Stimulation of brain melanocortin MC4 receptors enhances neurogenesis and counteract cognitive decline in a transgenic mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is the most frequent cause of dementia in Western societies. The progression of AD occurs through the activation of pathophysiological pathways commonly involved in both acute and chronic neurodegenerative disorders. Besides neuroprotective approaches, also neurorestorative strategies for AD are under intensive investigations (Tayeb et al., 2012). Melanocortins are small endogenous peptides derived from the common precursor proopiomelanocortin. Melanocortins have been proved capable of inducing neuroprotection in different experimental conditions of acute neurodegeneration, with long-lasting cognitive recovery (Giuliani et al., 2012). Moreover, we reported that melanocortins are able to stimulate neurogenesis in an acute neurodegenerative disorder such as ischemic stroke (Giuliani et al., 2011).

Based on the studies previously carried out, the purpose of this work was to study the possible induction of cognitive improvement and neurogenesis also in a model of chronic neurodegeneration as AD.

Tg2576 transgenic mice of 24 weeks of age (at the beginning of the study) carrying the human transgene APPswe were treated once a day for 50 days with a nanomolar dose of the syntetic analog [Nle4, D-Phe7] α-melanocyte-stimulating hormone (NDP-α-MSH) or equivalent volume of saline. Animals were prepared for 5-bromo-2'-deoxyuridine (BrdU) labeling of proliferating cells at days 1-11 of the study, and histological and immunohistochemical studies of the brain were performed. For the study of cognitive performance, animals were subjected, at the twenty-seventh week (starting 14 days after the first BrdU injection) and thirty-first week of age, to behavioral Morris water maze test. All values were analyzed by means of two-way repeated measures ANOVA (behavioral data) or one-way ANOVA (all other data), both followed by the Student-Newman-Keuls' test. A value of $p < 0.05$ was considered significant.

The treatment of Tg2576 mice (once daily on days 1-50) with NDP-α-MSH has led to a reduction in the levels of beta-amyloid deposits in the hippocampus and cortex and to an improvement of cognitive function, when compared with the animals treated with saline alone ($p < 0.001$). Despite the chronic treatment, no signs of toxicity were recorded. Immunohistochemical evaluation at day 50 (end of study) showed, in the dentate gyrus of the hippocampus of Tg2576 mice treated with NDP-α-MSH, a very large number of BrdU-immunoreactive cells that colocalized with NeuN (marker of mature neurons) and Zif268 (indicator of neurons functionally integrated), in comparison to Tg2576 animals treated with saline solution ($p < 0.001$). Animal pretreatment (20 minutes before each administration of NDP-α-MSH) with the selective melanocortin MC4 receptor antagonist HS024 prevented all favourable effects of NDP-α-MSH ($p < 0.001$).

Our data indicate that melanocortin MC4 receptor agonists are able to counteract the cognitive decline in Alzheimer's disease not only offering neuroprotection, but also causing intense neurogenesis. These agents could be candidates for an innovative strategy to prevent the progression of AD in humans.

Tayeb et al. (2012). *Pharmacol Ther.* 134, 8-25.
Giuliani et al. (2012). *Front Neuroendocrinol.* 33, 179-93
Giuliani et a. (2011). *Acta Neuropathol.* 122, 443–53.