BJP British Journal of Pharmacology

DOI:10.1111/bph.12772
www.brjpharmacol.org

COMMENTARY

PACAP and its receptors in migraine pathophysiology: Commentary on Walker *et al.*, Br J Pharmacol 171: 1521–1533

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Keywords
PACAP; PACAP receptors; trigeminal ganglion; migraine

Received
18 January 2014
Revised
25 April 2014
Accepted
30 April 2014

LINKED ARTICLE

This article is a Commentary on Walker CS, Sundrum T and Hay DL (2014). PACAP receptor pharmacology and agonist bias: analysis in primary neurons and glia from the trigeminal ganglia and transfected cells. Br J Pharmacol 171: 1521–1553. doi: 10.1111/bph.12541

Abbreviations

BBB, blood–brain barrier; CGRP, calcitonin gene-related peptide; PACAP, pituitary adenylate cyclase-activating peptide; VIP, vasoactive intestinal peptide

This is a Commentary on an article in BJP by Walker, Sundrum & Hay, Br J Pharmacol 2014; 171: 1521–1533. Walker *et al.* (2014) examined the action of pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), PACAP-27 and vasoactive intestinal peptide (VIP) on primary cultures of trigeminal ganglia neurons and glial cells derived from 3- to 5-day-old rat pups. They showed PACAP-responsive receptors that resemble transfected PAC_{1B} receptors. A complex PACAP receptor pharmacology was uncovered that should facilitate understanding of the role that PACAP receptors have in clinical conditions, particularly migraine headaches.

PACAP belongs to the VIP-glucagon growth hormone-releasing factor-secretin superfamily of signalling peptides (Vaudry *et al.*, 2000) and this peptide is encoded by the *ADCYAP1* gene, resulting in a pro-peptide of 175 amino acids. Following truncation, PACAP is expressed in one of the two forms containing either 27 or 38 amino acids, PACAP-27 and PACAP-38 respectively. PACAP-38 is more prevalent, representing about 90% of the PACAP forms in mammalian tissues (Bourgault *et al.*, 2008). PACAP is expressed throughout the CNS, as well as in peripheral organs and glands (Fahrenkrug and Hannibal, 2004). The peptide has been implicated in a wide range of biological functions but I will limit the present discussion to its relevance in migraine pathophysiology (Edvinsson and Uddman, 2005). A role for PACAP in migraine has been suggested by three observations: (i) PACAP levels are increased in the cranial circulation of the cat upon stimulation of the superior sagittal sinus (Zagami *et al.*, 1995); (ii) plasma levels of PACAP are increased during migraine attacks in humans (Tuka *et al.*, 2013); and (iii) infusion of PACAP in those known to have migraine results in migraine-like headache (Schytz *et al.*, 2009). The obvious, but unanswered, questions are; what are the sources of endogenous PACAP and how can systemic PACAP induce migraine? The peptide is a large molecule that does not pass the blood–brain barrier (BBB) (Erdling *et al.*, 2013), which suggests that the relevant targets are outside the BBB. Recently, it was observed that infusion of PACAP-38 resulted in marked dilatation of extracranial, but not intracranial, arteries. This response preceded the onset of migraine-like headache and was sensitive to triptan administration (Amin *et al.*, 2014).

Migraine is a complex disorder that is influenced by genetics and environmental factors. Evidence indicates that a

genuine migraine attack originates in the CNS. Brainstem regions, as well as the trigeminal and parasympathetic systems, are considered important for the expression of various symptoms in primary headache attacks (Akerman *et al.*, 2011). Cell bodies in the otic and sphenopalatine ganglia co-store VIP/PACAP and NOS, and a small population of cells also contain ChAT, the enzyme that synthesizes ACh (Edvinsson and Uddman, 2005). The trigeminal ganglion and trigeminal nucleus caudalis contain a subpopulation of neurons that store PACAP, but not VIP (Csati *et al.*, 2012a). Interestingly, sensory nerve fibres containing calcitonin gene-related peptide (CGRP), probably originating from the trigeminal ganglion, project to the cranial parasympathetic ganglia and there are CGRP receptors on satellite glial cells in the sphenopalatine ganglion (Csati *et al.*, 2012b). These findings provide morphological evidence for an interaction between the parasympathetic and sensory systems.

When released, PACAP may bind to three different GPCRs, which also can bind VIP as well. VIP, PACAP-38 and PACAP-27 all have equal affinity in binding to the VIP/PACAP receptors $VPAC_1$ and $VPAC_2$. The third receptor, PAC_1, has high affinity for both forms of PACAP, but has 100- to 1000-fold lower affinity for VIP (Dickson and Finlayson, 2009; receptor nomenclature follows Alexander *et al.*, 2013). The principal effect of $VPAC_1$/$VPAC_2$ or PAC_1 receptor stimulation is an increase in cAMP through AC activation. Activation of other second messenger systems, including PLC and PLD, has been demonstrated and may occur along with AC activation. Clinical experiments have shown that PACAP, but not VIP, elicits a migraine-like headache, suggesting the PAC_1 receptor as a putative anti-migraine target. Systemic administration of nitroglycerol or PACAP-38 produced photophobia and meningeal vasodilatation in wild-type, but in PACAP-knockout, mice (Markovics *et al.*, 2012). Those effects and an increased activation 4 h later in the trigeminal ganglion and in the trigeminal nucleus caudalis were attributed to stimulation of the peripheral terminals of PACAP-ergic trigeminal sensory nerves in the meningeal region in the wild-type, but not in the PACAP-knockout, mice.

All three PACAP receptors have been found in the migraine-related sphenopalatine and trigeminal ganglia and on intracranial blood vessels (Knutsson and Edvinsson, 2002; Erdling *et al.*, 2013). In their study, Walker and colleagues quantified PACAP-related signalling in primary cell cultures from trigeminal ganglion (neurons and glia) and showed that PACAP, but not VIP, induced cAMP production (Walker *et al.*, 2014). The response was antagonized by PACAP(6–38), which is consistent with PAC_1 receptor pharmacology (Harmar *et al.*, 2012). Interestingly, PACAP-38, but not PACAP-27 or VIP, also caused ERK1/2 activation in cultured glial cells but not in neurons. The task of in-depth analysis of PAC_1 receptors and development of receptor antagonists has not been easy because as many as 10 splice variants, displaying different intracellular coupling, have been reported (Blechman and Levkowitz, 2013). The research on PACAP and its receptors is still in its infancy. A critical unanswered question is similar to that for CGRP receptor antagonists – do PAC_1 receptor antagonists have to pass through the BBB in order to be effective? Current research points to the promise of PAC_1 receptor antagonists for migraine treatment, which gives impetus to the development of such antagonists for clinical studies.

Acknowledgements

The study was supported by the Swedish Research Council (Grant No. 5958), the Heart-Lund Foundation and a regional ALF grant.

Conflict of interest

The author declares no competing interests.

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