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Guanylyl cyclase-A mediated endothelial actions of natriuretic peptides are critically involved in postischemic reperfusion

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Background

Published studies have revealed protective actions of high levels of natriuretic peptides on vascular regeneration in response to ischemia. BNP overexpressed systemically in transgenic mice or gene transfer of CNP into ischemic muscles effectively accelerates angiogenesis [1]. These studies suggest that pharmacological levels of *exogenous* NPs might be used as a strategy of therapeutic angiogenesis. However, they do not reveal whether *endogenous* NPs exert (patho-) physiological vasculoprotective actions. To investigate this question, we studied the impact of genetic ablation of guanylyl cyclase-A (GC-A), the receptor for ANP and BNP, on postocclusive hindlimb ischemia in mice.

Methods

The right femoral artery and vein were excised under anesthesia. A Laser Doppler Perfusion Imager (LDPI) was used to estimate relative blood flow during seven weeks following surgery. These functional *in vivo* studies were complemented with studies on cultured primary murine lung endothelial cells (MLEC).

Results and conclusion

Serial blood flow measurements by LDPI revealed that postocclusive hindlimb perfusion was severly impaired in mice with global GC-A deletion (GC-A-/-) as compared to respective WT mice. The calculated perfusion ratio of ischemic to nonischemic hindlimb was 0.15 ± 0.02 for WT vs. 0.09 ± 0.007 for GC-A-/- mice at day 3 (P = 0.02). After 35 days, restoration of perfusion in GC-A-/- mice was still drastically reduced demonstrating that endogenous NPs, via GC-A, exert important vasculoprotective actions. To dissect the specific vascular cell type mediating this effect, we took advantage of two genetic mouse lines with conditional, cell-restricted deletion of GC-A either in smooth muscle (SMC GC-A KO) or in endothelial cells (EC GC-A KO), both previously generated in our laboratory [2,3]. In SMC GC-A KO mice the extent of restoration of perfusion at any time point was close to control littermates. In contrast, in EC GC-A KO mice postocclusive hindlimb perfusion was severely impaired during the whole observation period.

Incubation of cultured MLEC with ANP increased intracellular cGMP, activity of cGMP-dependent protein kinase I (PKG I) and phosphorylation of the extracellular signal regulated kinase ERK1/2. These responses were completely abolished in GC-A-deficient MLEC.

We conclude that endogenous ANP and/or BNP exert critical endothelium-mediated vasculoprotective effects after arterial occlusion. Our future studies will be directed to elucidate whether these effects are related to (PKG I, ERK-

dependent?) endothelial regeneration and angiogenesis or to endothelium-dependent vasodilatation.

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