REVIEW

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Neurogenic inflammation of the upper airway mucosa*

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SUMMARY

Chronic inflammation of the upper airway mucosa is most likely caused by multiple factors, but is frequently associated with local neurogenic inflammation. This phenomenon can be induced by the inhalation of exogenous particles and chemicals present in our environment, as well as irritants produced endogenously. These irritants, i.e. histamine, H+ or bradykinin, can stimulate the abundant afferent sensory nerves endings, epithelial and neuroendocrine cells present in the upper airways mucosa. These structures can interact with our immune and neural cells by producing pro-inflammatory neuropeptides, cytokines, chemokines and neurotrophins. This short review summarizes some of our current knowledge with regard to the role of airborne chemical stimuli and their possible implications in the development of chronic inflammation of the upper airways mucosa.

Key words: sensory nerves, takykinins, calcitonin gene-related peptide, nerve growth factor, brain-derived neurotrophic factor, neurotrophins, neurogenic inflammation, nasal mucosa, airway mucosa, neuroendocrine cells, epithelial cells

INTRODUCTION

The increasing prevalence of chronic airway diseases (CAD), including chronic rhinosinusitis (CRS) and bronchial asthma (BA), is associated with a significant reduction in patients' quality of life. Multifactorial pathophysiological mechanisms are very likely involved in the development of CAD. Among them, neurogenic inflammation, induced by stimulation of both sensory nerves and neuroendocrine cells present in the respiratory mucosa, has received increasing attention. For many years the airway epithelium was simply considered a protective physical barrier. However, recent studies suggest that the autonomic nervous system of the airways is involved, along with other, as yet, unknown mechanisms, in complex interactions between afferent sensory fibers and efferent nerves of sympathetic and parasympathetic origin.

The nose may be considered as an air conditioner involved in the protection of our fragile lower airways against inhalation of potentially harmful exogenous particles and chemical irritants present in our environment. Epithelial and neuroendocrine cells also seem to interact with our immune and neural cells, by producing pro-inflammatory neuropeptides, cytokines, chemokines and neurotrophins [1-6]. Increasing evidence supports the concept that upper and lower airways represent a continuum. Many nasal diseases influence the lower airways and vice versa [1].

Both upper and lower airway mucosa are densely innervated by sensory C and Aδ nerves which can be activated by thermal, mechanical and chemical stimuli [5,7]. Sensations of airway irritation, discomfort or pain inform our body about potential injury and may trigger protective responses such as sneezing, coughing, mucus production and airway narrowing [8]. These sensations involve the nociceptive system of our entire body, integrating local transduction with airborne irritants as stimuli, and with central nervous system cognitive and emotional processing [9,10].

This short review is an attempt to summarize some of our current knowledge with regard to the role of airborne chemical stimuli and their possible implications in the development of chronic inflammation of the airways and subsequent CAD.

NOCICEPTION IN THE AIRWAYS

Most airborne chemical stimuli appear to be capable of stimulating both olfactory receptors (1st cranial nerve), located in the olfactory cleft of the superior nasal cavities, as well as the dense network of free nerve endings of the trigeminal nerve (5th cranial nerve) [11]. The sensations derived from the trigeminal nerve stimulation are somatosensory and may include burning, stinging, itching, tickling, cooling, warming and various pain sensations. However, repeated or continuous olfactory stimulation also seems to elicit adaptation processes, confirmed by psychophysical measures, (i.e. decrease in perceived intensity), as well as by psychophysiological measures, (such as

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decrease of skin conductance response (SCR) amplitudes). Conversely, repeated trigeminal stimulation may induce differential responses due to variable inter-stimulus intervals (ISIs) as well as the nature of the chemical stimuli [12]. Specifically, trigeminal stimuli can produce increases in rated intensity with short ISI, a phenomenon called "sensitisation". Moreover, with long ISI, repeated trigeminal stimuli can produce marked decreases in intensity, a phenomenon referred to as "desensitisation".

Fibres of the trigeminal nerve, including C- and Aδ-fibres can induce a burning sensation when exposed to capsaicin, the pungent component of various chilli pepper plants [13-15]. The vanilloid receptor 1 (VR1) is activated by capsaicin and then causes a burning sensation. The VR1 receptors, present on sensory nerve endings, can also be stimulated and/or up-regulated by H+, adenosine tri-phosphate, prostaglandins, nicotine, bradykinin, as well as histamine [14].

Interestingly, the sensitivity of nociception may vary between individuals and seems be to up-regulated in some peoples suffering from allodynia. Desensitisation of sensory nerves endings could be characteristic of those who add capsaicin to their everyday diet without experiencing any discomfort. Neuropeptides are synthesized in the nucleus of sensory neurons and are then conveyed in vesicles to the nerve endings by slow axonal transport. When the amount of released sensory peptides following capsaicin exposure is higher than the amount of sensory neuropeptides available, desensitisation may occur [9,10,16]. Chronic exposure to capsaicin can also be associated with long-lasting functional impairment of sensory neurons [17].

Stimulation of sensory C and Aδ fibres leads to the release of multiple neuropeptides. They include structurally-related tachykinins, such as substance P (SP), neurokinin A (NKA), neuropeptide, K (NPK) and calcitonin gene-related peptide (CGRP) [3].

These neuropeptides are involved in vasodilatation and oedema associated with nasal obstruction in the upper airway, and bronchoconstriction (asthma) in the lower airway. In addition, sensory neuropeptides participate in plasma protein exudation, mucus secretion and inflammatory cell recruitment. This physiological response, called "neurogenic inflammation" [18,19], seems to contribute to the intensity of nasal obstruction, bronchoconstriction and mucus production, the most common symptoms in CAD associated with hyperreactivity.

PRO INFLAMMATORY MEDIATORS

The concentration of pro-inflammatory sensory neuropeptides has been shown to be increased in the airway mucosa of patients suffering from chronic upper and lower airway inflammation [16,20]. The amount of these sensory neuropeptides seems to be well correlated with the intensity of patients' symptoms. In contrast, the activity of the enzymes involved in the degradation of these sensory neuropeptides is markedly reduced. As a result, a marked decrease of dipeptidylpeptidase IV (DPPIV) activity within the human upper and airway mucosa has previously been shown to be closely correlated to the severity of both symptoms and histological features associated with chronic inflammatory airway diseases [21,22]. Unfortunately, there have been an increasing number of reports of harmful side effects, such as rhinopharyngitis and headaches, symptoms associated with "incretins" treatment, a DPPIV inhibitor prescribed for diabetes type II oral treatment [23].

Following the discovery of a very dense sensory innervation of the airways [3] neuroendocrine cells were identified within the airway mucosa. This is of growing interest, since an extensive interaction between sensory neurons, neuroendocrine cells and immune cells has been observed during chronic airway inflammation and persistent airway hyperreactivity. This neuro-immune cross-talk involves different groups of mediators, among them the neurotrophin family, which includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophins (NT-3/4). Neurotrophins modulate airway inflammation by enhancing sensory nerve excitability and the production of pro-inflammatory neuropeptides, as well as through interaction with different immune cell types [6,24,25].

The cellular sources of neurotrophins under physiological conditions appear to be primarily neurons and nerve-associated cells, such as glia cells, Schwann cells and fibroblasts. During inflammation, neurotrophins are also produced by haematopoietic cells including mast cells, macrophages, T cells and B cells. There is growing evidence now that neurotrophins are produced by a variety of non-neuronal and non-immune cell types such as endothelial, epithelial and neuroendocrine cells [26]. In the normal human airways, constitutive expression of BDNF and NGF has been found in nasal and bronchial epithelial and glandular cells, as well as in pulmonary lymphocytes and macrophages [27]. Neurotrophin concentration has been reported to be quite low in bronchoalveolar and nasal lavage fluid in asymptomatic patients, but increases dramatically during inflammation in allergic patients [28-31]. Neurotrophins and their receptors are expressed in human airways and are most likely involved in the pathophysiological mechanisms of allergic rhinitis [32]. Neurotrophins exert a dual role in the pathogenesis of asthma [33]. In the nervous system, neurotrophins enhance the number of tachykinin-producing nerve fibres surrounding the airways, sensitize C fibres to irritants and increase the synthesis and release of neuropeptides such as the tachykinins, SP, NKA and NKB. These neuropeptides are involved in several key features of chronic rhinosinusitis and asthma [34]. In the immune system, neurotrophins induce differentiation of B-lymphocytes, cytokine synthesis by T cells, promote the release of various pro-inflammatory mediators by mast cells and increase survival and activation of eosinophils [35].

CONCLUSION

In conclusion, the sensory nerves, epithelial and neuroendocrine cells of the airway mucosa seem to contribute to symp-

tomatic neurogenic inflammation of the airways by the release of several peptides provoked by exposure to airborne chemicals. However, one should keep in mind that neurogenic inflammation also seems to be partly modulated by the central nervous system, including its cognitive and emotional components.

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REFERENCES

1. Bousquet J, Van Cauwenberge P, Bachert C, et al. Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). Allergy 2003; 58: 192-197.
2. Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract. Part II. Am Rev Respir Dis 1991; 144: 1391-1399.
3. Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract. Part I. Am Rev Respir Dis 1991; 144: 1187-1198.
4. Barnes PJ. Neurogenic inflammation in the airways. Respir Physiol 2001; 125: 145-154.
5. Martling CR. Sensory nerves containing tachykinins and CGRP in the lower airways. Functional implications for bronchoconstriction, vasodilatation and protein extravasation. Acta Physiol Scand Suppl 1987; 563: 1-57.
6. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. J Allergy Clin Immunol 2007; 120: 1279-1284.
7. Stjarne P. Sensory and motor reflex control of nasal mucosal blood flow and secretion; clinical implications in non-allergic nasal hyperreactivity. Acta Physiol Scand Suppl 1991; 600: 1-64.
8. Angell James JE, Daly Mde B. Nasal reflexes. Proc R Soc Med 1969; 62: 1287-1293.
9. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature 2001; 413: 203-210.
10. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 2005; 115: 410-418.
11. Brand G. Olfactory/trigeminal interactions in nasal chemoreception. Neurosci Biobehav Rev 2006; 30: 908-917.
12. Cometto-Muniz JE, Cain WS. Thresholds for odor and nasal pungency. Physiol Behav 1990; 48: 719-725.
13. Caterina MJ, Schumacher MA, Tominaga M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997; 389: 816-824.
14. Taylor-Clark TE, Kollarik M, MacGlashan DW, Jr., Undem BJ. Nasal sensory nerve populations responding to histamine and capsaicin. J Allergy Clin Immunol 2005; 116: 1282-1288.
15. Nakagawa H, Hiura A. Capsaicin, transient receptor potential (TRP) protein subfamilies and the particular relationship between capsaicin receptors and small primary sensory neurons. Anat Sci Int 2006; 81: 135-155.
16. Lacroix JS, Buvelot JM, Polla BS, Lundberg JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy. 1991; 21: 595-600.
17. Papka RE, Furness JB, Della NG, Murphy R, Costa M. Time course of effect of capsaicin on ultrastructure and histochemistry of substance P-immunoreactive nerves associated with the cardiovascular system of the guinea-pig. Neuroscience 1984; 12: 1277-1292.
18. Celander O, Folkow B. The nature and the distribution of afferent fibres provided with the axon reflex arrangement. Acta Physiol Scand 1953; 29: 359-370.
19. Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. Br J Pharmacol Chemother 1967; 31: 138-151.
20. Stead RH, Bienenstock J, Stanisz AM. Neuropeptide regulation of mucosal immunity. Immunol Rev. 1987; 100: 333-359.
21. Grouzmann E, Monod M, Landis B, et al. Loss of dipeptidylpeptidase IV activity in chronic rhinosinusitis contributes to the neurogenic inflammation induced by substance P in the nasal mucosa. FASEB J 2002; 16: 1132-1134.
22. Landis BN, Grouzmann E, Monod M, et al. Implication of Dipeptidylpeptidase IV Activity in Human Bronchial Inflammation and in Bronchoconstriction Evaluated in Anesthetized Rabbits. Respiration 2008; 75: 89-97.
23. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007; 298: 194-206.
24. Fox AJ, Patel HJ, Barnes PJ, Belvisi MG. Release of nerve growth factor by human pulmonary epithelial cells: role in airway inflammatory diseases. Eur J Pharmacol 2001; 424: 159-162.
25. Pons F, Freund V, Kuissu H, et al. Nerve growth factor secretion by human lung epithelial A549 cells in pro- and anti-inflammatory conditions. Eur J Pharmacol 2001; 428: 365-369.
26. Jornot L, Grouzmann E, Lacroix JS, Rochat T. BDNF and DPP-IV in polyps and middle turbinates epithelial cells. Rhinology 2007; 45: 129-133.
27. Ricci A, Felici L, Mariotta S, et al. Neurotrophin and neurotrophin receptor protein expression in the human lung. Am J Respir Cell Mol Biol 2004; 30: 12-19.
28. Sieskiewicz A, Olszewska M, Olszewska E, et al. Neuroendocrine cells in the nasal mucosa - preliminary report. Folia Histochem Cytobiol 2007; 45: 123-127.
29. Fang SY, Shen CL, Ohyama M. Distribution and quantity of neuroendocrine markers in allergic rhinitis. Acta Otolaryngol 1998; 118: 398-403.
30. Boers JE, den Brok JL, Koudstaal J, Arends JW, Thunnissen FB. Number and proliferation of neuroendocrine cells in normal human airway epithelium. Am J Respir Crit Care Med 1996; 154: 758-763.
31. Weichselbaum M, Sparrow MP, Hamilton EJ, Thompson PJ, Knight DA. A confocal microscopic study of solitary pulmonary neuroendocrine cells in human airway epithelium. Respir Res 2005; 6: 115.
32. Raap U, Fokkens W, Bruder M, et al. Modulation of neurotrophin and neurotrophin receptor expression in nasal mucosa after nasal allergen provocation in allergic rhinitis. Allergy 2008; 63: 468-475.
33. Heymach JV, Jr., Kruttgen A, Suter U, Shooter EM. The regulated secretion and vectorial targeting of neurotrophins in neuroendocrine and epithelial cells. J Biol Chem 1996; 271: 25430-25437.
34. Goodman LJ, Valverde J, Lim F, et al. Regulated release and polarized localization of brain-derived neurotrophic factor in hippocampal neurons. Mol Cell Neurosci 1996; 7: 222-238.
35. Adriaensen D, Brouns I, Van Genechten J, Timmermans JP. Functional morphology of pulmonary neuroepithelial bodies: extremely complex airway receptors. Anat Rec A Discov Mol Cell Evol Biol 2003; 270: 25-40.

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