O-GlcNAcylation, and various enzymes involved, and biological parameters (urea, creatinine, pH, PCO2, PO2).

Cardiovascular function was strongly modified with a reduction in blood pressure (~25%) in LPS injected rats, while no improvement was reported neither after GLCN nor NbutGT treatment. An increase in global O-GlcNAcylation was only obtained under GLCN and NbutGT treatment. GLCN led to an increase in two enzymes involved in HBP regulation (GFAT and O-GlcNASe). LPS injected rats presented a lactate acidosis associating an increase in lactate (3.38±0.67 mmol/L v. 2.67±0.66) and drastic reduction in HCO3–. Urea and creatinine were increased suggesting an acute renal failure. Treatment with NbutGT but not GLCN corrected biological parameters (lactate: 2.6±1.00 mmol/L, pH: 7.41±0.03, HCO3–: 27.66±2.24 mmol/L).

Our study demonstrates the putative beneficial effect of O-GlcNAc stimulation during sepsis, especially by NbutGT. It remains to be determined whether the improved biological parameters are associated with a reduced mortality of rats.

0321
PTP1B gene deletion or pharmacological inhibition improves glucose metabolism and limits cardiovascular dysfunction in experimental septic shock

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Hyperglycemia is a feature of septic patient and has been associated with poor outcome and higher mortality. In contrast insulin has been shown to decrease mortality and to prevent the incidence of multi-organ failure but is often associated with deleterious hypoglycemia. Protein Tyrosine Phosphatase 1B (PTP1B) is a negative regulator of insulin signaling and NO production. Recently we showed that PTP1B gene deletion improves cardiovascular dysfunction during endotoxemia. However, the effect of PTP1B inhibition on glucose metabolism and cardiovascular insulin resistance during sepsis is unknown.

Thus, in order to address this question, we developed a Cecal Ligation and Puncture (CLP) model of sepsis which is known to reproduce metabolic disorders of clinical sepsis. Impaired glucose metabolism was found in mice 16 hours after CLP induction as shown by the disruption of glucose intake and insulin response during glucose (GTG) and insulin (ITT) tolerance tests. PTP1B−/− mice showed improved GTG and ITT (GTG 120min: CLP WT 20.1±2.1, CLP PTP1B−/− 12.5±2.4 mmol/L, p<0.001; ITT 120min: CLP WT 2.4±0.2, CLP PTP1B−/− 0.60±0.03 mmol/L, p<0.001) demonstrating an improvement of glucose metabolism. Insulin- and flow-mediated dilatation assessed in isolated-perfused mesenteric arteries was abolished by CLP and was improved by ex vivo PTP1B inhibition (% dilatation: Ins10-5M, CLP 0.7±0.4, CLP PTP1B 18±4%, p<0.01; 200 μl/min flow, CLP 1±1, CLP + PTP1B 13±3%, p<0.01). Arteries isolated from PTP1B−/− mice were protected against TNF-α induced impairment of dilation to insulin. We found that PTP1B−/− mice subjected to CLP had a higher survival rate compared to WT.

Thus, PTP1B gene deletion or inhibition limits sepsis-induced hyperglycemia and insulin resistance associated with reduced vascular dysfunction and increased survival. PTP1B inhibition may represent a new strategy in the treatment of sepsis insulin resistance with hyperglycemia.

0129
Pharmacological modulation of microparticle-mediated vascular response in a rat model of septic shock

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Introduction: Circulating procoagulant microparticles (MPs) take part in septic shock vascular dysfunction through pro-inflammatory and procoagulant detrimental effects. Aims were to study how circulating procoagulant MPs are involved in the vascular dysfunction of septic shock and to examine if the pharmacological modulation of MP could be beneficial.

Methods: In a first set of experiments, MPs were isolated from sham or septic rats obtained by cecal ligation and puncture, resuscitated and treated by activated protein C (aPC). Then, healthy recipients were inoculated with septic MPs and hemodynamic parameters were recorded during 4 hours. At the end of the record, blood and organs were harvested.

Results: Treating septic rats with aPC significantly reduced norepinephrine needs to reach the mean arterial pressure goal and leukocyte-derived MPs (6.2±2.1 vs 2.9±1.7 nM Phtleuc,Ser, p<0.05, n=16). MPs from septic rats significantly decreased the mean arterial pressure of healthy recipients (85±9 vs 107±2 mmHg), a deleterious hemodynamic effect also prevented by aPC treatment (120±5 mmHg), possibly through the elevation of MP thromboxane content (77.1±11.4 pg/ml vs 39.8±4.5 pg/ml in sham-NaCl MPs, p<0.001) and tended to return to baseline at the end of the follow-up period (p<0.05). No alteration in E-selectin (CD62E-MPs) levels could be detected. CD105-MPs (OR 6.55) and CD31-MPs (OR 4.9) were associated with early DIC in multivariate analysis and can originally predict it. Furthermore, leukocyte CD11a-MPs were also higher in DIC highlighting that endothelial cells and leukocytes are first impaired in the process of DIC.

Conclusion: Endothelial-derived MPs are relevant biomarkers of early vascular injury and endothelial dysfunction in septic shock-induced DIC and could prove useful for patients’ stratification.