JAK/ERK/STAT signalings are modulated by melanocortins in myocardial reperfusion via the vagus nerve

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Janus kinases (JAK), extracellular signal-regulated kinases (ERK) and signal transducers/activators of transcription (STAT) pathways are involved in the melanocortin-induced cardioprotection during myocardial ischemia/reperfusion (1). Here we investigated whether these effects occur via the vagus nerve-mediated cholinergic anti-inflammatory pathway (2,3). Ischemia was produced in rats by ligature of the left anterior descending coronary artery for 30 min; the effects of ischemia/reperfusion were evaluated on the heart and liver. During coronary artery occlusion, intravenous treatment with the melanocortin analog (Nle4, D-Phe7)α-melanocyte-stimulating hormone (NDP-α-MSH) induced a left ventricle up-regulation of the cardioprotective transcription factors pJAK2, pERK1/2 and pTyr-STAT3 (JAK-dependent), and a reduction in the levels of the inflammatory mediators tumor necrosis factor-α (TNF-α) and pJNK (also involved in apoptosis), as assessed by western blot analysis at the end of the 2-h reperfusion period. These beneficial effects of NDP-α-MSH were associated with heart over-expression of the pro-survival proteins heme oxygenase-1 (HO-1) and Bcl-XL. In the liver, NDP-α-MSH induced a decrease in the pJAK2, pTyr-STAT3 and pERK1/2 expression. In the liver of ischemic rats NDP-α-MSH also blunted pJNK and TNF-α expression, and up-regulated Bcl-XL. Bilateral cervical vagotomy prevented all effects of NDP-α-MSH, both in the heart and liver. These results indicate that in prolonged myocardial ischemia/reperfusion the vagus nerve mediates the melanocortin-induced modulation of the JAK/STAT/ERK signalings both in the heart and liver, with consequent mitigation of the inflammatory and apoptotic responses.

1. Ottani et al. (2013). *Pharmacol Res.* 72, 1-8.
2. Ottani et al. (2010). *Eur J Pharmacol.* 637, 124-30.
3. Giuliani et al. (2012). *Front Neuroendocrinol.* 33, 179-93.