Response to Letter Regarding Article, “Histone Deacetylation Inhibition in Pulmonary Hypertension: Therapeutic Potential of Valproic Acid and Suberoylanilide Hydroxamic Acid”

In their letter, Bogaard et al appreciate that HDAC inhibitors “may mitigate pulmonary vascular remodeling through effects on lung endothelial cells or vascular smooth muscle cells” but are concerned about the possibility that “HDAC inhibitors threaten the heart’s adaptive response to pressure overload.” These concerns, which were addressed in our articles, arise from their own study using trichostatin A, a broad-spectrum HDAC inhibitor, and valproic acid, which is not a broad-spectrum HDAC inhibitor, in a rat pulmonary artery banding model. In their study, trichostatin A (but not valproic acid) worsened right ventricular function and was associated with exaggerated right ventricular fibrosis and capillary rarefaction. Although these observations do indeed raise questions, we emphasize that this single report does not seem to be representative of the many reports demonstrating the beneficial effects of HDAC inhibitors in the stressed or failing heart.

Furthermore, it would suggest that rather than rejecting a promising class of drugs a priori, we should be asking what class of HDAC inhibitors should be employed in the context of pulmonary hypertension and what are the relevant biological pathways that should be selectively targeted.

The fortuitous discovery of an antihypertrophic action of HDAC inhibitors in cardiomyocytes nearly 10 years ago suggested a novel application for these compounds. Subsequent in vivo studies, focusing primarily on the left ventricle, have demonstrated that broad-spectrum HDAC inhibitors can effectively halt and even reverse pathological cardiac hypertrophy from a variety of stimuli: genetic, pharmacological, and mechanical. The remarkable efficacy of HDAC inhibitors shown in heart failure models is likely attributable to the ability of HDACs to target multiple cell types (eg, myocytes, fibroblasts, and immune cells) and diverse pathological mechanisms (eg, myocyte hypertrophy, fibrosis, and inflammation). The impact of HDAC inhibitors on inflammation in heart failure models has recently received particular attention and could be one of the principal mechanisms for their efficacious effects. Nontranscriptional effects of HDAC inhibitors in the heart have also been described.

Our data demonstrate that increases in class I–specific HDACs may be important in right ventricular pathological remodeling because they are specifically increased in this chamber in the setting of pulmonary hypertension, and inhibition with selective class I HDAC–specific inhibitors leads to a reduction in pulmonary hypertension and protection of the right heart. We agree it will be very important to perform mechanistic, preclinical safety and efficacy studies with class-specific HDAC inhibitors to determine whether isoform-selective HDAC inhibition provides a more favorable therapeutic index than broad-spectrum HDAC inhibitors for the treatment of chronic, nononcological indications, such as heart failure in the setting of pulmonary hypertension. However, we continue to believe that the many and varied effects that HDAC inhibitors have to improve cell function in the setting of heart failure warrant additional investigation of the role(s) of HDACs in right ventricular remodeling, especially since maintenance of right ventricular function in patients with pulmonary hypertension confers the survival advantage.

Disclosures

None.

References


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_Circulation_. 2013;127:e540
doi: 10.1161/CIRCULATIONAHA.112.154757

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/14/e540

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