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Aldosterone mediated dysfunction of human endothelial progenitor cells - Mechanisms and therapeutic opportunities

Thum T, Schmitter K, Fraccarollo D, Jakob M, Ertl G and Bauersachs J

Julius-Maximilians University, Internal Medicine I / Cardiology, Wurzburg, Germany

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Introduction:

Aldosterone is a well known risk factor associated with hypertension and cardiovascular injury. Bone marrow derived endothelial progenitor cells (EPC) play an important role in neovascularization and endothelial repair implicating a possible role as target for the prevention/therapy of vascular diseases.

Materials and Methods:

We examined the effects of aldosterone as well as the mineralocorticoid receptor (MR) antagonist eplerenone on EPC number and function *in vitro*, *in vivo* and a *clinical trial*.

Results:

Human EPCs expressed the MR both at gene and protein level. Aldosterone treatment of human EPC *in vitro* impaired cellular function, which could be rescued by MR antagonism. EPC from patients with primary hyperaldosteronism had a significant impairment in migratory potential compared

with age-matched healthy controls. Likewise, incubation of peripheral blood mononuclear cells with aldosterone (1-100 nmol/l) *in vitro* reduced EPC formation and development of colony forming units (CFU) in a concentration dependent manner. Co-treatment with the selective MR antagonist eplerenone alleviated this effect. Aldosterone reduced EPC migratory capacity and increased the intracellular production of reactive oxygen species (ROS), which was attenuated by MR blockade. While the protein kinase (PK) C inhibitor chelerythrine had no effect, co-treatment with the PKA inhibitor H-89 completely alleviated aldosterone effects on EPC migratory capacity and ROS production. Finally, eplerenone treatment improved number and function of circulating EPC in rats with secondary hyperaldosteronism due to heart failure.

Discussion and Conclusions:

We have shown impaired EPC number and function in both primary and secondary hyperaldosteronism. *In vitro*, aldosterone impaired EPC formation and function in a MR- and PKA-dependent manner involving

ROS formation. In vivo and clinical data additionally show a rescue of EPC function in hyperaldosteronism by specific targeting of the MR receptor. Beneficial effects of MR antagonists in cardiovascular disease prevention and therapy may be mediated in part by improved EPC biology.

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