Protective effects of the melanocortin NDP-α-MSH in a murine model of multiple organ dysfunction syndrome: evidence for an involvement of the “brain cholinergic anti-inflammatory pathway”

Alessandra Bitto  
Tutor: Prof. Salvatore Guarini

Current understanding of the pathophysiology underlying sepsis-induced multiple organ dysfunction (MODS) highlights the multiple cell populations and cell-signaling pathways involved in this complex condition. Melanocortins have been shown effective in reducing multiple organ damage and improved survival following circulatory shock. The ZIGI model has been recognized as the one that best resembles human MODS and it has been used widely to study systemic inflammation in relation to organ failure. Our aim was to demonstrate that NDP-α-MSH via MC4 receptor stimulation can be protective in zymosan-induced MODS.

The experiment was performed using C57BL/6 mice, 9 weeks old weighing 20–25 g. The ZIGI model for MODS consists of an aseptic intraperitoneal injection of 40 μg lipopolysaccharide (LPS; Escherichia coli, Sigma Chemical, St Louis, MO) dissolved in 200 μL of phosphate-buffered saline, followed 6 days later by zymosan (Sigma Chemical Co.) administration (day 0). Zymosan dose was of 0.8 mg/g body weight. Sham-ZIGI animals received only phosphate-buffered saline. Another group of animals received only the vehicle (Sham-MODS).

ZIGI mice were randomly divided into 3 groups:

Group 1: a daily treatment with vehicle.

Group 2: a daily treatment with NDP-a-MSH (340 ug/kg/day).

Group 3: a daily treatment concomitantly with NDP-α-MSH (340 ug/kg/day) and with nicotinic acetylcholine receptor antagonist chlorisondamine (0.25 mg/kg, subcutaneously).

Sham-MODS animals were randomly divided into 2 groups:

Group 1: Sham MODS receiving vehicle

Group 2: Sham MODS receiving a daily treatment with NDP-a-MSH (340 ug/kg/day).
Survival was evaluated 16 days after zymosan administration. At day 7, after zymosan injection 6 randomly assigned animals from each group were sacrificed, and their livers and lungs were collected. Total RNA was extracted and subsequently analyzed for TNF-α and IL-10 determination. NDP-α-MSH (340 ug/kg/day) significantly reduced ZIGI-induced TNF-α expression in either liver and lung and augmented IL-10 expression, suggesting a protective role of NDP-α-MSH in this experimental model. Moreover NDP-α-MSH (340 ug/kg/day) increased survival of ZIGI mice.