MEETING ABSTRACT

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Androgen-sensitive hypertension associated with soluble guanylate cyclase alpha1 deficiency is mediated by 20-HETE

Sara Vandenwijngaert¹, Ana C Dordea¹, Victor Garcia², Robert E Tainsh¹, Daniel I Nathan¹, Michael J Raher¹, Kaitlin Allen¹, Fan Zhang², Wolfgang S Lieb¹, Sarah Mikelman¹, Andrew Kirby³, Christine Stevens³, Robrecht Thoonen¹, Allyson Hindle¹, Patrick Y Sips⁴, Rajeev Malhotra¹, Mark J Daly³, Peter Brouckaert⁵, Kenneth D Bloch¹, Michael Schwartzman², Emmanuel S Buys^{1*}

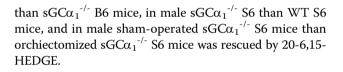
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Background

Dysregulated nitric oxide (NO) signaling contributes to the pathogenesis of hypertension. Previously, we reported gender- and strain-specific hypertension in mice deficient in the α 1-subunit of the NO receptor soluble guanylate cyclase (sGC α 1^{-/-}): male mice on an Sv129/J (S6) but not a C57BL6/J (B6) background are hypertensive.

Methods and results

Via linkage analysis, we identified a quantitative trait locus (QTL) associated with elevated blood pressure in male $sGC\alpha 1^{-1}S6$ mice. This OTL encompasses CYP4a12a, encoding the predominant murine synthase of the vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE). Renal expression of CYP4a12awas strain-, gender-, and testosterone-dependent:CYP4a12a gene expression was higher in male WT and sGC $\alpha_1^{-/-}$ S6 mice than in female S6 mice, or than in male and female, WT and sGC $\alpha_1^{-/-}$ B6 mice, higher in testosterone-treated S6 mice than in vehicle-treated S6 mice, and higher in sham-operated S6 mice than orchiectomized S6 mice. Also, 20-HETE levels were higher in renal preglomerular microvessels of male $sGC\alpha 1^{-/-}$ S6 than of $sGC\alpha 1^{-/-}$ B6 mice. Furthermore, the 20-HETE antagonist 20-6,15-HEDGE lowered blood pressure in male sGC $\alpha_1^{-/-}$ S6 but not WT mice. Finally, the more significant impairment of acetylcholine-induced relaxation of renal interlobar arteries in male sGC α_1^{-1} S6



Conclusion

Gender- and strain-specific hypertension and vascular dysfunction in sGC α 1^{-/-} S6 mice is associated with elevated *CYP4a12a* expression and 20-HETE levels, and is abrogated by antagonizing 20-HETE. These results corroborate our hypothesis that testosterone-induced *CYP4a12a* expression and a concomitant increase in 20-HETE production contribute to the hypertension associated with impaired NO-cGMP signaling and that *CYP4a12a* represents a candidate blood pressure modifying gene in the context of deficient NO-sGC signaling.

Authors' details

¹Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA. ²Department of Pharmacology, New York Medical College, Valhalla, NY 10595, USA. ³Center for Human Genetic Research, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA. ⁴Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA. ⁵Department for Biomedical Molecular Biology, Ghent University, Ghent, 9000, Belgium.

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^{*} Correspondence: ebuys@mgh.harvard.edu

¹Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA Full list of author information is available at the end of the article