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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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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.