FLUOXETINE AND VORTIOXETINE REVERSE DEPRESSIVE-LIKE PHENOTYPE AND MEMORY DEFICITS INDUCED BY AMYLOID-β(1-42) OLIGOMERS IN MICE: A KEY ROLE OF TRANSFORMING GROWTH FACTOR-β1

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Introduction: Depression is a risk factor for the development of Alzheimer's disease (AD), and the presence of depressive symptoms significantly increases the conversion of Mild Cognitive Impairment (MCI) into AD. A long-term treatment with antidepressants reduces the risk to develop AD and different second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are currently studied for their neuroprotective properties in AD. An impairment of neurotrophic factors signaling seems to be a common pathophysiological event in depression and AD. In particular a deficit of Transforming Growth Factor-β1(TGF-ß1) has been found both in depression and AD. In the present work the SSRI fluoxetine and the new multimodal antidepressant vortioxetine were tested for their ability to prevent memory deficits and depressive-like phenotype in a non-transgenic (non-Tg) model of AD by rescue of TGF-ß1signaling.

Materials and methods: We used a non-Tg model of AD obtained by intracerebroventricular (i.c.v.) injection of amyloid-β (1-42) ($A\beta_{1-42}$) oligomers in 2-month-old C57BL/6mice. Sterile 0.1M phosphate-buffered saline (PBS) was injected i.c.v. into control animals (vehicle). Memory deficits in Aß-injected mice were evaluated with the Novel Object Recognition Tests (ORT) and Passive Avoidance Test (PAT), while the Forced Swim test (FST) was used to assess depressive-like behavior. Starting from 7days before Aβ i.c.v. injection, fluoxetine (10 mg/kg) and vortioxetine (5and 10 mg/kg) were intraperitoneally injected daily, for 24or 26days. In order to correlate the preclinical efficacy of fluoxetine and vortioxetine with the effects on neuroinflammatory phenomena, we examined the mRNAs levels of different pro-inflammatory (IL-1β, TNF-α) and anti-inflammatory cytokines (IL-4, TGF-ß1) in the hippocampus by using quantitative real-time polymerase chain reaction (qRT-PCR), whereas active TGF-β1levels in the hippocampus were examined by western blot analysis.

Results: I.c.v. ($A\beta_{1-42}$) injection induced both memory deficits and a depressive-like behavior in mice. In particular mice treated with $A\beta_{1-42}$showed, 14days after Aβ injection, a significantly reduced latency time in PAT and an impairment of recognition memory in ORT when compared with vehicle control animals. Aβ injection also induced after 19days a significant increase in immobility time in FST. Chronic treatment with fluoxetine and vortioxetine (both at the dose of 10 mg/kg) was able to rescue the loss of memory assessed 14days after Aβ injection by the PAT and the ORT. Both antidepressants reversed the increase in immobility time detected 19days after Aβ injection by FST. Vortioxetine exerted significant antidepressant effects also at the dose of 5mg/kg. A significant deficit of TGF-β1, paralleling memory deficits and depressive-like phenotype, was found in the hippocampus of Aβ-injected mice. Fluoxetine and vortioxetine completely rescued hippocampal TGF-β1levels in Aβ-injected mice.

Discussion and conclusions: A chronic treatment with fluoxetine or vortioxetine can prevent both cognitive deficits and depressive-like phenotype in a non-transgenic animal model of AD with a key contribute of TGF-β1. Overall our data suggest that a deficit of TGF-β1might represent one of the neurobiological links between depression and AD and also that rescue of TGF-β1signaling with second-generation antidepressants might represent a new pharmacological strategy to prevent both amyloid-induced depression and cognitive decline in AD.