Role of PACAP in migraine headaches

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In the current issue of *Brain,* Amin and colleagues report their investigation of the incidence of migraine attacks, the changes in diameter of selected extra- and intracranial arteries and the changes in the plasma levels of pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) and vasoactive intestinal peptide (VIP) after the infusion of VIP and PACAP-38. Such an investigation is essential for migraine research, because it comprises a head-to-head comparison of the vascular and biochemical responses of these peptides with long-lasting observations of migraine attacks. The authors reported that 73% (n=16) and 18% (n=4) of their patients developed migraine-like attacks after PACAP-38 and after VIP infusion, respectively. Three of the four patients who developed migraine-like headache after VIP administration also reported attacks after PACAP-38 treatment. This study elegantly demonstrated that PACAP-38 infusion induces more migraine headache attacks than VIP.

VIP and PACAP-38 are potent vasodilators of cerebral and dural arteries. All three receptors for VIP/PACAP are present on cranial arteries. Amin et al. observed 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. The main difference in this effect was found to be that the PACAP-38-induced vasodilation was longer-lasting (> 2 h), whereas the VIP-induced dilatation was normalized after 2 h.

The plasma PACAP-38 level was observed to be increased at 1 h after the start of PACAP-38 infusion only in those patients who later reported migraine attacks. The source of the elevation in plasma PACAP-38 is unknown, but this finding suggests the possibility of the *de novo* synthesis or release of PACAP-38 during a migraine attack. However, the blood level of VIP was unaltered after the intravenous administration of PACAP-38.

It was concluded that infused PACAP-38 induced more migraine-like attacks and much longer-lasting dilatation of the extracranial arteries than did VIP and the plasma PACAP-38 is elevated before the onset of migraine attacks (Amin et al., 2014).

In recent years there has been considerable interest in the pathomechanism of migraine (Vécsei et al., 2013). Migraine, a primary form of headache, is a common, paroxysmal highly

disabling, neurovascular disease, with a high socio-economic and personal impact. It is a very complex disorder, involving head pain and a wide spectrum of concomitant clinical symptoms. It affects more than 16% of the general population. In spite of this, its genetic background has not been established in detail and appropriate prophylactic and clinical therapy for the treatment of attacks is not available.

In line with this study, it was earlier demonstrated that the intravenous administration of PACAP-38 causes headache in healthy subjects and migraine-like attacks in migraine patients without aura, on average 6 h after the start of the infusion (Schytz et al., 2009). It was further reported that PACAP-38 results in an increase in diameter of the superficial temporal arteries and a decrease in the mean blood flow velocity of the middle cerebral arteries (Schytz et al., 2009; Amin et al., 2012).

Connections of PACAP-38 and the trigeminovascular system

PACAP is a member of the VIP/secretin/glucagon neuropeptide superfamily and is considered to be a "brain-gut peptide", by virtue of its widespread expression and functions in the human organism. The peptide exists in two biologically active forms: PACAP-27 and (predominantly), PACAP-38. It is a pleiotropic peptide: it acts as a hypophysiotropic hormone, a neurotransmitter and a neuromodulator 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: $VPAC_1$, $VPAC_2$ and PAC_1 (Vaudry et al., 2009).

Since the 1990s, the central theme of migraine research has been the trigeminovascular theory (Moskowitz, 1992). The trigeminovascular system (TS) 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), VIP and PACAP, have essential roles in the activation mechanisms of the TS **(**Edvinsson, 2013). PACAP-38 is present in the TS, e.g. in the trigeminal ganglion (TRG) and caudal trigeminal nucleus (TNC) (Tajti et al., 2001).

PACAP-38 and light aversion (photophobia)

Markovics et al. investigated the pathophysiological changes induced in the TS by nitroglycerol (NTG) and PACAP in PACAP gene-deleted and wild-type mice. NTG is a well-known NO donor, which causes an immediate and a delayed migraine-like attack in migraine

patients without aura. After NTG administration, PACAP-deficient mice displayed a reduced level of light aversive behaviour (photophobia), and decreases in meningeal blood flow and c-fos expression in the TRG and TNC. Moreover PACAP-38 also elicited light aversion, similarly to that of NTG in wild-type 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.

PACAP-38 and TRG activation

Chemical (NTG) and electrical (square pulses) stimulation of the TRG in rats resulted in significantly elevated concentrations of PACAP-27 and -38 in the TNC. The plasma PACAP-38-like immunoreactivity (LI) was increased following electrical stimulation (Tuka et al., 2012). These data suggested that these peptides have marked effects of TS activation.

PACAP-38 and migraine phases (interictal and ictal)

In migraine patients in attack-free periods and during the headache phases, in migraine patients significantly lower PACAP-38 immunoreactivity was detected in the interictal plasma as compared with the healthy control group. In contrast, the PACAP-38 and CGRP concentrations were elevated in the ictal phase relative to the attack-free period in 21 migraineurs, while the PACAP-38-LI was higher in the overall population of migraineurs. A negative correlation was observed between the interictal PACAP-38 level and the disease duration. Interestingly, the plasma PACAP-38 release in the ictal period was significant only in menstruation cycle-independent migraineurs and those patients whose had no other chronic pain condition, such as low-back pain, lumbago or arthrosis (Tuka et al., 2013). This study revealed a clear association between the migraine phases and the changes in plasma PACAP-38 level.

The results obtained by Amin et al. (Amin et al., 2014) will have a considerable scientific impact. Their observations are milestones as concerns the role of PACAP and the pathomechanism of migraine. They elegantly demonstrate the difference between PACAP-38 and VIP-related migraine attacks, the extracranial vasodilation and the plasma concentrations of PACAP-38 in a head-to-head study. These findings open the way for further research to identify specific cause-related therapy.

References

Amin FM, Asghar MS, Guo S. Headache and prolonged dilatation of the middle menigeal artery by PACAP38 in healthy volunteers. Cephalalgia. 2012; 32:140-149.

Amin F, Hougaard A, Schytz H, Asghar M., Lundholm E, Parvaiz A, de Koning P., Andersen M, Larsson H, Fahrenkrug Jan, Olesen J, Ashina M. Investigation of the pathophysiological mechanisms of migraine attacks induced by PACAP38. Brain. 2014; (this issue).

Edvinsson L. Role of VIP/PACAP in primary headaches. Cephalalgia. 2013; 33(13): 1070-1072.

Markovics A, Kormos V, Gaszner B, Lashgarara A, Szőke É, Sándor K, Szabadfi K, Tuka B, Tajti J, Szolcsányi J, Pintér E, Hashimoto H, Kun J, Reglődi D, Helyes Zs. Pituitary adenylate cyclase-activating polypeptide plays a key role in nitroglycerol-induced trigeminovascular activation in mice. Neurobiology of Disease. 2012; 45:633-644.

Moskowitz MA. Trigeminovascular system. Cephalalgia. 1992; 12(3):127.

Schytz HW, Birk S, Wienecke T. PACAP38 induces migraine-like attacks in patients with migraine without aura. Brain. 2009; 132:16-25.

Tajti J, Uddman R, Edvinsson L. Neuropeptide messengers in the migraine generator region of the human brainstem. Cephalalgia. 2001; 21:96-101.

Tuka B, Helyes Zs, Markovics A, Bagoly T, Németh J, Márk L, Brubel R, Reglődi D., Párdutz Á, Szolcsányi J, Vécsei L, Tajti J. Peripheral and central alterations of pituitary adenylate cyclase activating polypeptide-like immunoreactivity in the rat in response to activation of the trigeminovascular system. Peptides. 2012; 33:307-316.

Tuka B, Helyes Zs, Markovics A, Bagoly T, Szolcsányi J, Szabó N, Tóth E, Kincses T, Vécsei L, Tajti J. Alterations in PACAP-38-like immunoreactivity in the plasma during ictal and interictal periods of migraine patients. Cephalalgia. 2013; 33:1085-1095.

Vaudry D, Falluel-Morel A, Bourgault S. Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. Pharmacol Rev. 2009; 61:283-357.

Vécsei L, Szalárdy L, Fülöp F, Toldi J. Kynurenines in the CNS: recent advances and new questions. Nat Rev Drug Discov. 2013; 12(1):64-82.

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