Melanocortins Protect Rats Undergoing Cardiac Arrest

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It is well-known that melanocortins and synthetic analogs induce cardioprotection in experimental myocardial ischemia/reperfusion (1), with involvement of the janus kinases (JAK), extracellular signal-regulated kinases (ERK) and signal transducers and activators of transcription (STAT) signalings (2). Here we studied the influence of the melanocortin analog [Nle4,D-Phe7]α-melanocyte-stimulating hormone (NDP-α-MSH) on pathological responses to cardiac arrest (CA) induced in rats by intravenous (i.v.) administration of potassium chloride, followed by cardiopulmonary resuscitation (CPR) plus epinephrine treatment. In CA/CPR rats i.v. treated with epinephrine (0.1 mg/kg) 48% returned to spontaneous circulation and at 1 h and 3 h after CPR we evaluated several parameters. We recorded low values of mean arterial pressure (MAP) and heart rate (HR), alteration of hemogasanalysis, left ventricle low expression of the cardioprotective transcription factors pJAK2 and pTyr-STAT3 (JAK-dependent), increase in oxidative stress, up-regulation of the inflammatory mediators tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and down-regulation of the anti-inflammatory cytokine IL-10. Treatment during CPR with epinephrine plus NDP-α-MSH (340 μg/kg, i.v.) improved survival rate by 81%, almost completely restored the basal conditions of MAP and HR, reversed metabolic acidosis, induced left ventricle up-regulation of pJAK2, pTyr-STAT3 and IL-10, attenuated oxidative stress, down-regulated TNF-α and IL-6 levels. These results indicate that melanocortins, in experimental conditions of CA/CPR, are able to improve return to spontaneous circulation, reverse metabolic acidosis, and inhibit heart oxidative stress and inflammatory cascade, these effects being seemingly mediated by activation of the JAK/STAT signaling pathway. The present findings should encourage further, long-term studies, because a treatment with melanocortins plus epinephrine might represent a novel and effective approach to the management of CA/CPR and consequent systemic responses, including neurological, renal, hepatic and pulmonary alterations.

1. Giuliani et al. (2012). *Front Neuroendocrinol.* 33, 179-93.
2. Ottani et al. (2013). *Pharmacol Res.* 72, 1-8.