Response to Overexpression of 5-Hydroxytryptamine 2B Receptor Gene in Pulmonary Hypertension: Still a Long Way to Understand its Transcriptional Regulation

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease, which involves pulmonary vasoconstriction and cardiovascular remodeling. Our present study shows that treatment with rosiglitazone, the peroxisome proliferator-activated receptor γ (PPARγ) agonist is able to attenuate 5-hydroxytryptamine (5-HT)–induced vasoconstriction of pulmonary arteries from monocrotaline- or hypoxia-treated rats and decreases the expression of serotonin receptor 2B, suggesting a potential mechanism for the benefit of PPARγ ligands in PAH.1

We thank Dr Maroteaux2 for the interest of our publication. In his Letter to the Editor, he raises several critiques of our study. Although his concern with the specificity of the 5-HT2A agonist TCB-2 is justifiable, the present study indicates a significant role of 5-HT2B pathological changes in the function and structure of rat pulmonary arteries by demonstrating that the 5-HT2B receptor antagonist LY279265, but not the 5-HT2A receptor antagonist ketanserin, attenuates the rosiglitazone-induced inhibition of 5-HT-evoked pulmonary artery constriction. In addition, both in vivo and in vitro treatment with rosiglitazone does not affect the expression of 5-HT2A receptor.

Previous studies show that the binding of the 5-HT2B receptor is elevated in pulmonary vascular beds of PAH mice,3 and mice with targeted deletion of PPARγ in smooth muscle cells develop spontaneous PAH,4 indicating a possible functional link between PPARγ and 5-HT2B receptors. We therefore investigated such hypothesis and observed the inhibitory effect of rosiglitazone on the 5-HT2B receptor-mediated signaling pathway in pulmonary artery smooth muscle cells. The most recent study from Dr Maroteaux’s group shows that mice with restricted ablation of the 5-HT2B receptor in bone marrow confers a complete resistance to PAH, and these new results appear to suggest a critical role of this receptor subtype in bone marrow-derived cells in the pathogenesis of PAH. Although they are potentially relevant of new findings reported by Dr Maroteaux, other contributory mechanisms involving pulmonary artery smooth muscle cells cannot be readily excluded with regard to the potential mobilization of bone marrow-derived cells into pulmonary arteries, where they interact with smooth muscle cells.5,6 Nevertheless, we agree with Dr Maroteaux on his concern concerning whether the AP-1–mediated induction of the 5-HT2B receptor and the feed-forward mechanism exist in vivo and their relevance to human disease. Clearly, these questions remain important and warrant further investigation.

The pathogenesis of PAH has, so far, remained poorly understood, and it appears to be heterogeneous. Notably, no animal models are available at present to completely recapitulate the human PAH. We thank Dr Maroteaux for his critical comments and agree that caution must be taken when one attempts to extrapolate the results from animal studies to human PAH.

Disclosures

None.

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