BMC Pharmacology

Poster presentation

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Mutation of three amino acids in the disulfide-ring of a CNP based chimeric natriuretic peptide alters its vascular properties

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from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P8 doi:10.1186/1471-2210-9-S1-P8

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P8

Clinical background

C-type natriuretic peptide (CNP) is a 22-amino-acid peptide produced mainly in the endothelium with potent cardiac unloading and blood pressure lowering actions, but minimal renal actions. Based on our previous knowledge, we recently fused a 6 aa sequence from BNP to the C-terminus and a 5 aa sequence from ANP to the N-terminus of CNP. This novel hybrid peptide, CBA-NP, has cardiac unloading actions and mild hypotensive effects similar to CNP. Importantly however, the N and C terminus alterations resulted in potent renal excretory actions. Here we test the hypothesis that the 3 aa GSM_{15-17} in the disulfide-ring mediate the vascular and hypotensive actions of CBA-NP. We therefore mutated GSM_{15-17} to REA_{15-17}, which we named ABC-NP and compared its *in vivo* and *in vitro* actions to CBA-NP.

Methods

We determined the cardiorenal and humoral actions of intravenous bolus administration of CBA-NP (n = 5) and ABC-NP (n = 5) at 25 mg/kg in two separate groups of normal anesthetized dogs. We also assessed the cGMP response of both peptides in human aortic endothelial cells (HAEC), human cardiac fibroblast (HCF) and isolated canine glomeruli. * $p < 0.05$

Results

IV bolus administration of CBA-NP and ABC-NP resulted in diuresis* and natriuresis*. There was a significant decrease in mean arterial blood (MAP) pressure with CBA-NP* but no change with ABC-NP. In addition, the reduction in pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) was significantly greater with CBA-NP as compared to ABC-NP. cGMP generation in HAEC and HCF was minimal with ABC-NP and was significantly higher with CBA-NP*. In contrast, cGMP generation was similar in isolated glomeruli between the two peptides.

Conclusion

Our studies demonstrates that mutation of three amino acid (aa) residues within the CNP ring of CBA-NP from GSM_{15-17} to REA alters the vascular but not the renal excretory properties. Hence by this minimal mutation within the ring of CBA-NP, we have designed a renal specific peptide ABC-NP resulting in new sequence specific functional information which can be used to design organ specific therapeutic peptides with unique properties tailored for a specific disease state.