World Neurosurgery: X 20 (2023) 100223

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Letter to the Editor Regarding Biomarkers in aneurysmal subarachnoid hemorrhage: A short review

ARTICLE INFO

Keywords
Aneurysmal subarachnoid hemorrhage
Neuropeptide
Vasospasm and biomarker

The recent article authored by Batista et al[1] provides a concise overview of the primary biomarkers that hold significance in subarachnoid hemorrhage. However, in order to further enhance the comprehensive understanding of this condition, it is imperative to include an overview of two noteworthy biomarkers associated with vasospasm, which may occur in specific cases of aneurysmal subarachnoid hemorrhage (aSAH). These biomarkers are the calcitonin gene-related peptide (CGRP) and neuropeptide Y (NPY).

aSAH represents approximately 5–10% of all stroke cases worldwide and is associated with a mortality rate as high as 50%. Therefore, the identification and utilization of biomarkers, as outlined by Batista et al.[1], are instrumental in estimating both the mortality and prognosis of patients following aSAH.[2]

Vasospasm, characterized by the constriction of cerebral blood vessels resulting in reduced blood flow and ischemic injury, is a prominent and deleterious complication observed in approximately 30%–40% of cases following aSAH.[3] The pathophysiology of vasospasm involves complex interactions between various molecular mediators, among which NPY and CGRP play crucial roles in the regulation of vascular tone and contribute significantly to this phenomenon.[3,4]

NPY, a 36-amino acid peptide, is a key vasoactive peptide in the brain. It is predominantly stored in sympathetic perivascular fibers with a higher density surrounding the major arteries of the anterior part of the circle of Willis, as well as in free nerve endings within the dura. NPY is recognized for its potent vasoconstrictive properties, leading to sustained constriction of both intra- and extraparenchymal cerebral blood vessels.[4,5]

The vasoconstrictive effects of NPY are independent of the endothelium, indicating a direct action on smooth muscle cells. By promoting vasoconstriction, NPY contributes to the narrowing of blood vessels and the development of vasospasm. Additionally, NPY has been implicated in the induction of a pro-inflammatory environment and the promotion of edema, further exacerbating the pathophysiological processes associated with vasospasm. These effects of NPY can result in neuronal apoptosis and worsen the overall outcome of aSAH.[4,6]

On the other hand, CGRP, a 37-amino acid peptide, plays a pivotal role in mediating vasodilation in the microvasculature. Within the cerebral circulation, CGRP is released by sensory fibers originating from the trigeminal ganglion. It exists in two variants, αCGRP and βCGRP, differing solely in their amino acid count.[3] CGRP acts as a potent vasodilator by interacting with nitric oxide, engaging both endothelium-dependent and endothelium-independent pathways regulated by cyclic AMP.[7]

The primary mechanism by which CGRP exerts its vasodilatory effects is through its endothelium-dependent action. It promotes the release of nitric oxide, leading to the relaxation of smooth muscle cells and subsequent vasodilation. Notably, CGRP retains its vasodilatory properties even in the absence of endothelium, indicating a direct impact on smooth muscle.[3]

In the context of vasospasm following aSAH, an imbalance between the vasoconstrictive effects of NPY and the vasodilatory effects of CGRP has been observed. Studies, including the investigation conducted by Bründl et al.[5], suggest that the release of NPY is predominant during the early phase of aSAH, contributing to vasoconstriction and vasospasm. Simultaneously, the release of CGRP may be impaired, leading to a diminished vasodilatory response and further promoting the development of vasospasm.[8]

In conclusion, a comprehensive understanding of aSAH is greatly enhanced by considering the roles of biomarkers, specifically NPY and CGRP, in the development of vasospasm, a significant complication following aSAH. NPY contributes to vasoconstriction and the narrowing of blood vessels, while CGRP acts as a vasodilator.[6] The imbalance between these biomarkers during vasospasm leads to impaired vasodilation and promotes the development of this condition.[8] Understanding the involvement of NPY and CGRP in vasospasm provides valuable insights for better management and treatment strategies for patients with aSAH.

CRediT authorship contribution statement

Juan Armando Mejía: Conceptualization, Investigation, Visualization, Writing – review & editing. **Luis Garcia Rairan:** Conceptualization, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Luisa Figueredo:** Conceptualization. **Claudia Niño:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial

https://doi.org/10.1016/j.wnsx.2023.100223
Received 18 May 2023; Accepted 12 June 2023

interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Batista S, Bocanegra-Becerra JE, Claassen B, et al. Biomarkers in aneurysmal subarachnoid hemorrhage: a short review. *World Neurosurg X*. 2023;19, 100205. https://doi.org/10.1016/J.WNSX.2023.100205.
2. Rodríguez-Rodríguez A, Egea-Guerrero JJ, Ruiz De Azúa-López Z, Murillo-Cabezas F. Biomarkers of vasospasm development and outcome in aneurysmal subarachnoid hemorrhage. *J Neurol Sci*. 2014;341(1–2):119–127. https://doi.org/10.1016/J.JNS.2014.04.020.
3. Schebesch KM, Herbst A, Bele S, et al. Calcitonin-gene related peptide and cerebral vasospasm. *J Clin Neurosci*. 2013;20(4):584–586. https://doi.org/10.1016/J.JOCN.2012.07.006.
4. Schebesch KM, Brawanski A, Kagerbauer SM, et al. The possible role of neuropeptide Y after spontaneous subarachnoid hemorrhage. *Acta Neurochir*. 2011;153(8):1663–1668. https://doi.org/10.1007/S00701-011-1056-8.
5. Bründl E, Proescholdt M, Schödel P, et al. Excessive release of endogenous neuropeptide Y into cerebrospinal fluid after treatment of spontaneous subarachnoid haemorrhage and its possible impact on self-reported neuropsychological performance – results of a prospective clinical pilot study on good-grade patients. *Neurol Res*. 2018;40(12):1001–1013. https://doi.org/10.1080/01616412.2018.1508547. https://pubmed.ncbi.nlm.nih.gov/30213237/.
6. Sun W, Zhang Z, Feng X, Sui X, Miao Y. Serum neuropeptide Y: a potential prognostic marker of intracerebral hemorrhage. *Dis Markers*. 2021. https://doi.org/10.1155/2021/7957013, 2021.
7. Shah KA, White TG, Powell K, Woo HH, Narayan RK, Li C. Trigeminal nerve stimulation improves cerebral macrocirculation and microcirculation after subarachnoid hemorrhage: an exploratory study. *Neurosurgery*. 2022;90(4):485–494. https://doi.org/10.1227/NEU.0000000000001854.
8. Juul R, Hara H, Gisvold SE, et al. Alterations in perivascular dilatory neuropeptides (CGRP, SP, VIP) in the external jugular vein and in the cerebrospinal fluid following subarachnoid haemorrhage in man. *Acta Neurochir*. 1995;132(1–3):32–41. https://doi.org/10.1007/BF01404845.

Juan Armando Mejía
Department of Neurosurgery, Fundación Santa Fe, Bogotá, Colombia

Luis Garcia Rairan*
Faculty of Medicine, Universidad El Bosque, Bogotá, Colombia

Luisa Figueredo
Department of Neurosurgery, Mayo Clinic, Jacksonville, FL, USA

Claudia Niño
Department of Neuroanesthesia, Fundación Santa Fe, Bogotá, Colombia

* Corresponding author. Universidad El Bosque, Ak. 9 #131a-2, 110111, Bogotá, Colombia.
E-mail address: Lagarciar@unbosque.edu.co (L. Garcia Rairan).