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Nerve growth factor in the aging brain: friend or foe?

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Motivation and Aim: It is well-known that nerve growth factor (NGF) plays an important role in the brain development and maturation in early ontogeny. It is considered that in the mature brain NGF controls survival of cholinergic neurons in the basal forebrain. However, possible contribution of NGF to the functioning of the adult and, particularly, aging brain is not completely known. In the present study, we investigated how neurotrophins and their receptors changed with aging and whether the NGF overexpression protected the brain in a model of cholinergic degeneration.

Methods: The experiments were performed in 3-, 17–18- or 22–24-month-old male Wistar rats. Animal behavior was studied using water maze. Brain samples were dissected and the levels of NGF or brain-derived neurotrophic factor (BDNF) were measured in hippocampus and frontal cortex using specific ELISA kits (Millipore, USA). The levels of TrkA, TrkB or p75NTR receptors were assayed using western-blot analysis with specific antibodies (SCBT or Millipore, USA).

Results: Aged 22–24-month-old rats exhibited slower rate of learning compared to young 3-month-old rats; however, long-term memory indices were similar in these groups. The content of NGF but not BDNF increased in both neocortex and hippocampus during aging. Significant age-dependent decrease in active, maximally glycosylated forms of TrkA (140 kDa) and TrkB (145 kDa) was revealed in the neocortex; while no major changes of partially glycosylated forms (110 and 95 kDa respectively) could be detected. In the hippocampus, similar decrease was revealed in the content of 95 kDa TrkB receptor whereas 110kDa TrkA receptor increased. Age-related changes in neocortical p75 receptor were similar to those of Trk receptors. Taken together, aging induced a complex decrease in neurotrophin receptors in the neocortex indicating significant alterations in neurotrophin signaling in the aged brain and these alterations were more pronounced in the NGF-associated processes.

Overexpression of NGF in the hippocampus significantly improved behavioral impairments induced in rats by administration of immunotoxin 192IgG-saporin into the medial septal nucleus, a model of Alzheimer-like cholinergic deficit. It was associated with a significant improvement of hippocampal neuroplasticity impaired after 192IgG-saporin administration. However, we did not find any effect of this treatment on survival of the basal forebrain cholinergic neurons or their functioning.

Conclusion: Thus, aging is accompanied by changes in the neurotrophin system in the neocortex and hippocampus and these changes were unidirectional in the neocortex and the opposite in the hippocampus. NGF overexpression in the hippocampus of rats with cholinergic deficit significantly improved animal behavior and neuropalsticity but did not protect cholinergic neurons from degeneration.

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