Letter by Cingolani et al Regarding Article, "Ventricular Phosphodiesterase-5 Expression Is Increased in Patients With Advanced Heart Failure and Contributes to Adverse Ventricular Remodeling After Myocardial Infarction in Mice"

To the Editor:

Pokreisz et al[1] recently published an interesting article in which they show increased cardiac left ventricular phosphodiesterase-5A (PDE5A) expression in patients with heart failure. They also generated a PDE5A transgenic mouse in which overexpression of this cGMP-selective phosphodiesterase worsened ventricular remodeling and function after myocardial infarction. Therefore, the obvious conclusion seems to be that inhibition of PDE5A might protect against postmyocardial infarction remodeling. Although the authors show cGMP to be related to these cardiac architectural changes, they raise new questions about the possible cGMP downstream signaling mechanisms involved. For the reasons outlined below, we believe a possible pathway that might explain the findings by Pokreisz et al is the one involving cGMP-protein kinase G (PKG)-Na^+/H^+ Exchanger (NHE-1) inhibition:

1. After coronary artery ligation, PDE5A inhibition by Sildenafil ameliorated postinfarction remodeling in rats.[2] This effect was evident without differences in infarct size between treated and untreated animals (such as in the article by Pokreisz et al) and was accompanied by an increase in PKG activity. In the same article, PDE5A inhibition by Sildenafil as well as by EMD360527/5 reduced NHE-1 activity whereas inhibition of PKG-1 activity by KT5823 restored NHE-1 normal function in Sildenafil-treated cardiac papillary muscles.[2]

2. Pokreisz et al, as well as others, reported that PDE5A localized mainly to the intercalated disks. NHE-1 also colocalizes to this site.[3,4]

3. It seems that neither inhibition nor overexpression of PDE5A influences cardiac function or remodeling under basal conditions. Interestingly, that also seems to be the case for the NHE-1. In another article published in Circulation,[5] inhibition of p90RSK, a kinase that phosphorylates and activates NHE-1, protected against ischemia/reperfusion and inhibited NHE-1 activity only after myocytes were exposed to an acidic load (as it usually occurs after myocardial infarction) but not under basal conditions. Inhibition of PDE5A also decreases NHE-1 activity only after cells are being challenged with an acidic load and not under basal conditions.[2]

4. Sildenafil has been shown to inhibit extracellular signal-regulated kinase (ERK) 1/2,[6] which phosphorylates p90RSK and activates NHE-1.[7]

In conclusion, we believe enough scientific evidence exists to consider NHE-1 as a possible downstream mediator in PDE5A inhibition-induced amelioration of ventricular remodeling, particularly in situations where the myocardium is exposed to acidic loading states, such as in the setting of acute myocardial infarction. Studies further exploring this intriguing pathway are warranted.

Disclosures

None.

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