JNK modulates the effect of caspases and NF-kappaB in the TNF-alpha-induced down-regulation of Na+/K+ATPase in HepG2 cells.

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An inhibition of the Na(+)/K(+)ATPase was previously shown to accompany and potentiate apoptosis in different experimental models. Since TNF-alpha is known to be a pro and anti-apoptotic cytokine, this work was undertaken to study the effect of TNF-alpha on the Na(+)/K(+)ATPase in HepG2 cells and to determine the signaling pathway involved. Cells were incubated for 1 h with TNF-alpha in presence and absence of PDTC, SP600125 and FK009, respective inhibitors of NF-KB, c-JNK, and caspases. The activity of the pump was assayed by measuring the ouabain-inhibitable release of inorganic phosphate, and changes in its expression were monitored by western blot analysis. TNF-alpha decreased significantly the activity and protein expression of the Na(+)/K(+)ATPase. NF-kappaB and caspases were found to be the main effectors of the cytokine, mediating respectively down-regulation and up-regulation of the pump. Their activity was however modulated at 1 h by c-JNK, which stimulated the caspases and inhibited NF-kappaB, resulting in a net inhibition of the ATPase, and probably favoring the apoptotic pathway.