Asian J. Exp. Sci., Vol. 23, No. 1, 2009; 349

Urokinase: An Enzyme Linking Kidney and Lung Function

Manoj G Tyagi
Department of Pharmacology,
Christian Medical College,
Vellore-632002 (Tamil Nadu); India.

Urokinase is an enzyme isolated from human urine and prepared from cultured human kidney cells. In normal kidneys, uPA most of which is secreted into the urine is produced in significant quantities by proximal tubules. However, several cells that are recruited or activated in the kidney in response to injury may produce uPA, including monocytes, macrophages. Urokinase is a key constituent of the pulmonary-renal cascade regulating multiple physiological functions like respiration, skeletal muscle control, blood formation and coagulation (Tyagi *et al.,* 2005). It is now evident that urokinase released from the kidney acts on peripheral receptors in the lungs and the brain. The urokinase receptor is known as CD87 and both single chain pro-uPA and two chain active protease may bind to this cellular receptor.

In the kidney, uPAR expression is up regulated after ureteral obstruction. uPA would appear to be a logical source of endogenous renal antifibrotic activity, due to its copious production by proximal and distal tubules. On the other hand the urokinase represents the predominant activator of the fibrinolytic activity in the alveolar compartment. Isolated alveolar or bronchial epithelial cells, which have shown to produce u-PA and plasminogen activator inhibitor–I *in vitro*. More studies have shown the importance of uPAR in the lungs. The urokinase receptor has been found to be expressed in the lung (Smith *et al.*, 2008). Urokinase has been shown to be present in the sputum of allergic asthma patients (Kowal *et al.,* 2008). Urokinase has an important role to contribute in idiopathic pulmonary fibrosis and has implications for its therapy (Gharee *et al.*, 2008). Moreover the enzyme has critical role in acute inflammatory and chronic interstitial lung disease (Wygrecka *et al.,* 2008).

To evaluate this linkage between the kidney and lungs, we conducted studies in groups of Guinea pigs (n=7) weighing between 500 to 700g. Urokinase was injected in a dose of 8000 units / kg intraperitoneally. The respiratory rate was measured before and 15 minutes after urokinase injection. Urokinase was found to increase the respiratory rate by 11.7 %. In another group of Guinea pigs (n=7), the gap junction intercellular communication (GJIC) inhibitor, Carbenoxolone (50mg/kg i.p) was found to attenuate this increase in the respiratory rate. These studies support the role of urokinase as a critical constituent of the "Pulmonary-renal cascade" and suggest that this enzyme is the linkage between kidney and lung function for physiological homeostasis.

References

Gharee Kermani M., Hu B., Phan S.H. and Gyetko M.R. (2008) The role of urokinase in idiopathic pulmonary fibrosis and implication for therapy. *Exp. Opin. Invest. Drugs*, **17 (6)**, 905-916

Kowal K., Szukowski, Moniuszko M., Bodcenta Lukaszyk A. (2008): Plasminogen activator inhibitor – 1 (PAI – 1) and urokinase plasminogen activator (uPA) in sputum of allergic asthma patients. *Folia Histochem Cytobiol*., **46 (2)**, 193-198

Smith L., Wagner T.E., Hulzar I. and Schnapp L.M. (2008): uPARAP expression during murine lung development. Gene expression (In Press)

Tyagi M.G., Velu S.T. and Gota V.S. (2005): Renal humoral modulation of skeletal muscle tone in mice; Implications for "The Pulmonary renal cascade ". *Ind. J Physiol. Pharmacol*., **49**, 403-410

Wygrecka M., Jablonska E., Guenther A., Preissner K.T. and Markart P. (2008): Current view of alveolar coagulation and fibrinolysis in acute inflammatory and chronic interstitial lung diseases. *Thromb. Haemost*., **99 (3)**, 494 - 501.