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NERVE GROWTH FACTOR IN THE CENTRAL NERVOUS SYSTEM: MORE THAN NEURON SURVIVAL

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INTRODUCTION

Since its discovery in nineteen-fifty by Rita Levi-Montalcini, nerve growth factor (NGF) has displayed an impressive pleiotropy, as suggested/indicated by its essential involvement both in physiological and pathological conditions within the central (CNS) and peripheral (PNS) nervous system and most peripheral tissues as well (34). The tremendous expansion of recent knowledge on high and low affinity receptors has highlighted molecular mechanisms and cellular effects mediated by NGF leading to either survival, differentiation or death of responsive cells (31). Born as growth factor for peripheral neurons, and then promoted as survival factor for cholinergic neurons in the CNS, NGF needs now to be re-defined as a biologically active molecule, due to the growing evidence and new information on biological processes in which this substance plays major roles; in fact it acts not only as a neurotrophin or a cytokine, but possibly also as a signalling molecule mediating intracellular regulation, including gene regulation, and extracellular effects leading to organism development, remodelling and repair. It has been estimated that at least 1000 transcripts are regulated in response to NGF, and 150 of the regulated transcripts have been matched to named genes (6, 7); NGF regulates genes encoding for cytoskeleton proteins (like dynein and proteins involved in actin gelation), DNA replication proteins, molecules involved in membrane trafficking and formation and transcription factors, thus suggesting an extremely complex protein network supporting its main biological effects. In extracellular environment the role of NGF includes regulation of angiogenesis through direct interaction with endothelial cells and growth factors, *in vitro* and *in vivo* (20), during development (39) and in postnatal (18) nervous tissue, in physiological (48) and pathological conditions and in peripheral tissues as well (34).

In this paper we will shortly review recent developments concerning NGF role in regulation of stem cells and progenitors in adult brain and spinal cord, in neuroinflammation and in myelin repair, centering upon the possible role of NGF in remyelination in the course of multiple sclerosis.

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NGF AND ADULT NEURAL STEM CELL

Neurotrophins are essential regulators of nervous tissue development and of brain and spinal cord building. NGF is the essential growth factor for differentiation and survival of sympathetic, sensory and central cholinergic neurons (35). A new, fascinating and expanding area in the field of neurotrophins is represented by their role in the regulation of adult neurogenesis and gliogenesis. It is known that neurogenesis and gliogenesis take place in the adult brain, starting from pools of progenitors located in the subventricular zone of the telencephalon (SVZ) (5), in the dentate gyrus of the hippocampus (26, 52) and maybe also in the spinal cord (30) and mesencephalon (21). Besides generating astroglial cells (56), newly generated neurons integrate in existing circuits in the hippocampus and olfactory bulb (32, 52) and could probably establish a pool of multipotent precursors for brain and spinal cord repair (10). The multiple roles of neurotrophins as mediators in cell cycle regulation and differentiation during development, point them out as likely candidates for physiological regulation of neural stem cell proliferation and differentiation in adult brain and also as possible targets for exogenous regulation of such processes in brain repair. The SVZ extending from the lateral ventricle to the olfactory bulb expresses high levels of $p75^{LNGFR}$-immunoreactivity (17). The positivity is distributed along the external surface of cell bodies in many cellular elements and double labelling experiments revealed that a percentage of proliferating cells (bromodeoxiduridine-uptaking cells) in the SVZ also expressed $p75^{LNGFR}$ immunoreactivity. The injection of radiolabelled-NGF in the lateral ventricles of developing rats induces an accumulation of NGF in a stream of cells extending from the SVZ to the olfactory bulb; moreover time-course experiments suggested that NGF-positive cells migrate from the SVZ toward the surrounding parenchyma (17). *In vitro* studies indicate that NGF, other neurotrophins and mitogens, like epidermal and fibroblast growth factors, participate in sequential actions that regulates proliferation and differentiation of neuronal stem cells, allowing generation of tri-lineage colonies for astrocyte, neuron and oligodendrocyte differentiation (9).

NGF AND NEUROINFLAMMATION

Altered NGF content in the cerebrospinal fluid and serum during inflammatory demyelinating diseases has been actively studied since first descriptions (11). Demyelinating diseases are extremely complex conditions in which brain inflammation and activation of different cell types occur, inducing demyelination and remyelination, following and interweaving each other. Altered NGF content and NGF receptor expression has been described in different cell types, areas and phases during experimental allergic encephalomyelitis (EAE), an inflammatory-demyelinating experimental disease associated with immune reaction, widely used as experimental model for multiple sclerosis (MS) (16). Several hypothesis have been formulated to explain such large fluctuations of NGF content in tissues and fluids during inflam-

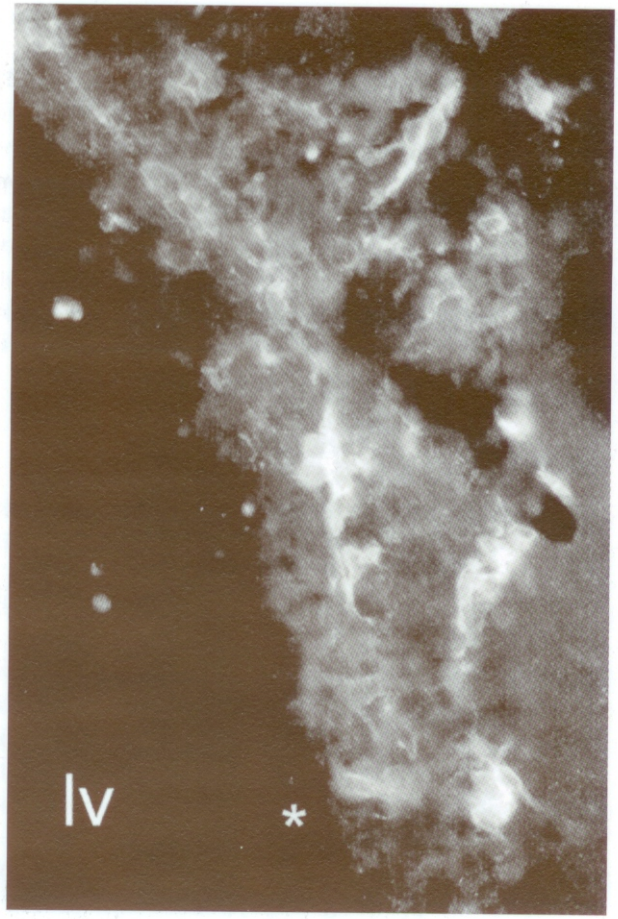

Fig. 1. - *$p75^{NGFR}$ -immunoreactive cells in the subventricular zone of adult rat.* Abbreviation: lv, lateral ventricle

matory-demyelinating conditions, including a proinflammatory role (36), contribution to remyelination (2, 22) and neuroprotection (27). We reported that the NGF content was significantly increased in the thalamus of EAE animals (16), concomitantly with the onset of clinical signs of central or peripheral inflammation, whereas in the cervical spinal cord and medulla oblongata a dramatic drop was observed; in control animals, NGF content in these areas is usually one-tenth as low as in the thalamus. This different regulation could be related to a dissimilar NGF synthesis capability in various tissues and CNS regions when exposed to appropriate stimuli, like proinflammatory cytokines. Cytokines involved in inflammation and immune responses during EAE, such as IL-1β and TNFα (28, 42) are potent inductors of NGF synthesis in peripheral tissues (38, 53) and in the CNS (24, 43). In areas where severe inflammation and demyelination occur, like spinal cord and medulla oblongata, increased request could account for the drop in NGF content. Modified NGF content also regulates high- (trkA) and low- ($p75^{LNGFR}$) affinity receptor expression. In EAE rats, p75- and trkA-like perivascular positivity involving glial and neural cells

appeared in several CNS areas, coincidentally with the appearance of perivascular inflammatory cellular infiltrates (16, 41) (Figure 1). Several reports indicated that NGF increase in inflamed tissues, concurrent with free-radical production and scar formation, could exert a protective effect from oxidative stress (44), which could be an important feature of NGF role in inflammatory-demyelinating conditions. In fact, during EAE and MS a severe neuronal injury, including axonal loss and neural death, occurs, leading to brain and spinal cord atrophy and possibly to the permanent disability that characterizes the later chronic progressive stage of MS (46; Giardino, submitted). More recently, it has been recognized that the detrimental effect of inflammation plays nonetheless a crucial role for remyelination attempts and neuroprotection (29). Therefore, it may be assumed that in this context NGF could exert a protective rather then detrimental role.

NGF AND MYELIN REPAIR: A ROLE IN INDUCING OLIGODENDROCYTE PRECURSORS TO DIFFERENTIATE INTO MYELINATING ELEMENTS?

MS is an inflammatory-autoimmune disease which, in its chronic phase, is characterized by multiple foci of demyelination in the CNS leading to severe functional impairment and permanent disability. While re-myelination in the CNS is a common event under experimental conditions (37), re-myelination attempts observed in early plaques in MS are not followed by repair (45) (Figure 2 A, B). The reason for this failure is still unknown, as it is so far not understood why a significant number of oligodendrocyte precursor cells, found in early lesions in MS tissue (12, 51), are in relatively a quiescent state in chronic lesions (57).

NGF role in re-myelination process has been postulated since years (47), but convincing data supporting this hypothesis have been obtained only recently: in fact the administration of human recombinant-NGF was shown to delay the onset of clinical EAE in marmoset, preventing the full development of inflammation and demyelination (55). In this study, widespread expression of TrkA and $p75^{LNGFR}$ was detected in CNS white matter cells morphologically similar to astrocytes and/or microglial cells, in oligodendrocytes and in a proportion of the mononuclear cells and macrophages comprising the inflammatory cellular infiltrates (Figure 2 C, D). Moreover, the demonstration of a close correlation between inflammation course and demyelination/re-myelination in NGF-treated animals meaningfully suggests a pleyotrophic role of NGF in regulating inflammatory processes and immune response also in neural tissue (47).

However, the positive role of NGF on EAE course may also involves oligodendrocyte precursors. We have reported that markers for endogenous precursor in gliogenic areas of the CNS are altered in EAE (17), including positivity for proliferating cells and $p75^{LNGFR}$ positive elements in the SVZ, which are expanded during the disease. Chains of small, ovoid $p75^{LNGFR}$ positive cells, extending from the border of the ventricle toward the white matter of the corpus callosum, were also observed in

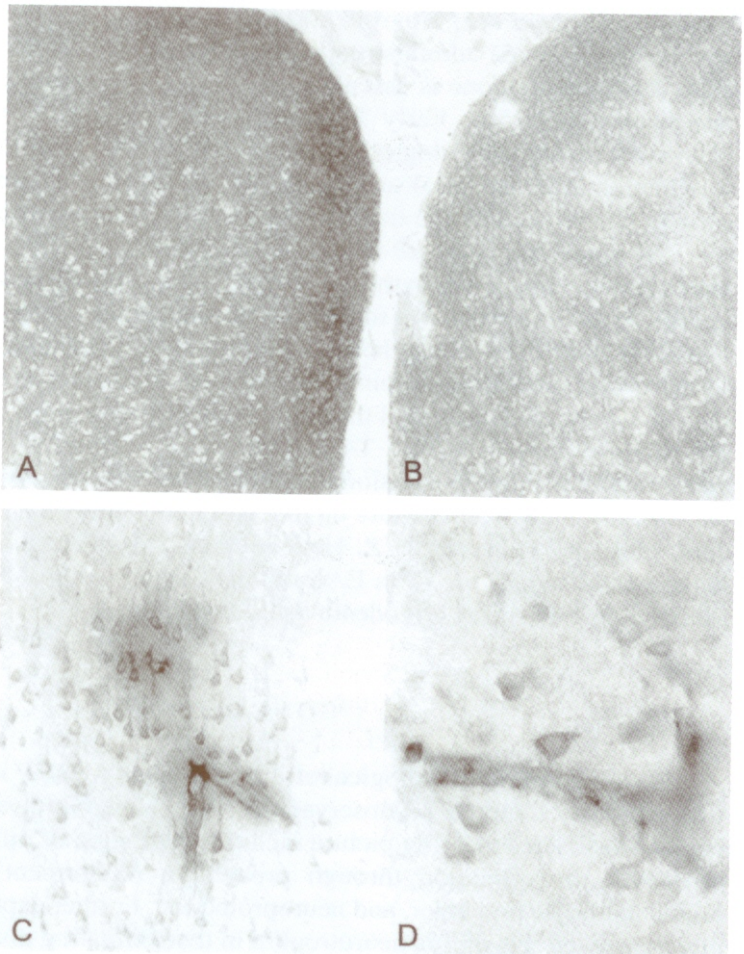

Fig. 2. - Sudan-black staining of the spinal cord (lumbar tract) in animals affected by experimetal allergic encephalomyelitis (B, 30 days after immunization) reveals an extensive vacuolization of the white matter tracts in the ventral funiculus as compared to control animals (A).
In the same stage of the disease, an up-regulation of $p75^{NGFR}$ (C) and trkA-immunostaining (D) was observed in neural and glial cells mainly in perivascular areas.

the acute phase. The finding supports the attractive hypothesis that neural and glial precursors in the adult brain and spinal cord require neurotrophins for migration and differentiation, maybe co-acting with cytokines. Cytokines, including those involved in acute EAE, have been proved to cause the elaboration of oligodendroglial progenitor and post-mitotic oligodendrocytes in a cellular system obtained from the SVZ (40); moreover TNFα modulates proliferation of progenitors in the SVZ of adult rat brain (58). *In vitro* studies indicated that NGF also protects oligodendrocyte from injury and death induced by TNFα (54). A direct role of NGF on oligodendrocytes in myelin formation is also supported by *in vitro* studies, indicating that NGF induces proliferation of oligodendrocytes isolated from adult pig brain (2) and activates trkA-mediated intracellular pathways leading to genomic effect (3), possibly participating to myelin formation (4).

We have previously shown that also treatments able both to increase endogenous synthesis of NGF and to regulate oligodendrocytes maturation may improve the clin-

ical course of EAE (25). Thyroid hormone, was used as a treatment, whose acute (1) and chronic (13-15) administration is known to increase endogenous synthesis of NGF. Thyroid hormone is essential for normal oligodendrocyte maturation and for myelination (49, 50). Early in development, thyroid hormone functions as an instructive agent, triggering cell cycle exit (8, 23). In post mitotic oligodendrocytes, it increases morphological and functional maturation by stimulating expression of various genes, such as the myelin-oligodendrocyte glycoprotein, myelin basic protein and glutamine synthase (8). As from our findings (19), also during a demyelinating process like EAE, in the spinal cord thyroid hormone was able to restore NGF content to control level and to activate endogenous oligodendrocyte precursors, by recruiting and channelling them toward complete maturation to myelinating cells. Moreover, in the SVZ and spinal cord of EAE animals a large number of proliferating cells were evidenced and the expression of markers for undifferentiated precursors (nestin) were increased. T4 administration reduced proliferation and nestin-IR and up-regulated the expression of markers for oligodendrocyte progenitors (PSA-NCAM, O4, A2B5) and mature oligodendrocytes (myelin basic protein) in the spinal cord, olfactory bulb and SVZ. Hence it can reasonably assumed that thyroid hormone administered *in vivo* in EAE animals decreases proliferation and favours differentiation toward the oligodendroglial lineage.

CONCLUSIONS

Among the multiple biological effects attributed to NGF in the CNS over the past fifty years, we focussed on observations related to NGF involvement in demyelinating diseases. The emerging picture includes regulation of inflammatory and immune processes, remyelination through protection, recruitment and differentiation of oligodendrocyte precursor, and neuroprotection. Further exploration of possible positive *in vivo* effects of this neurotrophin in demyelinating diseases is hindered by the very poor permeability of the blood-brain barrier to peripherally administered NGF. However, exploration of this field of research offers a fascinating view on the continuous up-dating and the multifaceted activity of this molecule.

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