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Role of natriuretic peptide receptor C signalling in obesity-induced heart failure with preserved ejection fraction with pulmonary hypertension

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To the Editor,

In a recent issue of the journal, Agrawal and colleagues[1] demonstrated that natriuretic peptide receptor C (NPRC) may contribute to right ventricular (RV) remodelling in obesity-induced pulmonary hypertension (PH)-heart failure with preserved ejection fraction (HFpEF) by increasing cardiomyocyte hypertrophy. The authors supported their findings by showing an association between RV hypertrophy and increased NPRC expression in vivo, and both an increase in cell size and activation of a hypertrophic gene program in vitro. The authors concluded that inhibiting NPRC signalling may thus represent a promising therapeutic target to prevent RV dysfunction in PH-HFpEF.

Although these findings make a valuable contribution to this field, one must be careful in jumping to any conclusions due to a very small sample size (five mice in each group for the PH-HFpEF experiments; three mice in each group for histologic analysis). The study may have been also underpowered to detect smaller early differences in pulmonary vascular remodelling. In addition, the authors did not, at least, discuss the rapidly growing and accumulating evidence suggesting a protective effect of NPRC in PH-HFpEF as opposed to a detrimental effect.

Miller and colleagues have elegantly showed that the development of PH in HFpEF may largely be determined by the presence and the severity of diastolic dysfunction,[2] which in turn has been shown to predict functional capacity and clinical worsening in PH.[3–5] Interestingly, alterations in NPRC signalling have been independently associated with the development of diastolic dysfunction in a random large cohort of people from Olmsted County (Minnesota, USA), suggesting the potential and crucial beneficial role of NPR-C signal transduction in the pathophysiology of PH-HFpEF.[6] Most importantly, the authors demonstrated that the development of diastolic dysfunction was independent of age, sex, BMI and arterial hypertension in the homozygotes for this NPR3 genotype with an odds ratio of 1.9 similar to that of arterial hypertension, a major risk factor for diastolic dysfunction.[4–6]

It is also possible that the observed disproportionate RV hypertrophy was due to an up-regulation of NPRC signalling in pulmonary vasculature, which in turn lowered RV systolic pressure and pulmonary vascular resistance. In fact, we recently demonstrated that a specific NPR-C agonist, the ring-deleted atrial natriuretic peptide analogue, cANF4-23 (cANF) may reduce the RV systolic pressure and the

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pulmonary artery systolic pressure as well as enhance cardiac performance, including left ventricular inotropy in an experimental model.[4,5,7] In addition, mice lacking NPRC exhibit right atrial dilation, hypertrophy of the RV free wall and trabeculae, tricuspid regurgitation as well as echocardiographic findings suggestive of RV pressure overload, including flattening and paradoxical bulging of the septum into the left ventricle during systole, which are all findings typically seen in humans with PAH.[4,5,8,9] Consistently, Doppler echocardiography assessment revealed a significantly higher RV systolic pressure compared with wild-type littermates.[4,5,8,9] These findings were also confirmed by resting right heart catheterization.[4,5,8,9]

Of critical importance, evidence also suggests that activation of NPR-C signalling pathway may have anti-proliferative effects.[8–10] Hailey and colleagues demonstrated that loss of NPR-C may exacerbate angiotensin II (Ang II)-mediated alterations in electrical and structural remodelling, whereas co-treatment with the NPR-C agonist cANF was protective.[11] In addition, Mackasey and colleagues showed that Ang II treatment in mice lacking NPRC (NPR-$C^{-/-}$) may exacerbate the progression of sinoatrial node (SAN) disease.[12] Specifically, NPR-$C^{-/-}$ mice treated with Ang II developed ventricular dilation with overt systolic heart failure (as opposed to compensated concentric hypertrophy in wild-type mice) and substantially more severe decline in SAN dysfunction.[12] On the other hand, co-treatment of wild-type mice with Ang II and a selective NPR-C agonist (cANF) was able to largely prevent development of SAN disease.[12]

In summary, based on the above evidence, NPR-C should be considered as a critical protective receptor in the heart.

Conflict of interest

Patent application on a related topic is under consideration: Method of treating pulmonary hypertension by administration of natriuretic peptide receptor C signalling pathway activators.

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