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Editorial comment

New insight in migraine pathogenesis: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) in the circulation after sumatriptan

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In this issue of the *Scandinavian Journal of Pain*, Jakob Møller Hansen and coworkers [1] report the effect of sumatriptan on circulating levels of two neuropeptides, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide-38 (PACAP-38) to provide new insights into migraine pathogenesis.

1. Trigeminovascular system in migraine

Dysfunction of the trigeminovascular system is one of many factors that have been considered in the pathogenesis of migraine [2]. It has long been known that the headache phase of migraine, at least in part, is associated with release of vasoactive substances and neuropeptides [3]. The role of several neuropeptides (e.g. substance P, calcitonin gene-related peptide (CGRP) and VIP) and a possible impact of these peptides on vascular and neuronal mechanisms associated with migraine have already been investigated [4,5]. Neuropeptides can cause dural neurogenic vasodilatation, plasma protein extravasation and sensitization of nociceptors, which have been documented in animal studies [6,7]. In humans, elevated concentrations of neuropeptides such as CGRP, VIP, and neurokinin A (NKA) have been found in plasma samples during migraine attacks [4,8–10]. Hence, one strategy to abort migraine is to block the release of neuropeptides or their receptor activation. Abortive agents in acute migraine management exert a modulatory effect on the levels of circulating neuropeptides [11].

2. Triptans in migraine

Triptans are 5-hydroxytryptamine (5-$HT_{1B/D}$) receptor agonists which are effective in acute migraine [12,13]. The 5-HT_{1D} receptors are of particular interest because they are expressed by trigeminal primary afferent fibres innervating cranial vasculature. The 5-HT_{1D} receptor has been found in trigeminal (sensory), superior cervical (sympathetic) and the sphenopalatine (parasympathetic) ganglia where in the latter, it may play a role in cluster headaches [14]. A possible mechanism of action of 5-HT_{1D} receptor agonists to abort headaches has been suggested to be the normalization of neuropeptide levels [10]. However, it is not known whether VIP and PACAP-38 circulating levels are influenced by sumatriptan. In the present study [1], both intra and extra cerebral circulatory levels of VIP and PACAP-38 were investigated prior to and following subcutaneous administration of sumatriptan. Under these conditions, sumatriptan did not affect basal levels of VIP and PACAP-38. This is likely due to the fact that basal levels of these peptides reflect mostly non-neuronal (e.g. gastrointestinal) release. In addition, only healthy volunteers were tested in the present study and no attempt was made to activate the trigeminovascular system with a headache inducing agent such as a nitric oxide donator or CGRP. Given the fact that in migraine some alterations in trigeminovascular system function have been proposed, it is possible that the effects of sumatriptan on vasodilatory neuropeptide levels would only be seen under conditions where the trigeminovascular system is activated to release neuropeptides. This idea is bolstered by the finding in the present study that PACAP-38 levels in healthy individuals were unaffected by sumatriptan.

3. Experimental models of acute headache and PACAP-38 and VIP

Experimental models predictive of acute anti-migraine action are based on the vascular or neurogenic theories of migraine and these models apply either artificial vasodilatation or neuronal sensitization to test drugs. For instance, headache induced by a nitric oxide donator (nitroglycerin) responds to sumatriptan [15]. Further studies are warranted to determine if, in a human model of trigeminal sensitization (or pain) in healthy volunteers, circulatory levels of VIP and PACAP-38 would be altered following administration of sumatriptan and whether this would have an association with headache. As a prerequisite, a normal range of basal levels of VIP and PACAP-38 neuropeptides would be essential if these peptides are being considered as future potential biomarkers in migraine. However, one of the existing issues is the fact that there

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is a considerable difference in the reported basal levels of these peptides in healthy volunteers in various studies [1,16,17]. This is to some extent surprising as it has been shown that concentrations of PACAP-38 present in human plasma are relatively stable in healthy volunteers and are not significantly changed due to sex, age, dietary factors or hormonal cycle in females [18]. Whether the inconsistency in reported basal levels of PACAP-38 among the studies originates from differences in assay methodologies or other factors, resolution of this issue will be necessary before considering whether PACAP-38 might be a useful biomarker of headache.

The possible role of VIP and PACAP-38 in migraine has been tested previously [19–22]. Half lives of these two peptides are short (3.5 and 1.0 min for PACAP-38 and VIP respectively) when given by infusion and within 2 h after infusion, plasma concentration of both is returned to baseline [23]. In human experimental studies, PACAP-38 induced cephalic vasodilatation and headaches in healthy volunteers and migraine-like headache in patients with migraine without aura, whereas VIP only induced a short lasting and mild headache in healthy controls and no migraine attacks in patients with migraine without aura. These observations may highlight a more profound contribution of PACAP-38 in comparison with VIP. Using high resolution magnetic resonance angiography, a recent study has shown that infusion of PACAP-38 produces a profound and long-lasting dilatation of the middle meningeal artery (but not middle cerebral artery) associated with headache in healthy volunteers [23]. In this study, subcutaneous injection of sumatriptan could not only reverse dilatation of the middle meningeal artery, but also in parallel reversed the delayed provoked headache without any effect on the middle cerebral artery. It has been proposed that the outcome might be due to the selective effect of PACAP-38 on PAC1 receptor. PACAP-38 and VIP have no effect on NOS activity in the trigeminovascular system and this pathway seems unlikely to be involved in PACAP-38 evoked vasodilation or headache (poster in *54th American Headache Society Annual Meeting 2012*). In animal models of migraine [6], utilization of selective antagonists for VIP/PACAP receptors (VPAC1 and VPAC2) or PACAP-selective receptor, PAC1, could be beneficial in unrevealing potential mechanism [24].

As suggested by the authors of the present study [1], testing the role of VIP and PACAP-38 neuropeptides in a population of migraine patients would also be beneficial to reveal any possible effect of abortive therapy (e.g. sumatriptan) on VIP and PACAP-38 levels in parallel with head pain intensity changes. In fact, an association between migraine periods and endogenous alterations in PACAP-38 has been demonstrated recently, where plasma levels of this peptide were higher in the ictal phase relative to the attack-free periods [16]. The difference in the plasma levels between the two phases may indicate that PACAP-38 is involved in the development of migraine attacks. Whether PACAP-38 contributes to headache pain through its known vascular effects or by sensitization of the trigeminal sensory fibres needs further investigation. Readers are referred to both the original paper [16] and its accompanying editorial [25] for further information.

4. The conundrum of VIP and PACAP-38 in relation to headache is still interesting and important

Sumatriptan levels in the intra or extra cerebral circulation have not been measured in parallel with VIP and PACAP-38 in the present study, but mean arterial blood pressure and heart rate were monitored [1]. Based on the results, sumatriptan did induce a significant increase in blood pressure but did not change the heart rate. Although this suggests that the drug was exerting its expected pharmacological effects, it would be interesting to know how the concentration of sumatriptan was altered in relation to regional and systemic blood levels of the neuropeptides' in human experimental models of vascular headache. In addition, testing other abortive agents would be interesting.

The present study suggests that sumatriptan does not affect basal levels of VIP and PACAP-38 in healthy individuals, but does not allow a firm conclusion on the possible contribution of VIP and PACAP-38 to migraine pathogenesis or the mechanism of action of sumatriptan in relation to modulation of these neuropeptides during migraine attacks. Nevertheless, the study results generate additional interest in clarifying both the role of VIP/PACAP-38 and their receptors in migraine pain and in determining how abortive agents or selective receptor antagonists modify the effect of these neuropeptides. Future studies to clarify these issues would definitely improve our understanding of trigeminal pain mechanisms and could eventually lead to better management of trigeminal pain and headaches.

References

[1] Hansen JM, Fahrenkrug J, Petersen J, Wieneck T, Olsen KS, Ashina M. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) in the circulation after sumatriptan. Scan J Pain 2013;4:211–6.
[2] Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. Neurobiology of migraine. Neuroscience 2009;161:327–41.
[3] Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. Cephalalgia 1994;14:320–7.
[4] Messlinger K, Fischer MJ, Lennerz JK. Neuropeptide effects in the trigeminal system: pathophysiology and clinical relevance in migraine. Keio J Med 2011;60:82–9.
[5] Messlinger K, Lennerz JK, Eberhardt M, Fischer MJ. CGRP and NO in the trigeminal system: mechanisms and role in headache generation. Headache 2012;52:1411–27.
[6] Buzzi MG, Tassorelli C. Experimental models of migraine. Handb Clin Neurol 2010;97:109–23.
[7] Benemei S, De Cesaris F, Nicoletti P, Materazzi S, Nassini R, Geppetti P. Migraine models. Methods Mol Biol 2010;617:105–14.
[8] Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extra cerebral circulation of humans during migraine headache. Ann Neurol 1990;28:183–7.
[9] Sarchielli P, Alberti A, Codini M, Floridi A, Gallai V. Nitric oxide metabolites, prostaglandins and trigeminal vasoactive peptides in internal jugular vein blood during spontaneous migraine attacks. Cephalalgia 2000;20:907–18.
[10] Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 1993;33:48–56.
[11] Brandes JL, Buchanan TM, Welch KM. Acute treatment of migraine. Handb Clin Neurol 2010;97:323–36.
[12] Ahn AH, Basbaum AI. Where do triptans act in the treatment of migraine? Pain 2005;115:1–4.
[13] Cologno D, Mazzeo A, Lecce B, Mundi C, Petretta V, Casucci G, d'Onofrio F. Triptans: over the migraine. Neurol Sci 2012;33(Suppl 1):S193–8.
[14] Ivanusic JJ, Kwok MM, Ahn AH, ennings EA J. 5-HT(1D) receptor immunoreactivity in the sphenopalatine ganglion: implications for the efficacy of triptans in the treatment of autonomic signs associated with cluster headache. Headache 2011;51:392–402.
[15] Iversen HK, Olesen J. Headache induced by a nitric oxide donor (nitroglycerin) responds to sumatriptan. A human model for development of migraine drugs. Cephalalgia 1996;16:412–8.
[16] Tuka B, Helyes Z, Markovics A, Bagoly T, Szolcsányi J, Szabó N, Tóth E, Kincses ZT, Vécsei L, Tajti J. Alterations in PACAP-38-like immunoreactivity in the plasma during ictal and interictal periods of migraine patients. Cephalalgia 2013. April 18. [Epub ahead of print].
[17] Elefsiniotis IS, Ketikoglou I, Kafiri G, Pantazis KD, Moulakakis A, Mavrogiannis C. Plasma pituitary adenylate cyclase activating polypeptide (PACAP) levels in chronic hepatitis B patients under lamivudine treatment. Eur J Gastroenterol Hepatol 2003;15:1209–16.
[18] Borzsei R, Mark L, Tamas A, Bagoly T, Bay C, Csanaky K, Banki E, Kiss P, Vaczy A, Horvath G, Nemeth J, Szauer E, Helyes Z, Reglodi D. Presence of pituitary adenylate cyclase activating polypeptide-38 in human plasma and milk. Eur J Endocrinol 2009;160:561–5.
[19] Schytz HW, Birk S, Wienecke T, Kruuse C, Olesen J, Ashina M. PACAP38 induces migraine-like attacks in patients with migraine without aura. Brain 2009;132:16–25.
[20] Birk S, Sitarz JT, Petersen KA, Oturai PS, Kruuse C, Fahrenkrug J, Olesen J. The effect of intravenous PACAP38 on cerebral hemodynamics in healthy volunteers. Regul Pept 2007;140:185–91.
[21] Hansen JM, Sitarz J, Birk S, Rahmann AM, Oturai PS, Fahrenkrug J, Olesen J, Ashina M. Vasoactive intestinal polypeptide evokes only a minimal headache in healthy volunteers. Cephalalgia 2006;26:992–1003.

[22] Rahmann A, Wienecke T, Hansen JM, Fahrenkrug J, Olesen J, Ashina M. Vasoactive intestinal peptide causes marked cephalic vasodilation, but does not induce migraine. Cephalalgia 2008;28:226–36.
[23] Amin FM, Asghar MS, Guo S, Hougaard A, Hansen AE, Schytz HW, van der Geest RJ, de Koning PJ, Larsson HB, Olesen J, Ashina M. Headache and prolonged dilatation of the middle meningeal artery by PACAP38 in healthy volunteers. Cephalalgia 2012;32:140–9.
[24] Bergerot A, Holland PR, Akerman S, Bartsch T, Ahn AH, MaassenVanDenBrink A, Reuter U, Tassorelli C, Schoenen J, Mitsikostas DD, van den Maagdenberg AM, Goadsby PJ. Animal models of migraine: looking at the component parts of a complex disorder. Eur J Neurosci 2006;24:1517–34.
[25] Edvinsson L. Role of VIP/PACAP in primary headaches. Cephalalgia 2013. April 10. [Epub ahead of print].