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Review

The role of neurotrophins in bronchial asthma

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Abstract

Allergic bronchial asthma is characterized by chronic inflammation of the airways, development of airway hyperreactivity and recurrent reversible airway obstruction. Target and effector cells responsible for airway hyperresponsiveness and airway obstruction include sensory and motor neurons as well as epithelial and smooth muscle cells. Although it is well established that the inflammatory process is controlled by T-helper (Th) 2 cells and the Th2-derived cytokines interleukin-4, airway hyperresponsiveness-5 and interleukin-13, the mechanisms by which immune cells interact with neurons, epithelial cells or smooth muscle cells still remain uncertain. Since there is growing evidence for extensive communication between neurons and immune cells, the mechanisms of this neuro-immune crosstalk in lung and airways of asthmatic patients are recently becoming the focus of asthma research. Neurotrophins represent candidate molecules regulating and controlling this crosstalk between the immune and peripheral nervous system. They are constitutively expressed by resident lung cells and produced in increasing concentrations by immune cells invading the airways under pathological conditions. They modify the functional activity of sensory and motor neurons, leading to enhanced and altered neuropeptide and tachykinin production. These effects are defined as "neuronal plasticity". The consequences are the development of "neurogenic inflammation" due to neuropeptide and tachykinin activities.

Keywords: Neurotrophin; Bronchial asthma; NGF (nerve growth factor)

1. Airway inflammation in bronchial asthma

Bronchial asthma is characterized by chronic airway inflammation, development of airway hyperreactivity and subsequently of airway remodelling. In allergic bronchial asthma, recurrent and reversible airway obstruction is induced by allergen inhalation (MacLean et al., 1988). In the late 1980s and early 1990s, the concept has been developed that Th-2 T cells orchestrate many aspects of pathologic immune responses including effector functions of the B cells, mast cells and eosinophils. Th-2 cells produce an array of cytokines including interleukin-4, interleukin-5, interleukin-9, and interleukin-13. In B cells, interleukin-4 and interleukin-13 are involved in isotype switching towards IgE (immunoglobulin E), while interleukin-5 processes pro-inflammatory properties including development, differentiation, recruitment and survival of eosinophils. The importance of T cells and T-cell-driven processes in these diseases is further underlined by the effectiveness of anti-inflammatory therapies including corticosteroids and others (Joos et al., 1997).

2. Airway hyperreactivity

Although the currently available anti-inflammatory drugs are effective in reducing symptoms and improving quality of life, they are not followed by complete disappearance of symptoms (Ichinose et al., 1990). This observation suggests that, in addition to the immunological dysregulation in allergy and asthma, other aspects need to be considered in the pathology of this complex disease. In this regard, airway hyperreactivity, for example, represents an important hallmark in the pathogenesis of the disease. Non-specific bronchial hyperresponsiveness may be defined as an increase in the ease and degree of airway narrowing in response to a wide range of bronchoconstrictor stimuli (Larsen et al., 1994). The development of airway hyperresponsiveness is mediated by multiple independent and additive pathways working in concert. The airway changes leading to airway narrowing mainly include (a) altered neuronal regulation of airway tone, and (b) increases in muscle content or function (Larsen et al., 1994; Iwamoto et al., 1993). Therefore, the mode of measuring airway hyperresponsiveness is critical for identifying the underlying mechanisms. Dependent on the method chosen for airway hyperresponsiveness measure-

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ment, different pathways can be distinguished. It has been previously shown that in vitro electrical field stimulation of tracheal smooth muscle segments reflects specific neuronal airway dysfunction since the addition of both atropin (dysruption of cholinergic pathways) and capsaicin (neuropeptide depletion sensoring neurons) completely blocks any reaction of the airway to electrical field stimulation (Wong and Koh, 2000; Virchow et al., 1995). Metacholine directly acts via muscarinic M_3 receptors on smooth muscle cells. Histamine stimulates histamine H receptors expressed on smooth muscle cells, sensory and motor neurons. Serotonin is an agonist of 5-HT receptors expressed on sensory and motor neurons (Undem et al., 1993; Weinreich et al., 1997). Many of these pharmacological stimuli have been used to assess the presence of airway hyperresponsiveness in patients with bronchial asthma. The complexity of the pathogenic mechanisms underlying airway hyperresponsiveness is further emphasized by the fact that these and other pharmacological stimuli act on various neuronal and non-neuronal cell populations present in the airways.

3. Innervation of the lung

The human airways are innervated via efferent and afferent autonomic nerves regulating many aspects of airway function, including airway smooth muscle tone, mucus secretion, bronchial micro-circulation, microvascular permeability as well as recruitment and subsequent activation of inflammatory cells (van der Velden and Hulsmann, 1999a). Innervation of the lung can be functionally divided into cholinergic, adrenergic and non-adrenergic non-cholinergic (NANC) pathways, which are not strictly anatomically separated. At least certain NANC effects are mediated by the release of neuropeptides from classical cholinergic or adrenergic nerves (van der Velden and Hulsmann, 1999a). The NANC system has been subdivided into the e-NANC and i-NANC system. The e-NANC system exhibits excitatory, bronchoconstrictory, C-fiber-mediated and tachykinin-dependent functions. In contrast, the i-NANC system is an bronchodilatory pathway located within parasympathetic nerves, mediating its effects mainly by nitric oxide (NO) and vasoactive intestinal peptide (VIP) (van der Velden and Hulsmann, 1999a).

4. The concept of "neurogenic inflammation"

Growing evidence indicates neuronal dysregulation on several levels in bronchial asthma (Sanico et al., 2000). Cholinergic nerves represent the dominant broncho-constrictory pathway, which shows increased activity in this disease. Possible underlying mechanisms include enhanced cholinergic reflex activity, increased acetylcholin release, enhanced sensitivity of smooth muscle to acetylcholin or increased sensitivity of muscarinic receptors on airway smooth muscle cells. It has been also shown that sensory nerves are able to modulate cholinergic functions. Cholinergic activities were shown to be increased by tachykinins (Fischer et al., 1996; Laurenzi et al., 1998). In animal models of hyperreactivity and asthma, increased release of acethylcholin has been demonstrated (Kannan et al., 1993).

The sympathetic nervous system is less prominent than the para-sympathetic nervous system within human airways. Compared to other species, there is a lack of sympathetic innervation of the human airways smooth muscle (Wilder et al., 1999; Lundberg et al., 1984; Bonini et al., 1999). The main neurotransmitters of this system are noradrenalin and neuropeptide Y.

The e-NANC system exhibits a high degree of plasticity in inflammatory conditions. Substance P and neurokinin A are closely related members of the neuropeptide family termed tachykinins. They are preferentially released by sensory C-fibres. They are synthesized preferentially in cell bodies of the sensory ganglia by a complex biosynthetic pathway. These neuropeptides are then transferred via axonal transport not only to pre-synaptic axon endings in the spinal cord and the nucleus of the solitary tract, but also to peripheral sensory nerve endings (Weinreich et al., 1995). Upon stimulation by mechanical, thermal, chemical or inflammatory conditions, tachykinins are released from nerve cells through a local (axon) reflex mechanism (Kay, 1996). Tachykinins act in a dual fashion as afferent neurotransmitters to the central nervous system as well as efferent neurosecretory mediators diffusion into the peripheral tissue. Increased levels of substance P have been detected in the airways of asthmatic patients (Herz et al., 1998) and allergen challenge increased neurokinin A levels in bronchoalveolar-lavage fluids of asthmatic patients (Dmitrieva et al., 1997). There is evidence for an increase in both the number and length of substance P immuno-reactive nerve fibres in airways from bronchial asthma patients as compared to airways from healthy subjects (Perretti and Manzini, 1993). Reasons for increased levels of substance P and neurokinin A in lung and airways of asthmatic patients may be related either to enhanced production and release of these neuropeptides or to impaired degradation of tachykinins. Tachykinins are degraded and inactivated by neutral endopeptidase, a membrane-bound metalopeptidase located mainly in the surface of airway epithelial cells and also present in airway smooth muscle cells, submucosal glands and fibroblasts. Allergen exposure, inhalation of cigarette smoke and other respiratory irritants have been associated with a reduced neutral endopeptidase activity, thus enhancing the effects of tachykinins within the airways (van der Velden and Hulsmann, 1999b; Fujino et al., 1997; Kaltreider et al., 1997; van Hagen et al., 1994).

A substantial amount of studies provide evidence that neuropeptides and neuromediators released from the nerve endings of the para-sympathetic, sympathetic and sensory system directly influence immune cells and, thus, partici-

pate in airway inflammation. A few examples illustrate this important capacity of neuropeptides and neurotransmitters.

Acetylcholin, the major neurotransmitter of para-sympathetic nerves, augments anti-CD3 induced mRNA expression of interleukin-2 and interleukin-2 receptors as well as T-cell proliferation (Ek et al., 1998). In this regard, acetylcholin acts via functional muscarinic receptors M1 and M2. Macrophages express the muscarinic M_3 receptor and subsequent stimulation with acetylcholin triggers the release of chemotactic substances by alveolar macrophages (Nagata et al., 1995).

The tachykinin family binds to the free tachykinin NK-1, NK-2 and NK-3 receptors, although with different affinities. NK-1 shows higher affinity for substance P, NK-2 for neurokinin A, and NK-3 for neurokinin B, respectively (Barnes, 1996).

In the airways, tachykinin NK-1 receptors are primarily responsible for mediating the inflammatory effects of tachykinins, while tachykinin NK-2 receptors represent the main mediators of bronchoconstriction (Joos et al., 1987). This is in line with tachykinin NK-1 receptor expression on immune cells such as B cells, T cells (Braun et al., 1999b), monocytes, macrophages (Ho et al., 1997), eosinophils and neutrophils (Iwamoto et al., 1993). Like VIP receptor, tachykinin NK-1 receptor expression by lung-infiltrating leukocytes in systemically and subsequently intratracheally allergen-challenged mice is strongly elevated (Kaltreider et al., 1997). Since substance P binds to tachykinin NK-1 receptors with the highest affinity, it is the predominant mediator of immunomodulatory effects among tachykinins. The activities of substance P on immune cells include a broad range of functional responses from neutrophils, eosinophils, mast cells, monocytes/macrophages and lymphocytes (reviewed in van der Velden and Hulsmann, 1999a). Substance P stimulates a number of neutrophil functions, including chemotaxis, superoxide production and adherence to epithelium and endothelium. Most of these effects require high concentrations of substance P whereas at low doses, substance P primes the response to other stimuli that otherwise would be ineffective. Substance P has a degranulating effect on eosinophils and induces human eosinophil migration in vitro. In an in vivo study with allergic rhinitis patients, it was shown that substance P administered after repeated allergen challenge enhanced the recruitment of eosinophils. It has been demonstrated that substance P can cause histamine release from human lung mast cells (Heaney et al., 1995). This is underlined by an in vitro model using trachea from the substance P-hyperresponsive Fisher 344 rat, in which substance P stimulation of mast cells represented a major factor leading to bronchoconstriction (Joos et al., 1997). Moreover, substance P activates monocytes to release inflammatory cytokines, including TNF-α (tumor-necrosis-factor α), interleukin-1, interleukin-6 and interleukin-10. In lymphocytes, substance P inhibits glucocorticoid-induced thymocyte apoptosis (Dimri et al., 2000), stimulates

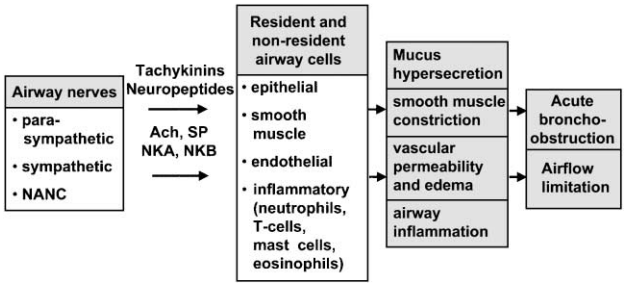

Fig. 1. The concept of neurogenic inflammation. Upon stimulation, airway nerves produce a variety of tachykinins and neuropeptides. Receptors for acetylcholin, substance P, neurokinin A and B are expressed on a variety of resident and non-resident airway cells. Pathophysiological consequences of enhanced neurotransmitter secretion are increased vascular permeability and formation of edema, smooth muscle constriction, mucus hypersecretion and airway inflammation. Subsequently, these effects result in acute broncho obstruction and airflow limitation.

proliferation, cytokine production, chemotaxis (van der Velden and Hulsmann, 1999a) and a Th1/Th2 phenotype switch in T cells (Levite, 1998; Levite et al., 1998) and induces differentiation and immunoglobulin switching in B cells (Braun et al., 1999b).

Functional consequences of neuropeptide and neurotransmitter activities in bronchial asthma include mucus hypersecretion, recruitment of inflammatory cells via upregulation of endothelial adhesion molecules, plasma extravasation and formation of edema via enhanced vascular permeability; activation of endothelial cells and smooth muscle bronchoconstriction are also immediate consequences of neurotransmitter and neuropeptide activity. The enhanced activity of neuropeptides and neurotransmitters followed by their functional effects on epithelial cells, airway smooth muscle cells and inflammatory cells resulted in the concept of "neurogenic inflammation" (Fig. 1). One important question which has been left unanswered so far is related to the mechanism of increased neuronal activity in bronchial asthma.

5. The putative role of neurotrophins in the pathogenesis of bronchial asthma

Some of the most effective mediators involved in inflammatory hyperalgesia are the neurotrophins nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF) (Donnerer et al., 1992; Dmitrieva et al., 1997; Mannion et al., 1999). NGF is a mediator with functions on both immune and nerve cells (Levi-Montalcini et al., 1996). It is a well-studied example of a target-derived neurotrophic factor that is essential for development, differentiation, maintenance and survival of peripheral sympathetic and neural crest-derived sensory nerve cells (Levi-Montalcini et al., 1995). NGF upregulates expression of neuropeptides in sensory neurons (Lindsay and Harmar, 1989) and contributes to inflammatory sensory hypersensitivity (Donnerer et al., 1992). In the central nervous sys-

tem, NGF is a trophic factor for basal forebrain cholinergic neurons. The biological effects of neurotrophins are mediated by binding either to the specific high affinity (K_d 10^{-11}) glycoprotein receptors trkA (for NGF), trkB (for BDNF) and trkC (for NT-3) or the low affinity (K_d 10^{-9}) pan-neurotrophin receptor p75 (NTR). Neurotrophin receptors are widely expressed in the peripheral and the central nervous system as well as on cells of the immune system (Lewin and Barde, 1996).

6. Sources of neurotrophins in allergic disease

Based on their expression profile, neurotrophins are excellent candidates for mediating immune–nerve cell interactions. During the inflammatory processes, NGF is produced by a wide range of immune cells including mast cells, macrophages, T cells and B cells (for review, Braun, 2000). Analysis of a murine model of allergic airway inflammation revealed that T cells, B cells and macrophages represent sources of enhanced NGF production (Fig. 2). In vitro, allergen stimulation of mononuclear cells from sensitized mice resulted in enhanced NGF synthesis (Braun et al., 1998). In addition, NGF production was enhanced by antigen stimulation in murine and human Th2 cell clones (Lambiase et al., 1997; Otten et al., 1994; Otten and Gadient, 1995). BDNF synthesis has been detected in activated human T cells, B cells, macrophages, mast cells and in platelets (Kerschensteiner et al., 1999; Braun et al., 1999a; Radka et al., 1996). In addition to a constitutive production of BDNF by respiratory epithelial cells, we have demonstrated that activated murine macrophages and T cells, but not B cells, produce BDNF in allergic rhinitis and mild allergic asthma (Sanico et al., 2000; Virchow et al., 1998). Histological analysis of the inflamed lung revealed strong NGF and BDNF production by cells within the peribronchial inflammatory infiltrate (Braun et al., 1998, 1999a).

As of recently, there is also evidence for enhanced neurotrophin production in allergic patients. Patients with allergic bronchial asthma display increased levels of NGF in serum and broncho-alveolar lavage (Undem et al., 1999; Bonini et al., 1996, 1999). Increased neurotrophin production in response to allergen provocation was demonstrated in airways of subjects neurotrophin content in broncho-alveolar lavage increased markedly in allergen exposed lung segments as opposed to in saline exposed control segments. Notably, this upregulation was seen during the allergic late phase response but not in the early phase (Virchow et al., 1998).

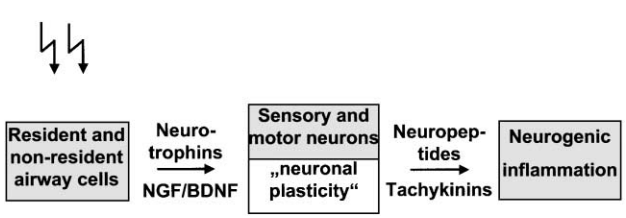

Fig. 2. Neurotrophins act as mediators of neurogenic inflammation. Resident and non-resident airway cells secret neurotrophins upon activation. Receptors for NGF and/or BDNF are expressed on sensory and motor neurons of the airways. In these cells, neurotrophins modify the level and degree of activity in a qualitative and/or quantitative fashion. As a consequence, neurotrophins control the level and pattern of neuropeptide and tachykinin release.

7. Neuronal plasticity and airway hyperresponsiveness in response to neurotrophins

Neuronal plasticity in the peripheral nervous system is as of yet not well characterized. To some extent inflammation-induced hyperalgesia shows remarkable similarities to airway hyperresponsiveness, particularly with respect to the effects of neurotrophins. Hyperalgesia can be defined by a decrease in the threshold for painful stimuli and heightened reflex pathways in sensory neurons (Carr et al., 2001). It is well established that neurotrophins play a central role in inflammation-induced hyperalgesia (Woolf et al., 1997; Safieh-Garabedian et al., 1995).

There is some evidence suggesting that sensory neurons innervating the lung are also responsive to neurotrophins since local increase of neurotrophins in the lung could mediate similar neuronal changes in animal models as seen during allergic inflammation (Undem et al., 1999; Hunter et al., 2000) (Fig. 1). It has been well established that visceral sensory neurons localized in the nodose and dorsal root ganglia require neurotrophins for survival during development (Snider, 1994). In adults, functional properties of neurons are also affected by neurotrophins (Chalazonitis et al., 1987). NGF was shown to upregulate neuropeptide production in sensory neurons and to contribute to inflammatory hypersensitivity (Donnerer et al., 1992). Though cultured nodose ganglion neurons do not require NGF for survival, their substance P production is regulated by NGF (MacLean et al., 1988). In transgenic mice overexpressing NGF in airway restricted Clara-cells, a marked sensory and sympathetic hyperinnervation and increased neuropeptide content was observed in projecting sensory neurons (Hoyle et al., 1998). In addition, these mice demonstrated airway hyperresponsiveness in response to capsaicin. In a guinea pig model, tracheal injection of NGF induced substance P production in mechanically sensitive "Aδ" fibres that do not produce substance P under physiological conditions (Hunter et al., 2000). These NGF-mediated effects are comparable to neuronal changes observed during allergic inflammation (Undem et al., 1999). The induction of neuropeptides in mechanically sensitive neurons may lead to exaggerated reflex responses to innocuous stimuli (Hunter et al., 2000). In a murine model of allergic airway inflammation, we were able to demonstrate that blocking of NGF by local treatment with anti-NGF antibodies prevented the

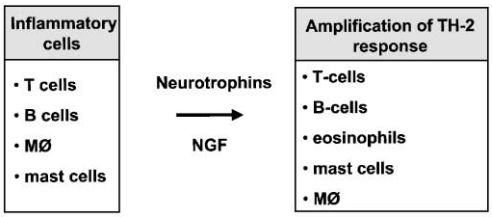

Fig. 3. NGF amplifies Th-2 mediated allergic inflammation—immunological plasticity. NFG is produced by resident and non-resident cells in the airways, including inflammatory cells (T cells, B cells, macrophages, mast cells). Inflammatory cells present in the airways during the allergic inflammation express functional NGF receptors. Stimulation of these cells with NGF results in the amplification of the locally upregulated Th-2 response.

development of airway hyperresponsiveness (Braun et al., 1998). Therefore, it is not surprising that NGF treatment induces airway hyperresponsiveness in the guinea pig. Along this line, de Vries et al. could block NGF induced airway hyperresponsiveness to histamine with the specific tachykinin NK-1 receptor antagonist SR 140333, thus pointing again to the central role played by tachykinins in this condition (de Vries et al., 1999). Taken together, these data provide further evidence that neurotrophins are central signaling molecules in immune–nerve cell communication as it occurs in pathophysiological conditions including bronchial asthma (Braun et al., 2000) (Fig. 2).

8. Immunological plasticity in response to neurotrophins

In addition to the effects of neurotrophins on neuronal plasticity, there is growing evidence as well for a sustained action of neurotrophins on immune cells involved in allergic inflammation, including mast cells, eosinophils, B cells and T cells. One of the first reports demonstrating that neurotrophins can modulate immune cell activities came from Aloe et al. After injection of NGF into neonatal rats, they observed an increased number of mast cells in these animals (Aloe and Levi-Montalcini, 1977). Further studies characterized NGF as an important growth and differentiation factor for mast cells and basophils (Burgi et al., 1996; Kannan et al., 1993; Matsuda et al., 1991; Tam et al., 1997). Since NGF is the best characterized neurotrophin, most of the available data pertains to it. NGF stimulates rapid degranulation of mast cells and basophils (Horigome et al., 1993, 1994; Bischoff and Dahinden, 1992), promotes differentiation, activation and cytokine production of mast cells, granulocytes and macrophages (Kannan et al., 1993; Matsuda et al., 1991; Susaki et al., 1996; Welker et al., 1998), activates eosinophils (Hamada et al., 1996), promotes proliferation of B- and T-cell subsets (Otten et al., 1989; Thorpe and Perez-Polo, 1987), enhances Th-2 cytokine production and IgE synthesis in a murine asthma model (Braun et al., 1998) and induces differentiation of activated B cells in Ig-secreting plasma cells (Brodie and Gelfand, 1994). It needs to be emphasized that the majority of NGF effects have been observed in pre-activated cells. NGF by itself does not appear to activate the immune cells in physiologically relevant concentrations, but rather modulates their threshold to other triggering stimuli (Levi-Montalcini et al., 1996). Most of these investigations, however, were performed in vitro. Therefore, the physiological function of NGF in vivo remains to be elucidated. Compared to NGF, there are few data available about possible functions of other neurotrophins in the immune system. The presence of a variety of neurotrophin receptors on developing and mature immune cells, however, suggests that the effects of other neurotrophins have to be considered as well.

Recent studies demonstrated the expression of neurotrophins and their receptors in bone marrow and thymus cells. Since bone marrow and thymus are the preferential organs for immune cell maturation and differentiation, this suggests that neurotrophins play a role in immune cell differentiation as well (Laurenzi et al., 1998; Labouyrie et al., 1999). Findings of higher neurotrophin transcript levels at fetal as compared to at adult stages further support such a notion (Labouyrie et al., 1999). Similar results were demonstrated in the thymus, where trkB on T cells inversely correlated with stages of maturation (Maroder et al., 1996). Therefore, Maroder et al. (1996) hypothesized that stroma cell derived neurotrophins have a direct influence on developing thymocytes.

Taken together, these data provide evidence that NGF is involved in the development of “immunological plasticity” (Fig. 3). Immunological plasticity may be defined as a long-lasting change in immunological functions including cell differentiation, mediator production and release, or sensitivity to activating stimuli. Since the immune and nervous system share many features including recognition of and reaction to unknown stimuli, it is not surprising that both systems use similar mediators and mechanisms to perform their tasks.

9. Conclusion

We are just at the beginning of revealing the complex interaction between the nervous and immune system. Inter-

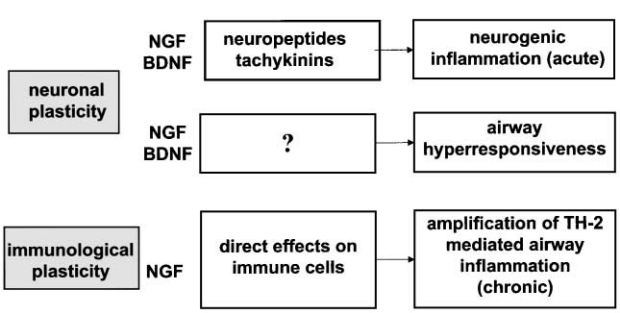

Fig. 4. The putative role of neurotrophins in the pathogenesis of bronchial asthma.

action between the two systems occurs on several levels (Fig. 4). Lung and airways are innervated by cholinergic non-cholinergic, adrenergic and non-adrenergic pathways. The neurotrophins are produced in increasing concentrations by both immune and non-immune cells in the asthmatic patient. Neurotrophins act on these peripheral nerves and result in "neuronal plasticity". This is defined by qualitative and/or quantitative changes in the functional activity and capacity of peripheral neurons. One important effect of neuronal plasticity is the enhanced production of neurotransmitters and neuropeptides, following activation of the neurons. This has the following functional consequences: (a) development of "neurogenic inflammation" as an acute and immediate effect; (b) development of airway hyperresponsiveness; (c) amplification of the Th-2 mediated inflammatory response via direct action of neurotrophins on T cells, eosinophils, mast cells and B cells. These effects are rather long lasting as compared to the effects of neuropeptides. This activity is described by the term "immunological plasticity". The above developed concepts now await further exploration, particularly in suitable in vivo models. Ultimately, this concept requires to be proven using suitable interventional strategies.

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