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 Liu1 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 pathophysiological 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.2 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.3

Previous studies showed that the rat fundus contraction was mediated via the 5-HT2B receptor subtype and reported potency (pEC50) for BW723C86 of 7.9.4 Watts et al5 identified the 5-HT2A receptor in mediating the BW723C86-induced contraction of rat jugular 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 Ki value for (4-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (TCB-2) is at the 5-HT2A receptor, but the affinity at 5-HT2B or 5-HT2C receptors is not defined.

Our recent article6 showed that mice with restricted expression of 5-HT2B receptors on bone marrow cells developed hypoxia- or monocrotaline-induced increase in pulmonary pressure, 5-HT2B receptor expression, and vascular remodeling, whereas restricted elimination of 5-HT2B receptors on bone marrow cells conferred a complete resistance. This was indicative that activation of 5-HT2B receptors was required for the development of PAH7 on bone marrow lineage progenitors, but not on lung-resident cells. The use of resident pulmonary artery smooth muscle cells on Figures 5 and 6 of Liu’s article are therefore not relevant to the pathological cells that express 5-HT2B receptors in PAH lungs. Furthermore, the authors missed the presence of a 5′-noncoding exon in mouse, rat, and human HTR2B gene. In addition, using the transcription element search system (http://www.cbil.upenn.edu/cgi-bin/tess/tess), we found that the transcription factor activator protein-1 (AP-1)–binding sites identified in the 5′-flanking region of rat HTR2B by Liu are not evolutionarily conserved. As shown on Figure 1, a weak AP-1–binding consensus is found 5′ of the first exon in mice and rat, but not human, promoter. For the 3′ (intrinsic) site, a weak double AP-1 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,6 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 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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