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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 (PPAR γ) and 5-hydroxytryptamine 2B (5-HT_{2B}) receptor in pulmonary arterial hypertension (PAH). Previous studies, including ours, demonstrated that 5-HT participates in PAH. A pathophysiological role of 5-HT_{2B} receptors was supported by the increased 5-HT_{2B} receptor expression in rodent lungs of hypoxia- or monocrotaline-induced PAH and corroborated by the genetic or pharmacological inactivation of 5-HT_{2B} receptors that prevented PAH development.² Other evidence already showed that the PPAR γ agonist rosiglitazone was beneficial in preventing PAH, and PAH developed spontaneously in mice with smooth muscle cell- or endothelial cell-specific deletion of PPAR γ .³

Previous studies showed that the rat fundus contraction was mediated via the 5-HT_{2B} receptor subtype and reported potency (pEC50) for BW723C86 of 7.9.⁴ Watts et al⁵ identified the 5-HT_{2A} 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 vasoconstriction in rats with pulmonary hypertension is mediated by 5-HT_{2B} receptors, although the pEC50 value for the 5-HT_{2B} agonist BW723C86 (<6 on Figure 3) is closer to that for 5-HT_{2A} receptors, questioning the implication of 5-HT_{2B} receptors. The only reported Ki value for (4-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (TCB-2) is at the 5-HT_{2A} receptor, but the affinity at 5-HT_{2B} or 5-HT_{2C} receptors is not defined.

Our recent article⁶ showed that mice with restricted expression of 5-HT_{2B} receptors on bone marrow cells developed hypoxia- or monocrotaline-induced increase in pulmonary pressure, 5-HT_{2B} receptor expression, and vascular remodeling, whereas restricted elimination of 5-HT_{2B} receptors on bone marrow cells conferred a complete resistance. This was indicative that activation of 5-HT_{2B} receptors was required for

the development of PAH⁶ 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-HT_{2B} receptors in PAH lungs. Furthermore, the authors missed the presence of a 5'-noncoding exon in mouse, rat, and human *HTR_{2B}* 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 *HTR_{2B}* 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' (intronic) site, a weak double AP-1 site in rat is partially conserved in human, but not in mouse, sequence. Finally, chronic exposure to 5-HT_{2B} receptor antagonists prevented PAH and plasma 5-HT increase, but not 5-HT_{2B} receptor overexpression,⁶ excluding, at least in vivo, a feed-forward regulatory mechanism, as suggested by Liu.

To sum up, the relation between PPAR γ and 5-HT_{2B} receptors needs further research to determine if the *Htr_{2B}* is a direct target of PPAR γ 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 *Htr_{2B}* promoter.

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Disclosures

None.

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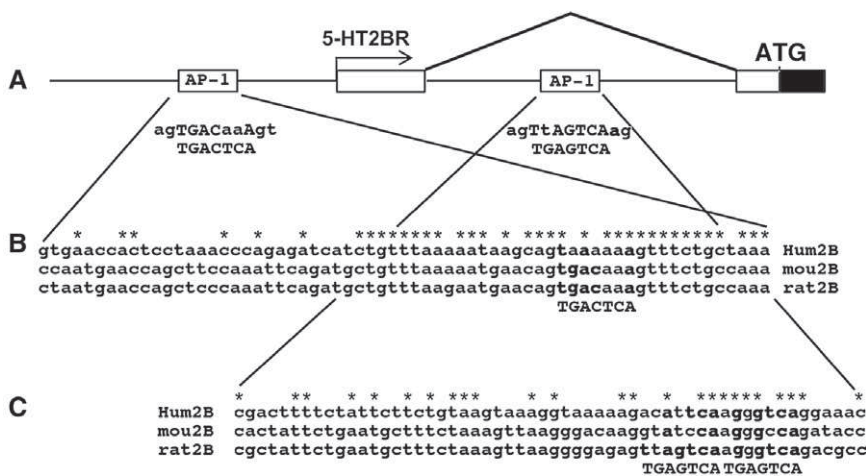


Figure. A, Promoter region of *Htr_{2B}* (white box, noncoding exons; black box, coding region). B, Putative 5' AP-1-binding site sequence. C, Putative 3' AP-1-binding site (in the first intron). DNA sequence alignments have been obtained using ClustalO program. Stars identify the conserved bases in human, mouse, and rat promoter sequences.

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