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Chapter 4

Nerve Growth Factor and Sepsis

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Additional information is available at the end of the chapter

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1. Introduction

Neurotrophins are a family of growth factors that are polypeptide in structure and are necessary for the development and maintenance of the vertebrate nervous system. The first member of this family, nerve growth factor (NGF) was discovered in 1952 by an Italian group of scientists led by Rita Levi-Montalcini. She received a Nobel Prize in 1987 for her team's discovery. A few decades after the discovery of NGF, brain-derived neurotrophin factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and neurotrophin-5 (NT-5) were discovered, followed by neurotrophin-6 (NT-6) and neurotrophin-7 (NT-7) [1-3].

2. NGF Structure

There are two forms of NGF isolated from the short arm of human chromosome 1, a high molecular weight 7S NGF and a low molecular weight 2.5S NGF. The 7S form is a complex with three subunits (α, β and γ) and has a molecular weight of 130-140 kDa. Two beta subunits, each 118 amino acids long, are linked together by disulfide bonds and are responsible for the biological activity of NGF. The alpha and gamma subunits are members of the kallikrein protein family, and while the role of the alpha subunit is unknown, the gamma subunit is an epidermal growth factor (EGF) binding protein and has a role in the functions of the beta subunit. The 2.5S form has a molecular weight of 26 kDa and is formed by non-covalent interactions of two different subunits. NGF is synthesized and stored mostly in the mouse submandibular gland for reasons still unknown despite extensive research [3,4].

3. NGF receptors

Recently, it has been demonstrated that neurotrophins have many roles. Nerve growth factor has two receptors, p75NTR and tyrosine kinase A (Trk A), whose signaling pathways can be synergic, antagonistic or independent of each other [5].

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The p75NTR receptor is a transmembrane glycoprotein with an extracellular domain and a member of the TNF receptor family; it has low affinity for NGF. The p75NTR is a pan-neurotrophin receptor and, in addition to NGF, binds to other neurotrophins, such as BDNF, NT-3, and NT-4/5. It induces the NFκB and c-Jun kinase transduction pathways with varying effects depending on the pathway. The p75 receptor has been shown to act as a co-receptor in the presence of high affinity receptors and as an antagonist in their absence. The p75NTR receptor is thought to act as a mediator in the pro-apoptotic process induced by NGF. p75NTR increases the production of ceramides and activates gene transcription or programmed cell death in cells [5,6].

Receptor protein-tyrosine kinases A, B, and C (Trk A, B, C) are specific, high-affinity neurotrophin receptors. Trk receptors have transmembrane, extracellular, and intracellular domains. The portion of the Trk receptor responsible for tyrosine kinase activity, and thus for signal transduction, is located in the cytosolic domain. While p75 receptors bind to all neurotrophins, the tyrosine kinase receptor family binds to different receptors with different affinities. The Trk A receptor binds with high affinity to NGF but also binds to NT-3, NT-4, and NT-5 with low affinity. The Trk B receptor binds to BDNF and NT-4 with high affinity and to NT-3 with lower affinity. In contrast, the Trk C receptor only binds to NT-3 [5,7]. The Trk A receptor only has high affinity for NGF, and most NGF activity takes place through Trk A receptors. Trk A is a 140 kDa transmembrane protein encoded by proto-oncogenes on chromosome 1. The binding of NGF to a Trk A receptor induces tyrosine kinase receptor autophosphorylation, leading to the activation of parts of signal transduction cascades. These cascades are mainly mitogen-activated protein kinase (MAPK)-Ras-Erk, phospholipase Cy1, inositol triphosphate, and SNT pathways. Mutagenesis studies of the Trk A receptor showed that Trk A has significant effects on the development of the nervous system, and loss of Trk A results in neuronal loss. The Trk A receptor also induces gene transduction in cells [5,7].

4. Nerve growth factor and the nervous system

Neurotrophins are a group of structurally and functionally similar proteins that are secreted by a target tissue; they play a role in the development of the nervous system and in signal transmission. The largest concentrations of neurotrophins are found where major cholinergic pathways are present, such as in the hippocampus and cerebral cortex. In neonatal rats, when NGF is applied intracerebroventricularly, it increases the activity of choline acetyltransferase in the cortex and hippocampus. In addition, intracerebraventricular application of anti-NGF antibodies reduces the activity of choline acetyltransferase [7,8].

NGF plays a role in growth, differentiation, maintenance, regeneration, neurotransmitter function, neurotoxin resistance, and lesions in nerve cells [7,8]. Under normal conditions, neurons are largely responsible for the synthesis of NGF; however, brain damage can cause glial cells to produce NGF as well. The blockade of the glutamate receptors and/or stimulation of the GABAergic system reduces NGF mRNAs in hippocampus and NGF

protein in hippocampus and septum [9]. The level of NGF in the nervous system and cerebrospinal fluid has been found to decrease with age [10,11]. During the fetal and early post-natal periods, neurons are NGF-dependent; however, at later stages, they become NGF-sensitive. NGF levels were found to be high in blood, tissue and cerebrospinal fluid of patients with pathological conditions, such as hypoxia, ischemia, age-related cerebral atrophy, and increased intracranial pressure [7,12].

The increase in NGF levels after cerebral injury is required for neuronal recovery. Many studies have shown that neurotrophic factors control cellular calcium homeostasis, regulate cerebral blood flow, reverse the effects of ischemia, and inhibit the formation of free radicals by increasing antioxidant enzyme levels. However, the underlying mechanism of the neuroprotective role of NGF is unknown [13, 14].

Neurotrophic factors were used in *in vivo* and *in vitro* studies of neurodegenerative diseases. Many of the neurotrophic factors were only used in primate models, while some were tested as treatment for human neurogenerative diseases. However, none of these studies provided satisfactory results due to technical problems, side effects, and insufficient activities. Studies have argued that, because of its beneficial effects, NGF may be a new potential therapeutic tool for the treatment of neurodegenerative diseases, especially Alzheimer's disease [15]. In addition, NGF has been shown to be involved in cognitive functions, especially learning [16].

5. Nerve growth factor and sepsis

Sepsis and associated clinical manifestations are the main causes of mortality and morbidity in intensive care units outside coronary intensive care units [17, 18]. Despite the high mortality, the pathophysiology of sepsis is not completely known. However, infection with a microorganism is known to be the first step in the development of sepsis. In order for the inflammatory response to occur, the activation of endogenous mediators is also required. There are numerous complex endogenous mediators, including the coagulation system, complements, kinins, cytokines, metabolites of arachidonic acid, myocardial depressant factor, endorphins, histamines, lysosomal enzymes, platelet activating factors, and free oxygen radicals. In addition to increased inflammation, mechanisms such as anti-inflammatory cytokine secretion, anergy, and apoptosis cause immunosuppression [18-21].

When interactions between NGF and the mechanisms involved in sepsis pathogenesis are examined, NGF is found to be associated with inflammatory events and apoptosis.

6. NGF and inflammation

In studies conducted before the interaction of neurotrophins with the inflammation process was discovered, interactions between neurotrophins and immune organs and immune cells were investigated. In recent decades, detailed studies on the cellular localization and tissue distribution of neurotrophins have been completed. These studies determined that

neurotrophin and its receptors are present in all lymphoid organs, including the thymus and bursa of Fabricius [3, 22-25]. The first immune cell shown to associate with NGF was the mast cell, and its close localization to the nerve cells suggests the functional interaction between the nervous system and the immune system. Exogenous NGF was shown to activate mast cells in some peripheral tissues and to increase their number, size and degranulation [26, 27]. In addition to mast cells, NGF receptors are expressed in T and B lymphocytes, monocytes, macrophages, and granulocytes. Studies have shown that NGF is not only synthesized in immune cells, but also interacts with them [22,24,26].

Increased NGF serum and tissue levels were also found in patients with other inflammatory conditions, such as allergies, asthma, cystitis, immune diseases and cardiopulmonary bypass [28-33]. It was determined that, when NGF is administered systemically, the bronchial hyperactivity induced by histamines is increased, while bronchial hyperactivity is inhibited by anti-NGF application. NGF interacts with tachykinins causing the increase in bronchial hyperactivity [32]. Human fibroblast, airway smooth muscle, and lung epithelium A549 cells have the ability to synthesize NGF. Synthesis in this cells is induced by pro-inflammatory cytokines (IL-1β, TNF-α) and inhibited by glucocorticoids [34-39]. In mouse models of arthritis, stimulation with IL-1β has been demonstrated to increase the synthesis of NGF, which results in the increase of TNF-α [40]. According to some uncertain data, NGF has a causal role in inflammation, most likely in pro-inflammatory processes based on the interaction of NGF with pro-inflammatory cytokines, such as TNF-α and IL-1β.

On the other hand, application of NGF resulted in dramatic shrinkage or disappearance of lesions in chronic vasculitic ulcers and allergic encephalomyelitis, and accelerated wound healing, which suggested an anti-inflammatory role for NGF as well [41-44]. In studies which investigated NGF's interaction with anti-inflammatory cytokines, a strong interaction between NGF and IL-10 was found. In inflammatory processes, changes in the levels of NGF and IL-10 were correlated, each up-regulating the other. The effect of IL-10 on increasing the secretion of NGF is dose-dependent, and the application of anti-IL-10 blocks the secretion of NGF [42,45-47].

In addition to pro-inflammatory and anti-inflammatory cytokines, NGF has been noted to interact with Toll-like receptors (TLR), which are involved in the pathogenesis of sepsis, and other inflammatory mediators. In the conjunctival epithelial cells obtained from patients with vernal conjunctivitis, NGF has been shown to modulate the expression of TLR-4 and TLR-9 [48]. TLR-4 signaling in the dendritic cells may activate the p38MAPK and NFκB pathways and induce the expression of NGF and p75 [49]. The human leukocyte antigen-DR (HLA-DR), CD40, CD80, CD83, CD86, and CCR7 expression induced by LPS is thought to cause the secretion of IL-12p40 and pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α. In addition, NGF was noted to inhibit the degranulation of natural killer (NK) cells; however, NK cells are not the cause of NGF production [50].

In monocyte and microglial cell cultures induced by lipopolysaccharaide (LPS), LPS was shown to activate mRNA expression and protein release of NGF in a dose and time-dependent manner [51,52]. The use of NFκB inhibitor pyrrolidine dithiocarbamate was also

shown to inhibit LPS-induced synthesis of NGF, and it was concluded that NFκB modulates expression of LPS-induced NGF [51]. The only study that showed the interaction between NGF and sepsis was conducted by Bayar et al [53]. In rats with sepsis experimentally induced by LPS, blood was obtained before the intervention, 2, 12, 24 and 72 hours after LPS injection, and serum NGF levels were measured using the Emax Immunoassay method. Twenty-four hours after LPS injection, NGF levels were significantly higher in sepsis-induced rats compared to the control group. It was observed that anti-NGF administered in the early period, one hour before induction of sepsis, reduced the level of NGF observed two hours after injection. However, administration of the same dose of anti-NGF after sepsis was induced did not result in any change in the NGF levels. The dose of anti-NGF might have been inadequate to reduce NGF levels, as NGF synthesis increases after sepsis begins.

The use of anti-NGF to eliminate the effects of NGF is a method employed in studies of the interaction between inflammation and NGF. While some studies have shown that NGF decreases inflammation in groups which have received anti-NGF [29,54], others have reported no change [55] or increased inflammation [56,57].

In one study, application of anti-NGF decreased the early allergic reaction in an experimental model of asthma induced by intratracheal administration of ovalbumin [54]. In a second study using a respiratory syncytial virus (RSV) infection model, high levels of NGF and NGF receptors were observed in both young and adult rats. In the same study, the inflammatory effect of NGF was shown to decrease with age. When NGF was administered exogenously, expression of the neurokinin 1 (NK1) receptor, which is a sign of neurogenic inflammation, increased in the lungs, and pre-treatment with anti-NGF antibody decreased the expression of NK1 and, thus, alleviated the neurogenic inflammation [58]. In the rat model of inflammation generated by inoculation of *Trisinella spiralis*, the application of anti-NGF prevented intestinal dysmotility in rats; however, it had no effect on inflammation [55].

When latent herpes simplex virus (HSV-1) infected rabbits were administered anti-NGF antibodies, the anti-NGF was shown to react with ocular HSV-1 [57]. In another study, in which colitis was induced using trinitrobenzene sulfonic acid, and damage was assessed four weeks later, pre-treatment with anti-NGF and anti-NT-3 increased the intensity of inflammation 2-3 folds [56]. In acute and chronic experimental colitis models, neuropeptides, such as substance P and CGRP, serve a protective function and are regulated by NGF; when neurotrophins are experimentally and selectively blocked, the inflammation is significantly increased [56]. Present studies suggest that NGF has more anti-inflammatory effects than inflammatory. In a study investigating the interaction between sepsis and anti-NGF, anti-NGF was applied and its effect on apoptosis was evaluated during both the early period, when no manifestations of sepsis are present, and the late period, when manifestations of sepsis are established [53].

Studies involving NGF and anti-NGF have reported that NGF has both pro-inflammatory and anti-inflammatory effects. The difference might be a result of using different models of inflammation, applying different NGF and anti-NGF doses, and/or using different administration techniques. However, at the 2002 NGF meeting, it was reported that NGF

and Trk A weaken immune response primarily through inhibition; in other words, they mainly have immunosuppressant effects. Researchers argue that NGF is a potent and complier neuroimmunomodulator that secretes, and is secreted by, inflammatory mediators, and that, NGF's proinflammatory or anti-inflammatory role can change depending on the type and stage of inflammation [59].

7. NGF and apoptosis

The term apoptosis was used for the first time in 1972 by Kerr, Wyllie, and Curie and means the falling of leaves from a tree in Greek. Apoptosis is the genetically controlled programmed cell death mechanism used by organisms to harmlessly dispose of damaged or unnecessary cells. Numerous physiological, adaptive, and pathological events may occur after apoptosis in the organism [60,61].

Cell proliferation and cell death are balanced in tissues to provide continuity of tissue volume. In a 1992 study by Buchman et al., apoptosis was triggered in an experimental sepsis model induced by LPS [62]. In a postmortem study by Hotchkiss et al., cases that died from sepsis demonstrated that apoptosis occurred particularly in lymphocytes and intestinal epithelial cells. Although neutrophil apoptosis is known to be delayed overall during sepsis, a recent clinical study showed that neutrophil apoptosis increased in the earlier periods of sepsis. This phenomenon was explained as a mechanism to compensate for the inflammatory response [63]. Another study suggested that, among the immunosuppression mechanisms observed in sepsis, lymphocyte apoptosis is one of the most important and is a primary response, rather than a compensatory response [64].

The interaction between nerve growth factor and apoptosis was first suggested in 1952 by Rita Levi Montalcini. She demonstrated that, during the development of sympathetic and sensory neurons, NGF levels were half those of normal neurons. The increase in NGF-sensitive neurons, due to exogenous NGF application, and in neuronal death, due to anti-NGF administration, supported her data. At the same time, NGF had an effect on regulating cell death in the bursa of Fabricius of chickens and in human memory B lymphocytes [65-67]. Autocrine regulation of the cell cycle in vascular smooth muscle cells was attributed to NGF. The presence of NGF was detected in aortic endothelial cells. It was determined that NGF levels increased with pro-inflammatory cytokine IL-1ß, and after anti-NGF application, the cell count during S and G2/M phases and the ratio of hypodiploid cells were both increased [68]. In yet another study, the application of anti-NGF antibodies resulted in a 5-fold increase in the hypodiploid DNA of LPS-activated monocyte/macrophage cultures compared to the control group. Morphological changes, such as round-shaped dense chromatin and DNA fragmentation, were also observed in apoptotic cells [52]. It was determined that Trk A activity inhibited cell development in PC 12 pheochromocytoma and neuroblastoma cells, and high expression of Trk A was correlated with neuroblastoma prognosis [69,70]. In a recent study, NGF was shown to inhibit the induction of cyclins, as well as, cyclin interaction with corresponding cyclin-dependent kinases, thus, preventing progression through the G1 phase of the cell cycle [71]. Cell death induced in trigeminal

ganglions by tunicamycin, another drug that stops the cell cycle at the G1 phase, is suppressed by NGF in mouse embryos [72].

In a study of normal and NGF transgenic mice that underwent middle cerebral artery occlusion (MCAO), investigators evaluated infarct volume and antioxidant enzyme activity in the tissue that caused the occlusion. They observed higher NGF protein level increases in the cortical regions after ischemic damage in transgenic mice compared to the controls. In addition, the infarct volume and density of apoptotic cells were lower in transgenic mice. As a result, it was concluded that NGF had antioxidant and antiapoptotic properties [73]. Yang et al. reported that NGF applied after MCAO reduced apoptosis, and NGF's neuroprotective effect lasted up to five hours [74]. NGF eye drops applied to a rat model of experimental glaucoma improved the long-term function of the optic nerve, widened the visual field, and inhibited apoptosis in retinal ganglion cells [75].

Nine people volunteered for a study in which erythemas were generated with UV radiation. Skin biopsies were performed afterwards, and by using anti-NGF dye, the number of NGF-positive melanocytes and keratinocytes were determined to have decreased [76]. In another study of rat peritoneal mast cell cultures, the effect of NGF on age-associated apoptosis was evaluated. It was determined that NGF prevents apoptosis in a dose-dependent manner, and when anti-NGF antibody is applied, NGF's antiapoptotic effect is completely blocked [77]. NGF has been reported to have a protective effect on respiratory syncytial virus (RSV)-induced apoptosis of airway epithelial cells, and therefore, it has been proposed as a new approach to the maintenance of respiratory tract infections [78].

Another study evaluated neurotrophins and their receptors on diffuse large B-cell lymphoma (DLBCL) cells with different rituximab sensitivities. NGF secretion was induced by DLBLC cell exposure to rituximab, and Trk-inhibitor K252a exposure produced additive cytotoxic effects to rituximab [79]. Using immunohistochemical staining, bevacizumab, a drug used in cancer treatment, was determined to decrease the level of NGF protein, and thus, via NGF down-regulation, bevacizumab increases apoptosis [80]. Diabetic rats subjected to treadmill exercise produce increased levels of NGF to suppress apoptotic cell death in muscles [81].

The hematoxylin-eosin, and other immunohistochemical stains, such as those for Bcl-2 and Bax, were used to stain liver, lung, and intestinal tissues in the above mentioned study which evaluated the effects of both early and late period anti-NGF application on apoptosis in experimental rat models of sepsis [53]. In this study, the increase in apoptosis was determined by H/E staining of all tissues from all sepsis groups. The ratio of apoptotic cells was more distinct in the sepsis group and in the group which received anti-NGF treatment in the early period. When the two groups were compared, rats from the early anti-NGF application group had distinctly increased levels of apoptosis in their liver and intestinal tissues. In addition, when early and late anti-NGF application groups were compared, the early anti-NGF application group exhibited a more prominent increase in apoptosis in the intestinal tissue compared to the late application group. When Bcl-2 staining of all tissues was compared, all sepsis groups were determined to have low Bcl-2 expression in the liver

tissue compared to the control groups. When lung tissue was stained, all sepsis groups had low Bcl-2 expression compared to the control group. However, the results from the sepsis group without any treatment was significantly lower. In addition, when intestinal tissue was stained, all sepsis groups had low Bcl-2 expression compared to the control group. However, the results from the sepsis group without any treatment and the early NGF application groups were significantly lower. All groups with sepsis had increased Bax expression in the lung and intestinal tissues compared to the control group. In the liver tissue, all groups had increased Bax expression; however, the sepsis and early anti-NGF groups had had the highest levels of Bax expression. When the early and late NGF application groups were compared, Bax expression in all tissues was higher for the early NGF application group. The study concluded that early application of anti-NGF causes apoptosis at least as much as sepsis by itself; however, the application of anti-NGF after sepsis has been established causes less apoptosis compared to sepsis cases not treated with anti-NGF. The level of apoptosis was more distinct in the group with early anti-NGF application, which caused a prominent decrease in serum NGF levels. However, in the group with late application of anti-NGF and relatively stable NGF levels, less apoptosis was detected.

In conclusion, no clinical study addressing the role of NGF in the pathogenesis of sepsis has been completed to date. However, based on the last study, the application of anti-NGF before the start of inflammation increases inflammation and apoptosis. The application of anti-NGF after the start of inflammation causes less inflammation and apoptosis compared to sepsis cases which do not receive any anti-NGF treatment. Based on the data demonstrating that anti-NGF increases inflammation and apoptosis in sepsis, it can be suggested that NGF has anti-inflammatory and antiapoptotic properties in sepsis cases.

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