Neuro–immune interaction in allergic asthma: role of neurotrophins

C. Nassenstein*1, J. Kutschker*, D. Tumes† and A. Braun*

*Immunology and Allergology, Fraunhofer Institute of Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, Hannover, Germany, and †School of Molecular and Biomedical Science, University of Adelaide, Adelaide, Australia

Abstract
The nature of persistent airway hyperreactivity and chronic inflammation in asthma remains unclear. It has been suggested that bi-directional neuro–immune interaction plays an important role in the pathogenesis of this disease, leading to enhanced airway narrowing after contact with unspecific stimuli, as well as infiltration, activation and degranulation of several immune cell subtypes. Important mediators in neuro–immune cross-talk are neurotrophins, which are produced by cells at the site of inflammation. In addition to modulating the function of several leucocyte subsets, they play an important role in the synthesis of neuropeptides by sensory nerve cells. Neuropeptides have been shown to cause smooth-muscle contraction and, in addition, modulate the production of pro-inflammatory molecules by leucocytes. The aim of the present review is to provide an overview of the molecular mechanisms by which neurotrophins and neuropeptides are involved in neuro–immune cross-talk in allergic asthma.

Airway inflammation and airway hyperreactivity

Allergic asthma is characterized by recurrent and reversible episodes of broncho-obstruction, airway inflammation and an increased disposition to airway constriction (airway hyperreactivity) in response to various unspecific stimuli including smoke, ozone and cold air. The underlying pathophysiological mechanisms by which airway hyperreactivity is initiated and becomes an allergen-independent and persistent entity of asthma are not fully understood. Recent reports indicate that airway hyperreactivity is due to various changes in the morphology and function of structural cells within the lung and that allergic airway inflammation may play an important role in this context [1]. Thus it was hypothesized that inflammatory mediators, including cytokines, chemokines and growth factors, contribute to the pathogenesis of airway hyperreactivity by affecting bronchial smooth-muscle cells and bronchial glands. These structures are under close control of the pulmonary autonomic nervous system, which predominantly consists of the NANC (non-adrenergic non-cholinergic) and the cholinergic nerves. Recent studies indicate that allergen exposure leads to sensory neuroplasticity in the airways, which may contribute to airway hyperreactivity [1a]. Sensory neuroplasticity is associated with changes in neuronal excitability and is characterized by an enhanced synthesis of neuropeptides in nodose primary afferent neurons, which is at least partly due to an increased number of tachykinin-immunoreactive nodose ganglion neurons projecting into the airways [2]. The rapid release of neuropeptides from peripheral nerve endings is thought to contribute not only to airway smooth-muscle contraction, but also to the modulation of allergic airway inflammation by direct interaction with immune cells (neurogenic inflammation) (reviewed by Barnes [3]).

Since inflammation enhances both sensory nerve excitability and production of tachykinins, which in turn modulate airway inflammation, neuro–immune cross-talk may be an important phenomenon in asthma. Herein, we review the molecular mechanisms of neuro–immune cross-talk and its role in airway hyperreactivity.

Neuro–immune interaction

Spatial relationship of nerves and immune cells
Communication between nerves and immune cells requires either co-localization of immune cells and nerves, including membrane-to-membrane contacts, and/or the release of soluble mediators coupled with expression of the appropriate receptors by target cells.

Spatial association of immune cells and nerves has been shown in various tissues, including the lung. Pulmonary sensory nerves, which can be found in and around the bronchi, bronchioles and occasionally in alveoli [4], form a dense network surrounding the epithelium, goblet cells and arterioles [5]. Sensory nerve fibres often form close contacts with mast cells, cells of the macrophage/monocyte cell lineage and lymphoid cells [6].

These findings raise two important questions: (i) which mediators are involved in bi-directional cross-talk of nerves and immune cells and (ii) what relevance does neuro–immune interaction have for the pathogenesis of allergic asthma?
Neuro–immune interaction in allergic asthma

Neurotrophins are released by different immune cell subtypes (a). Owing to their function as autocrine and paracrine survival factors, they increase airway inflammation (b) and also sensitize sensory nerve fibres and increase neuropeptide production (c). Neuropeptides are released upon contact with irritants (d) and can modulate the allergic inflammatory response (neurogenic inflammation) (e). In addition, neuropeptides cause airway smooth-muscle contraction, vasodilatation and hypersecretion, leading to broncho-obstruction.

**Figure 1** | Neuro-immune interaction in allergic asthma

Neurotrophins are released by different immune cell subtypes (a). Owing to their function as autocrine and paracrine survival factors, they increase airway inflammation (b) and also sensitize sensory nerve fibres and increase neuropeptide production (c). Neuropeptides are released upon contact with irritants (d) and can modulate the allergic inflammatory response (neurogenic inflammation) (e). In addition, neuropeptides cause airway smooth-muscle contraction, vasodilatation and hypersecretion, leading to broncho-obstruction.

**Functional relationship of nerves and immune cells**

Growing evidence suggests that neurotrophins and neuropeptides, which can be found in elevated concentrations after allergen provocation in bronchoalveolar lavage fluid [7–10], are important candidates of neuro–immune cross-talk.

Neurotrophins, such as NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), NT-3 (neurotrophin–3) and NT-4, are synthesized by ciliated bronchial epithelium, bronchial smooth-muscle cells, neurons, satellite cells of intrapulmonary ganglia, blood vessels, fibroblasts and different leucocyte subtypes including macrophages, T-cells and eosinophils. Several pro-inflammatory mediators, including neuropeptides such as SP (substance P) and NKA (neurokinin A) modulate neurotrophin synthesis in immune cells (reviewed in [11]).

Neurotrophins exert a dual role in asthma pathogenesis (Figure 1). They promote airway inflammation by interaction with different immune cell subtypes and contribute to an altered neuronal control of the airways. In the immune system, neurotrophins act like cytokines and increase survival and activation of eosinophils, induce differentiation in B-lymphocytes, augment cytokine synthesis in T-cells and increase proliferation, differentiation and production of various mediators in mast cells. In the nervous system, neurotrophins are known to enhance the number of tachykinin-producing nerve fibres surrounding the airways, to sensitize afferent C-fibres to various irritants and regulate neuropeptide synthesis of sensory neurons (reviewed in [11]).

Although the underlying molecular mechanisms by which neurotrophins sensitize pulmonary sensory nerves remain unclear, the modulation of response to TRPV1 (transient receptor potential vanilloid 1) ligands may be involved. TRPV1 is selectively expressed in afferent C-fibres and can be activated by endogenous ligands such as bradykinin, anandamide and lipoxygenase (reviewed in [12]) and exogenous ligands including noxious heat and capsaicin. Local application of TRPV1 agonists causes cough and bronchoconstriction, as well as microvascular leakage and hypersecretion within the airways (reviewed in [13]). Interestingly, patients with asthma are more sensitive to the tussive effect of TRPV1 agonists [13]. Similar changes are observed in a murine model of allergic asthma. Capsaicin aerosol challenge results in a prolongation of centrally mediated nerve reflexes and these reflexes lead to changes in the breathing pattern that can be used as an indicator of sensory nerve hyperreactivity [14,15]. Since local application of antibodies to NGF or BDNF reduces sensory nerve hyperreactivity in vivo [14,15], it is suggested that neurotrophin-induced sensitization of TRPV1 may play a relevant role in the pathogenesis of allergic airway diseases.

The biological activities of neurotrophins are mediated by the low-affinity pan-neurotrophin receptor p75NTR and the tyrosine kinases TrkA (tropomyosin receptor kinase A), TrkB and TrkC, which are characterized by high affinity as well as high specificity. NGF binds to TrkA, BDNF and NT-4 to TrkB, and NT-3 to TrkC.

Expression of both p75NTR and Trk receptors has been shown in nerve fibres within the airways [16,17], and initial studies indicate that both might be involved in the sensitization of nerve fibres. Second messengers of the Trk cascade are activated in response to NGF-induced rapid sensitization of sensory neurons to thermal stimuli [18]. In previous studies, neutralization of Trk receptors in guinea-pig tracheal smooth-muscle cells inhibited the direct allergen-induced tracheal contraction and decreased hyperreactivity to histamine [19], indicating that neurotrophin-mediated signalling via Trk receptors may also play a prominent role in the pathogenesis of allergic asthma. Interestingly, disruption of p75NTR-mediated signals alone also inhibited sensory nerve hyperreactivity [17]. We therefore speculate that Trk receptors and p75NTR may form complexes that contribute to the high-affinity binding of neurotrophins [20].

Activation of sensitized neurons can lead to broncho-obstruction both by the central reflex pathway facilitating efferent parasympathetic nerve activity and by local axon reflexes characterized by release of tachykinins including the pro-inflammatory SP and NKA from sensory endings [21].

Tachykinin receptors have been divided into three subclasses, NK-1 (neurokinin-1), NK-2 and NK-3. Although naturally occurring neuropeptides can act as an agonist to all three receptors, NK-1 is preferentially activated by SP, NK-2 by NKA and NK-3 by NKB respectively (reviewed in [22]). The expression pattern of these receptors suggests pleiotropic effects of neuropeptides, with neurokinin receptors expressed in submucosal glands, airway epithelial cells, airway smooth-muscle cells and diverse immune cells (reviewed in [22]).

Release of neuropeptides causes airway smooth-muscle contraction and modulates immune cell functions, which then
leads to neurogenic inflammation [3]. A variety of studies have revealed the involvement of neurogenic inflammation in the pathophysiology of inflammatory diseases, including allergic asthma [3,22]. Neuropeptides promote chemotaxis, activation and degranulation of eosinophils, increase lymphocyte proliferation, chemotaxis and adhesion, and inhibit Th1 cytokine synthesis. Additionally, neuropeptides promote the release of histamine, leukotriene C4, interleukin-6, prostaglandin D2 and tumour necrosis factor α by mast cells [22]. Since neuropeptides also modulate neurotrophin synthesis in immune cells [23], it has been suggested that a type of positive feedback mechanism originates, which might explain long-lasting changes in the airways of patients with asthma.

The in vitro relevance of neurogenic inflammation, however, is still controversial, with some reports indicating conflicting data.

Depletion of sensory nerves in a rat model of allergic airway inflammation did not affect the number of inflammatory cells in peripheral blood, the number of eosinophils in lung tissue, or the distribution of eosinophils in the adventitial tissue of blood vessels [24]. Conversely, neurotrophin-mediated airway inflammation in a murine model of allergic asthma was partly reduced by application of a dual NK-1/NK-2 receptor antagonist [25]. Studies in patients with allergic disorders also show conflicting results. Although local nasal application of capsaicin in patients suffering from allergic rhinitis caused leucocyte influx, albumin leakage and glandular secretion [26], initial clinical studies using strategies to block neurogenic inflammation have not been encouraging [3]. The lack of efficacy may however be explained by the low potency or defective pharmacokinetics of the compounds tested to date [22].

**Conclusion**

Neuro–immune cross-talk is one mechanism that may explain long-lasting airway inflammation and the persistent airway hyperreactivity in patients with allergic asthma. Neurotrophins and neuropeptides, which both exert pleiotropic activities, seem to be the key players in neuro–immune interaction. Despite promising in vitro and in vivo evidence indicating that neurogenic inflammation may be a candidate for the effective design of therapies against allergic disorders, the clinical implications have yet to be fully determined and should be the subject of future investigation.

---

**References**


Received 7 April 2006

©2006 Biochemical Society