REVIEW

Cellular approaches to central nervous system remyelination stimulation: thyroid hormone to promote myelin repair via endogenous stem and precursor cells

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Abstract

Brain and spinal cord repair is a very difficult task in view of the extremely limited repair capability of the mature central nervous system (CNS). Thus, cellular therapies are regarded as a new frontier for both acute and chronic neurological diseases characterized by neuron or oligodendroglia degeneration. Although cell replacement has been considered as the primary goal of such approaches, in recent years greater attention has been devoted to the possibility that new undifferentiated cells in damaged nervous tissue might also act in autocrine–paracrine fashion, regulating the micro-environment through the release of growth factor and cytokines, also regulating immune response and local inflammation. In this review, repair of demyelinating disease using endogenous cells will be discussed in view of the critical role played by thyroid hormones (THs) during developmental myelination, focusing on the following points: 1) endogenous stem and precursor cells during demyelinating diseases; 2) TH homeostasis in the CNS; 3) cellular and molecular mechanism regulated by TH during developmental myelination and 4) a working hypothesis to develop a rationale for the use of THs to improve remyelination through endogenous stem and precursor cells in the course of demyelinating diseases.

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Introduction

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MS: a puzzling disease in which myelin repair fails

MS is an inflammatory demyelinating disease of the CNS with unknown aetiology, which progresses over decades, ultimately leading to permanent motor disabilities, cognitive and affective disorders (Compston & Coles 2002). It is the most frequent non-traumatic disabling neurological disease among young adults, with 12 000 new diagnoses per year in the United States alone (Hirtz et al. 2007).

Different pathogenic events involving many cell types occur in the course of the disease. According to the classical view, inflammation and immune attack due to
CNS invasion by peripheral Th1 lymphocytes are pre-eminent in the early phase of the disease; then demyelination and oligodendrocyte (OL) death prevails, leading to the lesion of the myelin sheaths and the appearance of multiple areas of demyelination widespread in the white and grey matters of the entire CNS. It has been also proposed that the early apoptotic death of OLs triggers microglial activation, with Th1 invasion as a secondary event (Barnett & Primeas 2004, Barnett & Sutton 2006). In any case, axonal pathology and neuron death have been recognized as major early events in the chronology of disabilities, correlating with both permanent disabilities and brain atrophy in advanced MS (Lassmann et al. 2007). Several pathogenic processes, such as inflammation, immune reaction, demyelination, OL death, axonal damage and neuron death, follow each other and overlap over the long course of the disease, all providing possible targets for therapeutic intervention. Indeed, several drug combinations are under active investigation as potential disease-modifying therapies (Lopez-Diego & Weiner 2008).

Myelin repair is possible and may be effective also in terms of functional outcome, as it is the only truly competent repair mechanism operating in the mature CNS (Miller & Mi 2007, Franklin & ffrench-Constant 2008, McTigue & Tripathi 2008). This capability is largely guaranteed by the presence of a relatively recently described cell population in the CNS, which is identified by the presence of the membrane-associated chondroitin sulphate proteoglycan (NG2) and the α receptor for platelet-derived growth factor (PDGFαR). These cells, which are not astrocytes, OLs or microglial cells, were originally identified as oligodendrocyte precursor cells (OPCs; Nishiyama et al. 1999, Dawson et al. 2000). OPCs are generated during development (de Castro & Bribián 2005) and migrate over the entire CNS during late development, so that they are disseminated in the white and grey matter of the mature CNS, where they account for 5–8% of the total cell population (Levine et al. 2001). These cells have the remarkable capability of proliferating and migrating in the case of injury, and also of being able to differentiate into mature myelinating OLs (Barakscay et al. 2007). Moreover, new OPCs might be also generated by precursor cells, which are located in tissue niches in the mature CNS, including the subventricular zone (SVZ; Komitova et al. 2009) and the vascular niche (Araï & Lo 2009). The SVZ is the largest germinative zone in the adult brain, which contains a well-characterized stem cell niche. While most studies highlight the neurogenic potential of progenitors, recent data indicate that SVZ cells become reactivated in response to different pathological cues, such as trauma, ischaemia, neurodegeneration, inflammation and demyelination. A severe desegregation of the niche, with enhanced proliferation and recruitment of progenitors into myelin lesions, has been demonstrated in experimental models of demyelination in rodents (Calza et al. 1998a,b, Picard-Riera et al. 2002) and in MS (Nait-Oumesmar et al. 2007). Inflammation seems to be critical for activation of OPCs and progenitors and, ultimately, for successful myelin repair (Calza et al. 2005, McQualter & Bernard 2007). Remyelination is observed in areas of active inflammation in MS (Foote & Blakemore 2005, Setzu et al. 2006), whereas it is impaired in mice lacking proinflammatory cytokines (Mason et al. 2001) or in the case of macrophage depletion (Kotter et al. 2005, Schonberg et al. 2007). At the same time, as a Janus phenomenon, chronic inflammation is detrimental in many pathological conditions leading to excitotoxic lesion and altered redox balance (Sanders & De Keyser 2007), and also impairs the capability of progenitors to generate new OLs (Pluchino et al. 2008).

In spite of the fact that a significant number of OPCs also newly generated from the SVZ are present and proliferate in early lesions in MS (Wolswijk 2002, Wilson et al. 2006), for some unknown reason OPC differentiation into myelinating OLs is blocked (Kuhlmann et al. 2008) and remyelination progressively fails in MS. The inefficiency or failure of myelin-forming OLs to remyelinate axons and preserve axonal integrity remains a major impediment of the repair of MS lesions and the factor principally responsible for axonal and neuronal degeneration, leading to chronic disability and brain and spinal cord atrophy. The reason for incompetent myelin repair in MS is still obscure (Miller & Mi 2007, Rodriguez 2007, Dubois-Dalcq et al. 2008). Successful remyelination requires an orchestrated interplay among OPCs, extracellular matrix and axons. OPCs need to be appropriate in number, in the right position and prone to differentiate into mature OLs; the extracellular matrix, which provides the tissue architecture, has to properly regulate intercellular communication and cellular migration; axons have to provide appropriate membrane and soluble signals to OPCs (Camara & ffrench-Constant 2007, Simons & Trotter 2007). Moreover, other cellular and molecular players, including ependymal, endothelial, peripheral inflammatory cells, microglia, astrocytes, hormones, growth factors, etc. are in the arena of the ‘battle between destruction and repair’ in MS (McQualter & Bernard 2007, Rodriguez 2007).

Cell therapy to repair lesions in MS: in search of a rationale

Autologous hematopoietic cell transplantation has been proposed for immune modulation/ablation in MS. Clinical trials have been completed and others
are in progress. This type of cell therapy is not considered in this review. Stem cell transplantation has been also proposed to replace lost OLs also in MS, and tested in different rodent models of demyelination. Different cell types were used, deriving from syngenic, allogenic or xenogenic donors, including embryonic stem cells and adult somatic cells. Adult somatic stem cells, such as neural, hematopoietic and mesenchymal stem cell, but also other cell types, such as olfactory ensheathing cells, Schwann cells and differentiated OLs have been proposed (Lindvall & Kokaia 2006, Aharonowiz et al. 2008, Chandran et al. 2008, Duncan 2008, Duncan et al. 2008, Einstein & Ben-Hur 2008, Hommes 2008, Karussis & Kassis 2008, Kulbatski et al. 2008, Payne et al. 2008, Sher et al. 2008, Yang et al. 2009). Also, more recently, autologous induced pluripotent stem cells appeared on the scene (Abeliovich & Doege 2009).

In view of the fact that multifocal lesions in MS spread from the spinal cord to the optic nerve, the first issue to address was the route of administration in order to allow cells to penetrate the blood–brain barrier and reach the lesion sites. Intracerebroventricular and multiple intraparenchymal injections were used, but also i.v. peripheral administration, since inflammation renders the blood–brain barrier permeable in defined time-windows during the disease (Muller et al. 2005). Even if it is accepted that donor cells migrate preferentially to the site of tissue injury also after i.v. system administration, currently available data suggest that only a small percentage of systemically administered cells migrate in the CNS and few of them differentiate into myelinating cells (Pluchino et al. 2003).

This is largely due to the intrinsic properties of mature nervous tissue. In spite of the considerable structural and functional plasticity required to guarantee the normal functioning of the CNS, the possibility of structural rewiring after lesions also involving exogenous cells is extremely limited due to the intrinsic properties of cellular players and, probably even more important, due to the non-permissive adherent and soluble molecules that are present in the extracellular micro-environment. In the meantime, recent data regarding the beneficial effects of cell therapy in various animal models of demyelinating diseases indicate that transplanted or i.v injected stem cells possibly exert a positive effect through mechanisms other than cell replacement, such as attenuating deleterious inflammation, protecting remaining cells from degeneration, providing trophic or ‘chaperone’ support to the injured tissue and enhancing endogenous recovery processes (Pluchino et al. 2005, Einstein et al. 2007, Rosser et al. 2007).

At the same time, another obvious therapeutic approach is the attempt to improve myelin self-repair capability by unblocking OPCs and pushing them toward becoming mature myelinating OLs (Dubois-Dalcq et al. 2005). They are directed toward antagonizing myelin inhibiting factors, such as LINGO (Rudick et al. 2008) or boosting promoting factors, such as THs.

**Embryology offers precious advice for myelin repair strategies based on endogenous stem and precursor cells**

Cellular and molecular events in successful myelin repair in adult CNS derive from the recapitulation of developmental myelination and lead to the synthesis of new myelin to ensheathe naked axons (Miller & Mi 2007). Molecular, cellular and morphogenetic processes during myelination require a spatially, temporally and quantitatively orchestrated sequence of genetically and epigenetically driven events, which also includes exposure to hormones and vitamins. THs play a key role in the development in all animal species and are crucial in early brain development, when proliferation and migration are predominant, and in later stages, also postnatally, when the maturation of different cell types, initiation of axonal and dendritic growth, myelination and synapse formation take place (Oppenheimer & Schwartz 1997, Koibuchi & Chin 2000, Howdeshell 2002, Koenig & Neto 2002, Boelaert & Franklyn 2005).

**TH and CNS**

Thyroxine (T4) is the principal product of the thyroid gland and the most abundant circulating TH; however, 3,3’,5-triiodothyronine (T3) is the active form (Fig. 1). Transthyretin, synthesized by the choroid plexuses (CP), has an important role in transporting T4 from blood to cerebrospinal fluid and to the brain (Chanoine et al. 1992, Chen et al. 2006, Kassem et al. 2006), where all cell types are TH-sensitive. Because of the lipophilic nature of TH, it was thought that it traversed the plasma membrane by simple diffusion. However, in the past decade, membrane transport systems for TH have been demonstrated, i.e. organic anion transporters and amino acid transporters, among which MCT8 is strongly expressed in the CP, capillary endothelial cells and selected neuronal populations (Jansen et al. 2005, Taylor & Ritchie 2007, Heuer & Visser 2009). The biological activity of TH on target cells is determined by intracellular T3 concentration, which is dependent on the level of circulating T4 and T3, the presence of transporters on the plasma membrane and the activity of tissue specific deiodinases (Ds). Three distinct tissue-specific Ds have been identified (Gereben et al. 2008): D2 is the active isoform in the brain, converting T4 into T3, whereas D3 converts T3 into the inactive rT3. Most classic TH actions are
genomically mediated by T₃ binding to nuclear receptors (TRs), which belong to the nuclear receptor superfamily (Yen 2001). TRα and TRβ genes encode for TRs. Alternative splicing of TRα mRNA gives rise to TRα₁ and TRα₂, and the expression of the alternative DNA strand yields Ref-Erb-A (Aα₁, Aα₂), but neither TRα₂ nor Ref-Erb-A binds T3. Likewise, the alternative activation of promoters in the case of TRβ mRNA yields TRβ₁, TRβ₂ and TRβ₃. More recently, two additional rat TRβ isoforms, TRβ₃ and TRΔβ₃, have been cloned (Williams 2000). The various TR isoforms are expressed in temporospatial-specific patterns during development and in distinct ratios in adult tissues and different cell types, suggesting that TR subtypes and isoforms play different roles in cell proliferation, differentiation, growth and maturation (Forrest et al. 1990, 1991, Puymirat et al. 1992, Sarlieve et al. 2004, Lemkine et al. 2005; Fig. 2). TRs have a central DNA-binding domain containing two ‘zinc fingers’ and a carboxy-terminal ligand-binding domain (LBD) as well as a domain coupling with another T₃ receptor or other nuclear receptors (e.g. retinoic acid X receptor) to form dimers. In most cases, interaction between the T₃ and its receptor prompts the binding of accessory protein cofactors that either activate or repress a specific gene’s transcription. Acting as transcription factors, TRs play a vital role during embryonic development and metamorphosis, regulating cell cycle, cell growth and maturation (Calzá et al. 2000, Bassett et al. 2003). Expression of gene batteries is directly or indirectly regulated by TR in the brain and peripheral tissues (Dong et al. 2009). They include transcription factors, intracellular signalling molecules, hormones, such as GH and thyrotrophin-releasing hormone, cell-specific genes, such as the cerebellar Purkinje cell protein-2 and OL-specific genes (Calzá et al. 1997, Bernal et al. 2003).

Finally, a plasma membrane receptor site for TH on integrin αVβ3, which is linked by signal-transducing mitogen-activated protein kinase to mitogen-activated protein kinase-mediated intranuclear events, has been identified, opening up a completely new perspective for TH’s role in architectural sculpture and tissue and organ maintenance (Calzá et al. 1997, Davis et al. 2005, Visser et al. 2008).

**TH and CNS myelination**

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cerebellum of rats, as measured by real-time PCR, in which the cerebellum at post-natal days 2/3, 14, 30 and 135 in the appropriate times. More generally, T3 seems to be part of the division leading to terminal differentiation at appropriate times (Furlow & Neff 2006; Fig. 3).

view of cellular programming and micro-environmental fundamental cell activities, including cell cycle, in complex timing molecular system that regulates expression of TRs (Maruvada et al. 1998, Obregon et al. 2007), have provided abundant evidence that TH plays an important part in regulating OL lineage and maturation in vivo. THs induce more OLs to form from multipotent neural stem cells (Register et al. 1999, Fernández et al. 2004b) and regulate several stages of OL development and maturation (Baas et al. 1997). 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; Durand et al. 1997, Durand & Raff 2000, Lu et al. 2008). According to the hypothesis developed by Raff's group for OL generation and maturation (Durand & Raff 2000, Raff 2006) and further confirmed by other groups for different cell types (Papaioannou et al. 2007, Tsui et al. 2008), T3 is a major component of the molecular machinery that regulates OPC proliferation and differentiation through a mitogen-dependent intrinsic cell timer. When OPCs proliferate, they become sensitive to T3 after eight cell divisions (or corresponding time), probably because of a cell cycle-dependent expression of TRs (Maruvada et al. 2004). T3 stops cell division leading to terminal differentiation at appropriate times. More generally, T3 seems to be part of the complex timing molecular system that regulates fundamental cell activities, including cell cycle, in view of cellular programming and micro-environmental signals (Furlow & Neff 2006; Fig. 3).

The TR isoform involved in proliferation arrest is still disputed: the β1 isoform increases parallel to p27 during OL differentiation (Gao et al. 1998), but transfection experiments in mouse fibroblast have indicated that TRα but not TRβ causes the drastic arrest of proliferation (Sarlieve et al. 2004). A cell cycle-dependent balance among the different TR isoforms could regulate the differential hormonal sensitivity and thus the transcriptional response to T3 in the different phases of the cell cycle (Maruvada et al. 2004). This is true not only during development, but also in mature CNS. TRα expression seems to decline as soon as OPCs progress toward myelinating OLs, whereas TRβ1 seems to be associated with terminal maturation (Sarlieve et al. 2004). Finally, THs stimulate the morphological and functional maturation of OLs by stimulating the expression of various genes, such as the myelin-OL glycoprotein, myelin basic protein (MBP) and glutamine synthase (Rodriguez-Pena 1999, Baumann & Pham-Dinh 2001).

**TH and CNS remyelination**

In view of the key role of TH in developmental myelination, and since successful remyelination is a recapitulation of developmental myelination (Miller & Mi 2007), an appropriate TH drive should be critical also for remyelination in MS. Thus, we have extensively explored the use of THs to favour oligodendroglial lineage and maturation from endogenous precursors in order ultimately to improve remyelination in animal models of MS. Our approach attempts to combine cellular and molecular notions regarding the role of TH in oligodendroglial commitment from undifferentiated precursors and myelination during development, and an accurate knowledge and use of the animal models of MS (Calzà et al. 2005). In particular, we focused on two facts that seem to be critical in remyelination failure in MS. First, there is an extensive proliferation of OPCs (and progenitors in the SVZ) during the acute phase of experimental allergic encephalomyelitis (EAE) and in fresh MS plaques. Second, proliferating OPCs are unable to withdraw cell cycle and progress toward mature myelinating OLs; this differentiation block has been indicated as a cause of remyelination failure (Kuhlmann et al. 2008).

This altered cell regulation is possibly related to the exposure to a cytokine mix due to early inflammation. Exposure to cytokine mix including interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α) and interleukin-1β, which are those found in the inflammatory phase in EAE and MS (Frohman et al. 2006), increases the number of OPCs, blocking their differentiation (Kuhlmann et al. 2008). Moreover, exposure of OPCs to IFN-γ prevents differentiation and cell cycle withdrawal, and significantly attenuates MBP expression (Chew et al. 2005). Prolonged exposure to proinflammatory cytokines further impairs the capability of progenitors to generate OPCs (Pluchino et al. 2008), thus contributing to OPC depletion in chronic lesions.

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Figure 2 The expression of the different thyroid hormone receptor isoforms is temporally and spatially regulated in the CNS. The graph illustrates the expression of TRα, TRα2, TRβ1 in the cerebellum at post-natal days 2/3, 14, 30 and 135 in the cerebellum of rats, as measured by real-time PCR, in which the expression level observed in adult rats (P135) is 1. The expression of α isoforms is higher in early post-natal age, whereas β1 increases post-natally.
A proinflammatory cytokine mix could be also responsible for an inappropriate TH-drive of OPC maturation. Indeed, one accepted concept is that TH action at cellular level (but also T₃ serum level) is locally regulated by D activity and TR expression, and this is relatively independent of TH serum concentration (Bianco & Kim 2006, Gereben et al. 2008, St Germain et al. 2009). In particular, D2 activation increases intracellular T₃ concentration, and this saturates local TRs, significantly regulating transcription of T₃-responsive genes (Gereben et al. 2008). The opposite effect is produced by D3 activation. Proinflammatory cytokines are able to alter Ds activity, thus leading to a decreased local T₃ production and reduced rT₃ degradation, a biochemical condition leading to local hypothyroidism (Papanicolau 2000). Proinflammatory cytokines also inhibit TRβ1 gene expression (Tauchmanová et al. 2005, Kwakkel et al. 2007). A reduced T₃ production by D2 inhibition or due to a dysregulation of TR expression triggered by interleukin 1β and TNFz has been described in the hypothalamus (Boelen et al. 2004), hepatic cells (Boelen et al. 2006, Kwakkel et al. 2007) and pituitary cells (Baur et al. 2000).

Immune activation and brain injury itself decreases the activity of D2 (Fekete et al. 2004, Margaill et al. 2005). According to this hypothesis, a decrease in tissue availability of T₃ or an impairment of nuclear receptors or TH transporter expression due to inflammation deprives OPCs of a key signal for cell cycle exit and maturation into myelinating OLs.

This could explain the beneficial effects of TH administration on the clinical and pathological evolution of EAE and cuprizone demyelination as observed by us and others. We have shown that TH administration improves EAE clinical course and the remyelination process in Lewis and Dark-Agouty rats and in the non-human primate Callithrix jacchus (marmoset), favouring remyelination and neuroprotection without resulting in hyperthyroidism (Calzá et al. 2002, 2005, Fernández et al. 2004a,b, Giardino et al. 2007). This effect occurs when TH is administered in the acute phase of the disease, when OPCs and progenitors proliferate actively (Calzá et al. 1998a,b). We found that TH treatment reduces the number of proliferating cells in SVZ and spinal cord, and favours OPC differentiation in EAE rats. The in vitro formation
of new OLs has been tracked using different markers for OPC differentiation, such as oligodendroglial committed precursor (nestin and PSA-NCAM), A2B5 and PDGFRz as progenitor and pre-OL; O4 as pre-OL and immature OL; O4, NG2 and MBP as non-myelinating and myelinating mature OL. TH treatment induces the onset of O4-positive cells and up-regulation of A2B5-IR and PDGFRz in EAE, but not in control animals. T3 administration completely restores the capability to produce MBP (mRNA and protein), which reflects a mature stage of the OL and is impaired in EAE. Finally, myelin organization and sheath thickness are restored by TH treatment. Moreover, T3 also up-regulates mRNA expression of Olig1, which is one of the early genes expressed by neural stem cells during oligodendroglial lineage, thus suggesting that new OPCs are formed during EAE under the T3 drive. The clinical course of EAE rats and non-human primates is also positively affected, as indicated by the less severe relapse in treated animals.

Recently, the rationale proposed by us for improving myelin self-repair through stimulation of OPCs was successfully applied on cuprizone demyelination in rats and mice. In particular, Franco et al. (2008) showed that remyelination in the corpus callosum of T3-treated rats improved markedly when compared with saline-treated animals. In the white matter of saline-treated demyelinated animals, OLs decreased and OPCs increased and the SVZ showed an increase in early progenitor cell numbers, dispersion of OPCs and inhibition of Olig and Sonic hedgehog (Shh) expression compared to non-demyelinated animals. The changes triggered by demyelination were reversed after T3 administration, confirming that THs could be regulating the emergence of remyelinating OLs from the pool of proliferating cells residing in the SVZ. Harsan et al. (2008) analysed T3 effect on cuprizone demyelination in mice, using a combination of in vivo diffusion tensor magnetic resonance imaging (MRI) and histological analyses. T3 restored the normal diffusion tensor (DT)–MRI phenotype accompanied by an improvement of clinical signs and remyelination. T3 also increased the expression of Shh and the numbers of Olig-2 and PSA-NCAM-positive precursors and proliferative cells.

The effect of exogenous administration of TH in regulating the demyelination/ remyelination ratio in animal models of MS might also involve other cell types, as almost all animal cells are sensitive to TH. The immune cells contain T3 (Pallinger & Csaba 2008), supporting the view of a complex and still poorly understood interaction between TH and immune function (Klecha et al. 2006). TH also regulates the expression of cytoskeleton protein during axon growth and regeneration (Schenker et al. 2002), thus indirectly modulating the axon-OL interplay that provides for proper white matter development and organization (Berbel et al. 1994, Guadano Ferraz et al. 1994). Finally, astrocytes, which are critical players in the complex scenario of inflammatory/demyelinating disease, are the cells that produce T3 in the CNS and, at the same time, provide a target for T3 action. TH regulates several aspects of astrocyte differentiation and maturation, including the production of extracellular matrix proteins and growth factors, and thus controls neuronal growth and neuritogenesis (Trentin 2006). T3 alters the expression and organization of several extracellular matrix proteins including laminin, fibronectin and syndecan, which are produced by astrocytes (Mendes-de-Aguirar et al. 2008). Since the extracellular matrix 3D organization is severely altered in EAE and MS (Maier et al. 2005), this could also be a target for T3 effects.

In conclusion, endogenous stem and precursor cells could represent an important resource for cell therapies applied to myelin repair. To successfully pursue the attempt to involve these cell populations in self-repair, a greater knowledge of the disease’s progression as well as of endogenous stem and precursor cell biology is needed.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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