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Vascular Effects of Endothelin in Experimental Lung Injury

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ABSTRACT

Acute lung injury remains a frequent and life threatening consequence of severe sepsis. This thesis has investigated the role of the endothelin (ET) system in sepsis-induced lung injury, with special reference to its effects on two hallmarks of this syndrome - formation of edema and pulmonary hypertension. This was explored in a porcine endotoxin model of sepsis *in vivo*, as well as *in vitro* using isolated porcine pulmonary vessels.

In paper I we show that endotoxemia *via* ET-dependent mechanisms predominately increases pulmonary downstream resistance and subsequently augment pulmonary capillary hydrostatic pressure. In addition, we demonstrate that ET_B-receptor stimulation constricts pulmonary veins more than arteries *in vitro*. In paper II, we show that endotoxin-exposure induces differentiated effects in isolated pulmonary arteries and veins. In veins, endotoxin increases ET-receptor dependent constriction, whereas the response to α1-adrenergic stimulation, predominantly acting on arteries, is reduced. In addition, we demonstrate that the changes in response to ET-receptor stimulation are not induced by alterations in expression or distribution of ET-receptors in the preparations. In paper III we find that inhalation of a dual ET-receptor antagonist, tezosentan, during porcine endotoxemia potently reduces pulmonary hypertension without causing systemic effects. In paper IV we show that endotoxemia induces a marked degranulation of polymorphonuclear neutrophils with increased plasma levels of the highly permeability and edema promoting heparin-binding protein (HBP/CAP37). Treatment with tezosentan distinctly counteracts this increase and simultaneously reduces pulmonary edema, improves respiratory system compliance and decreases hemoglobin concentration, all suggesting that tezosentan treatment reduces transcapillary fluid passage.

In conclusion, our studies show that endotoxemia increases pulmonary capillary filtration pressure, raises levels of the powerful permeability promoting mediator HBP and induces pulmonary edema. Systemic treatment with a dual ET-receptor antagonist markedly counteracts these changes. In addition, inhaled tezosentan efficiently and selectively reduces pulmonary hypertension during endotoxemia. Taken together, these results show that the ET-system is extensively involved in the pathophysiology of endotoxin-induced lung injury. These findings need to be further elucidated, in other experimental conditions and in humans.

Key words: acute lung injury, sepsis, endothelin, extravascular lung water, pulmonary capillary pressure, pulmonary edema, heparin-binding protein, CAP37, tezosentan, pig, pulmonary circulation

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