Impairment of neurotrophin signaling in Alzheimer's disease: searching for new pharmacological targets

F. Caraci[1,2]

[1]Dept. of Drug Sciences, University of Catania, Catania, Italy
[2]IRCSS Associazione Oasi Maria S.S., Institute for Research on Mental Retardation and Brain Aging, Troina, Italy

An impairment in the signaling of different neurotrophins such as Brain-derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF) and Transforming-Growth-Factor-ß1 (TGF-ß1) has been demonstrated in Alzheimer's disease (AD) brain in an early phase of the disease.

ß-amyloid (Aß) accumulation is an early event in AD pathogenesis which can lead to pro-inflammatory processes even before the onset of cognitive decline.A strong neurobiological link has been found in AD brain between this early pro-inflammatory process and the deficit of neurotrophic factors such as NGF and TGF-ß1. A dysfunction in the extracellular metabolism of NGF that compromises Pro-NGF maturation and exacerbates its subsequent degradation has been recently proposed as a contributor to cholinergic neuron dysfunction in AD and Down Syndrome (DS), and hence to cognitive decline (Iulita and Cuello 2014). However, it is not known whether these CNS alterations are reflected in periphery and finally if a relationship exists between Aβ accumulation, peripheral biomarkers related to inflammation and NGF dysfunction in lymphocytes from DS patients with AD. We are currently examining whether DS lymphocytes from DS individuals can reflect, in the periphery, a deficit of NGF known to occur in DS brain in a preclinical stage of AD (Iulita, Caraci & Cuello 2015).

TGF-β1 is an anti-inflammatory cytokine that exerts neuroprotective effects against Aβ-induced neurodegeneration. Recently, we have identified a key role for TGF-β1 in recognition memory formation demonstrating that this neurotrophic factor is essential for the transition from early to late Long-Term-Potentiation (Caraci et al. 2015). An impairment of TGF-β1 signaling pathway has been demonstrated to be specific to the AD brain, and particularly to the early phase of the disease. Deficit of TGF-β1 seems also 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 into AD. Plasma TGF-ß1 levels are reduced in major depressed patients, and, interestingly, different second-generation antidepressant drugs increase circulating TGF-ß1 levels in depressed patients. In addition, it is known 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 have examined the neuroprotective activity of fluoxetine and sertraline both in pure and mixed rat neuronal cultures challenged with synthetic Aß(1-42) oligomers (100nM).We found that fluoxetine and sertraline, at therapeutic concentrations (100nM-1μM), significantly prevented Aβ-induced toxicity in mixed cultures, but not in pure neuronal cultures, via a paracrine mechanism mediated by TGF-ß1. 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 mature TGF-ß1.

Our data demonstrate that second-generation antidepressants are neuroprotective *in vitro* against Aß-induced neurodegeneration by rescuing TGF-β1 signaling and also suggest that drugs able to increase the release of active TGF-β1, such as fluoxetine and sertraline, might represent new neuroprotective tools for the treatment of AD.

Caraci et al.(2015), 5:11252.
Iulita F, Caraci F & Cuello AC. (2015).AD/PD Conference, 2015.
Iulita F& Cuello AC, (2014).TIPS.2014,35:338-348.