Comorbid depression in Alzheimer's disease (AD): novel observations from a longitudinal study in the triple-transgenic mouse model

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Alzheimer's disease (AD) is characterized by progressive impairment of memory accompanied by neuropsychiatric disturbances such as anxiety and depression (Assal and Cummings, 2002). Patients with mild cognitive impairment and depression have more than twice the risk of developing AD-type dementia than patients without depression (Modrego and Ferrández, 2004).

The triple transgenic mouse model of AD (3×Tg-AD) harbouring the mutant human genes $PS1_{M146V}$, APP_{Swe}, and Tau_{p301L} shows cognitive decline with amyloid-beta (Aβ) and tau pathology in a regional- and age-dependent manner that mimics the disease progression in humans (Oddo et al., 2003). We have recently demonstrated that 3×Tg-AD mice exhibit depressive-like behavior at the advanced stage of their AD-like pathology (Romano et al., 2015).

In the present work we evaluated more comprehensively the depressive-like phenotype of 3×Tg-AD mice and their wild-type littermates (Non-Tg) in parallel to the progression of their brain pathology in the frontal cortex (FC) and ventral hippocampus (vHIPP), two areas mostly affected in AD and highly involved in the regulation of depressive-/anxiety-related behavior. In particular, we conducted a longitudinal study testing the animals at 2 (pre-pathologic phase), 6 (presence of intraneuronal Aβ immunoreactivity) and 12 (Aβ deposits and early stages of tau pathology) months of age. Their behavior was examined in the Porsolt forced swim test (FST), the tail suspension test (TST), and the sucrose preference test (SPT), three paradigms that are broadly accepted as models to explore depressant- and anxiety-like behavior in mice and that respond to the acute administration of anti-depressant drugs. At the end of the behavioral studies, animals were sacrificed and their brains were analysed by immunohistochemistry.

Both in the FST and TST, 3×Tg-AD mice showed age-related behavioral alterations. Depressive-like behavior was first detected at 6 months of age, when 3×Tg-AD mice spent significantly more time in immobility as compared to Non-Tg mice. Similar differences were observed in 12-month-old mice. The behavioral differences in these tests were even more evident following the acute administration of the antidepressant drug desipramine (20 mg/kg. i.p.), which was able to decrease the immobility time in old Non-Tg mice, but was totally ineffective in 3×Tg-AD mice.

3×Tg-AD mice showed also significant decrease in sucrose preference, with respect to Non-Tg mice, at both 6 and 12 months of age. The two genotypes did not show any behavioral difference at 2 months of age.

Results from immunohistochemistry showed a significant increase of Aβ staining in 6-month-old 3×Tg-AD mice in both FC and vHIPP, while no tau immunoreactivity was found at this age. At 12 months of age we found dense Aβ and tau deposition in FC and vHIPP. None of these immunoreactive structures were detected in the Non-Tg brains.

These results suggest that cognitive alterations in 3×Tg-AD mice are paralleled by depressive-like and anhedonia-like behavior that appears at 6 months of age, thus suggesting that Aβ alteration can impact not only on the learning and memory but also on the non-cognitive domain in this model of AD.

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