BRADYKININ INCREASES P GLYCOPROTEIN EXPRESSION IN HUMAN TUBULAR CELLS EXPOSED TO ALBUMIN

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Objectives:

Sustained proteinuria and tubulointerstitial damage have been closely linked to progressive renal failure. Upon protein endocytosis, tubular epithelial cells are thought to produce mediators that promote inflammation, tubular degeneration, and fibrosis. Previous studies demonstrated that genes encoding membrane transporters in renal tubular cells were up- or down-regulated by proteinuria.

P-glycoprotein (Pgp) is a glycoprotein involved in the ATP-dependent transmembrane efflux of a wide range of compounds leading to a decrease in drug concentration within the cell. In the kidney Pgp is mainly expressed in the proximal tubule. The influence of albumin on expression and function of Pgp in HK-2 proximal tubular cells has been demonstrated. Bradykinin (BR) is involved in inflammation, and increasing clinical evidence suggests that bradykinin could play a role in the beneficial effect of ACE inhibitors in diabetic nephropathy. BR inhibited morphological alterations in HK-2 cells exposed to albumin.

AIM. In this study we investigated the influence of albumin on expression and function of Pgp in HK-2 proximal tubular cells.

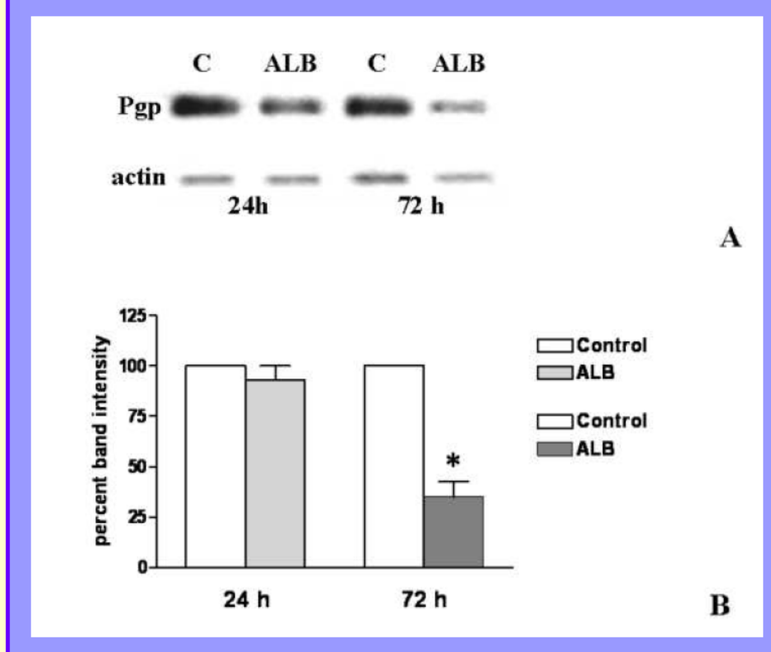
Methods:

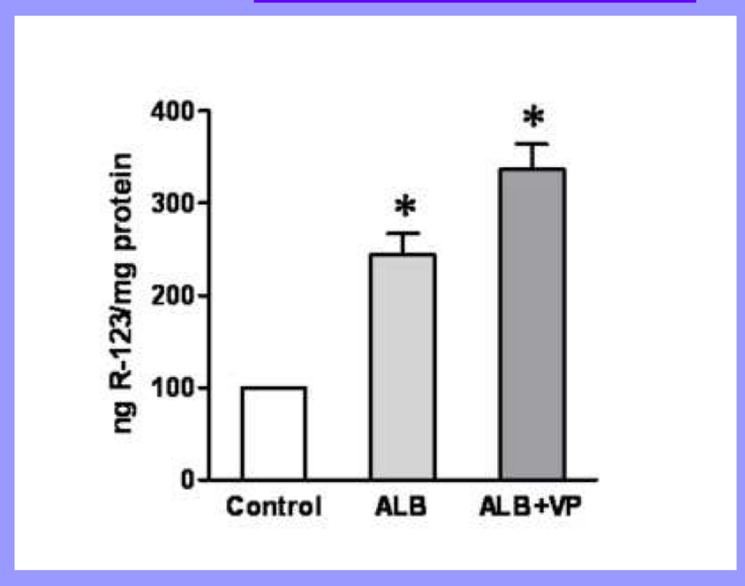
HK-2Tubular cells were cultured in presence of albumin (15 mg/ml, Scipac Ltd, UK) for 72 hours. Pgp protein expression was assessed by Western Blot (WB) mAb anti-Pgp clone F4, SIGMA. Semi-quantitative RT-PCR was performed to study ABCB1 gene expression.

Pgp transport function was evaluated by the test of intracellular accumulation of rodhamine-123.

BR (20 nM) was added in culture medium for 72 hours. p42/p44 MAP kinase assessed by WB using the Rabbit mAb Phospho-p44/42 MAPK Thr202/Tyr204, Cell Signaling Technology

Results:





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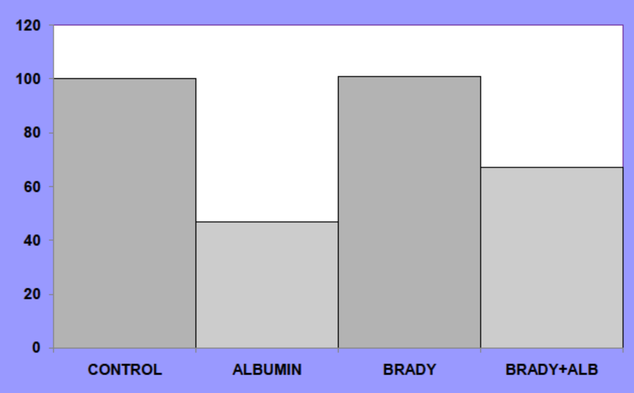
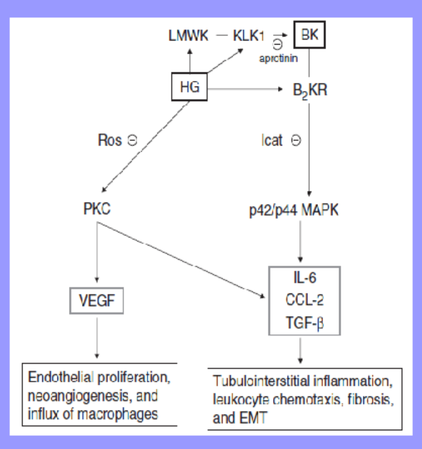
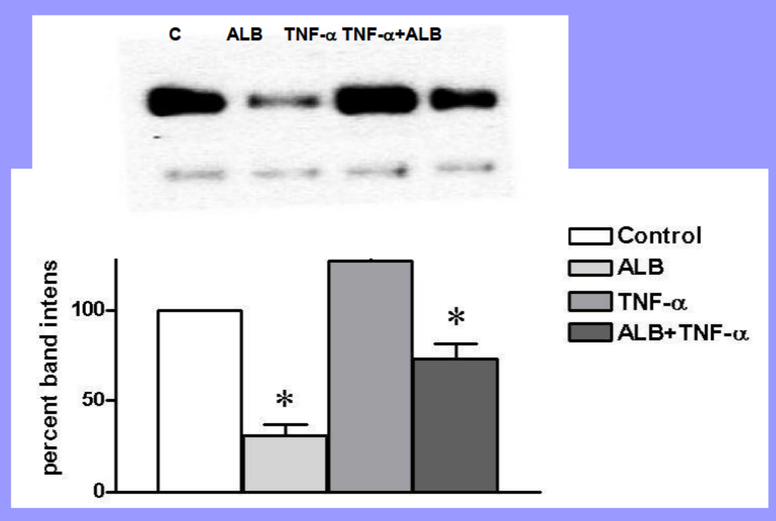
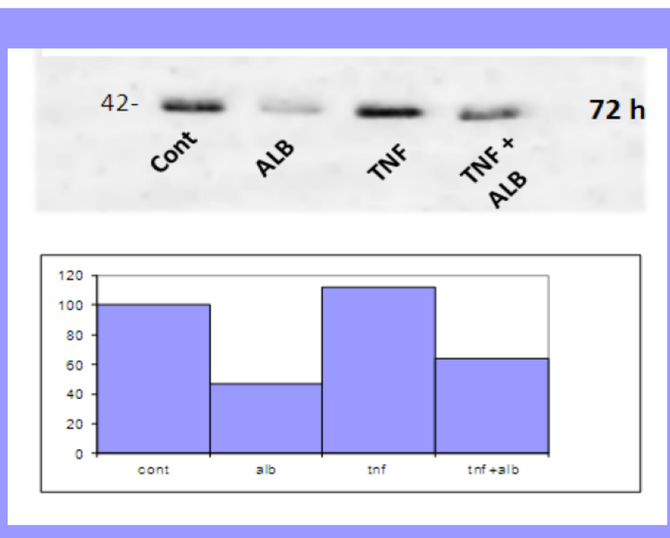
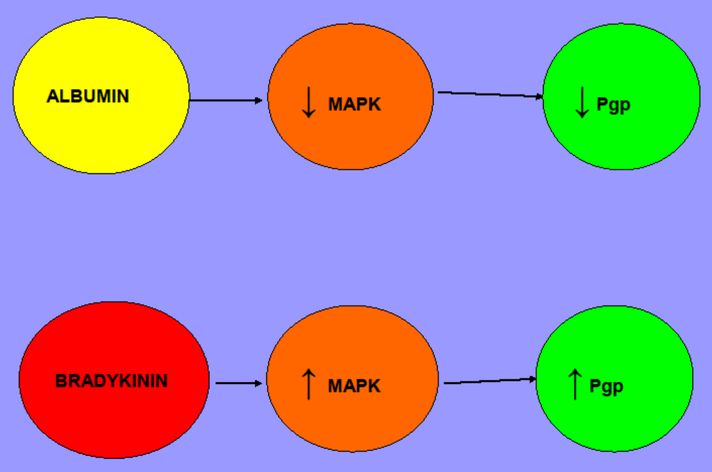




- Schema for the activation of renal tubular cells by glucose (HG) and bradykinin (BK) in promoting tubulointerstitial inflammation, fibrosis and neovascularization
- ACE inhibitors potentiate the effects of BK not only by decreasing its degradation but also by enhancing sensitivity to BK at a receptor level







Conclusions:

CONCLUSIONS

Tubular cells exposed to albumin show a reduction in the expression of Pgp with ensuing impairment in the membrane transport function. The albumin down-regulation of Pgp can be reversed by BR through MAPK pathway. These data provide further knowledge on the pathophysiology of tubular injury induced by proteinuria. The Pgp transport impairment induced by albumin may increase the sensitivity of tubular cells to chemicals leading to progression of renal damage observed in proteinuric diseases. Kinin system may make tubular cells less sensitive to protein damage and provide additional information on ACEI positive influence in proteinuric kidney diseases.

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