Second-generation antidepressant drugs exert neuroprotective effects against Aßtoxicity via an increased secretion of the anti-inflammatory cytokine Transforming-Growth-Factor-ß1

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Transforming-Growth-Factor-β1 (TGF-β1) is an anti-inflammatory cytokine that exerts neuroprotective effects against ß-amyloid (Aβ)-induced neurodegeneration. An impairment of TGF-β1 signaling pathway has been demonstrated to be specific to the Alzheimer's disease (AD) brain, and particularly to the early phase of the disease (Tesseur et al. 2006).
Deficit of TGF-β1 seems to be a common pathophysiological event both in depression and AD. Depression is a risk factor for the development of AD and the presence of depressive symptoms significantly increases the conversion of Mild Cognitive Impairment (MCI) into AD. Unpredictable chronic mild stress (UCMS), an animal model of depression, exacerbates Aß accumulation in the 3×Tg-AD mouse model of AD (Rothman al. 2012). The +10 CC genotype of TGF-ß1 gene, which affects the levels of expression of TGF-ß1, increases the risk to develop Late-Onset AD (LOAD) and is also associated with depressive symptoms in AD (>5-fold risk) (Caraci et al. 2012).Plasma TGF-ß1 levels are reduced in major depressed patients, and, interestingly, different second-generation antidepressant drugs, including venlafaxine, paroxetine and sertraline, increase circulating TGF-ß1 levels in major depressed patients. In addition, Kessing et al. (2009) reported that continued long-term antidepressants treatment is associated with a reduction in the rate of AD. Whereas these data identify TGF-β1 signaling as a potential common target for both depression and AD, the potential neuroprotective activity of antidepressant drugs against Aβ-induced neurodegeneration *in vitro* has been only partially explored.
We examined the neuroprotective activity of fluoxetine and sertraline both in pure and mixed rat neuronal cultures challenged with synthetic Aß(1-42) oligomers (100nM) for 48 hours.Aß(1-42) oligomers were prepared according to the original protocol of Klein's group (Gong et al. 2003), and administered to cell cultures in the presence of ionotropic glutamate receptor antagonists to avoid the potentiation of endogenous glutamate toxicity. Aß(1-42) oligomers induced the apoptosis of about 20-30% of the total neuronal population. At therapeutic concentrations (100nM-1μM), fluoxetine and sertraline significantly prevented Aβ-induced toxicity in mixed cultures, but not in pure neuronal cultures. A neutralizing antibody against TGF-ß1 (2μg/ml) prevented the neuroprotective effects of antidepressant drugs against Aβ-induced neurodegeneration in mixed cultures. Consistent with a glia-mediated effect, a 24 hr treatment of astrocytes with fluoxetine and sertraline promoted the release of TGF-β1 in the culture media by increasing the conversion of Pro-TGF-ß1 to TGF-ß1.
Our data demonstrate that second-generation antidepressant drugs are neuroprotective *in vitro* against Aß-induced neurodegeneration and suggest that drugs able to increase the release of TGF-β1, such as fluoxetine and sertraline, might represent new neuroprotective tools for the treatment of AD.

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