medical sciences forum

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Abstract

Prodrugs Activated by Vascular Ectopeptidases: Proof of Concept †

François Marceau

Faculté de Médecine, Université Laval, Quebec City, QC G1V 4G2, Canada; francois.marceau@crchudequebec.ulaval.ca

† Presented at the 8th International Electronic Conference on Medicinal Chemistry, 1–30 November 2022; Available online: https://ecmc2022.sciforum.net/.

Abstract: Several vascular ectopeptidases reside in blood vessels and efficiently regulate peptide hormones. For instance, bradykinin (BK) is inactivated by angiotensin converting enzyme (ACE) or arginine-carboxypeptidases (Arg-CPs), and aminopeptidase N (APN) cleaves several substrates. Whether such peptidases may activate latent prodrugs of vasoactive agents has been tested. The contractility of the isolated human umbilical vein, radioligand binding assays, immunolocalization of peptidases, the internalization cycle of fluorescent receptors (microscopy), blood pressure measurements in anesthetized rats, and specific inhibitors of peptidases have been exploited to show the feasibility of prodrug activation by vascular peptidases. L-alanyl-histamine has virtually no affinity for the human histamine H1 receptor, but releases histamine and contracts the vein following cleavage by endogenous APN. Prolonged sequences of BK, such as BK-Arg, Arg^0-BK-Arg-Arg, and BK-His-Leu have little affinity for the BK B2 receptor, but are contractile in the umbilical vein and hypotensive in anesthetized rats via their action on this receptor type following cleavage of the C-terminal extensions by Arg-CPs for the first two peptides, as well as by ACE for the last two. Vascular ectopeptidases were shown to activate latent agonists of the H1 and B2 receptors, a concept that could be extended to various classes of drugs for a local action on the vasculature.

Keywords: prodrug; vascular ectopeptidases; angiotensin converting enzyme; arginine carboxypeptidases; aminopeptidase N; bradykinin; histamine

Citation: Marceau, F. Prodrugs Activated by Vascular Ectopeptidases: Proof of Concept. *Med. Sci. Forum* **2022**, *14*, 89. https://doi.org/10.3390/ECMC2022-12906

Academic Editor: Maria Emília Sousa

Published: 19 September 2022

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/ECMC2022-12906/s1.

Funding: This research was funded by the Canadian Institutes of Health Research, grant number MOP-93773, and by a Studentship Award from the Fonds de recherche du Québec-Santé to the trainee X. Charest-Morin.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of CHU de Québec-Université Laval (protocol 2012-323, approved in 2012 and annually renewed) for studies involving humans. The animal study protocol was approved by the Institutional Review Board of Université Laval (protocol code 2014036-1, approved in March 2014 and annually renewed).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: No new primary data are included in this presentation. References to previous publications are included in the presentation.

Conflicts of Interest: The author declares no conflict of interest.