

POSTER PRESENTATION

Open Access

A novel natriuretic peptide

Hanna Höfeld¹, Fritz Buck², Ralf Middendorff¹, Dieter Müller^{1*}

From 5th International Conference on cGMP: Generators, Effectors and Therapeutic Implications
Halle, Germany. 24-26 June 2011

Background

Receptors for the natriuretic peptides (NPs) ANP, BNP and CNP are highly expressed in lung, suggesting that this organ is an important physiological target for NP signalling. By stimulating vaso- and bronchodilation and inhibiting cell proliferation and fibrotic processes, NPs may have therapeutic potential in various lung diseases. Mechanisms responsible for the relatively short half-life (few min) of NPs and the control of their local concentrations include (i) receptor-mediated internalization by the so called clearance receptor (NPR-C) and (ii) degradation by a membrane metalloprotease, called neutral endopeptidase (NEP) or neprilysin (1). The velocity of peptide degradation/inactivation differs between ANP, BNP and CNP. Interestingly, cleavage of NPs by insulin-degrading enzyme (IDE) (2) may have a particular role in NP signalling by generating peptide fragments that are hyperactive in receptor stimulation (3).

The physiological significance of NEP was supported by several studies in rodents showing that NEP inhibition leads to increased NP concentrations and activity. Moreover, we found that NEP inhibition is necessary and sufficient for detection of GC-A and GC-B by affinity labelling experiments with radioactive ANP or CNP in mouse and rat lung membrane preparations. Analogous assays, however, failed to label these receptors in human lung membranes, suggesting potent NP-degrading activity of NEP inhibitor-insensitive proteases.

Methods and results

ANP degradation by lung membranes in either the absence or presence of NEP inhibitors was analyzed by thin-layer-chromatography and mass spectrometry (2). We found that NEP inhibition strongly reduces ANP degradation by rat and mouse but not human membranes. ANP-degrading activity in human lung

membranes under conditions of NEP inhibition was very potent and even detectable with 1 ng of membrane protein. Like ANP, CNP was rapidly hydrolyzed. In both peptides, initial cleavage occurred at the same position within the conserved peptide ring structure being essential for biological activity. A second cleavage each was localized to the amino-terminus (behind Arg-4 or Lys-4, respectively). The cleavage sites are unrelated to those by NEP and IDE and indicate trypsin-like enzyme activity. Unlike ANP and CNP, BNP is a poor substrate and shows a completely different and complex cleavage pattern after prolonged incubation. The NEP inhibitor-insensitive protease was also detectable, albeit at much lower levels, in membranes from human aorta and mesenteric arteries, but not at all in placenta. Studies with various protease inhibitors revealed that leupeptin exposure potently inhibits NP degradation by this activity.

Conclusion

A novel trypsin-like enzyme activity, but not NEP, is the major natriuretic peptide-degrading membrane protease in human lung. The accumulated expression of this enzyme in human pulmonary tissue favours potential therapeutic interventions in lung diseases. Leupeptin may act as a beneficial agent in this regard.

Author details

¹Institute of Anatomy and Cell Biology, University of Giessen, Germany.

²Institute of Clinical Chemistry, University of Hamburg, Germany.

Published: 1 August 2011

References

1. Potter LR, Abbey-Hosch S, Dickey DM: Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. *Endocrine Rev* 2006, **27**:47-72.
2. Müller D, Schulze C, Baumeister H, Buck F, Richter D: The rat insulin-degrading enzyme: cleavage pattern of the natriuretic peptide hormones ANP, BNP and CNP revealed by HPLC and mass spectrometry. *Biochemistry* 1992, **31**:11138-11143.

* Correspondence: hans-dieter.mueller@anatomie.med.uni-giessen.de

¹Institute of Anatomy and Cell Biology, University of Giessen, Germany

Full list of author information is available at the end of the article

3. Ralat LA, Guo Q, Ren M, Funke T, Dickey DM, Potter LR, Tang WJ: **Insulin-degrading enzyme modulates the natriuretic peptide-mediated signaling response.** *J Biol Chem* 2011, **286**:4670-4679.

doi:10.1186/1471-2210-11-S1-P50

Cite this article as: Höfeld *et al.*: A novel natriuretic peptide. *BMC Pharmacology* 2011 **11**(Suppl 1):P50.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

