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Adrenomedullin reduces Staphylococcus aureus alpha-toxin-induced rat ileum microcirculatory damage.

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OBJECTIVE: Increased microvascular permeability and perfusion mismatch are hallmarks of sepsis or septic shock. The intestinal mucosa is very sensitive to tissue hypoxia. Intestinal mucosa dysfunction may allow translocation of bacteria and their products, thereby perpetuating sepsis and inflammation. Staphylococcus aureus alpha-toxin is a major pathogenicity determinant of this bacterium, provoking cardiovascular collapse. Current evidence suggests that the endogenous peptide adrenomedullin stabilizes circulatory homeostasis in systemic inflammatory response. Using alpha-toxin as a well-defined strong initiator of an inflammatory reaction, we tested the hypothesis that exogenously applied adrenomedullin stabilizes gut microcirculation. **DESIGN:** Prospective, experimental study. **SETTING:** Research laboratory at a university hospital. **SUBJECTS:** Isolated, perfused ileum from male Sprague-Dawley rats and human umbilical vein endothelial cells. **INTERVENTIONS:** Administration of S. aureus alpha-toxin before or after infusion of adrenomedullin. **MEASUREMENTS AND MAIN RESULTS:** Injection of a bolus of 1 microg of alpha-toxin in the superior mesenteric artery in a constant-flow, blood-perfused preparation of rat ileum increased perfusion pressure and relative hemoglobin concentration and decreased mucosal hemoglobin oxygen saturation. Continuous infusion of adrenomedullin (0.1 micromol/L) significantly reduced these alpha-toxin-related effects. Severe microvascular hyperpermeability observed in alpha-toxin-exposed ileum was abolished by adrenomedullin pretreatment. In addition, adrenomedullin blocked alpha-toxin-induced endothelial myosin light chain phosphorylation, endothelial cell contraction, and subsequent loss of endothelial barrier function in vitro. Treatment of alpha-toxin (infusion of 0.05 microg/mL)-exposed ileum with adrenomedullin (0.1 micromol/L) started 10 mins after onset of toxin application also significantly reduced superior mesenteric artery pressure and permeability increase. **CONCLUSIONS:** In summary, these data suggest that exogenous adrenomedullin protects ileum by reducing alpha-toxin-induced microcirculatory disturbances and by stabilizing endothelial barrier function.

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