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ALZHEIMER DISEASE

NGF gene therapy activates neurons in the AD patient brain

Genetic delivery of nerve growth factor (NGF) could activate neuronal trophic responses in patients with Alzheimer disease (AD), according to results from a phase I clinical trial, published recently in *JAMA Neurology*. The findings suggest that genetic delivery of growth factors might help prevent or reduce loss of cholinergic neurons in AD. "This is the largest series of humans that have undergone postmortem analysis of the brain to evaluate the effects of growth factors," says Mark Tuszynski, who led the study.

Degeneration of cholinergic neurons is an early and prominent contributor to cell loss and cognitive decline in AD. Previous studies in animal models of AD have shown that NGF can stimulate cholinergic neurons and prevent their death. However, growth factors are a potent class of biologically active proteins, and can cause off-target adverse effects, necessitating a targeted delivery strategy to control their localization and spread in the brain.

Tuszynski and colleagues from the University of California, San Diego, USA, used viral vectors for controlled amplification of NGF secretion in the basal forebrains of 10 patients with early AD. After the patients' deaths—on average, 5.4 years later—their brains were harvested and the effects of *NGF* gene therapy on cholinergic neurons were evaluated via immunohistochemical analysis.

"We found a neuronal growth response to the presence of NGF in every patient," says Tuszynski. Axons—including those of neurons that exhibited tau pathology—sprouted toward the local source of NGF. The investigators did not observe any adverse pathological effects related to NGF.

According to the authors, the degenerating neurons retained an ability to sense and respond to NGF up to 10 years after *NGF* gene transfer. The safety and consistent, long-lasting effects of *NGF* gene therapy support expansion of the investigations. A phase II multicentre, sham-surgery-controlled trial of NGF in AD will be completed later in 2015. This trial will also compare the cognitive outcomes of *NGF* gene therapy and sham surgery in patients with AD.

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According to Tuszynski, brain-derived neurotrophic factor (BDNF) also has potential applications in AD; moreover, its effects could be broader than those of NGF. "BDNF might counteract the loss of key memory circuits in the brain and improve their function," Tuszynski hopes.

To date, the majority of clinical trials in AD have targeted amyloid pathology, and the results have been largely disappointing. As growth factors do not target amyloid, they could provide an alternative or complementary strategy to slow down neuronal atrophy in AD.

The findings support the general rationale for testing growth factor therapies in human neurodegenerative disorders. Indeed, a phase II trial of glial cell line-derived neurotrophic factor gene therapy in Parkinson disease is currently underway.

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