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The synthetic antimicrobial peptide 19-2.5 interacts with heparanase and heparan sulfate in murine sepsis *in vivo* and in human sepsis *ex vivo*

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Introduction

Heparanase is an endo-β-glucuronidase that cleaves highly potent heparan sulfate (HS) from its proteoglycan, thereby triggering the inflammatory response in [1]. Thus, new anti-infective agents that interact with heparanase may be promising tools for sepsis therapy. As a novel anti-infective agent, peptide 19-2.5 (pep2.5) belongs to the class of synthetic anti-lipopolysaccharide peptides, however its activity is not restricted to Gram-negative bacterial infection [2,3].

Objectives

To evaluate the interaction of pep2.5 with heparanase in murine sepsis *in vivo* and in human sepsis *ex vivo*.

Methods

First, we used a model of murine cecal ligature and puncture (CLP) sepsis to study the impact of pep2.5 on heparanase *in vivo* in 12 NMRI mice. Mice were treated with pep2.5 or NaCl 0.9%. Plasma was sampled 24h after CLP. Second, we investigated whether pep2.5 interacts with heparanase in human plasma samples *ex vivo*. We added pep2.5 (20μg/ml) to plasma of 18 septic shock patients according to the ACCP/SCCM definitions and to plasma of 10 healthy volunteers. Heparanase-levels, HS-levels and heparanase activity were measured using ELISA (AMS Biotechnology, Oxon, United Kingdom). All data are given as mean ± standard deviation. A t-test with Holm-Šídák correction was used and a p-value < 0.05 was considered significant.

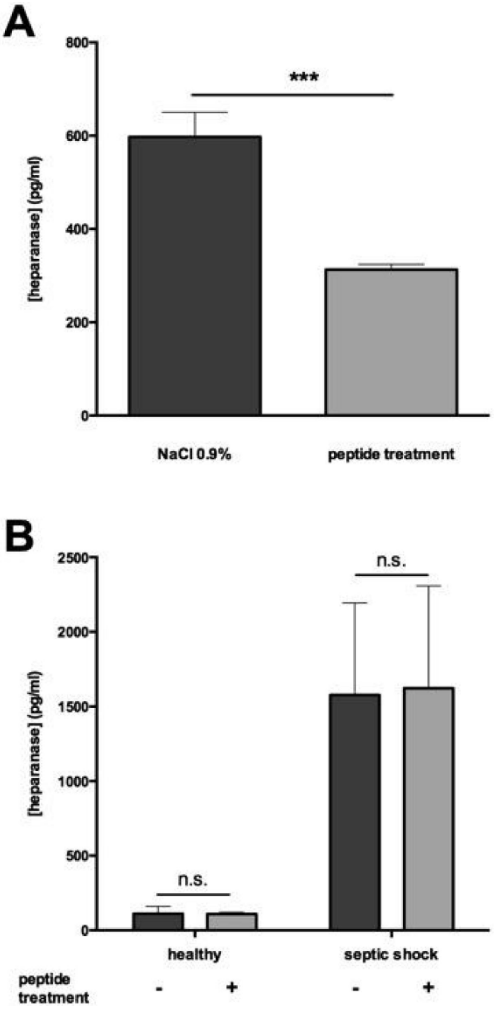

Figure 1 (**A**) Heparanase level in CLP-mice. (**B**) Heparanase level in human.*p < 0.05, **p < 0.005, ***p < 0.001.

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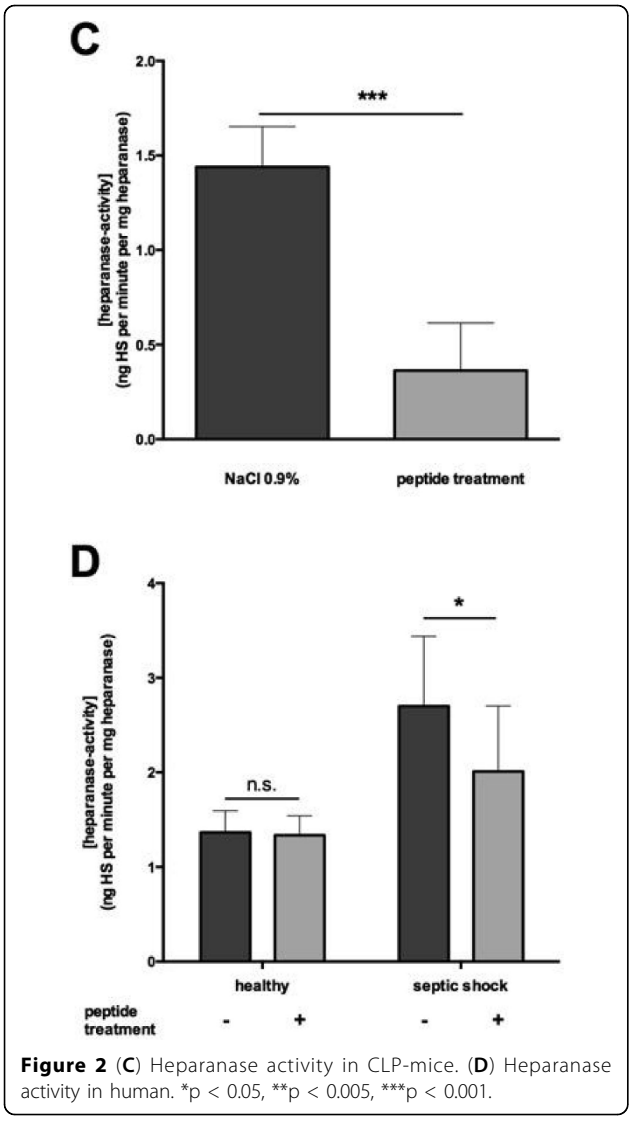

Figure 2 (**C**) Heparanase activity in CLP-mice. (**D**) Heparanase activity in human. *p < 0.05, **p < 0.005, ***p < 0.001.

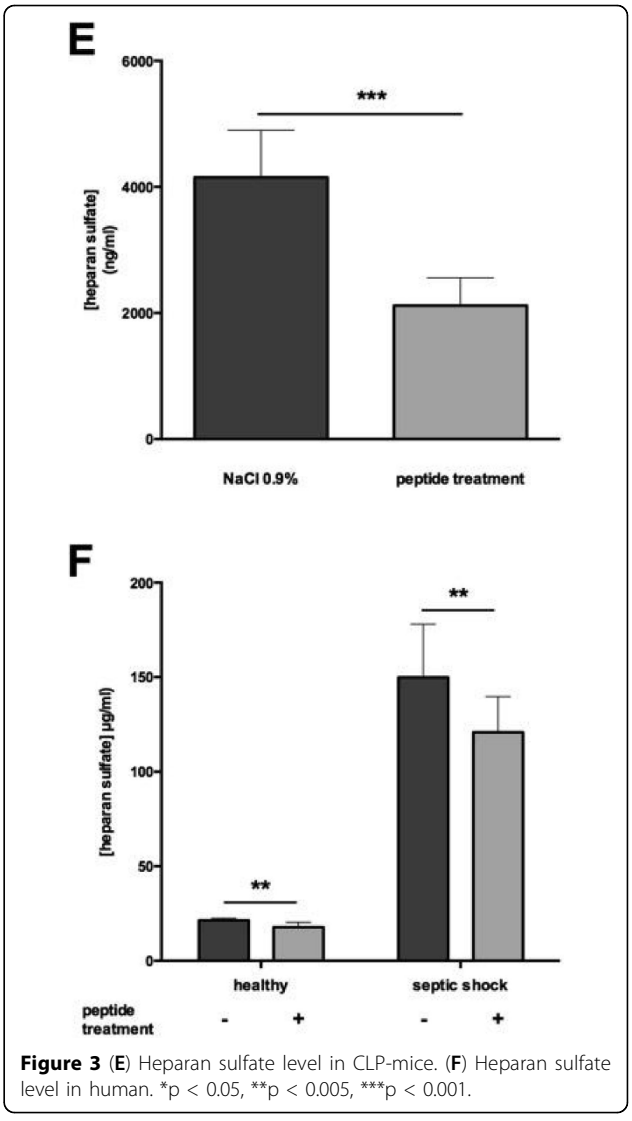

Figure 3 (**E**) Heparan sulfate level in CLP-mice. (**F**) Heparan sulfate level in human. *p < 0.05, **p < 0.005, ***p < 0.001.

Results

Mice subjected to CLP without treatment displayed higher heparanase levels in plasma compared to mice treated with pep2.5 ($p < 0.0001$). Treatment with pep 2.5 resulted in lower heparanase activity ($p < 0.0001$) and reduced HS-levels ($p < 0.0001$), compared to untreated animals (Figure 1).

Septic shock patients (78% male) were 70 ± 15 years old and healthy volunteers (50% male) were 67 ± 19 years old. Plasma heparanase levels, heparanase activity and HS-levels were significantly higher in individuals with septic shock than in healthy individuals (all $p < 0.0001$). The *ex vivo* addition of pep2.5 did not impact heparanase levels, however heparanase activity and HS-levels were decreased by adding pep2.5 to plasma of septic shock patients (all $p < 0.05$, Figure 1).

Conclusions

The synthetic antimicrobial peptide 19-2.5 interacts with heparanase in human and murine sepsis and reduces levels of highly potent HS. Thus, peptide 19-2.5 may have the potential for further development as a new anti-infective drug in sepsis therapy.

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