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Review

Peripheral tachykinin receptors as targets for new drugs

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Abstract

Tachykinins are widely distributed in the peripheral nervous system of the respiratory, urinary and gastrointestinal tract, stored in enteric neurons and in peripheral nerve endings of capsaicin-sensitive primary afferent neurons from which are released by stimuli having both pathological and physiological relevance. The most studied effects produced by tachykinins in these systems are smooth muscle contraction, plasma protein extravasation, mucus secretion and recruitment/activation of immune cells. The use of tachykinin receptor-selective antagonists and knockout animals has enabled to identify the involvement of tachykinin NK_1, NK_2 and NK_3 receptors as mediators of peripheral effects of tachykinins in different systems/species. The bulk of data obtained in experimental animal models suggests that tachykinins could contribute to the genesis of symptoms accompanying various human diseases including asthma/bronchial hyperreactivity, cystitis of various aetiology, inflammatory bowel diseases and irritable bowel syndrome. Tachykinin receptor antagonists are expected to afford therapeutically relevant effects.

Keywords: Tachykinin; Tachykinin receptor; Respiratory system; Gastrointestinal system; Urinary system

1. Introduction

1.1. Mammalian tachykinins

Tachykinins are a family of peptides which share the common C-terminal sequence Phe-Xaa-Gly-Leu-Met-NH_2. This sequence is crucial for their interaction with specific receptors and for producing the most of their biological effects. However, other domains of the tachykinin peptide sequence have been recognized to be determinant for producing certain effects (e.g. mast cell degranulation encoded by the N-terminal sequence of substance P) (see Maggi et al., 1993, for review). The first peptide of this family, substance P, was discovered by Von Euler and Gaddum as early as in 1931; more than 50 years elapsed before two other mammalian tachykinins, neurokinin A and neurokinin B, were disclosed (Maggio, 1988, for review). To date, substance P, neurokinin A and neurokinin B are three mammalian tachykinins that have reached an established status of neurotransmitters. Two genes have been identified in mammals encoding peptides of the tachykinin family: the preprotachykinin I gene (PPT-I or PPT-A) which encodes both substance P and neurokinin A, and the preprotachykinin II gene (PPT-II or PPY-B) which encodes neurokinin B. The primary RNA transcript of the PPT-I gene is spliced to yield four different forms of messenger ribonucleic acids (mRNA) termed α, β, γ and δ forms (Nawa et al., 1983, 1984; Krause et al., 1987; Nakanishi, 1987). α and δ PPT-I mRNAs code for the synthesis of substance P whereas β and γ PPT-I mRNAs code for the synthesis of both substance P and neurokinin A. In addition, β and γ PPT-I mRNAs encode the synthesis of two N-terminally extended forms of neurokinin A (known as neuropeptide K and neuropeptide γ, respectively): both peptides are capable to produce full biological responses (e.g. Takeda and Krause, 1989a,b) but their role as neurotransmitters awaits to be proven. On the other hand, the PPT-II gene encodes neurokinin B only (Maggio, 1988, for review). The PPT-I gene has been detected in both central and peripheral nervous system, in enteric neurons of the gut and in various cells of the immune system. In contrast, the PPT-II gene is expressed almost exclusively in the central nervous system (Maggi et al., 1993; Maggi, 1995 for review). Recently, the molecular cloning of a further preprotachykinin gene (termed PPT-C) has been described from cDNA of murine hematopoietic cells (Zhang et al., 2000). PPT-C mRNA was detected in pro- and pre-B lymphocyte cells from bone marrow, whereas it was undetectable in nonhematopoietic cells. The novel tachykinin encoded by PPT-C gene (termed

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hemokinin I) may act as an autocrine factor for the growth of hematopoietic cells. Zhang et al. (2000) have also suggested that hemokinin I may stimulate a specific receptor, distinct from any other known tachykinin receptor. However, further experimentation is needed to clearly define the role of hemokinin I in mammals. Owing to the lack of PPT-II gene expression in peripheral tissues, substance P and neurokinin A are the only tachykinins detected in appreciable amounts at this level. In normal, noninflamed tissues, tachykinins originate from neuronal cells, being present in (i) peripheral endings of capsaicin-sensitive primary afferent neurons (Maggi, 1995, for review) and (ii) enteric neurons of both submucousal and myenteric plexuses innervating all layers of the gut (Holzer and Holzer-Petsche, 1997a,b, for review). In addition, certain immune cell types synthesize and possibly release tachykinins during inflammation, thus representing a non-neuronal source of releasable tachykinins in inflamed tissues (De Giorgio et al., 1998; Lai et al., 1998; Maggi, 1997 for review).

1.2. Mammalian tachykinin receptors

The existence of multiple tachykinin receptors was first suggested by the observation that several nonmammalian tachykinins (i.e. eledoisin and kassinin) possess much higher potency than substance P in certain mammalian isolated tissues (Erspamer, 1981). Following the discovery of neurokinin A and neurokinin B in the early 1980s, several groups have presented evidence, based on functional or radioligand binding data, for the existence of three distinct receptors (termed NK_1, NK_2 and NK_3) mediating the biological actions encoded by the common C-terminal sequence of tachykinins. Substance P, neurokinin A and neurokinin B were initially considered to be the "preferred" ligands for the tachykinin NK_1, NK_2 and NK_3 receptors, respectively. (see Regoli et al., 1989; Guard and Watson, 1991; Mussap et al., 1993; Maggi et al., 1993; Maggi, 1995 for reviews). However, this concept has been challenged by radioligand binding and functional experiments that have shown both neurokinin A and neurokinin B to be as potent as substance P at stimulating the tachykinin NK_1 receptor (Hastrup and Schwartz, 1996; Maggi and Schwartz, 1997). It is also worth-noting that all three mammalian tachykinins (substance P, neurokinin A and neurokinin B) are capable to act as full agonists on each one of the three receptors, albeit at different concentrations. In 1996, the cloning of a further tachykinin receptor showing a high degree of structural homology and a similar binding profile to the previously identified NK_3 receptor protein has been reported (Donaldson et al., 1996; Krause et al., 1997). However, a recent attempt to isolate this receptor (referred to as "NK_4" or "NK_{3B}" in literature) or identify the corresponding gene by the use of various molecular biological techniques in human and other species was unsuccessful (Sarau et al., 2000). In view of these latter results, any update of the current tachykinin receptor classification aiming at including the "NK_4" receptor seems to be premature. Likewise, the possible existence of a hemokinin I-operated tachykinin receptor, as proposed by Zhang et al. (2000), needs to be confirmed in further investigations. The tachykinin NK_1, NK_2 and NK_3 receptors belong to the superfamily of rhodopsin-like, G-protein-coupled receptors with seven transmembrane spanning segments. Stimulation of phosphoinositol breakdown is a common effector system coupled to each one of the three tachykinin receptors, although other intracellular pathways are triggered upon occupation of tachykinin receptors as well, e.g. leading to cAMP formation and increased arachidonic acid metabolism (Henderson et al., 1990; Eistetter et al., 1991, 1993; Arkinstall et al., 1994; Catalioto et al., 1998b). Marked species-related differences in pharmacology exist for all three tachykinin receptors, revealed by the use of selective tachykinin receptor antagonists (see Patacchini and Maggi, 1995; Maggi, 1995 for review). Stimulation of peripheral tachykinin receptors leads to specific biological effects including: smooth muscle contraction, neuronal stimulation, endothelium-dependent vasodilation, plasma protein extravasation, chemotaxis and activation of immune cells, stimulation of secretion (Maggi, 1995, for review). The introduction of the first potent and selective tachykinin receptor antagonists at the beginning of the 1990s has allowed to assess the (patho)-physiological role of tachykinins in the central and peripheral nervous system. Either preclinical and clinical trials have shown that centrally acting tachykinin NK_1 receptor antagonists are endowed with anti-depressant, anxyolitic and anti-emetic therapeutic potential (Rupniak and Kramer, 1999; for review). On the other hand, clinical evidence supporting the use of tachykinin antagonists acting at peripheral level for treatment of human diseases is not available yet. Nevertheless, there is a general expectation that tachykinin receptor antagonists may prove useful for treatment of a variety of human diseases at visceral level. This review is focused on the pathophysiological role played by tachykinins in the respiratory, genitourinary and gastrointestinal systems, and on the preclinical evidence indicating a possible therapeutic use of antagonist compounds acting at peripheral tachykinin receptors.

2. Airways

Since the first demonstration that tachykinins are the sensory neuropeptides released by capsaicin from primary afferent nerve endings innervating the guinea-pig airways to produce smooth muscle contraction (Szolcsanyi and Barthò, 1982; Lundberg and Saria, 1982) and that tachykinin-containing nerve fibres are present in normal, but not in capsaicin-pretreated animals (e.g. Lundberg and Saria, 1982; Lundberg et al., 1983), a large number of studies

have been undertaken to assess the hypothesis that tachykinins may be involved in airways pathophysiology. Taken as a whole, these investigations have suggested that tachykinins, released from capsaicin-sensitive sensory nerves innervating upper and lower airways of several species including man (Lundberg et al., 1984; Martling et al., 1988), may participate in the genesis of asthma/bronchial hyperreactivity and rhinitis. Tachykinins have been shown to produce a variety of responses at respiratory level, including tracheal/bronchial smooth muscle contraction in man and other species (e.g. Maggi et al., 1991a,b; Naline et al., 1989), stimulation of secretions in both upper (e.g. Geppetti et al., 1988; Petersson et al., 1989) and lower (e.g. Coles et al., 1984; Meini et al., 1993) respiratory tract, development of bronchial hyperreactivity following exposure to inflammatory agents (antigens and others) (e.g. Saria et al., 1983; Boichot et al., 1995; Schuiling et al., 1999), plasma protein extravasation (e.g. Saria et al., 1983), recruitment of inflammatory cells and stimulation of resident immune cells (e.g. alveolar macrophages; Brunelleschi et al., 1990; Maggi, 1997, for review), sneezing (e.g. Stjärne et al., 1989) and nasal obstruction (Devillier et al., 1988). It is worth-mentioning that most stimuli capable of releasing tachykinins from sensory nerves in the airways are of pathological rather than physiological relevance. Evidence for tachykinin release from peripheral primary afferent terminals has been provided for the following: (a) administration of antigens to sensitized animals, (b) inhalation of irritants (like capsaicin, cigarette smoke, acid media, cold air, occupational sensitizers as toluene diisocyanate and others), (c) administration of pro-inflammatory autacoids like bradykinin and histamine (Maggi, 1995; Advenier et al., 1999; Kraneveld et al., 2000; Lecci et al., 2000).

2.1. Tachykinin receptors mediating pathophysiological effects of tachykinins in the airways

The introduction of tachykinin receptor selective antagonists since the middle 1980s has allowed to investigate more properly the relative contribution of each tachykinin receptor type to the biological effects produced by tachykinins at respiratory level. Bronchoconstriction of human airways caused by tachykinins is an effect mediated by tachykinin NK_2 receptors only (Naline et al., 1989; Dion et al., 1990; Ellis et al., 1993), while tachykinin NK_1 receptors are partially contributing to this effect in other species (e.g., Maggi et al., 1991b). Plasma protein extravasation and mucus secretion are two other effects mainly (if not exclusively) mediated by tachykinin NK_1 receptors in all species examined (Maggi, 1995; Lecci et al., 2000, for reviews). Recruitment and activation of inflammatory leukocytes induced by tachykinins are further effects mainly mediated by tachykinin NK_1 receptors (Advenier et al., 1997; Maggi, 1997), although stimulation of tachykinin NK_2 receptors produces infiltration of neutrophils and lymphocytes in airways of ovoalbumin-challenged guinea-pigs (Schuiling et al., 1999).

2.2. Clinical trials in human airways

Only few clinical studies are currently available, describing tachykinin receptor antagonists challenged to counteract asthmatic reactions provoked by different stimuli. In the first of these reports, Ichinose et al. (1992) claimed the effectiveness of the dual (NK_1/NK_2) tachykinin receptor antagonist (FK 224), in preventing both cough and bronchoconstriction elicited by inhaled bradykinin in asthmatic patients. However, further investigations with FK 224 failed to prove this compound capable of preventing neurokinin A-induced bronchoconstriction in asthmatics (Joos et al., 1996) or to ameliorate symptoms/lung function in patients suffering of mild to moderate asthma (Lunde et al., 1994). The use of a tachykinin receptor antagonist selective for the NK_1 receptor, the nonpeptide compound (CP 99994), did not afford better results, since CP 99994 (intravenously administered to mild asthmatic patients) failed to prevent bronchoconstriction and cough induced by hypertonic saline (Fahy et al., 1995). Likewise, the tachykinin NK_1 receptor-selective antagonist FK 888 failed to afford beneficial effects on exercise-induced bronchoconstriction in asthmatics, but significantly shortened the recovery times (Ichinose et al., 1996), suggesting a possible role of tachykinin NK_1 receptors in the late bronchoconstrictor response to exercise. On the other hand, the tachykinin NK_2 receptor-selective antagonist (SR 48968, saredutant; Emonds-Alt et al., 1992) is the first compound proven active (by oral route) in reducing bronchoconstriction provoked by inhaled neurokinin A in mild asthmatic patients (Van Schoor et al., 1998). The capability of tachykinin NK_2 receptor-selective antagonists to inhibit neurokinin A-induced bronchoconstriction in asthmatics has been further demonstrated by the use of nepadutant (Catalioto et al., 1998a) in a double-blind, placebo controlled cross-over trial (Joos et al., 2000). Nevertheless, a recent study (Kraan et al., 2001) has reported that saredutant (100 mg once a day, per os) was unable to reduce airways hyperresponsiveness caused by adenosine 5′-monophosphate in allergic asthmatic patients. Further trials are awaited to prove efficacy of tachykinin receptor blockers in asthmatic responses caused by allergens producing bronchoconstriction, bronchial hyperreactivity and airways inflammation.

3. Urinary tract

All the organs of upper and lower urinary tract of various species, including man, are densely innervated by peripheral projections of capsaicin-sensitive primary afferent neurons, which represent the main if not the sole source of tachykinins at this level. (Hua et al., 1987;

Edyvane et al., 1992; Edyvane and Marshall, 1990). Tachykinins can be released from capsaicin-sensitive primary afferent neurons in the urinary tract by a number of different stimuli, having pathological rather than physiological relevance including: acid media (Geppetti et al., 1990), various irritants like xylene (Maggi et al., 1988a) and cyclophosphamide (Maggi et al., 1992a), products of bacterial metabolism (Giuliani et al., 1991), certain constituents of urine like K^+ (Maggi et al., 1989b) and bradykinin (Maggi et al., 1989a).

3.1. Tachykinin receptors mediating pathophysiological effects of tachykinins in the urinary tract

Smooth muscle contraction is one of the most studied effects produced by tachykinins throughout the urinary tract. The urinary bladder detrusor muscle and urethra of various species (man included) respond with a contraction to exogenously applied tachykinins while, in selected species, nerve-mediated urinary bladder contractions produced by endogenous tachykinins can be observed upon application of capsaicin or electrical nerve stimulation (Maggi, 1995, for review). Tachykinin NK_1 and/or NK_2 receptors, working alone or in combination, are the mediators of tachykinin-induced contractions in animal species. In man the tachykinin NK_2 receptor exclusively mediates tachykinin-induced urinary bladder contraction (Maggi et al., 1988b), and it is also present in the urethra (Parlani et al., 1990; Palea et al., 1996) and ureter (Patacchini et al., 1998). In the spontaneously active guinea-pig renal pelvis tachykinins, exogenously applied or released by capsaicin or electrical nerve stimulation, produce both inotropic and chronotropic effects (Maggi et al., 1992b). Plasma protein extravasation is an acute inflammatory response that is produced by exogenously applied tachykinins in organs of the urinary tract, or by agents that stimulate the release of tachykinins from sensory nerves, like capsaicin (Eglezos et al., 1991), xylene (Giuliani et al., 1993b), cyclophosphamide (Ahluwalia et al., 1994) or antigens in sensitized animals (e.g. Ahluwalia et al., 1998) (Lecci and Maggi, 1995, for review). As in the airways, tachykinin-mediated plasma protein extravasation in the urinary tract requires activation of tachykinin receptors of the NK_1 type. The involvement of tachykinin NK_1 receptors in mediating this effect was proven since the introduction of the first receptor-selective agonists and antagonists (e.g. Eglezos et al., 1991). Recently, the involvement of the NK_1 receptor has been confirmed by the failure of cyclophosphamide to produce plasma protein extravasation in the urinary bladder of NK_1 receptor knockout mice (Laird et al., 2000). Owing to the ability of exogenously administered tachykinins to stimulate ureteral peristalsis and activate the micturition reflex (Maggi, 1995; Santicioli and Maggi, 1998), it could be hypothesized that endogenous tachykinins, released into the bladder wall, take part into the voiding mechanism of the urinary bladder. However, Lecci et al. (1993, 1998b) provided evidence against a peripheral role of tachykinins in initiating volume-evoked micturition reflex in rats, by showing that peripherally acting tachykinin NK_1 and/or NK_2 receptor selective antagonists are unable to modify the urodynamic parameters of distension-induced micturition under physiological conditions. By contrast, endogenous tachykinins acting via NK_2 receptors contribute to detrusor hyperreflexia generated by noxious stimuli, as shown by the ability of tachykinin NK_2 (but not NK_1) receptor-selective antagonists to correct altered urodynamic parameters (micturition frequency and bladder tone) following intravesical administration of irritant agents in rats (like capsaicin, prostaglandin E_2, xylene, *E. coli* lipopolysaccharide,) (Pietra et al., 1992; Ishizuka et al., 1994, 1995; Lecci et al., 1997, 1998c). To this regard, it may be speculated that tachykinins mediate chemically induced hyperreflexia by directly stimulating afferent nerve fibers in the mucosal layers of the bladder, on which are expressed specific (NK_2) receptors. Alternatively, tachykinins might act indirectly by stimulating generation of other local transmitters like prostanoids (see Lecci et al., 2000 for discussion). The bulk of data collected in in vitro and in vivo studies on animal models suggests that tachykinins could be involved in producing symptoms accompanying cystitis of different aetiology. Nonetheless, the therapeutical potential of tachykinin receptor antagonists in human diseases of the urinary tract has not yet been investigated.

4. Gut

The main source of tachykinins in the gastrointestinal tract is represented by intrinsic enteric neurons, including cholinergic motoneurons localized in the myenteric plexus and projecting to circular and longitudinal smooth muscle layers. The rest of tachykinin content is contributed by extrinsic fibres of capsaicin-sensitive primary afferent neurons, and by immune cells (Costa et al., 1987; Maggi, 1995, 1997; Holzer and Holzer-Petsche, 1997a). Tachykinins stored in primary afferent nerves are released by the same stimuli, mainly of irritative nature, which induce their release in the airways and urinary tract. Tachykinins stored in enteric neurons can be released by mechanical (i.e. intestinal wall distension) or chemical (synaptic input) stimuli having a physiological relevance (Maggi, 1995; Holzer and Holzer-Petsche, 1997a, for review).

4.1. Tachykinin receptors mediating pathophysiological effects of tachykinins in the gut

As seen in the organs belonging to respiratory or urinary tract, tachykinins are potent spasmogens in almost all intestinal regions so far investigated. A large part of their contractile effects originates from direct stimulation of tachykinin NK_1 and/or NK_2 receptors present on smooth

muscle cells/cells of Cajal of the circular and longitudinal muscle layers (Holzer and Holzer-Petsche, 1997a). In addition, indirect contractile responses can be evoked by tachykinins through stimulation of tachykinin receptors (mainly of the NK_3 type) present on intestinal neurons, from which either acetylcholine or tachykinins themselves are released (Patacchini et al., 2000). It is worth-mentioning that the release of inhibitory transmitters (e.g. nitric oxide) has also been reported upon stimulation of tachykinin NK_1, NK_2 and NK_3 receptors (Maggi et al., 1997). A great number of studies have reported that both direct/indirect excitatory motor responses elicited in mammalian intestine by application of electrical or mechanical (i.e. intestinal wall distension) stimuli, are mediated by endogenous tachykinins which add to the major effective excitatory transmitter, acetylcholine (Maggi, 1995; Holzer and Holzer-Petsche, 1997b; Maggi et al., 1997 for review). In this respect, it is noteworthy that the contribution of endogenous tachykinins to intestinal peristalsis is hardly appreciable under normal conditions, unless muscarinic receptors are blocked. Giuliani et al. (1993a, 1996) have shown that in atropine-pretreated animals, distension-evoked intestinal reflex contractions can be elicited and that tachykinin NK_1 and NK_2 receptor-selective antagonists inhibit these atropine-resistant responses, proving the involvement of endogenous tachykinins. Similar results were obtained by Lecci et al. (1998a) studying colonic propulsive activity in anaesthetized atropine-pretreated guinea-pigs, and by Holzer et al. (1998) studying in vitro peristalsis of isolated segments of guinea-pig small intestine. However, the former studies have also proven that tachykinins do not play a major role in intestinal motor activity under normal conditions, due to the modest/null ability of tachykinin receptor antagonists to modify normal peristalsis. This concept would be supported by recent studies performed in unanaesthetized dogs (Giuliani et al., 2001) and in healthy volunteers (Lördal et al., 1999) in which the tachykinin NK_2 receptor-selective antagonist nepadutant (Catalioto et al., 1998a) did not affect gastrointestinal normal motor activity per se. However, Tonini et al. (2001) showed that simultaneous administration of three tachykinin receptor antagonists, each one selective for the NK_1, NK_2 or NK_3 receptor type, produced a 50% inhibition of velocity of propulsion of a balloon inserted in distal colon isolated segments from guinea-pig. More convincing evidence exists on the role of endogenous tachykinins in producing exaggerated intestinal motility associated with various inflammatory and infectious intestinal diseases (Holzer, 1998 for review). In this context, tachykinin NK_2 (and partially NK_1) receptor antagonists have been reported to prevent increased fecal excretion and colonic giant contraction in castor-oil induced diarrhea in rats (Croci et al., 1997), without producing constipation. Besides excitatory motor responses, inhibitory motor effects have been reported following stimulation of tachykinin NK_1, NK_2 or NK_3 receptors (Maggi et al., 1997; Lecci et al., 2000). Either stimulation of tachykinin (NK_2) receptors present on sympathetic ganglia and subsequent activation of inhibitory sympathetic nerves (Giuliani et al., 1988), or activation of tachykinin (NK_1, NK_2 or NK_3) receptors present on enteric inhibitory neurons which in turn release nitric oxide, have been proposed as possible mechanisms of tachykinin-induced inhibitory motor effects at intestinal level (Holzer and Holzer-Petsche 1997b; Lecci et al., 1999; Zagorodnyuk and Maggi, 1995). To this regard, it may be speculated that tachykinin receptor antagonists may result useful in abnormal (inhibited) intestinal motility, as the post-surgical ileus. As a matter of fact, preliminary evidence has been obtained indicating that the tachykinin NK_2 receptor antagonist nepadutant (Catalioto et al., 1998a,b) reduces the inhibition of jejunal motility induced by abdominal surgery in rats (Bueno et al., unpublished observations). Besides affecting smooth muscle motility of the gut, tachykinins have been reported to enhance electrolyte and/or fluid secretion from both small and large intestine. At this level tachykinins would act as endogenous modulators by acting on secretomotor neurons which in turn release acetylcholine and other noncholinergic transmitters which in turn cause ion and fluid secretion (Maggi, 1995; Holzer and Holzer-Petsche, 1997b for review). For example, Cox et al. (1993) showed that in the rat descending colon mucosa under voltage-clamp conditions, tachykinins evoked increases in short-circuit current (I_{sc}) responses by activating a combination of NK_1, NK_2 and NK_3 receptor types. In a recent study, Patacchini et al. (2001) showed that in the rat distal colon muscularis mucosae, tachykinin NK_2 receptor-mediated contractile responses are produced by activating an indomethacin-insensitive effector mechanism, whereas tachykinin NK_2 receptor-mediated ion transport in the colon mucosa is a largely indomethacin-sensitive phenomenon. These results along with the observation that nepadutant blocks with different kinetics (competitive vs. noncompetitive, respectively) the two responses, provide indirect evidence that different intracellular effector mechanisms are triggered by the tachykinin NK_2 receptor in the intestine and lead to different biological responses.

Several animal models of ileocolitis are presently available, in which inflammatory reactions are obtained by administration of chemical irritants (like trinitrobenzensulfonic acid, TNBS, dextran sulphate, formalin), γ-irradiations, bacterial infection (e.g. *Trichinella spiralis*, *Salmonella*, *Nyppostrongylus brasiliensis*) or bacterial toxins (e.g. *Clostridium difficile* toxin A and *T. spiralis* toxin A). Endogenous tachykinins have been reported to mediate hypersecretory and inflammatory reactions of the gut induced by these agents, while administration of tachykinin NK_1 receptor antagonists has been shown to exert protective effects in various models of intestinal injury/inflammation (Holzer, 1998; Evangelista, 2001; Lecci et al., 2000 for reviews). The role of the tachykinin NK_1 receptor in mediating inflammatory reactions of the gut has recently

been supported by the use of tachykinin NK_1 receptor-knockout mice, which showed reduced intestinal damage produced by *C. difficile* toxin A or TNBS compared to control animals (Castagliuolo et al., 1998). In addition to mediating abnormal motility and inflammatory reactions in various experimental pathological conditions of the gut, tachykinins have also been shown to take part in visceral nociception (Holzer, 1998, for review). In particular, tachykinin NK_2 receptor antagonists have been found effective in reducing reflex responses (e.g. abdominal contractions) caused by painful stimuli as rectal wall distension (Julia et al., 1994) or intraperitoneal administration of acetic acid (Julia and Bueno, 1997) in rats. Moreover, tachykinin NK_2 receptor antagonists have been proven to be effective in animal models of visceral hyperalgesia induced by inflammation (e.g. McLean et al., 1997) or stress (Toulouse et al., 2000). The results obtained by Toulouse et al. (2000) showing the ability of nepadutant to inhibit rectal hypersensitive responses in rats pretreated with TNBS or previously subjected to restraint, suggest that the tachykinin NK_2 receptor is a main target mediating visceral allodynia/hyperalgesia. The role of tachykinin NK_2 receptors is further supported by the observation that nepadutant prevents the increased expression of either c-*fos* and c-*jun* protooncogene markers in spinal cord and dorsal root ganglia neurons from rats pretreated with TNBS (Kiss et al., 1999) and by Laird et al. (in press), who have shown nepadutant capable of preventing the hypersensitivity of single spinal cord neurons responding to colorectal distension or pelvic nerve stimulation in rats pretreated with intracolonic acetic acid. It is worth-mentioning that nepadutant had no significant effect on responses evoked in animals with noninflamed colon (Laird et al., in press).

The precise site at which tachykinin NK_2 receptors mediate visceral pain is yet to be identified, although the peripheral (vs. central) level seems more likely for several reasons (Laird et al., in press; Holzer, 1998). Nevertheless, the effectiveness of tachykinin NK_2 receptor antagonists in animal models of visceral hyperalgesia leads to speculate that these agents could be useful for the treatment of functional gastrointestinal disorders characterized by visceral pain as irritable bowel syndrome.

5. Conclusions

A huge amount of preclinical data indicates that both tachykinin NK_1 and NK_2 receptors are consistently expressed in the peripheral nervous system of several animal species, including humans. Tachykinin NK_3 receptors are also expressed in the peripheral nervous system of certain species, but their role in human peripheral nervous system is much less documented. The results obtained with selective receptor antagonists in animal models of various diseases indicate that tachykinin receptor antagonists might have a potential therapeutic effect in asthma/bronchial hyperreactivity, cystitis, inflammatory bowel disease and irritable bowel syndrome. To test this hypothesis several compounds are presently under clinical investigation.

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