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Chronic rhinosinusitis and neuropeptides

J. S. Lacroix

Summary

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. In the airways, activation of sensory C and Aδ fibres 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. The concentration of sensory 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.

Key words: rhinosinusitis; neuropeptides

Nasal obstruction, rhinorrhea and headaches lasting over 3 months are the most common symptoms in chronic rhinosinusitis [1]. The nasal mucosa blood vessels, the muco-ciliary transport system and inflammatory cells are the main tissue components involved in these clinical manifestations. The functions of these elements are influenced, at least in part, by biologically active agents released from both sensory and efferent autonomic nerves [2]. In order to protect the lower airways against inhalation of exogenous particles and airborne irritants, the nasal mucosa is densely innervated by sensory nerves. When stimulated, these nerve endings are involved in protective reflexes such as sneezing, rhinorrhea and nasal congestion [3].

Several polypeptides have been demonstrated by immunohistochemistry in a subpopulation of nasal sensory nerves beneath and within the epithelium, around blood vessels and glands [3]. They include structurally related tachykinins such as substance P (SP), neurokinin A (NKA), neuropeptide K (NPK) and calcitonin gene-related peptide (CGRP) [2]. In the airways, activation of sensory-C and Aδ fibres leads to the release of multiple neuropeptides. In addition to their involvement in vasodilatation, plasma protein exudation and mucus secretion [2], sensory neuropeptides also participate in inflammatory cell recruitment [4].

The 37-amino acid peptide CGRP is co-localised with SP and NKA in capsaicin-sensitive sensory-C fibres [2], which are found in close association with mast cells around blood vessels in numerous tissues [2, 5]. CGRP plays a dominant role in neurogenic inflammation by increasing vascular permeability and inflammatory cell chemotaxis (figure 1) [2, 4]. The release of CGRP-like immunoreactivity (LI) can be experimentally induced by sensory-C fibre stimulation with capsaicin, bradykinin (BK) and histamine [6–8].

Capsaicin, the pungent principle ingredient of red chilli pepper, is a direct stimulant of the sensory-C fibres, producing the release of CGRP [5] and other tachykinins [9]. Systemic pre-treatment of adult guinea-pigs with capsaicin induces tissue depletion of CGRP as well as destruction of sensory-C fibre terminals [10]. In the pig nasal mucosa, local intra-arterial (i.a.) injection of capsaicin induces CGRP-LI release with concomitant vasodilatation of both capacitance and resistance blood vessels [7]; capsaicin probably does not stimulate mast cell histamine release directly [11, 12]. In patients suffering from chronic rhinosinusitis, the concentration of sensory neuropeptides has been found to be very well correlated with the intensity of their symptoms and the density of inflammatory cells. Repeated intranasal applications of capsaicin induced a significant reduction of both the symptoms and the amount of sensory neuropeptides found in the nasal mucosa [13].

Bradykinin (BK) is a polypeptide involved in nociception, and produces marked vasodilatation and increased capillary permeability. In the nasal mucosa, BK receptors have been demonstrated in arteries, venous sinusoids and submucosal nerve

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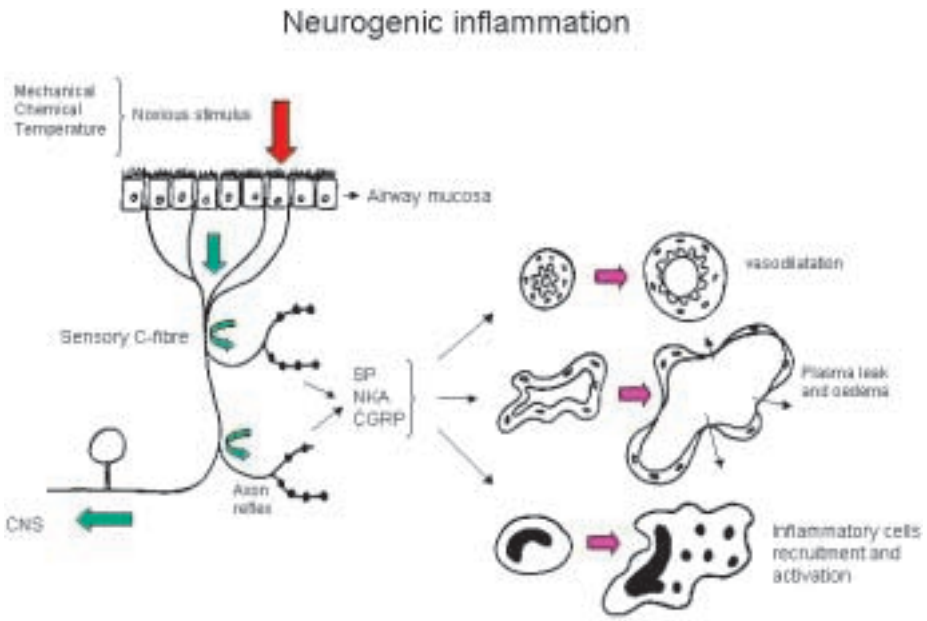
Figure 1

Schematic illustration of neurogenic inflammation in the upper airway mucosa associated with chronic rhinosinusitis. Activation of trigeminal sensory nerve endings in the nasal airway epithelium by mechanical, chemical or thermic stimuli induce a spread of action potentials in branches of capsaicin-sensitive sensory C fibres in afferent nerves via axon reflexes (curved arrows). The nasal mucosa vascular bed is richly innervated by substance P (SP), calcitonin gene-related peptide (CGRP) and neurokinin A (NKA) – containing sensory nerves. Upon release, sensory neuropeptides induce vasodilatation, increased plasma protein permeability and inflammatory cells recruitment and activation.



fibres [14]. BK may produce CGRP- and possibly SP-release from primary sensory-C fibres *via* capsaicin-independent mechanisms [15].

Intranasal histamine application in several species including man produces CGRP and SP release from sensory C-fibres, probably via type H_1-receptors [16, 17]. The vasodilatation evoked by topical application of histamine in pig skin could be decreased following systemic capsaicin pretreatment associated with CGRP and SP depletion [11]. These observations suggest that histamine may activate sensory C-fibres. In turn, CGRP probably stimulates histamine release from mast cells and potentiates histamine action, though less potently compared to SP [18–21]. This possible indirect, CGRP-mediated histamine release following sensory nerve stimulation can be experimentally confirmed by attenuation of CGRP-induced vasodilatation following pre-treatment with histamine blockers. Therefore, histamine release from mast cells appears to require co-action of sensory neuropeptides [22].

The inflammatory response in the nasal mucosa is characterised by local infiltration with mast cells, lymphocytes, and eosinophils [23]. The activity of the enzymes involved in the degradation of tachykinins and CGRP such as angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP), most likely modulates neurogenic inflammation in the airways mucosa [24]. Dipeptidylpeptidase IV (DPPIV) is a serine exopeptidase that cleaves Xaa-Pro dipeptides from the N-terminus of oligo- and polypeptides such as SP [25]. SP is sequentially cleaved by DPPIV from the N-terminus to generate fragments: first SP3–11, then after a second cleavage, SP5–11 [25].

Since DPPIV and NEP cause the degradation of peptides most likely involved in the pathophysiology of rhinosinusitis and asthma [2], the activity of these enzymes has been studied in nasal mucosa biopsies from patients suffering from chronic rhinosinusitis. It was found that DPPIV is expressed at specific and distinct sites within the human nasal mucous gland. The localisation of the enzyme DPPIV in the apical position of nasal exocrine cells in seromucous glands suggests a role of this enzyme in the protective function of the mucus. The presence of DPPIV was observed in vascular endothelial cells and in T-cells. This finding is in line with earlier histochemical studies of DPPIV in human and other mammalian tissues [26–27], as well as with more recent reports of the distribution of human DPPIV [28–30]. DPPIV immunoreactivity was also observed in some intraepithelial cells of the nasal mucosa. These cells were most likely not Langerhans cells since they did not express CD 1A or Protein 100 immunoreactivity on their surface.

The activity of the enzymes NEP and DPPIV was found to vary considerably among patients with chronic rhinosinusitis. Both enzymes' activity was also observed to be inversely related to the severity of the inflammation [31–33]. Conversely, high NEP and DPPIV enzymatic activity correlated with small numbers of inflammatory cells in the nasal mucosa. Also, the fact that the enzymatic

activity increased after treatment of chronic rhinosinusitis adds support to the involvement of the enzyme in this pathology. The potential clinical application of exogenous DPPIV as a new treatment of chronic rhinosinusitis is under study.

In conclusion, increased sensory neuropeptide activity and a reduction of their catabolism seems to be associated with an augmentation of nasal mucosa vasodilatation, as well as plasma exudation and an increased density of inflammatory cells. This neurogenic inflammation appears to contribute to the intensity of the nasal symptoms in patients with chronic rhinosinusitis and local hyperreactivity.

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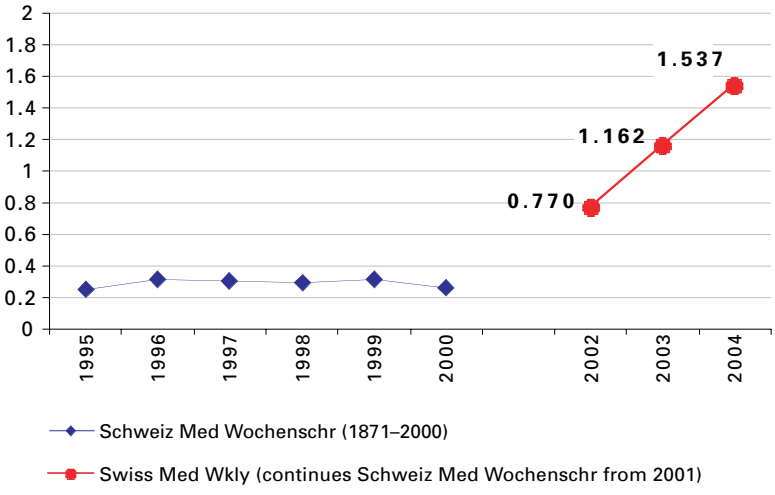

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