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Cardiorenal actions of a novel chimeric natriuretic peptide, CD-NP, as compared to C-type natriuretic peptide, in the normal dog

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Background

The novel chimeric natriuretic peptide, CD-NP, is a Mayo-designed cGMP-activating synthetic peptide that consists of the 22-amino-acid (AA) residues of C-type natriuretic peptide (CNP) and the 15-AA C-terminal extension of *Dendroaspis* natriuretic peptide (DNP) [1]. The rationale for the design of CD-NP was to transform CNP, which activates natriuretic peptide receptor-B (NPR-B) and is natriuretic, diuretic and less hypotensive than ANP and BNP which activate NPR-A into a CNP-like peptide with added renal actions. The goal of this investigation was to directly compare the cardiorenal profile of CD-NP to that of CNP.

Materials and methods

Normal anesthetized dogs were given CD-NP 50 ng/kg/min i.v. (n = 10) or an equimolar dose of CNP (29.3 ng/kg/min i.v., n = 7) for 75 min. Four 30-min clearances were performed at the following time points: pre-infusion (pre-I), at 30 and 60 min of I, and post-I. Blood and urine samples were collected for each clearance. Glomerular filtration rate was determined by inulin clearance. Comparisons were made within group *vs* pre-I (mean ± SEM, $P < 0.05^{*}$, $<0.01^{\dagger}$) and between groups ($P < 0.05^{\ddagger}$, $<0.01^{\S}$, <0.001) using repeated measures ANOVA.

Results

CD-NP significantly increased plasma cGMP (7 ± .4 to 25 ± $3^{\dagger}$ to 36 ± $3^{\dagger}$ to 23 ± $3^{\dagger}$ pmol/ml) and urinary cGMP excretion (978 ± 145 to 3170 ± $205^{\dagger\ddagger}$ to 5919 ± $616^{\dagger}$ to 3077 ± $298^{\dagger}$ pmol/min) *versus* CNP (7.8 ± .8 to 9.1 ± .3 to 10.1 ± $.6^{\dagger}$ to 8.1 ± .6 pmol/ml; 1099 ± 101 to 1193 ± 119 to 1301 ± 142 to 1003 ± 146 pmol/min, respectively). CD-NP significantly increased urinary sodium excretion (19 ± 4 to 168 ± $24^{\dagger\S}$ to 237 ± $26^{\dagger}$ to 96 ± $12^{\dagger}$ μeq/min) *versus* CNP (39 ± 14 to 68 ± 12 to 85 ± 31 to 81 ± 29 μeq/min). Urine flow (ml/min) was augmented by CD-NP (0.2 ± .06 to 1.3 ± $.2^{\dagger}$ to 1.8 ± $.3^{\dagger}$ to 0.8 ± $.2^{\dagger}$) and CNP (0.5 ± .1 to 1.0 ± .2 to 1.3 ± $.3^{*}$ to 1.0 ± .3). Glomerular filtration rate was enhanced by CD-NP (37 ± $2^{*\ddagger}$ to 48 ± $3^{\dagger}$ to 51 ± $3^{\dagger}$ to 53 ± $4^{\dagger}$ ml/min) and was preserved by CNP (55 ± 5 to 57 ± 6 to 52 ± 4 to 50 ± 6 ml/min). Pulmonary capillary wedge pressure was significantly reduced by CD-NP (5.7 ± .7 to 4.1 ± 1^{*} to 3.2 ± $.7^{\dagger\ddagger}$ to 4.3 ± .8 mmHg), but not by CNP (5.8 ± .7 to 5.7 ± .8 to 6.7 ± .7 to 7.4 ± $.9^{\dagger}$ mmHg). Right atrial pressure was significantly reduced by CD-NP (1.8 ± .4 to 1.1 ± $.4^{\dagger}$ to 0.9 ± $.5^{\dagger\S}$ to 1.3 ± .5 mmHg), but not by CNP (2.7 ± .3 to 2.6 ± .3 to 3.2 ± .3 to 3.9 ± $.4^{\dagger}$ mmHg). Neither CD-NP nor CNP induced systemic hypotension (mean arterial pressure 127 ± 4 to 124 ± 5 to 122 ± 6 to 126 ± 7 mmHg; 121 ± 5 to 126 ± 4 to 127 ± 5 to 126 ± 4 mmHg, respectively).

Conclusion

This study demonstrates the successful transformation of CNP to a CNP-like peptide, which is cGMP-activating, natriuretic, diuretic, GFR-enhancing, and cardiac unloading, and has minimal blood pressure lowering effects. This cardiorenal profile of CD-NP is highly attractive as a drug

for the treatment of acute decompensated heart failure, warranting further investigation.

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