Abstract:
Tumour necrosis factor alpha (TNF-α) has been implicated in the development of diabetic nephropathy and the accompanying increase in sodium retention. Inhibition of renal Na⁺/K⁺ ATPase was reported to accompany cell death. As TNF is known to induce both apoptosis and cell survival, this work investigated the effect and mechanism of action of TNF-α on the Na⁺/K⁺ ATPase and the Na⁺K⁺2Cl⁻ symporter using LLC-PK₁ cells, a porcine renal proximal tubules cell line. Materials and methods

Cells were incubated for 2 h with TNF-α in presence and absence of pyrrolidinedithiocarbamate, SP600125 and FK009, respective inhibitors of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), c-Jun N-terminal kinase (JNK) and caspases. The activity of the pump was assayed by measuring the ouabain-inhibitable release of inorganic phosphate. Changes in its expression and the expression of the symporter were monitored by western blot analysis.

Results
TNF-α up-regulated both transporters. NF-κB, JNK and the caspases were all mediators of the cytokine action. TNF up-regulated the Na⁺/K⁺ pump by stimulating JNK which in turn, activated NF-κB and inhibited the caspases. TNF effect on the cotransporter was also mediated via activation of JNK which however inhibited NF-κB and by so doing prevented activation of caspases. As caspases were demonstrated to down-regulate the two transporters, their inhibition by TNF is responsible for the observed up-regulatory effect.

Conclusions
It was concluded that the Na⁺/K⁺ ATPase and Na⁺K⁺2Cl⁻ are both targets of TNF-α and the effect of the cytokine favours cell survival over cell death.

Keywords: Caspases; JNK; Na+/K+ ATPase; Na+K+2Cl--; NF-κB; TNF-α

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