EFFECT OF MELANOCORTINS IN A TRANSGENIC MOUSE MODEL OF SEVERE ALZHEIMER'S DISEASE

Eleonora Vandini[1], Antonietta Vilella[1], Eleonora Daini[1], Letizia Manca[1], Alessandra Ottani[1], Michele Zoli[1], Salvatore Guarini[1], Daniela Giuliani[1], Carlo Baraldi[1], Anita Calevro[1]

[1]Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università di Modena e Reggio Emilia, Modena - Italy

Introduction: Alzheimer's disease (AD) is a chronic disorder characterized by progressive neurodegeneration associated with cognitive decline and behavioral deficits. Furthermore, inflammatory, apoptotic and excitotoxic responses play an important role in the above mentioned pathophysiological pathways. Melanocortins (MC) are endogenous peptides of the adrenocorticotropin/melanocyte-stimulating hormone family and acting via five different melanocortin G protein-linked receptors (MC1-MC5). MCs and their agonist synthetic analogs, like [Nle4,D-Phe7]α-melanocyte-stimulating hormone (NDP-α-MSH), have been reported to possess a multitude of protective actions, including anti-inflammatory and neuroprotective actions also in early and mild experimental AD. It is well know that neuroprotective effects of MCs are mediated by central nervous system MC_4receptors and occur through an inhibition of the main mechanisms of brain damage (inflammation, apoptosis and excitotoxicity). Low melanocortin levels have been found in occasional studies performed in AD-type dementia patients. Aim of this study has been to investigate whether melanocortins induce neuroprotection and reduce cognitive decline in a transgenic mouse model of severe AD.

Materials and methods: Transgenic mice (5XFAD) 30-weeks-old (at the start of the study) and their wild-type littermates were used. Transgenic mice were treated for 50 days, intraperitoneally (i.p), with the MC agonist NDP-α-MSH (NDP, 320 μg/kg); 5XFAD controls, as well as wild-type animals, were treated with an equal volume of saline solution i.p. To investigate learning and memory, at the day 50 of the experiment, mice underwent 4consecutive days of Morris water-maze (MWM) test, followed by a Probe test. At the end of the last behavioral test, animals were sacrificed and mice brains were removed and processed for histological and biomolecular examination.

Results: Control 5XFAD mice treated with saline showed impaired ability (as compared with wild-type mice) in cognitive performance. On the contrary, in 5XFAD animals treated with NDP a significant improvement in learning and memory performance occurred, compared with saline-treated control mice . Surprisingly, NDP did not preserve brain histological parameters as GFAP, Amyloid-beta and IBA1. Also parameters of inflammation and apoptosis weren't decreased by chronic treatment with the melanocortin.

Discussion and conclusions: Recently our studies have shown that chronic treatments with MCs prevent/slow neurodegeneration in early and mild AD experimental models. Here, for the first time, we demonstrate that, in a murine model of severe AD, melanocortins confirm protection against the weakening of cognitive performance, but this effect was not accompanied by a blockage of histological and biomolecular neurodegeneration in the hippocampus, in cortex and in the Gyrus Dentatus. These data open a new hypothesis on the neuroprotective mechanism of MCs which would imply not only anti-inflammatory and apoptotic actions (effective in early and mild AD) but also other pathways still unknown. In conclusion, the current data show, for the first time, that melanocortins could induce neuroprotection in AD not only through previously found mechanisms. This will be the goal of future studies.