Role of PACAP in migraine headaches

Migraine is a complex disorder with a wide spectrum of clinical symptoms, and affects more than 16% of the general population. Despite its high heritability, the genetic basis of migraine remains unclear in most cases, and appropriate prophylactic and clinical therapy is not always available. Recent years have nevertheless seen considerable progress in understanding the cellular and circuit mechanisms of migraine (Vécezi et al., 2013). In this issue of Brain, Faisal Amin and colleagues add to this progress by identifying the PAC1 receptor as a potentially important candidate therapeutic target (Amin et al., 2014).

Since the 1990s, a central theme of migraine research has been the trigeminovascular theory (Moskowitz, 1992). The trigemino-vascular system provides an important pain-transmission link between the vascular (dural and cortical) and neuronal (brainstem and thalamus) regions. The sensory trigeminal unit is controlled by the descending pathways from the monoaminergic nuclei, and a number of neuropeptides, such as calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP), have essential roles in activation of the trigeminovascular system (Edvinsson, 2013). PACAP is a member of the VIP/secretin/glucagon neuropeptide family and exists in two biologically active forms: PACAP27 and (predominantly) PACAP38. It is a pleiotropic peptide: it acts as a hormone on the pituitary gland, a neurotransmitter and a neuro-modulator in the nervous system, and it exerts neuroprotective, anti-apoptotic and differentiation-inducing effects in the developing nervous system. The effects of PACAP are mediated through G-protein-linked receptors: VPAC1, VPAC2 and PAC1 (Vaudry et al., 2009). PACAP38 is present in the trigeminal ganglion and caudal trigeminal nucleus (Tajti et al., 2001), and plasma PACAP38-like immunoreactivity is increased after electrical stimulation of the trigeminal ganglion (Tuka et al., 2012).

Intravenous administration of PACAP38 causes headache in healthy subjects and migraine-like attacks in migraine patients without aura, beginning on average 6h after the start of the infusion (Schytz et al., 2009). PACAP38 infusion also increases the diameter of the superficial temporal arteries and decreases the mean blood flow velocity of the middle cerebral arteries (Schytz et al., 2009). Amin et al. (2014) compare the vascular and biochemical effects of infusion of PACAP38 to those of the structurally and functionally related neuropeptide, VIP, in female migraineurs without aura. They show that 73% (n = 16) of their subjects developed migraine-like attacks after PACAP38 infusion, compared to 18% (n = 4) after VIP infusion. Three of four patients who developed migraine-like headache after VIP administration also reported attacks after PACAP38 treatment. Both VIP and PACAP38 are potent vasodilators of cerebral and dural arteries, and all three VIP/PACAP receptors are present on cranial arteries. Amin et al. (2014) report that both neuropeptides caused pronounced dilations of the extracranial (the superficial temporal artery, the middle meningeal artery, the external carotid artery and the cervical segment of the internal carotid artery), but not the intracranial arteries. However, VIP-induced dilatation was normalized after 2h, whereas PACAP38-induced vasodilation was longer lasting.

Plasma PACAP38 levels were increased 1h after the start of PACAP38 infusion only in those patients who later reported migraine attacks. Blood levels of VIP, in contrast, were unaltered after intravenous administration of PACAP38. This suggests the possibility of de novo synthesis or release of PACAP38 during migraine.

These results are consistent with previous evidence implicating PACAP38 in migraine. Markovics et al. (2012) compared the effects of nitroglycerol and PACAP on the trigeminovascular system of PACAP knockout and wild-type mice. Nitroglycerol is a well-known NO donor, which causes both immediate and delayed migraine-like attacks in migraine patients without aura. Nitroglycerol administration also induced photophobia in wild-type mice, as well as increases in meningeal blood flow and c-fos expression in the trigeminal ganglion and caudal trigeminal nucleus. These changes were reduced in PACAP-deficient mice compared with wild-type animals. Furthermore, PACAP38 elicited photophobia in wild-type mice.
mice, but not in PACAP-deficient mice (Markovics et al., 2012). These results suggest that PACAP is an important mediator of light aversion and meningeal blood flow regulation.

A link has also been reported between migraine phase and changes in plasma PACAP38 levels (Tuka et al., 2013). Plasma PACAP38 immunoreactivity was lower in interictal migraine patients than in a healthy control group. By contrast, PACAP38 and CGRP concentrations were elevated in the ictal phase relative to the attack-free period in 21 migraineurs. A negative correlation was observed between interictal PACAP38 level and overall disease duration. Plasma PACAP38 release in the ictal period was significant only in menstruation cycle-independent migraineurs and those patients with no other chronic pain condition, such as lower back pain, lumbar or arthrosis. This study thus revealed a clear association between migraine phase and changes in plasma PACAP38 levels.

The results obtained by Amin et al. (2014) will have considerable scientific impact, elegantly demonstrating, in a head-to-head study, the differences between PACAP-38 and VIP-related migraine attacks, including differential effects on extracranial vasodilation. Their observations are key milestones for elucidating the role of PACAP and the mechanisms of migraine, and will pave the way for further research into therapies tailored to specific causes of the disease.

László Vecsei,1,2 Bernadett Tuka1,2 and János Tajti1
1Department of Neurology, University of Szeged, Szeged, Hungary
2MTA-SZTE Neuroscience Research Group, Szeged, Hungary

Correspondence to: László Vecsei
E-mail: vecsei.laszlo@med.u-szeged.hu
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Deepening understanding of the neural substrates of chronic pain

Chronic pain has been labelled the silent health crisis, afflicting hundreds of millions of people worldwide. Chronic pain causes more disability than cancer and heart disease, and the annual monetary cost of treatment and lost productivity is above $500 billion per annum in the United States alone (Institute of Medicine, 2011). Once considered simply a response to disease or injury, chronic pain is increasingly recognized as a group of mechanistically separable nervous system processes produced and maintained by a variety of abnormal cellular signalling pathways (Woolf and Salter, 2000).

A growing number of signalling pathways in the peripheral and central nervous systems have been implicated in chronic pain, along with neuron–glia as well as neuron–neuron interactions (Beggs et al., 2012b), and genetic sensitivity (Mogil, 2012) coupled with epigenetic modulation (Stone and Szyf, 2013). Nevertheless, a core unresolved question is which neurons in the pain processing and transmission circuitry in the spinal cord provide the pathological output believed by most to drive the brain’s pain network in chronic pain. And how is the firing activity of those spinal cord neurons altered? In the current issue of Brain, Yves De Koninck and colleagues take a major step forward in answering these questions through their elegant investigation of de novo changes in neurons in the spinal dorsal horn after peripheral nerve injury (Lavertu et al., 2014). The authors leveraged work from a number of groups that had indicated that loss of Cl−-mediated inhibition, particularly in neurons in the superficial laminae of the dorsal horn of the spinal cord (Moore et al., 2002; Coull et al., 2003), is critical for chronic pain hypersensitivity.

In particular, De Koninck’s group had previously discovered that disinhibition may come about through downregulation of the function and/or expression of KCC2, the K-Cl co-transporter...