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Review

Thyroid hormone and remyelination in adult central nervous system: a lesson from an inflammatory-demyelinating disease

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Abstract

Re-myelination in the adult CNS has been demonstrated in different experimental models of demyelinating diseases. However, there is no clear evidence that re-myelination is effective in multiple sclerosis (MS), the most diffuse demyelinating disease. Moreover, chronic disabilities in MS are believed to be due to remyelination failure and consequent neuron damage and degeneration. Due to the presence of numerous oligodendrocyte precursors inside demyelination plaques, reasons for remyelination failure are unknown. In this paper, we reviewed data from embryonic development and in vitro studies supporting the primary role of thyroid hormone in oligodendrocyte maturation. We also reviewed personal data on the possibility of promoting myelination in chronic experimental allergic encephalomyelitis (EAE), a widely used experimental model of MS, by recruiting progenitors and channeling them into oligodendroglial lineage through the administration of thyroid hormone.

Theme: Development and regeneration
Topic: Cell differentiation and migration

Keywords: Remyelination; Experimental allergic encephalomyelitis; Thyroid hormone; Oligodendrocyte precursor cell; Neural stem cells

Contents

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS), which can progress over decades and ultimately lead to permanent

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disabilities in humans. Different pathogenic events, i.e. inflammation, immune attack, demyelination and oligodendrocyte death, scar formation, axonal pathology, neuron distress and death, can occur in the different phases of the disease, involving many cell types, i.e. ependymal and endothelial cells, peripheral inflammatory and immune cells, including mast cells, macrophages and lymphocytes, astrocytes, microglia and neurons [32,53,68]. Moreover, also immature cells, e.g. neural stem cells and oligodendrocyte precursor and/or progenitor cells (OPCs), seem to be actively involved in repair attempts [26].

The main pathological feature in MS is lesion of the myelin sheaths, leading to the appearance of multiple areas of demyelination in the CNS and to axonal pathology. Axonal pathology and subsequent degeneration, which has been recognized as a major early event for the chronology of disabilities, correlate with both permanent disabilities and brain atrophy in advanced MS [85]. In spite of the severity of the damage, demyelination could be repaired, since a large number of oligodendrocyte precursor cells (OPCs) are present in the CNS. When labeled using antisera against the proteoglycan NG2, it has been estimated that OPCs account for 5–8% of the total number of cells in the adult CNS [56]. However, although there is evidence of remyelination in different experimental conditions in the adult central nervous system (CNS), re-myelination attempts observed in early plaques in MS are not followed by repair of the lesion [63]. In particular, myelin is inappropriately thin for the corresponding axon and internodes are shorter, so that the resultant remyelination is morphologically and functionally inadequate [38,76]. The reason for this is still unknown, also considering that a significant number of OPCs and premyelinating oligodendrocytes are found in early lesions in MS tissue [30,73], although they are in a quiescent state in chronic lesions [81]. There are many possible speculative explanations of re-myelination failure in MS [38,76], including quantitatively inadequate recruitment and/or differentiation of OPCs [74]; axons not receptive to remyelination [30]; inappropriate support of growth factors by astrocytes and/or other inflammatory cells [67]; and unfavorable or hostile extracellular microenvironment with regard to matrix proteins, adhesion and soluble molecules [75].

The possibility that an inadequate number of OPCs is present in demyelination plaques in MS suggested attempting to introduce a larger number of cells able to differentiate into myelinating oligodendrocytes in order to promote remyelination [34,39,40,65,76]. Different attempts at cellular therapy, using engineered, olfactory ensheathing, Schwann, oligodendrocytes, OPCs, embryonic and adult neural stem cells, have been proposed with contradictory results. However, the rationale for this approach is not clear, since it is widely accepted that MS lesions contain a substantial number of premyelinating oligodendrocytes, indicating that the potential for repair is not limited by the loss of these cells. On the contrary, the number of OPCs is greater than before demyelination in early MS, meaning that new oligodendrocytes are generated during the disease [27]. Overall, the positive effects on clinical course described in some of these attempts have been attributed not to the newly generated myelin-forming cells, but to the growth factor release promoted by these cells.

Another possible explanation for remyelination failure in MS is that OPCs are unable to turn into remyelinating oligodendrocytes in MS. According to this view, attention should be devoted to the attempt to rescue endogenous OPCs and to turn reluctant OPCs into myelinating oligodendrocytes by acting on the OPCs themselves, or by potentiating extracellular signals from axons, astrocytes or other cells type favoring this.

2. Remyelination in adult CNS and during inflammatory-demyelinating diseases

Remyelination, the process by which myelin sheaths are restored to demyelinated axons, is one of the few spontaneous regenerative processes that occur within the adult mammalian CNS. It is generally accepted that the process of remyelination represents a recapitulation of myelination during development. For example, the Notch pathway, which is implicated in cell fate determination in premyelinating oligodendrocytes during development, is re-expressed in MS tissue [50]. A widely accepted model of remyelination proposes that new adult OPCs are generated by division, these newly generated cells being able to migrate into demyelinated areas thanks to the guidance provided by molecules released by different cells during inflammation, toxic or immune attack, and subsequently differentiating into myelinating cells [56,76]. OPCs are disseminated within the white and gray matter of the adult CNS, and can be also be generated from stem cells present in different areas of the CNS. Consequently, a potentially unlimited number of myelinating cells could be recruited in the adult CNS. In experimental inflammatory-demyelinating diseases, but also in MS, OPCs [29,66] and also neural stem cells [20,64,71] re-enter the cell cycle and proliferate, also due to the effects of proinflammatory cytokines which are secreted during acute EAE [31]. Moreover, newly generated PSA-NCAM-positive cells, which are believed to be precursors of OPCs [13], appear during acute EAE [20]. Although the molecular signals responsible for this activation have not yet been identified, it is likely that inflammation and remyelination are linked [26]. In fact, inflammation enhances the migration of OPCs [78], the depletion of macrophages impairs myelination [55] and different growth factors affecting cell cycle regulation are expressed in inflammatory cells in both EAE and MS [54].

Strategies to enhance reluctant myelination are under active investigation, as remyelination failure is one of the most frustrating questions in MS research [38]. Different strategies have been proposed to achieve this therapeutic

goal. As already described, the rationale for cell-based therapies aimed to bring more myelinating cells into MS plaques is weak. Moreover, practical clinical application of cell transplant in MS therapy is unlikely considering the necessity to transplant multiple (in the order of tens) and interspersed plaques of demyelination all over the rostro-caudal extension of the brain and spinal cord and intravenous delivery of cells leads to homing very few cells [65]. Neurotrophins, like NGF [79], mitogens, like bFGF and PDGF, insulin growth factor I [76] and alfa-TNF [7] have been administered to promote endogenous remyelination. However, the very low permeability of the blood–brain barrier to these proteins represents a limiting factor for the application of such strategies in human disease, as it imposes invasive delivery procedures. Moreover, effective myelination is the result of a complex interplay between axon and oligodendrocyte. Electrical activity within the axon is not only involved in regulating the differentiation and survival of oligodendrocyte precursors during development [10] but also plays a key role in the induction of myelination [33]. Axonal pathology in MS may contribute to further impairment of myelination [16,37]. Thus, neuroprotective strategies may also find a place in MS therapy [17,52].

3. Turning OPLs into myelinating oligodendrocytes: development and in vitro evidence for a key role of thyroid hormone

Thyroid hormones play a crucial role in brain development, as dramatically testified by the severe morphological, functional and cognitive impairment in congenitally hypothyroid infants [6]. They act by providing a signal at an appropriate stage of development that leads to differentiation and maturation [5,61]. There are two circulating thyroid hormones, i.e. thyroxine and tri-iodothyronine. Thyroxine, the principal product of the thyroid gland and the most abundant circulating thyroid hormone, is converted to tri-iodothyronine in the cytoplasm and nucleus of target tissues by three distinct tissue specific deiodinases [69]. Most classic thyroid hormone actions are believed to be mediated genomically by tri-iodothyronine binding to nuclear receptor (TRs). TRs have been shown to belong to a large superfamily of nuclear hormone receptors that include the steroid, vitamin D, and retinoic acid receptors, as well as "orphan" receptors for which there are no known ligand or function [84]. TRs share a similar domain organization with other family members as they have a central DNA-binding domain containing two "zinc fingers" and a carboxy-terminal LBD as well as a domain coupling with another tri-iodothyronine receptor or other nuclear receptors (e.g. retinoic acid X receptor) to form dimers. The receptors bind to DNA at sites with certain specific orientations of paired thyroid response elements with specific hexameric oligonucleotide sequences (e.g. AGGTCA) that are typically located in the 5¢ regulatory regions of thyroid hormone-responsive genes. In most cases, the interaction between the tri-iodothyronine and its receptor prompts the binding of accessory protein cofactors that either activate or repress a specific gene's transcription. TR isoforms are encoded on separate genes, designated as TRα and TRβ, on human chromosomes 17 and 3, respectively. Alternative splicing of the initial RNA transcript of the TRα gene generates two mature mRNAs that each encode two proteins: TRα-1 and c-*erbA*-2. The latter binds TREs weakly but cannot transactivate TH-responsive genes. There are also two TRs derived from the TRβ gene, designated as isoform TRβ-1 and TRβ-2. Acting as transcription factors, TRs play a vital role during embryonic development and metamorphosis, regulating cell cycle, cell growth and maturation [6,11,23]. The expression of gene batteries is directly or indirectly regulated by TR in the brain and peripheral tissues. They include transcription factors, like the member of the Sp/KLF family basic transcription element binding (BTEB), intracellular signaling molecules, like the substrate for calmoduline binding and protein kinase C RC3, hormones, like growth hormone and thyrotropin releasing hormone, cell-specific genes, like the cerebellar Purkinje cell protein-2 (Pcp-2) and oligodendrocyte-specific genes including genes encoding for the most abundant proteins in the myelin sheath, i.e. myelin basic protein (MBP), myelin-associated glycoprotein (MAG) and proteolipid protein (PLP) [14,15].

Thyroid hormones are crucial in both early brain development, when proliferation and migration are predominant, and in later stages, also postnatally, when the maturation of different cell types, the initiation of axonal and dendritic growth, myelination and synapse formation take place [6]. Moreover, in late brain development the proliferation, the migration and maturation of myelin forming oligodendroglia can be observed [70]. Finally, TH also contribute to neural and glial phenotype in the adult brain and after different lesions [18,22,28,42–45].

Studies in genetically modified animals [9,62], such as analysis of myelination in hypo- and hyperthyroid animals [49], have provided abundant evidence that TH plays an important part in regulating oligodendrocyte lineage and maturation in vivo. Thyroid hormone is known to induce more oligodendrocytes to form from multipotent neural stem cells [71]. A 120-bp enhancer element region in the gene encoding for the intermediate filament protein nestin in progenitor cells contains putative binding sites for nuclear hormone receptor (thyroid hormone), suggesting that nuclear receptors for thyroid hormone play a role in regulating this neuroectodermal marker [58]. Moreover, thyroid hormone influences several stages of oligodendrocyte development and maturation [8], acting through different isoforms. Early in development, TH functions as an instructive agent, triggering OPCs (O-2A cell) cell cycle exit in close cooperation with platelet-derived growth factor (PDGF) [35,36]. Raff and colleagues have demonstrated

that O-2A cells become TH-sensitive after eight cell divisions: At that time, TH specifically causes the O-2A cell to withdraw from the cell cycle and to undergo terminal differentiation [35]. However, it seems that the so-called "intrinsic mechanism" does not operate by counting cell division, but by measuring the elapsed time. The cyclin-dependent kinase inhibitor p27 seems to be part of the timing component, while TH activates the effector component. The TRs isoform involved in proliferation arrest is still disputed: The β1 isoform increases parallel to p27 during oligodendrocyte differentiation [41], but transfection experiments in mouse fibroblast have indicated that TRα but not TRβ provoke the drastic arrest of proliferation [72]. In other cell lines, the tumor suppressor protein p53 is the molecular

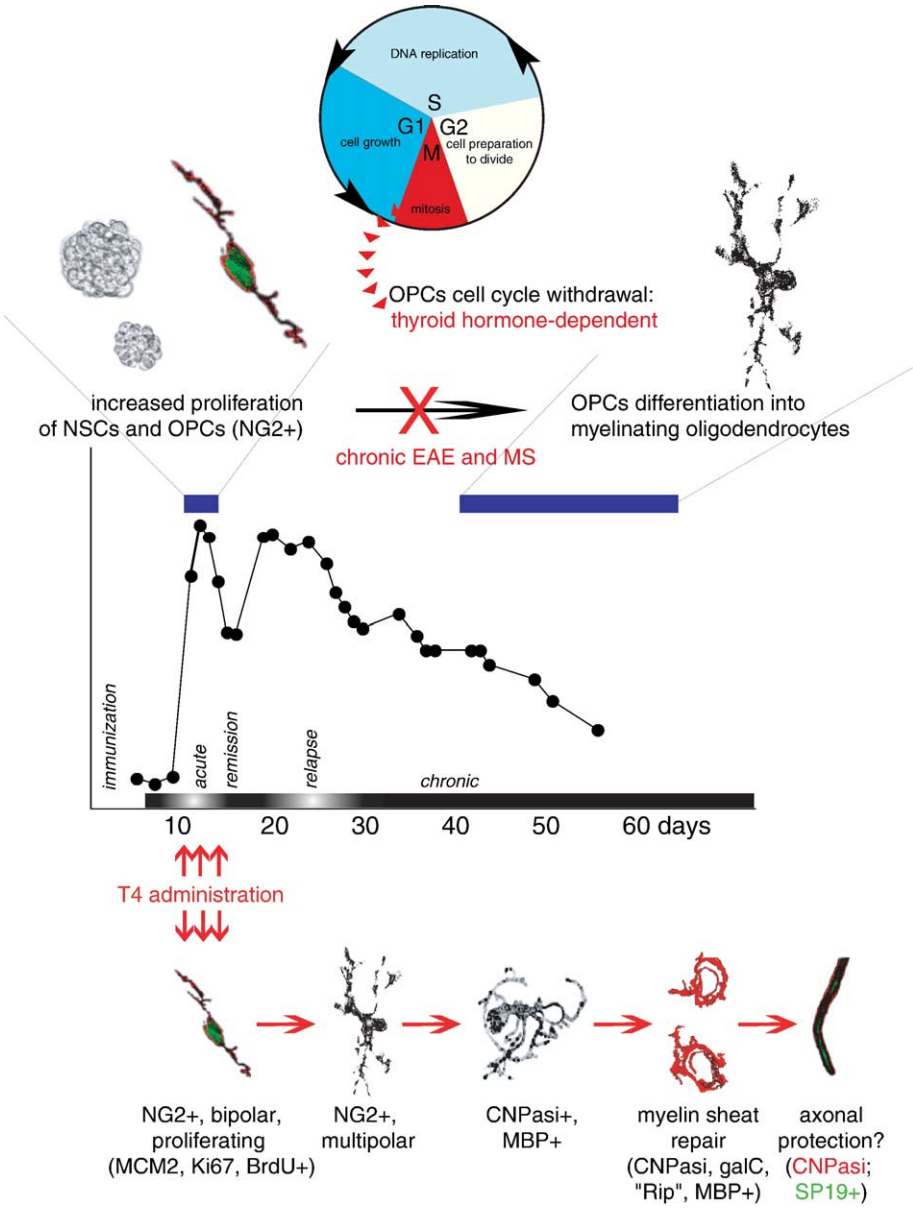

Fig. 1. The schema illustrates the rationale for thyroid hormone administration to improve remyelination during chronic EAE in DA rats. Graph reports the clinical course of EAE in DA rats immunized with guinea pig spinal cord in CFA. After the acute phase, a remission is observed which is followed by a severe, long-lasting relapse. During the acute phase, a spontaneous increase in NSCs and OPCs proliferation, in the SVZ and spinal cord, and in everywhere in the CNS, respectively, is observed. For unknown reasons, OPCs are unable to turn into myelinating oligodendrocytes in MS. OPCs differentiation into myelinating oligodendrocytes is thyroid hormone-dependent. OPCs become thyroid hormone-sensitive after a define number of cell cycles, due to p27 accumulation or to a switch of expression between thyroid hormone isoforms. Thus, we have administered thyroid hormone during the acute phase in EAE, when a large number of cycling cells are present. This treatment causes a decrease in NSCs and OPCs proliferation, the expression of markers for OPSs and myelinating oligodendrocytes increases and myelin sheaths are rapidly repaired. This could also protect neurons from axonal pathology [17,24,26]. Abbreviations: CNPasi, 2′,3′-cyclic nucleotide 3′-phosphodi-esterase; CNS, central nervous system; EAE, experimental allergic encephalomyelitis; galC, galactocerebroside; MCM2, mini-chromosome maintenance 2; MBP, myelin basic protein; MS; multiple sclerosis; NG2, proteoglycan NG2; NSCs, neural stem cells; OPCs, oligodendrocyte precursor cells; "Rip", mature oligodendrocyte; SP19, alfa subunit of voltage gated sodium channel.

partner for TRβ1 in cell cycle regulation [82]. A cell cycle-dependent balance among the different TR isoforms could be the way to regulate the differential hormonal sensitivity and, thus, transcriptional response to T3 in the different phases of cell cycle [60]. This is true not only during development, but also in mature CNS. TRα expression seems to decline as soon as OPCs progress toward myelinating oligodendrocytes, whereas TRβ1 seems to be associated with terminal maturation [72].

Post-mitotic oligodendrocytes contain about the same number of TR binding sites per cell as neurons, that is two to three times more than in astrocytes [84]. TH increases the morphological and functional maturation of oligodendrocytes by stimulating the expression of various genes, such as the myelin-oligodendrocyte glycoprotein, myelin-basic protein (MBP) and glutamine synthase [12,70]. In addition, TH provides a survival signal by rescuing developing oligodendrocytes from death induced by TNFα and IL-1β apoptosis [51]. Finally, MRS study has shown that thyroxin therapy can reverse abnormal myelination in congenital hypothyroidism even when thyroxin therapy was initiated beyond the age limit when abnormalities in myelinogenesis are considered irreversible [49].

4. Thyroid hormone administration enhances and accelerates remyelination in EAE

Starting from the facts listed above and in particular: (1) more OPCs are generated from NSCs during EAE; (2) OPCs re-enter mytosis in experimental and spontaneous demyelinating-inflammatory diseases; (3) newly generated OPCs are unable, for unknown reasons, to turn into myelinating oligodendrocytes in MS; (4) thyroid hormone stimulates cell cycle withdrawal and terminal differentiation of OPCs at the appropriate time, i.e. after a definite number of cell cycles, we have explored the possibility of promoting myelination in EAE, by recruiting stem and/or progenitor cells and channeling them into oligodendroglial lineage through the administration of thyroid hormone, in order to ameliorate repair capability of myelin sheet through non-invasive methods [24,26]. The rationale and timing of this experiment are illustrated in Fig. 1. These experiments have been carried out in Lewis female and congenic Dark Agouti (DA) female rats. These strains have a different susceptibility to EAE and related demyelination: Lewis develops sparse demyelination, whereas DA immunized with spinal cord homogenate develops an extensively demyelinating encephalitis [57] (Fig. 2).

We have analyzed the proliferation (Ki67-IR and bromodeoxyuridine (BrDU) uptake) and expression of markers for neuroectodermal cells (nestin), oligodendroglial committed precursor (nestin and PSA-NCAM), oligodendrocyte progenitors at different stages of differentiation (A2B5 and PDGFR as progenitor and pre-oligodendrocyte; O4 as pre-oligodendrocyte and immature oligodendrocyte; O4, NG2 and MBP as non-myelinating and myelinating mature oligodendrocyte; [12]) in the spinal cord, subventricular zone (SVZ, where a large population of neural stem cells is localized in the adult brain, [4]) and olfactory bulb. We found that thyroid hormone treatment reduces the number of proliferating cells in SVZ and spinal cord, and favors precursor oligodendrocyte differentiation in EAE rats. The expression of markers for undifferentiated precursors (nestin) actually decreases in EAE animals treated with thyroid hormone. Thyroid hormone treatment induces the onset of O4-positive cells and the up-regulation of A2B5-IR. Also mRNA for PDGF-receptor α (PDGFRα) is up-regulated by thyroid hormone treatment in EAE animals. Platelet-derived growth factor (PDGF) is a powerful inductor of oligodendrocyte lineage from stem cells. More importantly, myelin basic protein (MBP), which decreases in EAE animals, is significantly up-regulated in thyroid hormone treated EAE animals. Finally, myelin organization and sheath thickness, as evaluated by confocal laser microscopy using different markers of mature oligodendrocytes (CNPase, galC, MBP) and image analysis, are restored by T4 treatment. The clinical course of EAE animals is also positively affected, as indicated by the less severe relapse in treated animals.

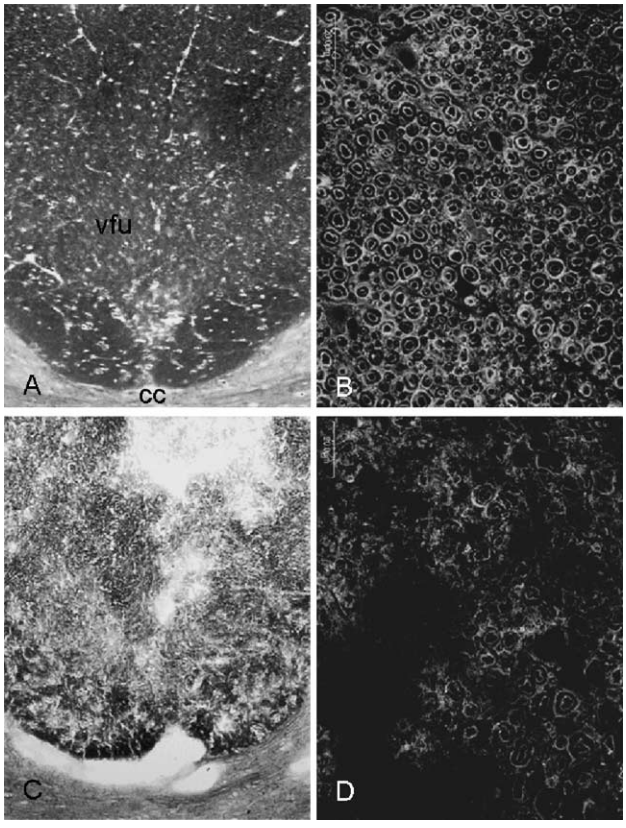

Fig. 2. Histological (A, C: Sudan Black) and immunohistochemical (B, D: "Rip"-IR, confocal microscopy image) staining of myelin in the ventral funiculus of the lumbar tract of the spinal cord showing the severe myelin damage in EAE-DA rats (C, D) with respect to control animals (A, B). Scaler bar: 20 μm. Abbreviations: cc, central canal; vfu, ventral funiculus.

5. Thyroid hormone and synthesis of neurotrophins in mature CNS and during inflammatory-demyelinating diseases

Although OPCs and oligodendrocytes appear as the most reliable target for TH action during EAE, we cannot exclude other possible cellular targets. In fact, TRs are widely expressed in different cell types in the CNS and peripheral tissues [83]. Due to the complex pathology of EAE (and MS), this should also be considered to explain any positive effects of TH in EAE rats. Indeed among treatments able to improve the clinical course of EAE, it has been reported that the administration of human recombinant-NGF delayed the onset of clinical EAE in marmoset, preventing the full development of inflammation and demyelination [79]. Several research groups over the past 20 years have indicated a relationship between thyroid hormone and NGF synthesis not only during development, but also in the mature brain and after lesion [18,19,22,46,47,59,69]. It is known that under physiological conditions, thyroid hormone regulates the endogenous synthesis of NGF [53–55] and a single injection of T4 is able to raise NGF content in the brain [80]. We reported that NGF content in the spinal cord drops in the acute phase of EAE [20] and that T4 administration restores NGF to control animal content [24]. Thus, also an NGF rise due to TH administration could be part of the process. NGF also protects oligodendrocyte from damage induced by tumor necrosis factor (TNF) [77], a pro-inflammatory cytokine strongly implicated in the pathogenesis of EAE [48]. However, the positive role of NGF in the EAE course could also involve oligodendrocyte precursors [21,23]. For example, immunoreactivity not only for proliferating cells but also $p75^{LNGFR}$ positive elements is expanded in the SVZ during EAE. Chains of small, ovoid $p75^{LNGFR}$ positive cells extending from the border of the ventricle toward the white matter of the corpus callosum are observed in the acute phase and an active uptake of NGF is also observed in the germinal zones in the brain. Finally, a direct role of NGF on oligodendrocytes for myelin formation is also supported by in vitro studies, indicating that it induces the proliferation of oligodendrocytes isolated from adult pig brain [1], activates trkA-mediated intracellular pathways leading to genomic effect and [2] possibly participates in myelin formation [3].

6. Conclusions

The data reviewed suggests that thyroid hormone administration favors myelin sheath repair in chronic EAE developed in DA rats. Thyroid hormone could exert its positive effects through different actions: by favoring OPCs generation from NSCs, by favoring OPCs maturation, by enhancing MBP and other myelin protein expressions, or by increasing NGF endogenous synthesis, which could then act as neuroprotector to prevent TNFa-induced apoptosis of OPCs, and as an immunomodulator.

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Further reading

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