
بسم الله الرحمن الرحيم
وقُل رَّبِّ زِدْنِي عِلْماً
صدق الله العظيم
سورة طه .. الآية ١١٤

الجديد في دور هرمونات الغدة الدرقية في الأمراض النفسية والعصبية

رســـــالـــــة

مقدمة توطئـة للحصـول على درجـة الماجستير

في **الأمراض النفسية و العصبية**

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٢٠١٣

Updates of The Role of Thyroid Hormones in Neuropsychiatric disorders

الجديد في دور هرمونات الغدة الدرقية في الأمراض النفسية والعصبية

A Review of Literature Submitted For Partial Fulfillment of The Master Degree in Neuropsychiatry

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Aim of the work

To highlight the recent updates concerning the role of thyroid hormones in neuropsychiatric disorders in order to reach a better management of patients with such disorders

Neuroendocrinology is the study of the interactions between the nervous system and the endocrine system.

Neuroendocrinology concepts are used as an integral part of understanding and treating neurobiological brain disorders

Brain development proceeds through precisely coordinated events in time and space that are largely determined by genetic factors

However thyroid hormones are the major physiological regulator of mammalian brain development.

Cell differentiation, migration and gene expression are altered as a consequence of thyroid hormones deficiency or excess. The physiological role of thyroid hormones can be defined so as to ensure and accelerate the timed coordination of different developmental events through its effect on the rate of cell differentiation and gene expression.

The hypothyroid brain presents many structural defects, Increases in cell density in the cerebral cortex, with Lower cell numbers, also it was noticed that there is a decreased number of GABAergic interneuron's in the cerebellum with accumulation of neuronal precursors. *(Manzano et al 2007).*

furthermore the interneuron's in the cerebral cortex shows reduction in number in neonatal hypothyroidism and changes of dendritic spine number are also observed in the cortex and hippocampus even after adult onset hypothyroidism, and are reversible with thyroxin treatment *(Gilbert et al 2007).*

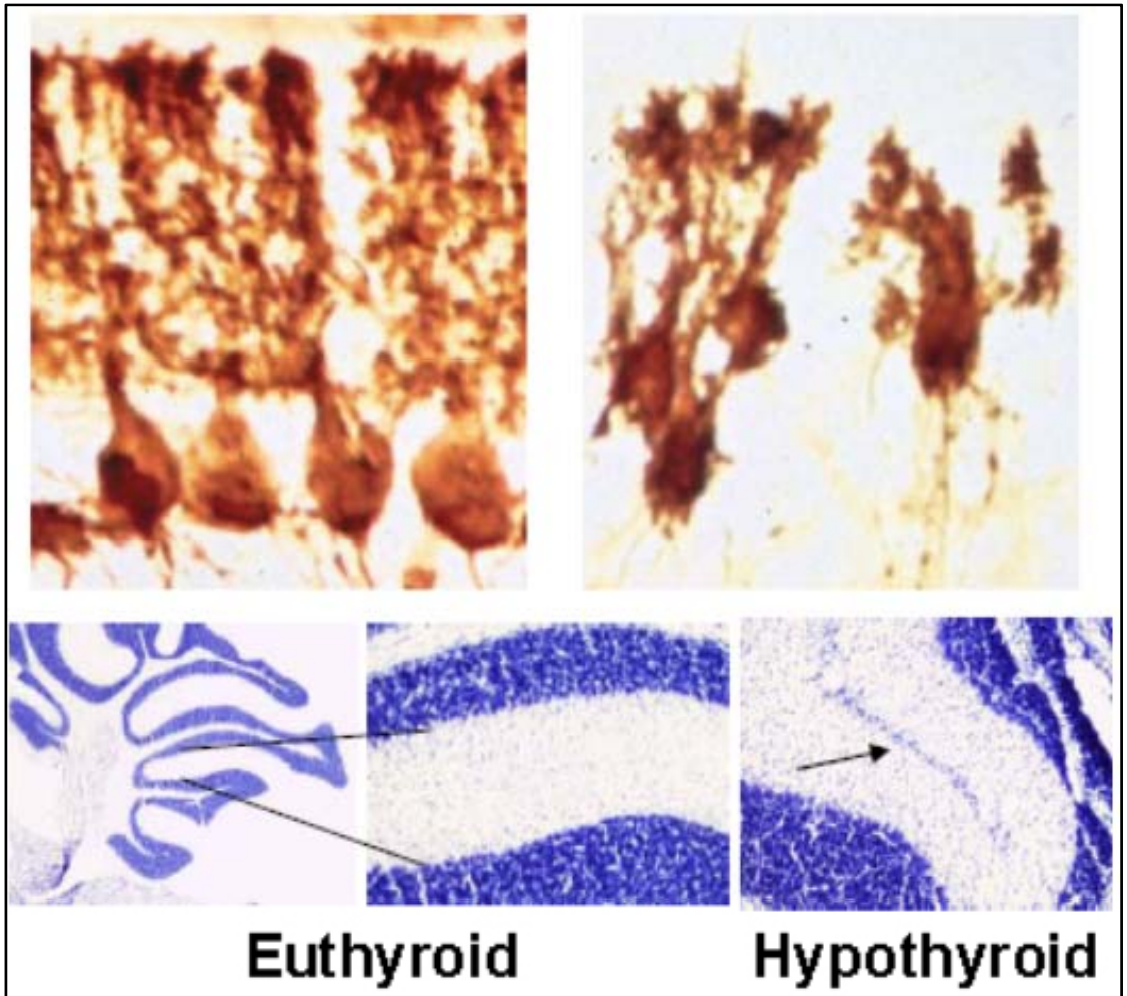

Figure 11: Postnatal morphological changes in the rodent cerebellum after neonatal hypothyroidism. Upper panel: Purkinje cells in a normal (left) and hypothyroid rat (right). Lower panel: persistence of the external granular layer (arrow) in a hypothyroid mouse cerebellum from Juan Bernal (2009): Thyroid Hormones in Brain Development and Function in thyroid disease manager

It has been described that hypothyroidism depresses, and thyroid hormone administration stimulates neurogenesis *(Ambrogini et al 2005, Montero-Pedrazuela et al 2006).*

Even the neuronal migration in the cerebral cortex have been noticed to be extremely sensitive to thyroid hormones, and any minor deficiency will be associated with migration defects *(Ausó et al 2004)*, Moderate thyroid hormone deficiency during pregnancy had been noticed to cause neuronal ectopias in the corpus callosum *(Goodman and Gilbert 2007).*

One mechanism by which thyroid hormones may influence neuronal migration in the cerebral cortex is through the regulation of the expression of the Reln gene *(Alvarez-Dolado et al 1999).*

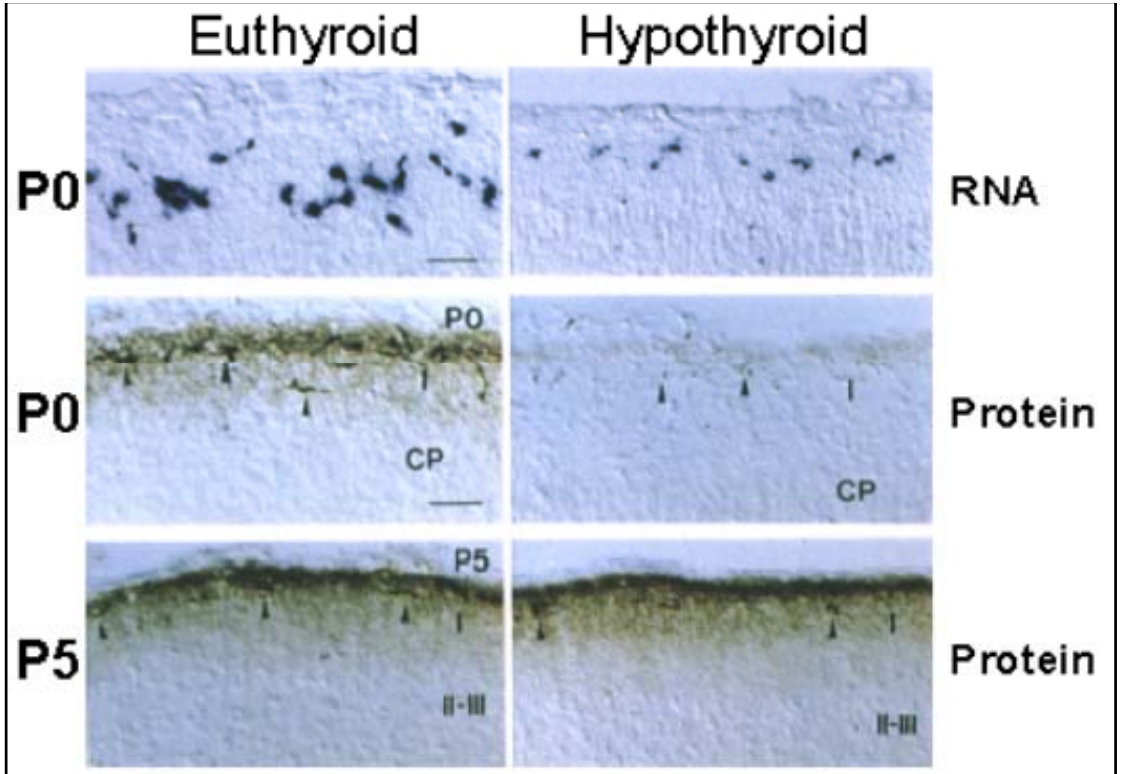

Figure 12: Regulation of Reelin by thyroid hormone. The figure shows slices of the cerebral cortex from euthyroid and hypothyroid newborn rats. The upper panels show in situ hybridization for Reelin RNA. The middle and lower panels show immunohistochemistry of Reelin protein. The RNA is present in isolated cells of layer I, known as Cajal-Retzius cells. The RNA is very low in the hypothyroid animals. The Reelin protein is a matrix protein, seen in these slices concentrated also in layer I. On P0 there is no Reelin protein in the hypothyroid animals, but on P5, the amount of reelin protein is normal (from Alvarez-Dolado M et al, J Neurosci. 19:6979-3, 1999).

Hypothyroidism causes delayed and poor deposition of myelin whereas hyperthyroidism accelerates myelination *(Adamo et al 1990).*

Thyroid hormones exert important effects on differentiation of oligodendrocytes, the cells that produce myelin. During development, hypothyroidism delays oligodendrocyte differentiation and myelin gene expression, *(Berbel et al 1994).*

In a study performed to evaluate the effect of local administration of triiodothyronine (T3) at the level of transected rat sciatic nerve showed an increase in the number and diameter of regenerated axons after administration *(Voria et al 2005)*.

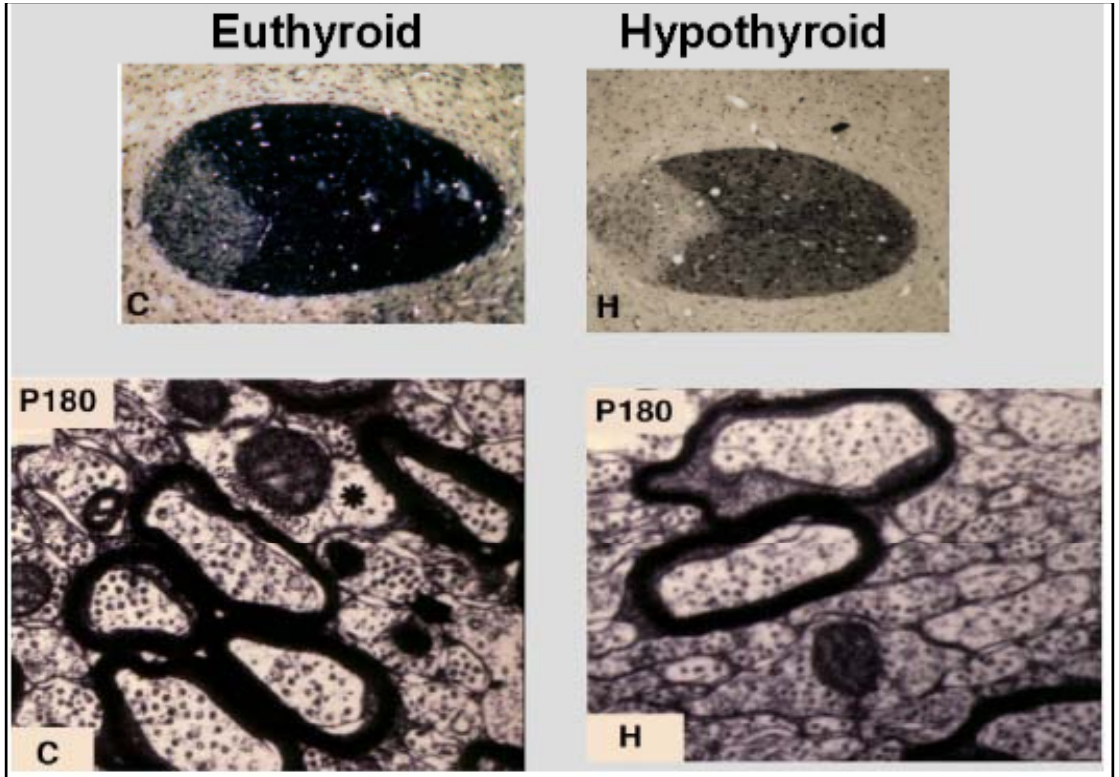

Figure 13: Myelination in the anterior commisure of euthyroid and hypothyroid rats. Hypothyroidism was produced during the neonatal period, and the rats were analyzed at 6 months of age. He upper panels show transversal section of the anterior commisure stained for myelin. The lower panels show electro microscopy analysis. The number of myelinated axons is reduced in the hypothyroid rats in parallel to an increased number of small diameter axons. Those axons reaching a critical size have near normal myelin content, but still present structural defects (From Berbel P et al, Behav Brain Res. 64:9-14, 1994).

In the last few years a number of genes have been identified as regulated by thyroid hormone in the brain. The regulated genes encode proteins of myelin, mitochondria, neurotrophins and their receptors, also proteins of the cytoskeleton, transcription factors, splicing regulators, cell matrix proteins, adhesion molecules, and proteins involved in intracellular signaling pathways. The identification of the gene network regulated by thyroid hormone during brain development, the elucidation of the mechanism of regulation and the clarification of the physiological roles of the regulated genes remain major goals for future studies

recently it was observed that L-thyroxin therapy induces a large down regulation of the primary transcripts of the non-coding microRNA pair miR-206/miR-133b. So that physiological levels of TH regulate a myriad of genes in human skeletal muscle. The identification of TH-responsive genes may provide the molecular basis of clinical effects in subjects with different TH status. The observation that TH regulates microRNAs reveals a new layer of complexity by which TH influences cellular processes *(Visser et al 2009).*