GHRELIN PROTECTS MUSCULOCUTANEOUS TISSUE FROM ISCHEMIC NECROSIS BY IMPROVING MICROVASCULAR PERFUSION

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ABSTRACT

Introduction: Persistent ischemia in musculocutaneous tissue may lead to wound-breakdown and necrosis. The objective of this experimental study was to analyse, whether the gastric peptide ghrelin prevents musculocutaneous tissue from necrosis and to elucidate underlying mechanisms. Method: Thirty-two C57BL/6 mice equipped with a dorsal skinfold chamber containing ischemic musculocutaneous tissue were allocated to 4 groups: 1. Ghrelin; 2. N(Ω)-nitro--L-arginine methyl ester (L-NAME); 3. Ghrelin & L-NAME; 4. Control. Microcirculation, inflammation, angiogenesis and tissue survival were assessed by fluorescence microscopy, inducible and endothelial nitric oxide synthase (iNOS, eNOS), vascular endothelial growth factor (VEGF) as well as nuclear factor κB (NF-κB) by Western blot analysis. Results: Ghrelin-treated animals showed an increased expression of iNOS and eNOS in critically perfused tissue when compared to controls. This was associated with arteriolar dilation, increased arteriolar perfusion and a sustained functional capillary density (FCD). Ghrelin further upregulated NF-κB and VEGF, and induced angiogenesis. Finally, ghrelin reduced microvascular leukocyte--endothelial cell interactions, apoptosis and overall tissue necrosis ($p<0.05$ vs. Control). Inhibition of nitric oxide by L-NAME did not affect the anti-inflammatory and angiogenic action of ghrelin, but completely blunted the ghrelin-induced tissue protection by abrogating the arteriolar dilation, the improved capillary perfusion and the increased tissue survival. Conclusions: Ghrelin prevents critically perfused tissue from ischemic necrosis. Tissue protection is the result of a NOS-mediated improvement of the microcirculation, but not due to induction of angiogenesis or attenuation of inflammation. This might represent a promising, non-invasive and clinically applicable approach to protect musculocutaneous tissue from ischemia [**Am J Physiol Heart Circ Physiol. 2011 Dec 9**.;Epub ahead of print]

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