Endothelial mineralocorticoid receptor activation enhances endothelial protein C receptor and decreases vascular thrombosis in mice

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Résumé en anglais	Previous studies have shown that aldosterone, which activates the mineralocorticoid receptor (MR), promotes thrombosis in animal models. Our objective was to determine whether MR activation/expression in the vascular endothelium could modify thrombotic risk in vivo and to examine thrombin generation at the surface of aortic endothelial cells (HAECs). MR was conditionally overexpressed in vivo in vascular endothelial cells in mice (MR-EC mice) or stimulated with aldosterone in HAECs. Thrombosis after ferric chloride injury was delayed in MR-EC mice compared with controls as well as in wild-type FVB/NRj mice treated with aldosterone (60 mug/kg/d for 21 d). Thrombin generation in platelet-poor plasma did not differ between MR-EC mice and controls. In MR-EC mice, aortic endothelial cell protein C receptor (EPCR) expression was increased. Aldosterone (10(-8) M) attenuated thrombin generation at the surface of cultured HAECs, and this effect was associated with up-regulation of expression of EPCR, which promotes formation of activated protein C. Aldosterone increases EPCR expression via a transcriptional mechanism involving interaction of MR with the specificity protein 1 site. These findings demonstrate that MR activation acts on endothelial cells to protect against thrombosis in physiological conditions and that MR-mediated EPCR overexpression drives this antithrombotic property through enhancing protein C activation.
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