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Modulating cGMP in heart failure by novel natriuretic peptides

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An emerging concept in cardiorenal therapeutics is the design and synthesis of chimeric drugs that are single-chemical entities that combine structural and biological components of different molecules resulting in novel agents possessing highly desirable properties. Such a strategy optimizes favorable actions of a least two different molecules and often reduces unwanted adverse effects.

We recently reported the design, synthesis and biological actions of a novel chimeric natriuretic peptide (NP) fusing the 22-amino acid (AA) sequence of mature C-type natriuretic peptide (CNP), a member of the NP family that is highly conserved among species, with the 15-AA C-terminus of Dendroaspis natriuretic peptide (DNP) that was isolated from the venom of the eastern green mamba snake (Dendroaspis angusticeps).

The rationale of the design of this novel chimeric NP was based upon our knowledge that CNP, principally an endothelial cell derived peptide, has favorable venorelaxing properties that would unload the heart in states of volume overload but when compared to atrial NP (ANP), B-type NP (BNP) or urodilatin (URO), which are marked arterial vasodilators, would be less hypotensive thus better preserving renal perfusion pressure. Such hemodynamic properties are a consequence of CNP activation of the NP receptor-B (NPR-B) that is highly expressed in veins as compared to arteries. In contrast, ANP and BNP which function via the NP receptor-A (NPR-A) principally vasorelax arteries where NPR-A is highly expressed. A therapeutic limitation of the use of CNP in volume overload states is that in contrast to ANP and BNP, CNP lacks renal actions limiting its utility in states of sodium and water retention or altered glomerular function.

The second principle in the design of CD-NP was based upon our understanding of DNP. Indeed, previous studies from our laboratory have demonstrated that DNP is potently natriuretic and diuretic but also markedly hypotensive. More recently, studies have established that DNP like ANP and BNP is a ligand for NPR-A. Further, Lisy et al have reported that the 15-AA C-terminus of DNP possessed mild natriuretic and diuretic actions, which provided the rationale for the hypothesis that the C-terminus of DNP in a chimeric design would provide CNP with the ability to activate NPR-A and transform CNP into a natriuretic and diuretic peptide lacking significant hypotensive actions. Indeed, in recent studies in cells overexpressing either NPR-A or NPR-B, CD-NP activated both NPR-B and NPR-A with predominate stimulation being NPR-B. Specifically, CD-NP was able to activate in cells expressing either NPR-A or NPR-B the generation of cyclic guanosine monophosphate (cGMP) that is the second messenger for both NP receptors.

Here we will review both preclinical development and the first clinical studies including first in humans and studies in human heart failure.