

EDITORIAL

Do neurotrophins play a role in allergic diseases and asthma?

The article of Noga and co-workers, published in this issue of the journal [1], provides well-documented evidence that human peripheral eosinophils produce, store and release neurotrophins. The study confirms one previous observation in subjects with mild blood eosinophilia [2] and adds new information by showing that eosinophils from asthmatic subjects produce higher amounts of nerve growth factor (NGF) and lower amounts of brain-derived neurotrophic factor (BDNF) than eosinophils from healthy controls. On the basis of data presented, the authors suggest that neurotrophins may play a role in the pathogenesis of allergic inflammation and asthma.

This editorial aims at challenging this novel hypothesis addressing some reflections which might hopefully stimulate further research in this area.

Are neurotrophins important in allergic inflammation and asthma?

Some years ago Robinson and Holgate [3] extended Koch's postulates to asthma by suggesting that the following conditions have to be answered when advocating the potential role of a new mediator in asthma:

- 1 The mediator must be present in elevated amount in the serum and biological fluids of asthmatic subjects.
- 2 The mediator must be produced by inflammatory cells involved in the pathogenesis of the disease.
- 3 The putative new mediator must reproduce *in vitro* and *in vivo* the signs and symptoms of the disease.
- 4 Specific antagonism of the mediator should prove useful in reversing physiopathological changes and symptoms of asthma.

Well, all these conditions seem to have been answered by recent studies of NGF and neurotrophins. In fact, NGF and neurotrophins are increased in serum, bronchoalveolar lavage, nasal washings and tears of subjects with allergic diseases as well as over-expressed in tissues of allergic subjects. They are produced, stored and released by mast cells, eosinophils and CD4⁺/Th2 type cells. Their administration in experimental models of asthma induce bronchial hyper-reactivity and eosinophilic inflammation. Anti-NGF treatment is able to inhibit the effects of ovalbumin challenge in sensitized animals (Table 1; see also [4] for references).

Therefore, it seems quite well-documented that neurotrophins can be included among the actors of allergic inflammation. But how important are they? Do they play a relevant role in initiating and maintaining the process or are they innocent bystanders/minor contributors to it, just present on the scene as products of the mast cells, eosinophils and Th2 lymphocytes recruited at the site of allergic inflammation?

It has long been known that NGF promotes differentiation of mast cells and basophils [5, 6]. We have also recently shown that

CD34⁺ haematopoietic stem cells produce NGF and express its high affinity receptor TrkA on their membrane [7]. Moreover, the expression of NGF and both its high and low affinity (p75) receptors in several immune and inflammatory cells strongly supports the concept of an autocrine circuit potentially effective in modulating the allergic and inflammatory response [8]. Finally, the above mentioned effects of neurotrophins in experimental models reproducing the pathophysiological changes of allergic diseases and asthma, whether confirmed in humans, should be decisive for assigning to these molecules an important role among key players of allergic inflammation. However, more functional and pharmacological studies are still needed to establish the relative relevance of NGF and neurotrophins vs. other allergy and asthma mediators.

Do neurotrophins play a role in tissue remodelling?

Independently from the answer about the role of neurotrophins in initiating and sustaining allergic inflammation, the findings of Noga and co-workers [1] raise a second not less intriguing issue about the role of neurotrophins in allergic diseases and asthma.

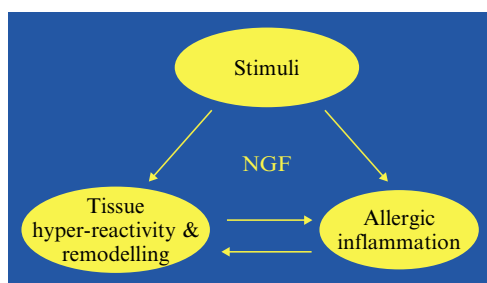
In fact, extensive evidence exists about the interactions between eosinophils and structural cells – such as epithelial cells and fibroblasts – as well as about the role of eosinophils in tissue remodelling. Do the substantial amounts of NGF and other neurotrophins which are present in the microenvironment of tissues undergoing an allergic reaction influence the structural changes associated with late-phase reactions and tissue remodelling in allergic diseases and asthma?

In vitro, NGF displays strong stimulatory effects on skin and lung fibroblasts, particularly with reference to fibroblast migration, smooth muscle actin expression and embedded-fibroblasts gel contraction [9]. Moreover, the NGF immunoreactivity is increased in biopsies from scar skin and in interstitial fibrotic lung disease [9]. Finally, *in vivo*, we had previously shown that topical administration of NGF in humans produces healing of both neurotrophic [10] and autoimmune [11], otherwise untreatable, corneal ulcers.

On the other hand, well-documented evidence also exists about the expression of NGF and NGF receptors on structural cells and particularly on lung [12], nasal [13] and conjunctival [14] epithelium, which is also a source of NGF. Therefore, it might be speculated that the effects of NGF (and possibly of other neurotrophins) do not have to necessarily descend from allergic inflammation, but that NGF and neurotrophin can act on bronchial hyper-reactivity and remodelling processes also through a direct effect on nerves and on the epithelial-mesenchymal trophic unit [15]. NGF released in response to different stimuli might in fact directly act on nerves, endothelial and epithelial cells – including mucus-producing cells – and

Table 1. Evidence for the role of NGF in allergic inflammation

NGF is increased at both systemic and local level in allergic subjects	
Blood	[16,17]
BAL	[20]
NLF	[21]
Tears	(Unpublished data)
Tissues	[22, 23]
NGF is produced by effector cells of allergic inflammation	
Mast cells	[24]
Th2 cells	[25]
Eosinophils	[26]
NGF modulates allergic inflammation	
Differentiation, chemotaxis and activation of allergic inflammatory cells	[8]
Tissue hyper-responsiveness	[17, 27–28]
Block of NGF inhibits signs and symptoms of allergic inflammation	
	[29]

**Fig. 1.** The central role of Nerve Growth Factor (NGF) in allergic inflammation, hyper-reactivity and tissue remodelling.

fibroblasts being responsible for an alternative pathway of structural and functional changes of tissues (Fig. 1).

Does the role of NGF neurotrophins extend to other Th2 mediated diseases?

In spite of the pleiotropic activity of neurotrophins, their role in human diseases is still poorly investigated.

Since mast cells, CD4⁺ Th2 type cells and eosinophils, as shown by Noga and co-workers [1], are major sources of NGF, this neurotrophin might be viewed as a Th2 cytokine. In fact, we found NGF is increased in vernal keratoconjunctivitis [16] and in other allergic diseases and asthma [17]. Accordingly, it might also be hypothesized that NGF should be increased in other Th2 diseases or in conditions where collagen activation/tissue fibrosis following mast cell/eosinophil interaction is present (such as pulmonary eosinophilia and fibrosis, scleroderma, etc.). At present, NGF has been reported to be up-regulated in sera of patients with systemic lupus erythematosus [18] and in skin of patients with scleroderma but also in some other inflammatory conditions with a Th1 cytokine profile [8]. Further studies about the relationships between different cytokine profiles (Th1, Th2, regulatory Tc Type) and neurotrophins might better elucidate the inflammatory/anti-inflammatory role of these molecules and the complex relationships between inflammation and neurotrophins.

In conclusion, the study of Noga and co-workers [1] adds another interesting contribution to the expanding field of neurotrophins in human diseases. I do hope that these reflections will stimulate further research in this exciting area of investigation.

References

- 1 Noga O, Englmann C, Hauf G, Grützkau A, Seybold J, Kunkel G. The production, storage, and release of the neurotrophins NGF, BDNF and NT-3 by human peripheral eosinophils in allergics and non-allergics. *Clin Exp Allergy* 2003; 33:648–53.
- 2 Solomon A, Aloe L, Pe'er J, Frucht-Pery J, Bonini S, Bonini S, Levi-Schaffer F. Nerve growth factor is preformed in and activates blood eosinophils. *J Allergy Clin Immunol* 1998; 102:454–60.
- 3 Robinson C, Holgate ST. The role of leukotrienes in asthma: evidence from clinical investigations. *Adv Prostaglandin Res* 1990; 20:209.
- 4 Bonini S, Lambiase A, Bracci-Laudiero ML et al. Nerve growth factor and asthma. *Allergy* 2002; 57:13–5.
- 5 Tsuda T, Wang D, Dolovich J, Bienenstock J, Marshall J, Denburg JA. Synergistic effects of nerve growth factor and granulocyte-macrophage colony-stimulating factor on human basophilic cell differentiation. *Blood* 1991; 77:971–9.
- 6 Aloe L, Levi Montalcini R. Mast cells increase in tissue of neonatal rats injected with the nerve growth factor. *Brain Res* 1977; 133:358–66.
- 7 Bracci-Laudiero ML, Celestino D, Starace G et al. CD34⁺ progenitors in human cord blood express nerve growth factor and its affinity TrkA receptor. *J Neuroimmunol* 2003; 136:130–9.
- 8 Aloe L. The role of nerve growth factor: from neurotrophic activity to immunologic diseases. *Allergy* 1997; 52:885–94.
- 9 Micera A, Vigneti E, Pappo O et al. Nerve growth factor displays stimulatory effects on human skin and lung fibroblasts demonstrating a direct role for this factor in tissue repair. *Proc Natl Acad Sci USA* 2001; 98:6162–7.
- 10 Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998; 338:1174.
- 11 Lambiase A, Bonini S, Aloe L, Rama P, Bonini S. Anti-inflammatory and healing properties of nerve growth factor in immune corneal ulcers with stromal melting. *Arch Ophthalmol* 2000; 118:1446–9.

- 12 Hglund O, de Blay F, Oster JP et al. Nerve growth factor levels and localisation in human asthmatic bronchi. *Eur Respir J* 2002; 20:1110–6.
- 13 Sanico AM, Stanis AM, Gleeson TD et al. Nerve growth factor expression and release in allergic inflammatory disease of the upper airways. *Am J Respir Crit Care Med* 2000; 161:1631–5.
- 14 Lambiasi A, Bonini S, Micera A, Rama P, Bonini S, Aloe L. Expression of NGF receptors on ocular surface in healthy subjects and during inflammatory diseases. *Invest Ophthalmol Vis Sci* 1998; 39:1272–5.
- 15 Holgate ST. Epithelial damage and response. *Clin Exp Allergy* 2000; 30:37–41.
- 16 Lambiasi A, Bonini St, Bonini Se et al. Increased plasma levels of nerve growth factor in vernal keratoconjunctivitis and relationships to conjunctival mast cells. *Invest Ophthalmol Vis Sci* 1995; 36:2127.
- 17 Bonini Se, Lambiasi A, Bonini St et al. Circulating nerve growth factor levels are increased in humans with allergic diseases and asthma. *Proc Natl Acad Sci USA* 1996; 93:10955.
- 18 Bracci-Laudiero L, Aloe L, Levi Montalcini R et al. Increased level of nerve growth in sera of systemic lupus erythematosus patients. *Neuro Report* 1993; 4:563–5.
- 19 Tuberi MA, Passiu G, Mathieu A, Aloe L. Nerve growth factor and mast cell distribution in the skin of patients with systemic sclerosis. *Clin Exp Rheumatol* 1993; 11:319–22.
- 20 Udem BJ, Hunter DD, Liu M et al. Allergen-induced sensory neuroplasticity in airways. *Int Arch Allergy Immunol* 1999; 118:150–3.
- 21 Sanico AM, Stanis AM, Gleeson TD et al. Nerve growth factor expression and release in allergic inflammatory disease of the upper airways. *Am J Respir Crit Care Med* 2000; 161:1631–5.
- 22 Bresciani M, Laliberté MF, Nicol S, Bonini S, Bousquet J, Laliberté F. Cellular localization of nerve growth factor in perennial rhinitis. *Allergy* 2000; 55(S63):70.
- 23 Kassel O, de Blay F, Duvernelle C et al. Local increase in the number of mast cells and expression of nerve growth factor in the bronchus of asthmatic patients after repeated inhalation of allergen at low-dose. *Clin Exp Allergy* 2001; 31:1432–40.
- 24 Leon A, Buriani A, Dal Toso R et al. Mast cells synthesize, store, and release nerve growth factor. *Proc Natl Acad Sci USA* 1994; 91:3739–43.
- 25 Lambiasi A, Bracci-Laudiero L, Bonini S et al. Human CD4⁺ T cell clones produce and release nerve growth factor and express high-affinity nerve growth factor receptors. *J Allergy Clin Immunol* 1997; 100:408–14.
- 26 Solomon A, Aloe L, Pe'er J et al. Nerve growth factor is preformed in and activates human peripheral blood eosinophils. *J Allergy Clin Immunol* 1998; 102:454–60.
- 27 de Vries A, Dessing MC, Engels F, Henricks PA, Nijkamp FP. Nerve growth factor induces a neurokinin-1 receptor-mediated airway hyperresponsiveness in guinea pigs. *Am J Respir Crit Care Med* 1999; 159:1541–4.
- 28 Sanico AM, Koliatsos VE, Stanis AM, Bienenstock J, Togias A. Neural hyperresponsiveness and nerve growth factor in allergic rhinitis. *Int Arch Allergy Immunol* 1999; 118:154–8.
- 29 Braun A, Appel E, Baruch R et al. Role of nerve growth factor in a mouse model of allergic airway inflammation and asthma. *Eur J Immunol* 1998; 28:3240–51.

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