THE ROLE OF PROSTAGLANDINS

IN

OXIDANT-INDUCED PULMONARY EDEMA

by

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CHAPTER VII

SUMMARY

The lung has considerable capacity to synthesize and release prostaglandins (PGs) into the pulmonary circulation, and these PGs are known to play a key role in normal pulmonary vascular regulation. Therefore, agents that damage lung endothelium can result in dramatic alterations in lung PGs. One such agent that has been demonstrated to injure the pulmonary system is PQ. The biochemical mechanism of toxicity is believed to be related to the cyclic oxidation-reduction of PQ that occurs in the pulmonary cells. This leads to continued production of high levels of superoxide anion (O_2^-) and other cytotoxic O_2 free radicals. This PQ-induced lung damage is mechanistically similar to lung damage associated with exposure to hyperoxia. This general type of damage is referred to as oxidant-induced lung damage.

These experiments were undertaken to determine if oxidant-induced lung damage (paraquat, high oxygen concentrations) resulted in altered PG levels. Also investigated were possible cause-and-effect relationships between induced PG changes and the lung pathology seen. These relationships not only include direct action of the PGs but also stimulating the release of other vasoactive mediators into the circulation.

The model used to study PG metabolism following paraquat-induced damage was the isolated perfused rat lung preparation. This model allows the retention of the structural and functional integrity of the lung. With this *in vitro* system, physical parameters can be measured and frequent perfusate sampling accomplished. Both of these are difficult to accomplish *in vivo*. Lungs perfused with paraquat (PQ), 1 x 10^{-7}M to 1 x 10^{-2}M, showed significant elevations in $PGF_2\alpha$ prior to detectable functional and pathological changes (increases in airway resistance, vascular resistance, and edema). No changes in PGE were observed. $PGF_2\alpha$ elevation in the perfused lungs exhibited a dose related response following PQ exposure (up to 300% increase over control values). Lungs perfused with PQ and ventilated with high oxygen (another oxidant) instead of air, demonstrated a dramatic potentiation in the selective increase of $PGF_2\alpha$. These levels reached over 1 ng/ml (a 2600% increase over control values).

Identification of PGs in the venous effluent during altered organ function does not establish causality. Therefore, the responsibility of these PG changes for the pathological sequelae was investigated. The addition of exogenous $PGF_2\alpha$ to the perfusate, without PQ, initiated edema in a dose related fashion. This indicates the potential of $PGF_2\alpha$ as a causative agent in lung edema formation from PQ injury. The addition of ibuprofen (a nonsteroidal anti-inflammatory agent) to the perfusion media blocked endogenous release of $PGF_2\alpha$ in lungs perfused with PQ. Ibuprofen also prevented the onset of edema. This provides further evidence that $PGF_2\alpha$ is

linked to oxidant-induced edema.

Another important mechanism by which PG alterations may contribute to lung injury is by stimulating the release of other vasoactive mediators into the circulation. It was demonstrated that oxidant-induced damage resulted in histamine release which significantly altered pulmonary vasculature permeability. This histamine release may have been stimulated by the selective rise in $PGF_2\alpha$. This was supported by evidence that inhibition of $PGF_2\alpha$ synthesis significantly lowered histamine release.

These data demonstrate that in the perfused lung: 1) PQ caused a selective increase of $PGF_2\alpha$ which was potentiated by a second oxidant agent; 2) this selective increase occurred prior to the onset of edema; 3) exogenous $PGF_2\alpha$ alone induced pulmonary edema; 4) ibuprofen, in doses which blocked $PGF_2\alpha$, also prevented edema formation; 5) PQ also released histamine which may be a secondary event following $PGF_2\alpha$ release. The elevated hydrostatic pressure ($PGF_2\alpha$) in combination with increased permeability (histamine) resulted in a potentiation of the pulmonary edema. This suggests the possibility that nonsteroidal anti-inflammatory agents may be clinically useful in the treatment of oxidant-induced lung damage, a pathological condition without present treatment.

The direct physiologic effects of $PGF_2\alpha$ elevations, in combination with the stimulation of other mediators, indicate that $PGF_2\alpha$ alterations play a pivotal role in the pathophysiology of oxidant-induced lung damage.

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