A Janus-Faced Role for Atrial Natriuretic Peptide in Myocardial Infarction?

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The biological significance of atrial natriuretic peptide (ANP) has been studied exhaustively from a physiological, pathological, pharmacological, and diagnostic standpoint. This member of the natriuretic peptide family exerts a profile of complementary effects in the cardiovascular system, including natriuretic, diuretic, vasodilator, anti–renin–angiotensin–aldosterone system, antihypertrophic, and lipolytic activity to regulate blood volume, blood pressure, and maintain cardiac structure and function.1 Despite this extensive cytoprotective profile, pharmacological manipulation of ANP and natriuretic peptides in a more general sense has not been exploited therapeutically to the extent that might have been anticipated. Recombinant ANP (Carpertide) and brain natriuretic peptide (BNP; Nesiritide) are licensed for treatment of acute heart failure in some territories without overwhelming evidence from large-scale, randomized controlled trials. Only recently, LCZ696, a novel molecule combining the angiotensin receptor blocker valsartan with sacubitril, an inhibitor of neutral endopeptidase (an enzyme that hydrolyses and inactivates natriuretic peptides and many other vasoactive mediators), was shown to produce an approximate 20% reduction in cardiovascular death and hospitalization compared with enalapril in patients with heart failure and is now licensed for this disorder2 (LCZ696 produced an increase in urinary cGMP levels, inferring that it was increased natriuretic peptide biology that underpinned its therapeutic effect). Besides these limited examples, ANP and BNP have also been shown to reduce infarct size and improve left ventricular function after acute myocardial infarction (MI) in early phase trials.3 Could this represent a further indication in which harnessing natriuretic peptide bioactivity will be valuable therapeutically? In an intriguing and pertinent study published in this issue of Circulation Research, Chen et al4 report that PDE2 expression is upregulated in endothelial cells by hypoxia and tumor necrosis factor–α (TNF-α; with simultaneous downregulation of cGMP-dependent protein kinase-I) and results in attenuated cGMP formation in response to ANP, an effect restored by addition of the selective PDE2 inhibitor BAY 60-7550. Cross talk with the cAMP system is also demonstrated using a novel FRET sensor. Using this approach, ANP is shown to produce a rise in cellular (specifically submembrane) cAMP that is blocked in the presence of TNF-α via upregulation of PDE2; again, BAY 60-7550 is able to reverse this phenotype. To substantiate these findings, intravital microscopic analysis of dextran leak from the cremaster circulation revealed that the increase in permeability in response to a threshold dose of TNF-α is significantly enhanced by ANP (and BNP), indicating cGMP/cAMP cross talk, an effect lost in endothelial GC-A knockout or mice treated with BAY 60-7550; extravasation of leukocytes followed an essentially identical pattern. Collectively, these observations demonstrate that release of ANP after MI can facilitate a GC-A/cGMP/PDE2/cAMP signaling cascade that promotes endothelial permeability, facilitates neutrophil recruitment, and aggravates injury.

These new findings add further complexity to the pathological roles of ANP in the cardiovascular system and particularly those related to MI. GC-A activation has traditionally been associated with an endothelial barrier protective function; certainly, from a pharmacological perspective, molecules that potentiate the biological activity of natriuretic peptides, such as neutral endopeptidase inhibitors, promote endothelial barrier integrity and prevent leukocyte recruitment to extravascular sites of injury and inflammation.6 In the present study,4 the hyperpermeability induced by ANP is ultimately elicited via breakdown of cAMP (which is primarily thought to be protective in terms of endothelial permeability and barrier

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function). Cross talk between the cGMP and cAMP systems is determined ostensibly by the activity of 2 cGMP-regulated cAMP-hydrolyzing phosphodiesterases; PDE2 contains a GAF-B domain at its N terminus that binds cGMP to allosterically upregulate activity, whereas for PDE3, cGMP is a high-affinity inhibitor at the substrate-binding site because of its low hydrolytic \( V_{\text{max}} \) (versus cAMP). Previous studies have intimiated that inhibition of PDE3 and reduced permeability tend to occur at lower cGMP concentrations, whereas ANP-facilitated cAMP hydrolysis and increases in permeability predominate at higher cGMP concentrations. This has important implications for MI because hypoxia and TNF-\( \alpha \) both promote PDE2 expression, and the pathological release of ANP or BNP in this setting must be commensurate with sufficient GC-A stimulation to promote activation of PDE2. However, endothelial-specific deletion of GC-A per se increases intra-vascular volume, suggesting that even under physiological conditions, ANP/GC-A/cGMP primarily couples with PDE2 rather than PDE3, at least in the endothelium. Yet, the picture is more complicated; in the lung, pharmacological administration of ANP protects against edema, and ANP knockout mice exhibit augmented lipopolysaccharide-induced injury. In addition, various agents that promote endothelial permeability seem to differentially affect the expression of PDE2 versus PDE3. For example, in the study by Chen et al., TNF-\( \alpha \) increased PDE2 expression, thereby favoring enhanced cAMP (and cGMP) breakdown in the face of GC-A activation; TNF-\( \alpha \) also concomitantly reduces cGMP-dependent protein kinase-1 and PDE3 expression to tip the balance even further. However, other mediators that increase endothelial permeability, such as thrombin, can activate PDE3\(^{10}\); in this scenario, the net result on permeability and leukocyte flux might be different. These disparate outcomes almost certainly illustrate a shift between the interaction of cGMP with PDE2 or PDE3 in organ-specific environments.

The spatial and temporal differences in cyclic nucleotide dynamics demonstrate the need to more fully understand the phenomenon of compartmentalized signaling before it will be possible to elucidate why natriuretic peptides have the capacity to exert both positive and negative effects on endothelial permeability and barrier function. Regardless, the interchange between PDE2 and PDE3 seems to proffer a flexible but finely tuned regulation of many functional consequences of cyclic nucleotide signaling and is now a relatively well-established phenomenon, particularly in the myocardium. For instance, in human atrial myocytes, lower concentrations of cGMP augment L-type Ca\(^{2+} \) channel activity through inhibition of PDE3, whereas higher concentrations of cGMP reduce such currents via PDE2 activation. Furthermore, the principal phosphodiesterase responsible for cGMP/cAMP breakdown can shift as a result of disease. This facet is highlighted by the observation that in healthy myocardium, cGMP generated by natriuretic peptides is almost exclusively regulated by PDE2, whereas in the failing heart, C-type natriuretic peptide at least can potentiate \( \beta \)-adrenoceptor-induced increases in force of contraction via cGMP-driven inhibition of PDE3.

Do the findings of Chen et al. imply that PDE2 inhibitors might be a useful adjunctive therapy for MI to optimize the beneficial effects of cardiac natriuretic peptide bioactivity? Perhaps, but the outcome is difficult to predict. In the pulmonary vasculature and right ventricle, PDE2 expression is downregulated in response to hypoxia, and enzyme inhibitors are effective in preventing and reversing the pulmonary hypertensive phenotype, lowering pulmonary pressure, limiting pulmonary vascular remodeling, and abrogating the right ventricle hypertrophy; in a similar context, blockade of PDE2 reduces the development of pulmonary edema after acute lung injury by accentuating a cAMP-driven reduction in permeability.

In sharp contrast, in the failing left ventricle, upregulation of PDE2 has been suggested to represent a protective mechanism, limiting detrimental cAMP-dependent \( \beta \)-adrenergic signaling (although some evidence suggests PDE2 regulates a local, antihypertrophic pool of cAMP). In actual fact, this right–left heart discrepancy might be explained, at least in part, by differential activity of cAMP and cross talk with cGMP systems because long-term potentiation of cAMP-dependent pathways (eg, \( \beta \)-agonists and PDE3 inhibitor) increases mortality in patients with LV dysfunction, whereas pharmacologically targeting cAMP signaling via the use of prostacyclin analogues offers a survival advantage in right heart failure (ie, PH patients). Thus, the organ-, tissue-, and cell-specific nature of the pathways involved suggests that if the injurious effect of GC-A/cGMP activation to increase endothelial permeability and leukocyte extravasation after MI is to be abrogated therapeutically, then specific targeting of endothelial PDE2 might be the ultimate, although challenging, goal. Furthermore, because the study by Chen et al. explored barrier function and leukocyte flux after MI primarily from the perspective of endothelial GC-A deletion, it would also be interesting to know if by using pharmacological GC-A stimulators (ie, agonists) in this context, it might be possible to optimize dose and time of administration to exploit the recognized salutary effects of ANP and BNP (eg, vasodilator, natriuretic/diuretic, sympatholytic, anti–renin–angiotensin–aldosterone system, antihypertrophic, and anti fibrictic) while minimizing or avoiding activation of PDE2.

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