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Rescue of TGF- β 1 signalling as a new strategy for neuroprotection in AD: Role of antidepressant drugs

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Transforming-Growth-Factor- β 1 (TGF- β 1) is an anti-inflammatory cytokine that exerts neuroprotective effects against β -amyloid (A β)-induced neurodegeneration. An impairment of TGF- β 1 signaling pathway has been demonstrated in an early phase of Alzheimer's disease (AD) pathogenesis. Deficit of TGF- β 1 seems to be a common pathophysiological event both in depression and AD. Depressive symptoms may be among the earliest symptoms of preclinical stages of AD and a long-term treatment with antidepressants is known to reduce the risk to develop AD. Plasma TGF- β 1 levels are reduced in depressed patients, and, interestingly, different second-generation antidepressants increase circulating TGF- β 1 levels in depressed patients. Whereas these data identify TGF- β 1 signaling as a potential common target for both depression and AD, the potential neuroprotective activity of antidepressants against A β -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 A β (1-42) oligomers (100 nM) for 48 hours. We found that therapeutic concentrations (100 nM-1 μ M) of fluoxetine and sertraline significantly prevented A β -induced toxicity in mixed cultures, but not in pure neuronal cultures. A neutralizing antibody against TGF- β 1 (2 μ g/ml) prevented the neuroprotective effects of antidepressant drugs against A β -induced neurodegeneration in mixed cultures. Consistent with a glia-mediated effect, a 24 hr treatment of astrocytes with fluoxetine promoted the release of active TGF- β 1 in the culture media. Our data demonstrate that second-generation antidepressants are neuroprotective *in vitro* against A β -induced neurodegeneration by rescuing TGF- β 1 signaling and suggest that these drugs might represent new neuroprotective tools for the treatment of AD.

Biography

Filippo Caraci is Assistant Professor of Psychopharmacology at the Department of Educational Sciences of the University of Catania. He has worked in the field of Neuropharmacology focusing his attention on the neurobiology of Alzheimer's disease with the aim to identify new pharmacological targets. He has published more than 60 papers in peer reviewed journals and serving as referee for several international journals in the fields of pharmacology. He is an associate faculty member of F1000 and he is also Reviewing Editor of Frontiers in Experimental Pharmacology and Drug Discovery.

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