Angelo Azzi Zdenek Drahota Sergio Papa (Eds.)

Molecular Basis of Membrane-Associated Diseases

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Prof. Dr. ANGELO AZZI
Institut für Biochemie und Molekularbiologie
Universität Bern
Bühlstraße 28
CH-3012 Bern

Prof. ZDENEK DRAHOTA
Institute of Physiology
Czechoslovak Academy of Sciences
Videnska 1083
CS-142 20 Praha 4

Prof. SERGIO PAPA
Institute of Medical Biochemistry
and Chemistry
University of Bari
Piazza G. Cesare
I-70124 Bari

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Nerve Growth Factor (NGF): Physiological Functions and Regulation of Its Synthesis

D. LINDHOLM[1], R. HEUMANN, G. D. BORASIO and H. THOENEN

1 Introduction

The physiological role of NGF as a neurotrophic factor in the peripheral nervous system is well established. NGF is essential for the development and maintenance of specific functions of peripheral sympathetic and neural-crest derived sensory neurons. NGF acts as a retrograde messenger between the target organs and the innervating neurons. The regionally different quantities of NGF in target tissues reflect the density of innervation by NGF-responsive neurons, which transport NGF in membrane-confined compartments to the perikaryon after NGF is bound via specific membrane receptors. Although the physiological function of NGF is well documented and a large number of NGF-specific effects on target neurons have been identified, there are two main questions which remain to be elucidated, namely the nature of the second messenger(s) evolving from the binding of NGF to its receptor and the mode of regulation of NGF synthesis in the target tissues. A better understanding of this regulation would provide the prerequisite for a rational approach to the pharmacological modification of NGF synthesis. This is of particular interest because it has recently become apparent that NGF is essential for the preservation of the function of the cholinergic neurons of the basal forebrain nuclei. These neurons are consistently affected in Alzheimers's disease and their impaired function seems to be largely responsible for the cognitive deficits of this disease.

2 Physiological Functions of NGF

Earlier work on NGF was mainly focussed on the role of NGF in embryonic development and differentiation of the peripheral nervous system (Levi-Montalcini 1987). NGF has been shown to regulate the survival of peripheral sympathetic and neural-crest derived sensory neurons during restricted periods of development (cf. Levi-Montalcini and Angeletti 1968; Greene and Shooter 1980; Thoenen and Barde 1980). This has been conclusively demonstrated in experiments on neonatal rodents where administration of anti-NGF antibodies leads to

Department of Neurochemistry, Max-Planck-Institute for Psychiatry, Am Klopferspitz 18 A.D-8033 Martinsried/Munich, FRG
[1]To whom correspondence should be addressed

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enhanced cell death in the NGF-responsive neuronal population, whereas exogenous NGF can rescue neurons which normally would die during the period of natural cell death. In addition, NGF is also required for differentiation and maintenance of function of the peripheral sympathetic and sensory neurons in adult life. Thus, NGF has been shown to regulate synthesis of specific enzymes which are involved in neurotransmitter production, such as tyrosine hydroxylase and dopamine β-hydroxylase as well as a series of neuron-specific peptides (cf. Otten 1984; Johnson E.M. et al. 1986; Thoenen et al. 1987). In the peripheral target fields NGF is synthesized in very low amounts and is retrogradely transported to the cell bodies of NGF-responsive neurons after being taken up via specific cell surface receptors (cf. Schwab et al. 1982). It has also been shown that the density of innervation of target organs by NGF-responsive neurons correlates with the levels of NGF and its mRNA (Korsching and Thoenen 1983; Heumann et al. 1984; Shelton and Reichardt 1984). Moreover, interruption of the retrograde axonal transport of NGF following axotomy or by pharmacological interference (e.g. colchicine treatment which results in disassembly of microtubuli) leads to degenerative changes in the NGF-responsive neurons, demonstrating that NGF acts as a retrograde messenger between the periphery and the innervating neurons (cf. Thoenen et al. 1987).

In contrast to sympathetic neurons in the peripheral nervous system, central adrenergic neurons neither respond to NGF nor carry NGF receptors (Konkol et al. 1978; Schwab et al. 1979). However, evidence for a trophic role of NGF in the central nervous system became apparent when it was shown that the cholinergic neurons of the basal forebrain nuclei express NGF receptors and exhibit specific retrograde transport of NGF (Schwab et al. 1979; Seiler and Schwab 1984). The cholinergic neurons have also been shown to respond to NGF with an increase in the levels of choline acetyltransferase (ChAT), the enzyme responsible for synthesis of the cholinergic neurotransmitter acetylcholine. This has been shown both in neonatal rats (Gnahn et al. 1983), in aggregate cultures of fetal forebrain (Honegger and Lenoir 1982), and in adult rats after partial fimbria lesions, i.e. of the septo-hippocampal connection (Hefti et al. 1984). The cell bodies of the cholinergic neurons are situated in the medial septal nuclei, in the diagonal band of Broca and in the basal nuclei of Meynert. Their fiber tracts project to the hippocampus, neocortex and olfactory bulb (cf. Cuello and Sofroniew 1984) and these innervated areas exhibit relatively high levels of NGF and NGF-mRNA as compared to other brain regions (Korsching et al. 1985; Whittemore et al. 1986; Shelton and Reichardt 1986). In analogy to the situation in the peripheral nervous system, there is a close correlation between the levels of NGF and its mRNA and the density of cholinergic innervation. Even within the rat hippocampus there are differences between NGF levels of various regions, e.g. the CA3, CA4 and dentate gyrus region have higher levels of NGF protein compared with the CA1-CA2 region and this is reflected in the density of cholinergic innervation (cf. Korsching 1986; Thoenen et al. 1987). Recent autoradiographic receptor binding studies on sections from adult rat brain have clearly demonstrated the presence of NGF receptors on these cholinergic neurons (Riopelle et al. 1987; Raivich and Kreutzberg 1987). Moreover, NGF levels and ChAT activity in rat hippocampus

increase in parallel during postnatal development, further supporting a role of NGF in this septo-hippocampal system (Auburger et al. 1987). Likewise, fimbria lesion experiments have shown that exogenous NGF administrated through an infusion pump can rescue cholinergic neurons of the basal forebrain nuclei which would otherwise degenerate following the transection (Hefti 1986; Kromer 1987; Williams et al. 1986).

3 Mechanism(s) of Action of NGF

Although many actions of NGF on target neurons have been described, the overall mechanism by which NGF exerts its effects is still unknown. This also holds true for the most important long-term effect of NGF, namely its survival-promoting activity on NGF-responsive neurons. NGF receptors on sensory (Sutter et al. 1979) and sympathetic neurons (Godfrey and Shooter 1986) and on PC12 pheochromocytoma cells (Hosang and Shooter 1985) have been identified and antibodies to the NGF receptor have been produced (Chandler et al. 1984; Ross et al. 1984). Moreover, binding studies have shown the existence of both high- and low-affinity NGF receptors on target cells which are encoded by the same mRNA. However, the mechanism for conversion between the two forms is not known but the high-affinity receptor seems to be responsible for most of the biological action of NGF, at least in PC12 cells (Green et al. 1986). Recently, both human and rat NGF receptors have been cloned (Johnson D. et al. 1986; Radeke et al. 1987) and the molecular data demonstrate that the NGF receptor belongs to a novel class of membrane receptors which lack an intrinsic tyrosine kinase activity. NGF is also known not to affect neuronal proliferation which is in contrast to most growth factors which have a mitogenic activity on their target cells (cf. Thoenen et al. 1987).

Previous studies have shown that intracellular microinjection of NGF into the cytoplasm of PC12 cells, bypassing the receptor, fails to elicit differentiation which is readily seen with NGF in the culture medium (Heumann et al. 1981). Conversely, microinjected, function-blocking, anti-NGF antibodies do not inhibit NGF action on PC12 cells. These studies led to the conclusion that NGF acts by a distinct second messenger system, the nature of which remains to be elucidated (Heumann et al. 1981). The results of recent studies have suggested a role for the ras oncogene product in NGF signal transduction. Introduction of purified, activated, ras protein into PC12 cells can elicit differentiation (Bar-Sagi and Feramisco 1985), and microinjected, anti-ras antibodies are able to block the effect of NGF on these cells (Hagag et al. 1986). The exact site of action of ras or of ras-like proteins in the signal transduction cascade induced by NGF is not known. Further downstream, transcriptional activators are most probably involved in regulating NGF-specific gene expression. Interestingly, NGF (Greenberg et al. 1985) as well as ras protein (Stacey et al. 1987) are known to transiently increase expression of the c-fos proto-oncogene product which is thought to be involved in transcriptional regulation. Milbrandt (1987) has recently described another putative transcriptional activator gene whose transcription is strongly induced in PC12 cells by short-term NGF treatment.

4 Regulation of NGF Synthesis and Implications for Treatment of Alzheimer's Disease

In Alzheimer's disease the cholinergic neurons of the basal forebrain nuclei are consistently affected and there is an atrophy and/or loss of these neurons during the course of this disease (Coyle et al. 1983; Pearson et al. 1983). Moreover, the impaired synthesis of acetylcholine is one of the earliest detectable signs of Alzheimer's disease and correlates well with the cognitive deficits observed (Francis et al. 1985). In view of the fact that these cholinergic neurons are also the target of NGF in the central nervous system, the hypothesis was put forward that NGF could play a role in this disease (Hefti and Weiner 1986). The idea that Alzheimer's disease results from an insufficient supply of NGF for these neurons has recently been disputed by Goedert and co-workers (1986). These authors demonstrated that the levels of NGF-mRNA in the cerebral cortex of patients with Alzheimer's disease are not different from the corresponding levels found in age-matched controls. Nevertheless, the following observations support the notion that pharmacological amounts of NGF are of potential value in treatment of Alzheimer's disease by supporting the cholinergic neurons undergoing atrophy or degeneration. Thus, it has been demonstrated that chronic administration of NGF over a period of 4 weeks can improve memory function, as shown by behavioural tests, and can counteract cholinergic cell body atrophy observed in a subpopulation of aged rats (Fischer et al. 1987). Moreover, studies on septo-hippocampal lesions clearly show that exogenous NGF has a beneficial effect in preventing cholinergic cell degeneration in the septal area after a transection of the fimbria (Hefti 1986; Kromer 1987; Williams et al. 1986). Likewise, NGF injections (Will and Hefti 1985) or transplantation of fetal cholinergic neurons into the hippocampus (Dunnett et al. 1982; Gage and Björklund 1986) can improve both learning and memory deficits observed in rats after such a lesion.

In view of these findings it seems justified to consider NGF supplementation as a possible therapeutic approach for the treatment of patients suffering from Alzheimer's disease. This could be achieved by either local administration of recombinant human NGF, of peptides with NGF-like functions or by enhancing endogenous NGF synthesis by pharmacological agents. However, a prerequisite for such an intervention is a better understanding of the physiological mechanisms by which NGF is regulated in vivo. Recent studies in the peripheral nervous system have shown that specific polypeptide factors are involved in the control of NGF synthesis in the nonneuronal cells. Using the rat sciatic nerve as a model system under conditions of degeneration and regeneration after a nerve lesion, we were able to show that macrophages play an important role in NGF regulation (Heumann et al. 1987; Thoenen et al. 1988). Interleukin-1, a lymphokine produced by these cells, was found to be the responsible agent increasing NGF-mRNA levels in the nonneuronal cells (Lindholm et al. 1987). Recent studies indicate that the action of IL-1 involves activation of phospholipase A2 and that IL-1 has a dual effect on NGF-mRNA. Thus, IL-1 enhances NGF gene transcription and also increases the stability of NGF-mRNA in cultured sciatic nerve fibroblasts (Lindholm et al. 1988).

The studies on the regulation of NGF synthesis in the central nervous system are less advanced compared with the peripheral nervous system. We have recently obtained evidence that IL-1 and other mesenchymal growth factors can influence NGF-mRNA levels in cultured rat astrocytes. We are currently studying the complex interplay of various growth factors in controlling NGF-mRNA synthesis in the central nervous system both in vivo and in vitro. Moreover, since it has very recently been reported that hippocampal neurons can also express NGF-mRNA (Rennert and Heinrich 1986; Ayer-LeLievre et al. 1988) this adds a new dimension to studies concerned with the regulation of NGF synthesis in the central nervous system.

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