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Migraine and neuropeptides

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ABSTRACT

Migraine is a common disabling neurovascular primary headache disorder. The pathomechanism is not clear, but extensive preclinical and clinical studies are ongoing. The structural basis of the leading hypothesis is the trigeminovascular system, which includes the trigeminal ganglion, the meningeal vasculature, and the distinct nuclei of the brainstem, the thalamus and the somatosensory cortex. This review covers the effects of sensory (calcitonin gene-related peptide, pituitary adenylate cyclase-activating polypeptide and substance P), sympathetic (neuropeptide Y) and parasympathetic (vasoactive intestinal peptide) migraine-related neuropeptides and the functions of somatostatin, nociceptin and the orexins in the trigeminovascular system. These neuropeptides may take part in neurogenic inflammation (plasma protein extravasation and vasodilatation) of the intracranial vasculature and peripheral and central sensitization of the trigeminal system. The results of human clinical studies are discussed with regard to the alterations in these neuropeptides in the plasma, saliva and cerebrospinal fluid during or between migraine attacks, and the therapeutic possibilities involving migraine-related neuropeptides in the acute and prophylactic treatment of migraine headache are surveyed.
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Contents

Abbreviations: C2, spinal cervical 2; CGRP, calcitonin gene-related peptide; CLR, calcitonin receptor-like receptor; CNS, central nervous system; CSF, cerebral spinal fluid; DORA-12, dual orexin receptor antagonist-12; DRG, dorsal root ganglia; -ir, -immunoreactive; LC, locus coeruleus; MCAs, middle cerebral arteries; MMAs, middle meningeal arteries; MRI, magnetic resonance imaging; NK1, neurokinin 1; NOP, nociceptin; NPY, neuropeptide Y; NRM, nucleus raphe magnus; NTG, nitroglycerine; OX1, orexin 1; OX2, orexin 2; OXA, orexin A; OXB, orexin B; OX, orexin; PAC1, pituitary adenylate cyclase-activating polypeptide receptor type 1; PACAP, pituitary adenylate cyclase-activating polypeptide; PAG, periaqueductal grey matter; PNS, peripheral nervous system; RAMP-1, receptor activity-modifying protein 1; SGCs, satellite glia cells; SP, substance P; SPG, sphenopalatine ganglia; SST, somatostatin; TNC, trigeminal nucleus caudalis; TRIG, trigeminal ganglia; TS, trigeminovascular system; VIP, vasoactive intestinal peptide; VPAC1, vasoactive intestinal polypeptide receptor 1; VPAC2, vasoactive intestinal polypeptide receptor 2.

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1. Introduction

Migraine is a highly prevalent devastating primary headache disorder that affects around 16% of the adult population, with a female to male ratio of 3:1 (Lipton et al., 2001; Rasmussen et al., 1991; Smitherman et al., 2013). The 1-year prevalence of migraine has been reported to be 10–12% (Tfelt-Hansen et al., 2014). It is ranked among the top 10 causes of disability worldwide (Smitherman et al., 2013; Steiner et al., 2014; Vos et al., 2012). The two main subtypes of this primary headache syndrome are migraine with and migraine without aura. This pain syndrome is typically characterized by recurrent attacks of unilateral, pulsating headache of moderate or severe intensity, which is aggravated by physical exercise (Headache Classification Committee of the International Headache Society (IHS), 2013). Migraine-associated symptoms include nausea and/or vomiting, photophobia or phonophobia and allodynia. The aura phenomenon usually precedes the headache; this phase is characterized by the development of transient focal neurological symptoms, the most common being a visual disturbance (Headache Classification Committee of the International Headache Society (IHS), 2013). In spite of intensive scientific research activities, the exact pathomechanism of migraine remains unknown. Controversies persist concerning the origin of the migraine headache, e.g. vascular or neuronal, cortical or brainstem (Tajti et al., 2011, 2012). Among the several hypotheses relating to migraine, the leading ones are connected with the activation of the trigeminovascular system (TS), the cortical hyperexcitability and the neuronal and glial interactions (Buzzi and Moskowitz, 1992; Pietrobon and Moskowitz, 2013).

In this review, we focus on the pivotal role of the neuropeptides calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), pituitary adenylate-cyclase activating polypeptide (PACAP), neuropeptide Y (NPY), substance P (SP), somatostatin (SST), nociceptin (NOP) and the orexins (OXs) in the modulation of the TS and the other migraine-related nervous system structures. The alterations in these peptides during migraine attacks or headache-free periods are surveyed, together with the presumed roles of these neuropeptides and their receptors in the acute and prophylactic therapy of migraine.

2. The detailed description of several neuropeptides and their effects on migraine

2.1. CGRP

CGRP is a 37-amino acid neuropeptide derived from the gene encoding calcitonin on chromosome 11 (Alevizaki et al., 1986; Terenghi et al., 1985) (Table 1).

The basic function of CGRP in the pathomechanism of migraine was proposed more than two decades ago (Edvinsson, 1991). Human CGRP has two isoforms: α-CGRP and β-CGRP (Emeson et al., 1989; Tippins et al., 1986). α-CGRP is widely distributed in the central (CNS) and peripheral nervous systems (PNS) (Russell et al., 2014). Most of the cranial vasculature is innervated by α-CGRP-containing C and Aδ sensory nerve fibres (Edvinsson and Uddman, 2005; Russell et al., 2014). β-CGRP, which differs from α-CGRP by 3 amino acids, is located in the enteric nerve terminals (Mulderry et al., 1988).

Table 1
Properties of the migraine-related neuropeptides.

Neuropeptides	Numbers of amino acid residues	Receptors (G protein-coupled receptors)	Chromosome location (in humans)	Migraine-related functions	Ref.
CGRP	37	CLR, RAMP-1	Chromosome 11	Craniocervical vasodilatation, peripheral and central sensitization, neuron–glia interaction	(Edvinsson and Uddman, 2005; Edvinsson et al., 2012; Goadsby et al., 1990; Ho et al., 2010; Messlinger et al., 2011)
VIP	28	VPAC1, VPAC2	Chromosome 6	Craniocervical vasodilatation	(Couvineau and Laburthe, 2012; Dickson and Finlayson, 2009; Edvinsson and Uddman, 2005; Said, 1984; Said and Mutt, 1970; Zagami et al., 1990)
PACAP	27 38	PAC1, VPAC1, VPAC2	Chromosome 18	Craniocervical vasodilatation, peripheral and central sensitization	(Arimura, 1992; Kimura et al., 1990; Laburthe et al., 2007; Miyata et al., 1989; Schytz et al., 2009, 2010; Tuka et al., 2013; Vaudry et al., 2009)
NPY	36	NPY	Chromosome 7	Craniocervical vasoconstriction	(Edvinsson et al., 1987; Goadsby and Edvinsson, 1993)
SP	11	NK1	Chromosome 7	Craniocervical vasodilatation, plasma protein extravasation	(Chang et al., 1971; reviewed by Moskowitz, 1993)
SST	14 28	SST	Chromosome 3	Antinociceptive effect in the TNC	(Bartsch et al., 2005; Vecsei and Widerlov, 1988; Vecsei et al., 1992)
NOP	17	NOP	Chromosome 8	Suppression of the neurogenic dural vasodilatation	(Bartsch et al., 2002; Ertsey et al., 2005)
OXs	33 (OXA) 28 (OXB)	OX1, OX2	Chromosome 17	Attenuation of the neurogenic dural vasodilatation, peripheral and central sensitization	(Cady et al., 2014; Hoffmann et al., 2014; Holland et al., 2005, 2006)

Abbreviations: CGRP: calcitonin gene-related peptide; CLR: calcitonin receptor-like receptor; NK1: neurokinin 1; NOP: nociceptin; NPY: neuropeptide Y; OX1: orexin 1; OX2: orexin 2; OXA: orexin A; OXB: orexin B; OXs: orexins; PAC1: pituitary adenylate cyclase-activating polypeptide receptor type 1; PACAP: pituitary adenylate cyclase-activating polypeptide; RAMP-1: receptor activity-modifying protein 1; Ref.: references; SP: substance P; SST: somatostatin; TNC: trigeminal nucleus caudalis; VIP: vasoactive intestinal peptide; VPAC1: vasoactive intestinal polypeptide receptor 1; VPAC2: vasoactive intestinal polypeptide receptor 2.

The TS includes the pseudounipolar neurons of the trigeminal ganglia (TRIG). The peripheral branch of these first-order neurons innervates the intracranial meningeal vasculature, while the central nerve endings project to the nociceptive second-order neurons in the trigeminal nucleus caudalis (TNC). The migraine pain-related secondary nociceptive neurons receive convergent synaptic input from the spinal cervical 2 (C2) dorsal root ganglia (DRG) and from the meningeal innervated part of the TRIG. From the second-order neurons, the information is conveyed to the third-order neurons in the thalamus and then to the sensory cortex (Buzzi and Moskowitz, 1992; Edvinsson and Uddman, 2005; Edvinsson et al., 2012; Noseda et al., 2011).

In the mid-1990s, the Weiller group made use of high-resolution positron emission tomography in their elegant demonstration that the blood flow of specific brainstem nuclei, called "migraine generators" (the locus coeruleus – LC, the periaqueductal grey matter – PAG, and the raphe nuclei), and the cerebellum was increased during spontaneous migraine attacks (Weiller et al., 1995). CGRP is widely expressed in the migraine-related structures such as the TRIG, the TNC and the upper part of the cervical spinal cord and the human LC (Tajti et al., 1999, 2001; Uddman et al., 2002). A high density of expression of CGRP-receptor components, e.g. the calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein (RAMP)-1, is found in the nerve fibres in the TNC (Eftekhari and Edvinsson, 2011). Recent observations suggest the role of the cerebellum and the CGRP in the modulation of pain (Edvinsson et al., 2011; Eftekhari et al., 2013; Moulton et al., 2010).

In the TRIG, CGRP is co-expressed with SP, 5-hydroxytryptamine (5-HT), nitric oxide synthase and PACAP (Eftekhari et al., 2015; Hou et al., 2001; Tajti et al., 1999). The satellite glia cells (SGCs) of the TRIG express the CLR and RAMP-1 (Eftekhari et al., 2010; Vause and Durham, 2010). Recent data point to the pivotal role of the neuron–glia interaction in the TRIG (Thalakoti et al., 2007; Vollbracht and Rapoport, 2013). The release of CGRP during the neuronal activation of the TRIG stimulates the SGCs, which release proinflammatory cytokines, thereby further modulating the neuronal response (Bigal et al., 2013; Thalakoti et al., 2007; Vecsei et al., 2015; Vollbracht and Rapoport, 2013). This observation permits a new approach to an understanding of the intraganglionic signalling process.

The CGRP-immunoreactive (-ir) peripheral branch of the neuronal elements of the TRIG supplies mainly the pial arterioles of the cortical surface and the vasculature of the intracranial dura mater (Edvinsson and Uddman, 2005; Edvinsson et al., 2012). CGRP is a very potent endogenous vasodilatory neuropeptide in the cerebral vasculature (Edvinsson and Uddman, 2005; Edvinsson et al., 2012). During activation of the TS, CGRP gives rise to neurogenic inflammation (vasodilatation and plasma protein extravasation) in the meningeal vasculature and to mast cell degranulation; this process leads to peripheral sensitization (Bigal et al., 2013; Lennerz et al., 2008; Messlinger et al., 2011; Raddant and Russo, 2011; Strassman et al., 1996). The clinical manifestation of this peripheral sensitization is the throbbing nature of the migraine headache, while routine physical activity worsens the headache during migraine attacks (Goadsby, 2005). In the brainstem, CGRP causes central sensitization of the second-order neurons in the TNC and in the third-order neurons in the thalamus (Bigal et al., 2013; Ho et al., 2010; Messlinger et al., 2011) (Fig. 1). This process leads to cephalic and extracephalic allodynia clinically (Burstein et al., 2000; Goadsby, 2005).

An immunohistochemical study revealed CGRP-ir fibres in the vicinity of the neurons of the sphenopalatine ganglia (SPG), and CLR and RAMP-1 immunoreactivity in the SGCs (Csati et al., 2012b). It is presumed that the sensory system influences the parasympathetic cranial ganglia, e.g. the SPG, during the activation of the TS (Csati et al., 2012b).

CGRP could act as a biomarker of migraine (Durham and Papapetropoulos, 2013). Elevated levels of CGRP in the serum in the cranial outflow at the external jugular and cubital vein, and in the saliva, have been detected during spontaneous migraine attacks, and enhanced CGRP plasma levels are observed in nitroglycerine (NTG)-induced migraine attacks (Ashina et al., 2000; Cady et al., 2009; Goadsby et al., 1990; Juhasz et al., 2005; Sarchielli et al., 2000). Increased CGRP levels have also been measured in the peripheral blood in the cubital vein outside migraine attacks (Cernuda-Morollon et al., 2013; Tuka et al., 2013). One research group did not confirm an elevated CGRP level in the external jugular venous blood during migraine without aura attacks (Tvedskov et al., 2005). Another research group reported a significant decrease in the CGRP level in the cubital venous plasma during migraine attacks without aura as compared with the level outside the attack period (Kovács et al., 1991). The differences observed between CGRP levels in plasma obtained from the external jugular and the cubital vein might be explained by the short half-life of the peptide, e.g. a fast degradation within the plasma (Kovács et al., 1991). The baseline level of CGRP in the saliva has been found to be significantly elevated between attacks in migraine subjects as compared with controls (Bellamy et al., 2006). A clinical study revealed that an increased level of CGRP in the saliva was predictive of responsiveness to a 5-$HT_{1B/1D}$ receptor agonist, rizatriptan (Cady et al., 2009). In female migraineurs during NTG-induced migraine attacks the plasma CGRP concentration proved to be decreased in parallel with the headache intensity score after the administration of sumatriptan (Juhasz et al., 2005). An increased CGRP level has been reported in the cerebral spinal fluid (CSF) in chronic migraine subjects as compared with control subjects (Sarchielli et al., 2007). Intravenous administration of CGRP caused migraine-like attacks both in migraineurs with aura and in those without aura (Hansen et al., 2010; Lassen et al., 2002). In contrast, CGRP infusion did not cause migraine attacks in a rare subgroup of migraineurs, familial hemiplegic migraineurs (Hansen et al., 2011).

Overall, CGRP may play a crucial role in the neurogenic inflammation and in the peripheral and central sensitization of the TS as concerns the pathomechanism of migraine, and it could be a possible biomarker of migraine headache.

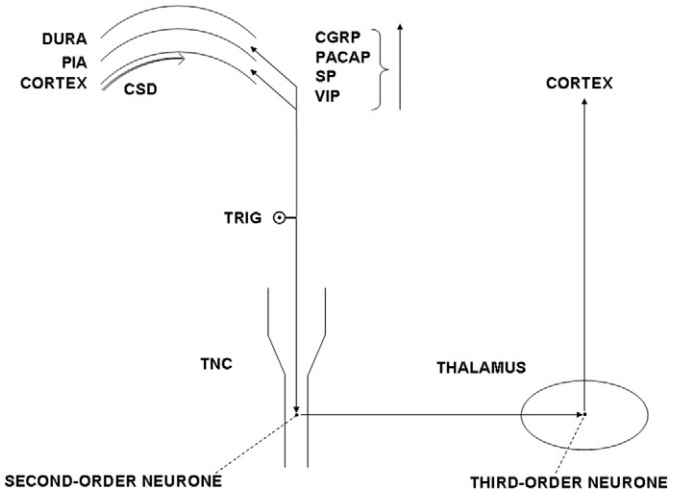

Fig. 1. Putative mechanism of the activation of trigeminovascular system (modified from Pietrobon and Moskowitz, 2013; Tajti et al., 2012). Hypothetically, cortical spreading depression may activate the meningeal nociceptors of trigeminal sensory afferents, resulting in a consequent release of vasoactive neuropeptides (CGRP, SP, PACAP, VIP). These peptides evoke vasodilatation in the meningeal vasculature, plasma protein extravasation and mast cell degranulation, eventually leading to the sensitization of the peripheral nerve branch of the TRIG (peripheral sensitization). This process subsequently leads to the activation and sensitization of the second-order neurons in the TNC and the third-order neurons of the thalamus (central sensitization). Abbreviations: CSD: cortical spreading depression, CGRP: calcitonin gene-related peptide, PACAP: pituitary adenylate cyclase-activating polypeptide, SP: substance P, TNC: trigeminal nucleus caudalis, TRIG: trigeminal ganglion, VIP: vasoactive intestinal peptide.

2.2. VIP

VIP, first isolated from the ovine intestine, consists of 28 amino acids (Said, 1984; Said and Mutt, 1970). It belongs in the secretin/glucagon/VIP superfamily of neuropeptides. It acts through the family of seven transmembrane G protein-coupled receptors, e.g. vasoactive intestinal polypeptide the receptors 1 and 2 (VPAC1 and VPAC2) (Couvineau and Laburthe, 2012; Dickson and Finlayson, 2009). VIP is a marker of the parasympathetic nervous system and exerts a strong vasoactive capability influence on the cranio-cervical vasculature (Edvinsson and Uddman, 2005). In the early 1990s, a clinical study revealed that the level of VIP in the plasma was elevated during spontaneous migraine attacks in patients who demonstrated symptoms of parasympathetic activation (Goadsby et al., 1990). Peripheral stimulation of the peripheral branch of the neuronal elements of the TRIG (superior sagittal sinus) in the cat revealed a markedly increased level of VIP in external jugular vein blood samples (Zagami et al., 1990). Immunohistochemical studies later revealed VIP-ir nerve fibres in the "migraine generators", e.g. the nucleus raphe magnus (NRM) and PAG (Tajti et al., 2001). VIP-ir nerve fibres were not seen in the TNC or at the C1 and C2 levels of the spinal cord (Uddman et al., 2002).

A recent clinical study demonstrated that increased VIP levels were detected in chronic and episodic migraine patients in the attack-free period versus controls (Cernuda-Morollon et al., 2014). In another study, the VIP levels in the peripheral blood interictally in chronic migraineurs were found to be higher than those in control subjects (Cernuda-Morollon et al., 2014). Administration of onabotulinumtoxin type A is efficacious as treatment for chronic migraine (Dodick et al., 2010). VIP acts as a potential predictor of onabotulinumtoxin type A responders versus non-responders (Cernuda-Morollon et al., 2014). During spontaneous migraine attacks, the VIP level was significantly reduced in the external jugular venous blood after rizatriptan administration (Sarchielli et al., 2006b). In the saliva, the VIP level was significantly elevated interictally in migraine subjects as compared with controls, and following sumatriptan treatment the VIP level was significantly decreased during the migraine attack (Bellamy et al., 2006).

These VIP data suggest that the parasympathetic system may play a role in the initiation of the migraine attack. This statement is supported clinically by the finding that roughly 30% of migraine patients develop cranial autonomic parasympathetic symptoms such as lacrimation, rhinorrhoea and eyelid oedema (Avnon et al., 2003, 2004; Barbanti et al., 2002; Gupta and Bhatia, 2007; Obermann et al., 2007). Immunohistological findings have revealed CGRP-ir nerve fibres in the SPG, CLR immunoreactivity in the SGCs and RAMP-1 immunoreactivity in the neurons and SGCs in the SPG (Csati et al., 2012b). These data suggest an interaction between the sensory and parasympathetic systems in the cranial ganglia (Csati et al., 2012b).

VIP exerts a strong vasodilatatory effect on the craniocervical vasculature (Edvinsson and Uddman, 2005). One clinical study revealed that a VIP infusion causes strong dilatation of the superficial temporal artery, but none of the patients reported migraine attacks (Rahmann et al., 2008). It was recently reported that a VIP infusion induced marked dilatation of the extracranial, but not the intracranial arteries in female migraineurs without aura, and only 18% of the migraine patients experienced migraine-like attacks (Amin et al., 2014).

Overall, therefore, VIP is a strong vasodilator with a low capability to induce a migraine attack.

2.3. PACAP

PACAP, a potent stimulator of adenylate cyclase and a biologically active, important neuropeptide, was first isolated from the ovine hypothalamus more than 25 years ago (Miyata et al., 1989). The gene of PACAP is localized on chromosome 18 (Kimura et al., 1990). There is a more dominant 38 amino acid-containing form, PACAP-38, and a C-truncated form, PACAP-27 (Arimura, 1992; Vaudry et al., 2009). These peptides exhibit structural and functional similarities to VIP (Miyata et al., 1989). Both forms can bind to G-protein-coupled VIP ($VPAC_1$ and $VPAC_2$) and specific PACAP (PAC_1) receptors (Laburthe et al., 2007; Schytz et al., 2010; Vaudry et al., 2009). PACAP-38 is widely distributed in many organs and is therefore implicated in various biological functions. In human and animal tissues, PACAP and its receptors have been detected in the sensory TRIG (Hou et al., 2003; Tajti et al., 1999) and the parasympathetic SPGs and otic ganglia (Csati et al., 2012a; Edvinsson et al., 2001; Uddman et al., 1999). Moreover, they are closely related to the vascular smooth muscles (Baun et al., 2011) and are present at different levels of the CNS and PNS (Arimura, 2007; Moller et al., 1993; Mulder et al., 1994; Pettersson et al., 2004). High concentrations of PACAP-38 have been detected among others in the human TNC (Uddman et al., 2002) and the LC (Palkovits et al., 1995), with moderate PACAP expression in the PAG (Palkovits et al., 1995; Tajti et al., 2001), the raphe nuclei (Legradi et al., 1994), the thalamus (Koves et al., 1991, 1994) and the spinal trigeminal nucleus (Hannibal, 2002; Vaudry et al., 2009). PACAP binding sites have been identified in the cortex, the thalamus, the hypothalamus, the brainstem (Akerman and Goadsby, 2009; Vaudry et al., 2009), the TRIG (Chaudhary and Baumann, 2002; Knutsson and Edvinsson, 2002), human mast cells (Kulka et al., 2008), the middle cerebral arteries (MCAs) (Erdling et al., 2013) and the middle meningeal arteries (MMAs) (Syed et al., 2012).

PACAP exerts various peripheral effects (Helyes et al., 2007; Nemeth et al., 2006) and it has a pro-nociceptive role in the CNS (Amin et al., 2014; Markovics et al., 2012; Schytz et al., 2009; Tuka et al., 2012). It has functions in neuroinflammation (Helyes et al., 2007) and sensitization (Sandor et al., 2009). Three synergistic theories (vascular, neuronal and mast cells) have been postulated to underlie the possible effects of PACAP in the mechanisms of migraine. The role of PACAP has been investigated in the NTG-induced animal model of the activated TS. NTG evoked marked migraine-like changes in wild-type mice, but not in PACAP-deficient mice. The systemic administration of PACAP-38 elicited the symptoms of photophobia, elevated the meningeal blood flow and exerted neural activation in the TRIG and TNC in wild-type mice, whereas the corresponding alterations were significantly less pronounced in the lack of the PACAP gene (Markovics et al., 2012). In another experiment, the administration of NTG generated increases in the levels of PACAP-27 and PACAP-38 immunoreactivity in the TNC in the rat. Similarly, significantly elevated peptide levels were observed in the TNC and also in the extracranial blood flow 90 and 180 min after electrical stimulation of the TRIG in the rat, another model of activated TS (Tuka et al., 2012). These data suggest that PACAP may elicit peripheral and central sensitization and evoke meningeal vasodilatation. An investigation of the direct vascular effects of PACAP-38 led to the finding that stimulation of the superior sagittal sinus in the cat causes the extracranial release of PACAP (Zagami et al., 1995). Moreover, a magnetic resonance imaging (MRI) angiographic study revealed that, in contrast with the MCAs, PACAP-38-induced headache is associated with significant dilatation of the MMAs, an effect which can be attenuated by the application of sumatriptan (Amin et al., 2012). The importance of the PAC_1 receptor has been emphasized (Syed et al., 2012), but there are results that intradermally injected PACAP-38 or VIP can elicit mild, short-lasting cutaneous pain in healthy volunteers, this being mediated primarily by the VPAC receptors (Schytz, 2010). It has additionally been observed that PACAP or VIP has lower potency and efficacy in the meningeal vessels than in the coronary arteries, leading to the conclusion that the PACAP-induced migraine-like headache might not involve meningeal vasodilatation (Chan et al., 2011). Although the vascular action of PACAP-38 cannot be excluded, it appears likely to be a slight and indirect vasodilator effect (Baun et al., 2011). It has been demonstrated clinically that the intravenous administration of PACAP-38 induces delayed migraine-like attacks and vascular alterations in patients with migraine without aura (Schytz et al., 2009), whereas merely a simple headache occurs in healthy volunteers. A more recent 24-h follow-up study revealed that the infusion of

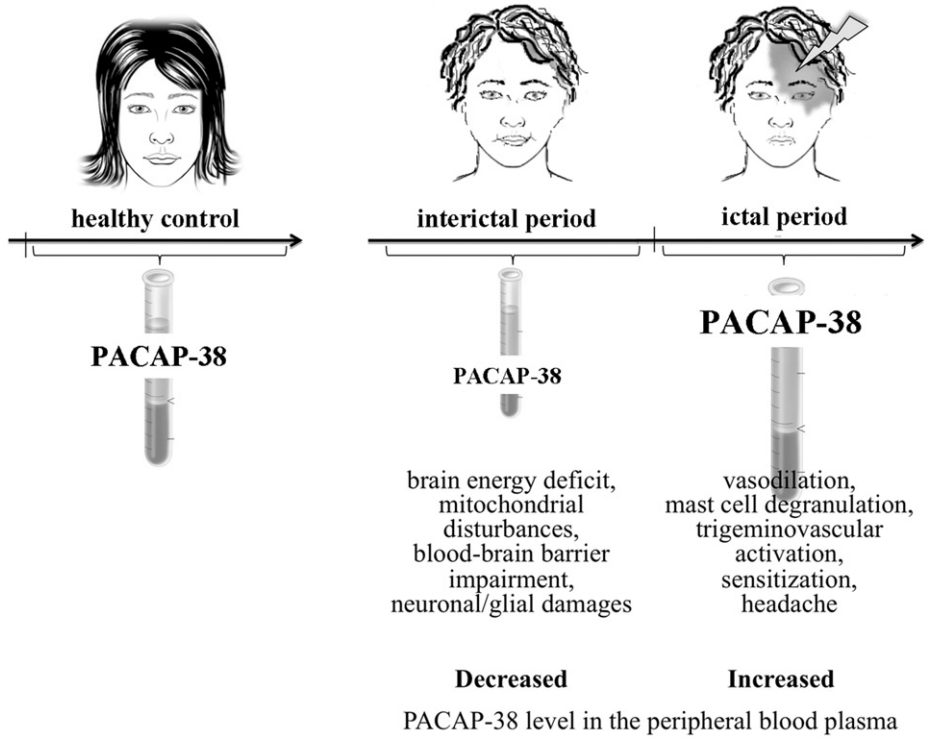

Fig. 2. Alterations in the plasma PACAP-38 concentrations in healthy subjects and migraineurs (modified from Tuka et al., 2013). The concentration of PACAP-38 may be decreased in the plasma in the interictal period of migraineurs as compared with healthy subjects. It is assumed that brain energy deficit (lactate, magnesium, etc.), mitochondrial disturbances, impairment of the blood–brain barrier (matrix metalloproteases, etc.) and neuronal/glial damages may also potentiate the decrease in PACAP-38 levels. Unknown trigger(s) can evoke elevated plasma PACAP-38 level during the attack phase, which can led to vasodilation, mast cell degranulation, neurogenic inflammation, trigeminal activation, contributing to the development of sensitization and serious migraine headache.

PACAP-38 rather than VIP generates pronounced migraine-like attacks and sustained vasodilatation of the extracranial arteries in migraineurs (Amin et al., 2014). Although elevated plasma PACAP-38 concentrations were recorded before the onset of the attacks, changes were not observed in the levels of VIP and tryptase in the blood after the PACAP-38 infusion, which suggests the role of the PAC_1 receptors (Amin et al., 2014). In another human study, significantly increased PACAP-38 levels were detected in the ictal phase of migraineurs relative to the attack-free period, while significantly lower plasma peptide concentrations were measured in the interictal period of migraineurs as compared with the healthy control group (Fig. 2). A slight negative correlation has been demonstrated between the interictal plasma PACAP-38 level and the disease duration, suggesting that PACAP has vascular effects related to migraine (Tuka et al., 2013) and it can sensitize the trigeminal sensory fibres directly (Schytz et al., 2009), but the mast cells also have a considerable role in these processes (Baun et al., 2012; Mori et al., 1994; Odum et al., 1998; Schytz, 2010) (Fig. 3). It seems that PACAP-38-induced MMA dilatation is probably caused by indirect, phopholipase C-mediated mast cell degranulation, which might be implicated in the mechanisms of migraine (Baun et al., 2012; Bhatt et al., 2014).

The experimental and clinical evidence lends support to the mediator role of PACAP in the initiation and/or promotion of migraine attacks (Vecsei et al., 2014). Recognition of the receptorial and signalling mechanisms of PACAP might open up new perspectives for the development of non-peptide, receptor-specific drugs.

2.4. NPY

NPY, a 36-amino acid peptide, is a marker of the sympathetic nerve endings with long-lasting vasoconstrictor properties, and therefore has a crucial role in the control of the cerebral circulation (Abounader et al., 1995; Goadsby, 2013; Goadsby and Edvinsson, 1993). In relationship with the craniocervical blood vessels, the sympathetic innervation is supplied by the superior and inferior cervical ganglia and the stellate ganglion (Arbab et al., 1988; Edvinsson and Uddman, 2005). In the sympathetic nerve terminals, NPY is co-stored and co-released with norepinephrine (De Potter et al., 1995; Miserez et al., 1992). Immunohistochemical investigations have revealed that one of the distinct brainstem nuclei in humans, the LC, as a “migraine generator”, contains the C-terminal flanking peptide of NPY immunoreactivity in the neurons, illustrating their adrenergic nature; the LC sends noradrenergic-containing nerve fibres to the TNC, indicating that the TNC is influenced by the adrenergic LC (Tajti et al., 2001).

NPY-ir nerve fibres densely innervate the cerebral dura mater, pial blood vessels and cerebral arteries (Edvinsson et al., 1987, 1994; Keller and Marfurt, 1991).

In young migraineurs with aura, the plasma NPY level is increased during attacks, but reduced in the interictal period, suggesting the role of NPY in the pathomechanism of migraine with aura (Gallai et al., 1994).

After lumbar puncture, the NPY immunoreactivity in the CSF was reported to be higher in migraineurs during the attacks as compared with controls (Valenzuela et al., 2000), whereas another research group did not observe an NPY immunoreactivity elevation in the suboccipital CSF or plasma during attacks and attack-free periods of patients with migraine without aura (Vecsei et al., 1992). In migraine patients with or without aura, the NPY immunoreactivity in the external jugular venous blood did not alter during migraine attacks (Goadsby et al., 1990).

In summary, NPY is a good marker of the intracranial sympathetic innervation, but the evidence relating to its potent role in the pathomechanism of migraine pain is not pronounced.

2.5. SP

SP, a member of the tachykinin neuropeptide family, consists of 11 amino acids (Chang et al., 1971). Its endogenous receptor is the

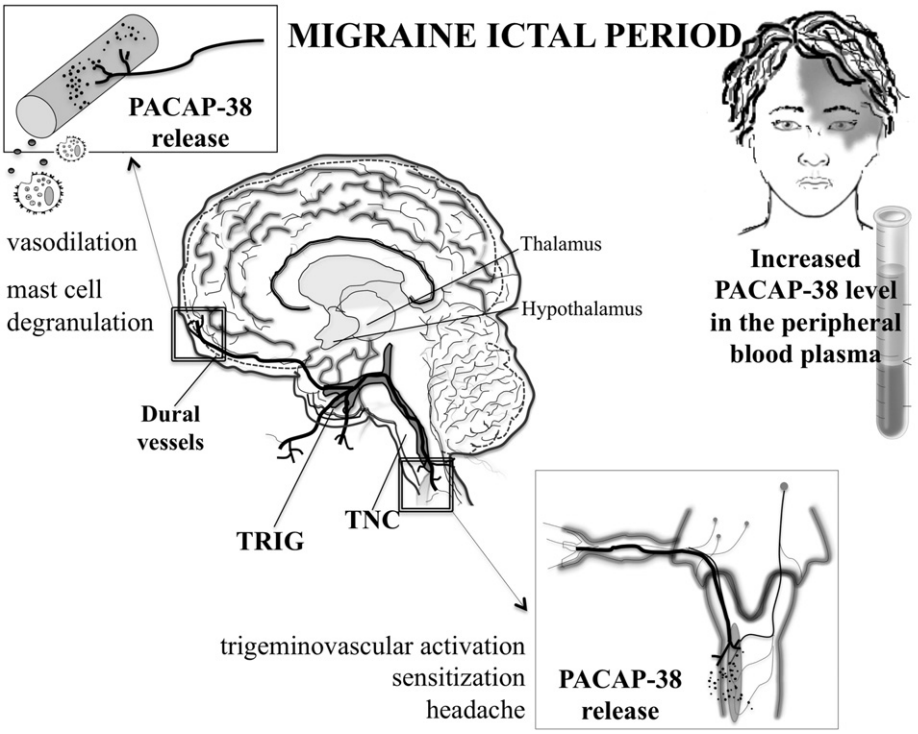

Fig. 3. PACAP-38-induced alterations in the trigeminovascular system in the ictal period of migraineurs (modified from Tuka et al., 2013). It is assumed that PACAP-38 can be released from peripheral and central terminals of the primary sensory neurons in the attack phase of migraineurs. PACAP-38 has direct and indirect sensitizing effects (vasodilation, mast cell degranulation, trigeminovascular activation and sensitization) on meningeal vessels and in the area of second-order trigeminal sensory neurons in the brainstem. The peptide may enter the circulatory system and an elevated PACAP-38 level can contribute to the development of migraine headache.

neurokinin 1 (NK1) receptor (Gerard et al., 1991). SP is widely expressed in the trigeminal sensory nerve fibres (Beattie et al., 1995). Dense SP-ir nerve fibres have been observed in the "migraine generators", e.g. the NRM, the LC and the PAG (Tajti et al., 2001). In the TNC and in the dorsal horns at the spinal C2 level, numerous SP-ir nerve fibres have been detected (Uddman et al., 2002). SP has a potent function in pain transmission in the different regions of the PNS and the CNS (Furst, 1999; Saria, 1999). During activation of the TS, SP induces plasma protein extravasation and vasodilatation in the cerebral dura mater (Moskowitz, 1993); this is blocked by the selective NK1 receptor antagonists (Beattie et al., 1995; May and Goadsby, 2001). In the TNC, SP performs nociceptive conduction (May and Goadsby, 2001; Pearson and Jennes, 1988). The NK1 receptor antagonists also have the ability to inhibit the activation of the second-order neurons in the TNC after electrical stimulation of the TRIG (May and Goadsby, 2001). Preclinical studies have revealed that stimulation of the peripheral branch of the TRIG, e.g. electrical stimulation of the superior sagittal sinus, results in elevations of CGRP and VIP, but not NPY and SP (Zagami et al., 1990). No elevation of SP in the cranial venous outflow was detected during spontaneous migraine attacks (Edvinsson and Goadsby, 1995; Goadsby et al., 1990), whereas the salivary SP immunoreactivity was increased during spontaneous migraine attacks without aura versus the level in control subjects (Nicolodi and Del Bianco, 1990). In chronic migraine patients, the plasma and saliva levels of SP were higher than those in control subjects, and associated with pain intensity (Jang et al., 2011). The plasma SP concentration was observed to be enhanced in episodic migraineurs during the headache-free periods (Fusayasu et al., 2007). In a further study, the SP level in the platelets was higher in migraineurs than in the controls (Nakano et al., 1993).

Overall, SP has a strong plasma protein extravasation effect, but to date the role of SP in the pathomechanism of migraine has not been fully confirmed.

2.6. SST

SST (previously termed the somatotropin release-inhibiting factor) plays a pivotal role in the regulation of the neuroendocrine system, as an inhibitor of the secretion of growth hormone, thyrotropin-releasing hormone, insulin, glucagon, cholecystokinin, secretin, gastrin, motilin, calcitonin and parathyroid hormone (Brazeau et al., 1973; Vecsei and Widerlov, 1988). Its precursor molecule, prepro-SST (116 amino acids), undergoes cleavage to furnish two forms, SST-14 (14 amino acids) and SST-28 (28 amino acids) (Bersani et al., 1989; Patel and O'Neil, 1988). The SST-containing neurons are widely distributed in the CNS, e.g. in the cerebral cortex, hippocampus, hypothalamus, brainstem and spinal cord (Johansson et al., 1984; Tuboly and Vecsei, 2013). SST acts on six different SST receptor subtypes belonging in the G-protein-coupled receptor family (Hannon et al., 2002; Olias et al., 2004; Tuboly and Vecsei, 2013).

A preclinical animal study has revealed that blockade of the SST receptors by the administration of cyclo-SST to the posterior hypothalamic area of the rat resulted in an antinociceptive effect on the dural electrical and facial thermal inputs in the TNC (Bartsch et al., 2005). In an early clinical study, the SST immunoreactivity in the suboccipital CSF was decreased in migraine patients without aura during the attack-free periods, subsequently further decreasing and reaching statistically significant difference as compared with a mixed neuropsychiatric group of patients (Vecsei et al., 1992). CSF obtained by lumbar puncture exhibited a lower SST immunoreactivity level in chronic migraine patients than in controls (Sarchielli et al., 2006a). In a double-blind parallel group trial, the treatment of migraine attacks with the subcutaneous administration of a long-acting SST analogue (octreotide, SMS 201–995) resulted in a significant reduction of headache pain (Kapicioglu et al., 1997). In a clinical study involving migraine patients with or without aura, withdrawal of the intravenous infusion of SST

did not lead to immediate or delayed migraine-like headaches in migraineurs or control subjects (Levy et al., 2003).

Overall, further preclinical and clinical investigations are needed to clarify the putative role of SST in the pathomechanism of migraine.

2.7. NOP

NOP (orphanin FQ), a 17-amino acid opioid-related peptide, is an endogenous ligand for the orphan-like receptor 1, a member of the opioid receptor family (nowadays termed the NOP1 receptor) (Meunier et al., 1995; Mollereau et al., 1994). The NOP1 receptor is widely distributed in the CNS, e.g. in the hypothalamus, the brainstem and the dorsal horn of the spinal cord (Bridge et al., 2003; Mollereau and Mouledous, 2000). NOP has multidirectional effects in the CNS, exerting algesic, hyperalgesic and analgesic properties, while in the PNS it displays antinociceptive effects (Ertsey et al., 2005; Giuliani et al., 2000; Meunier et al., 2000; Reinscheid et al., 2000). In tracing experiments with immunohistochemical visualization, NOP-ir fibres of trigeminal origin were detected in the dorsal horn of the cervical spinal cord (Marfurt and Del Toro, 1987). In the human TRIG, 78% of medium-sized neurons (30–60μm) express NOP immunoreactivity (Hou et al., 2003). About 61% of the NOP-ir neurons are co-localized with CGRP, and 68% of them contain PACAP (Hou et al., 2003). Interestingly, the human intracranial arteries (basilar and MCAs) do not demonstrate NOP1 receptor mRNA expression, and similarly the human extracranial temporal artery does not possess NOP immunoreactivity (Hou et al., 2003; Mork et al., 2002). NOP does not influence the contractile properties of the human cerebral arteries (Hou et al., 2003). The migraine-related CNS structures, such as the TNC, LC, PAG, raphe nuclei, thalamus and sensory cortex, display NOP1 receptor expression (Ertsey et al., 2005). The meningeal vasculature is densely innervated by trigeminal sensory nerve fibres (unmyelinated C-fibres and thinly myelinated Aδ fibres), and their activation can result in neurogenic inflammation as a source of migraine pain (Edvinsson and Goadsby, 1998; Edvinsson and Uddman, 2005). After electrical stimulation of the MMA, neurogenic dural vasodilatation was observed in an animal model of a closed cranial window (Bartsch et al., 2002). In this experimental set-up, intravenously administered NOP dose-dependently suppressed the neurogenic dural vasodilatation via NOP1 receptor activation (Bartsch et al., 2002). A clinical study of the circulating NOP revealed a lower plasma NOP level in migraine patients without aura during the headache-free period than in controls, and the level correlating with the attack frequency (Ertsey et al., 2005).

Thus, the action of NOP on the NOP1 receptor may play a role in the regulation of the vasomotor response of the cerebral dura mater and may be involved in the modulation of the release of the neuropeptide from the trigeminal sensory nerve terminals.

2.8. OXs

The OXs (also called hypocretins), derived from prepro-OX (130 amino acids), are orexin A (OXA) (33 amino acids) and orexin B (OXB) (28 amino acids) (Holland and Goadsby, 2007; Lee et al., 1999; Sakurai, 2005; Sakurai et al., 1998; Soll and Beck-Sickinger, 2000). OXA is selectively bound to the OX1 receptor (OX1R), while both OXA and OXB are bound to the OX2R (Holland and Goadsby, 2007; Kim et al., 2004; Lee et al., 1999). OXA and OXB are exclusively synthesized in the lateral, posterior and paraventricular nuclei of the hypothalamus (Gotter et al., 2012; Hoffmann et al., 2014; Holland, 2014; Sakurai, 2005). OX-containing neurons project to the different nociceptive areas of the brain, e.g. the cerebral cortex, cingulate cortex, paraventricular thalamic nuclei and “migraine generators”, e.g. the LC, PAG and NRM (Burdakov and Alexopoulos, 2005; Holland and Goadsby, 2007; Nambu et al., 1999; Peyron et al., 1998). OX1R is selectively expressed in the LC, while OX2R is expressed in the NRM (Holland, 2014; Trivedi et al., 1998). A functional imaging ($H_2^{15}O$ positron emission tomography) study demonstrated hypothalamic activation (increased regional cerebral blood flow) during spontaneous migraine attacks without aura (Denuelle et al., 2007).

The OXs have the ability to modulate the TS (Bartsch et al., 2004; Holland et al., 2006). The OX-ergic system can attenuate neurogenic dural vasodilatation via OX1R activation, which means inhibition of the TS (Holland et al., 2005). On the other hand, the OXs can facilitate the TS via the OX2R (Holland, 2014). As concerns the OX-containing neurons in the migraine-related structures, this activation is highest during wakefulness and inhibited during sleep (Holland, 2014). The function of the OXs in sleep is the promotion of waking (Sakurai, 2007). Clinical studies have revealed a high level of OXA in the CSF in chronic migraine patients, and mainly in those with medication overuse headache (Sarchielli et al., 2008).

The simultaneous antagonism of the OX1R and the OX2R with dual OX receptor antagonist-12 (DORA-12) inhibited trigeminal sensory neuronal activation in the TRIG after the injection of complete Freund's adjuvant to the temporomandibular joint in the rat (Cady et al., 2014). A recent experimental study in rats yielded evidence that DORA-12 resulted in attenuation of the trigeminal nociceptive activity in the TNC after electrical stimulation of the dural trigeminal afferents (Hoffmann et al., 2014). However, a randomized double-blind placebo-controlled pilot trial revealed that an OX receptor antagonist (filorexant, 10mg nightly) failed to provide effectiveness as migraine prophylaxis (Chabi et al., 2015).

Overall, it emerges that the OX1R and the OX2R may play a role in modulation of the nociceptive transmission in the TS, and the OX-ergic hypothalamic activation may be linked to the pathomechanism of migraine.

To summarize, the above selected neuropeptides might have a role in the pathomechanism of migraine by the modulation of the TS and the other migraine-related nervous system structures. These neuropeptides might influence the neurogenic inflammation of the dural vasculature and the peripheral and central sensitization of the TS resulting in the development of migraine headache.

3. The neuropeptide-related migraine therapy

3.1. SP

The role of NK1 as a receptor of SP has been investigated in preclinical and clinical studies (Table 2).

Under experimental conditions, the NK1 receptor antagonists proved highly potent in blocking plasma protein extravasation and diminishing the firing of second-order neurons in the TNC (May and Goadsby, 2001). However, human clinical studies failed to confirm the efficacy of NK1 receptor antagonists (May and Goadsby, 2001; Munoz and Covenas, 2014).

Orally administered lanepitant (LY-303,870), an NK1 receptor antagonist has been evaluated for both the acute and the preventive treatment of migraine. A double-blind placebo-controlled cross-over trial demonstrated that lanepitant was not superior to placebo in acute migraine therapy (Goldstein et al., 1997; May and Goadsby, 2001). In a 12-week double-blind study, lanepitant was not effective in preventing attacks of migraine with or without aura (Goldstein et al., 2001).

Another orally administered NK1 receptor antagonist, RPR100893, evaluated in a double-blind, randomized, placebo-controlled study, proved ineffective in the treatment of acute migraine (Diener and Group, 2003).

Likewise, single dose of the intravenously administered vofopitant (GR-205,171) was not effective relative to placebo in the treatment of a single attack of migraine with or without aura (May and Goadsby, 2001; Munoz and Covenas, 2014). Intravenous infusion of fosaprepitant (L-758,298), a prodrug of the NK1 receptor antagonist L-754,030, did not abort the migraine pain during the headache attack in a double blind study (May and Goadsby, 2001; Munoz and Covenas, 2014).

To summarize, NK1 receptor antagonists administered either orally or intravenously failed to demonstrate superiority to placebo in either acute or preventive migraine therapy.

3.2. CGRP

For the purpose of the therapy of migraine form the aspect of CGRP, pharmaceutical innovations have been introduced that target the CGRP receptors; these primarily involve the development of antagonists for the acute treatment of migraine and the creation of fully humanized monoclonal antibodies against CGRP itself and the CGRP receptors for the preventive treatment of migraine (Vecsei et al., 2015).

3.2.1. CGRP receptor antagonists

Small-molecule CGRP receptor antagonists have been developed for clinical use in acute migraine treatment, e.g. olcegepant (BIBN4096BS), telcagepant (MK-0974), MK-3207, MK-1602, BMS-694153, BMS-927711 and BI44370TA (Negro et al., 2012). Telcagepant has also been evaluated for the prevention of migraine (Ho et al., 2014).

Olcegepant and telcagepant have been investigated intensively. Intravenously administered olcegepant was effective relative to placebo for the acute treatment of migraine in a multicentre double-blind randomized study (Olesen et al., 2004), and telcagepant administered orally for acute migraine therapy was similarly more effective than placebo (Ho et al., 2008). A randomized, double-blind, placebo-controlled multicentre trial revealed that telcagepant reduced the number of migraine headache days as compared with placebo in a migraine prophylaxis therapy (Ho et al., 2014). Despite the favourable effects of the gepants in acute and preventive migraine therapy, their liver toxicity (elevation of the liver transaminases) limits their widespread clinical use (Vecsei et al., 2015).

3.2.2. CGRP-targeting monoclonal antibodies

Three monoclonal antibodies (LY2951742, ALD403, and LBR-101) developed that target the CGRP have so far been for the prophylactic treatment of migraine. Besides their effectiveness, the favourable dosing (once or twice per month) promotes the adherence of migraine patients to the treatment (Bigal and Walter, 2014; Bigal et al., 2014; Vecsei et al., 2015; Vollbracht and Rapoport, 2014). An unfavourable feature is the route of administration, which is subcutaneously or intravenously instead of orally (Bigal and Walter, 2014).

Only one monoclonal antibody that targets the CGRP receptor is currently available: AMG 334 (Bigal and Walter, 2014). The subcutaneous administration of AMG 334 once per month is undergoing investigation for prevention of the episodic or chronic state of migraine, but clinical data have not yet been published (Bigal and Walter, 2014). The data reported to date indicate that fully humanized monoclonal antibodies are promising therapeutic options for migraine prevention.

In summary, neuropeptides may well have a role in the acute and preventive therapy of migraine headache. Among the different neuropeptides, at present only CGRP seems to be a possible target for migraine therapy. Currently, the safety issues of the CGRP-receptor antagonists limit their use, but antibodies targeting CGRP or its receptors seem to be valuable candidates for migraine prevention in the near future.

4. Conclusions

Although migraine dramatically influences the quality of life of the patients, the precise pathomechanism of this type of primary headache disorder is still lacking. The neuropeptides discussed here may have a fundamental role in the processes of meningeal neurogenic inflammation and pain transmission in the TNC, and peripheral and central sensitization of the TS. Animal experimenters in the field of migraine research still face the problem that on appropriate animal migraine model does not yet exist. Moreover, from a clinical aspect in spite of the alterations in these neuropeptides in the different types of migraine (e.g. migraine with or without aura, or episodic or chronic migraine), they have not achieved a function as biomarkers. Notably, however, the actual level of any neuropeptide is determined by the rate of biosynthesis and the rate of degradation. Therefore, the measured levels reflect a steady state, from which far-reaching consequences cannot be drawn without the investigation of the turnover. Further preclinical and clinical research is needed for a better understanding of the roles of the

Table 2
Neuropeptide-related migraine therapy.

Targets	Route of administration	For acute treatment	For preventive treatment	Effectiveness in clinical trials	Comments	Ref.
NK1 receptor antagonists						
Lanepitant (LY-303,870)	p.o.	Yes	Yes	No effect	–	(Goldstein et al., 1997, 2001)
RPR100893	p.o.	Yes	No	No effect	–	(Diener and Group, 2003)
Vofopitant (GR-205,171)	i.v.	Yes	No	No effect	–	(May and Goadsby, 2001; Munoz and Covenas, 2014)
Fosaprepitant (L-758,298)	i.v.	Yes	No	No effect	–	(May and Goadsby, 2001; Munoz and Covenas, 2014)
CGRP-receptor antagonists						
Olcegepant	i.v.	Yes	No	Effective	Poor safety profile (liver toxicity)	(Olesen et al., 2004)
Telcagepant	p.o.	Yes	Yes	Effective	Poor safety profile (liver toxicity)	(Ho et al., 2008, 2014)
CGRP-targeting monoclonal antibodies						
LY2951742	s.c.	No	Yes	No data available	Under clinical evaluation	(Bigal and Walter, 2014; Bigal et al., 2014; Vollbracht and Rapoport, 2014)
ALD403	i.v.	No	Yes	No data available	Under clinical evaluation	(Bigal and Walter, 2014; Bigal et al., 2014; Vollbracht and Rapoport, 2014)
LBR-101	s.c	No	Yes	No data available	Under clinical evaluation	(Bigal and Walter, 2014; Bigal et al., 2014; Vollbracht and Rapoport, 2014)
CGRP receptor-targeting monoclonal antibody						
AMG 334	s.c.	No	Yes	No data available	Under clinical evaluation	(Bigal and Walter, 2014)

Abbreviations: CGRP: calcitonin gene-related peptide; i.v.: intravenous; NK1: neurokinin 1; p.o.: orally; Ref.: references; s.c.: subcutaneous.

neuropeptides in the pathomechanism of migraine headache. These neuropeptides and their receptors could well be valuable targets for the acute and prophylactic treatment of migraine in the near future.

Conflict of interest

The authors declare that they have no conflict of interest and have received no payment in the preparation of their manuscript.

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