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Neuregulin-1 compensates for endothelial NO synthase deficiency in the heart and kidney

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Background: Decreased eNOS activity is the hallmark of endothelial dysfunction and is associated with cardiovascular and renal disorders. Besides NO, endothelial cells produce numerous other small molecules, peptides, and proteins, which modulate the function of adjacent cells. For instance, neuregulin-1 (NRG-1) is an endothelium-derived growth factor, which plays crucial roles in cardiovascular development, has cardioprotective properties, and induces growth and differentiation of cell types in different organs, including the kidney.

Purpose: Although the cardioprotective effects of endothelium-derived NO and NRG-1 are well established, their interaction is not clear. Therefore, we studied the interaction between the NO/eNOS and NRG-1/ErbB signalling pathways in a transgenic eNOS knock-out mouse model (eNOS–/–) treated with subpressor doses of angiotensin II (AngII).

Methods: eNOS–/– mice and their wild type (WT) littermates (n=64, 15 weeks old) were randomized for implantation of osmotic minipumps with AngII (400 ng/kg.min) for 28 days or sham surgery. Mice were randomized to receive either daily NRG-1 injections (20 μg/kg, intraperitoneal) or vehicle for 4 weeks (n=8/group). Hypertrophy and fibrosis were measured in left ventricle (LV) and kidneys using echography and immunohistochemical staining.

Results: Although blood pressure was higher in eNOS–/– mice compared to their WT littermates, it was unaffected by a subpressor dose of AngII. Masson's trichrome staining showed that AngII significantly increased LV (interstitial and perivascular) and renal fibrosis in eNOS–/– mice, but not in WT controls (see figure for LV data). NRG-1 reversed this AngII-induced LV and renal fibrosis caused by eNOS deficiency. There was also significant hypertrophy of LV and kidneys in eNOS–/– mice treated with AngII, which was again normalized by NRG-1 treatment. Moreover, NRG-1 significantly attenuated albuminuria induced by eNOS deficiency under AngII treatment.

Conclusions: This study demonstrates that the anti-fibrotic and anti-hypertrophic effects of NRG-1 are independent from the NO/eNOS pathway in both heart and kidney. Strikingly, NRG-1 is able to compensate for some of the negative effects of eNOS deficiency, at least in conditions of AngII stimulation.