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Review

Extending the understanding of sensory neuropeptides

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Abstract

The tachykinins substance P and neurokinin A are present in human airways, in sensory nerves and immune cells. Tachykinins can be recovered from the airways after inhalation of ozone, cigarette smoke or allergen. They interact in the airways with tachykinin NK_1, NK_2 and NK_3 receptors to cause bronchoconstriction, plasma protein extravasation, and mucus secretion and to attract and activate immune cells. In preclinical studies they have been implicated in the pathophysiology of asthma and chronic obstructive pulmonary disease, including allergen- and cigarette smoke induced airway inflammation and bronchial hyperresponsiveness and mucus secretion. Dual NK_1/NK_2 or triple $NK_1/NK_2/NK_3$ tachykinin receptor antagonists offer therapeutic potential in airway diseases such as asthma and chronic obstructive pulmonary disease.

Keywords: Tachykinin; Substance P; Neurokinin A; Asthma; Chronic obstructive pulmonary disease; Airway inflammation

Contents

1. Introduction

The inflammation that results from the release of substances from primary sensory nerve terminals is called neurogenic inflammation. Already more than one century ago the first

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observations were made that activation of dorsal root ganglia neurons result in vasodilatation. Since then, abundant evidence has been accumulated to suggest that activation of peripheral terminals of sensory neurons by local depolarisation, axonal reflexes, or dorsal root reflexes release bioactive substances. These substances act on target cells in the periphery, such as mast cells, immune cells, and vascular smooth muscle cells, to produce inflammation (redness and warmth, swelling, hypersensitivity) (Richardson and Vasko, 2002).

The neuropeptides substance P and calcitonin gene-related peptide are considered to be the major initiators of neurogenic inflammation (Lembeck and Holzer, 1979; Barnes, 2001; Groneberg et al., 2004). Substance P and neurokinin A are members of the tachykinin peptide family and are potent vasodilators and contractors of smooth muscle (Severini et al., 2002). In studies on rodent airways substance P and neurokinin A have been implicated as the neurotransmitters mediating the excitatory part of the nonadrenergic, noncholinergic (NANC) nervous system. (Barnes, 1986; Lundberg, 1996).

The tachykinins substance P and neurokinin A have various effects that could contribute to the changes observed in the airways of patients with asthma and chronic obstructive pulmonary disease (COPD). These include smooth muscle contraction, submucosal gland secretion, vasodilatation, increase in vascular permeability, stimulation of cholinergic nerves, stimulation of mast cells, stimulation of B- and T-lymphocytes, stimulation of macrophages, chemo-attraction of eosinophils and neutrophils and the vascular adhesion of neutrophils. In the present review, data on the role of sensory neuropeptides obtained in animal models are reviewed. Moreover, an update on findings in human airways is presented. Finally, the prospects for development of tachykinin receptor antagonists as possible treatment for asthma and chronic obstructive pulmonary diseases are discussed.

2. Localisation and production of tachykinins in the airways

Tachykinins (substance P, neurokinin A and neurokinin B) 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 (Severini et al., 2002; Pennefather et al., 2004). Furthermore, mRNA expression studies suggests that the tachykinin hemokinin 1 has a unique distribution outside neuronal tissues (Patacchini et al., 2004).

In the airways, a distinct subpopulation of primary afferent nerves that are characterized by their sensitivity to capsaicin are considered as the principal source of substance P and neurokinin A (Lundberg et al., 1983a, 1984). Although they can also be expressed in capsaicin resistant neurons (Hunter et al., 2000; Carr et al., 2002), capsaicin pretreatment of experimental animals caused an almost total depletion of substance P and neurokinin A immunoreactivity (Lundberg et al., 1984; Nilsson et al., 1990). Radioimmunoassay and immunohistochemistry demonstrated the presence of substance P- and neurokinin A-immunoreactive nerves beneath and within the epithelium, around blood vessels and submucosal glands and within the bronchial smooth muscle layer (Lundberg et al., 1984; Luts et al., 1993). In guinea pigs, airway sensory nerves containing tachykinins are easily demonstrated but in human airways, tachykinergic innervation is sparse. Additional, nonneuronal sources of tachykinins in the airways have been reported. Chu and colleagues demonstrated staining for substance P in the airway epithelium (Chu et al., 2000) and Maghni and coworkers reported the presence of substance P in airway smooth muscle cells (Maghni et al., 2003). There is also evidence for the production of substance P by eosinophils, monocytes and macrophages, lymphocytes and dendritic cells (Lai et al., 1998; Aliakbar et al., 1987; Ho et al., 1997; Lambrecht et al., 1999). Immunoreactivity for neurokinin B has not been found in the airways yet. PCR-techniques demonstrated transcripts of the mouse and the human *TAC4* gene in lung tissue (Page et al., 2003; Duffy et al., 2003), which may result in the formation of the hemokinin 1, representing another source of tachykinins in the airways.

3. Airway tachykinin receptors

The biological activity of tachykinins depends on their interaction with three specific receptors, the tachykinin NK_1, NK_2 and NK_3 receptor (Maggi, 1993; Almeida et al., 2004). The tachykinin receptor displaying highest affinity for substance P was termed the tachykinin NK_1 receptor. The receptor showing highest affinity for neurokinin A was termed the tachykinin NK_2 receptor and the receptor with the highest affinity for neurokinin B was called the tachykinin NK_3 receptor (Maggi, 2000). Hemokinin 1 and its elongated forms act as tachykinin NK_1 receptor preferring agonists (Kurtz et al., 2002). It should be emphasized however that all tachykinins can act as full agonists on the three different receptors but with lower affinities than on the preferred receptor (Maggi et al., 1993).

An overwhelming amount of functional data demonstrates indirectly the broad expression of tachykinin NK_1 end NK_2 receptors in the airways. Also functional evidence for the presence of tachykinin NK_3 receptors exists, including human airways (Joos et al., 2001b; Myers et al., 2005). mRNA for the tachykinin NK_1 and NK_3 receptor has been found in human pulmonary veins, arteries and bronchi. mRNA for the tachykinin NK_2 receptor was abundantly expressed in human bronchi whereas a low expression of this receptor was found in human pulmonary veins and arteries (Pinto et al., 2004). In a study on surgical specimens, using specific antibodies, tachykinin NK_1 and NK_2 receptor protein was detected in human bronchial glands, bronchial vessels and bronchial smooth muscle. Tachykinin NK_1 receptors were occasionally found in nerves and tachykinin NK_2 receptors in inflammatory cells, such as T-lymphocytes, macrophages and mast cells (Mapp et al., 2000). A study on endobronchial biopsies revealed immunoreactivity for the tachykinin NK_1 receptor in the epithelium and the submucosa. Goblet cells appeared to be the cells with the strongest staining. In the submucosa, staining was localized on the endothelial cells of the blood vessels, the surfaces of inflammatory cells, and some smooth muscle cells