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Review

Tachykinins and their functions in the gastrointestinal tract

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Abstract. In the gastrointestinal tract, tachykinins are peptide neurotransmitters in nerve circuits that regulate intestinal motility, secretion, and vascular functions. Tachykinins also contribute to transmission from spinal afferents that innervate the gastrointestinal tract and have roles in the responses of the intestine to inflammation. Tachykinins coexist with acetylcholine, the primary transmitter of excitatory neurons innervating the muscle, and act as a co-neurotransmitter of excitatory neurons. Excitatory transmission is mediated through NK1 receptors (primarily on interstitial cells of Cajal) and NK2 receptors on the muscle. Tachykinins participate in slow excitatory transmission at neuro-neuronal synapses, through NK1 and NK3 receptors, in both ascending and descending pathways affecting motility. Activation of receptors (NK1 and NK2) on the epithelium causes fluid secretion. Tachykinin receptors on immune cells are activated during inflammation of the gut. Finally, tachykinins are released from the central terminals of gastrointestinal afferent neurons in the spinal cord, particularly in nociceptive pathways.

Keywords. Substance P, neurokinin A, enteric nervous system, tachykinin receptor, primary afferent neuron, neuropeptide, excitatory transmission.

Tachykinins, originally identified as substance P (SP), but later shown to include a number of pharmacologically and chemically related peptides, were first isolated from brain and intestine [1] and the first strong evidence for their transmitter roles was also in the intestine. Thus, the history of their discovery and roles in the intestine are interesting. Despite the long period over which these substances have been studied, particularly in the gastrointestinal tract (GI), new information on their functions continues to emerge.

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A brief history of the investigation of tachykinins in the GI tract

Extracts prepared from the brain and intestine of horse were found to have strong effects in lowering blood pressure and in contracting the small intestine [1]. For their work in 1931, von Euler and Gaddum prepared a dried powder from their extracts, which they referred to by the abbreviation 'P' for powder. From this shorthand the designation substance P evolved. The active substance(s) in the extracts were stable to acid and to heat, but could be degraded by peptidases. SP was eventually isolated from bovine hypothalamus and its amino acid sequence was

determined in 1970 [2]. Soon after, the identity of the peptide from the original source, horse intestine, was confirmed by extraction and sequencing [3]. At about this time, methods to generate antibodies against small peptides, and to use the antibodies to locate the peptides, were developed. Very effective and quite specific antibodies against tachykinins (using SP coupled to a carrier protein as the immunogen) were produced and applied to the GI [4–7] and the distribution of tachykinins has now been mapped in the gut of numerous species, including mouse, cat, guinea pig, rabbit, rat, human, dog, pig, horse and non-mammalian primates.

These studies have shown quite conclusively that tachykinins are almost entirely confined to neurons (nerve cells and axons) in the GI tract. Most of the axons are intrinsic (from the enteric nervous system, with cell bodies in the enteric ganglia), but some come from extrinsic sources, primary afferent neurons with cell bodies in spinal sensory ganglia. The major innervation from enteric sources is of enteric ganglia themselves, the muscle of the gut, interstitial cells of Cajal (ICC) and the mucosal epithelium. In addition, a high proportion of spinal extrinsic primary afferent neurons that innervate blood vessels (small arteries and arterioles) of the GI contain tachykinins [8–10]. Pharmacological analysis had suggested that excitatory transmission to the muscle of the gut had an unexplained non-cholinergic component [11, 12]. Following the chemical identification of SP, and the immunohistochemical evidence that it occurred in enteric neurons innervating the muscle, a number of laboratories set about investigating its possible role as an enteric neurotransmitter. Although the pharmacological tools available at the time were poor, it was quickly established that non-cholinergic transmission could be antagonized by desensitization of tachykinin receptors, or by peptide analog with tachykinin receptor antagonist properties [13–17].

Tachykinin peptides and their genes

The tachykinins have in common a C-terminal amidated amino acid region, Phe-X-Gly-Leu-MetNH_2, where X is an aromatic or hydrophobic residue [18]. This is the minimal sequence for producing biological activity. The identification of SP was followed by other tachykinins, neurokinin A (NKA) and neurokinin B (NKB). A little later, elongated forms of NKA, named neuropeptide K and neuropeptide-γ, were also discovered [19, 20]. NPK and NPγ are expressed in sensory neurons and in neurons of the central and enteric nervous system [18, 21, 22]. The novel peptides of the tachykinin family, hemokinin-1 and its elongated forms, endokinin A (EKA) and endokinin B (EKB), are primarily expressed in non-neural cells [23–25].

The three best known tachykinins, SP, NKA and NKB, are encoded on two different genes that are now called the tachykinin precursor 1 (*TAC1*) gene [originally known as preprotachykinin (PPT)-A or PPT-I] and the *TAC3* gene (originally known as PPT-B or PPT-II) [26] (Fig. 1). The *TAC1* gene consists of seven exons and transcription of the gene produces four splice variants, α, β, γ, and δ [26–30]. SP can be produced from all of the mRNA isoforms, whereas NKA production is confined to α and γ-*TAC1* [26, 28]. This means that SP can be expressed alone, but NKA is always produced along with SP. The elongated forms of NKA, neuropeptide K and neuropeptide-γ, are formed from β- and γ-*TAC1*, respectively [19, 20, 31].

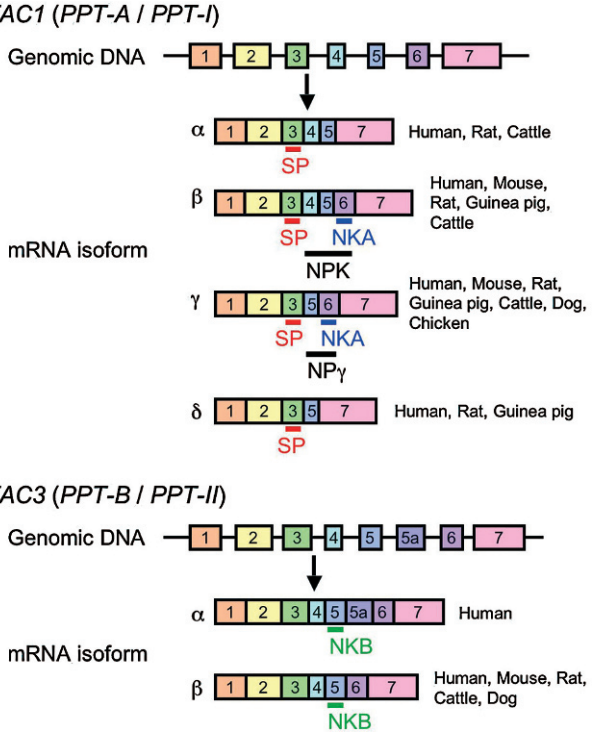

Figure 1. Splice variants of preprotachykinin genes (*TAC1* and *3*). Exons are shown as boxes. The positions of the predicted tachykinin peptides (SP, NKA, NKB, NPK, and NKγ) are indicated by underlining. The registered sequences from databases were used to draw the scheme (accession numbers: NM_013996, NM_003182, NM_013997, NM_013998, NM_001006667, NM_013251, NM_009311, BC119122, M68908, M68909, NM_009312, M34184, M15191, M34183, X56306, NM_019162, Z50784, Z50783, Z50782, X00076, X00075, NM_174193, M68911, M68912, NM_181017, XM_532472, XM_843938 and XM_418674).

TAC3 gene transcription results in three different mRNA isoforms (α-, β- and γ-*TAC3*), while only the α- and β-*TAC3* are translated into NKB [32]. In the rat

GI tract, *Tac3* transcripts have not been identified [33, 34], being in agreement with experiments that have failed to detect NKB immunoreactivity in the gut [18, 35–37].

Tachykinin receptors

Tachykinins act on specific membrane receptors that belong to the family of G-protein-coupled receptors [38–40]. Three tachykinin receptors, termed NK1, NK2, and NK3, with considerable sequence homology, have been identified so far and characterized at a molecular level [41–44]. These receptors can be fully activated by all tachykinins with moderate selectivity [45, 46]. In various bioassay systems, it has been demonstrated that the potency order of tachykinins is SP > NKA > NKB for NK1, NKA > NKB > SP for NK2 and NKB > NKA > SP for NK3 receptors [39, 45, 46].

The mammalian tachykinin receptors couple with the Gq-protein and binding with ligands results in production of 1,4,5-inositol triphosphate and elevation of intracellular Ca^{2+} though the activation of phospholipase C [43, 47–49]. It has also been reported that the receptors are capable of coupling with Gs-protein that leads to production of cAMP as a second messenger [48, 50]. The responses of the intestine to SP fade quickly, a phenomenon known as tachyphylaxis, and subsequent exposure of tissue results in diminished responses, indicating a desensitization of target cells to SP [51–53]. The tachyphylaxis and desensitization of NK1 receptors appears to be the result of rapid receptor phosphorylation followed by receptor internalization [54, 55]. The internalization is followed by intracellular sorting and return of receptor to the surface. Internalization is associated with a loss of functional binding sites on the cell and thereby contributes to reduction of responsiveness to tachykinins. However, there is evidence that initial desensitization depends on receptor phosphorylation but does not require internalization [54]. Recently, Simmons [56] has demonstrated that SP preferentially produces desensitization rather than a Ca^{2+} response at lower concentrations, whereas a related peptide, ranatachykinin C, is more effective at activating a Ca^{2+} response relative to its ability to produce desensitization. N-terminal regions of peptides may be related to the differential effects on the Ca^{2+} response versus desensitization of NK1 receptors [57]. These data are interesting because they suggest that it may be possible to develop ligands of NK1 receptors, which can predominantly produce signal activation or desensitization.

Recycling, ligand dissociation and dephosphorylation of the receptors can restore responsiveness [55, 58]. NK1 receptor trafficking can be markedly influenced by the SP concentration. High SP (10 nM) induced translocation of the NK1 receptors to perinuclear sorting endosomes where the receptors remained for a long time, whereas low SP (1 nM) caused translocation of the NK1 receptors to early endosomes located immediately beneath the plasma membrane, followed by rapid recycling of the receptors [59]. Furthermore, there may be an additional mechanism for restoration of responsiveness. It has been shown that the restoration of responsiveness of NK1 receptors to SP can precede receptor recycling [60]. This may result from a conversion of non-functional NK1 receptors to functional receptors at the plasma membrane.

One of the typical characteristics of the mammalian tachykinin receptors is a marked species difference in affinity for synthesized tachykinin antagonists [61, 62]. Molecular biological techniques including exploitation of chimeric and point-mutated receptors have revealed amino acid residues responsible for the species selectivity. For example, two non-peptide NK1 receptor antagonists exhibit opposite potency for the human and rat NK1 receptors. CP 96345 shows selectivity for the human receptor, whereas RP 67580 shows selectivity for the rat receptor. Substitution of two residues (valine-116 and isoleucine-290) in the transmembrane domain of the human NK1 receptor by the rat homologs, leucine and serine (V116L and I290S), reproduces the antagonist-binding affinities of the rat receptor [61]. Species selectivities of CP 96345, FK 888, and SR 48968 can also be accounted for by the differences in these amino acid residues between human and rat [62]. Since these amino acid residues are not the direct binding sites for the antagonists, it can be postulated that the local three-dimensional structure would define the binding affinity for antagonists.

Localization of tachykinins in the GI tract

Immunohistochemical studies have provided strong evidence that tachykinins are expressed by intrinsic neurons with cell bodies within the intestinal wall, i.e., in myenteric or submucosal ganglia, and by enteric axons with cell bodies outside the gut wall, e.g. nodose or dorsal root ganglia [6, 9, 21, 34, 63]. Early work, up until about 1995, utilized antibodies raised against SP and the neurons were referred to as SP neurons. It was later discovered that the neurons contain other closely related tachykinins (see above) that are recognized by most antibodies against SP, and so the immunoreactivity is now referred to as tachykinin immunoreac-

tivity. Tachykinin immunoreactivity has been localized to nerve fibers forming a dense network around ganglionic cell bodies of the myenteric and submucosal plexuses and in the circular and longitudinal smooth muscle layers. In addition, axons containing tachykinins form a perivascular network around submucosal arteries and contribute to the paravascular nerves following these arteries in the intestine of the mouse, human, rat, dog, guinea pig, and pig [4, 5, 8, 63–68], and presumably in all mammals. Tachykinin immunoreactive axons are also found in the mucosa, but the density of innervation of the mucosa differs between species [64, 69].

Lesions of nerve pathways and retrograde transport from targets are used to establish the projections and the intrinsic or extrinsic origins of the nerve fibers observed within the intestine. Interruption of the nerve pathways can be achieved by cutting the vagus nerves, mesenteric nerves, pelvic nerves and different nerve pathways within the wall of the intestine. The full description of a given class of enteric neurons usually requires a combination of lesion studies, retrograde transport, cell morphological studies, and immunohistochemical double-labeling. The results of such studies indicate that there could be at least eight types of tachykinin-containing neurons, six of which are intrinsic, supplying nerve terminals to a range of effectors in the small intestine. Extrinsic neurons are the sources of two projections, one to submucosal blood vessels and one to the enteric ganglia, but the majority of the tachykinin-positive axons are of intrinsic origin. Intrinsic neurons located in the submucosal ganglia supply the villi and have collaterals to myenteric ganglia. Five projections arise from the myenteric plexus, a very short projection ending either within the same row of ganglia or within the adjacent rows of ganglia on both sides, a longer projection within the myenteric plexus, a projection to the circular muscle, a projection to the submucosal ganglia where the axons surround most of the submucosal nerve cell bodies, and a projection to the villi [63, 70–73]. Tachykinins are probably involved not only in local reflexes but also in the transmission of sensory information from the gut to the central nervous system (CNS) [9, 21].

Innervation of the muscle

Tachykinin-containing fibers are numerous in smooth muscle [6, 73, 74] and direct comparison of the density and pattern of muscle innervation indicates little variation between species [69]. The circular muscle layers of the small intestine and colon in the dog and other large mammals have dual sources of tachykinin-containing intrinsic nerve supply: the myenteric ganglia supply fibers primarily to the outer part of the muscle and the submucosal ganglia supply fibers to the inner muscle, whereas the muscle supply in small mammals is entirely, or almost entirely, from myenteric ganglia [67, 75]. By combining immunohistochemical techniques with myotomy and myectomy operations, neurons with tachykinin-immunoreactivity have been shown to project both locally and orally (ascending projection) in the mouse small and large intestine [76], in the guinea pig small and large intestine [71, 77, 78], dog small intestine [67, 72], and rat small intestine and colon [65]. Retrograde tracing, by application of DiI to the inner part of the circular muscle, also revealed that myenteric neurons project locally and orally to the circular muscle in the guinea pig small intestine [77]. Pharmacological studies show that the tachykinin neurons innervating the muscle are excitatory neurons (see below).

Interneurons

In the guinea pig small intestine, neurons that project orally to innervate myenteric ganglia have tachykinin immunoreactivity [79]. However, not only ascending projections but also descending (anally directed) projections of neurons with immunoreactivity for tachykinin have also been documented in the rat [66] and dog [72] small intestine. Some of these neurons are possibly interneurons.

Intrinsic primary afferent neurons

Intrinsic primary afferent neurons (IPANs), identified by the characteristic Dogiel type II shapes of their cell bodies, have tachykinin immunoreactivity in the guinea pig and human small intestine [79–81]. Myenteric IPANs project locally, to provide dense networks of terminals in ganglia close to their cell bodies. In the small and large intestine, the majority of tachykinin immunoreactive terminals probably arise from these neurons. It is notable that tachykinin immunoreactive nerve terminals do not disappear when ascending and descending pathways connecting with myenteric ganglia are both cut [82]. Retrograde tracing shows that myenteric, tachykinin immunoreactive, Dogiel type II neurons project to the submucosa and mucosa [83].

Following the application of DiI to the surface of a single myenteric ganglion, retrogradely labeled nerve cell bodies were labeled with tachykinin in the submucosal plexus of the guinea pig small intestine [84]. Thus IPANs with cell bodies in the submucosa project to the myenteric ganglia. They also project to the mucosa [85]. Retrograde tracing shows that tachykinin-immunoreactive neurons located in the submucosal plexus in the pig small intestine [86] and guinea pig large intestine [87] also project to the mucosa. Moreover, in humans, neurons labeled from

the mucosa were located in all ganglionated nerve networks, including the myenteric plexus, in the small intestine and they were immuoreactive for tachykinins [88].

Stomach

Since the stomach almost completely lacks a ganglionated submucosal plexus, the somata of enteric neurons innervating the muscle or the mucosa have to be located within the myenteric plexus or extrinsic (vagal or spinal) ganglia. Removal of areas of longitudinal muscle and myenteric plexus from the corpus resulted in the loss of fibers reactive for tachykinins from both the circular muscle and mucosa in the area covered by the lesion [89]. Consistent with this, retrograde tracing with DiI from the mucosa, circular and longitudinal muscles labeled myenteric neurons encoded by tachykinins [90]. Tachykinin immunoreactivity occurred in about 50 % of spinal gastric afferents and less than 10 % of vagal afferents in the rat, mouse and guinea pig stomach [9, 10]. The spinal afferent neurons are generally also CGRP immunoreactive. The main targets of spinal afferent neurons of dorsal root ganglia are gastric blood vessels and the mucosa. The numbers of tachykinin-immunoreactive fibers in the mucosa was largely reduced by vagotomy in the rat stomach [91]. Keast et al. [69] noted marked species differences in the density of tachykinin-containing nerve fibers in the gastric mucosa. Such fibers are fairly numerous in human and pig, moderate in number in rat and guinea pig, and absent altogether from the mucosa of the dog stomach [69, 92]. Generally, tachykinin-containing fibers are numerous in the intramural ganglia and in the smooth muscle [6, 73]. Thus, in the stomach, as in other regions, tachykinins are found in intrinsic excitatory muscle motor neurons and in interneurons. There are few or no IPANs with Dogiel type II morphology in the stomach.

By combining localization studies, including lesion and tracing studies, and physiological and pharmacological studies, tachykinins are deduced to be contained in excitatory motor neurons to the longitudinal and circular muscle cells of all species, to occur in intrinsic primary afferent neurons and their excitatory synapses with other neurons, in some interneurons and in extrinsic (spinal) primary afferent neurons.

Localization of tachykinin receptors in the GI tract

Initial microscope studies of the distributions of tachykinin receptors used radioligand binding and autoradiography [37, 93–96]. Although these studies were useful to show in general where receptors are located, autoradiography does not have the resolution to show which cell types in enteric ganglia express the receptors, it relies on the receptor specificity of the ligands that can be labeled, and it is ill-suited for double-labeling to identify the cell types that show the signal. Thus ligand autoradiography has been largely supplanted by immunohistochemical and fluorescent-ligand-binding methods. It has been consistently shown that NK1 and NK3 receptors occur on enteric neurons [97–99], that NK2 receptors are dominant on muscle [100] and that NK1 receptors occur on ICC [101–103] (Fig. 2).

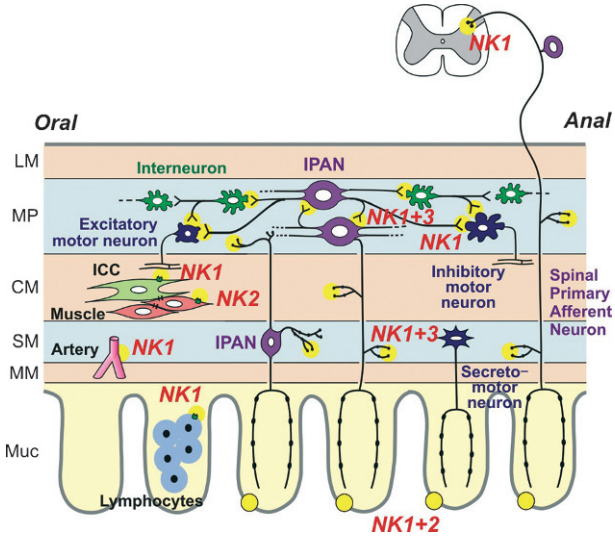

Figure 2. Schematic representation of the distribution of tachykinin receptors in the intestine and their relation to neurons, which are the major sources of tachykinins that can act at these receptors. Muscle motor neurons, intrinsic primary afferent neurons (IPANs) and spinal primary afferent neurons all contain and release tachykinins. Some ascending interneurons in the myenteric plexus may also utilize tachykinins as transmitters. IPANs make synaptic connections with other IPANs where tachykinins act on NK1 and NK3 receptors. They also affect inhibitory motor neurons at NK1 receptors. Both IPANs and spinal primary afferent neurons release tachykinins from their nerve endings in the mucosa. This tachykinin release can increase fluid secretion by acting on the mucosa (NK1 and NK2 receptors) and can contribute to inflammatory reactions by acting on lymphocytes and other immune-related cells. The excitatory motor neurons act through NK1 receptors on the interstitial cells of Cajal (ICC), and on smooth muscle, primarily through NK2 receptors. The layers of the intestine are indicated: LM, longitudinal muscle; MP, myenteric plexus; CM, circular muscle; SM, submucosal plexus; MM, muscularis mucosae; Muc, mucosa.

Tachykinin receptors of neurons

NK1 receptors have been observed in enteric neurons of a range of species and regions [97, 99, 103–106]. Functional classes of neuron that bear the NK1 receptor have been examined in the guinea pig ileum by means of simultaneous immunofluorescence labeling with other neuronal markers [104]. NK1-

receptor-immunoreactive neurons are nitric-oxide-synthase-immunoreactive inhibitory motor neurons, choline acetyltransferase (ChAT)/tachykinin-immunoreactive excitatory neurons to the circular muscle, ChAT/neuropeptide Y/somatostatin-immunoreactive secretomotor neurons, ChAT/calbindin myenteric neurons (IPANs), and ChAT/tachykinin submucosal neurons (also IPANs). These locations are congruent with a role of NK1 receptors in regulating motility, neuronal excitability, and mucosal water and ion transport (see below).

In myenteric ganglia, NK3 receptors were present on the IPANs, excitatory motor neurons and ascending interneurons, inhibitory motor neurons, descending interneurons, and secretomotor neurons. In submucosal ganglia, NK3 receptors were on secretomotor/vasodilator neurons, secretomotor neurons, and were completely absent from tachykinin-immunoreactive IPANs [107]. Nerve cell bodies immunoreactive for NK3 receptor were seen in the myenteric and submucous plexuses of the small and large intestine, but NK3 immunoreactivity may be absent in the stomach and esophagus, where IPAN-like neurons are also thought to be absent, or very rare [99]. Similar to these observations, NK3 immunoreactivity occurs in myenteric neurons of the small and large intestines, but is almost absent from enteric ganglia of the esophagus and stomach in the mouse [108]. The authors found that NK3 receptors were mostly on Dogiel type II neurons, which is consistent with electrophysiological studies (see below) that show that slow excitatory post-synaptic potentials (EPSPs) in these neurons are mediated by NK3 receptors.

Generally, NK2 receptors are considered to be expressed by muscle and epithelial cells (see below) only, and physiological studies indicate that the functional receptors on neurons are NK1 and NK3 receptors (see below). However, NK2 receptor immunoreactivity has also been detected in the varicose processes of nerve terminals in the gut in guinea pig, rat and human [105, 109, 110], but not in mouse [109]. In the guinea pig, NK2 receptor immunoreactivity was detected in nerve varicosities distributed at the myenteric and submucousal plexuses, around NK2-receptor-negative neurons and in nerve fibers running within ganglia [109]. In myenteric ganglia, these varicosities were most numerous in the ileum, frequent, but less dense, in the proximal colon and cecum, rare in the distal colon, extremely infrequent in the rectum and duodenum, and absent from the stomach and esophagus [100]. The immunoreactivity was weak in the myenteric cell bodies, suggesting that the protein is transported to the terminals and is not inserted into the cell body surface membrane, which is consistent with physiological studies. Nevertheless, the protein should be detectable in the cell bodies where it is synthesized, and cell body localization has been demonstrated [110].

Tachykinin receptors of ICC and muscle cells

As explained below in the section on transmission to the muscle, excitation of muscle involves both activation indirectly through ICC and direct effects on muscle. It has been consistently observed that ICC express NK1 receptors [101–103, 105]. Moreover, ICC are closely approached by tachykinin immunoreactive nerve fibers, especially at the deep myenteric plexuses [102, 103, 111–113]. The majority of NK1 receptor immunoreactivity in ICC is on the cell surface and the ICC are capable of binding SP, suggesting the receptors are functional [102]. In fact, recent evidence shows that SP can regulate pacemaker currents through the NK1 receptor in ICC [114]. There is little evidence for NK2 receptors on ICC.

NK2 receptors have been reported on circular and longitudinal muscle cells of several mammalian species, including human [97, 100, 101, 110, 115], as is supported by functional studies (see below). In general NK1 receptors are absent from the muscle, but Southwell and Furness [116] have observed NK1 receptor immunoreactivity on muscle throughout the small and large intestines from the guinea pig.

NK3 receptors are absent from smooth muscle in practically all regions, as shown by both localization and functional studies. However, NK3 immunoreactivity was found in smooth muscle cells of the muscularis mucosae of the rat esophagus [99]. They have also been reported to be expressed by smooth muscle cells of the human esophagus [117] and by a small number of smooth muscle cells of the inner portion of the circular muscle layers in the mouse, rat, and guinea pig small intestine [115].

A type of branched, elongated cell, which seems to be related to muscle cells, and which expresses α-smooth muscle actin, occurs in the mucosa. These cells, which have been called myoid cells, express NK1 receptors in humans [101]. NK1 immunoreactivity has also been reported on these cells in mouse, but not in rat or guinea pig [115].

Tachykinin receptors of epithelial cells

The intestinal epithelium expresses both NK1 and NK2 receptors. NK1 receptor immunoreactivity is present on epithelial cells in the human colonic mucosa [118], in the epithelial cells of the rat ileum [119] and in the crypts and some cells of the villi in the guinea pig small intestine [116]. NK2 immunoreactivity was found on the enterocytes located at the bases of crypts in the guinea pig proximal colon, and

was also present in other parts of the large intestine, cecum, distal colon, and rectum [100]. However, no NK2 immunoreactivity was present in the mucosal epithelial cells of guinea pig esophagus, corpus, antrum, duodenum, or ileum. These results support the idea that tachykinin receptors may mediate secretomotor effects in the small intestine and colon (see below).

Tachykinin receptors of immune cells

NK1 receptor has been suggested to be involved in the immune response in the gut [120]. In the human intestine, NK1 receptor immunoreactivity is present on lymphocytes of the lamina propria, and this expression is increased in inflammatory bowel disease [121]. NK1 receptors also occur on intestinal macrophages [122]. NK2 receptor mRNA and protein are localized to a few inflammatory cells of the lamina propria [118, 121, 123]. Pharmacological and knock-out experiments also point to an involvement of tachykinins in the regulation of gut immune and inflammatory responses (see below).

Pharmacological tools to investigate the roles of endogenous tachykinins in gut

The selective receptor agonists are mostly peptide analogs of tachykinins [21]. On the other hand, although the first selective antagonists were peptide analogues (stabilized by replacement of the specific L-amino acids with D-amino acids), these have been supplanted by potent and highly selective non-peptides. Most of the non-peptide antagonists are for the NK1 receptors [61, 124], but there are also effective antagonists for NK2 and NK3 receptors. Tachykinin receptor antagonists are summarized in Table 1.

The tachykinin-containing extrinsic afferent neurons can be selectively activated by capsaicin and piperine through their receptor, TRPV1 [157, 158]. Therefore, combinations of capsaicin/piperine, tachykinin receptor agonists, and tachykinin receptor antagonists are useful tools for investigating the roles of endogenous tachykinins in the gut.

Roles of tachykinins in transmission to GI muscle

Pharmacological analysis of transmission in the enteric nervous system has suggested that most enteric neurons release more than one transmitter. Consistent with this, immunohistochemical studies revealed that tachykinins co-exist with synthesizing enzymes for acetylcholine (ACh) in the same excitatory neurons. ACh is the primary transmitter of excitatory neurons innervating the muscle, because antagonists of muscarinic receptors for ACh, such as atropine, almost totally block the excitatory transmission, while blockage of the tachykinin receptors causes only a small reduction when cholinergic transmission is intact. However, in the presence of a muscarinic receptor blocker, excitatory transmission mediated by tachykinins can be observed clearly [159]. The tachykinin component of excitatory transmission appears to be more prominent at high rates of neuron firing, and can be blocked by a combination of NK1 and NK2 antagonists [15, 21, 160]. Thus, it is now well-established that tachykinins act as a co-neurotransmitter of excitatory neurons [161, 162]. Both SP and NKA appear to be involved in transmission to the muscle [163, 164].

Among the three receptors for tachykinins, there is good evidence that NK1 and NK2 receptors mediate the transmission from excitatory motor neurons to muscle [159]. Both NK1 and NK2 receptors are located on the muscle and NK1 receptors occur on the ICC (see above). It has been reported that fast non-cholinergic contraction induced by brief trains of electrical pulses is mediated by NK1, but not NK2, receptors, whereas delayed non-cholinergic contraction elicited by prolonged trains of electrical stimuli is sensitive to NK2 receptor antagonists [162]. This phenomenon can be explained by the differences in receptor localization. The fast contraction may be derived from the activation of ICC that are directly innervated, and thereby mediated by NK1 receptors. In contrast, the NK2-mediated late contraction may be caused by diffusion of the transmitter to the muscle. Investigation of NK1 receptor knock-out mice confirms that these receptors are primarily responsible for the non-cholinergic component of excitatory transmission to the muscle [165].

Consistent with the existence of co-transmission from excitatory neurons to the muscle, two components of muscle contraction during peristaltic reflexes have been identified, one component being cholinergic, the other due to tachykinin actions [13, 163, 166–168]. In general, the tachykinin component is more prominent at higher stimulus strengths.

Roles of tachykinins in neuro-neuronal transmission

NK1 and NK3 receptors are involved in neuro-neuronal transmission in the enteric nervous system. Fast and slow EPSPs can be recorded from myenteric and submucosal neurons. The fast EPSPs are caused by ACh though nicotinic acetylcholine receptors, 5-HT_3 receptors and purine, P2X, receptors [169]. In contrast, tachykinins have roles in the generation of slow EPSPs.

Table 1. Tachykinin receptor antagonists.

		Reference			Reference
NK1 antagonists					
Peptide					
Sendide	Ki = 4 pM (mouse)[1]	125	[D-Trp7]sendide	Ki = 0.023 nM (mouse)[1]	126
S18523	Ki = 0.8 nM (human)[1]	127	FK888	Ki = 0.69 nM (guinea pig) and 0.45 uM (rat)[1]	128
FR 113680	pA2 =7.53[2]	129			
Non-peptide					
CGP49823	IC50 = 0.22 (gerbil) and 7.8 uM (rats)[3]	130	CJ12255 (ezlopitant)	K(i) = 0.2 (human), 0.9 (guinea pig), 0.6 (ferret), 0.5 (gerbil) nM *[1]	131
CP96345	IC50 = 0.5 nM (human) and 35 nM (rat)[1]	61	CP99994	Ki = 0.25 nM (human)[1]	132
GR203040	Ki = 0.10 nM (human)[1]	133	L732138	IC50 = 2.3 nM (human)[1]	134
LY303870	Ki = 0.10 nM (human)[1]	135	MK0869 (aprepitant, L754030)	IC50 = 0.09 nM (human)[1]	136
NKP608	IC50 = 13 (gerbil) and 27 (rat)[1]	137	RP67580	IC50 = 20 nM (human) and 4 nM (rat)[1]	61
SDZ NKT 343	Ki = 0.16 nM (human)[1]	138	SR140333	IC50 = 0.3 (gerbil) and 1.06 uM (rats)[2]	130
SSR240600	K(i) < 0.10 nM (human)[1]	139	WIN51708	IC50 = 25 nM (rat) and >10 uM (human)[1]	140
NK2 antagonists					
Peptide					
MDL29913	Ki = 14 nM[4]	95	MEN 11420 (nepadutant)	Ki = 2.5 nM (human)[4]	141
Non-peptide					
GR159897	pKi = 9.5(human) and pKi =10.0 (rat)[5]	142	MEN15596	pKi =10.1(human)[4]	143
SR48968	Ki = 0.5 nM[4]	144	YM35375	IC50 = 84 nM[4]	145
NK3 antagonists					
Non-peptide					
GR138676	pKB = 8.3 (human)[6]	146	PD161182	Ki = 0.9 nM[7]	147
SB223412	pKb = 8.97[8]	148	SR142801	pKB = 9.15[9]	149
SSR146977	Ki = 0.26 nM (human)[10] IC50 = 7.8–13 nM[7] pA2 = 9.07[9]	150			
Dual NK1 and NK2 receptor antagonists					
Peptide					
FK224	IC50 = 1.7 (NK1)[1] and 1.9 uM (NK2)[4]	151	spantide	pA2 = 6.5 (NK1) and 6.5 (NK2)[11]	152
Non-peptide					
AVE5883	Ki = 5.6 (NK1) and 3.1 nM (NK2)	153	DNK333	IC50 = 0.5 (NK1)[1] and 24 nM (NK2)[4]	154
YM44778	IC50 = 18 (NK1)[1] and 16 nM (NK2)[4]	155			
Triple NK1, NK2, and NK3 receptor antagonists					
Non-peptide					
ZD6021	Ki = 0.12 (NK1)*[1], 0.64 (NK2)*[4] and 74 (NK3)*[12] nM	156			

[1] Inhibition of substance P (SP) binding to NK1 receptors.
[2] Inhibition of SP-induced guinea pig ileum contraction.
[3] Inhibition of depolarization of spinal motoneurons induced by the selective tachykinin NK1 receptor agonist septide.
[4] Inhibition of [^{125}I] or [^{3}H]neurokinin A binding to NK2 receptors.
[5] Inhibition of NK2 receptor antagonist radioligand [^{3}H]GR100679 to NK2 receptors
[6] Competition on neurokinin B-dependent arachidonic acid mobilization.
[7] Inhibition of senktide-induced inositol monophosphate formation or Ca^{2+} mobilization.
[8] Inhibition of ileal longitudinal muscle contraction by senktide in guinea pig
[9] Inhibition of [MePhe7]NKB-mediated contractions of guinea pig ileum
[10] Inhibition of radioactive neurokinin B binding to NK3 receptors.
[11] Inhibition of depolarization induced by selective agonists in isolated spinal cord of rat.
[12] Inhibition of [^{125}I]-MePhe7NKB binding to NK3 receptors.

Slow EPSPs in IPANs are mimicked by the NK3 receptor agonist, senktide, and are partially blocked by NK3 receptor antagonists, indicating a mediation through the NK3 receptors [170]. A further component of slow transmission is reduced by NK1 receptor block, indicating that both receptor types are involved in tachykinin transmission to the neurons [171]. The internalization of the NK1 receptor, detected by immunohistochemistry, also indicates that there is transmission to IPANs through this receptor type [172]. A major source of the tachykinin-mediated slow transmission to IPANs is probably other IPANs, which synapse with each other to form self-reinforcing circuits [173]. Transmission at IPAN to IPAN synapses is through slow EPSPs, and IPANs contain tachykinins.

Transmission within descending motility-controlling pathways involves tachykinins [174]. When the reflexes are evoked by mucosal stimulation, reflexes are reduced by NK3 receptor antagonist applied to the region in which the reflex is initiated, implying that transmission at the first synapse, between the IPAN and interneurons, is mediated by tachykinins [174]. There is also evidence that a component of transmission from IPANs directly to inhibitory muscle motor neurons is mediated by tachykinins acting through NK1 receptors. This was first suggested by internalization experiments. Agitation of villi of the guinea pig small intestine caused the internalization of the NK1 receptors in a subpopulation of myenteric neurons, which in previous work had been shown to be nitric oxide synthase (NOS) immunoreactive [175]. At the same time, it was shown that NK1 receptor antagonists reduced the amplitudes of descending excitatory reflexes [176]. Direct intracellular recording from the NOS-immunoreactive inhibitory motor neurons identified slow transmission that was reduced by NK1 receptor antagonists [177, 178]. Pharmacological analysis has revealed NK1 receptors on intrinsic inhibitory nitrergic neurons in local reflex circuits controlling esophageal motility [179–181].

Excitatory NK1 and NK3 tachykinin receptors also occur on submucosal secretomotor neurons [182, 183], where they are possibly also involved in neuroneuronal transmission.

Influences of tachykinins on mucosal transport

Tachykinins cause secretion of water and electrolytes when they are applied to the intestine [184, 185], and as they are found in nerve endings in the mucosa, there is a possibility that they could have a physiological role in controlling water and electrolyte transport. Moreover, pharmacological, immunohistochemical, and molecular studies all indicate that mucosal epithelial cells express NK1 and NK2 receptors [116, 184, 186, 187] (see above). However, the major transmitters of the motor innervation appear to be ACh and vasoactive intestinal peptide (VIP) [161]. On the other hand, tachykinins are present in the endings of extrinsic and intrinsic sensory neurons (IPANs) in the mucosa and could be released from these endings, perhaps as part of an axon reflex. Action potentials in one process of an IPAN traverse the cell body to invade other processes and the pattern of branching of the neurons indicates that action potentials could be conducted, as an axon reflex, between terminals that branch within the mucosa. Consistent with this idea, secretory responses to mucosal stroking in the guinea pig colon are partly reduced by blocking NK1 receptors for tachykinins [186].

Tachykinins in inflammation of the GI tract

SP participates in acute intestinal inflammation via binding to NK1 receptors. In the gut, both mucosal macrophages and T lymphocytes express NK1 receptors [122, 188]. There is also evidence that mucosal mast cells have NK1 receptors, and that tachykinins can be released from the mast cells and contribute to the secretion that occurs in inflammation [189]. Thus tachykinins released in the mucosa may contribute to inflammatory responses. The most likely sources of the tachykinin are the peripheral endings of spinal afferent neurons, which are known to release peptides when they are activated [168]. SP induces secretion of proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α (TNF-α) [122, 190–194] via activation of the transcription factor NF-κB in target cells [195, 196]. Conversely, the proinflammatory cytokines regulate expression of NK1 receptors [197]. This can explain the fact that NK1 receptor expression is increased during acute and chronic enterocolitis in animals and humans [35, 119, 123]. In addition, SP stimulates cyclooxygenase-2 and prostaglandin E2 expression through JAK-STAT activation in human colonic epithelial cells [198].

Pathogen-associated colitis is most commonly a consequence of *Clostridium difficile* infection. *C. difficile* produces enterotoxin A, which appears to interact with tachykinin neurons in producing secretion and inflammation [119, 199–201]. The intestinal effects of *C. difficile* toxin A are reduced by the NK1 receptor antagonist, CP 96345 [202]. Furthermore, mice genetically deficient in the NK1 receptor are protected from the secretory and inflammatory changes as well as from epithelial cell damage induced by toxin A, demonstrating a requirement for NK1 receptor in the

pathogenesis of acute inflammatory diarrhea [203]. There is also evidence for tachykinin involvement in the responses to other pathogens, including *Salmonella*, *Trichinella spiralis* and *Schistosoma mansoni* [120]. Furthermore, it has been shown that perturbation of gut flora by antibiotic treatment increased SP immunoreactivity in the colon and produced visceral hypersensitivity [204].

The dinitrofluorobenzene-induced colonic hypersensitivity model has been used to demonstrate an important role for SP and NK1 receptors in the development of colitis downstream from mast cell activation. Antagonizing the NK1 receptor in these animals resulted in significantly reduced colonic patch hypertrophy, leukocyte recruitment, and tissue damage. As a consequence, the formation of watery diarrhea could be completely abrogated [205]. Recent evidence suggests that SP may also play a protective role in chronic colonic inflammation [120]. SP, through NK1 receptors, possesses anti-apoptotic effects in the colonic mucosa by activating Akt, which prevents apoptosis and mediates tissue recovery during colitis [206].

Roles of tachykinins in spinal afferent neurons of the GI tract

Tachykinins are contained in a high proportion of the spinal afferent neurons that supply the gut. They may have effects, particularly on mucosal function (see above), when released from the peripheral ends of the neurons. Tachykinins are also released at the central synapses of the primary afferent neurons in the spinal cord and may thereby contribute to sensory signaling [207]. There is considerable evidence that tachykinin receptor antagonists reduce pain responses to intestinal distension [208, 209], although in the case of NK3 antagonists, the effect appears to be peripheral [210–212]. The visceromotor pain response to colonic distension is reduced by an NK2 antagonist, apparently by an effect in the spinal cord [208]. It has been demonstrated recently that noxious mechanical distension of the colorectum causes an acute change in the spinal level of SP, probably reflecting central release of the peptide from sensory neurons and contributing to the hypersensitivity following the noxious colorectal distension [213].

Utilization of tachykinin pharmacology in therapy

Although tachykinins regulate a variety of digestive functions, including smooth muscle contractility and GI propulsion, enteric microcirculation, secretory/absorptive processes, and nociceptive information transfer from the gut to the CNS, and effective antagonists of each receptor have been used in human trials, useful therapeutic agents have failed to emerge, except in the case of anti-emetic use of NK1 receptor antagonists, notably aprepitant for the treatment of chemotherapy-induced emesis [214, 215]. Moreover, NK1 antagonists which exerted potent visceral analgesic effects in animal studies failed to do so in humans [216]. Theoretically, tachykinin receptor antagonists may be expected to be useful for treatment of the functional bowel disorder, irritable bowel syndrome (IBS), but this expectation has not been realized in studies to date [217]. It has been suggested that NK3 antagonists could be effective in reducing motility, but only in cases where the activation of reflexes is intense [218].

The contribution of NK2 and NK3 receptors to visceral nociception has been identified in many animal studies [219, 220, and see above]. As is the case for propulsive motility [221], combinations of tachykinin receptor antagonists (e.g., NK1 + NK2) have been shown to reduce visceral hyperalgesia better than single antagonists [219]. The actual role of NK2 and NK3 receptor antagonists in humans remains to be established, nonetheless it is conceivable that simultaneous blockade of multiple tachykinin receptors by a tachykinin-receptor-specific, non-subtype-selective antagonist would achieve a better therapeutic outcome compared to a selective antagonist targeting a single tachykinin receptor.

A number of animal studies have implicated tachykinin receptors in inflammatory responses of the small intestine and colon, and yet there is no clinical trial information on the potential use of tachykinin receptor antagonists for inflammatory bowel conditions in humans [214]. It is thus necessary to investigate in more detail the pathogenesis of GI disorders so that the roles of tachykinins and their relation to other control systems can be better understood. With more advanced knowledge, effective therapies that target tachykinin receptors, perhaps in combination with other targets, may emerge.

Conclusions

Tachykinins, originally discovered in the intestine more than 70 years ago, have been a source of fascination ever since. They are now established to be excitatory co-transmitters to gastrointestinal muscle and to enteric neurons. They also have prosecretory effects and are involved in immune responses of the gut. However, tachykinin knock-out does not produce a GI phenotype, and drugs acting at tachy-

kinin receptors have not been efficacious thus far in treating GI disorders, with the exception of the use of NK1 receptor antagonists as anti-emetics. Additional studies are therefore necessary to elucidate further the mechanisms of control of gut function and malfunction. This better knowledge is necessary to develop treatments that may incorporate targeting of tachykinin receptors.

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