MOLECULAR BASIS FOR THE PROTECTIVE EFFECT OF MELANOCORTIN 4 RECEPTOR STIMULATION IN HEMORRHAGIC SHOCK

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We have previously shown that stimulation of melanocortin 4 receptors (MC4R) reverses hemorrhagic shock and improves survival. Here we investigated the molecular basis for the protective influences of MC4R stimulation. *Methods.* Severe hemorrhagic shock was produced in adult rats under general anesthesia. Rats were then treated with either the selective MC4R agonist RO27-3225 or saline. Analysis of the gene expression profile was performed in heart and liver samples using the Clontech Atlas Plastic Rat 4K Microarrays that contain long oligonucleotide probes from 4000 named rat genes. Array data were analyzed using the Significance Analysis of Microarrays procedure. Gene functional annotation and classification was performed using the Database DAVID 2007 (http://david.abcc.ncifcrf.gov). *Results.* Analysis of gene expression in the heart showed that treatment with the MC4R agonist RO27-3225 induced genes encoding the potassium channels Kcnh6 and Kcnmb1, glucose and adenosine transporters, proteins involved in response to oxidative stress (cytochrome C, protein tyrosine phosphatase, thioredoxin interacting protein), and α1-actin. Conversely, treatment markedly down-regulated acute phase response genes (α2-macroglobulin and coenzyme A dehydrogenase) and damage-associated molecular pattern proteins (Hmgb1 and S100 calcium-binding protein). Chloride, sodium and calcium channels and/or binding proteins were also down-regulated. Similar to the heart, RO27-3225 induced several potassium channels (Kcnab1, Kcnb2, Kcnc1, Kcnh7, Kcnk9, and Kcnn3) and repressed acute phase proteins (C-reactive protein, α1-antitrypsin, fibrinogen, complement component 3, and Mug1) in the liver. In addition, transcripts involved in synaptic transmission (catecholamine-O-methyltransferase, nicotinic cholinergic receptor, clathrin, neuroxin 2, and ionotropic kainate 3 glutamate receptor), regulatory transcription factors (Sp1, Sox10, Relax, and Nr2f1), adenylyl cyclases 4 and 6, and organic anion transporters were induced by treatment. Conversely, apolipoproteins A and E, gluthatione S-transferases Gstm2 and Mgst1, and ribosomal proteins were down-regulated by the MC4R agonist. *Conclusions*. The data indicate that MC4R stimulation during hemorrhagic shock protects the heart from acute damage, stabilizes membrane potential, preserves cellular viability, and sustains contractile function. Moreover, the reduced expression of inflammatory genes in the liver indicates control of the systemic inflammatory reaction.