Neurogenic inflammation in human airways: is it important?

Numerous peptides have been demonstrated in airway nerves and endocrine cells. Among the best studied are substance P and neuropeptide A which are peptides contained within sensory airway nerves. Both are members of the tachykinin peptide family. The tachykinins are potent vasodilators and contractors of smooth muscle which are co-localised with calcitonin gene-related peptide, a sensory neuropeptide with important vasodilator properties. In studies on rodent airways substance P and neuropeptide A have been implicated as neurotransmitters which mediate the excitative part of the non-adrenergic non-cholinergic (NANC) nervous system. These non-cholinergic excitatory nerves can be activated by mechanical and chemical stimuli – for example, bradykinin – generating antidromic impulses and a local axon reflex which leads to non-cholinergic bronchoconstriction, plasma protein extravasation, and vasodilatation. Jancsó et al first used the term "neurogenic inflammation" to describe the increase in vascular permeability, plasma extravasation, and tissue swelling which occurred in the skin and conjunctiva when sensory nerves were stimulated by topical administration of irritants such as capsaicin, hypertonic saline, mustard oil and formaldehyde, or by antidromic electrical stimulation.

In studies on animal and isolated human airways the effects observed following stimulation with tachykinins include smooth muscle contraction, stimulation of submucosal gland secretion, vasodilatation, and increased vascular permeability. Moreover, the sensory neuropeptides have important proinflammatory effects such as the stimulation of T lymphocyte proliferation, stimulation of macrophages, mast cells and eosinophils, and the chemotraction of eosinophils and neutrophils. Since the description of these effects the original concept of neurogenic inflammation put forward by Jancsó and coworkers has been broadened by some authors to include the various components of the efferent function of the sensory nerves. In view of their multiple effects the sensory neuropeptides have been implicated in the pathogenesis of several airway disorders including rhinitis and asthma.

The sensory neuropeptides substance P and neuropeptide A and their receptors have been localised to upper and lower human airways. Compared with rodents the nerve fibres containing substance P are less dense in human airway tissue. Studies on necropsic tissue, bronchoalveolar lavage fluid, and induced sputum have, however, suggested an increased amount of substance P in the airways of asthmatic patients compared with normal subjects. The major enzyme responsible for degradation of substance P and neuropeptide A is neutral endopeptidase which is present in both upper and lower human airways.

A considerable amount of research has been carried out on the effects of exogenously administered sensory neuropeptides on the upper and lower airways. Studies on human lower airways have focused on changes in airway calibre. Inhalation of substance P and neuropeptide A causes dose-dependent bronchoconstriction, neuropeptide A being more potent than substance P and asthmatic subjects being more responsive than normal subjects. The contractile effect of substance P and neuropeptide A is reduced in asthmatic patients pretreated with disodium cromoglycate or nedocromil sodium, suggesting that indirect mechanisms such as stimulation of inflammatory cells and/or nerves are involved. Pretreatment with anticholinergics offers only slight protection, whereas antihistamines have no effect on the bronchoconstriction caused by neuropeptide A. The exact mechanism by which substance P and neuropeptide A contract human airways in vivo remains to be determined. Apart from bronchoconstriction, other potentially important lower airway effects of the sensory neuropeptides include mucus hypersecretion – an effect which has been studied on human bronchi in vitro – and the enhancement of microvascular permeability – an effect which has been extensively studied in rodents. At present in vivo data on these effects in man are lacking.

The effect of exogenously administered substance P, neuropeptide A, and calcitonin gene-related peptide has also been studied in the nose. Topical administration of substance P and neuropeptide A increases nasal airway resistance in a dose-dependent fashion, substance P being more potent than neuropeptide A and methacholine. The increase in nasal airway resistance is more pronounced in patients with allergic rhinitis than in control subjects. Furthermore, in patients with allergic rhinitis, nasal challenge with substance P or neuropeptide A increases the amount of protein and albumin recovered, which is taken as evidence in favour of plasma protein extravasation. Substance P also increases the percentage of neutrophils recovered from nasal lavage. In contrast, application of calcitonin gene-related peptide to the nasal mucosa does not stimulate glandular or plasma protein extravasation, which is in agreement with animal studies showing that calcitonin gene-related peptide does not affect baseline plasma protein extravasation.

In animal airways neutral endopeptidase was found to be the major enzyme responsible for degradation of sensory neuropeptides. After inhalation of thiopran or phosphoramidon (two inhibitors of the degrading enzyme
neutral endopeptidase) the bronchoconstrictor effect of neurokinin A was enhanced both in normal and asthmatic subjects. These studies offered functional proof for an involvement of neutral endopeptidase in the in vivo breakdown of inhaled neurokinin A in man. Neutral endopeptidase was also found to be involved in the upper airway response to exogenously administered substance P; oral administration of the neutral endopeptidase inhibitor acetorphan potentiated the effects of substance P on nasal airway resistance. As in the patients with asthma, no difference was observed between the normal subjects and the subjects with allergic rhinitis. Moreover, angiotensin converting enzyme also seems to be involved in the breakdown of exogenously administered substance P in patients with allergic rhinitis.

Substance P and neurokinin A are thus present in human airway nerves and, when exogenously applied, have potent excitatory actions on both upper and lower human airways. Neutral endopeptidase is present in the airways and is involved in the breakdown of exogenously administered substance P. It is not known, however, whether sensory nerves release substance P and neurokinin A in airway disorders such as asthma and rhinitis.

One approach to this problem has been to measure the amount of substance P released in nasal or bronchoalveolar lavage fluid. Increased amounts of substance P have been recovered from nasal and bronchoalveolar lavage fluid after the administration of allergen in the nose or through the bronchoscope.18,19 These findings suggest that sensory neuropeptides can, indeed, be released from sensory nerves into the airways during an allergic reaction.

Another approach has been the use of the neurotoxin capsaicin. Capsaicin is an important pharmacological tool which has been used mainly in animal studies. It is the pungent ingredient present in a wide variety of red peppers of the genus Capsicum. In rodents capsaicin affects mainly (but not only) the thin unmyelinated sensory nerve fibres or C fibres; it causes an initial stimulation (pain, itch) followed by desensitisation to capsaicin and other sensory stimuli. With higher doses long term functional or even morphological ablation of the thin sensory neurones occurs.20 When inhaled, capsaicin causes cough and a mild, transient bronchoconstriction which is largely due to a parasympathetic reflex.21,22 In the guinea pig sensory neurones involved in these airway responses; evidence for such a mechanism in human airways is, however, lacking. Intranasal application of capsaicin to the nose has been used to study the role of the so-called “capsaicin sensitive nerves” (which is deliberately taken as synonymous with “substance P and neurokinin A containing nerves”). Capsaicin causes nasal irritation and burning pain, sneezing, nasal congestion, and secretion both in normal subjects and in subjects with allergic and vasomotor rhinitis.4,43,44,45 the effect being more pronounced in patients with vasomotor rhinitis.44,45 Capsaicin also induces a contralateral secretory response. As this response is almost completely blocked by pretreatment with a locally and systemically administered muscarinic receptor antagonist, the involvement of cholinergic parasympathetic reflexes has been suggested.46 Although capsaicin does enhance TAMEesterase, a presumable marker for glandular secretion,47 it does not increase albumin or total protein content in nasal lavage fluid.48 Thus, in contrast to substance P, capsaicin has no measurable effect on the vascular permeability in the nose.

In the present issue of Thorax (pages 225–229) Greiff and coworkers report on a study of the intranasal effects of capsaicin applied early and late in the birch pollen season in subjects with allergic rhinitis.47 As previously shown, capsaicin caused nasal pain. The pain provoking effect of capsaicin was more pronounced late in the season, suggesting that sensory nerves become more responsive during exposure to pollen. Moreover, capsaicin produced nasal blockage only at the end of the pollen season. In line with previous observations, capsaicin had no effect on the albumin levels in nasal lavage fluid before the pollen season and no change occurred in this parameter during the pollen season. Hyperalgesia therefore occurs during the pollen season but, as no changes in vascular permeability occurred, the involvement of neurogenic inflammation in allergic rhinitis was questioned.

Several questions still remain unanswered. Firstly, effects other than vascular permeability may be more important – for instance, in a study on 16 adults with chronic non-allergic rhinitis Lacroix et al found an enhanced vascular response to capsaicin compared with normal subjects.48 Both nasal vascular responses and subjective discomfort were considerably reduced after the fifth application of capsaicin and these changes in nasal response were accompanied by a 50% reduction in the content of calcitonin gene-related peptide in nasal biopsy specimens.49 Secondly, upper and lower airways have a different structure and behave differently towards inflammatory mediators (for example, histamine) and pharmacological agents (for example, methacholine). One therefore has to be cautious in extrapolating findings from the nose to the lower airways and there is a need to develop methods for the non-invasive measurement of plasma protein extravasation in the lower human airways. Thirdly, attention should be paid to the longer term effects of the sensory neuropeptides such as upregulation of cytokine expression and the influence on bronchial responsiveness40 which may be as important as the immediate bronchoconstrictor and vascular effects. Finally, as potent and specific antagonists for the neurokinin-1 and neurokinin-2 tachykinin receptors are being developed for clinical use, it will be possible to determine more precisely the contribution of the tachykinins to the pathophysiology of airway disorders such as asthma and rhinitis.50

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