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Progressive decline in circulating CNP with aging is associated with progressive cardiac fibrosis and myocardial impairment

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Background

Cardiac aging is associated with altered myocardial structure and function that may contribute to the development of heart failure (HF), particularly in the elderly. C-type natriuretic peptide (CNP) is of endothelial cell origin and represents the most potent anti-fibrotic peptide of the natriuretic peptide (NP) family. CNP activates the NP receptor-B (NPR-B), which is found in high abundance in cardiac fibroblasts. Further, selective cardiac knockout of NPR-B contributes to exaggerated cardiomyocyte hypertrophy in response to pressure overload. In addition, infusion of CNP suppresses post-myocardial infarction (MI) induced cardiac fibrosis in a rodent model of MI. The impact of aging on circulating CNP and associated left ventricular (LV) structure and function are undefined.

Objective

We hypothesized that a decrease in endogenous circulating CNP occurs with aging is associated with an increase in cardiac fibrosis and altered LV function and structure.

Methods

Studies were performed in 2, 11 and 20 month old male Fischer rats (n = 8/group). Standard echocardiography was used to assess LV structure and function. Left ventricles were harvested for gross and histopathologic analysis. Plasma CNP and BNP were measured.

Results

Aging from 2 to 20 months in male Fischer rats (equivalent to human aging from childhood to the 6th decade of life) was associated with progressive reductions in plasma CNP. Specifically, there was a significant incremental decrease in plasma CNP in the 2 month old group (30 ± 3 pg/ml) to the 11 month old group (21 ± 1 pg/ml) to the 20 month old group (9 ± 1 pg/ml). Significant and progressive cardiac fibrosis was observed with aging (from 9% to 15% to 21%, $p < 0.001$) Importantly, LV interstitial fibrosis, determined by picrosirius red staining, was inversely correlated with plasma CNP levels. In contrast, plasma BNP was slightly but significantly increased from the 2 month old group to 20 month old group (21 ± 2 to 26 ± 1 pg/ml, $p < 0.05$). Finally, the decrease in plasma CNP, seen from the 2 month old group to the 20 month old group, was also associated with a significant reduction in LV weight to body weight ratio (2.24 ± 0.02 to 1.79 ± 0.03, $p < 0.001$) and ejection fraction (88 ± 1% to 80 ± 1%, $p < 0.001$) and increases in LV end-diastolic chamber diameter (6.61 ± 0.09 mm to 7.48 ± 0.09 mm, $p < 0.001$).

Conclusion

We report for the first time that aging is associated with a progressive decline in circulating CNP and a progressive increase in cardiac fibrosis and systolic dysfunction. Further studies are warranted to explore the hypothesis that a

mechanism of myocardial aging with altered LV structure and function may include a decrease in the bioavailability of the paracrine and autocrine cardiovascular hormone CNP.