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Renal failure in experimental sepsis: role of endothelin and the Toll-like receptor 4

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Abstract

Sepsis is the leading cause of renal failure in critically ill patients, but the pathogenesis of septic kidney dysfunction is poorly defined. The current paradigm states that hypoperfusion and excessive renal vasoconstriction results in renal ischemia. However, experimental data also exist indicating a direct immune-mediated basis of septic renal impairment. This thesis aimed to investigate the contribution of both a potent vasoconstrictor peptide, endothelin-1 (ET-1), and a receptor that activates the immune system in response to a bacterial infection, the Toll-like receptor 4 (TLR4), to the renal failure caused by sepsis.

The first part of this thesis investigated the role of the endothelin system in renal microcirculatory and functional impairment caused by experimental septic renal failure, by studying the effects of dual endothelin type A and B (ETA/ETB) antagonism and selective ETA-antagonism during porcine endotoxemia. ET-1 is a vasoconstrictor peptide that is a potent modulator of microcirculatory blood flow. It is released in high amounts during sepsis and experimental data have shown that ET-1 reduces renal blood flow. In paper I and II pigs were subjected to lipopolysaccharide (LPS) infusion and the renal microcirculatory effects of dual ETA/ETB or selective ETA antagonism were investigated. The main findings were that dual ETA/ETB blockade attenuated the endotoxemia induced reduction in renal cortical microcirculation, as well as the increase in plasma creatinine levels (paper I). In addition, selective ETA antagonism reduced the decline in renal medullary microcirculation, but had no significant effect on diuresis or creatinine clearance (paper II).

The second part of this thesis investigated the role of TLR4 activation in renal failure caused by hyperdynamic endotoxemia or sepsis. Conscious surgically prepared sheep were subjected to LPS or live *Escherichia coli* infusion and observed for 24-36 hours. A main finding was that pretreatment with a TLR4-inhibitor attenuated renal failure and hypotension caused by endotoxemia in sheep. This effect was greater compared to norepinephrine treatment, in a dose that prevented hypotension (paper III). Moreover, it was observed that septic renal failure developed without renal hypoperfusion and that treatment with a TLR4-inhibitor reversed renal failure when administered 12 hours into sepsis (paper IV). This effect was independent of changes in systemic or renal hemodynamics but was associated with a reduced renal neutrophil accumulation.

In conclusion, despite no reduction in renal perfusion or arterial blood pressure, septic renal failure may still develop. During hyperdynamic sepsis, stimulation of the innate immune system, via TLR4 activation, may contribute to the development of renal failure. In addition, TLR4-inhibition is an effective treatment to improve renal function in ovine sepsis induced by *E.coli*. In hypodynamic endotoxemia, ET-1 contributes to renal vasoconstriction. By acting on ETA, ET-1 reduces renal medullary blood flow causing ischemia, but has no short-term effect on renal function.