGF injection (Aloe and Levi-Montalcini, 1977). A wide variety of NGF effects have been reported so far (Fig. 3): it stimulates differentiation and survival of mast cells (Kawamoto et al., 1995; Tam et al., 1997; Böhm et al., 1986; Aloe and De Simone, 1989; Matsuda et al., 1991; Horigome et al., 1994; Bullock and Johnson, 1996; Welker et al., 1998; Kanbe et al., 2000); it induces differentiation and proliferation of B and T lymphocytes (Thorpe and Perez-Polo, 1987; Otten et al., 1989; Brodie and Gelfand, 1992; Kronfeld et al., 2002) and proliferation of eosinophils (Hamada et al., 1996) and monocytes (La Sala et al., 2000); it induces the release of mediators from mast cells (Horigome et al., 1994; Bruni et al., 1982; Pearce and Thompson, 1986; Murakami et al., 1997; Tal and Liberman, 1997; Kawamoto et al., 2002), neutrophils (Kannan et al., 1991), basophils (Burgi et al., 1996; Matsuda et al., 1988; Bischoff and Dahinden, 1992; Heinemann et al., 2003) and macrophages (Barouch et al., 2001; Susaki et al., 1996); and it causes B lymphocytes to synthesise immunoglobulins (Kimata et al., 1991). Finally, NGF is involved in neutrophil chemotaxis and viability both in vitro (Kannan et al., 1991; Gee et al., 1983) and in vivo (Boyle et al., 1985).

4.3. NGF effects on structural cells

Recent studies suggest that NGF is capable of stimulating structural cells (Fig. 3). It induces contraction and migration of human pulmonary fibroblasts (Micera et al., 2001; Kohyama et al., 2002) and vascular smooth muscle cells (Donovan et al., 1995; Kraemer et al., 1998). It also causes endothelial cells to proliferate (Raychaudhuri et al., 2001; Cantarella et al., 2002): we recently demonstrated its proliferative effect on human airway smooth muscle cells in culture (Freund et al., 2003). Various neurotrophin receptors are involved in these effects. Recent observations of TrkA and $p75^{NTR}$ NGF receptor expression at the cell membrane of structural cells (Donovan et al., 1995; Kohyama et al., 2002; Freund et al., 2003) suggest NGF autocrine regulation in these cells.

5. Potential role of NGF in asthma

Numerous studies suggest that NGF is involved in asthma.

5.1. Expression and release of NGF in asthma

Elevated NGF concentrations have been observed in allergic and inflammatory diseases and reported to be related to asthma severity (Bonini et al., 1996). Serum NGF levels are higher in patients with asthma than in control subjects without asthma (Bonini et al., 1996). A similar increase has also been observed in bronchoalveolar lavage fluid (Olgart-Höglund et al., 2002). These reports suggest that NGF secretion is regulated locally in asthma. Already elevated NGF concentrations rise further after either segmental allergenic provocation (Virchow et al., 1998) or bronchial provocation with low-dose allergen (Kassel et al., 2001). Similar results are reported in the upper airways, where patients with allergic rhinitis have higher NGF levels than control subjects (Sanico et al., 2000). Here again, high concentrations rise still further after nasal allergen provocation.

5.2. NGF, innervation and bronchial hyperresponsiveness

Recent studies suggest that NGF plays a central role in bronchial hyperresponsiveness. First, Braun et al. (1998) reported that bronchial hyperresponsiveness induced by allergen challenge in a mouse model of allergic asthma was suppressed by anti-NGF blocking antibodies (Braun et al., 1998). Moreover, NGF pretreatment of the airways itself induces bronchial hyperresponsiveness, as shown in vivo in guinea pigs (Friberg et al., 2001; De Vries et al., 1999) and in vitro on tracheal segments (De Vries et al., 2001) and human isolated bronchi (Frossard et al., submitted for publication). An NK-1 receptor antagonist can block this NGF-induced bronchial hyperresponsiveness in vivo in guinea pigs, a finding that suggests the involvement of tachykinins in this process (De Vries et al., 1999). Additionally, preliminary treatment with anti-NGF blocking antibodies reduces bronchoconstriction induced by allergen challenge in vivo in mice (Braun et al., 1998) and guinea pigs (De Vries et al., 2002). The lack of bronchial hyperresponsiveness after sensitization and allergen challenge in $p75^{NTR}$ knock-out mice further supports the hypothesis that NGF activation of this receptor induces this hyperresponsiveness (Tokuoka et al., 2001; Kerzel et al., 2003).

NGF increases the sensitivity and excitability of peripheral neurons (Lewin et al., 1993, 1994; McMahon, 1996; Levi-Montalcini et al., 1996; Woolf et al., 1994). In addition, neutralisation of NGF by anti-NGF antibodies (Woolf et al., 1994) or its blockage by a fusion TrkA-IgG protein (McMahon, 1996) inhibits the inflammation of rat paw caused by injection of Freund's adjuvant or lipopolysaccharides (LPS), an inflammation associated with increased expression of sensory neuropeptides, substance P and CGRP. Neutralising anti-NGF antibodies also inhibit local hypersensitivity, comparable to cutaneous hyperalgesia (Woolf et al., 1996). Thus, NGF-induced neurogenic

inflammation in the airways is one possible mechanism by which this peptide induces bronchial hyperresponsiveness (Kerzel et al., 2003; Renz, 2001; Jacoby, 2003). Such a mechanism may involve intermediary cells, such as mast cells (Woolf et al., 1996). Additionally, NGF induces expression of the acid-sensing ion channel in neuronal cells (Mamet et al., 2003), which may also participate in the increased neural sensitivity.

5.3. NGF and airway inflammation

In a murine model of asthma, levels of IL-4 and IL-5, both Th2 cytokines, fall in the presence of anti-NGF blocking antibodies, even though the number of inflammatory cells infiltrated into the bronchial mucosa does not change (Braun et al., 1998). This is important in asthma, since Th2 cells participate in the development of asthma symptoms. IL-4 is essential to the synthesis of IgE immunoglobulins (Snapper et al., 1988).

A recent study also shows that NGF has a key role in acute phases of allergy (Päth et al., 2002). Transgenic mice that overexpress NGF in the bronchial epithelium develop greater airway inflammation than wild-type mice after allergen sensitization and challenge, while pre-treatment with anti-NGF blocking antibodies totally inhibits this airway inflammation (Päth et al., 2002). Recent findings also reveal the role of the $p75^{NTR}$ receptor in inflammation: blocking it in vivo in mice with an anti-$p75^{NTR}$ blocking antibody and deleting it in mice ($p75^{NTR-/-}$) prevent or at least disrupt inflammation (Tokuoka et al., 2001; Kerzel et al., 2003). These results suggest that NGF plays a functional role in allergic processes and in bronchial inflammation in asthma, particularly through activation of the $p75^{NTR}$ receptor.

5.4. NGF and bronchial remodelling

Airway structural cells and inflammatory cells infiltrated into the bronchial mucosa both release chemokines and growth factors, which in turn induce airway remodelling in patients with asthma (for review, see Chiappara et al., 2001; Stewart, 2001; Wilson and Bamford, 2001): sub-epithelial fibrosis with thickening of the basement membrane (Roche et al., 1989; Wilson and Li, 1997), increased vascularisation (Carroll et al., 1997; Li and Wilson, 1997), increased sensory innervation (Ollerenshaw et al., 1991), edema (Brown et al., 1995), bronchial smooth muscle hypertrophy and hyperplasia (Ebina et al., 1993).

Various recent studies suggest that NGF plays a role in this bronchial remodelling (Fig. 3). First, NGF stimulates the contraction and migration of pulmonary fibroblasts (Micera et al., 2001; Kohyama et al., 2002), as well as their differentiation into myofibroblasts (Micera et al., 2001). It also induces the release of pro-fibrotic factors, including TGF-β (Cosgaya and Aranda, 1995) and FGF-2 (fibroblast growth factor-2) (Chevet et al., 1999), and of cytokines involved in the remodelling mechanisms, including IL-4 from eosinophils (Noga et al., 2002) and IL-13 from basophils (Sin et al., 2001).

NGF stimulates fibroblasts in corneal ulcers to repair tissue (Lambiase et al., 1998; Lambiase et al., 2000). It also stimulates fibroblast production of type I collagen (Nithya et al., 2003) and increases expression of plasminogen activator inhibitor-I (PAI-I), an inhibitor of matrix metalloprotease-9 (MMP-9) proteolytic activity (Takahashi et al., 2000). These findings suggest that NGF is involved in regulating synthesis of the extracellular matrix. Finally, bronchial biopsy sections from 2 patients with interstitial pulmonary fibrosis (Micera et al., 2001) showed intense NGF labelling, which may suggest that its expression increases in fibrosing diseases.

In addition, NGF induces proliferation of endothelial cells (Raychaudhuri et al., 2001; Cantarella et al., 2002) and of vascular smooth muscle cells (Kraemer et al., 1998), as well as migration of the latter (Donovan et al., 1995). It stimulates angiogenesis directly (Puxeddu et al., 2003) or indirectly, by stimulating release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) (Calza et al., 2001). These results suggest NGF plays a role in the increased vascularisation observed in the airways of asthma patients. Overexpression of NGF in mouse airways increases sensory innervation (Hoyle et al., 1998). NGF also induces phenotypic modification of the neurons innervating guinea pig trachea so that substance P is expressed in neurons that do not express it constitutively (Hunter et al., 2000). These modifications may include increased sensory innervation, as described in asthmatic airways (Ollerenshaw et al., 1991). Finally, NGF stimulates proliferation of the bronchial smooth muscle cells (Freund et al., 2002) and might thus be involved in the smooth muscle hypertrophy observed in asthma.

6. Conclusion

In conclusion, elevated NGF concentrations are found in the airways of persons with asthma, and they rise even higher after allergen provocation. In vitro studies confirm increased expression of NGF in inflammatory conditions, an augmentation regulated by the anti-inflammatory glucocorticoids. These data suggest that NGF plays a role in airway inflammation, hyperresponsiveness and remodelling, all observed in patients with asthma. Accordingly, it is now thought that NGF may help mediate inflammation in the airways. A better understanding of its effects and its receptors in asthma could open new pathways for research into the treatment of this disease.

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