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MEETING ABSTRACT Open Access

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

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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 α1-subunit of the NO receptor soluble guanylate cyclase ($sGC\alpha1^{-/-}$): 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 $sGC\alpha1^{-/-}$S6 mice. This QTL encompasses *CYP4a12a*, encoding the predominant murine synthase of the vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE). Renal expression of *CYP4a12a*was 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 $sGC\alpha1^{-/-}$ S6 than of $sGC\alpha1^{-/-}$ 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 $sGC\alpha_1^{-/-}$ S6 than $sGC\alpha_1^{-/-}$ B6 mice, in male $sGC\alpha_1^{-/-}$ S6 than WT S6 mice, and in male sham-operated $sGC\alpha_1^{-/-}$ S6 mice than orchiectomized $sGC\alpha_1^{-/-}$ S6 mice was rescued by 20-6,15-HEDGE.

Conclusion

Gender- and strain-specific hypertension and vascular dysfunction in $sGC\alpha1^{-/-}$ 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.

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