NEUROPROTECTION BY GDNF AND A PHYSICAL EXERCISE THERAPY IN THE 3XTGAD MOUSE MODEL

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Background: AD is a neurodegenerative disorder clinically characterized by memory loss and cognitive damage. It is suggested that in a situation of cholinergic deficit, an imbalance between the excitatory glutamatergic and inhibitory GABAergic tone may be responsible for non-cognitive behavioral disturbances which result on neuropsychiatric symptoms (BPSD). Participation in a regular exercise program is increasingly proposed as an intervention that could prevent or reduce cognitive and mood disorders of age-associated dementias. An involved mechanism consists on neurotrophic factors induction. Recent studies have demonstrated in vivo the GDNF neurotrophic effects against the neuronal atrophy causing cognitive deficits.

Methods: We have over-expressed GDNF in hippocampal astrocytes by lentiviral vector transduction in male 3xTgAD mice. To evaluate the neuroprotective potential of astrocytes on cognitive and BPSD we used corner test, open field and Morris Water Maze assays. We also analyzed the effects of forced and voluntary exercise in male and female 3xTgAD mice to evaluate GABA-A and NMDA receptors functionality through radiometric binding methods in cerebral cortex.

Results: GDNF hippocampal astrocytes transfection of 3xTgAD mice induced an improvement of the spatial memory retention. Both exercise therapies recovered GABA-A receptor affinity in transgenic male mice. Voluntary exercise reversed the total NMDAR density in male 3xTgAD mice.

Conclusions: Results of GDNF over-expression in hippocampal astrocytes has allowed to consider this cell type as a good candidate for therapeutic intervention against neurodegeneration in AD. Voluntary exercise has demonstrated to be a promising coadyuvant therapy to ameliorate the imbalance between excitatory and inhibitory neurotransmisions in AD.