

The incretin hormone GLP-2 is secreted from pancreatic alpha cells during acute inflammation through IL-6 and protects against septic cardiomyopathy and shock

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BACKGROUND:

GLP-1 and GLP-2 (glucagon-like peptide-1/2) are incretin hormones that are co-secreted from intestinal L-cells in response to food intake. While GLP-1 is known to induce insulin secretion, GLP-2 has no direct insulinotropic effect. Functionally, GLP-2 enhances intestinal nutrient absorption and is clinically used for the treatment of patients with short bowel syndrome. Recently, GLP-2 has been found to be upregulated in patients with colitis with potentially protective effects through as yet unknown mechanisms. The aim of this study was to characterise the role of GLP-2 during systemic inflammation.

METHODS AND RESULTS:

To analyse whether the GLP-2 system is modulated by the immune system, we first measured circulating GLP-2 levels in patients under inflammatory conditions. 223 critically ill patients admitted to the ICU showed a 3.9 fold increase of total GLP-2 plasma levels in comparison to healthy controls (3.0 ng/mL versus 11.4 ng/mL; $p < 0.001$). Among the ICU cohort higher GLP-2 plasma concentrations were found in patients presenting with sepsis (9.4 ng/mL versus 6.4 ng/mL in none septic patients) and more severe disease (9.2 ng/mL in patients with Apache II score > 10 versus 5.8 ng/mL in patients with Apache II ≤ 10 ; $p = 0.002$). Moreover, GLP-2 levels were significantly correlated with markers of inflammation (IL-6, PCT, CRP) and septic cardiomyopathy (NTproBNP) and independently predicted mortality in critically ill patients.

To examine whether GLP-2 secretion could be directly regulated by the immune system we injected C57BL/6 mice with different LPS doses (i.p.). LPS increased GLP-2 secretion with a maximum of 17.2 ± 4 fold increase ($p < 0.01$) 210 minutes after injection of 1 mg/kg LPS. Further experiments in IL1R^{-/-} and IL6^{-/-} mice demonstrated that LPS-induced GLP-2 secretion is mediated by IL-6. To identify the source of GLP-2 secretion under inflammatory conditions, we injected LPS into transgenic Gcg^{-/-} mice (preproglucagon; precursor of GLP-2) with a tissue-specific reactivation of the Gcg gene in the gut (GcgRA^{ΔvilCre}) or the pancreatic alpha cell (GcgRA^{ΔPDX1-Cre}). Importantly, LPS-induced GLP-2 secretion was blocked in GcgRA^{ΔvilCre} mice, while GcgRA^{ΔPDX1-Cre} mice showed a marked increase of GLP-2, indicating that inflammation-dependent GLP-2 production is derived from the pancreas and not from the gut. Finally, we wondered whether inflammatory upregulation of GLP-2 has functional immunomodulatory relevance and administered GLP-2 (1-33) or saline as control per central vein catheter mice who underwent CLP (cecal ligation puncture; model for polymicrobial sepsis). GLP-2 treatment significantly improved LV-contraction (dp/dt_{max}) in septic cardiomyopathy (control 7361 vs. GLP-2 9500 mmHg/s; $p < 0.01$), as well as clinical sepsis score and inhibited sepsis-induced hypotension. Mechanistically GLP-2 inhibited CLP-induced myeloid cell (neutrophils, monocytes) infiltration into liver and heart tissue analysed by flow cytometry. Consistently, we found decreased tissue mRNA expression and serum levels of TNF- α , IL-6 and IL-1 β in the GLP-2 group.