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STATE-OF-THE-ART REVIEW

Innovative Therapeutics

Designer Natriuretic Peptides

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SUMMARY

Natriuretic peptides (NPs) are essential for the maintenance of volume homeostasis, and can be of myocardial, renal, and endothelial origin. Advances in peptide engineering have enabled the design of innovative designer NPs that go beyond native peptides in efficacy, specificity, and resistance to enzymatic degradation. Therefore, designer NPs provide an unparalleled opportunity for the treatment of cardiovascular disease. In this review, we report the conceptual framework of peptide engineering of the NPs that resulted in designer peptides for cardiovascular disease. We specifically provide an update on those currently in clinical trials for heart failure and hypertension. (J Am Coll Cardiol Basic Trans Science 2016;1:557–67) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The development of new drugs for cardiovascular (CV) disease continues to rapidly expand in recognition of the growing burden of CV disease worldwide (1). The approval of a small molecule, Entresto (Novartis, East Hanover, New Jersey), for heart failure (HF) has provided momentum for drug discovery in CV and related fields (2). The identification of paracrine-acting peptides released from cardiac cell-based therapies, and the role of peptides in the beneficial actions of Entresto via inhibition of neprilysin (NEP), have renewed interest in peptide therapeutics for disease syndromes such as HF and hypertension (HTN) (3,4). As stated by Jay and Lee (5), peptide therapeutics may permit more targeted approaches through well-characterized receptors and molecular pathways, as well as avoiding the off-target actions associated with small molecules. Furthermore, peptides possess larger surface areas than small molecules, which may optimize receptor activation. However, a major limitation to peptide therapies is rapid degradation, because >600 molecularly different proteases exist in humans, which limit the bioavailability of peptides compared with small molecules (6).

Breakthrough technologies in peptide engineering have markedly accelerated peptide therapeutics in disease areas such as diabetes with novel glucagon-like peptide 1 receptor activators, in HIV with therapeutics that target novel molecular markers, and even more recently in CV disease with the use of peptides such as seralaxin, and as discussed in this review, designer natriuretic peptides (NPs) (7–9). Insights into peptide and receptor biology have led to peptide modifications that have resulted in innovative analogues with enhanced activity. Thus, state-of-the-art peptide engineering holds the promise to create a wide variety of truly innovative therapies for CV disease that may have a high impact on reducing the burden of this growing area of human disease.

We review the current clinical use and trials of native NPs such as nesiritide (B-type natriuretic peptide [BNP]) in the United States, carperitide (A-type natriuretic peptide [ANP]) in Japan, and the

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ABBREVIATIONS AND ACRONYMS

ANP = A-type natriuretic peptide

AS-BNP = alternatively spliced variant of BNP

BNP = B-type natriuretic peptide

BP = blood pressure

CD-NP = cenderitide

cGMP = cyclic guanosine monophosphate

CNP = C-type natriuretic peptide

CV = cardiovascular

DNP = D-type natriuretic peptide

FDA = Food and Drug Administration

GFR = glomerular filtration rate

HF = heart failure

HTN = hypertension

NEP = neprilysin

NP = natriuretic peptide

NPR = natriuretic peptide receptor

pGC = particulate guanylyl cyclase

RAAS = renin-angiotensin-aldosterone system

SQ = subcutaneous

URO = urodilatin

VNP = ventricular natriuretic peptide

ZD100 = MANP

recently completed international trial of ularitide (urodilatin [URO]). We focus most on the rapidly developing area of designer NPs that may go beyond the native NPs in the treatment of CV disease. We discuss innovative peptide modification either based on rational design or genomic medicine that may impart enhanced receptor activation and/or reduced enzymatic degradation. We provide insights into the latest generation of designer NPs now being tested in models of CV disease and in clinical trials that may lead to a new generation of peptide therapeutics.

NATRIURETIC PEPTIDES

Peptides are biomolecules that consist of amino acids monomers and peptide (acid) bonds. The amino acid composition of these biomolecules is variable, and is considered an important factor that determines unique chemical and physical properties. The number of bound amino acids dictates the length of the peptides: dipeptides are the shortest peptides (2 amino acids and 1 single peptide bond), whereas polypeptides are long, continuous peptide chains. In contrast to biologically complex proteins, peptides have a rather simple biological composition and generally consist of ≤50 amino acids.

The family of NPs is a group of polypeptides that plays a pivotal role in maintaining the fluid homeostasis of the body by regulating intravascular volume, vascular homeostasis, and arterial pressure (**Figure 1**) (10). Recently, a role for the NPs in metabolic homeostasis has also been advanced (11–13). The NP system is highly preserved across species, and currently, the following 6 different NPs have been identified: ANP, BNP, C-type (CNP), D-type (DNP), ventricular NP (VNP), and the renal peptide, URO (14). NPs function as ligands for a set of transmembrane NP receptors (NPRs): CNP, evolutionarily the oldest of the NPs, mainly binds to the extracellular domain of the particulate guanylyl cyclase B receptor (pGC-B, NPR-B), whereas all other NPs bind to the transmembrane pGC-A (NPR-A) receptor (15). pGC-A receptors are expressed in various tissues, including heart, kidney, brain, adrenals, adipocytes, and vasculature (both arteries and veins) (16). pGC-B receptors are expressed in kidney, brain and veins, but less so in arteries (17).

A third NPR, called NPR-C, or the clearance receptor (18), actively eliminates endogenous NPs from the circulation using hydrolysis (ranked from the greatest to the lowest degradation rate: VNP = ANP ≥ CNP > BNP = DNP). Studies also suggest a signaling role for NPR-C via modulation of cyclic adenosine monophosphate (19–21). Clearance of NPs is furthermore regulated by the enzyme NEP, which is widely expressed in endothelium and lung with the highest abundance in the kidney. CNP is the least resistant to NEP-mediated hydrolysis (ranked from greatest to lowest degradation rate: CNP > ANP > BNP > DNP) (3,10,15,16). The differences in local NPR expression, degradation and clearance rates, and NP-binding affinity cause all 6 NPs to have unique and NP-specific properties (15).

Importantly, binding of a NP to a NPR activates the membrane-bound pGC-A and pGC-B receptors, and induces a variety of autocrine, paracrine, and endocrine effects. Activated pGC receptors produce the second messenger cyclic guanosine monophosphate (cGMP) that in turn activates protein kinase G. cGMP can also be produced in a nitric oxide–dependent manner; its production is then regulated via activation of the soluble guanylyl cyclase pathway (22).

ANP and BNP are believed to be the most important in controlling body fluid and blood pressure homeostasis (23,24). ANP has renin-inhibiting properties, is a potent aldosterone inhibitor, and is an antagonist to the mineralocorticoid receptor. In addition, via alternative processing of the ANP precursor (pro-ANP) it also contributes to renal sodium and water handling via generation of URO (25–27). BNP has been identified as an NP highly relevant to HF, which is due to its natriuretic, renin-angiotensin-aldosterone system (RAAS) inhibitory, vasodilating, and lusitropic properties (28–30), as well as its robust performance as a HF diagnostic and prognostic biomarker (31–33). CNP is an autocrine and paracrine factor that currently has limited use as a therapeutic for HF, particularly because of its rapid enzymatic degradation and paucity of renal protective actions (29), although its potent antifibrotic actions provide a therapeutic opportunity (34). Moyes et al. (21) elegantly demonstrated a role for CNP in vascular homeostasis that may involve binding and activation of NPR-C (21). DNP is a unique NP that has only been isolated from the venom gland of the Green Mamba snake (35). Its function has not been entirely clarified. Currently, VNP expression has only been confirmed in the hearts of primitive ray-finned bony fish, in which it is responsible for the maintenance of fluid and salt homeostasis (17).

Overall, NPs possess a wide variety of properties that are of value in diagnosis, prognosis, and treatment of CV disease, especially HF and HTN. Despite current optimal therapies, the prognosis for HF remains poor,