The Melanocortin Analog RO27-3225 Prevents Hemorrhage-Induced Alterations in Liver Gene Expression

D. Giuliani[1], C. Lonati[2], S. Gatti[2,3], P. Leonardi[3], A. Carlin[3], A. Ottani[1], M. Galantucci[1],A. Catania[2] and S. Guarini[1]

[1]Dept. of Biomedical, Metabolic and Neural Sciences, Section of Pharmacology and Molecular Medicine, University of Modena and Reggio Emilia, Modena, Italy; [2]Centro di Ricerche Chirurgiche Precliniche Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano, and [3]Dept. of Fisiopatologia Medico-Chirurgica e dei Trapianti, University of Milano, Milano, Italy

Hemorrhage triggers signaling events that promote induction of genes involved in stress and heat shock response, inflammatory reaction, and apoptosis. Systemic inflammation and organ damage can occur, and in the most severe cases multiple organ dysfunction syndrome, as a serious complication associated with high morbidity and mortality (Jastrow et al., 2009; Hierholzer and Billiar, 2001; Alam et al., 2002; Guarini et al., 2003). It has been previously found that melanocortin peptides improve hemodynamic parameters and prevent death during severe hemorrhagic shock (Bertolini et al., 1986; Giuliani et al., 2007, 2012). Of note, the anti-shock effect of melanocortins in experimental and clinical conditions has been recently highlighted by Corander et al. (2009) in an authoritative review aimed at spreading these relevant findings of basic science to clinicians. To gain further insights into the mechanisms of the anti-shock effect of melanocortins, in the present research we determined the influence of a synthetic melanocortin 1/4 receptor agonist on the molecular changes that occur in rat liver during hemorrhage. Indeed, liver biology is highly susceptible to ischemic injury associated with hemorrhagic shock, and impairment in liver function widely affects other organs (Alam et al., 2002; Guarini et al., 2003). Hemorrhage was performed in adult rats under general anesthesia by a stepwise blood withdrawal until mean arterial pressure fell to, and stabilized at, 40 mmHg. Then rats received either saline or the synthetic melanocortin 1/4 receptor agonist RO27-3225. Hemogasanalysis was performed throughout a 60-min period. Gene expression in liver samples was determined at 1 h or 3 h using quantitative real-time polymerase chain reaction. At 1 h, in saline-treated shocked rats there were significant increases in Atf3, Egr1, Hmox1, Fos, and Jun. These changes were prevented by RO27-3225. Increases in A2m, Hspa1a, Epo and Il-6 occurred at 3 h in shocked rats and were prevented by RO27-3225 treatment. At 3 h in shocked rats treated with RO27-3225 there were also significant increases in Tjp1 and Nr4a1, relative to sham animals. Further, treatment with RO27-3225 rapidly restored blood pressure, hemogasanalysis parameters and lactate blood levels. In conclusion, here we show that melanocortin treatment is able to significantly prevents most of the systemic and hepatic detrimental changes induced by hemorrhage. Indeed, treatment with the MC_1/MC_4 agonist RO27-3225 rapidly restores blood pressure, gradually reverses metabolic acidosis, prevents detrimental gene expression changes and causes induction of genes with a protective function. Because blood replacement alone does not inhibit hemorrhagic shock-induced systemic inflammation and tissue injury, our previous (Giuliani et al., 2007,2012) and present data suggest that a melanocortin-based treatment could exert substantial beneficial effects.

References

Alam et al (2002).*Resuscitation*. 54, 195-206.
Bertolini et al (1986). *Eur J Pharmacol*. 130, 19-26.
Corander et al (2009) *Circulation*. 120, 2260-8.
Giuliani et al (2007). *Br J Pharmacol*. 150, 595-603.
Giuliani et al (2012). *Front Neuroendocrinol*. 33, 179-93.
Guarini et al (2003). *Circulation,* 107, 1189-99.
Hierholzer and Billiar (2001). *Langenbecks Arch Surg*. 386, 302-8.
Jastrow et al (2009). *J Am Coll Surg*. 209, 320-31.