Buys et al. BMC Pharmacology 2011, 11(Suppl 1):P14
http://www.biomedcentral.com/1471-2210/11/S1/P14

BMC Pharmacology

POSTER PRESENTATION Open Access

Genetic mapping of a modifier locus affecting hypertension in soluble guanylate cyclase α_1 deficient mice

Emmanuel S Buys[1*], Michael J Raher[1], Andrew Kirby[2], Sarah R Hayton[1], Laurel T Tainsh[1], Patrick Y Sips[1], Peter Brouckaert[3], Mark J Daly[2], Kenneth D Bloch[1]

From 5th International Conference on cGMP: Generators, Effectors and Therapeutic Implications
Halle, Germany. 24-26 June 2011

Background

We previously reported that male mice deficient in the α_1 subunit of the NO receptor soluble guanylate cyclase ($sGC\alpha_1^{-/-}$ mice), an important nitric oxide (NO) receptor, are hypertensive [1]. The phenotype depends on the genetic background: $sGC\alpha_1^{-/-}$ mice on a 129S6 (S6) background ($sGC\alpha_1^{-/-S6}$) but not on a C57BL/6 (B6) background

($sGC\alpha_1^{-/-B6}$) develop hypertension [2]. These findings suggest that hypertension associated with $sGC\alpha_1$-deficiency is modulated by genetic factors. We aimed to identify modifier genes underlying the hypertension in $sGC\alpha_1^{-/-S6}$ mice.

Materials and methods

Mean arterial blood pressure (MAP) was measured invasively in 280 male F2 offspring from a $sGC\alpha_1^{-/-S6}$ X $sGC\alpha_1^{-/-B6}$ intercross ($sGC\alpha_1^{-/-F2}$). All mice were genotyped with a genome-wide panel of 150 SNP markers for linkage analysis using the Sequenom MassArray system and MAPMAKER/QTL. Renin-1c and renin-2d genotyping was performed using gene-specific primers. Plasma renin activity (PRA) and aldosterone were measured in anesthetized male S6 wild-type (WT^{S6}) and $sGC\alpha_1^{-/-S6}$ mice by radioimmunoassay and enzyme-linked immunoassay, respectively. The renin angiotensin system (RAS) was blocked by treating mice with either the aldosterone receptor antagonist, Spironolactone (100 mg/kg/day, subcutaneous pellet for 7 days), or the renin inhibitor, Aliskiren (200mg/kg/day, by gavage for 10 days).

Results

MAP in $sGC\alpha_1^{-/-F2}$ mice varied between values observed in $sGC\alpha_1^{-/-S6}$ and $sGC\alpha_1^{-/-B6}$ mice. Linkage analysis identified a locus on chromosome 1 with a highly significant logarithm of odds (LOD) score of 6.1. This region is syntenic with previously identified hypertension-related QTLs in the human and rat genome and contains the gene coding for renin. Importantly, B6 mice have one renin gene (renin-1c), and S6 mice have two renin genes (renin-1d and renin-2). Presence of the renin-1d and renin-2 genes correlated significantly with elevated MAP in the F2 mice ($P<0.0001$). PRA was higher in $sGC\alpha_1^{-/-S6}$ than in WT^{S6} mice (0.29±0.01 vs. 0.23±0.03 μg angiotensin 1/ml/hr, respectively, $P<0.05$). Similarly, plasma aldosterone levels were higher in $sGC\alpha_1^{-/-S6}$ than in WT^{S6} mice (0.47±0.03 vs 0.34±0.03 ng/ml, respectively, $P<0.05$). Treatment with Spironolactone or Aliskiren normalized blood pressure in $sGC\alpha_1^{-/-S6}$ (117±5 vs 146±2 mmHg, in Spironolactone and vehicle-treated mice, respectively, $P<0.001$, and 100±7 vs 148±4 mmHg, in Aliskiren and vehicle-treated mice, respectively, $P<0.001$).

Conclusion

Together, these data identify renin as a possible genetic modifier of blood pressure in a setting of deficient NO-cGMP signaling. Furthermore, these findings highlight the importance of sGC in the regulation of the renin-angiotensin system (RAS) and suggest that sGC may be a therapeutic target in RAS-dependent hypertension.

* Correspondence: ebuys@partners.org
[1]Department of Anesthesia Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
Full list of author information is available at the end of the article

Author details
[1]Department of Anesthesia Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA. [2]Department of Medicine, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA. [3]VIB Department of Molecular Biomedical Research, Ghent University, Ghent, Belgium.

Published: 1 August 2011

References

1. Buys ES, Sips P, Vermeersch P, Raher MJ, Rogge E, Ichinose F, Dewerchin M, Bloch KD, Janssens S, Brouckaert P: **Gender-specific hypertension and responsiveness to nitric oxide in sGCα_1 knockout mice.** *Cardiovasc Res* 2008, **79**:179-186.
2. Buys ES, Cauwels A, Raher MJ, Passeri JJ, Hobai M, Cawley SM, Rauwerdink KM, Thibault H, Sips PY, Thoonen R, Scherrer-Crosbie M, Ichinose F, Brouckaert P, Bloch KD: **sGC$\alpha_1\beta_1$ attenuates cardiac dysfunction and mortality in murine inflammatory shock models.** *Am J Physiol* 2009, **297**:H654-663.

doi:10.1186/1471-2210-11-S1-P14
Cite this article as: Buys *et al.*: Genetic mapping of a modifier locus affecting hypertension in soluble guanylate cyclase α_1 deficient mice. *BMC Pharmacology* 2011 **11**(Suppl 1):P14.