**UROCORTIN-MEDIATED STAT-3 ACTIVATION IS INDUCED BY EXPRESSION AND RELEASE OF IL-6**

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Treatment with urocortin (Ucn) of HL-1 cells was shown to induce Src-mediated phosphorylation and subsequent nuclear translocation of STAT3. In breast cancer cells, STAT3 was found to be activated by IL-6, while Ucn was shown to stimulate IL-1â and IL-6 secretion from mononuclear inflammatory cells. To verify whether cardiac myocytes can express and secrete IL-6, and, if so, to investigate the role of IL-6 in Ucn-mediated STAT3 activation, immortalized mouse atrial HL-1 cardiomyocytes were serum-starved for 16 to 20 hours. IL-6 enzyme-linked immunosorbent assay (ELISA) of the conditioned medium from starved HL-1 cells showed that 16 and 24 hours treatment with 10 nM Ucn significantly increased the secretion of IL-6, as compared to control cells. Conversely, Ucn did not induce the release in the culture medium of IL-1â, as documented by IL-1â ELISA. Quantitative real-time PCR confirmed the increased expression of IL-6, though not IL-1â, at the mRNA level. Interestingly, a concentration of Ucn as low as 0.01 nM, which can not activate Src kinase, was sufficient to stimulate expression and secretion of IL-6. TransAM STAT3 transcription factor assay (ELISA) of HL-1 nuclear extracts showed that nuclear translocation of STAT3 was significantly increased after 30 minutes incubation of 100 nM Ucn. STAT3 nuclear translocation was significantly reduced, though not abrogated, by incubation of HL-1 cells with anti-IL-6 polyclonal antibody. In conclusion, incubation of HL-1 cells with subnanomolar concentrations of Ucn induced the expression and secretion of IL-6, which resulted in STAT3 activation via an autocrine/paracrine mechanism independent from Src activation.