**UROCORTIN CAN MEDIATE CARDIOPROTECTION BY ACTIVATION OF THE SRC TYROSINE KINASE- STAT3 PATHWAY**

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Src tyrosine kinase family was recently identified as a novel upstream modulator of MAP kinase subfamily, p42/p44, whose activation is required for urocortin (Ucn)-mediated cardioprotection. Src kinase was also shown to reduce apoptosis in different cancer cell lines, enhancing phosphorylation and DNA binding affinity of Signal Transducer and Activator of Transcription (STAT) 3. In order to evaluate the effects of Ucn on the activation status of different STAT family members, HL-1 cardiac cells were incubated with Ucn (10nM) for increasing periods of time. STAT3 was rapidly phosphorylated at Tyr705, while neither phosphorylation at Ser727 nor induction of total STAT3 was observed. Pretreatment with PP2, a selective inhibitor of Src tyrosine kinase, reduced the pSTAT-T705 phosphorylation and transcriptional activity induced by Ucn in a dose-dependent manner. Overexpression of STAT3 in HL-1 cardiac myocytes pretreated with Ucn reduced the magnitude of cell death as compared to Ucn treatment alone, while transfection of HL-1 cells with a STAT3 mutant functionally inactive, acting as a dominant negative (DN-STAT3), enhanced the extent of cell death in a dose-dependent manner. In line with this finding, in HL-1 cardiac myocytes overexpressing STAT3 treated with Ucn, addition of the Src kinase inhibitor PP2 reversed the cytoprotective effects of Ucn, proving that the cytoprotective effects of Ucn are also mediated via the Src-pSTAT-T705 phosphorylation pathway. By immunocytochemistry, urocortin induced nuclear translocation of pST3-T705, which was inhibited by pretreatment with PP2. Together, these data strongly suggest that Ucn can mediate cardioprotection by activating the Src-pSTAT-T705 phosphorylation pathway.