Tumor necrosis factor alpha down-regulates the Na+-K+ ATPase and the Na+-K+2Cl-cotransporter in the kidney cortex and medulla.

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The effect of TNF-alpha on the renal Na+-K+ pump and the Na+-K+2Cl- cotransporter was investigated in the rat. Animals were injected with the cytokine, and 4h later, a homogenate from the cortical and medullary tissues was prepared and used to assay the activity of the Na+-K+ ATPase and the protein expression of the pump and symporter. TNF-alpha reduced the activity and expression of the pump in both cortex and medulla, and its effect disappeared when animals were pre-treated with indomethacin, suggesting that TNF-alpha acts via PGE2. Higher levels of PGE2 were detected by enzyme immunoassay, in kidney tissues isolated from rats treated with PGE2, thus confirming this hypothesis. The cytokine also down-regulated the Na+-K+2Cl- cotransporter but this effect was not abrogated by indomethacin. PGE2, injected into animals, exerted a dose-dependent effect. Low doses did not have any effect on the two transporters in the cortex while high doses inhibited and down-regulated the pump and up-regulated the cotransporter. In the medulla low doses increased the activity and expression of the pump but down-regulated the cotransporter while high doses exerted an exactly opposite effect on the two transporters. It was concluded that the effect of TNF-alpha on the pump is mediated via PGE2 which is released at relatively high doses. The effect of the cytokine on the cotransporter is, however, independent of PGE2.

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