A synthetic peptide designed to neutralise lipopolysaccharides attenuates metaflammation and diet-induced metabolic derangements in mice

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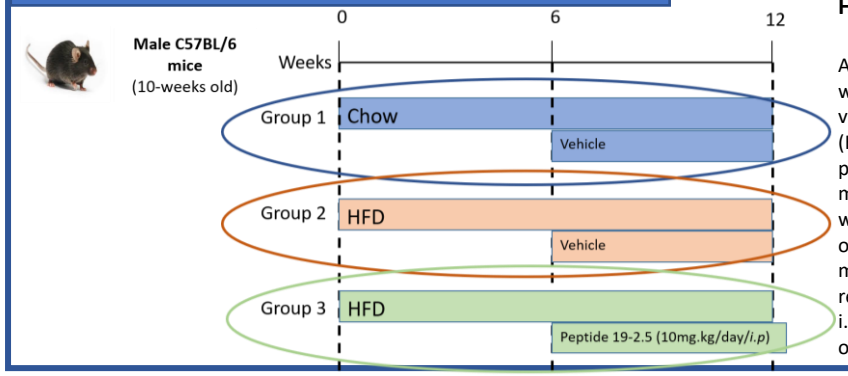
INTRODUCTION

LL-37 and Peptide 19-2.5

- LL-37 is the only member of the cathelicidin family of anti-microbial peptides (AMPs) expressed in humans.
- However, LL-37 cannot be utilised as a therapeutic intervention, as high doses of this peptide are toxic. Thus, synthetic antimicrobial peptides (AMPs), such as Peptide 19-2.5 (Pep2.5) , were developed with reduced toxicity as a potential lead candidate for the treatment of diseases in which AMPs may be useful including type-2 mellitus (T2DM).
- Pep2.5 was designed to have a maximal binding capacity for the lipid-A moiety of LPS and to neutralise LPS. Pep2.5 converts the lipid A part of LPS from a cubic aggregate into an inactive multi-lamellar structure and attenuates the systemic inflammation and organ injury/dysfunction associated with sepsis by binding to and inactivating LPS.

EXPERIMENTAL PROCUDURE



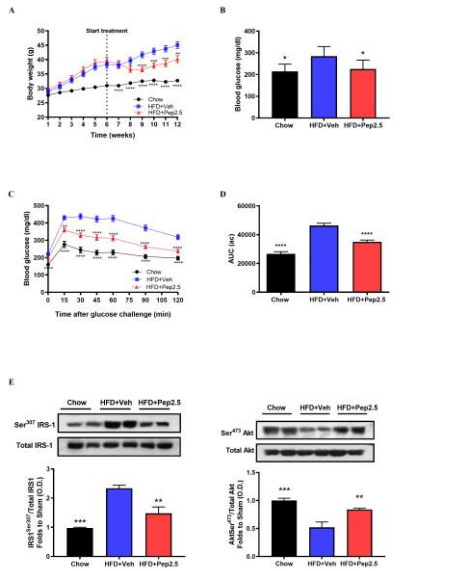
HFD-induced, murine model of T2DM

After 6 weeks of feeding mice a HFD, mice were randomly assigned to either receive vehicle (sterile saline, 0.9% NaCl i.p.) (HFD+Veh, n=20) or the drug treatment, peptide 19-2.5 (HFD+Pep2.5, n=20) (10 mg/kg x day i.p in vehicle) for 5 days per week from the end of week 6 until the end of the experiment at week 12. Chow-fed mice remained on the chow diet and received vehicle (sterile saline, 0.9% NaCl i.p.) from the end of week 6 until the end of the experiment at week 12.

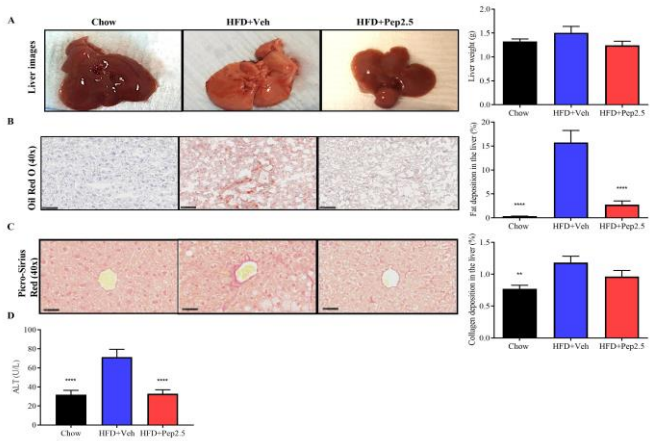
RESULTS

Peptide 19-2.5 ameliorated glycemic regulations by the improvement of insulin signaling in HFD-fed mice

- HFD-fed mice treated with Pep2.5, significantly attenuated the increase in weight gain from the start of drug treatment (from the end of week 6) until the end of the experiment (week 12) (FigA)
- HFD-fed mice treated with Pep2.5 reduced (i) the impairment in OGTT (ii) reduced calculated AUC (iii) the levels of non-fasting blood glucose levels at week 12 and (iiii) prevented the increase in the phosphorylation of serine 307 of IRS and, hence, reducing the phosphorylation of the downstream mediator AKT on Ser 473 the increase in insulin resistance.

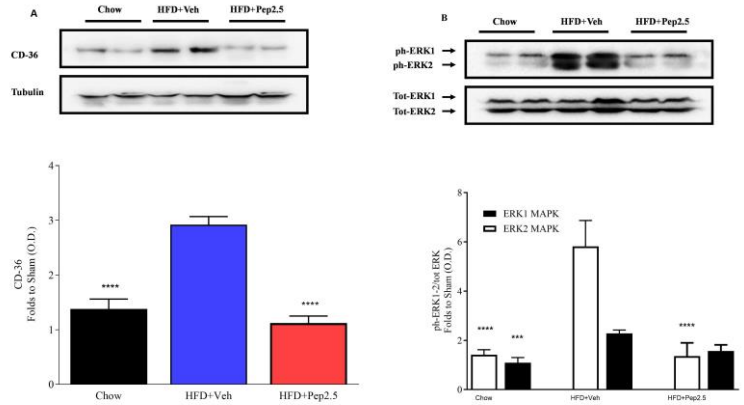


Peptide 19-2.5 abolishes steatohepatitis in HFD-fed mice



- Feeding mice, a HFD resulted in development of a larger fatty liver (steatosis) and associated with liver injury, both of which were abolished by treatment of HFD-mice with Pep2.5.

Peptide 19-2.5 reduces CD36 expression and the activation of ERK in the liver of HFD-fed mice



- Mice fed HFD treated with veh showed a significant increase in the expression of CD-36 and ERK1/2 in the liver
- However, treatment with Pep2.5 demonstrated a significant inhibition of the expression of CD36 and ERK1/2

CONCLUSION

The effects of LPS-binding proteins in experimental diabetes have not yet been investigated. To gain a better understanding of the role of LPS-binding AMPs in the pathophysiology of diabetes, we have challenged mice with a HFD for 12 weeks in the presence and absence of the LPS-binding protein, Pep2-5. We report here for the first time that Pep2.5 attenuates the IRS-1 phosphorylation in the liver, proteinuria, hypercholesterolemia and steatohepatitis caused by HFD in the mouse. The reductions in liver fat deposition and steatohepatitis (reduced activation of NF-κB, inflammasome and release of ALT) observed in HFD-mice treated with Pep2.5 are, at least in part, due to reduced expression of CD36 secondary to inhibition of ERK-1/2 in the liver. Although difficult to prove, a reduction in the degree of metabolic endotoxemia may also have importantly contributed to the observed beneficial effects of Pep2.5 in mice challenged with a HFD.