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Defensive and pathological functions of the gastrointestinal NK_3 receptor

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Abstract

In general, normal gut functions are unaffected by selective NK_3 receptor antagonists such as talnetant (SB-223412), osanetant (SR 142901) or SB-235375. However, NK_3 receptors may mediate certain defensive or pathological intestinal processes. The precise mechanisms, by which this role is achieved, are not fully understood. In summary, intense stimulation of the intrinsic primary afferent neurones (IPANs) of the enteric nervous system is thought to release tachykinins from these neurones, to induce slow excitation (slow EPSPs) of connecting IPANs. This is hypothesised to cause hypersensitivity and disrupt intestinal motility, at least partly explaining why NK_3 receptor antagonism can reduce the level of disruption caused by supramaximal distension pressures *in vitro*. Tachykinin release from IPANs may also increase C-fibre sensitivity, directly or indirectly. Thus, NK_3 receptor antagonists can inhibit nociception associated with intestinal distension, in normal animals or after pre-sensitisation by restraint stress. Importantly, such inhibition has been found with SB-235375, a peripherally restricted antagonist. SB-235375 can also reduce a visceromotor response to brief colorectal distension without affecting similar responses to skin pinch, providing additional evidence for intestinal-specific activity. NK_3 receptor biology is, therefore, revealing a novel pathway by which disruptions in intestinal motility and nociception can be induced.

Keywords: Tachykinins; NK_3; Intestinal motility; Visceral pain; Osanetant; Talnetant

1. Introduction

Substance P, neurokinin A (NKA) and NKB activate tachykinin NK_1, NK_2 and NK_3 receptors, with a characteristic rank-order of affinity. NKB has the highest affinity for NK_3 receptors, followed by NKA > substance P, which, in turn, have greater affinity for NK_2 and NK_1 receptors, respectively (Maggi, 2000). Each of these peptides is found in the gut, but the amounts of NKA may be low (Tsuchida et al., 1990). However, since the differences in the affinities of these peptides for the NK receptors are not large and 'agonist-promiscuity' is a real possibility, it is argued that NK_3 receptors can be activated by any of these tachykinins, when released in sufficient amounts (Grady et al., 1996; Sanger, 2004). Such an argument is consistent with observations that enteric tachykinin-containing neurones are not associated with clusters of NK receptors (Portbury et al., 2001), and that tachykinins diffuse for significant distances within the gut, as indicated by the detection of tachykinins in venous effluent or bathing solutions surrounding an intact, isolated intestine (Barthó and Holzer, 1985).

The gastrointestinal functions of exogenously applied tachykinins have been well reviewed (e.g., Holzer and Holzer-Petsche, 2001), but the current availability of selective NK_3 receptor antagonists now means that the roles played by endogenous tachykinins, acting at this receptor, can be better understood. For this purpose, it is important to understand which antagonists are incapable of crossing the blood–brain barrier and which can cross this barrier and gain access to the receptors within the brain and spinal cord. Thus, it is possible that tachykinins can directly influence gastrointestinal (GI) functions by acting within the gut itself at enteric nerve or at extrinsic nerve terminals, by acting within the brainstem to modulate vagal nerve activity, and/or by acting within the spinal cord to modulate systems affecting the transmission of sensations and pain. A summary of the important characteristics of

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the selective NK_3 receptor antagonists which have been most often studied is shown in Table 1.

2. Intestinal motility

2.1. Distribution of NK_3 receptors within the enteric nervous system

Tachykinins are localized to the Intrinsic primary afferent neurones (IPANs) of the intestine (Costa et al., 1996). IPANs are sensitive to chemical and/or mechanical stimuli and are characterised by morphology, location and electrophysiology. They have cell bodies in the myenteric and submucosal plexuses and multiple axons, including axons that project circumferentially to many different enteric neurones and axons that project to the mucosa. This anatomical arrangement plus an ability to generate slow excitatory postsynaptic potentials (EPSPs) or sustained slow postsynaptic excitation in response to appropriate stimulation (Morita and North, 1985; Clerc et al., 1999), and their responses to physiological stimuli such as luminal chemicals or mechanical distortion, means that IPANs are able to act as enteric sensory neurones. Further, since one IPAN can synapse with another, the generation of a slow EPSP in the second IPAN means that self-reinforcing networks can be created. Such a change in enteric sensitivity can, in turn, be transmitted by an IPAN forming excitatory synapses with longitudinally projecting excitatory and inhibitory inter-/motor neurones.

NK_3 receptors are found on the cell bodies of myenteric IPANs (Mann et al., 1997; Jenkinson et al., 1999; Lomax and Furness, 2000) and are also distributed to myenteric ascending excitatory and descending inhibitory motor and secretomotor neurones. In addition, NK_3 receptors are found in the submucosal plexus on secretomotor/vasodilator neurones, but not on the IPANs (Jenkinson et al., 1999). NK_3 receptors are found on myenteric neurones in guinea-pig gastric antrum and on myenteric and submucosal neurones in the ileum (Schemann and Kayser, 1991; Jenkinson et al., 1999). A similar distribution of the receptor has been reported in rat and mouse intestinal myenteric and (to a lesser extent) submucosal neurones. However, NK_3-immunoreactivity may be absent in the stomach and oesophagus, where IPAN-like neurones are also thought to be absent, or very rare (Grady et al., 1996; Mann et al., 1997; Wang et al., 2002). In the human sigmoid colon, intense NK_3-immunoreactivity was detected in the myenteric and submucosal plexus (Dass et al., 2002) but not on longitudinal and circular muscle, or on the muscularis mucosa. A similar localisation was found in the human gastric fundus, but with apparently lower levels in the myenteric plexus. The expression of the NK_3 receptor in the human gut has not yet been localised to particular neuronal types. However, in the absence of such data, the presence of substance P-containing neurones within the human intestine, morphologically similar to IPANs (Hens et al., 2001; Brehmer et al., 2004), suggests that the pattern of NK_3 receptor expression in humans could be similar to that observed in animals.

Table 1
Selective NK_3 receptor antagonists

Compound	Potency and selectivity at NK receptors	Ability to cross blood–brain barrier	References
Talnetant (SB-223412)	NK_3 Ki=2 (h), 0.8 (gpig), 43 (r) nM NK_2 Ki=144 (h), 17,071 (gpig IC_{50}), 4327 (r) nM NK_1 Ki>100,000 (h) nM	Crosses rat blood–brain barrier (23% at equilibrium) and active in CNS-mediated behavioural tests	Sarau et al., 1997
Osanetant (SR 142,801)	NK_3 Ki=0.21 (h), 0.11 (gpig), 0.42 (gerbil), 15 (r) nM NK_2 IC_{50}=38 (gpig) NK_1 IC_{50}=600 (h), >2000 (gpig), >10,000 (r) nM	Active in CNS-mediated behavioural tests	Beaujouan et al., 1997; Kamali, 2001
SB-235375	NK_3 Ki=2.2 nM (h), pA_2 8.3 (gpig ileum) NK_2 Ki=209 nM (h) NK_1 Ki >100,000 nM (h)	Does not cross blood–brain barrier during 23 h IV infusion of 1 mg/kg/h	Hay et al., 2002; Shafton et al., 2004

h=human, r=rat, gpig=guinea-pig.

2.2. Role of NK_3 receptors and IPANs in disturbed intestinal motility

A major function of intestinal NK_3 receptors appears to be linked to the role of the IPANs. Transmission between IPANs, via slow EPSPs, is mimicked by senktide and can also be greatly inhibited by NK_3 receptor antagonists in guinea-pig intestine (Neunlist et al., 1999; Alex et al., 2001; Sanger et al., 2002; Johnson and Bornstein, 2004). By comparison, the use of NK_1 receptor ligands suggests that either there is no involvement of this receptor on slow EPSP activity (Neunlist et al., 1999) or that there are a small number of neurones with short-latency (compared with those sensitive to NK_3 receptor antagonism) slow EPSP activity sensitive to NK_1 receptor antagonism (Johnson and Bornstein, 2004). Further, NK_3 receptor-mediated transmission between IPANs or between IPANs and ascending or descending interneurons may play a role in certain polarised reflexes of the intestine. This possibility is suggested by experiments in which the NK_3 receptor agonist senktide was used to desensitise NK_3 receptors, leading to the proposal that IPAN-evoked activation of the ascending excitatory pathway in guinea-pig intestine may be mediated by ACh and/or by tachykinins, acting at NK_3 receptors (Johnson et al., 1996). Similar experiments have also suggested that NK_3 receptors may also play a role in the descending inhibitory pathways (Johnson et al., 1998), involving NO-dependent and -independent neurotransmission (Lecci et al., 1996). The reasons why there is a requirement for the intestine to possess more than one motor neurotransmitter to mediate both ascending and descending motor pathways is not clear. One possibility is that for each pathway, the predominant motor neurotransmitter requires additional support in order to execute different types of movement in response to different types or intensities of intestinal stimulation. This possibility is suggested by a number of different pieces of evidence, including the work with selective NK_3 receptor antagonists.

Firstly, it would seem that, in general, IPANs do not release significant amounts of tachykinins in response to the intensities of