

Application of Nerve Growth Factor in Alzheimer's Disease

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Alzheimer's Disease (AD) is the most common form of dementia, which is characterized by a progressive decline in memory and cognitive function, accompanied with behavioral changes such as confusion, irritability and aggression, mood swings, language breakdown and eventually long-term memory loss. The most significant pathological findings in the brain affected by AD are senile plaques, neurofibrillary tangles, neuron loss or degeneration, particularly in the areas connected to the cerebral cortex and hippocampus, one of the most prominent among the regions being the basal forebrain cholinergic neurons. Although many basic and clinical studies have shown that drug treatment could improve the cognitive function and memory of AD patient, it is still a considerable challenge to delay and/or stop the neuron loss and degeneration.

Previous studies showed that imbalance of neurotrophic factors in the brain and lack of neurotrophic support causes neuronal atrophy and death. Among the neurotrophic factors, Nerve Growth Factor (NGF) is the best characterized one. Knockout of NGF in adult transgenic mice leads to severe neuronal death in basal forebrain cholinergic neurons. Several *in vivo* and *in vitro* studies have demonstrated that Intra Cerebro Ventricular (ICV) NGF administration completely prevents the retrograde degeneration of cholinergic neurons and increases learning and memory in the animal model of AD [1]. However, NGF is a large molecular protein that does not easily cross the blood-brain barrier. The delivery of NGF to the brain poses a major challenge for clinical application. Here, we will focus on the delivery strategies of NGF on brain and beneficial effects of delivered NGF on cholinergic neurons and functional recovery of AD.

ICV NGF Administration

The beneficial effects of ICV NGF administration in the AD model with fimbria-fornix transection have been studied nearly 30 years ago. Studies performed in aged animals showed that ICV NGF administration could reverse age-associated basal forebrain cholinergic neuronal degeneration and improve the learning and memory. Furthermore, in non-human primate brain, the ability of NGF could also prevent basal forebrain cholinergic neuronal degeneration and correct the learning and memory. One clinical trial was reported in 1998. In this study, three AD patients were treated with murine ICV NGF injection and showed certain beneficial effects. Two negative side effects occurred after NGF treatment, back pain and weight reduction [2]. Scientists keep seeking options to deliver NGF into the brain.

Gene Therapy

The idea method is to build genetically modified cells that could secrete NGF for a long time. After transplantation, genetically modified cells can secrete NGF in the brain. In 2005, Tuszynski et al. [3] reported that six AD subjects were transplanted with genetically modified autologous fibroblasts to express human NGF. Mini-Mental Examination and Scale-Cognitive Assessment showed improvement in the rate of cognitive decline. PET scans showed significant increases in cortical 18-fluorodeoxyglucose after treatment. Recent clinical study in Sweden showed that six AD patients were bilaterally implanted one or two human NGF biodelivery device, NsG0202. After 12 month

observation, no adverse events were related to NGF or the device. Positive findings in cognition, EEG and nicotinic receptor binding in 2 of 6 patients were detected [4].

NGF-Releasing Implant

First NGF-releasing implant is that NGF was encapsulated into ethylene vinyl acetate (EVA) to form several millimeter-thickness disks. NGF-releasing implants could release bioactive NGF. Furthermore, NGF-releasing implants could provide continuous stimulation of neurite growth in the PC12 cells for nearly 8 weeks. After transplantation in the brain, NGF-releasing implants placed within 1-2 mm of the treatment site enhanced the biological function of cellular targets [5].

NGF-Releasing Microspheres

NGF-releasing implants need an open operation to deliver them into the brain. This operation often causes surrounding tissue damage. In order to overcome this limitation, some groups developed NGF-releasing microspheres to deliver NGF into the brain. For drug delivery to the brain, the size of microspheres formulated is less than 100 μm . Microspheres can be easily injected using the stereotaxy technique into precise and functional areas of the brain, without causing damage to the surrounding tissues. Using water/oil/water (W/O/W) emulsion and solvent evaporation technique, Menei et al. [6] formulated NGF-releasing biodegradable microspheres. Intracerebral implantation of NGF-releasing biodegradable microspheres had a protection in striatum against excitotoxicity damage. Using similar technique, our group formulated recombinant human NGF (rhNGF)-releasing microspheres for the treatment of AD. rhNGF-releasing microspheres could sustain release NGF about 4-5 weeks *in vitro* and *in vivo*. Released rhNGF could stimulate neurite outgrowth in PC12 cells. After injection into the brain with fimbria-fornix transection, rhNGF-releasing microspheres promote survival of basal forebrain cholinergic neurons and improve memory impairments [7,8]. Moreover, glial derived neurotrophic factor (GDNF) was encapsulated into microspheres to formulate GDNF-releasing microspheres. Implantation of GDNF-releasing microspheres could increase dopaminergic survival and ameliorate the symptoms of Parkinson's disease (PD) [9].

Although NGF has been widely used for the treatment of neurodegenerative diseases studies, such as AD and PD, it is still not

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used for clinical application due to blood-brain barrier. How to find better ways to deliver NGF into the brain is still challenge.

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