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

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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 (WTS6) 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 $sGC\alpha_1^{\text{-/-F2}}$ mice varied between values observed in $sGC\alpha_1^{\text{-/-S6}}$ and $sGC\alpha_1^{\text{-/-B6}}$ 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 hypertensionrelated 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 $sGC\alpha_1^{-7-S6}$ 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 sGCa₁^{-/-} 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 reninangiotensin system (RAS) and suggest that sGC may be a therapeutic target in RAS-dependent hypertension.

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