NDP-α-MSH Preserves Brain Morphology and Cognitive Performance in Tg2576 Mice with Moderate Alzheimer's Disease

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Melanocortins are endogenous peptides with well-recognized anti-inflammatory and neuroprotective activity (1). They also induce neuroprotection in experimental Alzheimer's disease (AD) of mild severity (2). Aim of this study was to investigate whether melanocortins induce neuroprotection and reduce cognitive decline in AD with a medium level of severity by using APPSwe transgenic mice (Tg2576). Treatment for 50 days with saline induced in control Tg2576 mice (24 week-old at the start of the study) an impairment in spatial learning and memory, associated (at day 50) with hippocampus low levels of the synaptic activity-dependent gene Zif268, relevant morphological alterations in the cerebral cortex/hippocampus with increased level of β-amyloid (Aβ) deposit, and neuronal loss, in comparison with wild-type animals. Treatment of Tg2576 mice (once daily for 50 days) with the melanocortin analog [Nle4,D-Phe7]α-melanocyte-stimulating hormone (NDP-α-MSH) reduced cerebral cortex/hippocampus level of Aβ deposit, decreased neuronal loss, increased hippocampus Zif268 expression and reduced cognitive decline, relative to saline-treated Tg2576 mice. The MC4 receptor antagonist HS024 prevented all beneficial effects of NDP-α-MSH. All these data indicate that MC4 receptor-stimulating melanocortins improve cognitive performance in experimental AD of medium severity through induction of neuroprotection and improvement of synaptic transmission. If confirmed by further studies, these findings could have important clinical implications.

1. Giuliani et al. (2012). *Front Neuroendocrinol.* 33, 179-93.
2. Giuliani et al. (2014).*Neurobiol Aging*.35, 537-47.