



HAL
open science

Overexpression of 5-hydroxytryptamine 2B receptor gene in pulmonary hypertension: still a long way to understand its transcriptional regulation.

Luc Maroteaux

► **To cite this version:**

Luc Maroteaux. Overexpression of 5-hydroxytryptamine 2B receptor gene in pulmonary hypertension: still a long way to understand its transcriptional regulation.. *Hypertension*, 2013, 61 (4), pp.e28-9. 10.1161/HYPERTENSIONAHA.111.00702 . inserm-00996750

HAL Id: inserm-00996750

<https://inserm.hal.science/inserm-00996750>

Submitted on 28 May 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Luc Maroteaux

Hypertension. 2013;61:e28-e29; originally published online February 4, 2013;

doi: 10.1161/HYPERTENSIONAHA.111.00702

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2013 American Heart Association, Inc. All rights reserved.

Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://hyper.ahajournals.org/content/61/4/e28>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Hypertension* is online at:
<http://hyper.ahajournals.org/subscriptions/>

Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 500 words (typed double-spaced) plus 5 references in length and may be subject to editing or abridgment.

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.

Sources of Funding

This work was supported by the Centre National de la Recherche Scientifique, the Institut National de la Santé et de la Recherche Médicale, the Université Pierre et Marie Curie, and by grants from the Fondation de France, the French Ministry of Research (Agence Nationale pour la Recherche).

Disclosures

None.

Luc Maroteaux

INSERM UMR S-839, Université Pierre et Marie Curie
Institut du Fer à Moulin, Paris, France

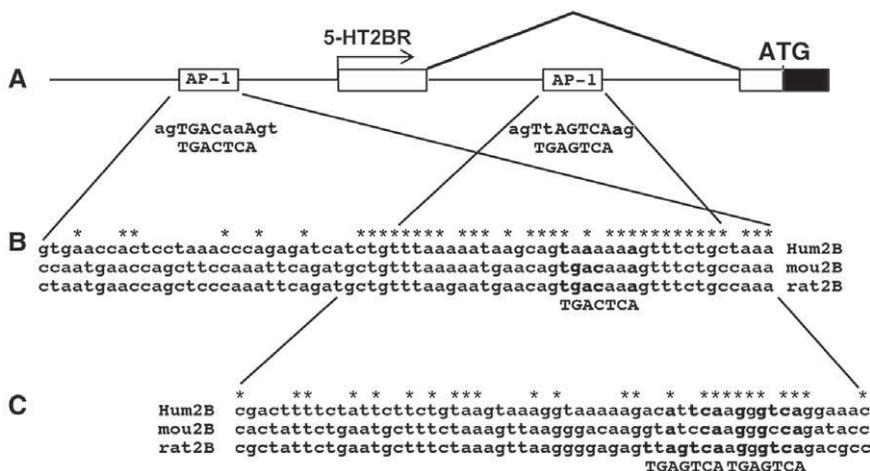


Figure. A, Promoter region of *Htr_{2B}* (white box, noncoding exons; black box, coding region). B, Putative 5' AP-1-binding site sequence. C, Putative 3' AP-1-binding site (in the first intron). DNA sequence alignments have been obtained using ClustalO program. Stars identify the conserved bases in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

(Hypertension. 2013;61:e28–e29.)

© 2013 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.111.00702

1. Liu Y, Tian XY, Mao G, Fang X, Fung ML, Shyy JY, Huang Y, Wang N. Peroxisome proliferator-activated receptor- γ ameliorates pulmonary arterial hypertension by inhibiting 5-hydroxytryptamine 2B receptor. *Hypertension*. 2012;60:1471–1478.
2. Launay JM, Hervé P, Peoc'h K, Tournois C, Callebert J, Nebigil CG, Etienne N, Drouet L, Humbert M, Simonneau G, Maroteaux L. Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. *Nat Med*. 2002;8:1129–1135.
3. Crossno JT Jr, Garat CV, Reusch JE, Morris KG, Dempsey EC, McMurtry IF, Stenmark KR, Klemm DJ. Rosiglitazone attenuates hypoxia-induced pulmonary arterial remodeling. *Am J Physiol Lung Cell Mol Physiol*. 2007;292:L885–L897.
4. Baxter GS. Novel discriminatory ligands for 5-HT_{2B} receptors. *Behav Brain Res*. 1996;73:149–152.
5. Linder AE, Gaskell GL, Szasz T, Thompson JM, Watts SW. Serotonin receptors in rat jugular vein: presence and involvement in the contraction. *J Pharmacol Exp Ther*. 2010;334:116–123.
6. Launay JM, Hervé P, Callebert J, Mallat Z, Collet C, Doly S, Belmer A, Diaz SL, Hatia S, Côté F, Humbert M, Maroteaux L. Serotonin 5-HT_{2B} receptors are required for bone-marrow contribution to pulmonary arterial hypertension. *Blood*. 2012;119:1772–1780.