Activation of Melanocortin MC_4 Receptors Slows Down Progression of Alzheimer's Disease in APP_{Swe} /$PS1_{M146V}$/Tau_{P301L} Transgenic Mice

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Melanocortins induce neuroprotection and neurogenesis in experimental acute neurodegenerative conditions (Giuliani et al., 2006, 2011, 2012), and low melanocortin levels have been found in occasional studies performed in Alzheimer's disease (AD)-type dementia patients (Facchinetti et al, 1984; Arai et al., 1986; Rainero et al., 1988). Because several pathophysiological pathways are common to acute and chronic neurodegenerative disorders (Lo, 2010), here we investigated the possible neuroprotective role of melanocortins in a chronic neurodegenerative disease, AD, by using 12 week-old (at the start of the study) triple-transgenic (3xTg-AD) mice harboring human transgenes APP_{Swe}, $PS1_{M146V}$ and tau_{P301L} (Oddo et al., 2003). Saline-treated 3xTg-AD mice showed an impairment in spatial learning and memory (assessed at 17 and 30 weeks of age), associated (at 30 weeks) with many brain changes such as cerebral cortex/hippocampus increased phosphorylation/level of biomarkers of the amyloid/tau cascade, malondialdehyde, nitrites, inflammatory and apoptotic mediators, as well as marked neuronal loss, in comparison with wild-type animals. Treatment of 3xTg-AD mice, once daily until the end of the study, with a nanomolar dose of the melanocortin analog [Nle^4,D-Phe^7]α-melanocyte-stimulating hormone (NDP-α-MSH) reduced, through an interaction with MC_4 receptors, cerebral cortex/hippocampus phosphorylation/level of all above AD-related biomarkers, decreased neuronal loss, induced over-expression of the synaptic activity-dependent gene Zif268 and improved cognitive functions, relative to saline-treated 3xTg-AD mice. In conclusion, our data show for the first time that MC_4 receptor-stimulating melanocortins are able to counteract the progression of experimental AD by targeting pathophysiological mechanisms up- and down-stream of Aβ and tau; these multiple beneficial effects might be due to a physiologically arranged self-defence machinery that is activated after the MC_4 receptor-mediated signal transduction of NDP-α-MSH, and that targets multiple AD-related pathophysiological pathways. These findings could be of clinical relevance.

References

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