Tachykinin receptors and airway pathophysiology

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ABSTRACT: The mammalian tachykinins (TKs), substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), have been shown to act as neurotransmitters (reviews [1-4]). SP and NKA are products of the same gene (preprotachykinin I), which is expressed both in the central and in the peripheral nervous system, whilst NKB is produced by a distinct gene (preprotachykinin II), which is selectively expressed in the central nervous system [3, 4].

TKs, particularly SP and NKA, are widely distributed in the airways and lungs of several species, including man [5-7]. The major, if not the sole, source of TKs in the airways is the peripheral endings of certain primary afferent nerves, which are sensitive to the stimulant and toxic action of capsaicin [8-10]. The preprotachykinin I gene is expressed by capsaicin-sensitive afferent neurons innervating the mammalian airways and, for this reason, SP and NKA are co-stored and co-released from sensory nerve terminals in the airways [7, 11, 12]. It should be remembered, that calcitonin gene-related peptide (CGRP) is also expressed by these primary afferent neurons, and is co-localized and co-released along with TKs in the airways [7].

Evidence from several laboratories (reviews [8-10]) has now established that the capsaicin-sensitive afferents play a dual, sensory and "efferent" function: these are determined by transmitter release from central and peripheral endings of primary afferent neurons, respectively. In the airways, the sensory function of these nerves deals with a number of reflex responses, including cough to inhaled irritants [13, 14]. The "efferent" function involves a variety of biological effects, including bronchoconstriction, vasodilatation, increase in plasma protein extravasation, recruitment of inflammatory cells etc.; effects which are collectively known as "neurogenic inflammation" [7, 11, 14]. These effects, mediated through specific receptors expressed by target cells in the airways, mimic several of the typical features of asthma. The recognition of this process has led to the speculation that neurogenic inflammation might play a role in the genesis of asthma/bronchial hyperreactivity [7, 11, 14], especially following processes (e.g. epithelial shedding) which cause damage to systems which, like neutral endopeptidase, limit the biological action of released TKs [15]. Accordingly, data obtained in several laboratories have indicated a significant role of neurogenic inflammation in animal models of asthma/bronchial hyperreactivity [7, 11, 14]. Such evidence has been chiefly based, until now, on the comparison of altered airway function in vehicle- versus capsaicin-pretreated animals. In fact, when administered in high doses to intact animals, capsaicin produces a long-lasting defunctionalization of the sensitive primary afferent neurons, along with neuropeptide depletion [8-10]. This approach undoubtedly demonstrates the overall importance of capsaicin-sensitive afferents in airways pathophysiology, but does not make it possible to recognize the relative importance of the individual neuropeptides released from the primary afferent nerves. A complementary approach to the use of capsaicin is the use of selective receptor antagonists for sensory neuropeptides. Since exogenously administered TKs reproduce the cardinal signs of asthma/bronchial hyperreactivity in the airways, and most of their effects are mediated through specific receptors, much attention has recently been focused on the discovery and development of selective receptor antagonists for TKs [4]. The basic idea behind these efforts is that TK receptor antagonists may eventually prove beneficial in treating certain forms of airway disease, and...
prove or disprove the idea of a pathogenic role of sensory nerves in airways disease.

The aim of this short review article is to present some of the most recent developments in this field, with special attention to advancements presented at the International Symposium on Substance P and Related Peptides, held in Shizuoka, Japan, November 3-6, 1992.

Tachykinins in the airways

The distribution of TKs in sensory nerve endings at airways level has been repeatedly reported in various mammalian species, including humans [5-7].

Human airways possess TK-containing nerve profiles [16], which are of extrinsic origin as they disappear after lung transplantation [17]. Density of TK innervation in the lungs varies depending on the localization (highest in lamina propria, ganglia and smooth muscle [18]), species (higher in rodents [16]), and pathology (higher in asthmatics [19]), although the latter results were not confirmed in another study [20]. Various TKs, including SP, NKA and the N-terminally elongated form of NKA, neuropeptide K, have been detected in extracts from the human lung [21], and in the bronchoalveolar lavage fluid. Indeed, SP has been found to be elevated in the fluid of allergic patients after allergen provocation [22].

In guinea-pig airways, nerve stimulation produces prominent bronchoconstrictor and inflammatory effects, which are mediated through release of TKs from peripheral endings of capsaicin-sensitive nerves: in this species, TKs fulfill all of the classical criteria used to define neurotransmitter status for a given substance [11]. Capsaicin, which on acute application produces TK release from sensory nerves, has been reported to produce contraction of the human isolated bronchus [23], which is enhanced by peptidase inhibitors [24], and may involve release of endogenous TKs. However, such a hypothesis needs to be confirmed with TK receptor antagonists.

Tachykinin receptors

With few, but notable exceptions (e.g. mast cells degranulation), the biological effects of TKs in the airways are mediated through their common C-terminal sequence. Based on the different rank order of potency of natural TKs, three distinct TK receptor types have been identified, which have been termed NK-1 (SP-preferring), NK-2 (NKA-preferring), and NK-3 (NKB-preferring) (reviews [3, 4]). The existence of three distinct receptor types which mediate TK actions has been strengthened by the development of selective receptor agonists (synthetic ligands which stimulate only one of the three receptors with high selectivity), by the development of receptor selective competitive antagonists (see next sections), and ultimately by the isolation and cloning of the three receptor proteins [4, 25].

With few exceptions, not involving the mammalian airways, the expression of the NK-3 receptor is confined to the central nervous system, whilst NK-1 and NK-2 receptors are expressed both in the central and peripheral nervous system [3, 4]. Thus, both SP and NKA are present in the airways, and are co-released from sensory nerves in a calcium-dependent manner [12]. Since both NK-1 and NK-2 receptors are present on target cells in the airways [11, 26], the expression of various receptor types on different target cells ultimately determines the biological consequences of TKergic co-transmission. For both physiological and, in perspective, therapeutic purposes, the precise assessment of the receptor types mediating the various biological actions of TKs in the airways and, especially, the assessment of the receptor types responsible for their biological actions in human airways becomes of paramount importance. The issue is complicated by several factors, which can be summarized as follows:

With the development of newer and more selective ligands it has become clear that pharmacological differences exist within the NK-1 and NK-2 receptors. Such differences involve both species-related variants of the main TK receptors and, probably, also the existence of true receptor subtypes (intraspescies variants) [4]. For the NK-1 receptor, it appears that some competitive receptor antagonists recognize with different affinities the receptor expressed in human, guinea-pig and rabbit species, as opposed to that expressed in the rat or mouse species [27, 28]. Furthermore, the existence of intraspecies heterogeneity of the NK-1 receptor has been proposed [29]. Recently, the existence of a novel, "septide-sensitive" receptor, which could represent an NK-1 receptor subtype, has also been proposed [30]. It appears that a septide-sensitive receptor exists in the guinea-pig bronchi [31], whilst it is not known whether it is present in human airways. This is an area of very rapid development, and no clear-cut conclusion has yet been drawn, especially with regard to nomenclature of the various receptor subtypes/species variants.

With regard to the NK-2 receptor, the existence of receptor subtypes (NK-2A and NK-2B) was proposed on the basis of the different pharmacological profiles detected in peripheral preparations from various species [4, 32-34]. Although cases for intraspecies heterogeneity have been presented, which support the idea of the existence of true receptor subtypes (e.g. NK-2A receptor on guinea-pig tracheobronchial smooth muscle, and NK-2B-like receptor on guinea-pig alveolar macrophages) [35-37], it is not yet clear whether the pharmacological criteria used to define NK-2A and NK-2B receptors chiefly recognize species variants of the NK-2 receptor. In various smooth muscle preparations, NK-2A receptor is expressed by the human, guinea-pig and rabbit species, whilst rat and hamster express NK-2B receptors [4].

The TK receptors which mediate the same effect may vary considerably with species. For the airways, one of the most striking examples is related to bronchoconstriction: this is mediated by NK-1 and NK-2A receptors in guinea-pigs and rabbits, by NK-2B receptors in hamsters, and NK-2A receptors in human bronchus [31-33, 38]. In mice, no bronchoconstriction is produced by TKs in the isolated bronchus, and bronchodilation may
be demonstrated through the release of prostanoids from the epithelium [39].

**Tachykinin receptor antagonists**

The first generation of TK receptor antagonists was developed at the beginning of the 1980s, based on insertion of multiple D-Trp residues on the backbone of SP (review [4]). The best known example of this first generation of TK receptor antagonists is the undecapeptide SP derivative, Spanide I. These compounds have been instrumental in assessing the status of SP as a neurotransmitter, especially in the peripheral nervous system. These ligands possess a number of drawbacks, however, which have seriously hampered basic research on TKergic transmission; furthermore, owing to their low potency and limitations linked to their peptide nature, these compounds have not been considered as serious candidates for application in humans.

In the last 5 yrs, a number of peptide ligands have been developed which represent the "second generation" of TK receptor antagonists (tables 1 and 2). Common features of these ligands are their remarkable improvement in potency and selectivity for only one of the three TK receptors and their peptide nature [4]. These ligands have been of special importance for establishing the relative role of NK-1 and NK-2 receptors (and by inference of

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>NK-1 receptor</th>
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<th>NK-3 receptor</th>
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<td>inactive*</td>
<td>6.16 (5.8-6.4)</td>
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<tr>
<td>(+)CP 96,345</td>
<td></td>
<td>inactive*</td>
<td>inactive*</td>
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<tr>
<td>RP 67,580</td>
<td></td>
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<tr>
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TK: tachykinin; NK: neurokinin; GPI: guinea-pig ileum in the presence of atropine, substance P methylester as an agonist; RPA: endothelium-denuded rabbit pulmonary artery, neurokinin A as an agonist; HT: hamster trachea, neurokinin A as an agonist; RPV: rat portal vein, Arg-neurokinin B as an agonist. Affinities are presented as pA2 values. 95% confidence limits are in brackets. *: inactive at 10 μM; **: inactive at 1 μM; ***: inactive at 3 μM.
SP and NKA) in examples of TKergic co-transmission (e.g. atropine-resistant bronchoconstriction in guinea-pigs) (see below). Some of these ligands also have characteristics (e.g. long duration of action in vivo) which could enable clinical testing.

Finally, a third generation of TK receptor antagonists arose from the discovery of potent nonpeptide ligands, which are highly selective for NK-1 receptor, such as CP 96,345 [27] or RP 67,580 [28], or for the NK-2 receptor, SR 48,968 [38, 40] (fig. 1). Because of their nonpeptide nature, these ligands are the most obvious candidates as drugs to be used in human therapy.

The use of second and third generation TK receptor antagonists has enabled some firm conclusions about TK receptors and airway pathophysiology to be drawn, especially in guinea-pigs. These recent advances could be summarized as follows:

Atropine-resistant bronchoconstriction is produced in guinea-pigs airways by nerve stimulation through TK release from sensory nerves. This prominent effect, which in guinea-pigs equals in magnitude the cholinergic bronchoconstriction, involves both NK-1 and NK-2 receptors, when exogenous TKs are administered either in vivo (e.g. recording changes of insufflation pressure), or in vitro (e.g. recording tension changes in isolated bronchi). However, when endogenous TKs are released by stimulating sensory nerves, activation of NK-2 receptors plays a dominant role in the overall bronchoconstriction, and the role of NK-1 receptors (as deduced by the effectiveness of NK-1 receptor antagonists) is negligible [33, 41, 42]. In the isolated guinea-pig bronchus, the relative contribution of NK-1 receptor to the overall bronchomotor response increases (and that of NK-2 receptors decreases) after pretreatment with peptidase inhibitors, suggesting that endogenous SP (NK-1 receptor preferring) is degraded at a faster rate than endogenous NKA [33].

Stimulation of TK release from sensory nerves produces a remarkable increase in plasma protein extravasation in both rat and guinea-pig airways. This reaction can be demonstrated not only following electrical stimulation of, e.g. vagal nerves in vivo, but also in response to inhalation of irritants such as cigarette smoke, administration of various mediators of inflammation, and antigen challenge [43]. Plasma protein extravasation produced by endogenous TKs in the airways is entirely mediated through NK-1 receptors, as documented by the ability of selective NK-1 receptor antagonists to abolish the response [44, 45]. Likewise, NK-1 receptors seem exclusively responsible for increased mucus secretion produced by TKs in the airways (46, 47), and see below.

The results of the above-mentioned studies indicate a clear specialization of NK-1 versus NK-2 receptors in mediating the inflammatory versus bronchomotor responses to endogenous TKs in guinea-pig airways. Whether exactly the same situation applies to human airways is not known, although it is suggested by some results. Thus, NK-2 receptors only mediate contraction of human isolated airways [38], NKA but not SP produces bronchoconstriction in asthmatics [48, 49] and NK-1 receptors mediate mucus secretion in human isolated trachea [47]. A preliminary study raised the possibility that NK-1 receptors may contribute to airway bronchoconstriction in asthmatics, owing to an over expression...
of NK-1 receptor messenger ribonucleic acid (mRNA) in asthmatic lungs [50]. If the situation which has been delineated from guinea-pig studies were fully applicable to human airways, it would be logical to conclude that an antagonist having mixed and possibly balanced affinity for NK-1 and NK-2 receptors could be therapeutically superior to a receptor selective antagonist [11]. At the present time, several examples of antagonists possessing very high affinity (in the nM range of concentrations) for NK-1 or NK-2 receptors are available (table 2 and fig. 1). Although the possibility of developing bifunctional receptor antagonists having high affinity for two distinct receptor proteins is theoretically feasible, the optimization process of lead compounds in classical structure-activity relationship studies required to increase the affinity for a given receptor is almost invariably paralleled by an increase in selectivity, i.e. development of a compound with high affinity (in the nM range of concentrations) for two distinct receptors is difficult to rationalize. It is not very difficult to find receptor antagonists which have similar but low potency (affinity in the μM range of concentrations) in blocking NK-1 and NK-2 receptors: several TK receptor antagonists of first generation, including Spantide I have this characteristic [4]. Recently, another compound of this type (FK 224), which is derived from Streptomyces violaceoniger, has been described [51, 52]. FK 224 possesses similar and relatively balanced affinity for NK-1 and NK-2 receptors, and blocks, at similar doses, both bronchoconstriction (NK-2 receptor mediated) and plasma protein extravasation (NK-1 receptor mediated) in guinea-pig airways. Although the potency of FK 224 for TK receptors is not very high, it might represent a new and interesting tool to assess the pathophysiological importance of TKs in airway diseases. Icmosov et al. [53] recently reported that inhalation of FK 224 inhibits bronchoconstrictor response to inhaled bradykinin in asthmatics, suggesting the involvement of endogenous TKs in the evoked response.

Tachykinins and cough

As mentioned earlier, cough to inhaled irritants is one of the major "sensory" functions produced by capsaicin-sensitive primary afferents at airway level. It is conceivable that TKs released from central endings of these afferent neurons act as neurotransmitter/modulators of the cough reflex in the central nervous system. No data are available, however, from the use of TK receptor antagonists to support this hypothesis.

Kohrogi et al. [54] reported that inhalation of extremely low concentrations of SP produces cough in guinea-pigs, and suggested a possible role of TKs released in the airways to produce cough. These findings have not been confirmed by others, however, [55]. A recent study by Takahama et al. [56] showed that inhalation of NKA also produces cough in conscious guinea-pigs; the response to the inhaled peptide was increased by phosphoramidon, and after induction of bronchitis by SO₂ inhalation, whilst being abolished by vagotomy. Interestingly, NKA-induced cough, contrary to SP- or capsaicin-induced cough, was unaffected by codeine [56]. These results give further support to the idea that local release of TKs in the airways may represent a potent stimulus to initiate the cough reflex. Owing to the availability of potent receptor antagonists for TK receptors, it appears of interest to evaluate whether these compounds may inhibit cough produced not only by inhaled TKs, but also that produced by other irritants.

Yoshihara et al. [57] reported a significant elevation (177% increase above control) of plasma SP levels during paroxysmal cough stage in pertussis patients. Plasma SP levels in such patients were significantly elevated, not only as compared to plasma SP levels measured in the same patients during the recovery stage, but were also significantly higher than those in asthmatic patients measured during and after asthmatic crisis [57].

Tachykinin and airway response to antigen

Various studies and lines of evidence suggest an activation of sensory nerves during allergic reactions in the airways. Earlier studies have reported an attenuation of allergic reactions to acute antigen exposure in capsaicin-pretreated guinea-pigs [43, 58]. The idea that sensory nerves contribute to the acute airway response to antigen has been supported by several recent reports, as follows:

Ellis and Undem [59] reported that application of threshold concentration of antigen to the isolated trachea from sensitized guinea-pigs determines a remarkable enhancement of the TK-mediated atropine resistant contraction produced by electrical stimulation of sensory nerves. The antigen-enhanced response was abolished by application of TK receptor antagonists, while the response to exogenously administered SP was not modified. Furthermore, the antigen-induced potentiation was blocked by pyrilamine, at concentrations which selectively block histamine effects [59]. The authors concluded that antigenic stimulation of resident mast cells releases endogenous histamine to produce prejunctional facilitation of TK release, possibly contributing to the immediate hypersensitivity reaction in the airways [59].

Kohrogi et al. [60] reported that application of the neutral endopeptidase inhibitor, phosphoramidon, known to potentiate TK action in the airways, enhances the contraction produced by ovalbumin application to isolated bronchi from sensitized guinea-pigs, and that capsaicin pretreatment prevents the phosphoramidon-induced potentiation. Phosphoramidon also enhanced the response to leukotriene C₄ and serotonin, whilst leaving contraction to histamine or platelet-activating factor (PAF) unchanged. These findings further suggest that mediators released during the immune reaction activate sensory nerves to release TKs which contribute to the overall bronchomotor response.

Bertrand et al. [61] reported that CP 96,345, a potent and selective nonpeptide antagonist of NK-1 receptor, produces an approximately 50% reduction in plasma protein extravasation in guinea-pig trachea, produced by administration of aerosolized ovalbumin to sensitized animals. The response was also enhanced by
phosphoramidon. Interestingly, the effect of both phosphoramidon and CP 96,345 could be demonstrated at 10 but not at 5 min after ovalbumin challenge, suggesting the involvement of TKs to the delayed phase of reaction to antigen challenge.

TKs stimulate guinea-pig alveolar macrophages to release prostanoids through NK-2B-like receptor [36, 62] Brunelleschi et al. [62] recently reported a dramatic (1-3 orders of magnitude for different TKs) increase in sensitivity to TKs in alveolar macrophages from sensitized guinea-pigs. Concomitantly, no change in the response to bacterial peptide l-formyl-l-methionyl-l-leucyl-l-phenylalanine (FMLP) was produced by immunization [62].

**Tachykinins and mucus secretion**

Various studies have established that TKs are powerful stimulants for mucus secretion in mammalian airways. Such an effect of TKs has been shown to involve mucus discharge from both seromucous glands and goblet cells [46, 47]. A recent study by Miani et al. [63] demonstrated, by the use of receptor selective agonists, that only NK-1 receptors mediate mucus secretion in ferret trachea. Furthermore, the presence of NK-1 receptors on submucosal glands and epithelium was demonstrated at autoradiography, whilst NK-2 receptors are present only on smooth muscle [63]. By the use of receptor selective antagonists, CP 96,345 [64] and FK 888 [65], the involvement of NK-1 receptors in mucus secretion of ferret trachea has finally been proven. FK 888 has also been shown to block noncholinergic mucus secretion produced by activation of intramural nerves, providing evidence for TKergic innervation via NK-1 receptors [65].

**Tachykinins, airway epithelium and inflammatory cells**

TK receptors are present on airway epithelial cells, and their stimulation leads to the release of epithelium-derived factor(s) [39, 66, 67]. A recent study [68] provides evidence that pM concentrations of TKs stimulate, through NK-1 receptors, the release of neutrophil chemoattractant factor(s) from bovine airway epithelial cells in culture. This report is of particular interest, because antidromic stimulation of sensory nerves produces leukocyte accumulation in the airways [69]. While application of exogenous TKs reportedly affects leukocyte function (review [11]), these direct effects are usually produced by high, nonphysiological concentrations of TKs, and their general significance and mechanisms are poorly understood. The findings of Von Essen et al. [68] raise the interesting possibility that leukocyte accumulation produced by TK release into the airways does not originate because of a direct chemotactic action of released peptides (i.e. through a concentration gradient) but may be related to a NK-1 receptor induced release of chemotactic factor(s) from airway epithelium.

Conclusions and considerations

In conclusion, a wealth of data is now available to indicate that TKs are neurotransmitters in the airways of various animal species, where they mediate motor and inflammatory reactions, which resemble those observed in various human diseases. There is little doubt that in small rodents TKs are important physiological mediators of airway response to a variety of stimuli, and TKs fulfill all of the classical criteria which are needed to prove neurotransmission at this level. Available evidence also indicates that TKs are present in human airways, and mediate some of the effects which have been extensively documented in small rodent species. The recent development of potent and selective TK receptor antagonists of second and third generation [4] now offers the exciting possibility of weighing the exact importance of TKs in airway pathophysiology. This will undoubtedly happen in the next few years, when TK receptor antagonists will undergo clinical evaluation for their potential role in treatment of airway diseases. When looking at asthma/bronchial hyperreactivity, it is clear that TKs could take part in both the chronic, inflammatory component of the disease and the genesis of the acute bronchospastic reactions. On the other hand, a plethora of mediators are involved in the genesis of the inflammatory and motor components of asthma, and it would be considered exceptional if TKs were the main mediators underlying this kind of pathology. Since sensory nerves are the only source of TKs in the airways, and owing to the peculiar chemosensitivity of these capsaicin-sensitive primary afferent neurons, it would be logical to expect that a local release of TKs in the airways might be especially important during exposure to irritants. Chronic bronchitis in smokers could be a suitable clinical conditions for testing such a hypothesis. Since TKs are transported to both central and peripheral endings of sensory neurons, their possible role as mediators of airway-targeted reflexes should also be considered: in particular a potential role of TK receptor antagonists in modulating the cough reflex in the central nervous system deserves attention.

In both guinea-pig and ferret airways, a clear specialization of different TK receptors occurs, with NK-1 receptor mediating the inflammatory and secretory components of TK action, and NK-2 receptors being responsible for the bronchomotor response. Whether a similar specialization occurs with the same characteristics in the human airways is not definitively proven, although it might be considered a reasonable assumption on the basis of the available data. If this were the case, a mixed NK-1/NK-2 receptor antagonist might prove therapeutically more effective than antagonists which are selective for only one of these two TK receptors. Since a highly potent, "bifunctional" TK receptor antagonist (possibly with affinity for TK receptors higher than that of natural TKs) is not available at the present time, data obtained with low potency receptor antagonists should be regarded with caution, when assessing the pathophysiological importance of this family of peptides in the genesis of airway diseases.
TACHYKININ RECEPTORS AND AIRWAY PATHOPHYSIOLOGY

References


