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Meeting abstract

The novel angiogenic cytokine secretoneurin promotes angiogenesis, arteriogenesis and vasculogenesis in the mouse hind-limb ischemia model

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Introduction

Secretoneurin (SN) represents a sensory, inflammatory neuropeptide which was recently demonstrated to act as an angiogenic and vasculogenic cytokine *in vitro* and *in vivo*. The present study was conducted to test the hypothesis that SN may be implicated in reparative angiogenesis. Furthermore, we challenged the healing potential of SN applied as a newly generated SN gene therapy vector in the setting of limb ischemia.

Methods and results

We cloned the human SN coding sequence into the pAAV plasmid containing a cytomegalovirus enhancer/promoter sequence. To establish the bioactivity of the constructed SN plasmid (p-SN), we transfected p-SN into COS cells and verified protein expression by SN-specific RIA. Bioactivity of recombinant SN was shown by proliferative and chemotactic activity on endothelial cells *in vitro*. Unilateral limb ischemia was induced in C57/bl6 mice by femoral artery resection. By real time PCR, western blotting, SN-specific RIA and immunhistochemistry, we documented that SN is up-regulated in ischemic muscles. We tested whether SN gene therapy may exert curative effects in this ischemia model. Injection of the SN plasmid into ischemic adductor muscles increased capillary (670 vs. 350/mm^2, n = 12, p = 0.02) and arteriole (16 vs. 8/mm^2, n = 12, p = 0.04) density, reduced endothelial cell apoptosis, and accelerated perfusion recovery as shown by laser Doppler perfusion imaging (LDPI; ratio ischemic/control leg after 28 days of ischemia: 1.1 vs. 0.7, n = 12, $p < 0.01$) in comparison to p-GFP (green fluorescent protein)-treated mice. Furthermore, SN gene therapy significantly reduced toe necrosis of ischemic limbs compared to control animals (26% vs. 50%, n = 12, $p < 0.05$). In bone marrow transplantation models, increased vascularity of ischemic hind-limbs after SN gene therapy was shown to be mediated, at least in part, by enhanced recruitment of bone marrow-derived endothelial progenitor cells.

Conclusion

These results suggest that the novel angiogenic cytokine secretoneurin is up-regulated by ischemia in skeletal muscle cells. Furthermore, results from gene therapy in this ischemia model suggest that secretoneurin represents a promising new substance for therapeutic angiogenesis.