JCI The Journal of Clinical Investigation

# Designer natriuretic peptides.

D G Gardner

*J Clin Invest.* 1993;92(4):1606-1607. https://doi.org/10.1172/JCI116744.

Research Article



# Editorial

The natriuretic peptides continue to amaze researchers in the field with their diversity of biological activity, ranging from reduction of blood pressure through regulation of renal tubular sodium handling to modulation of neuronal activity in the central nervous system (1). The article by Wei et al. (2) in the present issue of the *Journal* would suggest that even now we do not completely understand, nor have we fully exploited, all of the biological properties that these peptides have at their disposal.

The natriuretic peptide family consists of the atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and the C-type natriuretic peptide (CNP). These peptides operate through association with specific high affinity receptors located on the surface of target cells (3). The type A receptor associates with ANP and to a lesser extent with BNP, while the type B receptor recognizes CNP as its primary ligand. The type C receptor is believed to function predominantly in a clearance mode. It binds with relatively high affinity to each of the natriuretic peptides, as well as a number of structurally related homologues, but has yet to be linked to a specific physiological activity. The type A and B receptors share a common effector mechanism for regulating cellular activity. The intracellular component of each receptor contains a protein kinase–like domain near its amino terminus, which is believed to subserve a regulatory function, and a guanylate cyclase domain at its carboxy terminus. Ligand occupancy of the extracellular domain leads to activation of cyclase activity and accumulation of cellular cGMP, which is believed to signal most, if not all, effects of these peptides within the cell.

Although various members of the family share similar biological properties, there are clearly major differences within the group. ANP is the most natriuretic of the peptides, while CNP has only a modest effect on sodium handling in the kidney (4). BNP, in the systems where it has been tested, behaves like ANP, with equal or lower activity at comparable doses. CNP, on the other hand, is a very potent venodilator, while ANP is largely ineffective in this regard (5). Since the signaling mechanism would appear to be similar, if not identical, for these different ligands, the specificity of their individual biological response profiles appears to lie not at the level of signal transduction (i.e., different second messenger pathways) but, rather, with the distribution of their respective receptors in target tissues. The kidney is relatively deficient in CNP-sensitive type B receptors, which likely explains the limited natriuretic activity of this peptide (6). The dichotomy in sensitivity to ANP vs. CNP in the venous strips suggests a similar unequal distribution of the type A vs. B receptors in this tissue, in this case favoring the latter. This, obviously, is amenable to direct experimental testing.

Another important difference among the various peptides lies in their tissue distribution within the organism. ANP and, to a lesser extent, BNP are produced primarily within myocardial cells and secreted into the circulation, where they are carried to distant target tissues to act in true hormonal fashion. CNP, on the other hand, has not been found at high levels in the circulation (4). It has, however, been found at easily detectable concentrations in selected tissues such as vascular endothelium, brain, kidney, intestine, and heart. This suggests that CNP in these locations may function as a local autocrine or paracrine regulator of activity in neighboring cells with physiological implications that are quite distinct from those attendant to the hormonal peptides alluded to above. Such autocrine or paracrine regulation would, for example, be much more efficient in responding to local signals such as mechanical stress or regional ischemia and effecting changes that are confined to a specific vascular bed. Taken together, this diversity of peptide and peptide receptor expression increases the flexibility of the natriuretic peptide system substantially and, very likely, in a fashion that more directly addresses the needs of the organism.

These data collectively provide the substrate for the main theme of the Wei study (2), namely their attempt to bring together selected properties of the different natriuretic peptides by creating synthetic peptide hybrids that include structural features of each. Circulating ANP is a 28–amino acid peptide that requires an internal disulfide bridge, as well as five amino acids that extend carboxy terminal to the bridge, for full activity. The amino terminus is more flexible, tolerating significant manipulation without serious reduction in peptide activity. CNP, which appears to circulate as a 22–amino acid peptide (4), bears significant amino acid homology to ANP (7) and, like ANP, it harbors an intramolecular disulfide bridge that is critical for its activity. However, unlike ANP, it lacks the carboxy-terminal extension beyond the ring. Wei et al. (2) have carried out a simple and logical experiment to test their hypothesis. They created a hybrid peptide linking the CNP molecule, including the disulfide bridge critical to all natriuretic peptide activity, to the highly conserved carboxy-terminal tail of ANP to produce a structure that they call vasonatrin. Because it contains the entire structure of CNP together with sequence that is known to be important for ANP activity, they predicted that vasonatrin would display activity intermediate between the two. This peptide was examined in both in vivo and in vitro test systems, and provided some interesting and, in some cases, unexpected findings. It proved to have natriuretic activity in the whole animal and venorelaxant activity in vitro that was intermediate in potency between that seen with either ANP or CNP, confirming the authors' hypothesis. From a quantitative standpoint, it was closer to the latter than the former, as one might predict based on the relative contribution of CNP to the amino acid sequence of the hybrid. More importantly, vasonatrin displayed activity as an arterial vasorelaxant, which was not observed with either of the two native peptides in this system. This totally unpredicted finding could be explained in a number of different ways. As pointed out by the authors, it could reflect slower turnover/degradation of vasonatrin relative to the native peptides, perhaps through differential affinity for the type C receptor. While this could be a factor in vivo, it is unlikely to account for the differences seen in the in vitro system, where very high levels of the individual peptides were used. It could also reflect serendipitous binding to an as

J. Clin. Invest.

0021-9738/93/10/1606/02 $2.00
Volume 92, October 1993, 1606–1607

yet unidentified receptor either within or outside the natriuretic peptide receptor family. Alternatively, it is possible that vasonatrin simply functions as a better ligand than its native counterpart for one of the receptor subtypes. Both the A and B receptors have been cloned and selectively expressed in heterologous cells, making this hypothesis amenable to direct testing.

The findings of Wei et al. (2) raise some intriguing possibilities in that they suggest potential for designing novel natriuretic peptides with specific cardiovascular and renal activity profiles (e.g., hypotensive and diuretic activity) based solely on selection and incorporation of isolated structural determinants into the hybrid molecules. They also suggest the opportunity for creating totally unique activity profiles that are not available in any of the native peptides. Such predesigned peptides could prove to be even more useful than their natural counterparts and, potentially, more amenable to targeting to selected tissues or organ systems. This modular design is particularly attractive from a therapeutic standpoint, where many of the vasoactive pharmaceuticals presently available optimize one function (e.g., afterload reduction) while sacrificing another (e.g., renal perfusion). Peptides like vasonatrin, if developed for clinical use, could come to represent important tools in the management of disorders of renal and cardiovascular function.

David G. Gardner
Department of Medicine and Metabolic Research Unit
University of California at San Francisco

## References

1. Brenner, B. M., B. J. Ballerman, M. E. Gunning, and M. L. Zeidel. 1990. Diverse biological actions of atrial natriuretic peptide. *Physiol. Rev.* 70:665–699.

2. Wei, C.-M., C. H. Kim, V. M. Miller, and J. C. Burnett. 1993. Vasonatrin peptide: A unique synthetic natriuretic and vasorelaxing peptide. *J. Clin. Invest.* 92:2048–2052.

3. Wong, S. K.-F., and D. L. Garbers. 1992. Receptor guanylyl cyclases. *J. Clin. Invest.* 90:299–305.

4. Clavell, A. L., A. J. Stingo, C.-M. Wei, D. M. Heublein, and J. C. Burnett Jr. 1993. C-type natriuretic peptide: a selective cardiovascular peptide. *Am. J. Physiol.* R290–R295.

5. Wei, C. M., L. L. Aarhus, V. M. Miller, and J. C. Burnett, Jr. 1993. The action of C-type natriuretic peptide in isolated canine arteries and veins. *Am. J. Physiol.* 264:H71–H73.

6. Brown J., and Z. Zuo. 1992. Renal receptors for atrial and C-type natriuretic peptides in the rat. *Am. J. Physiol.* 263:F89–F96.

7. Sudoh, T., N. Minamino, K. Kangawa, and H. Matsuo. 1990. C-type natriuretic peptide (CNP): A new member of natriuretic peptide family identified in porcine brain. *Biochem. Biophys. Res. Commun.* 168:863–870.