Melanocortins modulate the JAK/ERK/STAT pathways in myocardial ischemia/reperfusion

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It is well established that the janus kinases (JAK), extracellular signal-regulated kinases (ERK) and signal transducers and activators of transcription (STAT) pathways play a cardioprotective role. Here we aimed to investigate the influence of cardioprotective agents, melanocortins, on the JAK/ERK/STAT signaling in cardiac and systemic responses to myocardial ischemia/reperfusion. Ischemia was produced in rats by ligature of the left anterior descending coronary artery for 30 min. At the end of the 2-h reperfusion, western blot analysis of the cardioprotective transcription factors pJAK2, pERK1/2, pTyr-STAT3 and pSer-STAT3, the inflammatory mediator tumor necrosis factor-α (TNF-α), the pro-apoptotic factors BAX and c-jun N-terminal kinases (pJNK), the anti-apoptotic protein Bcl-$_X$L, as well as of the cardioprotective enzyme heme oxygenase-1 (HO-1), was performed in the left ventricle, spleen and liver. Intravenous treatment, during coronary artery occlusion, with the melanocortin analogs [Nle^4, D-Phe^7]α-melanocyte-stimulating hormone (NDP-α-MSH) and adrenocorticotropic hormone 1-24 [ACTH-(1-24)], induced a left ventricle up-regulation of pJAK2, pERK1/2 and pTyr-STAT3 (JAK-dependent), and a reduction in pJNK and TNF-α levels; these effects of NDP-α-MSH and ACTH-(1-24) were associated with over-expression of the pro-survival proteins HO-1 and Bcl-$_X$L, and marked decrease of the myocardial infarct size. Melanocortin treatment did not affect left ventricle pSer-STAT3 (ERK1/2-dependent) and BAX levels. In the spleen and liver, NDP-α-MSH and ACTH-(1-24) induced similar effects on the expression of the above transcription factors/proteins, except for pERK1/2 (down-regulated) and HO-1 (unaffected). Pharmacological blockade of JAK and ERK pathways abrogated the myocardial infarct size reduction by NDP-α-MSH. These results indicate that melanocortins inhibit local and systemic detrimental responses triggered by prolonged myocardial ischemia/reperfusion, seemingly via modulation of the JAK/ERK/STAT signaling pathways.