Neuropeptide receptors as potential drug targets in the treatment of inflammatory conditions

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Keywords

calcitonin gene-related peptide, cortistatin, galanin, pituitary adenylate cyclase-activating polypeptide, somatostatin, tachykinin

Received

27 August 2012

Accepted

8 February 2013

Accepted Article Published Online

21 February 2013

Cross-talk between the nervous, endocrine and immune systems exists via regulator molecules, such as neuropeptides, hormones and cytokines. A number of neuropeptides have been implicated in the genesis of inflammation, such as tachykinins and calcitonin gene-related peptide. Development of their receptor antagonists could be a promising approach to anti-inflammatory pharmacotherapy. Anti-inflammatory neuropeptides, such as vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, α -melanocyte-stimulating hormone, urocortin, adrenomedullin, somatostatin, cortistatin, ghrelin, galanin and opioid peptides, are also released and act on their own receptors on the neurons as well as on different inflammatory and immune cells. The aim of the present review is to summarize the most prominent data of preclinical animal studies concerning the main pharmacological effects of ligands acting on the neuropeptide receptors. Promising therapeutic impacts of these compounds as potential candidates for the development of novel types of anti-inflammatory drugs are also discussed.

Introduction

Homeostasis of the body is under triple regulation by the nervous, endocrine and immune systems. Communication between these systems can take place via direct cell-to-cell contact or through soluble signalling molecules and their specific receptors on target cells. The most prominent groups of these regulator molecules are neuropeptides, hormones and cytokines. The classic definition of neuropeptides was modified in the past two decades, because they are not exclusively produced by the neurons but also by the inflammatory, immune and endocrine cells. Their receptors are also expressed in these cells; they are considered as neuro-endocrine-immune modulators. They have a crucial regulatory role in the cross-talk of the neuro-endocrine and neuro-immune systems.

A number of pro-inflammatory neuropeptides have been implicated in the genesis of neurogenic inflamma-

tion, such as tachykinins and calcitonin gene-related peptide (CGRP). Local release of tachykinins, as well as CGRP of neuronal origin, results in the sensitization of peripheral nerve endings and the activation of inflammatory and immune cells, contributing to the initiation and maintenance of neurogenic inflammatory processes. These neuropeptides exert their effects through the activation of G protein-coupled receptors. The development of antagonists acting on these receptors provides a new approach to anti-inflammatory pharmacotherapy.

Besides classical pro-inflammatory neuropeptides, numerous peptides of neuronal origin are known to ameliorate neurogenic inflammation and inhibit the function of inflammatory cells. These peptides have also been shown to be produced by non-neuronal sources, e.g. inflammatory cells. Anti-inflammatory neuropeptides are as follows: vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP),

α -melanocyte-stimulating hormone (α -MSH), urocortin (Ucn), adrenomedullin (AM), somatostatin (SST), cortistatin (CST), ghrelin, galanin and opioid peptides. All of these compounds act on G protein-coupled receptors that activate adenylate cyclase, with the notable exceptions of SST and CST, which act via $G_{i/o}$ -coupled receptors. Agonists of these neuropeptide receptors might offer lead compounds for the development of novel anti-inflammatory agents. Receptors are expressed in different immune-competent cells regulating the cAMP–protein kinase A pathway. Anti-inflammatory neuropeptides reduce the inflammatory response by downregulating the production of inflammatory mediators and upregulating anti-inflammatory mediators, including cytokines, chemokines and free radicals. Receptors of anti-inflammatory neuropeptides could also be promising targets in the treatment of inflammatory diseases.

Pro-inflammatory neuropeptides

Tachykinins

Pro-inflammatory tachykinins form an important, expanding family of neuropeptides, containing 10- to 12-amino-acid peptides, such as substance P (SP), neurokinin A (NKA), neurokinin B (NKB), hemokinin-1 (HK-1) and endokinin A–D (EKA–EKD). These peptides activate G protein-coupled mammalian tachykinin receptors, NK_1 , NK_2 and NK_3 , with varying affinity [1].

Tachykinins are involved in a broad range of biological actions, including pain transmission, inflammation, vasodilatation, platelet function, activation of the immune and endocrine systems, smooth muscle contraction and depression-like behaviour [2–5].

The discovery of SP, the first characterized neuropeptide, in 1931 has opened the research field of tachykinins. It is encoded by the preprotachykinin A (*PPT-A*, *TAC1*) gene and expressed predominantly in capsaicin-sensitive primary sensory neurons of the dorsal root and trigeminal ganglia, as well as in the central nervous system (CNS). Substance P preferentially binds to the NK_1 receptors. Substance P has been proved to participate in various pathophysiological processes, such as vasodilatation, plasma protein extravasation, leucocyte infiltration, mast cell degranulation, pain, anxiety, depression, nausea and vomiting.

Neurokinin A is the other tachykinin product of the *TAC1* gene. It is expressed mainly by capsaicin-sensitive sensory neurons and is a preferred binding ligand of the NK_2 receptors, expressed predominantly on smooth muscle cells. The most important mediated physiological effect of NKA is smooth muscle contraction, mainly in the respiratory and gastrointestinal systems.

Neurokinin B is derived from the preprotachykinin B (*PPT-B*, *TAC3*) gene. Both NKB and NK_3 receptors, which bind NKB with the highest affinity, are predominantly expressed

in the CNS, where NKB exerts neural activation. There is some evidence that NK_3 receptors also exist on the periphery, mainly in the joints [6], airways [7] and gastrointestinal tract [8].

In 2000, new members of the tachykinin family were discovered, encoded by the preprotachykinin C (*PPT-C*, *TAC4*) gene. The peptide products of the *TAC4* gene are HK-1 in mice and their respective peptides, endokinins (EKA–EKD) in humans [9].

Hemokinin-1 and EKA–EKD differ from other tachykinins by their predominantly non-neuronal expression pattern [10]. Remarkable expression of *TAC4* mRNA has been reported in various tissues and cells of the immune system, such as T and B lymphocytes, macrophages, dendritic and endothelial cells, suggesting that they have an important role in the activation and differentiation of inflammatory and immune cells as well as the promotion of angiogenesis [9, 11–14].

Hemokinin-1 most closely resembles SP in sequence and also exhibits immunological cross-reactivity. Moreover, similar preference has been described for the NK_1 receptor [10, 15–18]. However, several effects of HK-1 suggest the existence of presently unidentified receptors related to HK-1 [19].

NK_1 receptor antagonists

CP-96,345 – the first NK_1 receptor antagonist, discovered in 1991 [20, 21] – proved to be effective in several inflammatory conditions. In cerulein-induced pancreatitis of the rat, it was able to inhibit the pancreatic plasma extravasation and serum amylase increase [22]; in the zymosan-induced acute colitis of the rat, it decreased plasma extravasation [23]; while in murine experimental autoimmune encephalomyelitis (EAE), it could reduce the clinical and histological signs by stabilization of the blood–brain barrier and suppression of T-helper 1 immunity [24].

Effectiveness of two different NK_1 receptor antagonists has been reported in complete Freund's adjuvant (CFA)-induced arthritis of the rat. WIN51708 [25] and GR82334 decreased the mechanical hyperalgesia and destructive histological changes in the joint, when given intrarticularly [26].

Moreover, GR205171 also relieved mechanical hyperalgesia in CFA-induced arthritis in the rat, and it could inhibit joint swelling in animal models of neuropathic pain [27]. Besides arthritic pain, GR205171 was able to attenuate reductions in carotid arterial vascular resistance evoked by the tachykinin NK receptor agonist SP methyl ester 1 and produced a dose-dependent inhibition of plasma protein extravasation in the dura mater [28].

The NK_1 receptor antagonist L-703,606 was found to be effective in experimental animal models of carrageenin-induced arthritis. In rats, it was able to reduce the arthritic pain [29], as well as paw oedema [14].

RP67580 was tested in animal models of several different pathological conditions. Lam and Ng [30] reported that

RP67580 was even able to improve the efficacy of dexamethasone in reducing arthritic pain and joint swelling in the rat adjuvant-induced arthritis model. Furthermore, administration of RP67580 resulted in abrogation of watery diarrhoea and reduction of colonic patch hypertrophy, leucocyte recruitment, tissue damage and mast cell infiltration when applied in a dinitro-fluorobenzene (DNFB)-induced colonic hypersensitivity model [31]. In murine non-atopic airway inflammation, the development of both tracheal hyper-reactivity and neutrophil accumulation in the bronchoalveolar lavage fluid could be observed [32].

FK888 was also investigated in the inflammatory processes of the airways. Hirayama and colleagues found that FK888 was able to inhibit plasma exudation but not bronchoconstriction induced by vagal stimulation in guinea-pigs [33].

The NK₁ receptor antagonist SR140333 was described to decrease bodyweight loss, macroscopic and histological scores and reduced colonic myeloperoxidase (MPO) activity and tumour necrosis factor- α (TNF- α) tissue levels in dinitrobenzene sulfonic acid (DNBS)-induced colitis of the rat [34]. Recently, it was also reported to reduce endotoxin-induced fever effectively in rats if administered by the intracerebroventricular route [35].

Another NK₁ receptor antagonist, named MEN-11467, was observed to reduce the macroscopic damage, necrosis score and plasma protein extravasation in the early acute phase of acetic acid-induced rectocolitis in guinea-pigs [36].

CP-99,994 was described to abolish microvascular leakage in the rat trachea and main bronchi during toluene-induced respiratory tract irritation [37]. It was also discovered to have a remarkable antiemetic effect [38].

Rolapitant (SCH 619734), a functionally competitive antagonist, was active in both acute and delayed emesis models in ferrets [39]. In several different animal models, NK₁ antagonists, such as aprepitant (MK-869), L-733060, CP-122721 and L-760735, have been shown to exhibit antidepressant-like and anxiolytic effects [40–44].

In contrast to the successful experiments with various animal models, NK₁ receptor antagonists failed as anti-inflammatory compounds in most clinical trials. Early findings on the distribution and pharmacodynamics of SP and NK₁ receptors triggered numerous pharmaceutical companies – including Eli Lilly, GlaxoSmithKline, Merck, Parke-Davis and Pfizer – to develop selective nonpeptide NK₁ receptor antagonists for the therapy of painful conditions. However, these compounds did not exhibit significant analgesic activity in clinical trials and failed to reach the market for this indication. This story has been reviewed in detail by Hill [45] Urban and Fox [46] and Herbert and Holzer [27].

The early results showing that SP was more abundant in the dorsal horn of the spinal cord than in the ventral horn caught the attention of the pharmaceutical industry.

Localization of SP in thin unmyelinated sensory fibres seemed to support involvement of the peptide in sensory neurotransmission. Substance P had a slow, but long-lasting, excitatory effect on dorsal horn sensory neurons. NK₁ receptors are also present in dorsal horn neurons and dorsal root ganglia, such as in unmyelinated nerve fibres of the skin and dura mater [27].

Although the previous data presented strong evidence that SP participates in nociception, SP showed no algesic effect when injected intramuscularly or applied to the base of skin blisters. Substance P induced primary hyperalgesia in the knee joint of the rat and cat. Painful stimuli, inflammation and neuropathy were shown to influence SP content in primary afferent and dorsal root ganglion neurons [27].

In animal studies, NK₁ antagonists showed no effect in acute pain models, such as hotplate and tail-flick tests, but they exerted antihyperalgetic effects in some animal models of inflammation and neuropathic pain [27].

The only clinical trial that has found significant analgesic effect was performed with CP-99994, involving patients who underwent surgical extraction of the third molar. In contrast, aprepitant and CP-122721 were ineffective for tooth extraction pain. Aprepitant and LY 303870 also failed to relieve neuropathic pain in patients with postherpetic neuralgia or diabetic neuropathy. LY 303870 exhibited no effect on osteoarthritic pain. GR205171 and L-758298 (water-soluble prodrug of aprepitant) could not improve various types of headache, including migraine [27].

Several theories have been proposed to explain the therapeutic failure of NK₁ receptor antagonists as analgesics. Many of them have much higher affinity to the human NK₁ receptor than to that of the rat. Consequently, preclinical studies involving high doses of NK₁ antagonist applied to rats might have detected nonspecific effects, because functional magnetic resonance imaging and positron emission tomography could not be used to determine effective human doses of the drugs at that time. Species differences in the distribution of NK₁ receptors at supraspinal sites have also been blamed [27].

The lack of effect of NK₁ antagonists in osteoarthritis, diabetic neuropathy and various headache syndromes might be explained by involvement of multiple transmitters in these processes and a subordinate role of SP. Central and peripheral neurons of the nociceptive pathway contain multiple neurotransmitters. These are released together with SP and modulate the effect of each other. The peptide content of such neurons is influenced by inflammation, nerve injury or painful conditions. Some authors suggest that anxiolytic activity of NK₁ receptor antagonists has been misinterpreted as antihyperalgesic activity in preclinical trials. Although an anxiolytic effect of NK₁ antagonists has been described in animal models [47], L-759274 has recently failed to prove such efficacy in a placebo- and active-controlled, double-blind clinical trial [48].

NK₁ receptor knockout mice became available after the disappointing clinical data had been obtained. These animals exhibit normal acute nociception and acute inflammatory processes, except that they show a slighter 'wind-up' phenomenon in the dorsal horn. *TAC1* gene-deleted mice – lacking both SP and NKA – also have normal nociception. Earlier availability of genetically modified animals in the tachykinin field could have prevented pharmaceutical companies from investing vast resources into clinical development of NK₁ antagonist analgesics [27, 45].

Human studies investigating NK₁ receptor antagonists in airway inflammation were controversial. CP-99994 did not inhibit hypertonic saline-induced bronchoconstriction [49], in contrast to the results gained in animal experiments, but FK888 was capable to attenuate the recovery phase of exercise-induced airway constriction [50].

In contrast, based on previous promising results of animal experiments [38], NK₁ receptor antagonists have been developed as a new effective group of antiemetics. The presence and functional role of tachykinins have been identified in the ferret, in the brainstem nuclei involved in nausea and vomiting. Nucleus tractus solitarius is the proposed site of action. Tachykinins are also transmitters of vagal afferents projecting to the area postrema, which is the chemoreceptor trigger zone. Substance P-induced neuronal excitation was shown to be prevented by NK₁ antagonists with electrophysiological as well as positron emission tomographic examinations in animal studies [51].

Clinical trials confirmed the potent antiemetic effect of several NK₁ antagonists in cancer-chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting [52, 53]. Aprepitant and its injectible form, fosaprepitant dimeglumine (MK-0517), are in clinical use for the therapy of cancer-chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting [54]. Orally administered casopitant mesylate (GW679769B) was able to increase the efficacy of ondansetron in female patients at high risk for postoperative nausea and vomiting [55]. Maropitant (Pfizer) has been approved by the USA Food and Drug Administration for the treatment of motion sickness-evoked nausea and vomiting in dogs.

Furthermore, on the basis of former animal studies [47, 56], aprepitant, L-759274 and casopitant were investigated as new pharmacological tools of antidepressant as well as anxiolytic therapy and were proved to be effective in major depression [57, 58], but not in anxiety disorder [48].

NK₂ receptor antagonists

The NK₂ receptor antagonist saredutant (SR48968) was investigated particularly in inflammation of the airways. Some authors reported no effect on the hypersensitivity reaction in non-atopic airway inflammation [32], whereas others showed that SR48968 was able to inhibit airway hyper-responsiveness in the murine model of endotoxin-

induced acute pneumonitis [59]. In human studies of bronchial asthma, decreased bronchoconstriction in response to NKA was observed [60]. SR144190 could prevent airway hyper-responsiveness to acetylcholine in guinea-pigs as well as castor oil-induced diarrhoea in rats [61].

Nepadutant (MEN 11420) was capable of reducing the macroscopic damage, necrosis score, plasma protein extravasation and MPO activity in the early phase of acetic acid-induced rectocolitis in the guinea-pig [62]. It could also decrease spontaneous colonic hypermotility in the rat [63]. Furthermore, administration of nepadutant led to reduction of diarrhoea in a murine model of bacterial toxin-induced enteritis [63].

NK₃ receptor antagonists

In adjuvant-induced arthritis, the NK₃ receptor antagonist talnetant (SB-223412) reduced the inflammatory thermal hyperalgesia in rats, as well as normalizing the basal release of SP from spinal cord synaptosomes [6].

Another NK₃ antagonist, osanetant (SR142801), was found to reduce the increase in TNF- α and interleukin-6 levels as well as the matrix metalloproteinase-9 activity in murine endotoxin-induced airway inflammation [7].

Combined receptor antagonists

A combination of SR140333 and SR48968 (NK₁ and NK₂ receptor antagonists, respectively) in endotoxin-induced acute pneumonitis was investigated by several groups. Veron and colleagues [7] found that it diminished neutrophil cell accumulation and matrix metalloproteinase-9 activity in the bronchoalveolar lavage fluid, while another research group described the reduction of neutrophil accumulation and attenuation of MPO activity and interleukin-1 β production, suggesting the effectiveness of a combination of NK₁ and NK₂ receptor antagonists in airway inflammation [59].

The dual NK₁/NK₂ receptor antagonist FK224 showed no effect in asthmatic patients against NKA-induced bronchoconstriction [64, 65], although former human studies had revealed its protective effect against bradykinin-induced bronchoconstriction and cough [33]. After the controversial results with FK224, further dual NK₁/NK₂ receptor antagonists, such as DNK-333, AVE-5883 and MEN11420, seemed to be effective in the attenuation of airway hyper-responsiveness in later studies [64, 66–68].

However, DNK-333 was also tested in diarrhoea-predominant irritable bowel syndrome, where the reduction of abdominal pain/discomfort and global symptoms of diarrhoea-predominant irritable bowel syndrome were observed [69].

The triple NK₁/NK₂/NK₃ receptor antagonist CS-003 was able to decrease airway responsiveness in human bronchial asthma [70].

Table 1

Anti-inflammatory effects of tachykinin and calcitonin gene-related peptide (CGRP) receptor antagonists in animal models

Receptor	Antagonist	Anti-inflammatory effects in animal models
NK ₁	CP-96,345	Cerulein-induced pancreatitis in rats, zymosan-induced colitis in rats, EAE [22–24]
	WIN51708	Adjuvant-induced arthritis in rats [25, 26]
	GR82334	
	L-703,606	Carrageenan-induced arthritis in rats [29]
	RP67580	Adjuvant-induced arthritis in rats, murine DNFB-induced colitis, murine non-atopic airway inflammation [30–32]
	SR140333	DNBS-induced colitis in rats, endotoxin-induced fever in rats [34, 35]
	MEN-11467	Acetic acid-induced colitis in guinea-pigs [36]
	GR205171	SP-induced plasma protein extravasation in rats [28]
	CP-99,994	Toluene-induced respiratory tract irritation in rats, anti-emetic effect in ferrets and dogs [37, 38]
	Rolapitant (SCH 619734)	Anti-emetic effect in ferrets [39]
	Aprepitant (MK-869)	Anxiolytic and antidepressant effect in gerbils [40, 42–44]
	L-733060	Anxiolytic and antidepressant effect in gerbils [42–44]
	CP-122721	Anxiolytic and antidepressant effect in gerbils [42–44]
NK ₂	L-760735	Anxiolytic effect in gerbils [41]
	Saredutant (SR48968)	No effect in non-atopic [32], but protective effect in endotoxin-induced [59] murine airway inflammation
	SR144190	Acetylcholine-induced airway hyper-reactivity in guinea-pigs [61]
NK ₃	Nepadutant (MEN 11420)	Acetic acid-induced colitis in guinea-pigs, bacterial toxin-induced enteritis in mice [62, 63]
	Talnetant (SB 223412-A)	Inflammatory thermal hyperalgesia in rats [6]
	Osanetant (SR142801)	Endotoxin-induced murine airway inflammation [7]
Combination of NK ₁ and NK ₂ antagonists	SR140333 + SR48968	Endotoxin-induced murine airway inflammation [7, 59]
CALCRL-RAMP1	CGRP(8–37)	Endotoxin-induced acute pneumonitis in mice [59]

Abbreviations are as follows: CALCRL, calcitonin receptor-like receptor; DNBS, dinitrobenzene sulfonic acid; DNFB, dinitrofluorobenzene; EAE, experimental autoimmune encephalitis; NK, neurokinin receptor; RAMP, receptor activity-modifying protein; and SP, substance P.

Calcitonin gene-related peptide

Calcitonin gene-related peptide is a 37-amino-acid peptide derived from the calcitonin gene and produced by neurons. In particular, it plays a role in the regulation of the microcirculation, mediating vasodilatation and increased blood flow. Its main target structures are the skin and the trigeminovascular system [71]. Formerly, the biological effects of CGRP were suggested to be mediated by CGRP₁ and CGRP₂ receptors. The CGRP₁ receptor is now a pharmacologically and molecularly well-defined receptor, considered to be a heterodimer complex formed by the calcitonin receptor-like receptor (CALCRL) and receptor activity modifying protein 1 (RAMP1) [72]. The CALCRL-RAMP1 complex has been proved to be responsible for mediating the cardiovascular effects of CGRP. The CGRP fragment CGRP(8–37) acts as a selective antagonist of this receptor. In contrast, the precise structure, function and importance of CGRP₂ receptors still remain unclear [73].

Calcitonin gene-related peptide antagonists

Regarding the potential therapeutic use of CGRP antagonists as anti-inflammatory agents, in a murine model of endotoxin-induced acute pneumonitis, CGRP(8–37) was shown to diminish neutrophil accumulation, MPO level and interleukin-1 β production [59].

Olesen and colleagues [74] provided evidence that CGRP is a key element in the pathophysiology of migraine,

by showing in a phase II trial that intravenous administration of a small-molecule CGRP receptor antagonist, olcegepant (BIBN4096BS), showed efficacy comparable to the response rate obtained with triptans [75].

Telcagepant (MK-0974) was the first orally available and highly selective CGRP receptor antagonist. It effectively reduced pain and accompanying symptoms, such as nausea, photophobia and phonophobia, in phase II and III trials [75].

MK-3207 was tested as a further CGRP receptor antagonist with a higher oral bioavailability and potency than telcagepant, but despite its effectiveness in acute migraine it was stopped because of a higher concentration of liver transaminases [75].

A phase II trial with the oral CGRP receptor antagonist BI 44370 TA was recently completed and showed that the compound was well tolerated and effective against migraine-like headache [75].

The anti-inflammatory effects of tachykinin and CGRP receptor antagonists are summarized in Tables 1 and 2.

Anti-inflammatory neuropeptides

Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide

The 28-amino-acid VIP is found in the intestine, CNS, cardiovascular, respiratory, genitourinary and immune

Table 2

Anti-inflammatory effects of tachykinin and calcitonin gene-related peptide (CGRP) receptor antagonists in human trials

Receptor	Antagonist	Anti-inflammatory effects in human trials
NK ₁	CP-99,994	No inhibition of hypertonic saline-induced bronchoconstriction [49]
	FK888	Attenuation of the recovery phase of exercise-induced airway narrowing [50]
	Aprepitant (MK-869)	Acute and delayed chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting [52, 53]
	Fosaprepitant (MK-0517)	Chemotherapy-induced nausea and vomiting [54]
	Casopitant (GW679769B)	Postoperative nausea and vomiting [55]
NK ₂	L-759274	Major depression [56–58]
	Saredutant (SR48968)	Decreased bronchoconstriction on response to NKA [60]
Dual NK ₁ /NK ₂	FK224	No protective effect in NKA-induced bronchoconstriction [65]
	DNK-333	Decreased airway hyper-responsiveness, IBS-D [66, 69]
	AVE-5883	Decreased airway responsiveness, inhibition of bronchoconstriction [67]
	MEN-48968	Decreased airway responsiveness [68]
Triple NK ₁ /NK ₂ /NK ₃	CS-003	Decreased airway hyper-responsiveness in human bronchial asthma [70]
CALCRL-RAMP1	Olcegepant (BIBN4096BS)	Human migraine [74]
	Telcagepant (MK-0974)	Human migraine [75]
	BI 4370 TA	Human migraine [75]

Abbreviations are as follows: CALCRL, calcitonin receptor-like receptor; IBS-D, irritable bowel syndrome with diarrhoea; NK, neurokinin receptor; NKA, neurokinin A; and RAMP, receptor activity-modifying protein.

systems and the thyroid gland [76, 77]. The amino-acid sequence of VIP contains homologies with many gastrointestinal hormones and PACAP. PACAP is present as a 38 and also 27 amino acid containing peptide [78, 79]. Immunoreactivity for PACAP was shown to be present in the pituitary, throughout the CNS, respiratory, gastrointestinal, genitourinary, endocrine and immune systems and the skin (for review see [80]). PACAP is also released from peripheral nerve endings during neurogenic inflammation [81]. Vasoactive intestinal peptide and PACAP share the receptors VPAC₁ and VPAC₂. These receptors are present in the CNS, pituitary, eye, lung, endocrine organs, gastrointestinal tract, urinary tract, blood vessels and immune cells. Activation of these receptors on immune cells inhibits inducible nitric oxide synthase expression, inflammatory cytokine/chemokine production and co-stimulation of macrophages and dendritic cells [82]. PACAP also lessens the release of inflammatory neuropeptides from nerve endings [83]. Both peptides have been shown to exert beneficial effects in animal models of arthritis [83, 84], EAE [85, 86], colitis [87, 88], sepsis [89, 90] and pancreatitis [91, 92]. However, there is no consensus regarding which receptor is responsible for the anti-inflammatory actions. PAC₁ was suggested in models of septic shock, whereas VPAC₁ was suggested in cerulein-induced pancreatitis [90, 91, 93]. Vasoactive intestinal peptide was shown to decrease inflammatory cytokine and chemokine production of human synovial fibroblasts [94]. Moreover, a few conflicting studies are also available regarding the anti-inflammatory activity of these peptides. Mice genetically lacking VIP were reported to develop less severe EAE and sepsis [95]. Interestingly, PACAP knockout animals developed less severe experimental pancreatitis [92]. PACAP was

found to precipitate migraine headache in mice and humans and to initiate neurogenic inflammation of the skin in humans [96–98].

α-Melanocyte-stimulating hormone

α-Melanocyte-stimulating hormone is a 13-amino-acid peptide derived from pro-opiomelanocortin. It acts via melanocortin receptors, of which MC₁, MC₃ and MC₅ are responsible for anti-inflammatory effects [99]. α-Melanocyte-stimulating hormone is expressed in the CNS, pituitary, skin and immune system [82]. The receptors MC₁ and MC₃ are present in the CNS, immune cells and peripheral tissues. In peripheral tissues, MC₅ is ubiquitous, and it is also expressed on lymphocytes [99]. Underlying mechanisms of the effects of α-MSH include inhibition of nuclear factor-κB activation, inhibition of interleukin-1 receptor-associated kinase-1 and inhibition of T-lymphocyte proliferation and dendritic cell function [100–103]. Activation of melanocortin receptors had inhibitory effects in experimental models of sepsis, arthritis, inflammatory bowel disease and uveitis [104–107]. The melanocortin receptor agonist AP214 was found to be effective in murine coecal ligation-induced sepsis, zymosan-induced peritonitis and serum transfer-induced arthritis in K/BxN-transgenic mice [104, 105]. The MC₁, MC₃, MC₄ and MC₅ agonist AP405 has been evaluated in preclinical studies and suggested for topical treatment of atopic dermatitis.

Urocortins

Urocortin 1 is a member of the corticotropin-releasing factor (CRF) peptide family, acting via CRF₁ and CRF₂ receptors. Target cells possessing CRF₁ and CRF₂ receptors are located in the cardiovascular, gastrointestinal and immune

systems, CNS, pituitary, testis and skin [108]. Urocortin 1 was reported to ameliorate murine colitis and to modulate the immune response in rat colitis [109, 110]. Conflicting data are also available. Activation of CRF₂ was found to be pro-inflammatory in the human colon, and CRF₂-deficient mice expressed less intensive intestinal inflammation [111, 112]. Urocortin 1 ameliorated murine collagen-induced arthritis. The presence and participation of urocortins and their receptors were confirmed in human rheumatoid arthritis and osteoarthritis [113, 114]. Activation of CRF receptors is beneficial in EAE [115]. Urocortin was effective in a murine model of sepsis [89].

Adrenomedullin

Adrenomedullin is a highly conserved peptide belonging to the amylin peptide family. Adrenomedullin is ubiquitous and exerts its actions via the CALCLR-RAMP2 receptor complex. Target sites comprise the cardiorespiratory organs and immune cells [116]. Adrenomedullin has been shown to be anti-inflammatory in animal models of sepsis, pancreatitis, arthritis and colonic inflammation [117–120]. Adrenomedullin was also reported to inhibit cell proliferation and inflammatory mediator secretion by synovial fibroblasts of rheumatoid arthritis patients [121]. Adrenomedullin has not been tested in humans for inflammatory disease, but as an adjunct to reperfusion therapy of myocardial infarction [122].

Somatostatin

Somatostatin is synthesized in 14- or 28-amino-acid-containing native forms in the CNS, primary afferent and sympathetic neurons, endocrine and immune cells [123, 124]. Somatostatin binds to sst_{1–5} receptors. These are categorized further to group SRIF1, containing sst₂, sst₃ and sst₅, and SRIF2, consisting of sst₁ and sst₄ [125]. The SRIF2 family seems to be more important in relation to anti-inflammatory effects. Receptors have been found on sensory neurons and most immune cell types, including lymphocytes, monocytes, macrophages, endothelial cells, fibroblasts, synovial cells and dendritic cells [126]. Somatostatin inhibits neurogenic inflammation [127]. The sst₄-receptor-selective cyclic heptapeptide analogue TT-232 was effective in neurogenic and non-neurogenic inflammation of the skin, as well as lipopolysaccharide-induced acute and ovalbumin-induced chronic airway inflammation [128–130]. This analogue also has tyrosine-kinase-inhibiting properties in much higher doses. A nonpeptide selective sst₄ receptor agonist, J-2156, exhibited efficacy in similar animal models [128, 131]. Somatostatin also decreases proliferation, chemotaxis and cytokine and immunoglobulin secretion by lymphocytes, monocytes and macrophages [132–135]. The beneficial effects of the SST analogues octreotide and pasireotide in murine antigen-induced arthritis were found to be mediated via sst₂ and sst₁ receptors, respectively [136]. The sst₄-receptor-selective analogue J-2156 was also reported to inhibit the

CFA-induced arthritis in the rat [131]. Chronic intra-articular administration of SST14 seemed to be effective in the treatment of rheumatoid arthritis patients [137]. Octreotide showed efficacy in the treatment of human uveitic chronic macular oedema [138, 139]. Octreotide failed to produce any beneficial effect in glucocorticoid-treated ulcerative colitis patients [140]. However, it ameliorated TNF- α secretion in a rat model of Crohn's disease [141]. Octreotide proved to be effective in acetic acid-induced colitis, whereas SST was ineffective in dextran sulfate-induced colitis in rats [142, 143]. Likewise, octreotide alleviated sepsis-induced pelvic inflammation in rats, but SST failed to improve ovine sepsis [144, 145]. Somatostatin and octreotide treatments failed to improve acute human pancreatitis [146]. Octreotide was shown to inhibit cerulein-induced acute murine pancreatitis. Somatostatin was also reported to relieve rabbit pancreatitis in combination with growth hormone [147].

Cortistatin

Cortistatin is a cyclic peptide with great homology to SST. It is most abundant in the CNS and immune cells. Despite the structural homology, the effects of CST do not completely overlap with those of SST. This might be due to the ability of CST to activate ghrelin receptors as well as sst receptors [148]. Cortistatin inhibited neurogenic and non-neurogenic inflammation in rodent skin, abolished inflammatory cytokine and neuropeptide production and relieved heat-injury-evoked thermal hyperalgesia [149]. Cortistatin proved to be effective in experimental arthritis, a murine model of Crohn's disease and sepsis [150–152].

Ghrelin

Ghrelin, a 28-amino-acid peptide, is mainly produced by the gastric mucosa, but it has also been detected in the pancreas and gastrointestinal tract [153]. Ghrelin exerts its action via growth hormone secretagogue receptors (GHS-Rs). These are widely expressed in the CNS, pituitary, pancreas, cardiorespiratory and gastrointestinal tracts, pancreas and immune cells [154]. Ghrelin showed inhibitory effects in colonic inflammation, arthritis, pancreatitis and sepsis [155–158].

Galanin

Galanin is a 29-amino-acid peptide expressed in the CNS and peripheral nervous system [159]. Galanin exerts its actions via GAL₁, GAL₂ and GAL₃ receptors. The GAL₁ and GAL₂ receptors are expressed throughout the CNS, while GAL₃ dominates in non-neuronal tissues [159]. Galanin was beneficial in a cuprizone-induced mouse model of multiple sclerosis [160]. The peptide has also been shown to alleviate a rat model of Crohn's disease when administered chronically [161]. On the contrary, galanin may contribute to excess colonic fluid secretion in a murine model of ulcerative colitis [162]. Galanin was reported to play a pro-inflammatory role in cerulein-induced acute murine

pancreatitis. The disease was alleviated by galanin receptor antagonists and genetic deletion of galanin [163, 164]. Recent data indicate substantial involvement of GAL₃ in this model [165]. Galanin also participates in neurogenic and non-neurogenic inflammation of murine skin. Genetic lack of the galanin gene attenuates these processes [166].

Endomorphin-1 and endomorphin-2 (EM-1 and EM-2)

Endomorphin-1 and EM-2 are tetrapeptides binding to μ opioid receptors with high affinity and selectivity [167]. Endomorphins are widely distributed in the CNS and immune cells [168–170]. Endomorphins are also present in

primary afferent neurons [171]. Endomorphin-1 attenuated CFA-induced polyarthritis in rats. Endomorphin-1 and EM-2 have been shown to inhibit inflammatory cytokine secretion of isolated synoviocytes of rheumatoid arthritis and osteoarthritis patients [172].

The anti-inflammatory effects of neuropeptide receptor agonists are summarized in Tables 3–5.

Conclusions

According to the current literature, neuropeptide receptors and the potential clinical relevance of the ligand

Table 3

Data from animal experiments illustrating anti-inflammatory effects of neuropeptide receptor agonists

Receptor	Agonists	Anti-inflammatory effect in animal models
VPAC ₁ VPAC ₂ PAC ₁	PACAP	Neurogenic inflammation in rats and mice, murine collagen-induced arthritis, murine colitis, murine sepsis, murine cerulein-induced pancreatitis [81, 83, 85, 87, 90, 92]
VPAC ₁ VPAC ₂	VIP	Collagen-induced arthritis in rats, murine EAE, TNBS-induced murine colitis, murine sepsis, murine cerulein-induced pancreatitis [84, 86, 88, 89, 91]
MC ₁ MC ₂ MC ₃	AP214	Murine coecal ligation-induced sepsis, murine zymosan-induced peritonitis, murine serum transfer-induced arthritis [104, 105]
MC ₁ MC ₃ MC ₄ MC ₅	AP405	Completed preclinical phase for atopic dermatitis
CRF ₁ CRF ₂	Ucn 1	TNBS-induced colitis in mice and rats, murine collagen-induced arthritis, murine EAE, murine endotoxin-induced sepsis [89, 109, 110, 113, 115]
CRLR-RAMP2	AM	Murine DSS-induced colitis, murine collagen-induced arthritis, sepsis in rats, cerulein-induced pancreatitis in rats [117–120]
sst ₁ sst ₂ sst ₃ sst ₄ sst ₅	SST 28	Neurogenic inflammation in rats, inhibits proliferation, chemotaxis, cytokine and immunoglobulin secretion of lymphocytes, monocytes and macrophages, murine EAE, rabbit acute pancreatitis [127, 132–135, 147]
sst ₂ sst ₃ sst ₅	Octreotide	Murine antigen-induced arthritis, TNB-induced colitis in rats, sepsis-induced pelvic inflammation in rats, cerulein-induced murine pancreatitis, acetic acid-induced colitis in rats [136, 141, 143, 145, 146]
sst ₁ sst ₄	Pasireotide TT-232	Murine antigen-induced arthritis [136] Murine LPS-induced airway inflammation, skin and joint inflammation in rats, neurogenic cutaneous inflammation in mice and rats, neuropeptide release in rats, CFA-induced arthritis in rats [128–130]
	J-2156	Murine LPS-induced airway inflammation, neuropeptide release in rats, neurogenic and non-neurogenic cutaneous inflammation in rats, CFA-induced arthritis in rats [128, 131]
sst ₁ sst ₂ sst ₃ sst ₄ sst ₅ GHS-R	CST	Murine collagen-induced arthritis, murine TNBS-induced colitis, murine endotoxin-induced sepsis [150–152]
GHS-R	Ghrelin	Murine TNBS-induced colitis, murine endotoxaemia, cerulein-induced pancreatitis in rats [155–158]
GAL ₁ GAL ₂ GAL ₃	Galanin	Cuprizone-induced murine multiple sclerosis, TNBS-induced colitis in rats [160, 161]
μ	EM-1	CFA-induced arthritis in rats [172]

Abbreviations are as follows: AM, adrenomedullin; CALCRL, calcitonin receptor-like receptor; CFA, complete Freund's adjuvant; CRF, corticotropin-releasing factor; CST, cortistatin; DSS, dextran sulfate sodium; EAE, experimental autoimmune encephalitis; EM, endomorphin; GAL₁, galanin-1 receptor; GHS-R, growth hormone secretagogue receptor; LPS, lipopolysaccharide; MC₁, melanocortin 1 receptor; OA, osteoarthritis; PAC, pituitary adenylate cyclase-activating polypeptide receptor; PACAP, pituitary adenylate cyclase-activating polypeptide; RA, rheumatoid arthritis; RAMP, receptor activity-modifying protein; SST, somatostatin; sst₁, somatostatin receptor 1; TNB, trinitrobenzene; TNBS, trinitrobenzene sulfonic acid; Ucn 1, urocortin 1; VIP, vasoactive intestinal peptide; and VPAC, vasoactive intestinal peptide–pituitary adenylate cyclase-activating polypeptide receptor.

Table 4

In vitro data produced using human cells or tissues illustrating anti-inflammatory effects of neuropeptide receptor agonists

Receptor	Agonists	Anti-inflammatory effect in human <i>in vitro</i> experiments
VPAC ₁ VPAC ₂	VIP	Inhibits cytokine secretion of human synovial fibroblasts of RA patients [94]
CRF ₁ CRF ₂	Ucn 1	Altered levels in fibroblast-like synoviocytes from OA and RA patients [114]
CALCRL-RAMP2	AM	Inhibits synovial fibroblasts of RA patients [121]
μ	EM-1 EM-2	Inhibits cytokine secretion of synovial fibroblasts of OA and RA patients [172] Inhibits cytokine secretion of synovial fibroblasts of OA and RA patients [172]

Abbreviations are as follows: AM, adrenomedullin; CALCRL, calcitonin receptor-like receptor; CRF, corticotropin-releasing factor; EM, endomorphin; OA, osteoarthritis; RA, rheumatoid arthritis; RAMP, receptor activity-modifying protein; Ucn 1, urocortin 1; VIP, vasoactive intestinal peptide; and VPAC, vasoactive intestinal peptide-pituitary adenylate cyclase-activating polypeptide receptor.

Table 5

Data from clinical studies illustrating anti-inflammatory effects of neuropeptide receptor agonists

Receptor	Agonists	Anti-inflammatory effect in human trials
sst ₁ sst ₂ sst ₃ sst ₄ sst ₅	SST14	Human RA [137]
sst ₂ sst ₃ sst ₅	Octreotide	Human uveitic chronic macular oedema [138]

Abbreviations are as follows: RA, rheumatoid arthritis; SST, somatostatin; and sst₁, somatostatin receptor 1.

antagonists of pro-inflammatory neuropeptides have been at the forefront of clinical research. Unfortunately, this strategy has failed to produce a revolutionary breakthrough in the field of anti-inflammatory pharmacotherapy. The NK₁ receptor antagonists have proved to be useful in the clinical management of nausea and vomiting. Their role in the therapy of anxiety and mood disorders is still to be elucidated. The NK₂ receptor antagonists ibodutant and DNK-333 have completed phase II clinical trials as treatment of irritable bowel syndrome [69]. Calcitonin gene-related peptide receptor antagonists have participated in phase III clinical trials as a novel therapy for migraine headache. However, after cancellation of the studies on telcagepant owing to hepatotoxicity, they seem to be less promising.

Although numerous neuropeptides have been established to possess anti-inflammatory effects, the develop-

ment of agonists acting on their receptors is in a less advanced stage. On the basis of functional animal studies on different acute and chronic inflammation models, it is suggested that specific, selective, nonpeptide agonists of anti-inflammatory neuropeptides might open a new gateway in drug development.

Statement

The authors state that drug and molecular target nomenclature has been cited according to BJP's Guide to Receptors and Channels [173].

Competing Interests

There are no competing interests to declare.

The authors' work is supported by Hungarian Research Grants. This study was supported by Hungarian Grants OTKA K-81984, Baross Gábor Program, SROP 4.2.2.A-11/1/KONV-2012-0024, SROP 4.1.2.B-10/2/KONV-20/0-0002 and SROP-4.2.2/B-10/1-2010-0029, 34039/KA-OTKA/11-16.

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