The influence of lipopolysaccharide, insulin, glucose, and activated protein C in the sepsis pathogenesis and during acute inflammatory conditions

With focus on lymphocyte apoptosis

Jeppe Sylvest Nielsen, MD

This PhD dissertation was accepted by the Faculty of Health Sciences of the University of Aarhus, and defended on April 11, 2008.

Official opponents: Marie-Lise Gougeon, Anders Perner, and Marianne Hokland.

Supervisors: Else Tønnesen, Thomas Ledet, Anders Larsson, and Jan Krog.

Correspondence: Jeppe Sylvest Nielsen, Godthåbsvej 95, 3. tv., 2000 Frederiksberg, Denmark.

E-mail: sylvest@ki.au.dk

Dan Med Bull 2008;55:125

ABSTRACT

Sepsis, severe sepsis, and septic shock are complex syndromes associated with a high mortality and a narrow range of treatment modalities. Experimental studies in pigs have shown that the inflammatory response to endotoxemia is in many ways analogous to the human inflammatory response to infection. The aims of this PhD study were to evaluate the immunomodulating effects of insulin, glucose, and activated protein C (APC), which all reduce morbidity and mortality in septic patients. Because lymphocyte apoptosis has an important role in the pathogenesis of sepsis, this PhD thesis focuses on the role of lymphocyte apoptosis during endotoxemia and infectious conditions.

Firstly, we examined the effect of APC on plasma cytokine levels. APCs have been postulated to be an anti-inflammatory substance, and we sought to explore whether the anti-inflammatory effect was caused by modulation of plasma cytokines. In a porcine model of acute endotoxemia, we found no effect of APC on peak plasma cytokine levels. However, we observed a significant delay in peak TNF-α and Il-10 levels, but the relevance and consequences of this delay remain unknown.

Secondly, since normoglycemia achieved through intensive insulin therapy has proven beneficial in ICU patients and lymphocyte apoptosis is considered a detrimental part of sepsis pathogenesis, we sought to explore whether high insulin levels concomitant with normoglycemia (hyperinsulinemic euglycemic clamp (HEC)) influenced spleen lymphocyte apoptosis during acute endotoxemia. In vivo we found that not only does LPS induce apoptosis in B- and T-lymphocytes, but the HEC augments this response.

Finally, we examined whether the lymphocyte apoptosis observed in the second study also occurred in human lymphocytes and whether we could differentiate between the effects of glucose and insulin. In addition we assessed the apoptotic response in CD4+ and CD8+ T-cells, B cells and NK cells to different LPS types. We discovered that rough strain LPS (R-LPS) is a potent apoptosis inducer in CD4+ and CD8+ T-cells, and both smooth (S-LPS) and R-LPS appear to reduce apoptosis in human B-cells.

In conclusion, our results demonstrate that APC, insulin, and glucose all have possible immune-modulating effects. LPS-strain-type, insulin, and glucose all influence lymphocyte apoptosis, and they could be related to the immunosuppression seen in patients with Gram-negative infections.