The Many Possible Benefits of Natriuretic Peptides After Myocardial Infarction

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Natriuretic peptides (NPs) are well-known markers of the ventricular hypertrophic response, as documented in many studies performed either in animals or with cultured cardiomyocytes. In recent years, evidence has been mounting that NPs are in fact negative regulators of the hypertrophic response, as reviewed recently. In this light, NPs appear as endogenous cardioprotective agents of which expression increases in reaction to myocardial pathological conditions, but it is still unclear to which extent these agents may actually decrease mortality. In this issue of Hypertension, Nakanishi et al show that when myocardial infarction (MI) is induced by permanent occlusion of the coronary artery, mortality by heart failure is increased in knockout mice with inactivation of the gene coding for the NP receptor guanylyl cyclase-A (GC-A). Beyond these short-term effects, inactivation of GC-A also worsens post-MI chronic ventricular remodeling. Although the present study does not show whether these chronic remodeling processes also increase mortality at a later stage, the remodeling is accompanied by ventricular enlargement and decreased fractional shortening, both of which usually associate with poor prognosis. The importance of these data is enhanced by the fact that increasing numbers of studies are investigating the utility of recombinant NPs in humans. However, several questions remain concerning the particular modes of action of NPs.

One issue concerns the question of whether NPs work via peripheral mechanisms or via a direct action on the myocardium. Importantly, congestive heart failure is accompanied by volume expansion, and the present article shows that the natriuresis and diuresis are decreased in GC-A knockout animals during the 4 days that follow MI, thus possibly contributing to increased heart failure during that period. Diuretic drugs might have been used to test whether increased diuresis suffices to improve survival after MI. However, it is not certain whether such an experiment would have provided clear-cut answers because diuretic drugs also activate the renin-angiotensin system or trigger aldosterone secretion, both of which may have deleterious cardiac effects. Part of the action of NPs is to inhibit aldosterone secretion by acting directly at the level of the adrenals. Theoretically, these peptides may thus have a particularly beneficial profile because they induce diuresis while preventing (unlike diuretic drugs) aldosterone secretion, and recent studies suggest that aldosterone antagonists increase post-MI survival. However, the issue is further complicated by the recent concern that administration of nesiritide for decompensated heart failure may worsen renal function (compared with vasodilators or diuretics) or even increase the short-term risk of death. Therefore, more data are needed to understand the respective benefits of several compounds affecting diuresis during the post-MI period as well as their mechanism of action. The results obtained by Nakanishi et al in double-knockout animals indicate that the effects of GC-A on early mortality are independent of the angiotensin II type 1a (AT1a) receptor.

Beyond diuresis, NPs may improve survival by acting directly on the myocardium because they have been shown to inhibit left ventricular hypertrophy by a direct action on cardiomyocytes. Although atrial NP (ANP) and brain NP (BNP) signal via the GC-A receptor, genetic inactivation of the gene encoding for the precursor of each peptide has different consequences on the hearts of these animals. Thus, whereas ANP knockout mice display cardiomyocyte hypertrophy, BNP knockout animals have no ventricular hypertrophy but display cardiac fibrosis in response to cardiac overload. This may be explained partially by paracrine actions of different types of NPs produced by different types of cells in the heart. Indeed, BNP produced by cardiac fibroblasts themselves inhibit the production of collagen synthesis by these cells. In knockout mice in which GC-A (the receptor to ANP and BNP) is lacking, hypertrophy and fibrosis have been reported. However, a recent study has shown that C-type NP (CNP) also reduces hypertrophy and fibrosis significantly during the post-MI period. The GC-B receptor (which is recognized by CNP) is believed to be abundant in cardiac cells other than cardiomyocytes (fibroblasts or endothelial cells) but not in cardiomyocytes themselves. Thus, the antihypertrophic and antifibrotic actions of NPs after MI may involve multiple cell types and multiple receptors.

One complicating factor in the interpretation of the experiments of Nakanishi et al is the fact that cardiac ventricular mass is increased in GC-A mice even before the induction of MI. Left ventricular hypertrophy is a powerful risk factor for cardiovascular disease. In patients with uncomplicated hypertension, the relationship between left ventricular mass and risk of cardiovascular disease is so powerful that it is continuous over a wide range of LV mass values, even those extending below what is often considered as the “upper normal” limit. In mice, genetic alterations that attenuate the hypertrophic response to pressure overload prevent cardiac hypertrophy.
dysfunction despite increased wall stress. Therefore, additional experiments are needed to differentiate whether the increased mortality of GC-A knockout animals after MI is attributable to a “generic” effect of the pre-existing hypertrophic conditions or to a specific mechanism of action of the GC-A signaling pathway.

If NPs are beneficial after MI, are they good at all times? Intriguingly, the same group had reported in a previous publication that infarct size after ischemia-reperfusion was significantly smaller in either GC-A knockout mice or in the hearts of wild-type mice treated with a GC-A antagonist, suggesting that GC-A may be deleterious in that setting. The difference between the previous and present studies may reflect the fact that Nakinishi et al performed permanent coronary occlusion, a maneuver that has consequences different from that of ischemia-reperfusion injury. However, recombinant human ANP has been reported to reduce infarct size after coronary occlusion/reperfusion in dogs. Likewise, administration of BNP has been reported to decrease infarct size in isolated rat hearts after ischemia-reperfusion, presumably via activation of mitochondrial K_{ATP} channels. Additional work is needed to determine whether differences between studies are attributable to the different animal models used or whether they reflect specific sets of circumstances in which NPs may be less beneficial.

The molecular pathways via which NPs may exert their cardioprotective effects are still incompletely understood. Nakinishi et al provide some information concerning the late effects of NPs on ventricular remodeling because they show (using double-knockout animals) that in mice lacking GC-A, the presence of AT1a receptors is necessary to observe increased myocardial fibrosis 4 weeks after MI. Others have shown that drugs that inhibit angiotensin-converting enzyme (which is necessary to produce angiotensin II) or antagonize the receptor to aldosterone (which lies downstream of angiotensin II) attenuate cardiac fibrosis and ventricular dysfunction after MI. As for NPs themselves, it remains to be determined whether the inactivation of AT1a prevents fibrosis by blocking actions of angiotensin II at the level of the myocardium or whether these effects involve peripheral actions of angiotensin II (such as secretion of aldosterone from the adrenals).

Beyond therapeutics, the actions of NPs may have implications for elucidating genetics factors in cardiovascular risk. Accordingly, a mutation of the GC-A receptor has been shown to be associated with risk for MI in a Japanese cohort. In rats, naturally occurring ANP hypomorphic alleles have been shown to be associated with increased left ventricular mass. Therefore, the data of Nakinishi et al may mimic a situation in humans in which cardiovascular risk is increased in individuals with decreased ANP-mediated signaling.

Altogether, there is increasing evidence that NPs are endogenous agents that activate pathways that perform important cardioprotective actions. Although the results of Nakinishi et al may further encourage clinical investigators into exploring the utility of synthetic NPs in the clinical setting, the recent concerns raised about potential harmful effects of recombinant NPs underline the importance of understanding better at which level, on which cells, and via which receptor NPs are acting. Such information may help in the design of future strategies to treat patients with impaired cardiac function. A recent report indicates that even small-molecule approaches may be used to harness the benefits of the NP-signaling pathway. Genetic studies centered on genes associated with the NP-signaling pathway may also show promise for identifying individuals with increased cardiovascular risk.

References


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