

## 7. Summary

### **Adrenomedullin treatment abolishes ileal mucosal hypoperfusion induced by *Staphylococcus aureus* alpha-toxin – an intravital microscopic study on an isolated rat ileum**

In sepsis mucosal hypoxia, caused by diminished perfusion represents an important determining factor leading to intestinal-barrier failure. In this case the invasion of intestinal bacteria, toxins and other inflammatory mediators can further aggravate existing septic events.

Adrenomedullin is an endogenous vasoactive peptide produced by the mucosa of the gastrointestinal tract. In cases of experimentally induced sepsis it was found to exhibit protective properties, but the mechanism of this action is still unknown.

In the work presented here, the corrective influence of Adrenomedullin on microcirculatory disturbances of the intestine was investigated.

To evaluate mucosal microcirculation, an isolated rat ileum was selected as model and studied with intravital microscopy combined with spectrophotometric measurements of mucosal oxygenation. This way the model has allowed a detailed and isolated analysis of the microcirculation, while excluding systemic circulatory, neural and humoral influences. Microcirculatory disturbances were induced by the powerful bacterial pathogen  $\alpha$ -toxin from *Staphylococcus aureus*, infusing it continuously into the arteria mesenterica superior. The  $\alpha$ -toxin led to a considerable vasoconstriction of the mucosal blood vessels and thus resulted in an increased perfusion-resistance. Furthermore, a perfusion mismatch arose in the intestinal wall based on redistribution of the perfusion flow and caused a 50% reduction of the villus perfusion and mucosal hypoxia. The insufficient oxygen supply of the mucosa, caused by the  $\alpha$ -toxin, was also evident by the compromised oxygen uptake of the intestine. The rise of mucosal haemoglobin content was suggested to be consequenced by a postkapillary vasoconstriction und an increased fluid extravasation due to endothelial hyperpermeability. These  $\alpha$ -toxin effects may have contributed to diminished mucosal perfusion.

Administration of Adrenomedullin significantly reduced  $\alpha$ -toxin effects on mucosal microcirculation. As a result of a complete redistribution of the perfusion flow towards the mucosa the oxygenation of the mucosa was definitively improved. Moreover organ oxygen uptake was near control levels. It is thus to be assumed that the blood-vessel-dilating effect of Adrenomedullin is most pronounced in the area of the mucosa. Mucosa derived Adrenomedullin may act as paracrine mediator significantly involved in the regulation of intestinal mucosal blood flow.