Atrial Peptides Modify the Effect of Marinobufagenin on Sodium Pumps
Implications for Blood Pressure Control

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The demonstration that acute volume expansion released a blood borne natriuretic substance initiated a search for “natriuretic hormone.” It was initially thought that this factor might regulate blood pressure by regulating blood volume as an endogenous diuretic. Subsequently, it was suggested that natriuretic hormone might be “endogenous digitalis” and cause natriuresis and vasoconstriction by inhibition of renal tubular and vascular Na,K ATPase (NKA), respectively. The possibility that this factor might explain the link between sodium intake and hypertension provided an attractive hypothesis, but progress was hampered by difficulties identifying its biochemical structure. “Endogenous digitalis-like factor” has now been identified as multiple cardiotonic steroids of 2 classes, a glycoside indistinguishable from plant derived ouabain and several bufadienolides that are similar if not identical to those found in toads. Most of the endogenous cardiotonic steroids that have been studied cause natriuresis; however, none are yet firmly established as natriuretic hormones. On the other hand, endogenous digitalis-like factors have been implicated as causative agents in some experimental and human forms of hypertension, including digitalis-like factors have been implicated as causative agents in some experimental and human forms of hypertension, including preeclampsia. The exact role of the different types of steroids in the various hypertensive states remains to be determined.

By contrast with endogenous digitalis, the natriuretic factors discovered in cardiac atrial granules were rapidly identified as a family of small peptides derived from a larger precursor. Although the precise role of these peptides in plasma volume and blood pressure regulation is still not entirely clear, they inhibit renal tubular sodium reabsorption in multiple sites, and mice in which the precursor gene has been knocked out develop a salt-sensitive type of hypertension. Some atrial peptides have been shown to inhibit renal-derived NKA; however, they are clearly distinguished physiologically from digitalis-like factors by their vasodilator and blood pressure-lowering effects.

The fact that plasma volume expansion increases the plasma concentration of 2 classes of natriuretic factors with opposite effects on vascular tone suggests the possibility of some modulating interactions between them. Although this has long been recognized, few previous studies have addressed this question directly. The article by Fedorova et al in this issue of Hypertension demonstrates that such an interaction may occur at the cellular level and begins to explore the mechanisms of this potentially important phenomenon. Using normal Sprague-Dawley rats, they studied the interaction between 2 atrial peptides, human ANP and prepro-ANP 104 to 123 and marinobufagenin (MBG), an endogenous bufadienolide that has been shown to inhibit the ouabain-resistant α-1 NKA found in rat renal and vascular tissue. They showed that both ANP analogs and MBG inhibited NKA catalytic activity of microsomes from renal medulla and that these effects were additive. By contrast, in aortic vascular rings and sarcolemma, atrial peptides had no effect or slightly increased NKA activity and completely prevented the inhibitory effect of MBG. To explore the signaling mechanisms that might be involved in this interaction, they focused on the phosphorylation status of the α-1 subunit of NKA.

In the renal medulla preparation, atrial peptides increased phosphorylation of α-1 NKA by a protein kinase G (PKG)–dependent pathway. Previous studies have shown that NKA catalytic activity is reduced by phosphorylation of the α-subunit by protein kinases A and C; however, the intracellular signaling pathway by which atrial peptide-activated PKG increases NKA phosphorylation is not established. Inhibition of renal NKA by atrial peptides may require dopamine cAMP–regulated phosphoprotein (DARPP-32), because it was blocked by knocking out the gene for this protein. DARPP-32 is a major substrate of PKG, and the pathway suggested by these gene knockout studies (Figure) could have caused the effects in renal tissue observed by Fedorova et al. It should be noted that this proposed PKG-dependent pathway causes a similar effect on NKA as activation of PKA and PKC, providing an opportunity for cross-talk between the different protein kinases.

In aortic rings and sarcolemma, by contrast, atrial peptides had no effect or slightly stimulated NKA catalytic activity and reduced phosphorylation of α-1 NKA, again by a PKG-dependent pathway. Interestingly, in the presence of atrial peptides, the effect of MBG on NKA catalytic activity was inhibited, an effect also mediated through a PKG-dependent mechanism. Because the effects on both phosphorylation and catalytic activity were PKG dependent, Fedorova et al postulated that the dephosphorylated form of vascular NKA might be less sensitive to inhibition by a specific α-1 inhibitor, MBG. Compatible with this interpretation, previous work by this group had shown that phosphorylation of the α-1 subunit of human vascular NKA by a PKC activator phorbol 12, 13-diaceate caused the opposite effect shown in the present experiments, that is, inhibition of catalytic activity and potentiation of vasoconstriction by MBG.
The difference in atrial peptide effects on NKA phosphorylation and catalytic activity between vascular and renal tissues could be because of tissue-specific differences in PKG isoforms, as the authors suggest. However, the pathway by which PKG activation in aortic tissue might decrease phosphorylation of NKA remains to be determined. It could, as suggested for renal tissue, involve an interaction between kinases and phosphatases (Figure), but one that increases rather than decreases dephosphorylated NKA.

The role of phosphatases in the regulation of NKA activity was observed in previous studies of another cGMP/PKG agonist, NO. The NO donor sodium nitroprusside stimulated Na pump current in rabbit ventricular myocytes by a mechanism dependent on cGMP/PKG, an effect inhibited by the protein phosphatase-1 and -2A inhibitor okadaic acid.9 In this regard, it would be interesting to determine the effect of okadaic acid on the phenomena observed in vascular tissue by Fedorova et al5 because the signaling pathway by which NO and atrial peptides alter NKA activity could be similar. This possibility is suggested by the similar pattern of tissue heterogeneity demonstrated by both atrial peptides and NO on NKA activity.10

That hormone-activated protein kinases have opposite effects on NKA activity in different tissues is a well-known phenomenon.10 The current studies, however, suggest a potentially important translation of a specific instance of this phenomenon to the regulation of blood pressure and renal function. Thus, synergism between MBG and atrial peptides in the kidney would obviously facilitate the excretion of a salt load and contribute to the fine regulation of renal sodium excretion. It might also provide an important mechanism to explain the natriuretic effect of atrial peptides in the setting of acute volume expansion that has not been considered previously. In the vasculature, antagonism of the vasoconstrictor effect of MBG by atrial peptides would provide an explanation for how volume expansion might lead to an increase in renal sodium excretion mediated by digitalis-like factors without causing a rise in blood pressure. Conversely, absence of this interaction might lead to a salt-sensitive form of hypertension, such as that found in the atrial peptide precursor knockout mice. Studies of the intracellular signaling pathways that confer organ specificity to the interaction between 2 physiologically important vasoactive classes could lead to a better understanding of the cellular mechanisms underlying various forms of hypertension, especially the salt-sensitive types.

Disclosures
None.

References
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