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## NERVE GROWTH FACTOR AND ALZHEIMER'S DISEASE

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## Mini Review

# Nerve Growth Factor and Alzheimer's Disease

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### 1. Introduction

Nerve growth factor (NGF) is the first neurotrophic factor discovered in the snake venoms and mouse submaxillary glands in the 1950s. Mouse NGF is a protein consisting of 118 amino acids and physiologically maintains neuronal survival, facilitates neurite outgrowth and stimulates neuronal differentiation of the basal forebrain cholinergic neurons in addition to the peripheral sympathetic neurons and neural crest-derived sensory neurons. NGF is synthesized at the sites innervated by axons of NGF-responding neurons, taken into the axons from axonal terminals via a receptor and transported to the cell body in a retrograde fashion. Namely, NGF is believed to be a typical target tissue-derived neurotrophic factor. Not only immature neurons but also mature ones continue to respond to NGF especially for maintenance of neuronal functions and neuroprotection.

NGF has more than 50% amino acid sequence homology with each other and with brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3 or NT-4, and they form the neurotrophin family.<sup>1,2</sup> Each neurotrophin binds to a corresponding high affinity receptor, TrkA, TrkB or TrkC, and shows various neurotrophic actions, however, causes cell death through a low affinity neurotrophin receptor p75 commonly used in all neurotrophins.<sup>3</sup> Furthermore, it was found that precursor of NGF (proNGF) is secreted extracellularly, binds as high affinity ligand to p75, and transduces pleiotropic signals including death signal.<sup>4</sup> In other words, NGF is a double-edged sword to determine the life and death of cells including neurons, and elucidation of the regulatory mechanisms is strongly expected to understand the biological significance of NGF.

### 2. Neuroprotective effect of NGF and neurological diseases

#### 2.1 Alzheimer's disease:

Basal forebrain cholinergic neural pathway is significantly impaired in Alzheimer's disease, which correlates with a decrease in memory and learning ability.<sup>5</sup> Although it was believed that the action of NGF is confined to the peripheral nervous system for a while after the discovery, NGF had been found in the brain and suggested to act as a neurotrophic factor for basal forebrain cholinergic neurons.<sup>6</sup> Since attention has been focused on aging earlier in the western society (in the 1980s), Alzheimer's disease has become a serious social problem. A new treatment method

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utilizing the NGF has been greatly expected. However, there was a need for NGF to be injected into the brain because NGF cannot pass through the brain-blood barrier. Therefore, only few cases of clinical trials had been carried out. On the other hand, in a relation of NGF to the pathology, it was suggested that the "lack of NGF" theory of Alzheimer's disease may be correct. Amount of NGF produced in the cerebral cortex and hippocampus of patients is increased somewhat, but decreased in the septal area, a transport destination of NGF through cholinergic neuronal tracts. The axonal transport impaired by the neurofibrillary tangles and senile plaques may be responsible for a lack of NGF trophic for basal forebrain cholinergic neurons. This impairment leads to degeneration and drop out of the cholinergic neurons and results in reduced memory and learning ability. ProNGF has been reported to be increased in Alzheimer's brain.<sup>7</sup> Therefore, NGF may be concerned with the secondary pathological step of the disease, though it is not considered as a primary cause of the disease. Cerebrospinal fluid content of proNGF has recently been expected as a putative biomarker for early Alzheimer's disease.<sup>8</sup> Furthermore, a recent study<sup>9</sup> has shown that among 10 patients of Alzheimer's disease, degenerating neurons in the brain responded to NGF, and that all patients exhibited a trophic response to NGF in the form of axonal sprouting toward the NGF source. These observations suggest that administration of NGF is promising for the treatment of Alzheimer's diseases.

## **2.2 Peripheral neuritis:**

Diabetes complicated by peripheral neuritis in many cases. Diabetes has been studied in details using the I-type model. In this model, decrease of NGF level of peripheral tissues is found in parallel with the decrease of the motor nerve conduction velocity, and peripheral administration of NGF improves the neuropathic symptoms.<sup>10</sup> On the basis of these results, clinical trials for human were carried out, but no improvement was observed. Neurotrophic factors such as NGF is unlike the hormone over the blood. The difference of the production site and producing cells is closely related with the physiology. NGF is transported by diffusion and/or axonal transport in the tissues or organs from the production site to the action site. Therefore, the method of administration and the administration site must be in line with the physiology of NGF. Due to its susceptible degradation in the body as a protein, development of stable low-molecular-weight compounds with the NGF-like activity may be a promising approach. Specifically, the following activities are required to achieve this approach, 1) stimulatory activity to elicit physiological NGF production; and 2) NGF-like inducible activity with intracellular signals.<sup>11</sup> In fact, we administered low-molecular-weight compounds that promote NGF production, and succeeded in inhibition of onset and improving the symptoms of the neurological disorders of animal models.<sup>12-14</sup>

## **2.3 Neuropathic pain**

When acute inflammation occurs in the peripheral tissues such as skin, expression of NGF is enhanced there, and nerve growth-associated protein 43 (GAP43) and substance P are enhanced in dorsal root sensory neurons projecting axons to the inflamed skin. NGF is thought to be involved in the formation of inflammatory hyperalgesia and tactile hypersensitivity. These actions are inhibited by pre-injection of NGF antibody into the inflamed tissue.<sup>15</sup>

NGF synthesis is facilitated by interleukin-1 and various inflammatory mediators produced by macrophages in inflamed tissues, and the increased NGF is believed to enhance the nociceptive activity acutely and transiently. On the other hand, refractory chronic neuropathic pain is triggered by the spinal cord injury and peripheral nerve damage. Similar symptoms caused by chronic compression by ligation of the sciatic nerve are suppressed by continuous NGF infusion.<sup>16</sup> Chronic hypersensitivities is thought to be induced by increasing glutamate release that causes neuronal death and/or synapse reconstruction. NGF might inhibit these processes depending on its neurotrophic activity. The nociceptive actions of NGF have been recognized as side effects when used clinically. Genetically engineered NGF molecules with proper amino acid displacement are promising because such NGFs retain the original neurotrophic activity without nociceptive activity.<sup>17</sup>

## **3. NGF is a double-edged sword**

### **3.1 TrkA and p75 receptors:**

As described above, TrkA, and p75 are high and low affinity type NGF receptors, respectively.<sup>3</sup> TrkA

is a transmembrane receptor with intracellular tyrosine kinase. NGF binding to TrkA causes autophosphorylation of TrkA, and starts intracellular signal transduction. This signal is transmitted to different 3 signaling cascades such as ras/mitogen-activated protein kinase pathway, the phosphatidylinositol 3-phosphate kinase pathway and phospholipase C gamma-1 pathway. As a result, NGF exhibits typical neurotrophic effects, maintenance of neuronal survival and facilitation of neuronal differentiation including neurite outgrowth.

It has been considered that the high-affinity of TrkA is guaranteed by the interaction with p75, because TrkA and p75 are coexpressed in particular neurons. However, p75 is structurally belong to the tumor necrosis factor (TNF $\alpha$ ) receptor family, and has been shown to mediate cell death signals as similar to TNF receptor and Fas antigen. However, as the cell death through p75 is suppressed when TrkA is coexpressed, survival signal of TrkA is considered to be manifested in preference to cell death-inducing signal of p75. Therefore, NGF-induced cell death had been regarded only as a special case, i.e., it takes place in the cells with p75 and without TrkA. However, it has proposed in 2001 that proNGF induces neuronal cell death through the p75 receptor, and subsequent studies have revealed that the physiological ligand for p75 is proNGF rather than NGF.<sup>18</sup> P75 is located on the cell membrane surface in combination with sortilin, a type I transmembrane protein. ProNGF binds to p75-sortilin complex with high affinity. Namely, precursor domain binds to p75 and mature domain, to sortilin.<sup>19</sup> Thus, the paradigm on NGF signaling has changed greatly over the past decade.

### **3.2 Physiology of NGF precursor (proNGF)**

It had been believed that NGF is synthesized as precursor form in the endoplasmic reticulum and Golgi apparatus, converted to the active form (mature form) by specific cleavage enzymes such as furin, and secreted extracellularly as the cleaved mature form. However, following discoveries leads to a new paradigm, 1) proNGF is secreted from the cells transfected with NGF gene, 2) proNGF content is elevated in the brain of Alzheimer's disease, 3) proNGF induces cell death of oligodendrocytes in the injury site of the spinal cord. Namely, proNGF can be secreted out from cells under physiological or particular pathologic conditions and shows plural biological activities via p75.

Interaction between signals of cell death and survival is complicated. For example, proNGF induces apoptosis through binding to p75-sortilin complex of cells expressing TrkA, p75 and sortilin. However, if mature NGF is present, NGF binds to TrkA-p75 complex and generates survival signal to suppress cell death. Both types of signals seem to compete within the cells.<sup>20</sup> Increased proNGF in the brain of Alzheimer's disease patients might facilitate cell apoptosis, which will be one of the mechanisms to lead the pathogenesis of Alzheimer's disease.

### **3.3 Involvement of other neurotrophins in apoptosis**

BDNF, a member of neurotrophin family other than NGF, is a neurotrophic factor that has variety functions. BDNF plays roles for differentiation and migration of cells during neural development stages, and for cell survival and synaptic functions in adulthood.<sup>1</sup> Similar biological activities of BDNF precursor (proBDNF) to those of proNGF are reported.<sup>20</sup> That is, proBDNF also induces apoptosis via binding to p75-sortilin complex. How is the balance of mature form to precursor form of neurotrophins determined? Elucidation of this mechanism is valuable to understand the functions and diseases of nervous systems at molecular and cellular level, and also gives a lot of tips effective in disease treatment. Progress of future researches is expected.

## **4. References**

1. Skaper SD (2012). The neurotrophin family of neurotrophic factors: an overview. *Methods Mol Biol*, **846**, 1-12, doi: 10.1007/978-1-61779-536-7\_1.
2. Chao MV (2003). Neurotrophins and their receptors: A convergence point for many signalling pathways. *Nature Reviews Neuroscience*, **4**, 299-309.
3. Barbacid M (1995). [Neurotrophic factors and their receptors](#). *Curr Opin Cell Biol*, **7**, 148-155.

4. Beattie MS, Harrington AW, Lee R, Kim JY, Boyce SL, Longo FM, Bresnahan JC, Hempstead BL, Yoon SO (2002). ProNGF induces p75-mediated death of oligodendrocytes following spinal cord injury. *Neuron*, 36, 375-386.
5. Bartus RT, Dean RL 3rd, Beer B, Lippa AS (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science*, 30, 217, 408-414.
6. Korsching S, Auburger G, Heumann R, Scott J, Thoenen H (1985). Levels of nerve growth factor and its mRNA in the central nervous system of the rat correlate with cholinergic innervation. *EMBO J*, 4, 1389-1393.
7. Fahnstock M, Michalski B, Xu B, Coughlin MD (2001). The precursor pro-nerve growth factor is the predominant form of nerve growth factor in brain and is increased in Alzheimer's disease. *Mol Cell Neurosci*, 18, 210-220.
8. Counts SE, He B, Prout JG, Michalski B, Farotti L, Fahnstock M, Mufson EJ (2016). Cerebrospinal fluid proNGF: A putative biomarker for early Alzheimer's disease. *Curr Alzheimer Res*, 13, 800-808, Jan 28. [Epub ahead of print]
9. Tuszynski MH, Yang JH, Barba D, U HS, Bakay RA, Pay MM, Masliah E, Conner JM, Kobalka P, Roy S, Nagahara AH (2015). Nerve Growth Factor Gene Therapy: Activation of Neuronal Responses in Alzheimer Disease. *JAMA Neurol*, 72, 1139-1147. doi: 10.1001/jamaneurol.2015.1807.
10. Tomlinson DR<sup>1</sup>, Fernyhough P, Diemel LT (1997). Role of neurotrophins in diabetic neuropathy and treatment with nerve growth factors. *Diabetes*, Sep;46 Suppl 2, S43-49.
11. Furukawa S, Nitta A, Furukawa Y (1999). Stimulation of neurotrophin synthesis by 4-methylcatechol: a promising approach to the treatment of neurodegeneration. *Biomedical Rev*, 10, 45-54.
12. Hanaoka Y, Ohi T, Furukawa S, Furukawa Y, Hayashi K, Matsukura S (1992). Effect of 4-methylcatechol on sciatic nerve growth factor level and motor nerve conduction velocity in experimental diabetic neuropathic process in rats. *Exp Neurol*, Feb;115:292-296.
13. Hirakawa A, Shimizu K, Fukumitsu H, Soumiya H, Inuma M, Furukawa S (2010). 2-Decenoic acid ethyl ester, a derivative of unsaturated medium-chain fatty acids, facilitates functional recovery of locomotor activity after spinal cord injury. *Neuroscience*, 171, 1377-1385, 2010.
14. Shibata S, Inuma M, Soumiya H, Fukimitsu H, Furukawa Y, Furukawa S (2015). A novel 2-decenoic acid thioester ameliorates corticosterone-induced depression- and anxiety-like behaviors and normalizes reduced hippocampal signal transduction in treated mice. *Pharmacol Res Perspect*, Mar;3(2):e00132. doi: 10.1002/prp2.132. Epub 2015 Mar 25.
15. Koltzenburg M, Bennett DL, Shelton DL, McMahon SB (1999). Neutralization of endogenous NGF prevents the sensitization of nociceptors supplying inflamed skin. *Eur J Neurosci*, 11, 1698-1704.
16. Ren K, Thomas DA, Dubner R (1995). Nerve growth factor alleviates a peripheral neuropathy in rats. *Brain Res*, 699, 286-292.
17. Malerba F, Paoletti F, Bruni Ercole B, Materazzi S, Nassini R, Coppi E, Patacchini R, Capsoni S, Lamba D, Cattaneo A (2015). Functional Characterization of Human ProNGF and NGF Mutants: Identification of NGF P61SR100E as a "Painless" Lead Investigational Candidate for Therapeutic Applications. *PLoS One*, Sep 15;10(9):e0136425. doi: 10.1371/journal.pone. 0136425. eCollection 2015.
18. Lee R, Kermani P, Teng KK, Hempstead BL (2001). Regulation of cell survival by secreted proneurotrophins. *Science*, 294(5548), 1945-1948.
19. Nykjaer A, Lee R, Teng KK, Jansen P, Madsen P, Nielsen MS, Jacobsen C, Kliemann M, Schwarz E, Willnow TE, Hempstead BL, Petersen CM (2004). Sortilin is essential for proNGF-induced neuronal cell death. *Nature*, 427, 843-848.
20. Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen ZY, Lee FS, Kraemer RT, Nykjaer A, Hempstead BL (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. *J Neurosci*, 25, 5455-5463.