NGF in Early Embryogenesis, Differentiation, and Pathology in the Nervous and Immune Systems

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Abstract The physiology of NGF is extremely complex, and although the study of this neurotrophin began more than 60 years ago, it is far from being concluded. NGF, its precursor molecule pro-NGF, and their different receptor systems (i.e., TrkA, p75NTR, and sortilin) have key roles in the development and adult physiology of both the nervous and immune systems. Although the NGF receptor system and the pathways activated are similar for all types of cells sensitive to NGF, the effects exerted during embryonic differentiation and in committed mature cells are strikingly different and sometimes opposite. Bearing in mind the pleiotropic effects of NGF, alterations in its expression and synthesis, as well as variations in the types of receptor available and in their respective levels of expression, may have profound effects and play multiple roles in the development and progression of several diseases. In recent years, the use of NGF or of inhibitors of its receptors has been prospected as a therapeutic tool in a variety of neurological diseases and injuries. In this review, we outline the different roles played by the NGF system in various moments of nervous and immune system differentiation and physiology, from

We wish to dedicate this review to the late Prof. Rita Levi-Montalcini, a splendid mentor and physiologist.

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embryonic development to aging. The data collected over the past decades indicate that NGF activities are highly integrated among systems and are necessary for the maintenance of homeostasis. Further, more integrated and multidisciplinary studies should take into consideration these multiple and interactive aspects of NGF physiology in order to design new therapeutic strategies based on the manipulation of NGF and its intracellular pathways.

Keyword Neurotrophin · proNGF · NGF receptors · Neuronal degeneration · Inflammation

Abbreviations

CGRP	Calcitonin gene-related peptide
CIPA	Congenital insensitivity to pain with anhidrosis
CNS	Central nervous system
CREB	CRE-binding protein
DRG	Dorsal root ganglion
EAE	Experimental autoimmune encephalomyelitis
ERK	Extracellular signal-regulated kinase
IL	Interleukin
MAPK	Mitogen-activated protein kinase
NGF	Nerve growth factor
NPY	Neuropeptide Y
NT	Neurotrophin
p75NTR	p75neurotrophin receptor
PI3K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
PLC	Phospholipase C
PNS	Peripheral nervous system
SOS	Son of sevenless
SP	Substance P
TH	Tyrosine hydroxylase
TrkA	Tropomyosin-related kinase A

Contents

1 The Discovery of NGF

The discovery of nerve growth factor (NGF) is intimately linked to the development of the nervous system. More than sixty years ago, Levi-Montalcini's pioneer studies on nervous system differentiation, using Cajal's silver staining technique in chick embryos, lead to the identification of NGF (Levi-Montalcini 1987). Levi-Montalcini's scientific background as a neuroanatomist prompted her to re-investigate the effects of limb extirpation on the nervous system in chick embryos and to hypothesize that contrary to the prevailing opinion of the time, limb ablation resulted in a massive neuronal degeneration due to the impossibility of the neurons to form synapsis with their end organs. The massive death of peripheral neurons was also observed in normal chick embryos between E6 and E12, suggesting that there were more neurons in the developing nervous system than the periphery could support. This intuition was confirmed in experiments with supernumerary limbs, while an unexpected clue for the interpretation of this phenomenon was provided by the transplantation of solid tumors in chick embryos (Levi-Montalcini and Hamburger 1951). Here, the enlarged size of sensory and sympathetic ganglia, the increased number of surviving neurons, the abnormal distribution of fibers, that not only penetrated the sarcoma but also invaded the embryo viscera and the lumen of the veins, suggested that the tumor was releasing an unknown factor able to control the growth and survival of sensory and sympathetic neurons. The possibility to purify the newly discovered factor in huge amounts from male mouse submaxillary glands (Levi-Montalcini and Cohen 1960) and to produce antibodies against NGF (Levi-Montalcini and Booker 1960) was instrumental in understanding that the target organ, by producing limited amounts of NGF, was responsible for the survival of peripheral neurons during development. In vivo NGF deprivation, using neutralizing NGF antibodies, demonstrated, in a number of animal models, a massive destruction of immature sympathetic cells and a marked reduction in sensory neurons in dorsal root ganglia (DRG) (Levi Montalcini and Angeletti 1968; Aloe et al. 1981). Even though the technical approach at that time was limited to morphological and biochemical analysis, these findings, demonstrating the existence and effects of NGF, still represent a milestone in neurobiology. This was the beginning of what has been called "The NGF saga," since the spectrum of NGF activities is much broader and more complex than that was initially imagined (Levi-Montalcini 1997). More than 60 years after the discovery of NGF, our knowledge of its properties and functions is far from complete, as is evident from the astonishing number of papers published every year on NGF.

The study of NGF is indeed still a fertile terrain of discovery, as shown by the recent findings of a variety of biological activities of the immature form of NGF (pro-NGF) and the critical balance between pro-NGF and NGF concentrations within tissues for their neurotrophic activity, mediated by different receptors (i.e., p75NTR versus TrkA) and intracellular signaling pathways.

2 The NGF System: NGF Precursor, Mature Forms, and Their Receptors

NGF, isolated from mouse salivary glands, is a complex comprising three subunits: α, β, and γ, where only the β subunit has a biological effect (Bax et al. 1997). This high molecular weight complex, also known as 7S NGF, because of its sedimentation velocity, is present only in the mouse. In other species, NGF is present only as the β subunit, a dimer of two identical monomers of 118 amino acids, held together by non-covalent bindings. The crystallographic analysis of murine β-NGF shows that each monomer has an elongated shape and comprises antiparallel pairs of β-strands, forming a flat surface and four β-hairpin loop regions (McDonald et al. 1991). The monomer is also characterized by three disulfide bridges arranged in a peculiar ring structure, known as a "cysteine knot" that, first described for NGF, is also common to other growth factors (McDonald and Hendrickson 1993). The two monomers associate through the flat region (which is rich in hydrophobic residues) that gives stability to the homodimer, which shows a high association constant. NGF is synthesized in the endoplasmic reticulum as an immature form of 241 amino acids—the proNGF—which is either processed in the Golgi network within secretory vesicles by furin and other convertases (Seidah et al. 1996), or released in immature forms of different molecular weights, due to alternative splice variants and different levels of glycosylation (Bierl et al. 2005; Bierl and Isaacson 2007). In the extracellular space, pro-NGF is either processed into mature NGF by plasmin or rapidly degraded by metalloproteinases (Bruno and Cuello 2006). ProNGF has recently received attention because it appears to have biological effects (Lee et al. 2001) that are distinct from, or even opposite, to those of mature NGF in certain cell types (D'Onofrio et al. 2011). In vivo studies have shown that the prevalent form present in the brain (Fanhestock et al. 2001) and peripheral nervous tissues (Bierl et al. 2005) is proNGF and not the mature NGF. Levels of proNGF in the brain are also increased during aging (Bierl and Isaacson. 2007), in neurodegenerative diseases (i.e., Alzheimer's and Parkinson's diseases) (Fanhestock et al. 2001; Xia et al. 2013) and diabetic encephalopathy (Soligo et al. 2015).

Studies of the sequence of NGF led to the discovery of other molecules, sharing a high level of sequence homology with NGF and together constituting the neurotrophin family (Ebendal 1992). Neurotrophins are structurally related proteins, and all are key factors in the development and physiology of the nervous system. In addition to NGF, the neurotrophin family includes brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT-4/5). These neurotrophins have been found in all vertebrates, while two additional neurotrophins, closely related to NGF, neurotrophin-6, and neurotrophin-7, have been found only in fish, and Lf-NT and Mg-NT have been isolated only in lamprey and Atlantic hagfish (Agnatha) (Hallböök 1999; Lanave et al. 2007). Molecular evolution studies have shown that neurotrophins evolved early in vertebrate history, and the phylogenetic tree suggests the duplication of an ancestor *NGF* gene in two clusters of genes, one including *NGF*, *NT-3*, and *NT-6/7* and the other comprising

BDNF and *NT-4/5*. A second duplication separated the *BDNF* gene from that of *NT-4/5* and the *NGF* gene from that of *NT-3*, leading to the formation of a variety of proteins that have acquired multiple functions during the evolution of the vertebrate nervous system with its increasing complexity (Hallböök 1999). The rate of evolution of the *NGF* gene has been higher than that of other neurotrophin genes (Lanave et al. 2007), and this could possibly explain the greater diversity and complexity of functions requiring NGF, both within and without the nervous system, in comparison with the more conserved functions that require BDNF and NT-3 (Lanave et al. 2007).

The biological effects of NGF are directly dependent on its initial binding to specific cell surface receptors: p75NTR, a 75 kD glycoprotein, that belongs to the TNF receptor superfamily, and TrkA, a transmembrane tyrosine kinase of 140 kD. p75NTR is also known as a pan-neurotrophin receptor because it also binds the other neurotrophins with similar affinity, while the transmembrane tyrosine kinases, TrkA, TrkB, and TrkC, bind more specifically NGF, BDNF, and NT-3, respectively (Rodríguez-Tébar et al. 1991). Phylogenetic analysis of the *trk* genes shows that they originate from duplications of an ancestral gene during vertebrate evolution. These multiple *trk* genes coevolved in parallel with the neurotrophin genes, allowing preferred ligand–receptor interactions and the development of specific functions in different cell populations (Hallböök 1999).

The structure of TrkA is characterized by an extracellular domain that contains cysteine repeats, leucine-rich repeats, and two immunoglobulin domains, the second of which is the site that interacts with NGF. The binding of NGF to TrkA induces receptor dimerization and phosphorylation of specific tyrosine residues (Kaplan et al. 1991), which act as docking sites for cytoplasmic adaptor proteins that activate intracellular pathways (Fig. 1). Numerous studies have demonstrated that the activation of TrkA signaling regulates the survival and differentiation of neuronal cells. The best known pathways activated by NGF trough TrkA are the phosphatidylinositol 3-kinase (PI3K), MAPK, and PLC-γ (Reichardt 2006). The binding of Shc to the phosphorylated tyrosine residue Y490 leads to the activation of PI3K and the phosphorylation of Akt. Activation of Akt results in the inhibition of the forkhead transcription factor FKHRL1, which controls the transcription of pro-apoptotic genes such as Bim and Fas ligand (Fukunaga et al 2005), and in inhibition of GSK-3β, a point of convergence of many signaling pathways that influence the transcription of CREB, AP-1, and NF-κB (Beurel et al. 2010). The activation of PI3K pathway in neurons is involved in the maintenance of survival and in promoting axonal elongation.

The binding of Shc to residue Y490 also allows the recruitment of Grb2 and Sos, which leads to the activation of Ras and the downstream MAPK pathway, which results in Erk activation and CREB transcription. This pathway has a key role in regulating neuronal survival and differentiation.

Phosphorylation of the TrkA residue Y785 induces activation of PLC-γ and the formation of diacylglycerol (DAG) and inositol triphosphate (IP3). The increase in IP3 releases Ca^{++} from the intracellular stores, thus activating calcineurin and other enzymes sensitive to Ca^{++} levels. The accumulation of DAG induces activation of

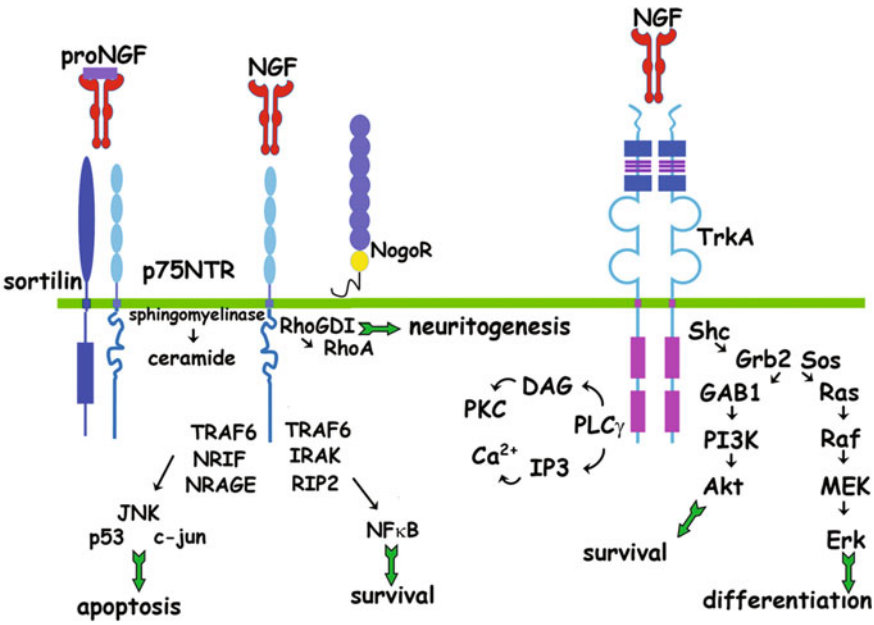

Fig. 1 The binding of NGF to TrkA dimers induces phosphorylation of tyrosine residues in the intracellular domain that results in activation of specific pathways. The presence of p75NTR increases the affinity and specificity of TrkA for NGF. p75NTR can interact with other co-receptors (i.e., sortilin, NogoR) and activates different intracellular adaptors and signaling pathways regulating a broad spectrum of diverse cellular responses

protein kinase C (PKC), which is involved in neurite outgrowth (for more detailed reviews on TrkA signaling see Reichardt 2006; Uren and Turnley 2014).

The majority of studies on TrkA signaling have been performed using either a cellular model of mouse pheochromocytoma, the PC12 cell line (Greene 1978), which in the presence of NGF differentiates in sympathetic neurons, or primary neuronal cells derived from different areas of the nervous system. The intracellular pathways activated by NGF binding to TrkA in non-neuronal cells are similar to those described in neuronal models, although they regulate other cell functions (Barouch et al. 2001; Torcia et al. 2001). For example, in masts cells, NGF acts as a chemotactic factor by binding to TrkA and activating MAPK and PI3K signaling (Sawada et al. 2000). However, in monocytes, NGF binding to TrkA plays a key anti-inflammatory role by activating the PI3K pathway and inhibiting the synthesis of inflammatory cytokines (Prencipe et al. 2014).

The expression of TrkA is considered necessary and sufficient to elicit NGF biological responses, but the role and contribution of p75NTR to NGF signaling and function is still debated and far from being univocally defined. For a long time, the role of p75NTR was considered limited to facilitating TrkA functions and enhancing its specificity. Indeed, the co-expression of p75NTR together with TrkA

increases the specificity and affinity of NGF binding. Both receptors have a similar affinity for NGF with a Kd in the range of 10^{-9} M; however, when they are co-expressed, the Scatchard analysis reveals the presence of a high-affinity-binding site with a Kd of 10^{-11} M. Different biochemical models, describing the possible interaction between p75NTR and TrkA, have been proposed to explain the increased binding affinity: p75NTR can either act as TrkA co-receptor, by concentrating NGF and presenting it to TrkA, or directly interacts with TrkA, inducing allosteric modifications that enhance its affinity for NGF (Chao and Hempstead 1995). A novel hypothesis is that there is no direct extracellular interaction between TrkA and p75NTR and that they interact through common downstream signaling pathways and shared adaptor molecules (Wehrman et al. 2007). What is now emerging as a critical factor in the regulation of NGF/proNGF activities is the relative levels of expression of p75NTR in comparison with the TrkA, since their ratio plays a role in determining which of the intracellular pathways and biological activities are triggered (Masoudi et al. 2009).

For a long time, p75NTR was considered unable to convey any signals by itself because, in common with the other members of the TNF receptor family, it lacks any intrinsic enzymatic activity in the intracellular domain. As studies on TNF-R signaling progressed (Cabal-Hierro and Lazo 2012), it also became clear that p75NTR, by interacting with specific co-receptors and intracellular adaptors, could activate intracellular pathways very distinct from those activated by TrkA. The intracellular region of p75NTR has a death domain, although it is not identical to the death domain of other receptors of the TNFR1 group. This p75NTR intracellular motif is not able to self-assemble and does not recruit signaling proteins containing death domains such as FADD or TRADD (Wang et al. 2001), but instead binds to TRAF6 (Ye et al. 1999; Yeiser et al. 2004) and to other adaptor molecules, which do not have a death domain, such as IRAK (Mamidipudi et al. 2002) RhoA (Yamashita et al. 1999), NRAGE (Salehi et al. 2000), and NogoR (Wang et al. 2002).

In common with other receptors of the TNF-R superfamily (Hehlgans and Pfeffer 2005), it is now clear that p75NTR can regulate a broad spectrum of extremely diverse biological responses, such as neurite outgrowth, proliferation, and cell differentiation, as well as cell survival and death. This depends on the cell types in which p75NTR is expressed, on their differentiation state and on co-expression with TrkA and other co-receptors, such as sortilin (Nykjaer and Willnow 2012). This variety of effects indicates an extremely complex regulation of p75NTR activity, which as yet is only partially understood. Some of the pathways now known to be regulated by p75NTR are the NF-kB, c-Jun kinase, RhoA, and ceramide pathways (for more extensive reviews on p75NTR signaling see Roux and Barker 2002; Kraemer et al. 2014).

Recently, much attention has been directed to sortilin, one of the p75NTR co-receptors belonging to the VPS10P-domain receptor family (Willnow et al. 2008), because it can significantly increase the affinity of p75NTR for proNGF (Nykjaer et al. 2004). A number of studies have shown that in the presence of low

levels of TrkA, p75NTR is structurally and functionally coupled with the transmembrane protein sortilin (Nykjaer et al. 2004; Teng et al. 2005; Domeniconi et al. 2007). This transforms p75NTR into a "death-promoting" receptor, whose activation drives neurons to apoptosis by binding proNGF with high affinity and activating caspase 6 (Lee et al. 2001; Majdan et al. 2001; Huang and Reichardt 2003; Fahnestock et al. 2004; Reichardt 2006).

3 NGF and Early Embryo Development

NGF and its receptors are expressed in the embryo well before the formation of the neural tube and the differentiation of neuronal cells (Fig. 2). This is not surprising, considering that NGF mRNA is found in oocytes, being present in small pre-vitellogenic as well as in fully grown oocytes (Carriero et al. 1991; Abir et al. 2005; Dissen et al. 2009). Although NGF and its receptors are involved in follicle formation and oocyte maturation (Dissen 1995; Dissen et al. 2009; Kerr et al. 2009; Linher-Melville and Li 2013), and NGF is expressed and accumulated in oocytes (Carriero et al. 1991), there are few indications of its possible role in early embryogenesis. The expression of p75NTR and TrkA appears in mouse embryos at the blastocyst stage, with the expression of p75NTR preceding that of TrkA, and both being confined within the inner mass of the blastocyst and absent from the trophoblast (Moscatelli et al. 2009). Mouse embryonic stem cell lines derived from blastocysts retain the expression of NGF receptors in vitro, and the addition of NGF, while increasing their number, maintains the expression of staminal markers of pluripotency such as Oct4 and Nanog (Moscatelli et al. 2009). Human embryonic stem cells (hESCs) also express neurotrophin receptors (Pyle et al. 2006; Schuldiner et al. 2000), and the addition of NGF results in an increase in cell survival (Pyle et al. 2006). In studies of the differentiation patterns of hESCs in a 3D culture environment, it was found that NGF, together with Retinoic Acid (RA), preferentially favors the differentiation of hESCs toward ectodermal and mesodermal lineages (Inanç et al. 2008).

In embryos, the expression of NGF receptors persists in specific areas during gastrulation and neurulation (Zhang et al. 1996), and their localization is not always identical (Wheeler et al. 1998), suggesting different functions of TrkA and p75NTR in cell differentiation and morphogenesis. During early embryogenesis, NGF expression is modulated in the ectoderm and seems to be involved in body shaping, but not in early neural differentiation (Bhargava and Modak 2002). Thus, NGF and its receptor are expressed well before the onset of neurogenesis, and their expression characterizes specifically non-neuronal tissues such as somites, notochord, and neural crest (Yao et al. 1994; Bhargava 2007; Tomellini et al. 2014). Indeed, neutralization of NGF in chick embryos in the first stages of development causes alterations of the embryo's axial rotation and influences a number of genes involved in developmental processes, cell movements in the notochord and somite formation,

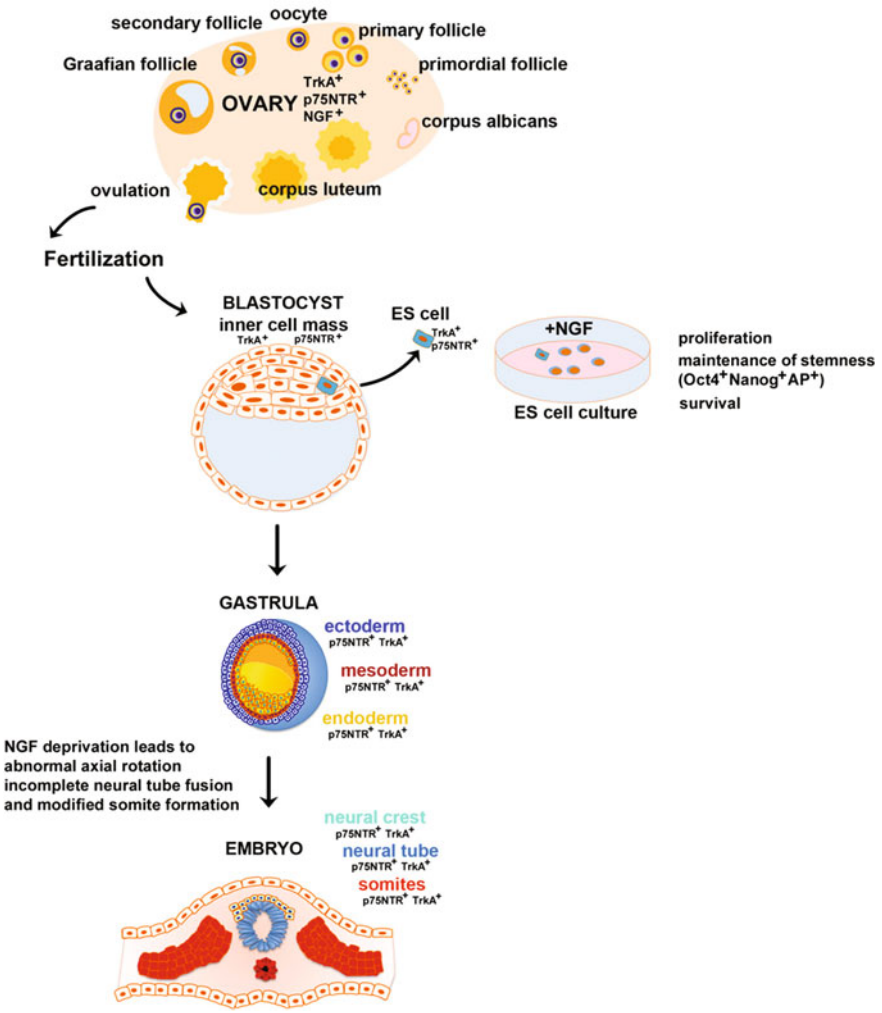

Fig. 2 NGF, p75NTR, and TrkA are expressed in the ovary during fetal life and contribute to follicle formation and at puberty onset they are involved in oocytes maturation. NGF mRNA is accumulated in the oocytes so that NGF mRNA is transferred to the embryo at fertilization. The novo synthesis of NGF and expression of TrkA and p75NTR are detected in the blastula. The embryonic stem cells that derive from the inner mass retain the expression of p75NTR and TrkA, and addition of NGF to the culture medium increases their proliferation and survival but does not alter the stemness potential as the unchanged expression of Nanog and Oct4 indicates. In the gastrula, the expression of NGF receptors characterizes all three germ layers. During morphogenesis and neurogenesis, there is a well-defined spatiotemporal expression of NGF, p75NTR, and TrkA that influences differentiation of both non-neuronal and neuronal cells in specific areas

cell cycle regulation, and proliferation (Manca et al. 2012). Neutralization of NGF or of p75NTR in chick embryos during somite formation reduces apoptosis of the sclerotome and dermomyotome (Cotrina et al. 2000). Interestingly, sonic hedgehog (Shh), a key factor regulating sclerotome differentiation (Resende et al. 2010) and survival (Britto et al. 2000), reduces the expression of p75NTR and NGF in somite explants, suggesting that the regulation of NGF is essential for maintaining control of programmed cell death in non-neuronal cells (Cotrina et al. 2000).

Neural crest cells begin to express p75 from E10.5, when they start to migrate (Wilson et al. 2004). These cells, although of ectodermal origin, acquire mesenchymal cell properties, migrating throughout the embryo to generate multiple tissues that include the majority of the cranial connective tissue and skeletal elements, neurons and glia of the peripheral nervous system, endocrine cells, smooth muscle cells, tendons, and pigment cells (Mayor and Theveneau 2013). During their migration and regulated differentiation, they express sequentially different Trk receptors (Davies 1997), thus acquiring responsiveness to one or other neurotrophin (Vogel 1993; Rifkin et al. 2000) that canalizes and defines the differentiative program of peripheral neuronal populations (for a more detailed review see Marmigère and Carroll 2014).

4 NGF in Health and Disease of the Peripheral and Central Nervous Systems

A large body of studies has discussed and demonstrated the crucial role of NGF in the development, maintenance, and regeneration of mammalian sympathetic and sensory neurons of the peripheral nervous system (PNS). NGF-sensitive neurons express both TrkA and p75NTR receptors, the activities of which are exquisitely balanced. The sensitivity and affinity of TrkA for NGF are increased by its functional interaction with p75NTR (Nykjaer et al. 2005; Wehrman et al. 2007) and are modulated by the changes in the expression levels of both receptors (Esposito et al. 2001).

During the development of neural circuits, intermediate and final neuron targets release gradients of NGF and support neuron survival via a main long-distance signaling initiating within distal axons (Levi-Montalcini 1987), which implies the retrograde transport of internalized NGF-TrkA receptors complexes. Once they reached neuronal cell bodies, these so-called signaling endosomes will regulate genes expression, promoting neuron survival, axon growth and pathfinding, and synaptogenesis (Miller and Kaplan 2001; Barker et al. 2002; Harrington and Ginty 2013; Howe and Mobley 2005; Reichardt 2006; Cosker et al. 2008; Pazyra-Murphy et al. 2009; Sharma et al. 2010), while enhancing sensitization to NGF and protecting from p75NTR-mediated apoptosis (Deppmann et al. 2008). Although another neurotrophin, NT-3, can also bind to TrkA receptors, only the TrkA/NGF complex is internalized and forms signaling endosomes supporting neuronal

survival. This mechanism relies on the inability of NT-3 to activate the intracellular signaling cascades regulated by Rac1, GTP, and cofilin proteins that promote F-actin depolymerization, a process essential to initiate the trafficking of signaling endosomes (Harrington et al. 2011). Fundamental evidence on the pro-survival role of NGF during development derives from pioneering in vivo studies on DRG and sympathetic ganglion neurons of NGF- and Trk-knockout mice (Snider 1994). In vitro studies, on the other hand, were decisive for identifying the molecular mechanisms through which NGF, proNGF, and their receptors operate (Campenot 1977; Ye et al. 2003; Mok and Campenot 2007; for review see Harrington and Ginty 2013).

Along with neuron survival, target-released NGF also regulates axon growth and retraction (Campenot 1977), synapse and neural circuit formation (Ladle et al. 2007; Sharma et al. 2010), and expression of neurotransmitters (Luo et al. 2007; Patel et al. 2003). In vitro studies, which use compartmentalized chambers, have shown that NGF applied directly to distal axons acts locally to support their extension; however, when only cell bodies are exposed to NGF, neurons fail to extend axons into a compartment that lacks NGF (Campenot 1977). In sympathetic neurons, NGF is also required for dendritic arborization, the degree of which strictly correlates with the size of the neuron's peripheral targets (Voyvodic 1989). Interruption of retrograde signaling by axotomy causes dendritic retraction, which persists as long as axons require regeneration (Purves 1975). Finally, retrograde NGF/TrkA signaling also drives synapse establishment and subsequent maintenance and plasticity in adults. In sympathetic neurons, appropriate coupling of pre- and postsynaptic specializations has been validated by several studies, in which retrograde signaling was abolished by either axotomy or the administration of NGF-blocking antibodies (Purves 1975; Mandai et al. 2009; Sharma et al. 2010).

Along with the "classic" and well-described mechanism of retrograde signaling, NGF/TrkA activity can also be purely local, through the tightly regulated activation of intracellular signaling cascades. This local signaling has been extensively studied during axon outgrowth, guidance, and regulation of preterminal branching. In general, neurotrophin-stimulated axon growth requires the activation of transcription factors, which regulate gene expression and subsequent synthesis of the proteins necessary for axon growth. However, in addition to gene expression, local signaling pathways are also required for the control of cytoskeletal dynamics, as elegantly described for the NGF by Campenot (1982a, b). The activation of a spatially controlled signal transduction based on PI3K-Akt activation at the growth cones, the major sites where neurons receive and integrate extracellular signals to direct axonal cytoskeletal dynamics (Baas and Luo 2001), has been demonstrated for filopodia formation and axon growth (Kuruvilla et al. 2000; Zhou et al. 2004; Ketschek and Gallo 2010). Fig. 3 shows the three major intracellular domains of sympathetic ganglionic neurons, in which NGF-TrkA exerts its activity: nucleus, for the modulation of gene expression by NGF signaling endosomes (control of neuronal survival, axon growth, and synaptogenesis); postsynaptic specializations, for a more local control by NGF signaling endosomes of synaptogenesis and

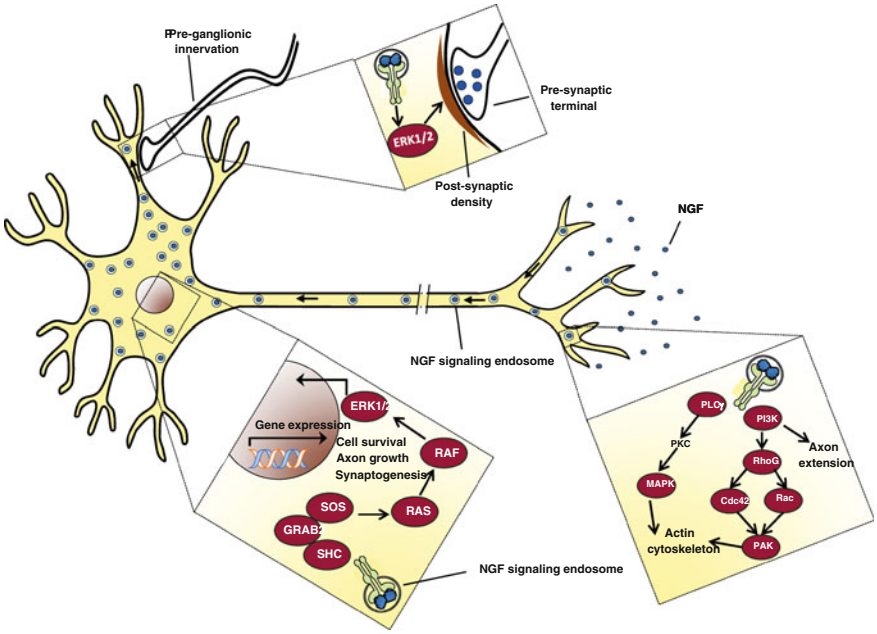

Fig. 3 In sympathetic neurons, NGF activates different intracellular signaling pathways. At the growth cones, NGF released by peripheral targets binds to TrkA receptors and elicits two main types of responses. In the first, the NGF-TrkA complex is internalized in signaling endosomes. These are retrogradely transported along the axon to the cell body, where they trigger an intracellular signaling cascade ending up in Erk1/2 activation and consequent modulation of gene expression. NGF-regulated genes encode proteins important for cell survival and differentiation, axon growth, and synaptogenesis. Signaling endosomes, after reaching cell bodies, can move into dendrites, where they will regulate processes related to synaptogenesis and local control of synaptic plasticity. Furthermore, the NGF-TrkA complex can also remain within the growth cone plasma membrane, initiating a local signaling cascade, involving MAPK and PAK activation, directed at promoting growth cone mobility and advancement through cytoskeletal remodeling, a process important during both development and axon regeneration

synaptic activity; and growth cones, for a local control of axon growth, which does not require NGF endocytosis.

The role of NGF in adult life is not only confined to the maintenance of neuronal survival and structure, but also includes the fine modulation of the chemical phenotype of neurons. It has been shown that in adult dorsal root ganglion neurons in vitro, the expression of mRNAs encoding the precursors of both substance P (SP) and calcitonin gene-related peptide (CGRP) is regulated by NGF (Lindsay and Harmar 1989). In vivo studies have also shown that the infusion of NGF after sciatic nerve transection reactivated α-CGRP, β-CGRP, and SP expression in DRG neurons (Verge et al. 1995). Similarly, in sympathetic neurons, the expression of tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis, is strictly NGF-dependent (Thoenen et al. 1971). Altogether, these findings provide

evidences of a continuous and dynamic regulation of peptide neurotransmitter/neuromodulator levels in adult neurons by NGF.

As with the PNS, a specific role for NGF has also been proposed for the cholinergic neuron population of the central nervous system (CNS). Cholinergic neurons are situated largely in different areas of the basal forebrain (BF), which are the major source of cholinergic innervation to the cerebral cortex, hippocampus, amygdala, and remaining portions of the cortical mantle (Niewiadomska et al. 2009). They are highly and critically dependent on NGF during both development and adulthood, including aging. When NGF is synthesized by target neurons, it is retrogradely transported to the cell bodies of the BF neurons, contributing to the maintenance of cell morphology (i.e., cell body size and extent of terminal arborization (Higgins et al. 1989), and physiology, i.e., up-regulation of choline acetyltransferase (ChAT) gene expression, protein levels and activity, synthesis and release of acetylcholine, and expression of the vesicular acetylcholine transporter (VAChT) (see Niewiadomska et al. 2011 for review). NGF expression is highly modulated by neuron activity (i.e., in the hippocampus, it is increased by glutamatergic and cholinergic neurotransmission, and decreased by GABAergic neurotransmission) (Huh et al. 2008), and by pathological events (i.e., it is up-regulated by seizures, forebrain ischemia, marked hypoglycemia, and tissue injury) (Lindvall et al. 1994). NGF is also synthesized by subpopulations of hippocampal and BF GABAergic interneurons (Zhang et al. 2007) and by astrocytes and microglia, the CNS glial cells. In both these cell types, NGF expression is significantly up-regulated by several factors, such as inflammation, cytokines, and the bacterial lipopolysaccharide (LPS) (Tonchev et al. 2008), indicating a role in brain protection and regeneration from injuries.

In the past, a reduction in NGF trophic support, which could derive from a decrease in the correct cleavage of the proNGF to form mature NGF, has been indicated as one of the causes of age-related cholinergic neuron atrophy and neurodegenerative diseases, i.e., Alzheimer's disease (AD) (Tuszynski and Blesch 2004). In effect, high levels of proNGF and sortilin in adult and AD patient brains have been described (Fahnestock et al. 2001; Nykjaer et al. 2004). However, the aging-related cholinergic atrophy and cell loss in normal brains are not always accompanied by the reductions in the levels of NGF (Katoh-Semba et al. 1998). This has led to the hypothesis that aging cholinergic neurons fail to respond to NGF. Indeed, NGF retrograde transport in aged rat BF cholinergic neurons is significantly reduced, with consequent NGF signaling impairment, cell atrophy, and changes in gene expression (Cooper et al. 1994; DeLacalle et al. 1996; Sofroniew et al. 2001). Similarly, mild cognitive impairment (a prodromal stage of AD) and early forms of AD are characterized by the loss of cholinergic function more than by neurodegeneration, as neither a loss of NGF receptor mRNA levels (Goedert et al. 1989) nor a failure of NGF synthesis (Scott et al. 1995) has been observed. This marks an important difference between the early stages of AD, and the massive cholinergic neuron death observed in advanced stages of late-onset AD and other

pathologies associated with cognitive deficits, such as Parkinson's disease (PD) and Down syndrome, among others (for review see Schliebs and Arendt 2010; Iulita and Cuello 2014). It is possible that the early formation and deposition of β-amyloid, the hallmark of AD, play a role in inducing an initial cholinergic dysfunction, which later evolves to become neuronal loss. This hypothesis is supported by a number of experimental findings showing that β-amyloid deposits may trigger cholinergic dysfunction in several ways: (i) by binding to α7-containing nicotinic acetylcholine receptors (a7nAChRs), thereby affecting their activity; (ii) by affecting NGF signaling; (iii) by mediating tau phosphorylation; (iv) by interacting with acetylcholinesterase (AChE); or (v) by specifically affecting the cholinergic neuron proteome (for review see Schliebs and Arendt 2011). Several in vivo studies have shown that age-related dysfunction of the cholinergic system may be ameliorated by treatment with NGF (for review see Niewiadomska et al. 2011). Another important aspect to be taken into consideration is the presence of prominent neuroinflammatory events triggered by the early deposition of intracellular Aβ oligomers (Ferretti et al. 2012). As demonstrated in transgenic animal models for AD, characterized by extracellular plaque deposition, neuroinflammation induces an increase in levels of metalloproteinase-9, one of the enzymes involved in NGF degradation in the extracellular space (Bruno et al. 2009). Amplified NGF degradation, together with a concomitant decreased in the conversion of proNGF into its mature form, results in a signaling deficiency of NGF and atrophy of basal forebrain cholinergic neurons (Cuello et al. 2012).

NGF may affect a variety of additional CNS neurons since its binding sites are present during early development in many neuronal systems, not necessarily of cholinergic origin, including the visual system (Vantini et al. 1989; Yan and Johnson 1988, 1989). Here, NGF and TrkA are expressed by almost all eye components. NGF released into the aqueous humor (Lambiase et al. 2002) and in the retina, the neural part of the eye, is produced and utilized by retinal ganglion cells, bipolar cells, and glial cells (Frade et al. 1999; Wang et al. 2014). During visual system development, NGF, TrkA, and p75 are highly expressed along the entire visual pathway, where NGF influences neuronal outgrowth, survival, apoptosis, and physiology (Roberti et al. 2014). Interestingly, topically applied NGF eye drops are able to reach the retina and the optic nerve (Ferrari et al. 2014), greatly enhancing the expectations regarding the clinical use of this neurotrophin for a number of ocular neurodegenerative diseases, such as glaucoma (Wang et al. 2014).

Finally, the presence of NGF in those limbic areas of the CNS involved in mood and cognition (i.e., the amygdala) and in the orchestration of neuroendocrine responses and circadian activities (i.e., the hypothalamus) indicates a much wider role for this NT than previously hypothesized. Several experimental studies currently suggest that NGF may also function as an intercellular messenger or humoral factor to help regulate endocrine responses to stress (for review see Berry et al. 2012).

5 NGF in Immune System Differentiation and the Immune Response

During embryo development, the expression of NGF receptors is finely modulated in primary and secondary lymphoid organs (Ernfors et al. 1988; Lomen-Hoerth and Shooter 1995; Ciriaco et al. 1996; Aloe et al. 1997) and declines during postnatal life (Ernfors et al. 1988; Ciriaco et al. 1996). In bone marrow and in the thymus, NGF receptor expression has been found in stromal cells, which release specific growth factors and signals (Pezzati et al. 1992; Cattoretti et al. 1993; Caneva et al. 1995; Ciriaco et al. 1996; Rezaee et al. 2010; Lee et al. 2008), that regulate the correct differentiation of myeloid and lymphoid precursors. In the thymus, the expression of NGF and of both its receptors is very high in the final stages of embryo development and in the early postnatal period and then decreases with age (Laurenzi et al. 1994; Aloe et al. 1997; Garcia-Suárez et al. 2001). In the Bursa of Fabricius, the lymphoid organ in which B cells differentiate in birds, the expression of NGF receptors (Ciriaco et al. 1996) is elevated during B-precursor differentiation in the epithelial follicles. The administration of NGF to chick embryos accelerates follicle formation (Bracci-Laudiero et al. 1991).

In immune organs, there is a local production of NGF (Laurenzi et al. 1994) that regulates sympathetic and sensory innervation, and neuropeptide and neurotransmitter synthesis in the embryo and in adult life (Madden and Felten 1995, Elenkov et al. 2000) These effects are directly and actively modulated by the amount of NGF available, as demonstrated in transgenic mice overexpressing NGF, which shows enhanced fiber density and modified innervation patterns in the spleen and lymph nodes (Carlson et al. 1995). The constant production of NGF in lymphoid organs (Laurenzi et al. 1994; Yamamoto et al. 1996; Aloe et al. 1997) also seems to be important for regulating the differentiation of hematopoietic stem cells. These hematopoietic stem cells express TrkA (Chevalier et al. 1994; Bracci-Laudiero et al. 2003), and its expression is at its highest levels in the more undifferentiated cells, declining during lineage differentiation. This modulated expression of TrkA suggests that NGF may play different functions depending on the state of differentiation of immune cell and functional activity. The possibility that NGF may be a key factor for haemopoiesis is supported by the fact that hematopoietic stem cells produce their own NGF in an autocrine fashion, probably regulating anti-apoptotic genes. In vitro studies have shown that the administration of NGF in semisolid cultures increases long-term survival of human hematopoietic cells (Bracci-Laudiero et al. 1993, Auffray et al 1996) and promote the commitment toward specific lineages in human and murine myeloid progenitor cells (Matsuda et al. 1988, 1991; Tsuda et al. 1991; Welker et al. 2000). Support for the possible pro-survival role of NGF in hematopoiesis is also provided by studies on leukemia showing a constitutive activation of TrkA in blasts from patients with de novo or secondary acute leukemia that affects survival of the leukemic cells in patients and in animal models (Li et al. 2009). A high expression of TrkA also characterizes Hodgkin–Reed/Sternberg cell lines, in which the constitutive activation of TrkA

and the Akt pathway promotes cell survival, which can be strongly reduced by using TrkA inhibitors (Renné et al. 2008).

Differentiation of B cells is also influenced by NGF. Studies of mature lymphoid cells have shown that NGF has a proliferative effect on both B and T cells (Brodie and Gelfand 1992) and causes the differentiation of B cells into immunoglobulin-secreting plasma cells (Kimata et al. 1991). NGF seems also to influence the survival and, consequently, the antibody production of pulmonary plasma cells via regulation of the Ire1/XBP-1 pathway (Abram et al. 2009). NGF stimulates B-lymphocytes to produce IgM, IgA, and IgG (Brodie and Gelfand 1994) and regulates the survival of B-memory cells (Torcia et al. 1996), which rapidly and efficiently counteract pathogens when re-encountering antigens during the secondary response, a key feature of immunological memory.

The effects of NGF do not seem to be restricted only to differentiation processes, and a growing body of data is accumulating to support the hypothesis that NGF and its receptors are also involved in modulating functions and activity of mature immune cells. Mature immune cells express much lower TrkA levels than hematopoietic stem cells (Bracci-Laudiero et al. 2003; Antonelli et al. 2003), but after antigenic or inflammatory stimulation, when strong functional activity is necessary, TrkA expression is strongly up-regulated (Ehrhard et al. 1993; Caroleo et al. 2001; Ralainirina et al. 2010). The activity of NGF on cells of the myeloid lineage is to enhance effector functions, such as the release of inflammatory mediators, chemotaxis, and proliferation (Kannan et al. 1991; Noga et al. 2002; Gibbs et al. 2005; Samah et al. 2008). In lymphocytes and monocytes, in addition to proliferation and survival, NGF influences cytokine release (Susaki et al. 1996; Bayas et al. 2003; Shi et al. 2012; Prencipe et al. 2014) and the production of neuropeptides that have an immunological role (Bracci-Laudiero et al. 1996, 2005). In differentiated cells of both myeloid and lymphoid origin, NGF appears to regulate their survival (Kawamoto et al. 1995; Bullock and Johnson 1996; Hamada et al. 1996; la Sala et al. 2000;) by inducing the expression of anti-apoptotic genes such as bcl-2 (Bullock et al. 1996; Torcia et al.1996; la Sala et al. 2000).

Altogether these data suggest that NGF has a specific function in the differentiation and activation of immune cells and can thus play an important role in regulating the immune response in vivo. Confirmation of this hypothesis has come from studies on patients with congenital insensitivity to pain with anhidrosis (CIPA), a rare autosomal peripheral sensory neuropathy caused by mutations in the gene encoding TrkA (Indo et al. 1996). These patients, in addition to neurological alterations and loss of pain and sensation, are also prone to recurrent infections, slow wound healing, and inflammatory complications that are related to the altered functions of certain immune cell populations. The chemotactic activity of neutrophils is significantly impaired (Beigelman et al. 2009), and B-lymphocytes show changes in the intracellular pathways (Melamed et al. 2004) and impaired anti-apoptotic activity (Sato et al. 2004).

Studies on inflammatory and autoimmune diseases have clearly demonstrated that NGF and its receptor expression are highly modulated during inflammatory response and disease progression. Inflammatory mediators and cytokines can

greatly enhance the synthesis of NGF in cells (Torcia et al. 1996; Caroleo et al. 2001; Kobayashi et al. 2002) and in tissues, and NGF concentrations appear to be correlated with clinical severity (Aloe et al. 2001). The biological meaning of this enhanced in vivo production of NGF at the site of inflammation and the ways in which NGF can affect inflammatory pathways, immune responses, and healing processes is far from being understood.

An example of the complexity of NGF activities in vivo can be extrapolated from studies on multiple sclerosis (MS). In MS patients, there is an increase in NGF concentration in the cerebrospinal fluid that correlates with the inflammatory state of the patients (Bracci-Laudiero et al. 1992; Caggiula et al. 2005). Administration of NGF in animal models of experimental autoimmune encephalomyelitis (EAE) delays the onset of clinical symptoms and prevents the full development of EAE lesions by directly reducing immune cell infiltrates (Villoslada et al. 2000; Parvaneh Tafreshi 2006). The administration of NGF exerts its effects directly on the activity of immune cells, by regulating T-lymphocyte response, monocyte infiltration, and the release of anti-inflammatory cytokines (Villoslada et al. 2000; Arredondo et al. 2001; Flügel et al. 2001; Parvaneh Tafreshi 2006). In EAE models, a local production of NGF (De Simone et al. 1996; Acosta et al. 2015) has also been observed in different brain areas during the acute phase of the disease. In addition to the immunological effects, this release of NGF also protects neuronal population (Linker et al. 2009), induces myelin repair (Øren et al. 2004; Acosta et al. 2013), and efficiently suppresses the formation of new lesions (Villoslada et al. 2000). This neuroprotective effect of immune cell-produced NGF also appears to be common to other neuropathologies characterized by different etiologies, as AD, PD, and spinal cord injury (Ebadi et al. 1997; Schulte-Herbrüggen et al. 2007; Saab et al. 2009; Colafrancesco and Villoslada 2011). This further confirms the integrative role that NGF has in human physiology and how the local increase of NGF in vivo can simultaneously have multiple effects on different cell types.

6 Conclusion

Much still remains to be elucidated regarding the highly complex physiology of NGF and its key role not only in the nervous system but in other systems as well. The complexity of NGF signaling, the number of receptors involved, and the diverse biological activities of immature and mature NGF are directly correlated with the need for the differential regulation of a variety of cell types in the various states of differentiation and activation. This intricate control of a multitude of activities, some of which have opposite effects, is necessary for a correct homeostasis. The pleiotropic effects of NGF are thus a demonstration of its major integrative role, and alterations in the NGF-NGF receptor axis can affect many cell types, tissues, organs, and systems. Manipulation of the production of NGF, its receptors, and intracellular pathways at different times and in selected cell types could become a powerful tool for the treatment of many neurological and immune

diseases, although more integrative and interdisciplinary studies are needed. As aptly described by Dr. Ibáñez in an editorial on the discovery of the biological effects of pro-NGF (Ibáñez 2002), the story of NGF resembles a "roller-coaster," still full of discoveries and surprises and, unusually for such an "old molecule," still unfolding.

References

Due to the vastness and complexity of the subjects treated in the present review, the list of bibliographic references is far from exhaustive and should be considered as merely representative. The authors apologize for not including the original work of many researchers who have helped to define the physiology of NGF and refer readers to other reviews for further informations.

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