Late-life depression accelerates cognitive impairment and tau-associated pathology in an Alzheimer´s disease model

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Clinical studies suggest that depression could be considered an important risk factor for the future development of cognitive impairment and Alzheimer's disease (AD). In fact, there is a strong association between late-life depression and AD. The age of AD onset has been shown to be accelerated in patients with mild cognitive impairment (MCI) with a history of depression, and women appear to be particularly more vulnerable to this condition. In addition, individuals with MCI who present depressive symptoms have an elevated burden of amyloid-beta (Aβ), the main toxic protein associated with Alzheimer's pathology, and a higher risk of developing AD compared to non-depressed MCI patients. Although it has been described that some transgenic models of AD can develop signs similar to depression in advanced stages, the induction of Alzheimer's pathology due to a depressive process has not been studied under experimental conditions to emulate late-life depression as a risk factor for AD. In this study, we induced chronic unpredictable mild stress (CUMS) in P301S tau transgenic mice to determine whether depression is a cause, rather than a consequence, of the development of AD pathology. Our results suggest that transgenic tau mice subjected to CUMS seem to develop a depressive state. This animals display enhanced cognitive impairment compared to controls. In addition, histological studies show increased tau deposition, suggesting that late-life depression could worse AD progression by accelerating tau aggregation and worsening clinical signs. The findings generated in this project could provide evidence of depression as a risk factor for AD, providing new insights on molecular mechanisms involved in AD onset and progression.