

# Expert Opinion

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Anti-inflammatory

## Potential therapeutic targets for neurokinin-1 receptor antagonists

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The peptide substance P and its tachykinin receptor, neurokinin-1 (NK1), have been the focus of considerable research for their role in a variety of both central and peripheral diseases. Recent preclinical data, as well as relevant clinical findings, support the potential therapeutic value of NK1 receptor antagonists in centrally mediated disease states, including anxiety and depression. In addition, a separate body of literature supports the use of NK1 receptor antagonists as inhibitors of centrally mediated emetic and cough responses. The role of NK1 receptor antagonists as analgesic agents with potential to treat migraine headache has also been investigated. NK1 receptors are also found in a number of peripheral regions, including the bladder, gastrointestinal tract and bone marrow. Preclinical models have been employed to address the potential therapeutic uses for NK1 receptor antagonists in diseases associated with inflammatory responses, including asthma, irritable bowel syndrome and cystitis of the bladder. Finally, other more recent publications suggest a role for NK1 receptor antagonists as tumour suppressants and haematopoietic agents. These applications for NK1 receptor antagonists are discussed in this review.

**Keywords:** anxiety, depression, emesis, inflammation, substance P, tachykinin

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### 1. Background

The peptide substance P (SP) was first discovered in 1931, yet its molecular target was not identified until several decades later. Early research to elucidate the role of this peptide focused on its behavioural and physiological effects in the central and peripheral nervous systems. When administered centrally, the peptide appeared to produce an anxiogenic state in animals, whereas administration into the spinal cord produced hyperalgesia [1]. Peripheral application of SP to isolated guinea-pig ileum resulted in contraction, whereas incubation of the peptide with bone marrow cells produced increases in B cell proliferation [2].

It was later found that SP belonged to the tachykinin family of peptides, that includes neurokinin A and neurokinin B, which are formed as splice variants of two genes, preprotachykinin A and B (*PPT-A* and *PPT-B*) [3], which have been redesignated *TAC1* and *TAC2* by the Human Genome Organisation. More recently, another group of peptides have been identified that belong to the tachykinin family and are coded for by another gene designated *PPT-C* or *TAC4*. These include hemokinin-1 [2,4], as well as endokinins A-D [5].

Three subtypes of tachykinin neurokinin receptors have been identified through molecular cloning techniques and have been designated NK1, NK2 and NK3 [6]. Each receptor subtype has varying affinities for these neuropeptides. The NK1 receptor, like the other tachykinin receptors, is a guanine nucleotide binding protein (G-protein) receptor that has a structure containing seven transmembrane spanning domains. The NK1 receptor was found to be coupled to the G-protein Gq and signals through calcium mobilisation within the cell. In addition, the NK1 receptor

was found to undergo rapid internalisation and desensitisation following agonist activation [7].

Based on *in vitro* binding affinity and functional response, the endogenous neuropeptide SP has the highest affinity for the NK1 receptor [8], although both NKA and NKB will activate the NK1 receptor at high concentrations. In addition, hemokinin-1 and the endokinins all have preferential affinity for the NK1 receptor with similar affinity and functional responses to SP [9,5]. Furthermore, hemokinin-1 produces similar behavioural effects in models of anxiety and depression as SP, with slightly reduced potency [10]. The function of these peptides is presently unknown and they are considered orphan peptides without an endogenous receptor.

Once the molecular target for SP was determined, the localisation of the receptor was determined using autoradiography [11,12]. The SP binding site distribution was found to correspond, somewhat, to the localisation of the peptide using immunohistochemistry [1]. In the central nervous system, the NK1 receptor is localised in high concentrations in the dorsal horn of the spinal cord, as well as the striatum, hippocampus, amygdala and, importantly, in the brainstem, in both the locus coeruleus and raphe nucleus. Peripherally, the NK1 receptor is found in epithelial cells throughout the gut, the lung and the bladder, as well as bone marrow [13].

Based on the physiological effects of SP and the localisation of NK1 receptors, it became apparent the NK1 receptor antagonists could be potential therapeutic agents for a number of both centrally and peripherally mediated disorders. It seems likely that blocking the response of this endogenous neuropeptide would provide a viable treatment for such varied disorders as depression, anxiety, cough, irritable bowel syndrome (IBS) and disorders of the bladder.

## 2. Medical need

### 2.1 Depression/anxiety

Anxiety and depression are mood disorders associated with a profound social and economic impact. It is estimated that up to 20% of the population worldwide will experience a depressive episode during their lifetime. The World Health Organization projects that by the year 2020, depression will be the second leading cause of disease burden due to disability [14]. Anxiety often accompanies depression and can make the patient feel further alienated.

There are multiple antidepressants and anxiolytics presently on the market. Most of these target monoaminergic systems, either through inhibition of enzymes associated with the degradation of the neurotransmitters serotonin or norepinephrine or through the inhibition of the re-uptake mechanisms that terminate the action of these neurotransmitters in the synaptic cleft. Both of these mechanisms result in an increase in one or both neurotransmitters at the receptor, which is thought to enhance mood.

However, a substantial number of patients (up to 15%) do not respond at all to the available therapies and as many as

50% do not achieve remission, defined as a reduction in Hamilton depression (HAM-D) scores to < 7 [15]. In addition, a significant percentage of patients report a recurrence of symptoms over time. Finally, the antidepressants available have considerable side effects that result in non-compliance, including sexual dysfunction, nausea and vomiting [1]. As a result of these compliance issues, compounds with novel mechanisms have been sought for the treatment of depression and anxiety.

### 2.2 Emesis

Emesis associated with chemotherapy is a major concern for oncologists and patients alike. There are two phases of chemotherapy-induced emesis: the acute phase immediately following treatment; and the delayed phase, which occurs up to 48 h after treatment. Both are thought to be centrally mediated via the nucleus of the solitary tract in the brain stem. Traditional treatments are effective for the acute phase, including serotonin 3 receptor (5-HT<sub>3</sub>) antagonists, but are less effective in blocking the delayed phase of emesis [16].

### 2.3 Asthma

Asthma is a disorder whose incidence has increased in recent years, particularly among children living in urban areas. It is a complex disorder that can be life-threatening if untreated and includes both inflammatory and immunological components. The symptoms include wheezing, shortness of breath and chest tightness or constriction, which are thought to be caused by a combination of inflammation, increased mucus production and constriction of the bronchi. Treatments include those that control the occurrence of symptoms, such as anti-inflammatory agents and long-acting bronchodilators, and those used for rescue during an asthma attack, such as fast-acting bronchodilators and anticholinergics to decrease mucus production. An alternative therapy with better efficacy for controlling symptoms is viewed as medically necessary.

### 2.4 Cough

The cough reflex involves both peripheral and central components, the latter via receptors in the nucleus of the solitary tract [17]. The most commonly used cough suppressant, dextromethorphan, works via the mu opioid receptor in this region. The reported abuse of this cough suppressant and the lack of novel therapeutic agents introduced have further fueled the need for a novel cough suppressant.

### 2.5 Migraine headache pain

Pain responses are mediated via a number of different fibre pathways that pass through the spinal cord before being relayed to higher brain centers. Migraine headache pain is thought to be related to activation of C-fibres leading to subsequent activation of inflammatory responses in the dura mater and the network of blood vessels surrounding the brain. SP is one of the major activators of C-fibres. Analgesic agents targeted specifically to migraine headache, such as sumatriptan, are

thought to act by inhibiting the inflammatory responses produced by C-fibre activation via 5-HT<sub>1D</sub> and histamine H<sub>1</sub> receptors [18]. In theory, therefore, inhibiting the activation of C-fibres with a NK1 antagonist could help prevent the initiation of the cascade of events leading to migraine headaches.

It should be noted that although NK1 receptor antagonists have a strong preclinical rationale for being analgesics, few positive clinical trials have been reported for other types of pain, including chronic, postsurgical and dental pain, as well as migraine headache (see Section 5), despite numerous attempts spanning decades [19].

### 2.6 Irritable bowel syndrome

IBS is a form of colitis that has a debilitating effect on patients and presents as a constellation of symptoms including diarrhoea alternating with constipation, abdominal pain and distension, as well as nausea and vomiting. The contractions of the wall of the intestine are thought to produce some of the symptoms, but as the causes of the syndrome are poorly understood, treatment often focuses on symptomatic relief and non-specific therapies, such as changes in diet or antianxiety medications. A therapy that more specifically targets the receptors located in the bowel that produce contractions could improve the long-term prognosis for this chronic disease.

### 2.7 Cystitis of the bladder

Cystitis of the urinary bladder is another painful and potentially debilitating condition that involves inflammation of the bladder wall without associated bacterial infection. One form of this disorder, referred to as interstitial cystitis, is quite painful and severely affects the patient's quality of life. The symptoms are similar to cystitis caused by a bacterial infection, including painful, frequent urination and disruption of urine flow, but are often more pronounced. The disorder is treated in much the same way as IBS, by treating symptoms, including opiate pain medications and psychiatric drugs. Again, a more specific treatment is needed.

## 3. Therapeutic class review

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This review details the potential therapeutic intervention of a single mechanism: NK1 receptor blockade. Presently, with the exception of the emesis [19] indication discussed below, there are no NK1 receptor antagonists on the market for the indications above. Although there is known clinical efficacy of NK1 receptor antagonists in emesis and there have been reports of clinical efficacy of NK1 receptor antagonists for depression [20-22], none of the other indications have been proven in clinical trials as yet. The preclinical evidence that supports the use of NK1 receptor blockade as a potential therapeutic target for these indications is discussed below.

Aprepitant (Emend®), an NK1 antagonist developed and marketed by Merck, came on the market in March 2003 as an adjunctive therapy for the treatment of chemotherapy-induced

emesis. It is a potent inhibitor of cytochrome P450 3A4 and, therefore, has known interactions with medications that are metabolised via this enzyme, including dexamethasone.

## 4. Current research goals

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One major goal of ongoing research in this area is to elucidate the role of SP and the NK1 receptor in various centrally and peripherally mediated disease states. The development of non-peptide NK1 receptor antagonists paved the way for the development of tools to determine the functional role of NK1 receptors, which in turn has led to potential clinical candidates. Many non-peptide NK1 receptor antagonists had variable species selectivity. Compounds with high affinity for the human NK1 receptor had lower affinity for the rat and mouse NK1 receptor [23]. This species difference in affinity was found to be caused by a single amino acid difference in the fourth and seventh cytoplasmic loops of the receptor [24]. The affinity difference between species for non-peptide NK1 receptor antagonists became an important consideration for the choice of animal models for drug discovery, particularly in the case of depression.

## 5. Scientific rationale

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### 5.1. Pain

The most widely studied effects of SP and the NK1 receptor relate to nociception. The receptor is localised in the dorsal horn of the spinal cord and activation by agonists produced hyperalgesia. Blockade of the receptor was, therefore, thought to be a promising target for analgesia. A number of clinical studies have been conducted over the years, but the promise of a novel analgesic without tolerance or dependence did not come to fruition [19,25]. A variety of reasons have been proposed for the presumed mismatch between the preclinical effects of NK1 receptor antagonists in animal models and their effects in the clinic, including the use of the species with different pain pathways than humans and differences in pharmacokinetic parameters [26,27]. A more recent clinical trial found that the NK1 antagonist CP-99,994 significantly reduced postoperative pain following oral surgery, with an efficacy at later time points similar to ibuprofen [27]. It has been suggested anecdotally that NK1 receptor antagonists may have a benefit in fibromyalgia [28,29], although clinical trials do not support this [26]. Recent papers on NK1 knockout (KO) mice suggest that the NK1 receptor may mediate descending inhibitory controls [30] that maybe related to neurogenic inflammation [31]. The conflicting evidence surrounding the potential clinical value of NK1 receptor antagonists as analgesics has led some companies to continue with active programmes in this area (see Table 1).

SP is one of the neuropeptides associated with activation of C-fibres through the trigeminal ganglion. It has been proposed that trigeminal nerve activation is a major contributing factor in migraine headache. Activation of C-fibres is believed

**Table 1. Summary of NK1 antagonists in clinical development.**

Company	Compound	Country	Mechanisms	Indications	Status	As of
Advanced Targeting Systems	SP	US	NK1 antag	Analgesic	Discovery	Jan-00
AstraZeneca	ZD-4794	UK	NK1 antag	Antidepressant	Discovery	Jan-00
	NA	UK	NK1/NK2 antag	Multiple	Discovery	Oct-02
Aventis	NA	US/Canada	NK1 antag/H1 antag	Allergy	Discovery	Jan-02
Bioglan Labs	BL-1832	UK	NK1 antag	Analgesic	Phase 3	Jan-01
	BL-1833	UK	NK1 antag	Analgesic	Discovery	Jan-01
	BL-1872	UK	NK1 antag/opioid agonist	Analgesic	Discovery	Jan-01
Esteve	E-6006	Spain	NK1 antag/ sigma opioid agonist	Depression	Phase 2?	Apr-03
GlaxoSmithKline	GW-597599	UK	NK1 antag	Depression/anxiety	Phase 2	Jan-03
	GW-679769	UK	NK1 antag	Depression/anxiety	Phase 1	Jan-03
Janssen	R-116301	US	NK1 antag	Analgesic	Discovery	Feb-00
Kyorin Pharm	KRP-103	Japan	NK1 antag	Urinary incontinence	Discovery	Oct-03
NIH	SP-PE toxin	US	NK1 antag	Analgesic	Discovery	Feb-00
Novartis	TKA-457	Switzerland	NK1 antag	Analgesic	Discovery	Nov-01
Merck	Aprepitant	US	NK1 antag	Emesis	Launched	Apr-03
	L-758,298	US	NK1 antag	Depression	Discontinued	Mar-04
		US	NK1 antag	Emesis	Phase 2	Jun-98
	L-760,735	UK	NK1 antag	Analgesic	?	Jul-03
		UK	NK1 antag	Antidepressant	Discovery	May-99
L-759,274	UK	NK1 antag	Antidepressant	Discontinued	Mar-04	
Nissan Chemical Industries	NIP-530	Japan	NK1 antag/H1 antag	Atopic dermatitis	Discovery	Jun-99
Pfizer	Ezlopitant	US	NK1 antag	IBS	Phase 2	Jul-00
	CP-122,721	US	NK1 antag	Emesis/depression	Phase 2	Sep-01
					Asthma/IBS	Discovery
	PD-154075	US	NK1 antag	Emesis/neuropathic pain	Phase 1	Jan-02
	CJ-17493	US	NK1 antag	Depression	Phase 1?	Jun-03
	CP-96,345	US	NK1 antag	HIV infection	Discovery	Oct-01
Hoffmann-La Roche	R-673	US/Japan	NK1 antag	Depression	Phase 2	Jan-03
	NA	Switzerland	NK1 antag	Depression	Phase 1	Aug-01
	NA	Switzerland	NK1 antag	Anxiety	Discovery	Aug-01
	R-1124	Switzerland	NK1 antag	Emesis	Phase 2	Sep-02
Sanofi-Synthelabo	Nolpitatanium besilate	France	NK1 antag	IBS	Phase 2	Jun-01
	SSR240600	France	NK1 antag	Micturition disorder	Discovery	Jul-02
UCB Pharma SA	NA	Belgium	NK1 antag/ 5-HT uptake inhibitor	Depression	Discovery	Nov-01

?: Unknown; 5-HT: Serotonin; Antag: Antagonist toxin; IBS: Irritable bowel syndrome; NA: Not available; NK: Neurokinin; SP: Saporin conjugate.

to produce a neurogenic inflammatory cascade, beginning with the extravasation, or leakage, of proteins from blood vessels within the dura mater [18]. Therefore, NK1 receptor antagonists would be suitable for blocking the cascade of events leading to migraine headache. Preclinical studies have shown that NK1 receptor antagonists block the neurogenic inflammatory response produced by administration of capsaicin [32,33] and electrical stimulation of the trigeminal ganglion [34]. As with other clinical pain trials, however, NK1 receptor antagonists for the treatment of migraine headache have been unsuccessful [25]. An alternative hypothesis is that

neurogenic vasodilation of meningeal blood vessels is the main component in the inflammatory process [18]. If this were the case, one would not expect NK1 receptor antagonists to produce the vasoconstriction necessary to halt the inflammatory process, which would explain the failed clinical trials.

### 5.2 Depression and anxiety

The discovery of non-peptide NK1 receptor antagonists with high affinity for the human NK1 receptor, coupled with the localisation of NK1 receptors in areas of the brain associated with mood, such as the amygdala, as well as the behavioural

effects of SP in rodents, led to an interest in the development of NK1 receptor antagonists as novel antidepressants and/or anxiolytics. A variety of preclinical evidence suggests that activation of NK1 receptors is associated with depression and anxiety and that NK1 receptor blockade produces both behavioural and physiological effects associated with antidepressant and anxiolytic activity. Due to the species differences in affinity found for non-peptide NK1 receptor antagonists, the traditional rat and mouse animal models for anxiety and depression had no utility, as the NK1 receptor amino acid sequences in these species rendered them poor targets for antagonists that targeted the human receptor. As a result, models were developed using other rodent species, including gerbils, guinea-pigs, hamsters and ferrets, where the NK1 receptor binding affinity of antagonists is similar to that seen for the human receptor.

NK1 receptor activation produces stress responses in rodents, including foot tapping in gerbils [35], vocalisation in guinea-pig pups [36] and decreased time spent in the open arms of an elevated maze [37]. These effects are inhibited or reversed by administration of NK1 receptor antagonists. NK1 receptor antagonists are also active in resident-intruder models in hamsters, as well as mouse models, using both NK1 receptor blockade or KO mice [38].

The pharmacological processes involved in these behavioural effects are now more fully understood. NK1 receptor occupancy in striatum by NK1 receptor antagonists has been correlated with the inhibition of foot-tapping in gerbils produced by these compounds [39], suggesting that this behavioural effect is mediated by NK1 receptor blockade. Guinea-pig vocalisations induced by stress or by intra-amygdala administration of SP were inhibited by NK1 receptor antagonists [40]. Another study showed that immobilisation stress in gerbils produced NK1 receptor internalisation in amygdala that was inhibited in the presence of the NK1 antagonist L-760,735 [36]. These studies suggest that activation of NK1 receptors by either the exogenous administration or stress-induced release of SP results in NK1 receptor internalisation that is blocked by NK1 antagonist administration.

More recent studies have demonstrated interactions between noradrenaline neurons in the locus coeruleus and 5-HT neurons in the dorsal raphe nucleus. NK1 receptor antagonists were found to produce burst firing of noradrenaline neurons in the locus coeruleus [41]. In addition, NK1 receptor antagonists alter the firing characteristics of 5-HT neurons in the dorsal raphe [42]. As known antidepressants are thought to exert their effects through monoaminergic systems in these brain regions, these studies suggest that the behavioural effects produced by NK1 antagonist administration may be mediated through interactions with monoaminergic systems in these regions as well.

Finally, recent evidence suggests that depression and stress are related to changes in synaptic modelling and a decrease in neurogenesis in the cortex and hippocampus. Antidepressant treatment has been shown to cause changes in synaptic

plasticity [43]. NK1 receptor antagonists have been found to reverse the stress-induced impairment of neurogenesis in a tree shrew model of psychosocial stress [44].

Two separate Phase II clinical depression/anxiety studies demonstrated a significant decrease in both Hamilton Anxiety (HAM-A) and HAM-D self-rating symptom scales following administration of two different NK1 receptor antagonists, aprepitant (MK869) [20] and a 'compound A' [21]. Compound A has recently been identified as L-759,274 in a report detailing the positive clinical results [22]. Importantly, in both studies, the incidence of adverse events was similar to placebo. Subsequent dose-finding clinical trials for aprepitant in depression failed as the HAM-A and HAM-D scores for both the positive control (fluoxetine) and aprepitant were similar to placebo. Similarly, the dose-finding trial for L-759,274 also failed for both the test compound and the positive control (paroxetine) [22]. It has been reported that Merck has ceased its development of L-759,274 for depression after a clinical trial in which aprepitant failed to show efficacy [22].

### 5.3 Emesis

Most of the preclinical studies for chemotherapy-induced emesis were conducted in ferrets, as this species exhibits the acute emetic response following cisplatin treatment, in addition to a delayed emetic response which can occur for 48 – 72 h following chemotherapy treatment. Aprepitant and its prodrug L-758,298 were found to inhibit both the acute and the delayed phase of cisplatin-induced emesis in the ferret model [45]. Importantly, the effect was enhanced with combined treatment with the presently available antiemetics dexamethasone and ondansetron. Other NK1 receptor antagonists, including CP-122,721, have been shown to be preclinically active in this model [46]. The antiemetic response of NK1 receptor antagonists was found to be dependent on brain penetration of the compound [47]. Finally, different species have shown activity of NK1 receptor antagonists against other emetic responses, such as the inhibition of motion-induced sickness in the house musk shrew [48].

### 5.4 Asthma

NK1 receptors are found in the epithelium of the bronchi of the lung where SP is in abundant supply. There is preclinical evidence that NK1 receptor blockade may influence more than one component of the asthmatic response, which is composed of constriction of bronchi as well as inflammatory and secretory processes, through both central and peripheral mechanisms. In the guinea-pig, the NK1 antagonist CP-99,994 inhibited SP-induced contractions in both isolated bronchi and lung, as well as *in vivo* [49]. NK1 receptor antagonists have also been shown to inhibit bronchoconstriction in a rabbit model of gastroesophageal acid reflux [50]. In addition, NK1 receptor stimulation has been shown to cause contractions in human isolated bronchi that are inhibited by both CP-99,994 and SR-140333 [51]. Although the response in the isolated tissues suggests that NK1 receptor antagonists

are exerting their effects peripherally, there is also evidence for a central component of this response through the nucleus tractus solitarius. Bronchopulmonary C-fibres are thought to synapse in this nucleus prior to sending their output to higher brain centres, thus providing a respiratory reflex characterised by cough and bronchoconstriction in response to SP [52]. This effect is inhibited by NK1 receptor antagonists such as SR-140333 [53]. Supporting this hypothesis of activation of C-fibres by SP in asthma is a report that preprotachykinin-A mRNA, from the gene that encodes SP, is increased 10-fold in the airway epithelium of smokers with chronic bronchitis, whereas no change in NK1 receptor mRNA was detected, suggesting an increase in SP without changes in receptor number [54].

The role of NK1 receptors in the inflammatory and secretory processes within the lung are tied to their role in plasma protein extravasation. Much like the blood vessels in the head are thought to trigger the inflammatory response resulting in migraine headache through a cascade of events beginning with leakage or extravasation of plasma proteins, a similar process is thought to take place in the lung. It is thought that outside stimuli, such as allergens, can trigger extravasation [55] and activate mast cells independent of NK1 receptor activation. The subsequent infiltration of neutrophils is believed to be mediated by NK1 receptors [56]. The resulting inflammatory cascade leads to airway hyper-reactivity and mucus secretion, both of which are affected by NK1 receptor antagonists. CP-99,994 was found to block the SP-induced submucosal gland fluid release in pigs [57]. Clinically, there is a suggestion that microvascular leakage of plasma protein occurs in human asthma patients exposed to SP ([58]; for review of the role of NK1, NK2 and NK3 receptors, see [59]).

### 5.5 Cough

Most of the interest surrounding the use of NK1 receptor antagonists in cough has been restricted to their involvement in the cough response in asthma. As in asthma models, irritants such as citric acid and capsaicin have been used in pharmacodynamic models to test the efficacy of NK1 receptor antagonists to block endogenous SP release. The central cough reflex described above in reference to the nucleus of the solitary tract is thought to play a role in the general cough response, although a local peripheral component is also involved. NK1 receptor antagonists, such as SR-140333 [60] and, more recently, NKP 608 [61], have been shown to inhibit citric acid-induced cough in the guinea-pig. CP-99,994 was also found to inhibit capsaicin-induced cough in the guinea-pig when administered both subcutaneously and intracerebroventricularly, suggesting that the compound exerts its effects both centrally and peripherally. Interestingly, when similar studies were performed using a mechanically induced cough in the cat, the compounds were much more potent when administered centrally, suggesting that this is the main site of action in the cat [18].

In a study conducted in asthmatic patients, CP-99,994 infused intravenously for 2 h prior to hypotonic saline challenge produced no significant improvement in bronchoconstriction or cough [62].

### 5.6 Irritable bowel syndrome

NK1 receptors are found throughout the intestine in smooth muscle cells of the myenteric plexus, where activation by SP produces muscle contraction [14]. The symptoms of bowel disorders, such as colitis and IBS, are thought to be caused at least in part by muscle spasms in the colon. It is also thought that inflammatory processes similar to those occurring in the lung may play a role in these disorders. The NK1 antagonist TAK-637 has been found to decrease stress-induced defecation in gerbils [63] and the abdominal muscle contractions induced by colorectal distention in rabbits [64]. In models of acute rectocolitis, the NK1 antagonist MEN-11467 reduced plasma extravasation and necrosis induced by rectal infusion of acetic acid in guinea-pigs, although this effect was seen only in the early phase of colonic inflammation [65]. In two models of colonic hypersensitivity produced by distention and chemical irritants, TAK-637 reduced abdominal contractions following both peripheral and central administration, suggesting that a central component of the response is likely [66]. Indeed, central administration of NK1 selective agonists was shown to exacerbate the inflammatory responses produced in two different chemically induced models of colitis in rats [67]. The visceral pain response produced by NK1 receptor activation may be transmitted through dorsal column neurons, where NK1 receptor immunoreactivity was found to be increased following colon inflammation [68].

A comparison of NK1 receptor expression in the intestine of healthy patients against that of patients with ulcerative colitis or Crohn's disease found marked upregulation of NK1 receptors in both inflamed and uninflamed mucosa. The increase was particularly marked in epithelial cells lining the surface of the mucosa and the endothelial cells of capillaries and venules – sites where plasma protein extravasation may take place [69].

### 5.7 Cystitis of the bladder

As in the case of the bowel, NK1 receptor activation in the bladder is thought to trigger an inflammatory response. As in the lung, bladder mast cell activation is not NK1 receptor dependent, while the subsequent inflammatory response characterised by plasma extravasation and migration of neutrophils is absent in NK1 KO mice [70]. In addition, similar to the results found for inflammation of the bowel, NK1 receptors in the visceral pain pathways through the spinal cord, specifically the lumbosacral portion, were found to be upregulated following chemically-induced chronic bladder irritation [71,72]. A recent report suggests that part of the inflammatory response in the bladder may be via the production of reactive oxygen species. Treatment with NK1 receptor antagonists reduced both the hyperactive bladder response

and the reactive oxygen species [73]. TAK-637 was shown to increase bladder capacity without affecting voiding efficiency in cats, presumably by inhibiting the afferent pathway through the spinal cord [74], suggesting that bladder function is not likely to be compromised by NK1 receptor antagonists.

In a clinical study, intravesical capsaicin was administered to patients with interstitial cystitis, the rationale for the therapy being to desensitize the afferent pathway through which visceral pain is transmitted. Four out of the five patients reported improvement in their symptoms and three out of five exhibited a trend toward decreased urinary SP [75]. Similarly, cooling the dorsal spinal cord to reduce neuronal overactivity following spinal cord injury has been shown to improve symptoms of reflex incontinence [76].

## 5.8 Other possible therapeutic uses

### 5.8.1 Pancreatitis

As with the other inflammatory processes described above, acute pancreatitis involves plasma protein extravasation. In rats, activation of NK1 receptors produced extravasation and neutrophil infiltration in endothelial cells, which was blocked by NK1 receptor antagonists. In NK1 KO mice, SP had no effect. In addition, the effects of a non specific agent cerulein were decreased by 60% in NK1 KO mice, suggesting that neurogenic inflammation through NK1 receptor activation is an important component of acute pancreatitis [77]. SP KO mice demonstrated almost complete protection against acute pancreatitis [78]. In a rat model of acute pancreatitis produced by retrograde infusion of radiological contrast media, intraductal co-administration of CP-96,345 decreased pancreatic inflammation caused by the contrast infusion [79].

### 5.8.2 Atopic dermatitis

There is also recent evidence that neurogenic inflammatory processes may be involved in skin disorders such as atopic dermatitis. Peripheral blood mononuclear cells from patients with atopic dermatitis showed increased expression of NK1 receptors. Addition of SP to these cells produced increases in TNF- $\alpha$  and IL-10 release, suggesting that SP may aggravate the symptoms of atopic dermatitis by both increasing the production of inflammatory cytokines and upregulation of the NK1 receptor [80]. The peptide antagonist spantide II was found to produce an anti-inflammatory effect in an allergic contact dermatitis model in rats [81].

### 5.8.3 Human immunodeficiency virus

A number of studies have reported on the effects of NK1 receptor activation on immune function. Both SP and the NK1 receptor are found in the bone marrow and have been reported to be involved with haematopoiesis [82]. In addition, NK1 receptors are present on monocytes and T lymphocytes and SP has been shown to alter the function of these immune cells. SP enhanced HIV-1 replication *in vitro* in a latently infected human immune cell line, an effect that is inhibited by NK1 receptor antagonists [83]. Some mechanisms by which

NK1 receptor activation may enhance HIV replication may be through its effects on the permeability of cells, where SP was found to increase permeability of endothelial cells exposed in culture to HIV-1, an effect that was blocked by spantide, an NK1 antagonist [84]. It has also been suggested that increased life stress and depression in HIV patients increases levels of SP, which then acts as a modulator of neuro-immune function, increasing the susceptibility of immune cells to HIV infection [85]. Indeed, levels of SP were found to be increased in HIV-infected men [86]. *In vitro* studies with human mononuclear phagocytes exposed to HIV showed that CP-96,345 inhibited HIV replication [87] and downregulated SP mRNA expression [88].

### 5.8.4 Cancer

The first reports concerning the role of NK1 receptor activation in tumour growth concerned their localisation on a high percentage of cells taken from a variety of certain human neoplasms, including astrocytomas and glioblastomas, where NK1 receptors were found on blood vessels [89]. Later reports showed upregulation of NK1 receptors in blood vessels around human colorectal cancer tumours that were not seen in healthy controls [90]. More recently, increased expression of mRNA for both SP and the NK1 receptor were found in human breast cancer cells [91].

Another group has focused on childhood lymphoblastic leukaemia and found increases in SP expression, measured with immunocytochemistry, in the cytoplasm of lymphoblasts of the T cell type, but not in lymphoblasts of the B cell type or in controls [92]. In a similar study, SP mRNA expression was increased in bone marrow from children with acute lymphoblastic leukaemia and the presence of SP immunopositive cells correlated with treatment failure and relapse [93]. Taken together, these studies suggest that activation of NK1 receptors may play a role in tumour growth, possibly through humoral factors.

Recent studies have reported that SP antagonist analogues inhibit proliferation of small lung cell cancer cell lines in the proliferative state only, suggesting that the effect was not due to cytotoxicity [94]. A peptide derivative of SP has been reported to act as an antagonist and to inhibit small cell lung cancer growth in preliminary clinical trials [95]. Similarly, the non-peptide antagonist MEN-11467 was shown to inhibit cell proliferation in pancreatic cancer cell lines [96]. These studies suggest that NK1 receptor blockade may have a potential therapeutic use for tumour suppression.

### 5.8.5 Substance abuse

There is increasing evidence in the literature that neuropeptide expression may be altered following chronic administration of opiates. SP gene expression in caudate putamen and nucleus accumbens was shown to be decreased with chronic morphine treatment [97]. NK1 KO mice have shown decreased morphine-induced hyperlocomotion, as well as impairment in detecting both the rewarding properties of

morphine and its withdrawal [98]. Although this study found no alterations in the rewarding properties of cocaine in NK1 KO mice, another study found that prolonged cocaine self-administration transiently increased SP mRNA levels in the shell of the nucleus accumbens [99].

Other groups have examined the influence of NK1 receptors on the development of both dependence and tolerance to morphine. Administration of increasing doses of morphine to rats elevated SP immunoreactivity in the dorsal horn of the spinal cord, whereas subsequent administration of naloxone to induce withdrawal decreased SP immunoreactivity. Pretreatment with NK1 antagonist SR-140333 attenuated both the withdrawal response and the decrease in SP immunoreactivity [100], suggesting that NK1 antagonists may be useful for alleviating the symptoms of opiate abuse. Furthermore, a subsequent study demonstrated that intrathecal co-administration of SR-140333 with morphine prevented analgesic tolerance in rats. In addition, NK1 antagonist treatment in cultured dorsal root ganglion neurons prevented the morphine-induced increase in the expression of calcitonin gene-related peptide *in vitro*, which is thought to contribute to the development of tolerance [101]. This opens up the possibility of co-administering NK1 antagonists to prevent the development of tolerance in patients using opioids for the treatment of chronic pain.

## 6. Competitive environment

Table 1 summarises the preclinical and clinical status of a number of companies interested in developing NK1 receptor antagonists for the indications described above. Only those companies that have reported activity in the area for the last 4 years are included. Several of the compounds listed have additional activities on proteins other than the NK1 receptor and these are noted. The list of companies in this research area ranges from small biotechnology firms to pharmaceutical giants. Several of the companies have multiple NK1 receptor antagonists in their pipelines for the same or several different indications and for markets in locations throughout the world. The most common indications for clinical development appear to be depression/anxiety and emesis, although Pfizer has five candidate compounds in their pipeline for at least five different indications.

As stated above, Merck's NK1 antagonist aprepitant is being marketed for the treatment of chemotherapy-induced emesis. Other companies have products in later stage clinical development, including Bioglan labs, GlaxoSmithKline, Merck, Pfizer, Hoffmann-La Roche and Sanofi-Synthelabo, for indications ranging from analgesia and depression to IBS and emesis.

Many of the companies have published preclinical and clinical data on their candidate compounds. However, this trend appears to be company specific and dependent upon the stage of development of the compound. The listing in Table 1 is

based on a search of the Investigational Drugs database (Copyright 2004, Derwent Information Ltd.) [201] which tracks the clinical development of known chemical entities. Many of the companies listed in Table 1 have not published data on their compounds in peer-reviewed journals, although they are listed in the database. Those studies which have been published on NK1 receptor antagonists in clinical development are outlined below.

Merck has published extensively on its non-peptide NK1 receptor antagonists, including a number of recent publications on clinical data on both aprepitant and L-758,298, its prodrug, in chemotherapy-induced emesis [102-104]. A Merck compound in clinical trials for depression in the UK is L-760,735, which has been shown to be active in animal models of depression and anxiety, including fear conditioning in gerbils [105]. This compound was also used in reports to illustrate the link between NK1 receptor blockade with changes in noradrenaline neurons in the locus coeruleus [41] and 5-HT neurons in the raphe nuclei [42]. As mentioned previously, Merck appears to have ceased its development of NK1 antagonists in the US with the failure of aprepitant to show efficacy in a recent depression trial [22].

Pfizer's ezlopitant is reported to be in Phase II clinical trials in the US for IBS. Most of the publications concerning this compound pertain to its metabolism [106-108], particularly its interaction with cytochrome P450 enzymes [109,110]. CP-122,721, which is in Phase II clinical trials for emesis and depression, has been reported to produce antiemetic effects in ferrets [46]. It was shown to be clinically active in a trial in postoperative vomiting following hysterectomy [111]. Pharmacological characterisation of CP-122,721 both *in vitro* and *in vivo* demonstrated that it acts as a non-competitive, irreversible antagonist [112]. The compound was also recently reported to be clinically active in depression [113].

Johnson & Johnson recently acquired Janssen's R-116301, which has been reported to produce antiemetic responses in ferrets, cats and dogs. It was also characterised for its inhibition of plasma protein extravasation in guinea-pigs and foot tapping in gerbils [114].

Esteve's NK1 antagonist E-6006 has been reported to be active in animal models of depression, including forced swim test in rats, tail suspension test in mice and isolation-induced vocalisations in guinea-pigs [115]. Its metabolite, E-6332, has been analysed in rat and dog plasma [116].

Finally, Sanofi-Synthelabo has SSR240600 in preclinical development. They recently reported on the pharmacological and biochemical characterisation of this compound, where it was reported to inhibit citric acid-induced cough in guinea-pigs [117,118].

## 7. Expert opinion and conclusion

NK1 receptor blockade produces far reaching and profound biochemical, physiological and behavioural effects in a

number of organ systems, including the bone marrow, gut, bladder, lung and brain. Based on the preclinical literature outlined above, it appears that blocking NK1 receptors generally produces positive effects related to the decrease in the receptor activation produced by SP, including producing anxiolytic and analgesic effects and decreases in smooth muscle contraction. Many of the effects of NK1 receptor antagonists also appear to be due to their effects on inhibiting inflammatory processes produced by endogenous SP release, as in the case of asthma, IBS and interstitial cystitis. A related mechanism is the effects on changes in epithelial cells associated with blood vessels, with evidence that NK1 receptor blockade may prevent the opening of the pores of these cells, decreasing not only the leakage of plasma proteins, but also decreasing permeability of the blood vessels to viral agents, such as HIV infection and possibly even tumour cells.

A major issue to be addressed is: how realistic is the assumption that NK1 receptor blockade will be effective against all of these varied therapeutic targets? Although preclinical evidence supports the use of NK1 receptor antagonists for all of these indications, there are a number of caveats to bear in mind when considering potential clinical outcomes for these indications. First, there is the strong possibility that *in vitro* models in cells do not mimic events *in vivo*. This is particularly true for the studies conducted using cultured immortalised cell lines, where NK1 receptor antagonists were shown to inhibit cell growth. Similarly, it is frequently argued that animal models do not necessarily mimic what occurs in humans in the clinic. One need only look at the failed clinical trials for NK1 receptor antagonists for analgesia to understand that although NK1 receptor blockade produced analgesia in several different animal models of pain, none of these models accurately predicted positive clinical results [19]. It is possible that the species differences in affinity seen for non-peptide NK1 receptor antagonists could have played a role in these failed trials, although it has also been suggested that NK1 receptor antagonists simply do not provide the level of sensory blockade necessary to produce analgesia in humans [25]. The opposing argument could be made for preclinical data on the therapeutic efficacy of NK1 receptor antagonists as antiemetics, where the data for the ferret clearly predicted efficacy in the human trials.

Given these caveats, it would appear that the only way to be certain of NK1 antagonist efficacy for a new indication is to conduct a human trial. This has been done for two of the above indications: emesis and depression. For the depression indication, there have been two positive trials reported for two separate compounds and also two failed trials for the same compounds, in addition to the recent report of a failed trial with aprepitant [22]. However, as has been pointed out, given that half of all clinical trials for depression fail [19], this finding is not surprising. Therefore, conducting multiple trials with various NK1 receptor antagonists for depression may yet lead to a drug for this indication.

For indications where inflammatory processes such as plasma extravasation are thought to be causative mechanisms of the disease, such as in asthma, NK1 receptor antagonists may be a useful adjunctive therapy to already established remedies to control the inflammatory response. The same rationale supports the use of NK1 receptor antagonists for the treatment of IBS, pancreatitis and cystitis of the bladder, where inflammatory processes are thought to be a contributing factor to the symptoms. Given the fact that there are presently no specific treatments for these disorders, proof of principle clinical trials for these indications are warranted. A note of caution must be exercised for the use of NK1 receptor antagonists to treat disorders of the bowel and bladder, however, if the symptoms result from the visceral pain signals through the spinal cord, where NK1 receptor antagonists have failed to provide analgesic effects in the clinic.

Finally, it may be premature to determine whether NK1 receptor antagonists will be efficacious in treating cancer and HIV infection. Most of the preclinical studies in these areas involve the use of cell lines and the limited number of clinical reports have been largely retrospective. This remains an exciting area of research, with the future utility of this mechanism for treatment to be determined.

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