Tumor necrosis factor alpha alters Na+-K+ ATPase activity in rat cardiac myocytes: involvement of NF-kappaB, AP-1 and PGE2.

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There has been increasing evidence that tumor necrosis factor alpha (TNF-alpha) is synthesized by cardiomyocytes and contributes to their impaired function and to cardiac failure. Because the Na(+)-K(+) ATPase is a key player in the contraction of cardiomyocytes, this work was undertaken to study the effect of TNF-alpha on the Na(+)-K(+) ATPase in rat heart. Sprague Dawley rats (Rattus norvegicus) were injected with TNF-alpha (270 ng/100 g body weight) and 4 h later the ventricles were isolated, homogenized and assayed for their Na(+)-K(+) ATPase activity. The effect of TNF-alpha on the pump was studied also in isolated myocytes treated in suspension. The involvement of PGE2 was investigated by pre-treating animals or cells with indomethacin, an inhibitor of COX enzymes. The involvement of NF-kappaB and AP-1 was studied using their respective inhibitors PDTC and curcumin. A time response study showed an increase in the activity of the Na(+)-K(+) ATPase in the left and right ventricles of animals treated with the cytokine, with no change in its protein expression. This effect disappeared in the presence of indomethacin suggesting an involvement of PGE(2) in the action of TNF-alpha. Rats and cells treated directly with PGE(2) showed a dose-dependent response. A decrease in the activity of the Na(+)-K(+) ATPase was observed at a low dose and an increase at a high dose in both ventricles. Since PGE(2) is suspected to be the active mediator in TNF-alpha signaling, inhibiting its synthesis by inhibiting some suspected transcription factors was attempted. PDTC abrogated fully, and curcumin partially the effect of the cytokine. It was concluded that TNF-alpha activates NF-kappaB and AP-1 and induces PGE(2) release which alters dose-dependently the activity of the pump by activating different EP receptors with different affinities for PGE(2).