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The effect of triiodothyronine on maturation and differentiation of oligodendrocyte progenitor cells during remyelination following induced demyelination in male albino rat

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ABSTRACT

Demyelination was induced by two weeks cuprizone treatment. Rats of +ve control and triiodothyronine (T3) then received three subcutaneous injections of either saline or T3 day after day and sacrificed at the end of the third and fifth weeks. Animals in −ve control group received only standard rodent chow. After one week of cuprizone withdrawal the corpus callosum in +ve control and T3 treated rats was still demyelinated as revealed by MBP immunohistochemistry. The assay of PLP gene showed significant increase of T3 treated group compared to both the −ve control and +ve control groups. After three weeks, significant improvement in myelination was detected in T3-treated group compared to +ve control as detected by both MBP immunohistochemistry and electron microscopy. After one week of cuprizone withdrawal, PDGFRα positive cells and gene expression showed significant increase in +ve control and T3-treated groups as compared to −ve control with insignificant difference in between the former two groups. After three weeks of cuprizone withdrawal, PDGFRα positive cells in T3-treated and +ve control groups decreased to the control levels. These results suggest that T3 was effective in improving remyelination when administered during acute phase and might direct progenitor lineage toward oligodendrocytes.

1. Introduction

Oligodendrocytes (OLG) provide myelin to axons which is essential for the proper function and maintenance of neurons in the brain. Myelin loss occurs in many demyelinating diseases such as multiple sclerosis (MS) and causes a variety of neurological disabilities in adults (De Groot and Woodroofe, 2001; Lassmann, 2001).

In demyelinating disease lesions, oligodendrocytes are lost either by apoptosis or necrosis (McTigue and Tripathi, 2008) and to promote functional recovery, lesions must be supplied with endogenous oligodendrocyte progenitor cells (OPCs) or with transplanted myelinating cells (Jeffery et al., 1999; Chari and Blakemore, 2002; Blakemore et al., 2002).

The adult mammalian subventricular zone (SVZ) of the lateral ventricle contains stem cells that give rise to neurons and glia (Doetsch et al., 1997). It generates the most abundant number of stem cells in the adult brain that are capable of migrating to a long distance (Maki et al., 2013). These endogenous progenitors react to demyelinating lesions and generate remyelinating oligodendrocytes (Nait-Oumesmar et al., 1999).

There is strong evidence supporting that thyroid hormone (TH) acts directly on oligodendrocytes differentiation and maturation processes which has been extensively studied during brain development (Franco et al., 2008). However, TH can also modify the proliferative activity and maturation of OPCs in mature brain (Fernandez et al., 2004) suggesting that OPCs in adult brain are still sensitive to signaling molecules known to regulate oligodendrogenesis during development (Franco et al., 2008).

The present study was designed to clarify the possible effect of T3 on differentiation and maturation of oligodendrocyte precursor cells using oligodendrocyte markers and confirming the result by gene expression.

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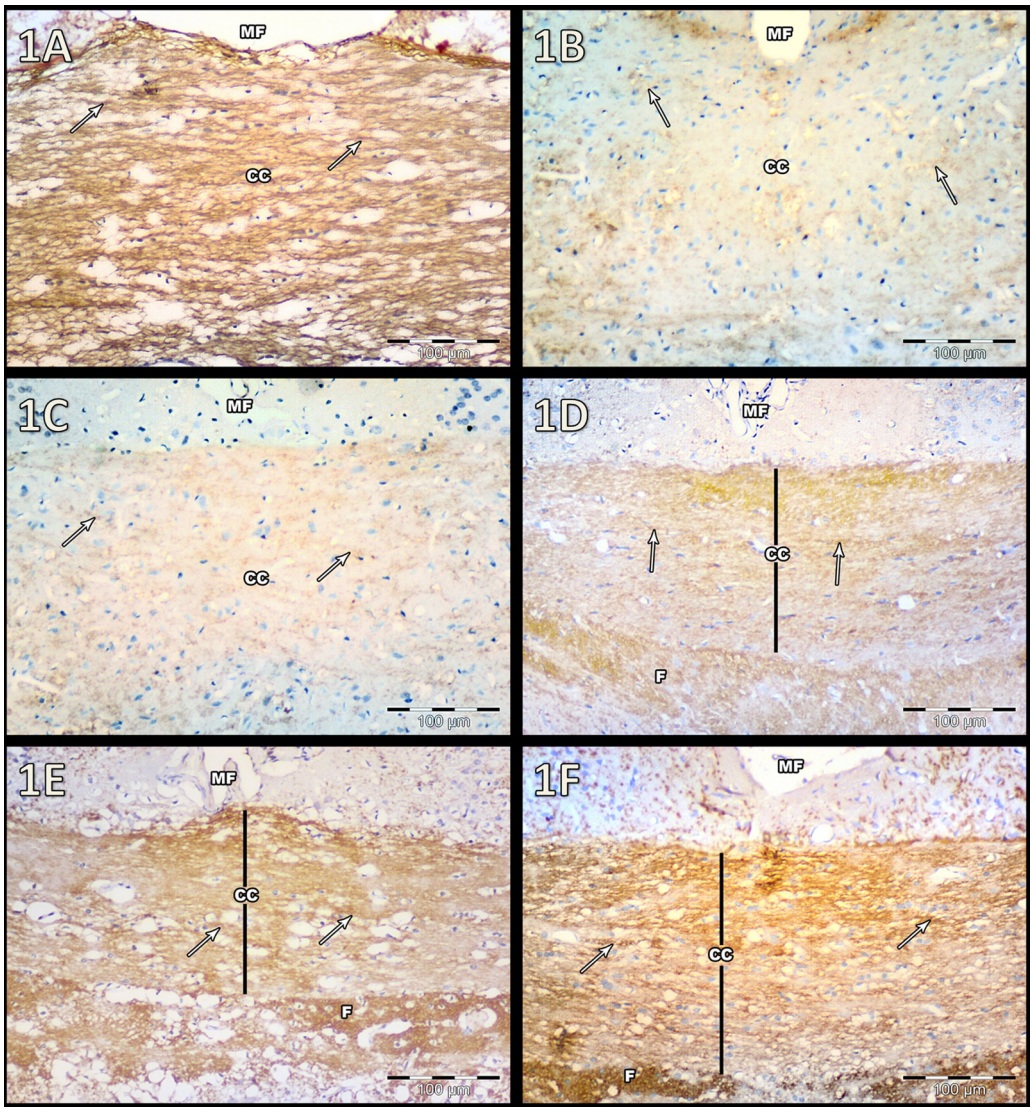

Fig. 1. (A) Photomicrograph of brain coronal sections of CC immunostained for MBP as indicator of mature OLGs show marked reduction in positive reactivity in cuprizone group (B) and +ve control (C) and T3-treated (D) groups after one week cuprizone withdrawal as compared to −ve control (A). More positively stained myelinated fibers can be seen in three weeks after cuprizone withdrawal in +ve control (E) and T3-treated (F) groups especially in the latter group as compared to cuprizone group (B). CC = corpus callosum. MF = median fissure.

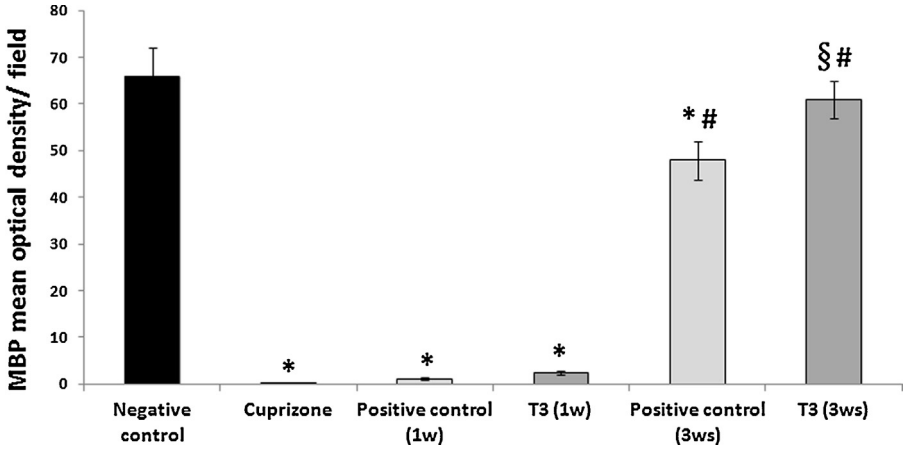

Fig. 2. Histogram of MBP mean optical density in CC of different groups demonstrating significant increase in three weeks (3ws) T3-treated group as compared to other treated groups. *Significant versus −ve control, #significant versus cuprizone group, one week (1w) +ve control and 1w T3 treated groups, § significant versus 3ws +ve control. $P < 0.001$. 1w, one week after cuprizone withdrawal, 3ws three weeks after cuprizone withdrawal.