

Poster presentation

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Renal targeted protein therapeutics in experimental overt heart failure with renal dysfunction

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Clinical background

C-type natriuretic peptide (CNP) is a 22-amino-acid peptide produced mainly in the endothelium and is a ligand for a guanylyl cyclase-coupled receptor, the NPR-B receptor. Recent studies have revealed that in overt heart failure (HF), the predominant natriuretic peptide (NP) receptor in the kidney is the NPR-B receptor. CNP has a potent cardiac unloading action and reduces blood pressure but has minimal renal actions. Based on our previous knowledge, we altered the amino acid (aa) sequence in the ring structure of CNP and fused a 5 aa sequence from ANP to the N-terminus and a 6 aa sequence from BNP to the C-terminus of CNP. We hypothesized that this novel hybrid peptide ABC-NP would maintain CNP's inherent cardiac unloading characteristics plus gaining renal enhancing properties without hypotensive effects.

Methods

We determined the cardiorenal and humoral actions of intravenous infusion of ABC-NP at 2 pmol/kg/min, 10 pmol/kg/min and 100 pmol/kg/min in 7 dogs with rapid ventricular pacing induced overt HF with cardiorenal dysfunction (240 bpm for 10 days). * $p < 0.05$.

Results

IV infusion of ABC-NP enhanced glomerular filtration rate (GFR), from 31 ± 5 to 45 ± 7 , 51 ± 6 and 60 ± 7 ml/min*, induce natriuresis (from 3 ± 2 to 12 ± 8 , 17 ± 13 and 29 ± 19 μ Eq/min*) and diuresis (from 0.13 ± 0.03 to 0.4

± 0.1 , 0.6 ± 0.2 and 0.8 ± 0.3 ml/min*) with a modest reduction in pulmonary capillary wedge pressure (PCWP) (from 21 ± 1 to 19 ± 1 , 20 ± 1 and 21 ± 1 mmHg*). Importantly, mean arterial blood pressure was maintained. These actions were associated with suppression of plasma renin and increases in urinary cGMP* excretion.

Conclusion

We report for the first time that this novel peptide ABC-NP has potent natriuretic and GFR enhancing actions without hypotensive properties in an experimental model of overt CHF. This renal specific peptide may have potential therapeutic benefit in states of renal dysfunction with volume overload to enhance GFR and sodium excretion without the detrimental side effect of hypotension.