

TRANSFORMING GROWTH FACTOR- β 1 PROTECTS RAT CORTICAL NEURONS AGAINST EARLY AND LATE β -AMYLOID TOXICITY

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Transforming growth factor β 1 (TGF- β 1) is a pleiotropic cytokine, which is known to exert a neuroprotective role in Alzheimer's disease. Estrogens enhance TGF- β 1 secretion in rat cortical astrocytes and the medium collected from estrogen-treated astrocytes is protective when transferred to cultured neurons challenged with β -amyloid (A β) (1). Several mechanisms have been proposed to explain the neuroprotective action of TGF- β 1 against A β -induced neurotoxicity, such as cell cycle inhibition or the increased expression of anti-apoptotic proteins. Nevertheless the specific molecular pathways involved in these phenomena are presently unknown.

We examined the neuroprotective properties of TGF- β 1 in pure cultures of rat cortical neurons challenged with the toxic A β fragment (25–35). When applied to mature pure rat cortical neurons, 25 μ M A β (25–35) (in the presence of 10 μ M MK-801 + 30 μ M DNQX) induced the apoptosis of about 40–50% of the total neuronal population at 24 hours. TGF- β 1 (10 ng/ml), similarly to the cell-cycle inhibitor flavopiridol (0.3 μ M), was able to rescue about 85–90% of A β -treated neurons when added 1 hour before the peptide. Interestingly, a similar extent of protection was observed when TGF- β 1 was added 6 hours after A β , an experimental condition in which flavopiridol was inactive. These data suggest a mechanism other than cell cycle inhibition in the neuroprotective effect of TGF- β 1 during the late phase of A β toxicity. A down-regulation of the Wnt pathway, with ensuing GSK3 β activation, is known to occur late in A β -induced neuronal apoptosis (2). Western blot analysis showed that TGF- β 1 prevented the activation of GSK3 β , the increase in tau phosphorylation and the down-regulation of β -catenin levels induced by A β at 24 hours. TGF- β 1 per se promoted the inactivation of GSK3 β via the PI3k/Akt pathway. The selective inhibitor of the PI3k/Akt pathway, LY294002 (10 μ M), significantly reduced the neuroprotective effects of TGF- β 1 by preventing the inhibition of the cell cycle and the inactivation of GSK3 β induced by TGF- β 1 in A β -treated neurons.

We conclude that TGF- β 1 both inhibits the cell cycle and rescues the Wnt signaling in A β -treated neurons via the PI3k/Akt pathway, thus affecting both the early and late phase of A β toxicity.

REFERENCES

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