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Review article

Neurogenic inflammation and allergy

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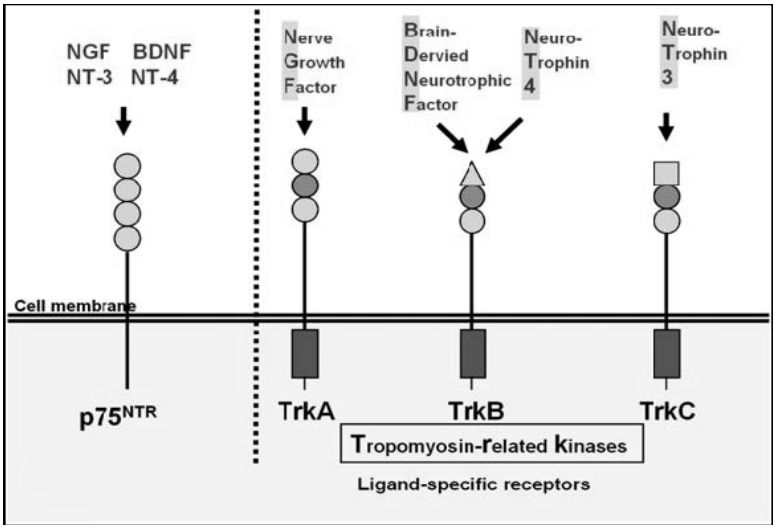
Neurogenic inflammation encompasses a series of vascular and non-vascular inflammatory responses, triggered by the activation of primary sensory neurons with a subsequent release of inflammatory neuromediators, resulting in a neurally mediated immune inflammation[1,2].

Neuromediators are mainly released from neurons. Immune and/or structural cells are secondary sources of these mediators during immune inflammation[3,4]. Neuromediators include neurotrophins and neuropeptides[4] (table 1).

Table 1. Mediators of neurogenic inflammation (neuromediators)[5,6].

Neurotrophins	Neuropeptides
Nerve growth factor (NGF)	Calcitonin gene-related peptide (CGRP)
Brain-derived neurotrophic factor (BDNF)	Vasoactive intestinal peptide (VIP)
Neurotrophin (NT)-3	Neuropeptide Y (NPY)
Neurotrophin-4/5	Tachykinins (substance P, neurokinin A and neurokinin B)
Neurotrophin 6 and 7	



BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor; NT: neurotrophin.

Figure 1. Signaling of neurotrophins via cell surface receptors.
Members of the neurotrophin family bind to ligand-specific (high affinity) tropomyosine-related kinase (Trk) receptors. In addition, all neurotrophins bind to the common pan-neurotrophin (low affinity) receptor p75NTR. The high affinity receptors mediate trophic effects, whereas the low affinity receptor may be involved in induction of apoptosis. (Quoted from Nockher and Renz, 2006)[5].

Neurotrophins are protein family of neuronal growth factors that control the survival, differentiation and maintenance of neurons in the peripheral as well as in the central nervous system in the embryonic and postnatal stages[7]. They induce a variety of responses in peripheral sensory and sympathetic neurons. These effects include chemotaxis, regulation of neurotransmitter production and excitability, establishment of functional synapses and control of metabolic functions and peripheral axonal branching. Overexpression of neurotrophins in peripheral body tissues results in sensory hyperinnervation[8]. Neurotrophins exert their cellular effects by interaction with two structurally unrelated receptors differing in specificity for ligand and signal transduction activities[9,10] (Fig. 1).

Tachykinins have previously been considered as a group of neuropeptides because of their widespread distribution in the central and the peripheral nervous system (capsaicin sensitive primary afferent neurons and capsaicin insensitive intrinsic neurons). This terminology is no longer held since their presence in a variety of non-neuronal structures has been demonstrated repeatedly[11,12]. The biological activity of tachykinins, the neurotransmitters of the excitatory part of the nonadrenergic, noncholinergic (NANC) nervous system, depends on their interaction with three specific tachykinin receptors, neurokinin (NK)1 (specific for substance P), NK2 (specific for neurokinin A) and NK3 (specific for neurokinin B) receptors[13-15]. The adequate stimuli for tachykinin release from the sensory nerves in the airways are of chemical nature (especially those chemicals that are produced during inflammation and tissue damage). VIP, an anti-inflammatory neuropeptide, is a neurotransmitter of the inhibitory part of the NANC nervous system[16].

Peptidases are involved in the breakdown of neuropeptides[17]. Both neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE) are involved in tachykinin breakdown[18]. NEP has been located to the airway mucosa and submucosa in contrast to ACE, which has been located in vascular cells. It has therefore been proposed that NEP is the main regulator of tachykinins in the airway, whereas ACE may influence tachykinins in the vascular space[19]. A decrease in NEP activity has been observed in response to substances which exacerbate asthma, such as smoking[18]. Smoking has also been found to promote the release of substance P (SP) from sensory nerves in addition to increasing NK1 and NK2 receptors in comparison to non-smokers[20]. Therefore, smoking could potentially act as a pro-inflammatory stimulus that upregulates tachykinin activity in the airway, partly due to the decrease in NEP activity. Sont and coworkers[21] found that NEP expression was higher in the airway epithelium from asthmatic patients using inhaled corticosteroids compared with steroid-naïve asthmatic subjects, suggesting that NEP is upregulated by steroid use. It has therefore been postulated that NEP activity may have an important role in the regulation of tachykinin induced responses in human asthma[18].

Neuroimmune interaction in allergy

Understanding the complex pathophysiology of allergic diseases has been a main challenge of clinical and experimental research for many years. During allergic inflammation, a bidirectional regulation of neuronal stimulation and allergic inflammation has been prospected. Neuromediators represent the key factor of this process, working on either immune or structural cells and exerting neuroimmunomodulatory functions[5]. Studies have demonstrated that in allergic inflammation, various cytokines, such as interleukin (IL)-1, mediate signals from the immune to the nervous system and stimulate neuromediator synthesis[22]. Vice versa, evidence has emerged that allergic inflammatory responses are controlled by neuromediators[5,23]. Therefore, signaling molecules that mediate inflammatory interactions among immune, neuronal, and structural cells (neuromediators) are becoming a focus of allergy research[5]. Because neuropeptides are short-lived signaling molecules that are rapidly degraded, their action is temporally limited and mainly restricted to the site of synthesis[24]. Neurotrophins, however, were found to be produced continuously during allergic inflammation. Thus, neuropeptides are considered to be the major initiators of allergic inflammation[19,25], while neurotrophins might act as long-term modulators, amplifying inflammatory signals between the nervous and immune systems during allergic inflammation[26,27].

Sources of neuromediators in allergy:

Under physiological conditions, the primary sources of neuromediators are neuronal cells and nerve-associated cells, such as Schwann cells, glial cells, or fibroblasts[28]. During allergic inflammation, cells of the immune system and structural cells are able to express both the neuromediators and their corresponding receptors[4,23].

Neuromediators and immune cells:

- ***Monocytes/macrophages:***

Alveolar macrophages produce neurotrophins after allergen challenge[29]. Monocytes isolated from human peripheral blood showed a constitutive expression of neurotrophins in patients with allergy compared with those obtained from healthy donors[30].

- ***Eosinophils:***

Eosinophils are potentially able to express cell surface receptors for all neurotrophins, but receptor expression may depend on the level of maturation or activation level of these cells[31]. In one study, circulating blood eosinophils from patients with allergy did not show any Trk expression, but more importantly, eosinophils obtained from the bronchoalveolar lavage fluid (BALF) after allergen provocation expressed all neurotrophin receptors[32].

- ***Lymphocytes:***

T lymphocytes have been shown to produce neuromediators, but the amount of synthesis depends on the activation level. T cells isolated from the inflamed lung showed high levels of BDNF synthesis, whereas T cells isolated from the spleen did not produce detectable BDNF. These differences may result from different T-cell populations in spleen and lung and/or a preactivation state of lung T cells at the site of local inflammation[33].

Neuromediators and structural cells:

There is growing evidence that structural cells are actively involved in the local inflammatory response through synthesis of cytokines and other mediators[28]. Constitutive expression of many neuromediators in mouse lung epithelial cells is markedly upregulated after repeated allergen challenges in a murine model of experimental allergic asthma[34]. This finding indicates that the airway epithelium may be an important source for increased expression of some neuromediators in the allergic lung[35]. In the skin, keratinocytes are recognized as a primary source of some neuromediators during inflammatory conditions[36].

How neuromediators result in progression and amplification of allergic inflammation?

A. Neuronal plasticity:

Local overproduction of neurotrophins during allergic inflammation results in increased neuronal release of neuropeptides such as tachykinins, exhibiting a great degree of functional plasticity defined as neuronal plasticity (Fig. 2). The consequences are the development of neurogenic inflammation[37,38]. Neuropeptides released by sensory neurons then modulate a broad range of functional responses of immune cells including lymphocytes, eosinophils, mast cells, and macrophages, leading to activation and differentiation of these cells[22,39]. Immune cells contribute to this process by virtue of their neurotrophin expression. Therefore, neurotrophins can influence the intensity and duration of a local immune response either by direct signaling through specific neurotrophin receptors or through upregulation of neuropeptide synthesis.

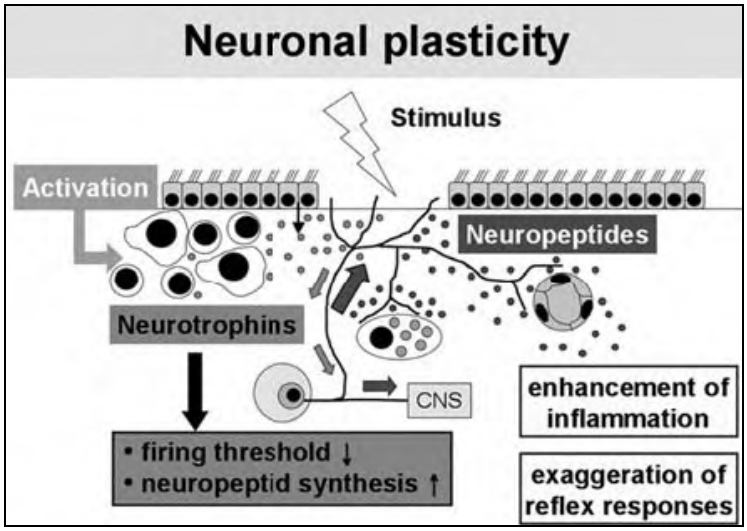


Figure 2. Neuronal plasticity mediated by neurotrophins. (Quoted from Renz et al., 2004)[38]

B- Immunological plasticity:

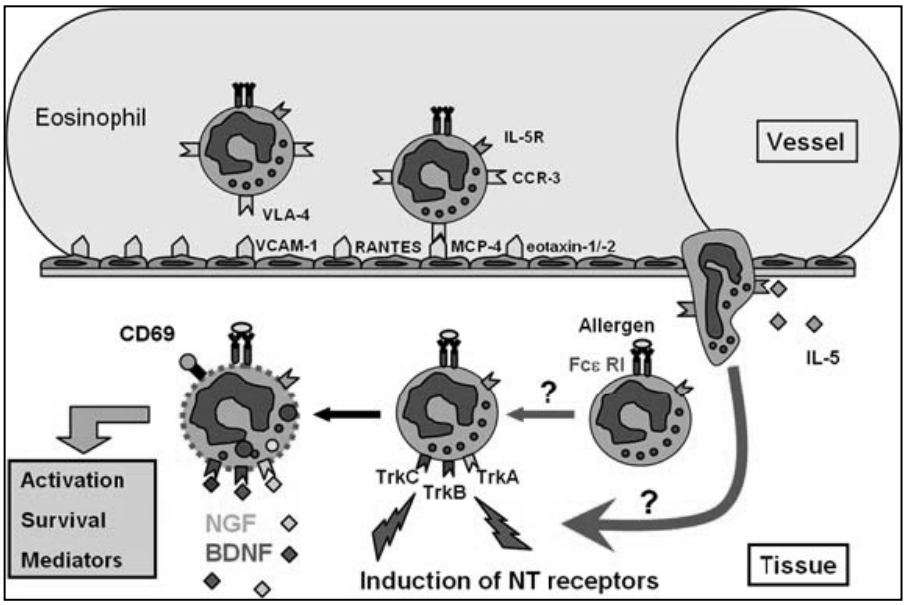
Neurotrophins act in autocrine as well as paracrine signaling. Because the pathophysiology of allergic diseases is characterized by the progression of allergic inflammation, the potential role of neurotrophins in progression and amplification of allergic inflammation is of a great interest. These effects are described by the term immunological plasticity that include enhancement of survival, differentiation, and/or proliferation of immune cells and activation of release of cytokines or mediators[5]. Therefore, neurogenic inflammation describes a vicious cycle of neuroimmune interactions that amplify allergic inflammation and neurotrophins are cross talks between immune and nervous systems in allergic inflammation[22,38,39].

Tissue mast cell numbers are dependent on factors controlling infiltration, local development, and survival in the tissues. An increase in mast cell numbers is a characteristic feature of the allergic inflammation[40]. Several studies have suggested

that NGF is involved in the development and maintenance of mast cell hyperplasia in the allergic airways[41]. In addition, NGF functions as a chemoattractant for mast cells[41,42] and also supports the survival of mast cells as a cofactor together with stem cell factor[43]. Neuromediators also regulate mast cell degranulation and mediator release[44]. Abrogation of NGF signaling by intranasal application of neutralizing antibodies inhibits allergen induced early phase reaction, which is mediated by mast cell degranulation[45].

In addition, neurotrophins can directly stimulate lymphocytes to produce T-helper-2 (Th2) cytokines, going in line with the Th2 type shifted immune response. This is supported by studies in murine asthma models showing that treatment of mice with anti-NGF antibodies decreases the function of Th2 T-cells[46]. Th2 cells orchestrate many aspects of pathologic immune responses including effector functions of B-cells, mast cells and eosinophils. These cells produce an array of cytokines such as IL4, IL-5, IL-9 and IL-13. In B-cells, IL-4 and IL-13 are involved in isotype switching towards IgE, while IL-5 possesses pro-inflammatory properties, for example the development, differentiation, recruitment and survival of eosinophils[47]. So far, no information is available that neurotrophins directly influence the switch of naive CD41 T cells into Th2 cells. However, at least in a transgenic mouse model, NT-3 selectively supports the activity of antigen-specific Th2 cells but not of Th1 cells because of an expression of the TrkC receptor on Th2 but not TH1 cells[46].

Neurotrophins also influence the developing immune response by acting as cytokines[23]. Moreover, in vitro studies have showed prolonged survival of BALF, but not blood eosinophils, by all members of mammalian neurotrophins due to their antiapoptotic effects[32]. Neurotrophin mediated survival of eosinophils (fig. 3) might contribute to the massive eosinophilia observed during asthma and it also contributes to increased airway inflammation. NGF and BDNF are also eosinophil chemo-attractants[27].



BDNF: brain-derived neurotrophic factor; MCP: monocyte chemoattractant protein**;** NGF: nerve growth factor; NT: neurotrophins; VCAM-1: vascular cell adhesion molecule 1; VLA-4: very late antigen 4.

Figure 3. Neurotrophins modulate biological effects of infiltrated eosinophils in the allergic airway. Within the inflamed tissue, expression of neurotrophins is increased. Eosinophils are then susceptible to neurotrophin-induced activation and survival. (Quoted from Nockher and Renz, 2006)[27]

C- Angiogenesis and microvascular remodeling:

Angiogenesis encompasses the formation of vascular tissue from pre-existing vessels. Microvascular remodeling involves structural alterations of arterioles, capillaries, or venules without the formation of new vessels. Both are complex events that are regulated by a large number of mediators such as cytokines and growth factors[48]. Both angiogenesis and microvascular remodeling mainly result from endothelial cell proliferation and often occur simultaneously. It has been recognized that neurotrophins and tachykinins are vasoactive

factors affecting endothelial cell biology and elicit angiogenesis[49]. Moreover, it has been shown that NGF induces matrix metalloproteinase expression in vascular smooth muscle cells which contributes to the migratory response of smooth muscle cells by releasing them from their surrounding extracellular matrix after injury[50,51].

Neurogenic inflammation in some allergic diseases:

Bronchial asthma

Bronchial asthma is characterized by chronic airway inflammation, development of airway hyperreactivity (AHR), recurrent reversible airway obstruction and airway remodeling[5]. Bronchial asthma is more than an immunological disorder and both peripheral and central neural mechanisms are also involved in the pathogenesis of asthma[52]. It is now clear that inflammation and AHR do not develop independently from one another, but they are associated through a bidirectional signaling between cells of the immune and nervous systems. Therefore, the search for bidirectional signaling molecules between immune cells and neurons has become a novel focus regarding asthma research[27].

Neurotrophins are constitutively expressed by resident lung cells and are produced in increasing concentrations by immune cells invading the airways during allergic inflammation [38] (Fig. 4). Neurotrophins modify the functional activity of sensory and motor neurons, leading to enhanced and altered neuropeptide and tachykinin production[38]. Tachykinins interact in the airways with tachykinin NK1, NK2 and NK3 receptors to cause bronchoconstriction, plasma protein extravasation, and mucus secretion and to attract and activate immune cells. In preclinical studies, tachykinins have been implicated in the pathophysiology of asthma [53].

AHR, an important hallmark in the pathogenesis of asthma, may be defined as an increase in the ease and degree of airway narrowing in response to a wide range of bronchoconstrictor stimuli due to enhanced cholinergic activity[54.] Cholinergic activities were shown to be increased by tachykinins[55,56]. Neurotrophin- induced neuronal plasticity may induce AHR[57] (Fig. 5). Neurotrophin-induced AHR may be the result of airway inflammation, as the infiltrating cells are capable of producing neurotrophins. NGF can induce AHR even without the background of inflammation, as NGF treatment of mice induced AHR. Thus, neurogenic inflammation describes a vicious cycle of neuroimmune interactions that amplify airway inflammation and AHR in allergic asthma[22,39].

NGF may be also involved in airway remodeling. Beside its effects on bronchial smooth muscle and hyperinnervation with sensory nerves, NGF induces fibroblast migration and differentiation into myofibroblasts, as well as collagen production[58,59]. Additionally, NGF plays a role in increased vascularisation by inducing endothelial cell and vascular smooth muscle cell proliferation and stimulating the release of proangiogenic factors[60].

Is there is a role for neurogenic inflammation in asthma in humans?

Whilst there is convincing evidence of neurogenic inflammation in various animal models of asthma, the evidence in humans is less clear. Replication of the experimental approaches in humans has proven difficult with conflicting results. In terms of human studies, the three main investigative approaches have been:

1. Studies to determine if pro-inflammatory neuropeptides and neurotrophins are elevated in the airways in asthma.
2. Studies to examine different functional effects of neuropeptides and neurotrophins in asthma.
3. Studies using inhibitors of pro-inflammatory neuropeptides to attempt to improve indices of asthma control in humans[61].

Atopic dermatitis and stress? How do emotions come into skin?

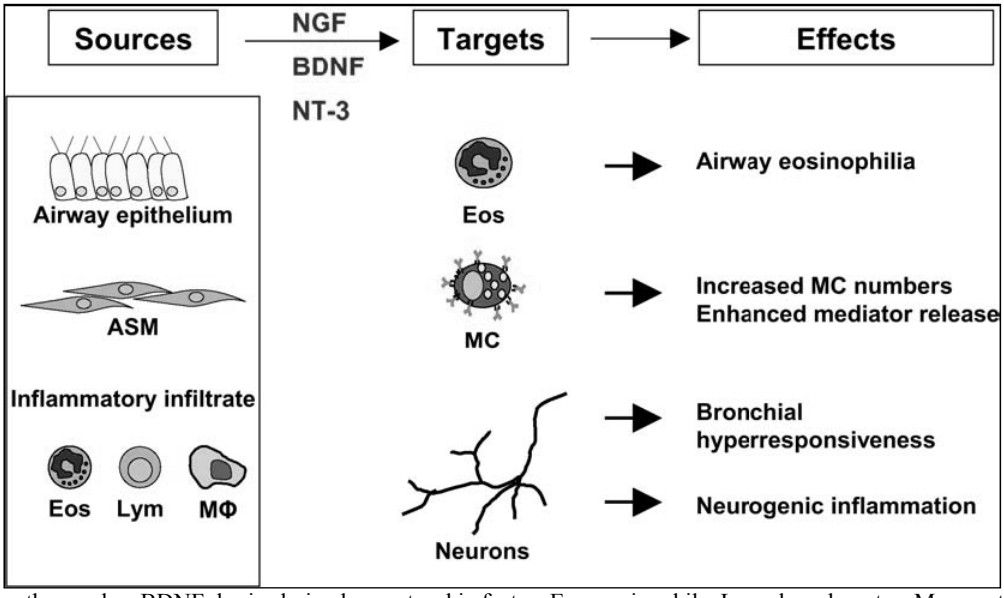
Several common skin diseases are now acknowledged to be worsened by psychological stress, particularly immunodermatoses such as atopic dermatitis (AD), psoriasis, seborrheic eczema, prurigo nodularis, lichen planus, chronic urticaria and alopecia areata. AD is a chronic inflammatory skin disease associated with cutaneous hyperreactivity to environmental triggers, and is often the first step in the atopic march resulting in asthma and allergic rhinitis[63]. AD is a complex disease traditionally involving interaction of genetic, environmental, and immunologic factors. Recent studies suggest that psychoneuro-immunologic factors and emotional stress are important in its evolution. The observations that external (psychologic) stressors may induce AD flares is explained by studies showing that stress impairs the skin barrier function and favors a shift in immunity toward a Th2 allergic response. Furthermore, patients with AD appear to have an inherited hypothalamic deficiency that impairs normal hypothalamic-pituitary-adrenal axis function. Psychologic and stress-reduction

interventions were recently shown to improve patient well-being, and to significantly improve cutaneous manifestations[64].

Mast cells play a key role in the development of inflammatory reaction to stress. Enhanced levels of neuropeptides released from nerve endings, resident cells (e.g., keratinocytes, fibroblasts, epidermal, dendritic and Langerhans cells) and immune cells influence the exacerbation of AD through enhancement of mast cell degranulation. This leads to the recruitment of inflammatory cells to the site of inflammation, vasodilatation and plasma extravasation, modulation of immunocyte function (e.g. mediator release from T-lymphocytes, induction of antibodies production from B cells and modulation of antigen presentation in Langerhans cells) and regulation of mediator release (cytokines, chemokines and growth factors). The epidermal keratinocytes are also affected by neurogenic inflammation (proliferation, apoptosis, spongiosis and edema). Modern biopsychosocial interventions can markedly benefit the well-being of AD patients, including improvement of skin manifestations (Fig. 6). Various forms of relaxation therapy, biofeedback, autogenic training, massage therapy, and hypnosis have been used in treating dermatologic diseases. Although aimed at decreasing stress and anxiety, controlled studies of these interventions in AD have encountered contradictory results[64,65].

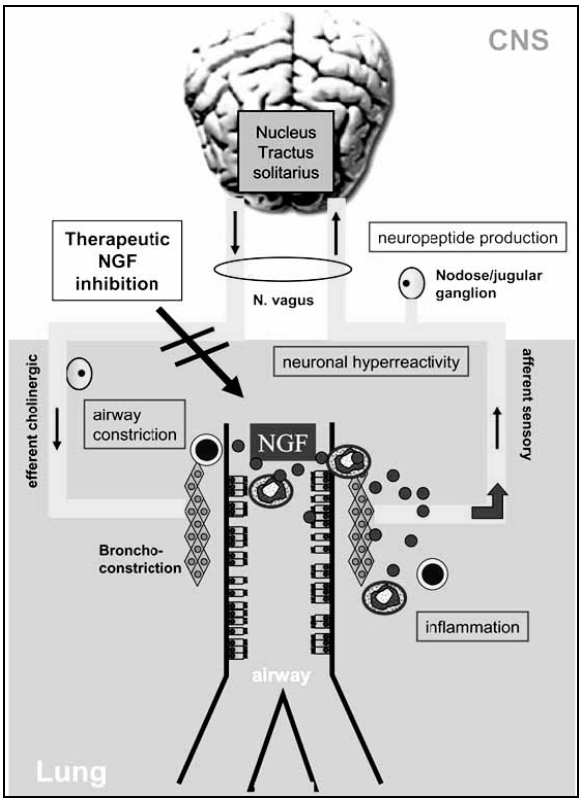
Allergic rhinosinusitis

The nose is an air conditioner and is involved in the protection of the lower airways against inhalation of exogenous particles and airborne irritants. The nasal mucosa is therefore densely innervated by sensory nerves containing several neuropeptides[66]. In the airways, activation of sensory nerves leads to the release of multiple neuropeptides. In addition to their involvement in vasodilatation, plasma protein exudation and mucus secretion, sensory neuropeptides also participate in inflammatory cell recruitment. This neurogenic inflammation contributes to the intensity of nasal obstruction, rhinorrhea and headaches, the most common symptoms in chronic rhinosinusitis[67]. The concentration of neuropeptides is increased in the nasal mucosa of patients suffering from chronic rhinosinusitis. In contrast, the activity of the enzymes involved in the degradation of these sensory neuropeptides is markedly reduced. These observations should contribute to a better understanding of the pathophysiological mechanisms of one of the most frequently occurring chronic inflammatory diseases[66].



ASM: airway smooth muscles; BDNF: brain-derived neurotrophic factor; Eos: eosinophils; Lym: lymphocytes; Mc: mast cells ; Mo: monocytes; NGF: nerve growth factor; NT-3: neurotrophin-3.

Figure 4. Production and effects of neurotrophins during allergic airway inflammation. (Quoted from Nockher and Renz, 2006)[5]



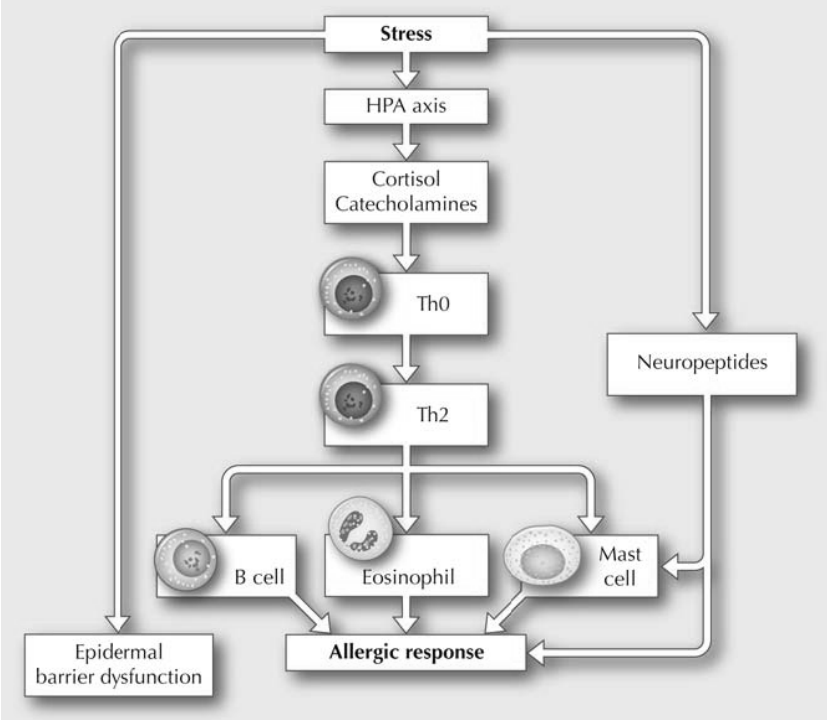
NGF, nerve growth factor

Figure 5. Neurotrophins in asthma bronchiale.
Inflammation derived neurotrophins such as NGF promote central features of allergic asthma. Neurotrophins induce neuropeptide production and neuronal hyperreactivity using a mechanism that is comparable to inflammatory pain. These events contribute to facilitated airway constriction (airway hyperreactivity). In addition, NGF can act directly as a proinflammatory cytokine-like factor. (Quoted from Schulte-Herbrüggen et al., 2007)[62]

Table 2. Some tachykinin receptors antagonists studies in humans.

Name	Inhibits	Clinical Effect
FK22494	NK1/ NK2	Inhibited bradykinin induced bronchoconstriction. No effect on NKA induced bronchoconstriction.
CP-99,99495	NK1	No effect on lung function/ hypertonic saline bronchoconstriction.
FK-88896	NK1	No effect on lung function / exercise induced bronchoconstriction (reduced recovery time).
SR 4896897	NK2	Inhibited NKA induced bronchoconstriction No effect on lung function / AMP challenge.
DNK33398	NK1/ NK2	Inhibited NKA induced bronchoconstriction.
AVE588399	NK1/ NK2	Inhibited NKA induced bronchoconstriction No effect (? Potentiation of allergen induced late phase response).

(Quoted from Butler and Heaney, 2007)[61]



HPA axis: hypothalamic-pituitary-adrenal axis; Th: T-helper lymphocytes.

Figure 6. Effects of stress on atopic dermatitis

When the brain identifies an external perceived stressor, corticotropin- releasing hormone (CRH) is secreted from the hypothalamus, transported through the portal circulation to the pituitary, and induces adrenocorticotropic hormone release from the anterior pituitary into the general circulation. Simultaneous sympathetic nervous system activation results in glucocorticosteroid, catecholamine, and neuropeptide secretion. Catecholamines and cortisol have a potent effect on the immune system. They mediate differentiation of naive T helper cells toward Th2 phenotype. This tilts the balance toward humoral immunity by increasing production of IL-4, IL-5, and IL-13; these activate B-cells, mast cells, and eosinophils, increasing the allergic inflammatory response, and exacerbating Th2-mediated diseases involving these pathways. Additionally, cutaneous neuropeptides (egg, substance P) stimulate mast cells and mediate AD deterioration. Another known effect of stress is disruption of the skin barrier function, leading to increased infections and possibly enhanced cutaneous penetration of allergens. (Quoted from Arndt et al., 2008)[64]

Ocular allergy

Ocular allergy is a common disorder affecting 20% of the population in developing countries. Ocular allergy comprises the acute (self-limiting) type-I hypersensitivity seasonal and perennial allergic conjunctivitis and the more complex, chronic and severe forms of atopic and vernal keratoconjunctivitis, and giant papillary conjunctivitis. Disease severity can range from mild itching and redness to the more serious vision threatening forms affecting the cornea[68]. As a recent point of view, during allergic states, several neuromediators are released from intracellular sites or their expression is changed. They drive the common signs of ocular allergic inflammation (pain, redness, swelling, heat), by acting directly on cells responsible for both early and late phase reactions as well as on epithelial cells and fibroblasts, leading to either self-limiting or chronicity states. In allergic conjunctivitis, the main mediator is histamine which is a vasoactive peptide that drives vasodilation, vascular permeability, cell proliferation, tissue growth and repair[69]. SP and NGF may drive histamine release from mast cells[70,71].

Neurogenic inflammation and allergy in clinical practice

1- Assessment of the severity of inflammation in some allergic diseases

Bronchoalveolar lavage, sputum and peripheral blood samples have been used to assess the presence of neuromediators and their receptors in allergic diseases[61]. In clinical practice, assessment of airway inflammation is difficult. Therefore, detection of biological markers of airway inflammation might offer help for proper monitoring of asthma severity for better management of this disease[72]. Sputum BDNF and serum CGRP levels were reported to be up-regulated during acute asthma exacerbations and

their levels positively correlated with eosinophil numbers in sputum and blood, respectively[73,74]. A recent study[75] conducted on 24 Egyptian children and adolescents during and after acute asthma exacerbations demonstrated that sputum NKA levels were up-regulated during acute asthma exacerbations and they positively correlated with exacerbation severity.

2-Therapeutic applications

Neurotrophin antagonism:

Neurotrophin antagonism for asthma therapy has not been tested in humans so far. However, there are now a number of highly specific antagonists under development[76-79] only tested in animal models of asthma[80]. Several pharmacological strategies were used in animal models of asthma:

1. Direct blocking of neurotrophins by antibodies[45,81,82].
2. Blocking the high affinity receptors Trks by decoy or antibodies[83].
3. Blocking the low affinity panneurotrophin receptor p75NTR by antibodies[84].
4. Blocking neurotrophin signal transduction by tyrosine kinase inhibitors like K252a or tyrphostin AG879[85].

These experiments demonstrated that blocking of neurotrophins or their receptors is able to inhibit the development of the key characteristics of asthma in preclinical models (mouse, rat and guinea pig). Blocking neurotrophins diminished the main features of human asthma like airway inflammation, airway hyperreactivity and allergen specific early phase response[70,86,87]. However, there are considerable concerns about the use of neurotrophin antagonists in human asthma. Neurotrophins are highly potent factors involved in many essential physiological conditions, especially in the central nervous system, where they can induce long lasting alterations. Thus, a careful balance with respect to the expected beneficial pharmacological actions in comparison to the possible side effects is essential. Since asthma has several effective conventional treatment options like steroids, the use of neurotrophin antagonists is critical for the treatment of asthma. However, there are patient subgroups with severe, difficult to treat asthma that might benefit from new therapeutic options[62].

Neuropeptides antagonism:

A number of strategies are possible to interfere with the action of sensory neuropeptides in the airways: that include:

1. Depletion of neuropeptides within nerves [e.g. by the neurotoxin capsaicin].
2. Inhibition of the release of sensory neuropeptides [e.g. by β2-adrenoceptor agonist, theophylline, cromoglycate or phosphodiesterase (PDE4) inhibitors].
3. Inhibition of tachykinin receptors by receptor antagonists. A number of receptor antagonists have been used such as dual NK1/NK2 or triple NK1/NK2/NK3 tachykinin receptor antagonists[88] (table 2), but they seem unlikely to confer any additional benefit to inhaled steroid therapy in humans. This is in contrast to the extensive and overwhelming data suggesting a role for tachykinins in asthma. There are several explanations for this apparent paradox[89,90]:

a. The lack of efficacy can be easily explained by the low potency or defective pharmacokinetics of the compounds tested so far. Potent tachykinin receptor antagonists have not been considered for application in airways diseases, but for depression or emesis[91].

b. Blocking either NK1 or NK2 receptor is probably an insufficient approach, as most of the effects of tachykinins in the airways are mediated by more than one tachykinin receptor.

c. In the application of a new tachykinin receptor antagonist to airway diseases, it is crucial that one first demonstrates that the antagonist is indeed able to block airway effects of an agonist (e.g. SP or neurokinin A). This allows to determine the in vivo activity of the antagonist under consideration and to determine dose and dosing frequency for further clinical study.

Once a potent drug is identified, that can be administered twice, or preferably once a day, clinical studies are to be conducted to define the potential therapeutic benefit in either asthma or chronic obstructive pulmonary disease. These clinical studies will need to last for at least 3, preferably 6 or 12 months, in order to demonstrate changes in relevant clinical outcomes. This is especially important to detect a possible effect on exacerbations of asthma or chronic obstructive pulmonary disease, situations where a release of tachykinins from human airway tissue has been suggested to occur[92,93].

Key Messages

Tissue and immune cells produce and respond to neuromediators. Studies of various allergic diseases performed over the period of the last 2 decades indicate that **neuromediators are upregulated in allergic diseases** such as bronchial asthma and atopic dermatitis and may act as inflammatory cytokines. There is a growing evidence that **neuromediators** are part of an

integrated adaptive response to several offending stimuli that **connect cells of the immune and nervous system together with structural cells**. On the basis of these observations, a more intense investigation of the complex biological functions of neuromediators might open new opportunities for the development of novel therapeutic intervention strategies beyond the currently available anti-inflammatory drugs.

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