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**A NOVEL SYNTHETIC, HOST-DEFENCE PEPTIDE PROTECTS AGAINST ORGAN INJURY/DYSFUNCTION IN A RAT-MODEL OF SEVERE HEMORRHAGIC SHOCK**

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# A novel synthetic, host-defence peptide protects against organ injury/dysfunction in a rat-model of severe hemorrhagic shock

**Background**: Hemorrhagic shock (HS) is still a common cause of death in severely injured patients. However, there is no specific pharmacological intervention that prevents MOF associated with HS. The underlying pathophysiology is characterized by impairment of organ perfusion and systemic inflammatory response, both of which triggers the release of endogenous host-defence/antimicrobial peptides.

**Objective**: To evaluate (i) levels of the host-defence/antimicrobial peptide LL-37 in patients with trauma and HS (ii) the effects of a synthetic host-defence peptide (Pep19-4LF) on MOF associated with HS in rats.

**Methods**: (i) LL-37 was measured in 47 trauma/hemorrhage patients (ISS-score greater than or equal to 16) admitted to an urban major trauma center, and 10 healthy volunteers. (ii) Male Wistar rats were submitted to HS or sham operation. HS was induced by withdrawal of blood from a catheter implanted in the carotid artery to reduce mean arterial blood pressure (MAP) to approximately 30 mmHg for 90 min. At 90 min after initiation of hemorrhage (or when 25% of the shed blood had to be re-injected to sustain target MAP), resuscitation was performed with the shed blood over a period of 5 min. The same volume of blood for maintenance of MAP was replaced by Ringer lactate on resuscitation. Rats were treated with Pep19-4LF [66 (n=8) or 333µg/kg x h (n=8)] or vehicle (n=12) for 4 h following resuscitation.

**Results**: Plasma LL-37 was 12-fold higher in patients with trauma/hemorrhage compared to healthy volunteers. When compared to trauma patients, the plasma levels of LL-37 were significantly higher in trauma hemorrhage patients. Increased levels were associated with (a) low systolic blood pressure, (b) high heart rate, (c) high lactate, and (d) low base deficit on admission.

HS-rats treated with high dose Pep19-4LF had a significant higher MAP at the end of the 4 h resuscitation period (79±4 vs. 54±5 mmHg). Pep19-4LF treatment (high dose) resulted in significantly attenuated renal dysfunction, liver injury and lung inflammation compared to HS-rats treated with vehicle. Pep19-4LF enhanced (kidney/liver) the phosphorylation of (i) protein kinase B and (ii) endothelial nitric oxide synthase. Moreover, Pep19-4LF (high dose) attenuated the HS-induced (i) translocation of p65 from cytosol to nucleus, (ii) phosphorylation of IKK on $Ser^{176/180}$ and (iii) phosphorylation of IκBα on $Ser^{32/36}$ resulting in inhibition of NF-□B and formation of pro-inflammatory cytokines.

**Conclusions**: Trauma-associated HS results in the release of LL-37. The synthetic host-defence/antimicrobial peptide Pep19-4LF attenuates the organ injury/dysfunction associated with HS. Thus, Pep19-4LF may be useful to reduce MOF caused by severe hemorrhage and resuscitations in patients with trauma.