PROTECTIVE EFFECT OF NDP-α-MSH ON HEART, SPLEEN AND LIVER, VIA THE VAGUS NERVE AND JAK/ERK/STAT SIGNALING, IN MYOCARDIAL ISCHEMIA IN RATS

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Background. Heart ischemia/reperfusion injury still represents a major problem into clinical setting, also for the preservation of other organs which could be damaged. Experimental evidence indicates that natural melanocortins and synthetic analogs also exert cardioprotective effects via janus kinases (JAK), extracellular signalregulated kinases (ERK) and signal transducers/activators of transcription (STAT) pathway (Ottani et al., 2013). There is evidence indicating that an efferent vagal fibre-mediated cholinergic pathway – called "cholinergic anti-inflammatory pathway – plays physiological protective roles, including a cardioprotective role. " (Giuliani et al., 2012).

Aim. Here we investigated whether melanocortin induced modulation of the JAK/ERK/STAT signaling occurs via the cholinergic anti-inflammatory pathway, focusing our study on cardiac, splenic and hepatic responses to prolonged myocardial ischemia/reperfusion.

Methods. Ischemia was obtained in rats by ligature of the left anterior descending coronary artery for 30 min. Five min before coronary occlusion, rats were subjected to bilateral cervical vagotomy by tying two silk sutures around each vagal trunk. Effects of ischemia/reperfusion were evaluated using Western blot of heart, spleen and liver proteins.

Results. Intravenous treatment, during coronary artery occlusion, with the melanocortin analog (Nle4, D-Phe7) α-melanocyte-stimulating hormone (NDP-α-MSH) induced a left ventricle upregulation 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 (a transcription factor also involved in apoptosis), as assessed at the end of the 2-h reperfusion period. Further, these beneficial effects of NDPα-MSH were associated with heart over-expression of the pro-survival proteins heme oxygenase-1 (HO-1) and Bcl-XL, and decrease of ventricular arrhythmias and infarct size. In the spleen and liver NDP-α-MSH induced a decrease in the pJAK2 and pTyr-STAT3 levels, and strongly reduced pERK1/2 expression. In the spleen and liver of ischemic rats NDP-α-MSH also blunted pJNK activity and TNF-α expression, and up-regulated Bcl-XL. Bilateral cervical vagotomy (performed 5 min before coronary occlusion) prevented all effects of NDP-α-MSH, both in the heart and liver.

Conclusion. These results support our hypothesis that melanocortins inhibit heart, spleen and liver damage triggered by prolonged myocardial ischemia/reperfusion. Likely, this occurs through the activation on vagus nerve that modulates the JAK/STAT/ERK signaling pathways. Present findings should also promote clinical studies for the potential use of

melanocortin analogs in the management of local and systemic reactions to myocardial

ischemia and reperfusion.

References

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