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

To the Editor:

I have read with great interest the recent report by Liu concerning putative interactions between peroxisome proliferator-activated receptor (PPARγ) and 5-hydroxytryptamine 2B (5-HT2B) receptor in pulmonary arterial hypertension (PAH). Previous studies, including ours, demonstrated that 5-HT participates in PAH. A pathophysiologic role of 5-HT2B receptors was supported by the increased 5-HT2B receptor expression in rodent lungs of hypoxia- or monocrotaline-induced PAH and corroborated by the genetic or pharmacological inactivation of 5-HT2B receptors that prevented PAH development. Other evidence already showed that the PPARγ agonist rosiglitazone was beneficial in preventing PAH, and PAH developed spontaneously in mice with smooth muscle cell- or endothelial cell-specific deletion of PPARγ.

Previous studies showed that the rat fundus contraction was mediated via the 5-HT2B receptor subtype and reported potency (pEC50) of BW723C86 of 7.9. Watts et al. identified the 5-HT2B receptor in mediating the BW723C86-induced contraction of rat juxtaglomerular vein with a pEC50 of 6.1. In Figures 3 and 4, Liu claims that the BW723C86 (<6 on Figure 3) is closer to that for 5-HT2A receptors, questioning the implication of 5-HT2B receptors. The only reported site in rat is partially conserved in human, but not in mouse, sequence. Finally, chronic exposure to 5-HT2B receptor antagonists prevented PAH and plasma 5-HT increase, but not 5-HT2B receptor overexpression, excluding, at least in vivo, a feed-forward regulatory mechanism, as suggested by Liu.

To sum up, the relation between PPARγ and 5-HT2B receptors needs further research to determine if the Htr2b gene is a direct target of PPARγ action on the vascular contraction and remodeling in PAH. Full set of research is also needed to demonstrate a putative role for 5-HT in transcriptional regulation of Htr2b promoter.

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Disclosures

None.

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