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CGRP and Migraine: Could PACAP Play a Role Too?

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Abstract

Migraine is a debilitating neurological disorder that affects about 12% of the population. In the past decade, the role of the neuropeptide calcitonin gene-related peptide (CGRP) in migraine has been firmly established by clinical studies. CGRP administration can trigger migraines, and CGRP receptor antagonists ameliorate migraine. In this review, we will describe multifunctional activities of CGRP that could potentially contribute to migraine. These include roles in light aversion, neurogenic inflammation, peripheral and central sensitization of nociceptive pathways, cortical spreading depression, and regulation of nitric oxide production. Yet clearly there will be many other contributing genes that could act in concert with CGRP. One candidate is pituitary adenylate cyclase-activating peptide (PACAP), which shares some of the same actions as CGRP, including the ability to induce migraine in migraineurs and light aversive behavior in rodents. Interestingly, both CGRP and PACAP act on receptors that share an accessory subunit called receptor activity modifying protein-1 (RAMP1). Thus, comparisons between the actions of these two migraine-inducing neuropeptides, CGRP and PACAP, may provide new insights into migraine pathophysiology.

Keywords

CGRP; PACAP; migraine; neuropeptides

Migraine

Clinical context of migraine

Migraine is far more than just another a headache. It is a complex and disabling neurological disorder (Goadsby et al., 2002). As defined by the International Headache Society, migraine is a headache that lasts for 4 to 72 hours and characterized by at least two of the following: unilateral localization; pulsating quality; moderate to severe pain intensity; and aggravation by movement such as walking (Headache, 2004). Furthermore, the headache must be accompanied with at least one of the following: nausea and/or vomiting; and photophobia and phonophobia (Headache, 2004). In addition, some migraineurs experience an aura, which typically precedes the headache during the premonition or prodrome phase

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(Headache, 2004; Kelman, 2004a). This often results in visual changes such as a scintillating scotoma that moves across the visual field (Kelman, 2004a; Purdy, 2011). The prodrome may also be accompanied by other symptoms such as fatigue, gastrointestinal issues, and mood changes (Kelman, 2004b). As a result, migraine sufferers are often incapacitated for extended periods of time.

Migraine is estimated to affect up to one in four households (Lipton et al., 2001). A highly prevalent disorder: 6 – 8% of men and 15 – 25% of women suffer from migraine (Pietrobon and Striessnig, 2003). The lifetime incidence is 43% in women and 18% in men (Stewart et al., 2008). Migraine is typically episodic (Goadsby et al., 2002); however, 3 – 5% of the general population experience chronic daily headaches occurring at least 15 days per month, often with migrainous characteristics (Couch, 2011). A 1999 study of migraine economic burden in the United States found a total of 112 million bedridden days per year by migraineurs (Hu et al., 1999). As a result, the indirect cost of migraine to employers was estimated at $11 billion annually in the US, primarily due to absenteeism (Hawkins et al., 2007). Additionally, the direct healthcare cost associated with migraine was estimated at $13 billion in the US (Hawkins et al., 2008). From a global perspective, the World Health Organization ranks migraine in the top twenty of disabling conditions. Consequently, migraine has not only a harmful impact on the individual, but also a significant impact on society.

Despite having a substantial effect on society, little advancement has been made in managing the disorder. For some migraineurs, non-steroidal anti-inflammatory drugs may be sufficient for pain relief (Diener et al., 2006; Silberstein and Goadsby, 2002). However, many migraineurs depend on oral triptans, which are 5-HT1B/D receptor agonists and the current gold standard in migraine abortive therapy, but the response rate is only 60% (Loder, 2010). Moreover, triptans have adverse effects including paresthesias, flushing, neck tightness, and chest pressure as well as possible cardiovascular risks (Loder, 2010). Preventatives such as propranolol, topiramate, and tricyclic antidepressants, such as amitriptyline, have also been used to reduce to the number of migraines attacks (Goadsby et al., 2002). Recently, botulinum toxin has been found to be an effective preventative (Rapoport, 2010). Despite these options, many migraineurs do not respond to medication (Tfelt-Hansen and Olesen, 2012) or develop chronic daily headaches due to medication overuse (Bussone, 2010).

Current understanding of migraine pathophysiology

The lack of therapeutic options in managing migraine reflects the limited understanding of the mechanisms behind migraine. Ironically, both the early development of triptan drugs and rationale for looking at CGRP in migraine were based on the old vascular migraine model. For decades, migraine had been considered a vascular disorder in which pain resulted from vasodilation of cranial arteries (Levy and Burstein, 2011). This theory was suggested after Wolff observed dilation of the superficial temporal artery during migraine (Wolff et al., 1953), an idea that gained further support due to various vasodilators found to induce migraine. These vasodilators are: CGRP, nitroglycerin, histamine, and PACAP-38 (Asghar et al., 2011; Christiansen et al., 1999; Iversen et al., 1989; Lassen et al., 1995; Schytz et al., 2009). Typically, these vasodilators have a biphasic effect with an initial mild headache experienced by both healthy controls and migraineurs, but a delayed migraine-like headache that meets the criteria described above is only experienced by migraineurs. However, the vascular theory has been challenged by evidence supporting a more neural basis of migraine (Brennan and Charles, 2010; Goadsby, 2009; Levy and Burstein, 2011). In addition, a simple role for vasodilation has been ruled out since some potent vasodilators, such as vasoactive intestinal peptide (VIP), do not induce migraine despite eliciting intracranial vascular dilation (Brennan and Charles, 2010; Rahmann et al., 2008). Importantly, while

migraine-triggering vasodilators initially cause dilation in both controls and migraineurs during the initial mild headache phase, there is no increase in intracranial arterial diameter during the migraine-like headache phase (Brennan and Charles, 2010; Schoonman et al., 2008). There is though one recent study that reported CGRP-induced dilation of both the middle meningeal artery and the middle cerebral artery in migraineurs during the migraine-like attack (Asghar et al., 2011). Hence, while the story is unfinished, it seems that vascular events alone are not necessary or sufficient to induce a migraine (Brennan and Charles, 2010). In its place, the neurovascular model, which combines both neural and vascular contributions, has gained general acceptance.

The neurovascular theory of migraine centers on activation of the trigeminovascular system (Goadsby et al., 2002; Messlinger, 2009) (Figure 1). This system consists of pseudo-unipolar neurons in the trigeminal ganglion with primary afferents innervating the pial and dural meningeal vessels surrounding the brain and efferent projections synapsing with second order neurons in the trigeminal nucleus caudalis (TNC) (Liu et al., 2008; Messlinger et al., 1993). The ganglion provides sensory fibers for all anterior cranial tissues and is subdivided into three topographical divisions with the ophthalmic division playing the predominate role in migraine (Messlinger, 2009). In particular, trigeminal ganglion provides afferent innervation to the meninges including the dura mater and intracerebral arteries (Messlinger, 2009). Almost exclusively nociceptive, meningeal afferents are polymodal, thus sensitive to mechanical, thermal, and chemical stimuli including capsaicin and H+ that activate TRPV1 and ASIC3 receptors (Bove and Moskowitz, 1997; Messlinger, 2009; Yan et al., 2011). Sensory trigeminal fibers project primarily to the TNC, which extends from the medullary dorsal horn to the first two cervical segments of the spinal dorsal horn (Messlinger, 2009). Stimulation of meningeal afferents leads to c-Fos positive neurons in the TNC (Hoskin et al., 1999; Kaube et al., 1993; Strassman et al., 1986). Neurons in the TNC then synapse with neurons in the thalamus, especially nuclei in the posterior thalamus, where ascending input is integrated and relayed to higher cortical areas (Burstein et al., 1998).

In addition to the trigeminal system, innervation from the sphenopalatine ganglia has also been implicated in the neurovascular model of migraine (Figure 1) (Bolay et al., 2002). This ganglion contains parasympathetic nerves involved in autonomic control of cranial vessel tone. Interestingly, the sphenopalatine ganglia and nerves contain PACAP and its receptors (Csati et al., 2012). As discussed below, both CGRP and PACAP may play roles in the trigeminal-autonomic reflex during migraine attacks.

Some studies have suggested trigger sites in the brainstem could activate the trigeminovascular system (see (Messlinger, 2009)), or that defective central processing allows non-noxious trigeminovascular input to be perceived as painful (Lambert, 2010; Lambert and Zagami, 2009). While these studies suggest the brainstem plays a role in migraine, the mechanisms are not yet clear.

In summary, the exact mechanisms of migraine remain elusive. This is not surprising given migraine is a very complex disorder with a variety of triggers and phenomena occurring throughout the CNS and intracranial tissues. While the old vascular theory has fallen from favor, it seems likely that the vasculature will still play a role and that model led to the finding that vasodilators, such as CGRP, can trigger migraine-like headaches. Importantly, other vasodilators do not, which raises the question as to what else CGRP does. Using that same logic, we have compared those activities with those of another migraine-inducing vasodilator, PACAP, to potentially reveal overlapping roles of CGRP and PACAP in migraine.

Calcitonin gene-related peptide (CGRP)

CGRP background

CGRP is a neuropeptide involved in a number of physiological and pathological processes in the body. CGRP is found in neurons throughout the body (Recober and Russo, 2009; van Rossum et al., 1997; Wimalawansa, 1996). Approximately 50% of trigeminal neurons express CGRP (Eftekhari et al., 2010; Tajti et al., 1999). There are two genes encoding nearly identical forms of CGRP. The CALCA gene encodes α-CGRP, a 37 amino acid peptide (Amara et al., 1982), which we will refer to simply as CGRP. This gene also encodes the originally identified splice variant, calcitonin, a hormone peptide produced in thyroid C-cells (Amara et al., 1982; Moya et al., 1975). The CALCB gene encodes β-CGRP, which differs from α-CGRP by only one amino acid. While the two peptides have nearly indistinguishable activities, they are differentially regulated and expressed in a distinct, but overlapping pattern (Russo et al., 1988). Note that trigeminal ganglia predominantly express α-CGRP (Amara et al., 1985).

The CGRP receptor consists of three separate subunits: calcitonin-like receptor (CLR); RAMP1; and receptor component protein (RCP) (Archbold et al., 2011; Barwell et al., 2012) (Figure 2). CLR, a G protein-coupled receptor, and RAMP1 are required for trafficking to the cell surface and for CGRP binding (McLatchie et al., 1998). RCP is an intracellular subunit that is required for Gαs coupling to the receptor (Barwell et al., 2012; Evans et al., 2000; Prado et al., 2002). RAMP1 appears to be the functional rate-limiting subunit of the receptor (Zhang et al., 2006; Zhang et al., 2007). Additionally, there is evidence that 2 RAMP1 subunits may cooperatively bind to a CLR dimer (Heroux et al., 2007; Zhang et al., 2007). Binding of RAMP2 or 3 subunits to CLR forms adrenomedullin receptors, AM1 or AM2, respectively, which have low affinity for CGRP (Walker et al., 2010). RAMP1 with the calcitonin receptor forms amylin subtype 1a receptor (Hay et al., 2006). After binding of CGRP to the cleft between CLR and RAMP1, a signal is transduced through the receptor, which can lead to activation of multiple pathways that modulate gene expression and ion channel activity (Walker et al., 2010). Via autoregulation, CGRP can increase CGRP promoter activity and mRNA levels (Zhang et al., 2007). Consequently, CGRP may initiate a positive feedback loop, which may in part explain why peripheral injection of CGRP leads to a delayed migraine-like headache several hours after injection.

Localization of CGRP and its receptor provides insight into the various actions that CGRP has throughout the body. Many of these areas have been implicated in migraine (Raddant and Russo, 2011). CGRP-immunopositive cell bodies and fibers are found in hypothalamic nuclei, ventral tegmental area, cerebellum, and various brainstem nuclei, including the periaqueductal grey (PAG) (Dobolyi et al., 2005; Edvinsson et al., 2011; Kresse et al., 1995; Ma et al., 2003). Furthermore, CGRP-binding sites have been localized throughout the CNS including the cortex, limbic areas (e.g. amygdala), hypothalamus, and brainstem, including PAG (Skofitsch and Jacobowitz, 1985a; van Rossum et al., 1997; Yashpal et al., 1992). In addition to neurons, satellite glia and possibly non-myelinating Schwann cells contain CGRP receptors although they do not normally produce CGRP (Eftekhari et al., 2010).

CGRP and migraine

Over the past years, a strong role has emerged for CGRP in the pathogenesis of migraine (Goadsby, 2005, 2006; Villalon and Olesen, 2009; Waeber and Moskowitz, 2005). This is primarily based on three lines of evidence from clinical studies.

1. Serum and salivary CGRP levels have been reported to be elevated in migraineurs during a spontaneous attack as well during a nitric oxide-induced attack (Bellamy et al., 2006b; Cady et al., 2009; Gallai et al., 1995; Goadsby et al., 1990; Ho et al.,

2010; Juhasz et al., 2003). CGRP levels have been reduced by triptans, coincident with pain relief (Goadsby and Edvinsson, 1993; Juhasz et al., 2005). Most of these studies used blood from the external jugular vein, so the most likely source of CGRP would have been perivascular release from peripheral trigeminal nerve fibers. However, another study did not find elevated CGRP during migraine (Tvedskov et al., 2005). The reason is not clear, but the lack of an increase in some patients may reflect heterogeneity of the pathology or different severity of the symptoms. So, while elevated CGRP in migraine seems likely, it remains controversial (Tfelt-Hansen and Le, 2009).

2. Intravenous injection of CGRP led to migraineurs experiencing a delayed headache roughly 2 – 4 h after injection with some of those headaches meeting criteria as a migraine (Asghar et al., 2011; Hansen et al., 2010; Lassen et al., 2002). Whereas, non-migraineurs only described an initial mild headache or fullness of head, and none met criteria for experimentally induced migraine (Hansen et al., 2010; Petersen et al., 2005). Interestingly, administration of sumatriptan was effective in reversing the CGRP-induced migraine (Asghar et al., 2011). The triptans are 5-HT1B/D receptor agonists that act by inducing vasoconstriction and inhibiting release of CGRP and other neuropeptides (Loder, 2010). They have been shown to down regulate nociceptive signaling in the spinal trigeminal nucleus (Levy et al., 2004), although the sites of triptan actions are not yet fully known. Sumatriptan also reversed a nitric oxide-induced migraine and reduced CGRP levels coincident with pain relief (Juhasz et al., 2005).

3. Selective CGRP receptor antagonists are effective in the management of migraine. In a phase II study, 66% of migraineurs responded to 2.5 mg of IV olcegepant (BIBN4096) compared to 27% subjects who received placebo (Olesen et al., 2004). It was superior to placebo based on a 2 h pain free rate as well as improved photophobia, phonophobia, and nausea (Olesen et al., 2004). In several phase III clinical trials, an oral antagonist, telcagepant (MK-0974) has been show to be effective and was as efficacious as rizatriptan and zolmitriptan (Connor et al., 2009; Ho et al., 2008a; Ho et al., 2008b).

In summary, these studies have demonstrated CGRP to be elevated during a migraine and that CGRP can induce a migraine-like state in migraineurs only, suggesting that sensitivity to CGRP may play a role in migraine susceptibility. Moreover, blocking the actions of CGRP can effectively reverse the symptoms of a migraine. However, somewhat surprisingly, CGRP and its receptor have yet to be genetically associated with migraine (Anttila et al., 2010; Chasman et al., 2011; Menon et al., 2011). This may reflect not only the heterogeneity of migraine, but may also reflect the possibility that other modifiers are needed in concert with CGRP. Furthermore, both the triptans and CGRP receptor antagonists are not effective for all patients and each drug class has limitations and drawbacks. For these reasons, more targets need to be investigated.

Given that CGRP is a key player in migraine, to identify new targets, one strategy is to consider how CGRP might be contributing to the symptoms? To understand how CGRP plays a role in migraine requires an appreciation for the multifunctional roles of this peptide. As a starting point, we have outlined CGRP actions in light aversion, nociceptive sensitization, neurogenic inflammation, cortical spreading depression, and nitric oxide generation.

CGRP and light aversion

Over the past few years, studies in animal models have revealed an unexpected role for CGRP in light aversive behavior that is suggested to be analogous to photophobia

experienced by migraineurs. Sensitized to CGRP as the result of RAMP1 over-expression, nestin/hRAMP1 mice demonstrated a significant decrease in time in the light zone of a dim light-dark box compared to vehicle-treated nestin/hRAMP1 mice and CGRP-treated control mice (Recober et al., 2010; Recober et al., 2009). Furthermore, CGRP decreased locomotor activity in the dark zone, which may reflect exacerbation of pain by movement that is often experienced during a migraine (Recober et al., 2010). Wildtype mice have also demonstrated these CGRP-induced behaviors, but required bright light and habituation to the chamber (Kaiser et al., 2012). While there is a difference in sensitivity in this assay between wildtype and nestin/hRAMP1 mice, it demonstrates that endogenous CGRP receptors are sufficient to convey this behavior. Triptans have attenuated the CGRP-induced behaviors in wildtype and nestin/hRAMP1 mice suggesting that light aversion in mice likely provides a preclinical model of migraine-type photophobia (Kaiser et al., 2012; Schwedt and Goadsby, 2010).

CGRP in central and peripheral nociceptive sensitization

CGRP plays a role in the nervous system as a neuromodulator of nociception. This is particularly evident in the trigeminal system. Trigeminal sensory fibers are CGRP-immunopositive at a higher ratio than sensory fibers in extracranial tissues (Messlinger, 2009). Consequently, CGRP is released from primary afferents in both the periphery and the TNC (Eberhardt et al., 2008; Ebersberger et al., 1999; Eltorp et al., 2000; Goadsby et al., 1988; Jenkins et al., 2004; Offenhauser et al., 2005). CGRP receptors are also located in the soma of trigeminal ganglion cells (Lennerz et al., 2008; Tajti et al., 1999). In the TNC, there is evidence of CGRP receptors on primary afferent terminals suggesting a potential role in modulating presynaptic activity to facilitate nociceptive transmission (Lennerz et al., 2008; Messlinger, 2009). Second-order neurons in the TNC project to the posterior thalamus (Burstein et al., 1998). In the thalamus, CGRP-immunopositive neurons are located in the peripeduncular nucleus, subparafascicular nucleus, and posterior thalamic nuclear group as well as areas ventromedial to this group (Kresse et al., 1995). Moreover, the ventral posteromedial nucleus is known to contain CGRP receptors, and CGRP receptor antagonists inhibit nociceptive activation of the ventral posteromedial nucleus (Summ et al., 2010). Interestingly, somatosensory and nociceptive activity is integrated and relayed from ascending pathways to higher cortical areas via CGRP-containing neurons of the subparafascicular thalamus and the caudal part of the posterior thalamic group (de Lacalle and Saper, 2000; Gauriau and Bernard, 2004). These CGRP containing fibers project to the secondary somatosensory cortex, amygdala, insula, and hypothalamus (Campeau and Watson, 2000; de Lacalle and Saper, 2000; Gauriau and Bernard, 2004) indicating roles in nociception, stress, autonomic responses, anxiety, and auditory perception (Raddant and Russo, 2011). Also the posterior thalamus has been implicated in migraine-type photophobia (Noseda et al., 2010). In efferent pathways, CGRP has also been found in the nucleus raphe mangus of rats leading to anti-nociceptive effects (Huang et al., 2000) and in A11 dopamine neurons located in the posterior hypothalamus that provide descending innervation to spinal gray matter including the TNC (Charbit et al., 2009).

CGRP release from central terminals of the trigeminal nerve can modulate second order-nociceptive neurons in the TNC (Fischer, 2010). This also occurs in the spinal dorsal horn, which can lead to central sensitization resulting in mechanical allodynia (Marquez de Prado et al., 2009). CGRP and its receptor co-localize with AMPA-type glutamate receptors in post-synaptic neurons in the spinal dorsal horn (Gu and Yu, 2007). Furthermore, CGRP was also found to enhance synaptic transmission of NMDA- and AMPA-type glutamate receptors (Ebersberger et al., 2000). Consequently, CGRP is thought to play a role in central sensitization (Seybold, 2009), which is a component in mitigating headache pain in migraine and likely also contributes to hypersensitivity to other senses leading to photophobia, phonophobia, and allodynia in migraine (Ho et al., 2010).

CGRP and neurogenic inflammation

Neurogenic inflammation includes vasodilation, plasma protein extravasation, mast cell degranulation, and release of proinflammatory and inflammatory molecules due to sensory nerve activation (Markowitz et al., 1987; Raddant and Russo, 2011). The process can activate meningeal nociceptors (Messlinger, 2009).

CGRP plays multiple roles in neurogenic inflammation. It is the most potent vasodilator peptide (Brain and Grant, 2004; McCulloch et al., 1986). Due to its effects on the coronary arteries, CGRP has been shown to be cardioprotective by limiting cardiac ischemia-reperfusion injury (Huang et al., 2008). Importantly, the CGRP receptor is found throughout the cerebral vasculature (Oliver et al., 2002) with CGRP acting as a particularly potent vasodilator in intracranial arteries, even more so than in coronary arteries (Edvinsson et al., 2002; Moreno et al., 2002). CGRP has been found to induce dilation of the middle cerebral artery and middle meningeal artery in migraineurs coincident with the induced migraine (Asghar et al., 2011); however, this has not been found in other studies (Goadsby, 2009; Lassen et al., 2008; Levy and Burstein, 2011). CGRP is indirectly involved with plasma extravasation, which is primarily caused by substance P and neurokinin A (Holzer, 1998). These peptides are often co-released with CGRP (Lee et al., 1985; Lundberg et al., 1985; Skofitsch and Jacobowitz, 1985b) and CGRP can increase substance P release (Zhang et al., 2007). CGRP in conjunction with substance P can trigger mast cell degranulation to release proinflammatory and inflammatory compounds (Brain and Grant, 2004; Ottosson and Edvinsson, 1997; Theoharides et al., 2005). Recently, it has been confirmed that dural mast cells express the CGRP receptor (Lennerz et al., 2008). Mast cell activation and degranulation leads to release of histamine, which has been shown to induce migraine (Lassen et al., 1995), along with prostaglandins, TNF-α, and other compounds. Mast cells can activate dural primary afferents, which subsequently leads to c-Fos immunoreactivity in the TNC (Levy et al., 2007). Similar to mast cells, satellite glia, which surround neurons in trigeminal ganglia (Hansson and Ronnback, 2003), contain CGRP receptors (Eftekhari et al., 2010; Lennerz et al., 2008). In response to CGRP, satellite glial cells can release proinflammatory cytokines such as TNF-α and IL-6 leading to sensory neuron sensitization (Capuano et al., 2009; De Corato et al., 2011; Thalakoti et al., 2007; Vause and Durham, 2010). Similar cascades occur in other inflammatory pain conditions (Cao and Zhang, 2008; Watkins et al., 2001). Moreover, satellite glia and neurons have been proposed to participate in a positive feedback loop of CGRP synthesis and release maintaining a state of heightened inflammation and sensitization (Raddant and Russo, 2011). This positive feedback loop may explain why transgenic mice overexpressing RAMP1 have higher CGRP levels in cerebrospinal fluid (Recober et al., 2009). Consequently, CGRP is apparently a key mediator of neurogenic inflammation in the trigeminovascular system.

However, a role for neurogenic inflammation in migraine has been diminished in part due to the lack substance P found in venous outflow during a migraine attack (Goadsby et al., 1990) and the lack of substance P receptor antagonist efficacy in migraine clinical trials (Diener, 2003; Ho et al., 2010). Still several animal models of migraine utilize an inflammatory soup consisting of bradykinin, 5-HT, histamine, and prostaglandin E2 buffered at low pH, which leads to sensitization of second-order neurons in the TNC (Burstein et al., 1998; Levy et al., 2004; Strassman et al., 1996). Consequently, these animal models have been widely used to model central sensitization in migraine (Messlinger, 2009). Other than a known role for histamine inducing migraine, it remains to be seen whether neurogenic inflammation plays a role in migraine in humans.

CGRP and cortical spreading depression

A potential trigger that may engage neuropeptides in the trigeminovascular system during migraine is cortical spreading depression (CSD), which is associated with aura (Ayata, 2010). CSD is a self-propagating wave of neuronal and glial depolarization initiated in the occipital lobe that spreads rostrally over the cortex at rate of 2 – 6 mm per min; this is followed by a prolonged neuronal suppression during repolarization (Olesen et al., 2009; Raddant and Russo, 2011). CSD leads to the release of various noxious substances such as glutamate, potassium, and adenosine triphosphate, which diffuse into the meninges, activating nociceptors, releasing CGRP and substance P from peripheral terminals, and triggering neurogenic inflammation (Levy, 2010). Activation of meningeal nociceptors after CSD (Bolay et al., 2002; Zhang et al., 2011; Zhang et al., 2010) leads to c-Fos expression in the TNC (Kunkler and Kraig, 2003; Moskowitz, 1993). Interestingly, animal models have shown CSD suppression in response to common migraine prophylaxis (Ayata, 2010; Ayata et al., 2006).

CGRP may play a role in CSD. It may lead to the initial hyperemia during CGRP based on studies with animal models of CSD in which CGRP receptor antagonists blocked pial dilation (Colonna et al., 1994; Wahl et al., 1994). A recent study using rat brain slices found that endogenous CGRP was released during CSD and that CGRP receptor antagonists inhibited CSD in vitro (Tozzi et al., 2012). In addition, one clinical study reported that CGRP infusion induced an aura in some subjects although this needs further study (Hansen et al., 2010).

CGRP and nitric oxide

As discussed above, CGRP can induce a migraine-like headache in migraineurs, but nitrovasodilators, which are nitric oxide (NO) donors, such as glyceryl trinitrate or sodium nitroprusside can elicit the same effect. Remarkably, CGRP levels were elevated following glyceryl trinitrate induced migraine (Juhasz et al., 2003). Nitrovasodilators have also been studied in animals (Messlinger, 2009). Interestingly, sodium nitroprusside was found in rats to induce an initial, transient phase of neuronal activation and then a delayed, long phase of high neuronal activity in the TNC, which closely mimics clinical trials with migraineurs (Koulchitsky et al., 2004). Furthermore, glyceryl trinitrate induced c-Fos immunoreactivity in the TNC (Martin and Martin, 2001; Tassorelli and Joseph, 1995a, b). This may occur in part because NO donors were found to increase the release of CGRP in rat dura in vitro (Strecker et al., 2002). Moreover, pre-treatment of trigeminal ganglia cultures with NO donors was also found to increase CGRP release in response to both depolarization and inflammatory mediators, which may have occurred due to NO donors increasing CGRP promoter activity (Bellamy et al., 2006a; Eberhardt et al., 2008). While NO donors have some functions independent of CGRP, their function in migraine may strongly relate to promoting CGRP production and release, adding to the CGRP-influenced pathways in migraine.

Pituitary adenylate cyclase-activating peptide (PACAP)

PACAP background

Like CGRP, PACAP is a multifunctional vasodilatory peptide that has recently been implicated in migraine pathogenesis. PACAP has roles in neurodevelopment, neuroprotection, neuromodulation, neurogenic inflammation, and nociception (Hashimoto et al., 2006; Vaudry et al., 2000). PACAP belongs to the VIP-glucagon-growth hormone releasing factor-secretin superfamily (Vaudry et al., 2000). PACAP is encoded by ADCYAP1 gene, which expresses two forms containing either 27 or 38 amino acids with PACAP-38 being the more prevalent, representing 90% of PACAP forms in mammalian

tissues (Bourgault et al., 2008). We will generally refer to PACAP-38 simply as PACAP. It is expressed throughout the CNS (Masuo et al., 1992; Uddman et al., 2002) as well as in peripheral organs and glands (Borzsei et al., 2009; Fahrenkrug and Hannibal, 2011; Koves et al., 1990; Reglodi et al., 2012). As a result, PACAP has various roles in cardiovascular, respiratory, gastrointestinal, and reproductive systems in addition to the nervous system (Vaudry et al., 2000). PACAP binds to three different G-protein coupled receptors, which have affinity for VIP as well. Receptors VPAC1 and VPAC2 have varying affinity for the following peptides: VIP > PACAP-38 > PACAP-27 (Laburthe and Couvineau, 2002). PAC1 is selective for PACAP-38 and PACAP-27 with 102 to 103 lower affinity for VIP (Laburthe and Couvineau, 2002). These different receptor affinities are likely to underlie the ability of PACAP-38, but not VIP, to induce migraine.

Like the CGRP core subunit CLR, the VPAC1 receptor can associate with all three RAMP subunits, including RAMP1, in a cell-based assay (Figure 3) (Christopoulos et al., 2003; Morfis et al., 2003). In contrast, VPAC2 did not show any interaction (PAC1 was not tested). Binding of PACAP and VIP to VPAC1 was not affected by any of the RAMPs (Christopoulos et al., 2003; Morfis et al., 2003). Interestingly, co-expression of VPAC1 and RAMP2 increased agonist-mediated phosphoinositide hydrolysis with no change in cAMP stimulation compared with VPAC1 receptor alone. While direct modulation by RAMP1 was not observed, we suggest that elevated RAMP1 could compete with RAMP2 association with VPAC1. This would effectively shift receptor coupling towards cAMP production. Such modulation of signaling will be dependent on the cell type, but it suggests a possible synergistic effect of increased RAMP1 levels on both CGRP and PACAP receptor cAMP signaling.

In the trigeminovascular system, PACAP is expressed in the TNC (Uddman et al., 2002) and found in the spinal cord, trigeminal ganglia, and TNC (Schytz et al., 2010). PACAP and its receptors are also expressed in sphenopalatine ganglia neurons that control dural vessel tone and cranial blood flow (Csati et al., 2012). Similar to CGRP, PACAP binds to a variety of sites throughout the CNS, including the hypothalamus, thalamus, various areas throughout the brainstem, and the dorsal horn of the spinal cord (Masuo et al., 1992; Narita et al., 1996; Tajti et al., 2001), and PAC1 is expressed throughout the brain, including the neocortex, limbic system, and brainstem (Hashimoto et al., 2006; Vaudry et al., 2000). As with CGRP, PACAP has been linked to anxiety-like behavior. PACAP and PAC1 knockout mice have decreased anxiety-like behavior (Hattori et al., 2012; Otto et al., 2001). Both transgenic mice show a variety of neurobehavioral phenotypes including increased hyperactivity, decreased depression-like behavior, and aberrant social interaction (Hattori et al., 2012; Otto et al., 2001). In addition, chronic stress increased PACAP mRNA expression within the bed nucleus of the stria terminalis, suggesting a likely role in stress and anxiety, which are both key triggers in migraine (Hammack et al., 2009; Hammack et al., 2010). Like CGRP and its receptor, PACAP is not expressed in satellite glia cells, and PAC1 and VPAC1 receptors are found in satellite glia (Csati et al., 2012).

Emerging role for PACAP in migraine

A role for PACAP in migraine is primarily based on two lines of clinical evidence. A very recent clinical study in migraineurs demonstrated that PACAP plasma levels were elevated during a migraine attack compared to their interictal levels (Tuka et al., 2013). A complication of this finding is that interictal PACAP levels were lower in comparison to healthy subjects, and ictal PACAP levels were comparable to healthy subjects (Tuka et al., 2013). The second line of evidence is that following peripheral injection of PACAP in migraineurs, 11 out 12 subjects experienced an initial headache, and 7 out of 12 subjects experienced a migraine-like headache that was delayed by 2–11 h with only one exception (Schytz et al., 2009). Injection in healthy subjects led to an initial headache in 12 out 12

subjects, and only 2 subjects experienced a migraine-like headache during the first two hours (Schytz et al., 2009). Hence, PACAP appears to have a similar ability to induce a delayed migraine-like headache as observed with CGRP. Similarly, PACAP induced an initial vasodilation of the middle cerebral artery and superficial temporal artery in both healthy and migraineur subjects, but only the migraineurs experienced a delayed migraine-like headache (Schytz et al., 2009). Like CGRP, migraineurs seems to be particularly sensitive to PACAP. This clinical evidence has garnished attention to the possible role of this peptide in migraine pathophysiology.

Comparisons of PACAP and CGRP activities relevant to migraine

A very intriguing shared activity of PACAP and CGRP is their ability to induce light aversion in mice. Peripheral injection of nitroglycerol and PACAP-38 has been shown to induce light aversive behavior in wildtype mice, but not in PACAP knockout mice (Markovics et al., 2012). These findings reflect similar studies with CGRP, which induces light aversion in CGRP-sensitized and wildtype mice (Kaiser et al., 2012; Recober et al., 2010; Recober et al., 2009).

Unlike CGRP, PACAP has been reported to be antinociceptive in the periphery (Helyes et al., 2007; Nemeth et al., 2006; Sandor et al., 2009; Sandor et al., 2010). However, a PACAP knockout mouse indicated that PACAP plays an excitatory role in pain transmission, suggesting a possible role in central sensitization (Sandor et al., 2010). Furthermore, a recent study has shown that injection of PACAP-38 into the paraventricular nucleus of the hypothalamus increased TNC activity, which could be inhibited by a PAC1 receptor antagonist (Robert et al., 2013). In addition, intrathecal injection of PACAP has been shown to induce hyperalgesia in mice (Narita et al., 1996).

Being vasodilatory peptides, both PACAP and CGRP are likely to contribute to vasodilation during neurogenic inflammation. PACAP-containing nerve fibers have been closely localized near cerebrovasculature containing VPAC1 receptors in rats (Fahrenkrug et al., 2000). PAC1, VPAC1 and VPAC2 have been localized to the smooth muscle within the cerebrovasculature of rodents (Erdling et al., 2013). This facilitates VIP-, PACAP-27-, and PACAP-38-induced vasodilation of the middle cerebral artery, but PACAP-38 is the least potent (Erdling et al., 2013). This may be due to greater abundance of VPAC1 receptors compared to VPAC2 and PAC1 receptors (Baun et al., 2011). However, in the middle meningeal artery, another study showed PACAP-38 to be as potent as VIP (Boni et al., 2009), but in the cerebellar arties, PACAP-38 was 1000-fold less potent (Syed et al., 2012). While VPAC2 and PAC1 antagonists were ineffective in blocking VIP and PACAP-38 induced vasodilation, VPAC1 antagonist PG97-269 was able to block PACAP-38 induced dilation (Boni et al., 2009), yet in another study, the same PAC1 receptor antagonist was effective in blocking vasodilation (Syed et al., 2012). Interestingly, maxadilan, a selective PAC1 receptor agonist, has not been shown to vasodilate the basilar artery or the middle meningeal artery in the rat (Baun et al., 2011). The contradicting nature of these findings leaves which of the three receptors are key in mitigating PACAP intracranial dilation unanswered. In human studies, PACAP-38 has also been shown to dilate human meningeal arteries, but not as potently as VIP (Chan et al., 2011). Considering that VIP does not induce a migraine and that PACAP38 is a likely a weak vasodilator in intracranial arties in comparison, it has been suggested that the ability of PACAP-38 to induce a migraine is not likely due its vasodilatory effects (Baun et al., 2011), but likely the result of its other central actions (Hashimoto et al., 2006).

Like its role in nociception, PACAP also has inconsistent roles in neurogenic inflammation. PACAP, like CGRP, is upregulated following inflammation in sensory neurons (Zhang et al., 1998). Also, PACAP has been reported to inhibit neurogenic inflammation in the

periphery (Helyes et al., 2007; Nemeth et al., 2006; Sandor et al., 2009; Sandor et al., 2010). Yet, PACAP-38 induces dural mast cell degranulation, and was significantly more potent than VIP and PACAP-27 (Baun et al., 2012; Theoharides et al., 2005). This suggests a possible role for PACAP, like CGRP, in triggering neurogenic inflammation within the dura, which may be relevant to migraine.

With respect to CSD, to our knowledge, PACAP in CSD has not been investigated, thus it remains to be seen whether PACAP plays any role in CSD similar to CGRP.

PACAP has also been linked to nitric oxide pathways. In rats, peripheral injection of nitroglycerin increased PACAP within the TNC, and electrical stimulation of the trigeminal ganglia increased PACAP within the plasma and TNC (Tuka et al., 2012). Also, nitroglycerol induced more vasodilation and neuronal activation in trigeminal ganglia and TNC in wildtype mice compared to PACAP knockout mice (Markovics et al., 2012). This suggests that PACAP and NO, like CGRP and NO, are coupled in the trigeminovascular system.

Conclusion

CGRP clearly plays an integral role in migraine based on several clinical studies. While its exact contributions in migraine are not known, it has known roles in several events associated with migraine, light aversion, nociceptive sensitization, neurogenic inflammation, cortical spreading depression, and nitric oxide generation. Thus, CGRP is well positioned to contribute to migraine symptoms. The ability of CGRP receptor antagonists to ameliorate migraine provides conclusive evidence of the involvement of CGRP in migraine. However, CGRP alone cannot account for migraine, but instead is likely to act with other modifiers, such as PACAP.

Although PACAP lacks some of the actions of CGRP that may contribute to migraine pathophysiology, it has some shared actions, such as ability to induce light aversion, neurogenic inflammation and neuromodulation of sensory neurons. These common features suggest CGRP and PACAP might act in concert. This commonality is even more intriguing at a molecular level since both CGRP and PACAP receptors share a RAMP1 subunit, which is functionally rate limiting for CGRP activity. Whether it is also limiting for PACAP activity remains to be tested. Much has to be learned about PACAP and its role in migraine, but it presents potential novel target in migraine therapy. It will be interesting to see if PACAP receptor antagonists are effective in acute migraine therapy as demonstrated with CGRP receptor antagonists (Charles, 2013; Schytz et al., 2010). Thus, these two migraine-inducing neuropeptides, CGRP and PACAP, may provide insight into migraine pathophysiology as future studies delve into the mechanisms shared by these peptides.

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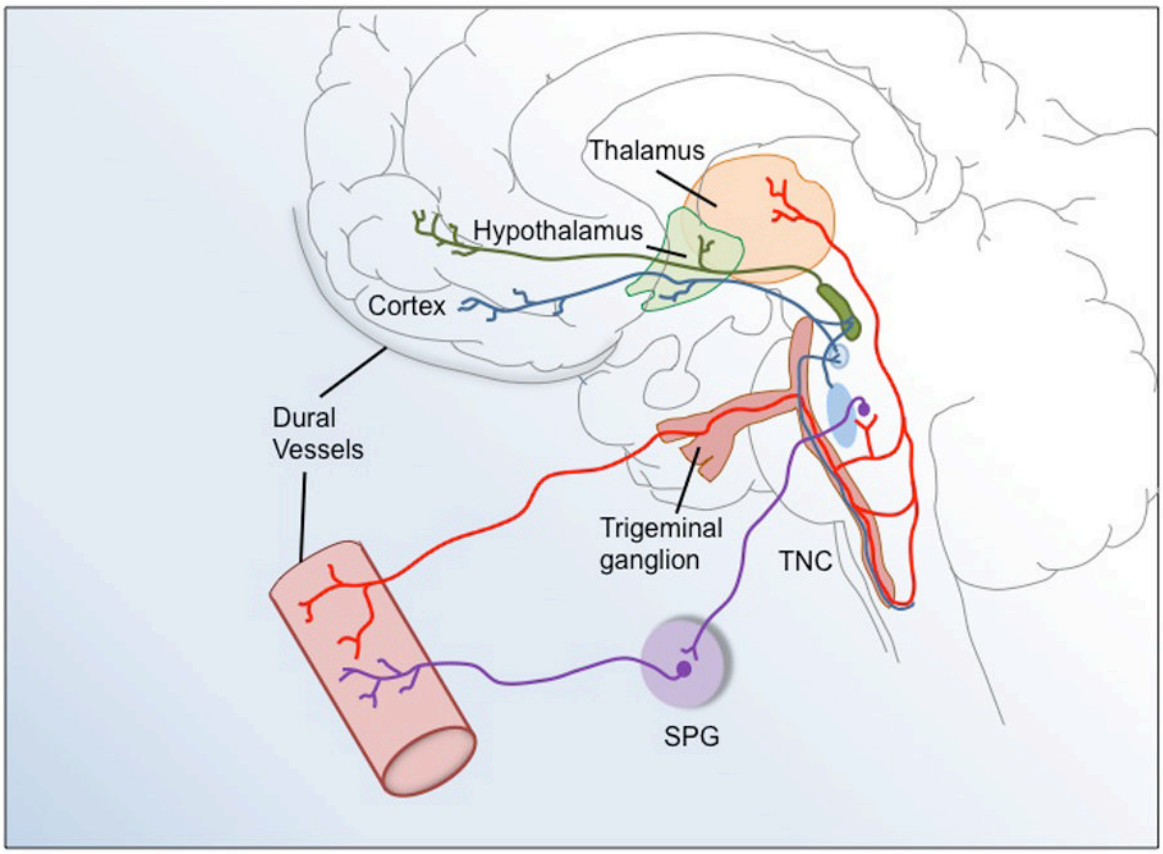

Figure 1.
Representation of the trigeminovascular system in migraine. Trigeminal afferents innervate the dural vasculature. The first-order trigeminal neuron is located in the trigeminal ganglion. Its central terminal projects to the trigeminal nucleus caudalis (TNC) that extends from the dorsal medulla to the dorsal spinal horn of the first two cervical segments. Second-order neurons of the TNC project to the posterior thalamus. The sphenopalatine ganglion (SPG) also provides reflex parasympathetic innervation to dural vessels. This illustration has been adapted from (Goadsby et al., 2002).

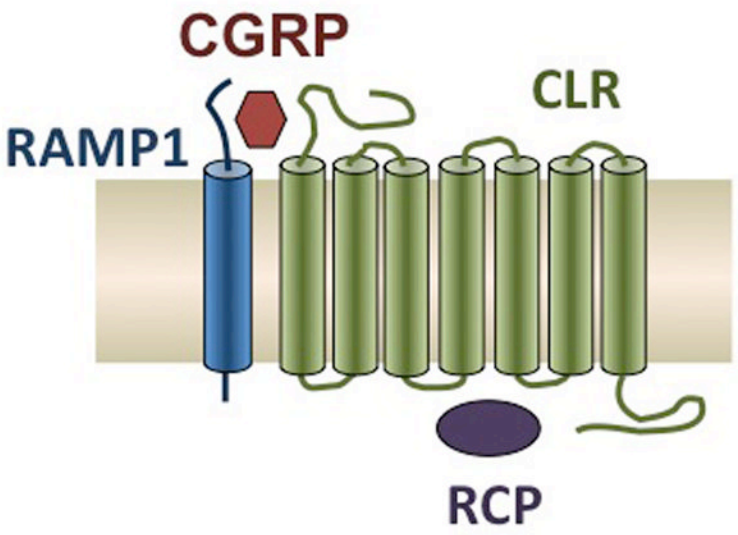

Figure 2.
Schematic of the CGRP receptor complex, which contains three subunits: CLR, RAMP1, and RCP. This figure has been modified slightly from (Russo et al., 2009).

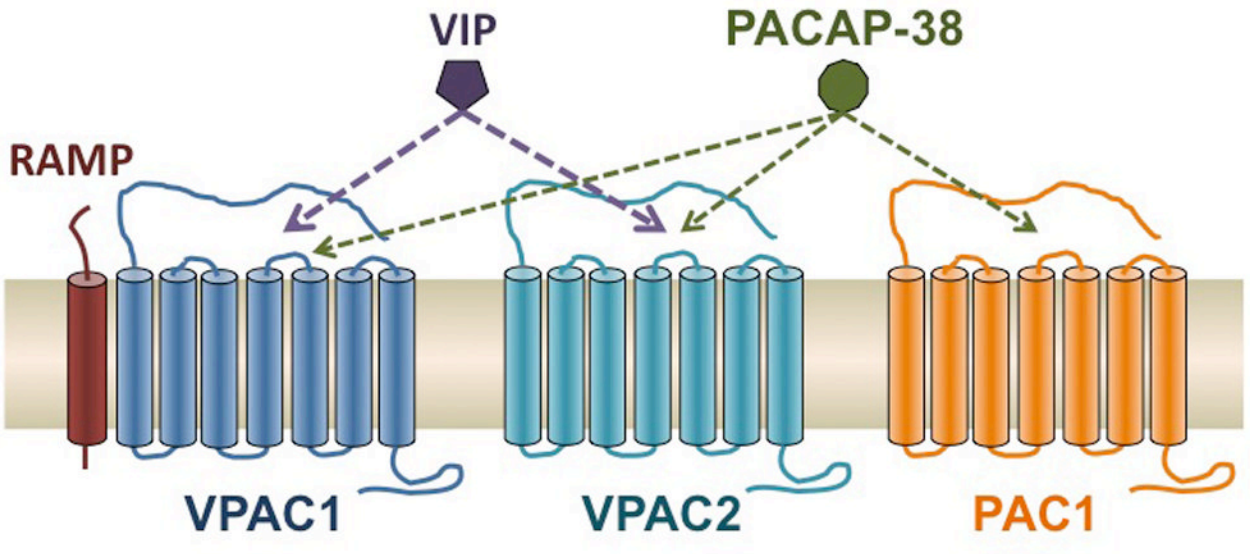

Figure 3.
Schematic of the VPAC1, VPAC2 and PAC1 receptors, which bind VIP and PACAP-38 with varying affinities. Compared to PACAP, VIP binds to PAC1 with 100–1000-fold lower affinity. PACAP-27 can also bind all three receptors (not shown). All three RAMPs can associate with VPAC1, but apparently not VPAC2 (PAC1 not known).