Peripheral projections of the trigeminovascular system as antimigraine target

Projeções periféricas do sistema trigeminovascular como alvo anti-enxaqueca

Alejandro Labastida-Ramírez[1]*
Antoinette Maassen Van Den Brink[1]

[1]Erasmus MC, Division of Vascular Medicine and Pharmacology - Rotterdam - Zuid Holland - Países Baixos.

Calcitonin gene-related peptide (CGRP) is a key neuropeptide, highly expressed in the central and peripheral trigeminovascular system, involved in craniofacial nociceptive modulation[1]. In migraine patients, CGRP infusion generates migraine-like headaches[2], and during spontaneous attacks this peptide is released in the extracerebral circulation[3]. The treatment of choice currently available for terminating migraine attacks are the triptans, 5-$HT_{1B/1D}$ receptor agonists, of which some also display affinity for the 5-HT_{1F} receptor[4]. These drugs have the ability to decrease elevated CGRP levels by inhibiting further release from trigeminal perivascular afferents and consequently decrease nociceptive transmission from the periphery to the central nervous system[3]. However, due to their coronary vasoconstrictor potential, they are contraindicated in patients with cardiovascular diseases. This concern has resulted in the development of novel drugs devoid of vascular side-effects, such as monoclonal antibodies targeting CGRP or its receptor. Moreover, these drugs have shown that migraine attacks can be prevented exclusively via peripheral blockade of CGRP. This thesis focused on the pharmacological modulation of the peripheral CGRPergic projections of the trigeminovascular system.

We investigated in rodents the modulation of trigeminal CGRP release by lasmiditan, a highly selective 5-HT_{1F} receptor agonist (ditan), and comparatively studied sumatriptan. CGRP release was diminished similarly by both drugs in all the trigeminovascular system components (dura mater, trigeminal ganglion and trigeminal nucleus caudalis) ex vivo. In vivo, lasmiditan or higher doses of sumatriptan significantly attenuated endogenous CGRP release, but not exogenous CGRP effects. These findings suggest that selective 5HT1F receptor activation (by lasmiditan) is sufficient to presynaptically inhibit CGRP release in peripheral and central trigeminal nerve terminals, and, consequently, attenuate nociceptive transmission in the trigeminovascular system[5]. Since activation of 5HT1F receptors is not associated with coronary vasoconstriction, lasmiditan may represent a cardiovascular safety advantage over the vasoactive triptans.

In addition to the trigeminovascular CGRP release inhibition by lasmiditan, further (antimigraine) mechanisms of action described with previous 5HT1F receptor agonists include modulation of glutamate release from sensory fibers[6]. The co-localization of 5HT1F receptors and glutamate in the vestibular nuclei of rats, suggests that the 5HT1F receptor might also modulate glutamate release in CNS structures[7]. Moreover, since glutamate receptor antagonism prevents the initiation of cortical spreading depressions (CSDs), a key pathogenic event in migraine with aura, 5-HT_{1F} receptor agonism could attenuate CSDs via a central inhibition of glutamate. Therefore, after taking into account these additional mechanisms, future experiments are needed to determine whether lasmiditan can: (I) inhibit glutamatergic neurons in the central nervous system, or (II) attenuate CSDs initiation and its associated hyperaemia; and if all or none of these mechanisms are associated with its clinical antimigraine efficacy.

COMPETING INTERESTS

The authors declare that they have no competing interests.

***Correspondence**
Alejandro Labastida-Ramírez
E-mail: a.labastidaramirez@erasmusmc.nl

Received: March 6, 2020.
Accepted: March 11, 2020.

DOI: 10.5935/2178-7468.20200007

REFERENCES

1. Hendrikse ER, Bower RL, Hay DL and Walker CS. Molecular studies of CGRP and the CGRP family of peptides in the central nervous system. *Cephalalgia*. 2019; 39: 403-19.
2. Hansen JM, Hauge AW, Olesen J, et al. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura *Cephalalgia*. 2010; 30: 1179-86
3. Goadsby PJ and Edvinsson L. The trigeminovascular system and migraine: Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 1993; 33: 48–56.
4. Rubio-Beltrán E, Labastida-Ramirez A, Haanes KA et al. Characterization of binding, functional activity, and contractile responses of the selective 5-HT_{1F} receptor agonist lasmiditan. *Br J Pharmacol* 2019; 176: 4681-4695.
5. Labastida-Ramirez A, Rubio-Beltrán E, Haanes KA et al. Lasmiditan inhibits calcitonin gene-related peptide release in the rodent trigeminovascular system. *Pain* 2020;161(5):1092-1099, doi: 10.1097/j.pain.0000000000001801.
6. Ma QP. Co-localization of 5-$HT_{1B/1D/1F}$ receptor and glutamate in trigeminal ganglia in rats. *Neuroreport* 2001; 13: 1589-91
7. SK A, Khalmuratova R, Jeon SY et al. Colocalization of 5-HT_{1F} receptor and glutamate in neurons of the vestibular nuclei in rats. *Neuroreport* 2009; 20: 111-5