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Drug effects on neuropeptides and their receptors: Big hopes but moderate success in the treatment of chronic pain

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Abstract

Neuropeptides, including tachykinins, CGRP, and somatostatin, are localized in a peptidergic subgroup of nociceptive primary afferent neurons. Tachykinins and CGRP are pronociceptive, somatostatin is an antinociceptive mediator. Intensive drug research has been performed to develop tachykinin and CGRP antagonists, and somatostatin agonists as analgesics. CGRP receptor antagonists are efficacious and well-tolerated drugs in migraine. Monoclonal antibodies against CGRP or its receptor are used for the prophylactic treatment of migraine. Tachykinin NK_1 receptor antagonists failed as analgesics but are used for chemotherapy-induced nausea and vomiting. New, orally active somatostatin 4 receptor agonists are promising drug candidates for treating various pain conditions.

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Introduction

Based on the International Association for the Study of Pain data, chronic pain affects approximately 20% of people all over the world. The presently available pharmacotherapy includes opioids, non-steroidal anti-inflammatory drugs, and adjuvant analgesics. These drugs are often ineffective and possess severe side effects, such as respiratory depression, constipation, nephropathy/nephrotic syndrome/interstitial nephritis, gastrointestinal disturbances/bleeding, or central nervous system pathologies. In the last 50 years, huge efforts have been made to find new drug targets by analysis of the mechanisms involved in the generation and progression of chronic pain, but the success rate has been minimal. Among others, neuropeptides were one of the most promising target families in the central nervous system and the periphery. They play important regulatory and fine-tuning roles in several physiological and pathological pain-related processes. Based on these, intensive drug development was started to utilize the antinociceptive potential of agents acting on neuropeptide receptors. Due to different factors, these efforts have led to only a moderate success. Some compounds and only some specific diseases/indications (e.g. migraine) have been approved in the last decades. The present review aims to summarize the present state and challenges of the neuropeptide field with special emphasis on calcitonin gene-related peptide (CGRP), tachykinins, and somatostatin (SOM).

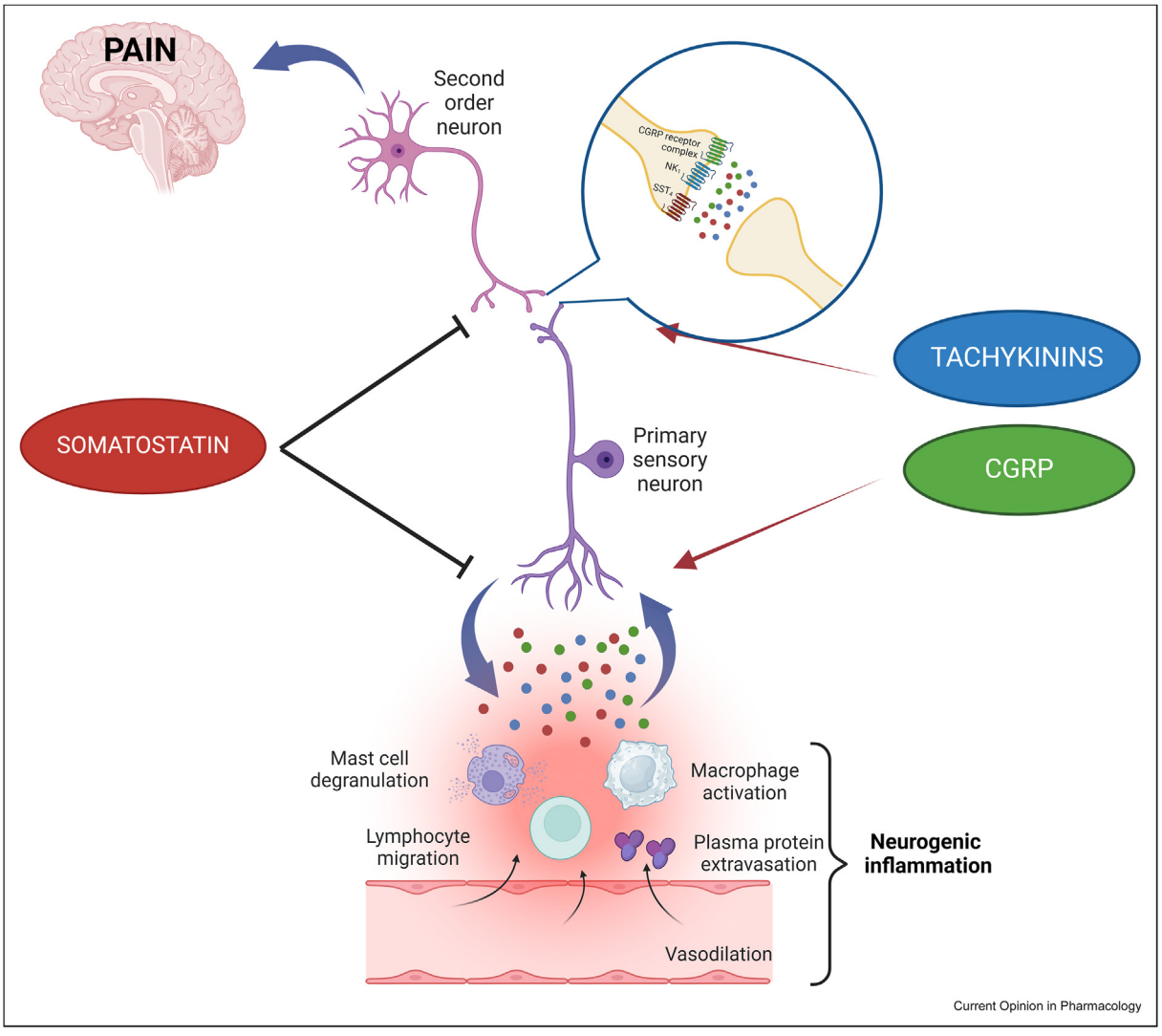
Calcitonin gene-related peptide

CGRP is a 37 amino acid-long peptide produced by alternative processing of the calcitonin gene, and thus, it is similar to calcitonin, amylin, and adrenomedullin. CGRP has two isoforms: α CGRP and β CGRP. CGRP is stored in the cell body, peripheral, and central terminals of a subgroup of nociceptive primary afferent neurons whose somata are found in the dorsal root, vagal, and trigeminal ganglia. Trigeminal fibers innervate external areas such as the skin and mucous membranes at the cranial part of the body, as well as internal ones, including the dura mater covering the brain. A strong association of CGRP with migraine headaches has been outlined over a research period of almost two decades. CGRP expression level is especially high in the trigeminovascular system, which includes the cell bodies of primary sensory neurons at the trigeminal ganglia with their peripheral axonal projections running in the trigeminal nerves to the vessels of the dura mater and with their central projections to the spinal trigeminal nucleus, plus corresponding parts of the thalamus and sensory cortex [1]. CGRP is stored predominantly in C-type trigeminal primary sensory neurons, while its receptors are found on Aδ neurons as well on blood vessels,

explaining the potent vasodilator effect of CGRP [2]. The CGRP receptor complex is composed of three parts [3,4]. The receptor activity-modifying protein 1 (RAMP1) is a single transmembrane protein chain, which increases the binding of CGRP to the major part, the calcitonin receptor-like receptor (CLR), composed of seven membrane-spanning α helices. Upon activation, CLR induces the coupling of the G_s protein's subunit with the CLR's intracellular domain, and this process is facilitated by the third part, the receptor component protein (RCP). $G_{s\alpha}$ activates adenylyl cyclase, thereby increasing cAMP levels and inducing vasodilation.

Activation of the trigeminovascular system causes the release of CGRP in the extracerebral circulation, leading to meningeal vasodilation [5]. In humans, CGRP release was observed during spontaneous migraine attacks, and it could be reduced by clinically used anti-migraine drugs [6,7]. Furthermore, CGRP infusion can cause migraine-like headaches in migraineurs [8]. Based on these data, a hypothesis has been formulated that CGRP is a key mediator in the development of migraine. According to a classical theory of migraine, neuropeptides, including CGRP and substance P (SP), are released from activated trigeminal nerve endings in the dura mater, and they evoke vasodilation, plasma extravasation, and mast cell activation, as shown in Fig. 1 [9]. Thereby, a so-called neurogenic inflammation develops, leading to peripheral sensitization, i.e. hyperexcitability of the meningeal trigeminal nociceptors, contributing to migraine headaches. Increased CGRP and SP release from the central terminals causes the facilitation of synaptic transmission onto the second-order neurons of

Figure 1



Proinflammatory and pronociceptive effects of CGRP and tachykinins (SP, NKA, NKB, HK-1) as well as anti-inflammatory and antinociceptive actions of SOM released from peripheral and central terminals of peptidergic primary sensory neurons (created with BioRender.com).

the trigeminal system, thus contributing to central sensitization.

Following the recognition that CGRP plays a significant role in the pathomechanism of migraine, CGRP antagonists have been sought for proof of concept and clinical testing. Olcegepant was the first selective CGRP receptor antagonist that proved effective and well-tolerated in patients with migraine attacks upon i.v. administration [10—12]. This "gepant" was followed by orally effective antagonists, including telcagepant, which were also effective, but some exhibited hepatic toxicity. Although hepatic injury precluded the approval of these early agents for clinical use, their studies further confirmed the pivotal role of CGRP in migraine attacks. After a pause, drug development was continued, resulting in ubrogepant, rimegepant, and atogepant, three orally effective CGRP antagonists without obvious hepatic toxicity [13]. The most recent drug in this category is zavegepant, applied as a nasal aerosol, which provides a rapid onset of action by a non-invasive route. The recent gepants possess high clinical efficacies in migraine attacks comparable to those of the triptans and are well-tolerated. The relatively long half-life of rimegepant raised the possibility that it could be used in migraine prophylaxis as well. Indeed, rimegepant and atogepant, both having half-lives over 10 h, are approved for the prophylactic use of migraine. Importantly, CGRP antagonists appear not to cause medication overuse headaches. The American Headache Society recommends the use of gepants if the patient's migraine headache is not responsive to two triptan drugs [14].

Another strategy to antagonize CGRP is using monoclonal antibodies against CGRP or its receptor [15]. The former category comprises fremanezumab, eptinezumab, and galcanezumab, whereas the latter contains erenumab only. All three antibodies against CGRP are humanized, meaning that only 10% foreign (murine) sequences are found in the immunoglobulin. In contrast, erenumab is a human antibody without foreign sequences that binds to CLR and RAMP1 parts of the CGRP receptor. These antibodies against CGRP/CGRP receptor proved effective and well-tolerated in clinical trials. Their important advantage is the long half-lives (around 1 month), which allow for once-monthly subcutaneous administration (eptinezumab is given i.v. every 3 months). It is much more convenient compared to conventional, small-molecule drugs used typically daily for the prophylactic treatment of migraine. The American Headache Society recommends these antibodies if the patient is not properly controlled by two other conventional drugs used for migraine prophylaxis [14]. In contrast, the European Headache Federation recommends them as first-line therapy [16]. Considering the choice between an antibody or gepant treatment for migraine prophylaxis, the advantage of the antibodies is the less frequent administration and better compliance, whereas the gepants offer a non-invasive, i.e., oral route of application.

Both small-molecule CGRP antagonists (gepants) and antibodies against CGRP or its receptor are likely to act outside the brain as they can hardly cross the blood—brain barrier. One of their likely sites of action is the dura mater, where the following effects of CGRP can be inhibited. CGRP released from the C-type trigeminal nerve endings causes dilation of the arterioles, thus contributing to neurogenic inflammation. In addition, the released CGRP can act on Aδ nociceptors in the dura, sensitizing them to various stimuli, thus contributing to the generation of headaches [17]. Recently, the existence of a special neuronal cross-talk has been proposed in which CGRP released from axonal varicosities of trigeminal C-fibers may act on CGRP receptors located on nodes of Ranvier along adjacent Aδ-fibers [18]. Another possible target is the trigeminal ganglion, lying outside the blood—brain barrier, where the cell bodies of the trigeminal primary afferent neurons are found. CGRP release from the somata of C-type neurons may activate nociceptive Aδ neurons, whose activity is then transmitted to the brain, contributing to central sensitization.

Potential adverse effects of the drugs against CGRP or its receptor include vasoconstriction, e.g., Raynaud's phenomenon, hypertension, and constipation. Raynaud's phenomenon has been reported in patients receiving gepants or monoclonal antibodies, but both incidence (around 5%) and severity were low [19]. Regarding hypertension, 5% of patients treated with anti-CGRP monoclonal antibodies developed a significant elevation of blood pressure [20]. The incidence of anti-CGRP therapy-induced constipation has been the subject of the debate. Although in some studies, a rate over 50% was observed, most other investigations reported drastically smaller values ranging between 5 and 25% [21,22]. Despite the above considerations, the safety profile of the anti-CGRP agents is outstandingly good. More care should be taken for patients receiving prophylactic, i.e., continuous therapies with anti-CGRP drugs, in particular those who have vasospastic diseases, hypertension, constipation, or predisposing factors for these pathologies. The advantageous pharmacokinetic and adverse effect profile of anti-CGRP drugs, as well as their significant effect on sensory nerve terminals, raised the possibility of their use in primary pain conditions, such as abdominal pain in irritable bowel syndrome, chronic temporomandibular pain, idiosyncratic facial pain, or trigeminal neuralgia. Ongoing studies (NCT06221111, NCT05162027, NCT04249427, NCT04054024) will hopefully end with success in these fields based on the promising preclinical data suggesting their analgesic efficacy in different conditions [23—25]. Further details on this topic are found in recent excellent reviews [26—29].

Tachykinins

Tachykinins are one of the biggest families of neuropeptides, exerting several regulating functions in the central nervous system and the periphery due to their wide distribution, receptorial and signaling diversity, and complex interactions with other systems [30–32]. SP acting on its tachykinin NK_1 receptor, for which it shows the highest affinity, is the most commonly and intensively investigated member, but also neurokinin A and B (NKA and NKB) and their NK_2 and NK_3 receptors, respectively, have been thoroughly mapped to understand their location and function under normal and pathological conditions [33–38]. The intensive research of the last decades resulted in plenty of preclinical data suggesting their role, among others, in pain, inflammation, cancer, or mood disorders [39]. The NK_3 receptor antagonist, fezolinetant has just been approved for the treatment of vasomotor symptoms in postmenopausal women [40–42]. Based on the animal data, intensive drug development was built on the NK_1 receptor antagonists, which were tested in different conditions [43], but one of the biggest expectations was the efficacy in pain. However, after the successful phase I studies, all NK_1 receptor antagonists examined (including aprepitant and fosaprepitant) failed to exhibit analgesic effects in phase II and III studies [44], indicating that the previous preclinical success could not be translated to humans. The few clinical conditions in which NK_1 receptor antagonists are found to be efficacious include chemotherapy-induced or postoperative nausea and vomiting [45–48] in combination with serotonin 5-HT_3 receptor blockers [49]. Consequently, no new clinical trials are registered in pain therapy targeting NK receptors. The combination of NK_1 receptor antagonists with opioids to reduce side effects, tolerance or endosomal inhibition of the opioid receptors could be a potential new direction [50–52]. Additionally, since CGRP and SP are co-localized in about 12% of the trigeminal neurons and both are involved in the response to sensory stimuli in the trigeminal system by acting on different signaling pathways, dual inhibition of CGRP and NK_1 or NK_2 receptors may be more effective than monotherapy in migraine [53].

The reason for the failure of NK_1 receptor antagonists as analgesics in humans is still unclear. Species differences can always be involved, but it must be mentioned that a new member of the tachykinin family, hemokinin-1 (HK-1), was discovered in 2000 [54], and growing evidence about this peptide may provide some explanation for the lack of success with NK_1 antagonists. HK-1 shows the highest affinity for the NK_1 receptor, similarly to SP, so the presence of HK-1 molecules in the vicinity of NK_1 receptors can modify SP actions (via competition to the binding site or allosteric modulation). Moreover, SP and HK-1 have very similar structures and immunogenicities, which means that previous studies are very likely to have measured and demonstrated both peptides in different biological samples. However, newer methods can differentiate between the two peptides [55]. Additionally, they do not exclusively act via NK_1 receptors but, e.g., on Mas-related G protein-coupled receptor-X2 (MRGPRX2) [56–59] or presently unknown targets [60–63]. Furthermore, the HK-1-encoding Tac4 gene encodes many more peptides in humans (e.g. endokinin A-D, human HK-1) [64,65].

Somatostatin

SOM is a pleitropic inhibitory neuropeptide of the nervous system. Via its five G_i protein-coupled receptors ($SST_{1\text{-}5}$), it can decrease hormone release (acting mainly on $SST_{2,3,5}$ receptors) and has remarkable anti-inflammatory and analgesic effects [66–68]. Somatostatin analogs/receptor agonists are widely used in clinical practice to treat endocrine diseases such as acromegaly and neuroendocrine tumors alone or in combination with radiotherapy [69–71]. This latter process, known as peptide receptor radionuclide therapy, serves as an alternative in treating advanced neuroendocrine tumors expressing a high number of SOM receptors [72,73]. Furthermore, it is also used as a vasoconstrictor in severe gastrointestinal bleeding [74–76].

The SST_4 receptor is proven to have an important inhibitory role in inflammation and pain and is not involved in the endocrine functions of SOM [77]. In the last decades, data has indicated the presence of the SST_4 receptor in pain pathways and its involvement in different pain states [78,79], as well as the antinociceptive effectiveness of its agonist [80–84]. Based on these results, the SST_4 receptor agonist, LY3556050, was investigated in clinical phase II studies in osteoarthritis and chronic low back pain (NCT04627038, NCT04874636). Although the studies were finished, results have not yet been published to show a clear outcome. Only one former study assessed the safety and efficacy of LY3556050 in diabetic peripheral neuropathic pain (NCT04707157), which was terminated due to slow enrollment-business decision. Still, a new study was also initiated at the end of 2023, which is in the recruitment phase with the same indication (NCT06074562).

Conclusions

In recent decades, intensive drug development has been built on neuropeptides using receptor agonists or antagonists/antibodies in different pain states. The biggest breakthrough can be linked to CGRP, which is considered one of the most promising therapeutic targets for drugs used in the prevention and treatment of migraine

Table 1

Current medical uses of neuropeptide inhibitors and their possible future analgesic and non-analgesic applications.

	CGRP inhibitors	NK_1 receptor antagonists	SST receptor agonists
	Fremanezumab, galcanezumab, eptinezumab, erenumab, atogepant, rimegepant (prevention) ubrogepant, rimegepant, zavegepant (acute treatment)	Aprepitant, fosaprepitant, netupitant, rolapitant	Octreotide, lanreotide, pasireotide
Current clinical uses	Migraine (prevention and acute therapy)	Chemotherapy-induced or postoperative nausea and vomiting	Acromegaly, gastrointestinal bleeding, neuro-endocrine tumors (diagnosis and therapy)
Pain-related clinical studies	Abdominal pain in irritable bowel syndrome, painful chronic temporomandibular disorders, idiosyncratic facial pain, trigeminal neuralgia	–	Low back pain, diabetic peripheral neuropathy, osteoarthritis
Possible future uses	Sinusitis, dry eye disease, and asthenopia, hot flashes in menopause	Drug dependence, posttraumatic stress disorders, incontinence, overactive bladder	Postoperative pancreatic fistula, diabetes

attacks. Hopefully, these compounds could also be used in other chronic primary pain states, such as irritable bowel syndrome, temporomandibular disorders, or neuralgia. NK_1 receptor antagonists are well-known agents relieving chemotherapy-induced nausea and vomiting, but further investigation of the tachykinin family may help understand the molecular mechanism of action of neurokinin receptors and unravel their real analgesic potentials. Moreover, the repositioning of these drugs to other, not analgesic indications can also be promising (Table 1). Since both SP and CGRP are important pronociceptive and proinflammatory neuropeptides released from the peptidergic nerve terminals [85], drugs acting on these neuropeptides and their receptors may have additive or potentiating effects in various pain states. Recent preclinical/clinical data are available about their interaction in migraine [53], simultaneous changes of expression and release in migraine [86–88], cancer pain [89], orofacial pain [90,91], visceral pain [92], neuropathy [93] or different action in bone fracture-related pain matrix changes [94] indicating a strong connection between the two peptides. To the best of our knowledge, despite these data, there is still no drug candidate that could influence the effects of CGRP and SP simultaneously. New, orally active SST_4 receptor agonists, which are under clinical investigation in different pain-related diseases, can serve as promising alternatives to classical analgesics in several fields.

Declaration of competing interest

We declare no conflicts of interest.

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- •• of outstanding interest

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