New therapeutic targets for the treatment of heart failure

Cyclic guanosine monophosphate (cGMP) is a cyclic derivative of the guanosine triphosphate (GTP) nucleotide, whose generation is mediated by the enzyme guanylate cyclase and acts as a second messenger in different intracellular signaling transduction pathways. Specifically, cGMP participates in signal transduction coupled to the synthesis of natriuretic peptide and nitric oxide (NO), stimulating protein kinase G phosphorylation (PKG). The increase in cGMP synthesis or the inhibition of its degradation by phosphodiesterase type 5A (PDE5A) blunts left ventricular hypertrophy (LVH) and its consequences. This has given rise to different studies showing that PDE5A inhibitors, such as sildenafil, can protect the heart preventing NO-derived cGMP degradation. However, stimulation of cGMP production induces PDE upregulation, attenuating a possible beneficial effect. In addition, the signaling pathways participating in NO generation are altered, especially in the context of LVH, explaining the negligible positive results observed in the clinical setting with PDE5A inhibitors.

In the present study, Lee et al. demonstrate that PDE9A, another subtype of PDE, can be expressed in the mammalian heart, including humans, and that this enzyme is upregulated in LVH and heart failure. Furthermore, the group led by David Kass suggests that PDE9A might be a possible alternative therapeutic target, as it specifically regulates natriuretic peptide signaling coupled to cGMP, independently of NO. They show that specific PDE9A inhibition decreases the development of LVH in mice with pressure overload produced by aortic constriction, through a natriuretic peptide-coupled pathway independent of NO. Moreover, in this model of pressure overload, PDE9A KO mice attenuated the fall of ejection fraction and reduced interstitial fibrosis, without left ventricular dilatation.

The administration of PDE9A inhibitors seems to be well tolerated in humans and its use is investigated in neurocognitive disease clinical trials [https://clinicaltrials.gov/ct2/show/NCT00930059](https://clinicaltrials.gov/ct2/show/NCT00930059). Thus, the results of Lee et al. suggest that these inhibitors may also be applied in heart disease.

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