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The Relationship Between Thyroid States, Oxidative Stress and Cellular Damage

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1. Introduction

The thyroid hormones play an important role in many physiological processes, such as differentiation, growth, development, and the physiology of all cells. One of the most studied effects of the thyroid hormone is the control of the basal metabolic rate. Modifications in its levels can produce several alterations including modifications in the ROS steady-state and the REDOX environment in the cells. There is much evidence that show both hyperthyroidism and hypothyroidism are related to oxidative stress and cellular damage. For hypothyroidism, there are other findings that point to its protective effects. In this chapter we show both findings and propose that hypothyroidism is a protective state against toxic agents.

2. Thyroid hormones

Thyroid hormones (THs) T₄ (thyroxine or 3',5',3,5-L-tetra-iodothyronine) and T₃ (3',3,5-triiodothyronine) are synthesized in the thyroid gland located in the anterior part of the trachea, just below the larynx. It consists of two lobes joined in the middle by a narrow portion of the gland. The major thyroid-secretor cells, known as follicular cells, are arranged into hollow spheres, each of which it forms a functional unit called a follicle. On a microscopic section, rings of follicular cells enclosing an inner lumen filled with colloid form the follicles (figure 1).

The principal constituent of the colloid is a large protein molecule, thyroglobulin, where thyroid hormones are incorporated in their various stages of synthesis. The follicular cells produce the two iodine-containing hormones derived from the amino acid tyrosine; T₄ and T₃, the thyroid hormones. The mechanism involved in thyroid hormone syntheses and their release from thyrolobulin are shown in figure 2. Iodine, an essential element of the thyroid molecule, is actively transported by the Na⁺-I⁻ symporter (NIS, encoded by the SLC5A5 gene) at the basolateral membrane of the thyrocyte and it diffuses by an exchanger, known as pendrin (PDS, encoded by the SLC26A4 gene) to the lumen at the apical membrane. At the extracellular apical membrane, thyroperoxidase (TPO, EC 1.11.1.8) with hydrogen peroxide (H₂O₂), generated by dual oxidase 2 (DUOX2, EC 1.6.3.1), oxidizes and binds iodine

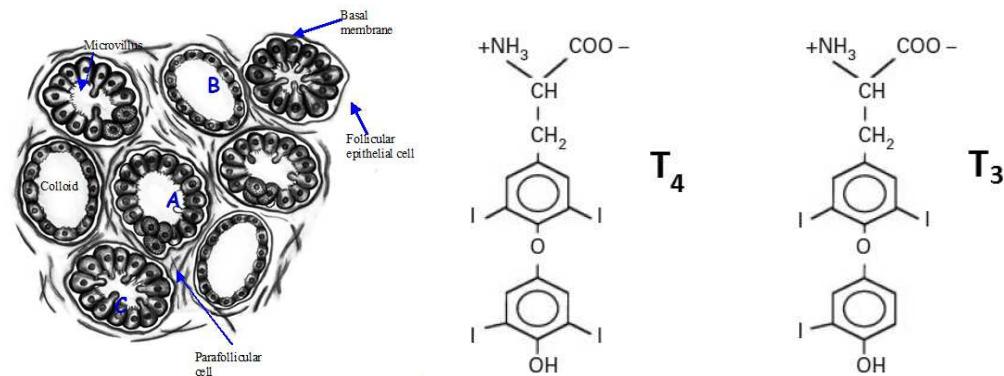


Fig. 1. Histological thyroid and the thyroid hormone structure. There are thyroid follicles with different activity. A: Thyroid follicle resting. B: Follicle with high activity.

covalently to tyrosyl residues, producing monoiodotyrosine (MIT) and diiodotyrosine (DIT) within the thyroglobulin macromolecule. The enzyme thyroperoxidase catalyzes the coupling of two iodotyrosine residues to produce the prohormone T_4 and smaller amounts of the active hormone T_3 . After endocytosis, iodinated thyroglobulin is hydrolyzed in the lysosomes by cathepsins and the thyroid hormone is released from the thyroglobulin backbone. The released MIT and DIT are deiodinated by a specific iodotyrosine deiodinase (TYD, or DEHAL1, EC 1.22.1.1), and the released iodine is recycled within the cell. The mechanism involved in the last step in the process, the thyroid hormone secretion, remains unknown (Di Cosmo et al., 2010). About 90% of the secretory product released from the thyroid gland is in the form of T_4 though T_3 is about four times more potent in its biologic activity. Most of the secreted T_4 is converted into T_3 by a group of enzymes known as iodothyronine deiodinases (D1 and D2, EC 1.97.1.10), which also include an inactivating deiodinase, the type 3 deiodinase (D3), that inactivates both T_4 and T_3 (Bianco et al., 2002)(table 1).

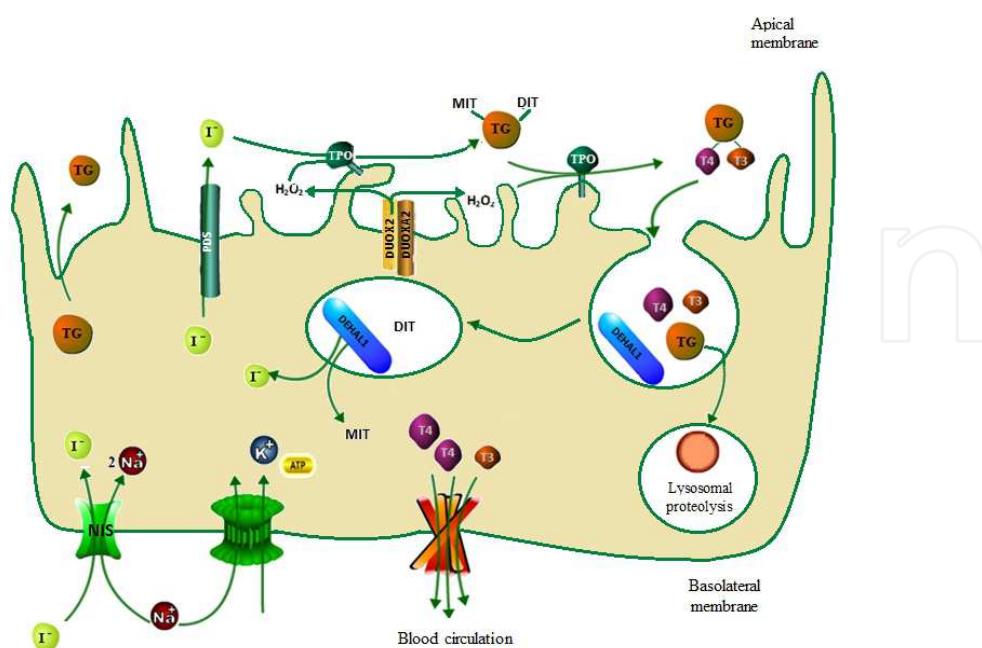


Fig. 2. Thyroid hormone syntheses in a follicular thyroid cell. Based on the model proposed by Di Cosmo (Di Cosmo et al., 2010)

The role played by the deiodinases is physiologically relevant. They have a role in various aspects of mammalian physiology, such as the maintenance of plasma T₃ concentration (Bianco et al., 2002), TSH and TRH feedback regulation (Christoffolete et al., 2006; Larsen, 1982), and the clearance of sulfated iodothyronines (Schneider et al., 2006).

Deiodinase	Tissue
D1	Liver, thyroid, kidney
D2	Brain, pituitary gland, BAT, thyroid, muscle
D3	Developing tissues and placenta, adult skin, brain

Table 1. Tissue distribution of deiodinases in humans (St.Germain et al., 2009).

2.1 Thyroid hormone regulation levels

Because the thyroid hormones have a crucial role in the function of every tissue in the body, their levels must be maintained relatively constant around an optimum level. This homeostatic-control mechanism primarily operates on the principle of negative feedback (figure 3). In this homeostatic-control mechanism, the hypothalamic thyrotropin-releasing hormone (TRH), the thyroid-stimulating hormone (TSH), and thyroid hormone all together form the hypothalamus-pituitary-thyroid axis. Thus, TRH in trophic fashion turns on the TSH secretion by the anterior pituitary, whereas thyroid hormone, in negative feedback fashion, turns off the TSH secretion. In the hypothalamus-pituitary-thyroid axis, inhibition is exerted primarily at the level of the anterior pituitary. As with other negative feedback loops, the one between thyroid hormone and TSH tends to maintain a stable thyroid hormone output (Hulbert, 2000).

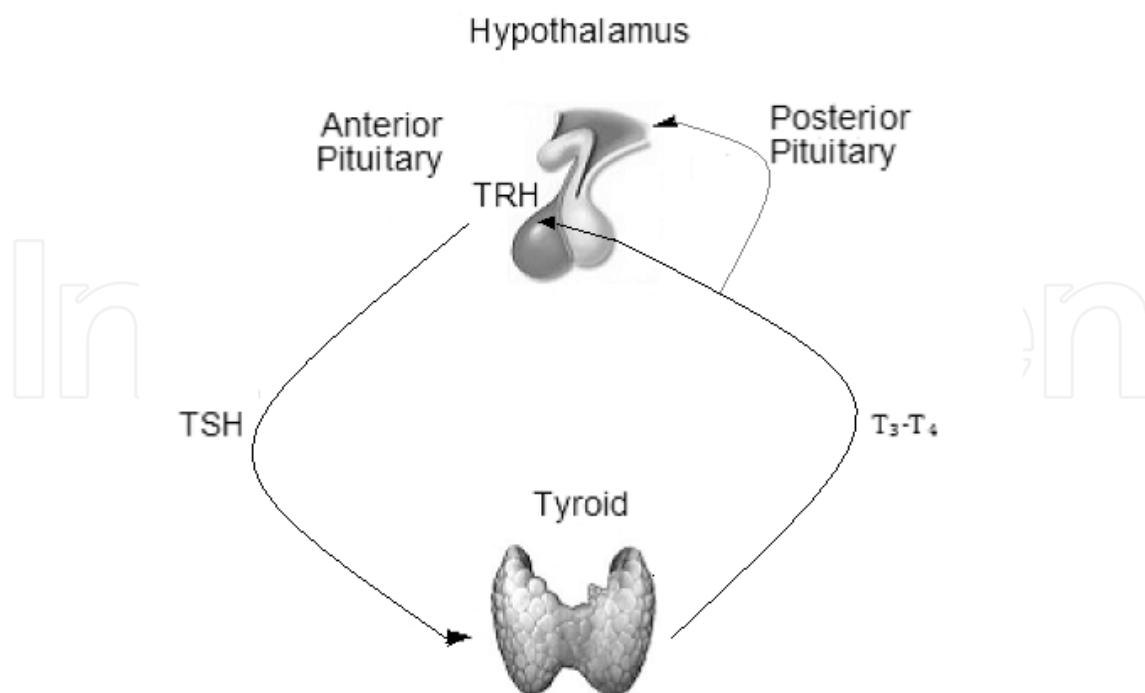
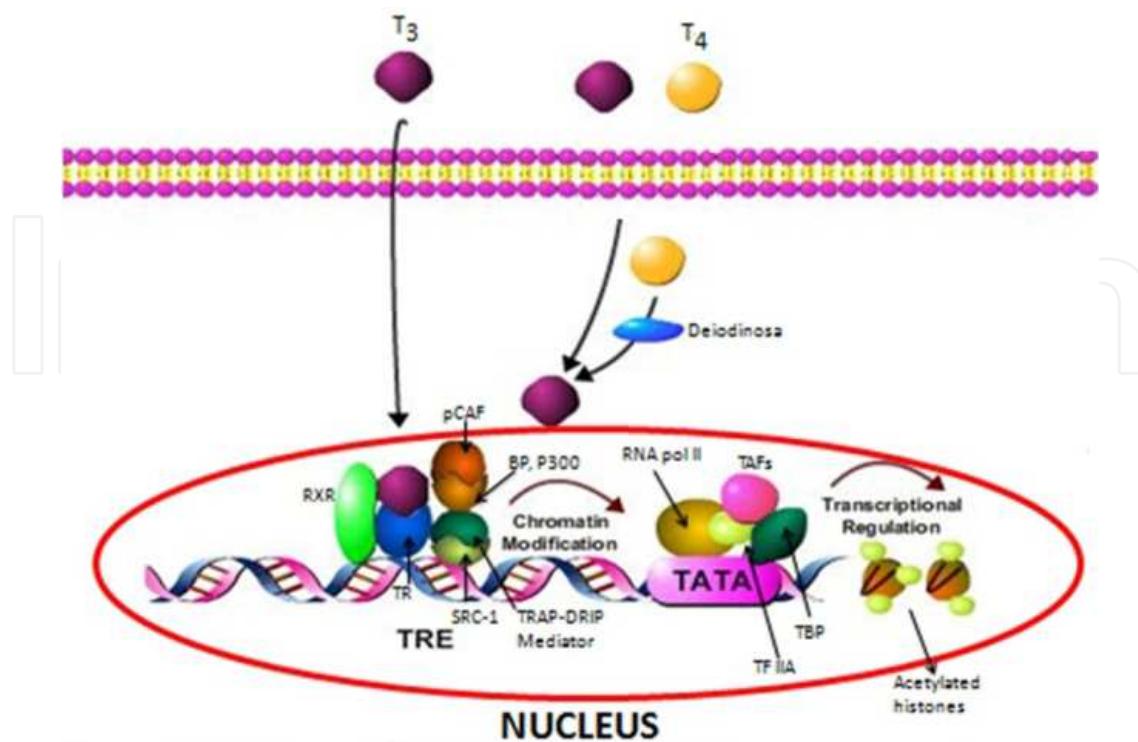


Fig. 3. Hypothalamus-pituitary-thyroid axes. In this image is shown the negative feedback exerted by a high T₃ concentration.

2.2 Mechanism of action of the thyroid hormones

Because thyroid hormones have been considered as lipophilic in their intracellular action, passive hormone diffusion through the lipid bilayer has been accepted. Because of the existence of nuclear receptors for thyroid hormones, it has long been believed that the THs caused effects only via genomic effects, however since the late 1980s it has been proposed that the THs may cause effects independently of genetic mechanisms, affecting membrane lipid composition or activation of enzymes (Lazar, 1993). Receptors for thyroid hormones (TRs) are proteins that act as transcription factors that belong to the superfamily of nuclear receptors, which includes steroids, vitamin D, retinoic acid, fatty acids, prostaglandins, and orphan receptors (Zhang & Lazar, 2000). The TRs have regions; the DNA binding domain (DBD), ligand binding domain (LBD), hinge region (HR), and amino terminal domain (A-B) (Sap et al., 1986). The THs cross the lipid membrane because of their hydrophobic nature. In the cytoplasm they can bind to newly synthesized TRs, however most THs bind to nuclear receptors. The TRs bound to the THs may regulate the transcription process by modifying the structure of chromatin, allowing other factors to exert their action on elements of the TH responses (figure 4). In addition, the THs interact, directly or indirectly, through bridge or coactivator molecules, with the transcriptional machinery of the process. A critical aspect in regulating the transcription process by the TRs is the conformational change that T₃ exerts on the receiver itself. The T₃ decreases the ability of the hydrophobic TRs and can modify the way in which the TRs, either as dimer or heterodimer, bind to DNA. The TRs bind to regulate transcription as a monomer, homodimer, heterodimer, or heteromultimer. The thyroid hormones binding to the TRs cause changes in the structure of these complexes thus modulating the interaction with other elements of the transcriptional apparatus to determine the type of response, enhancing or inhibiting (Cheng et al., 2010; Yen, 2001).



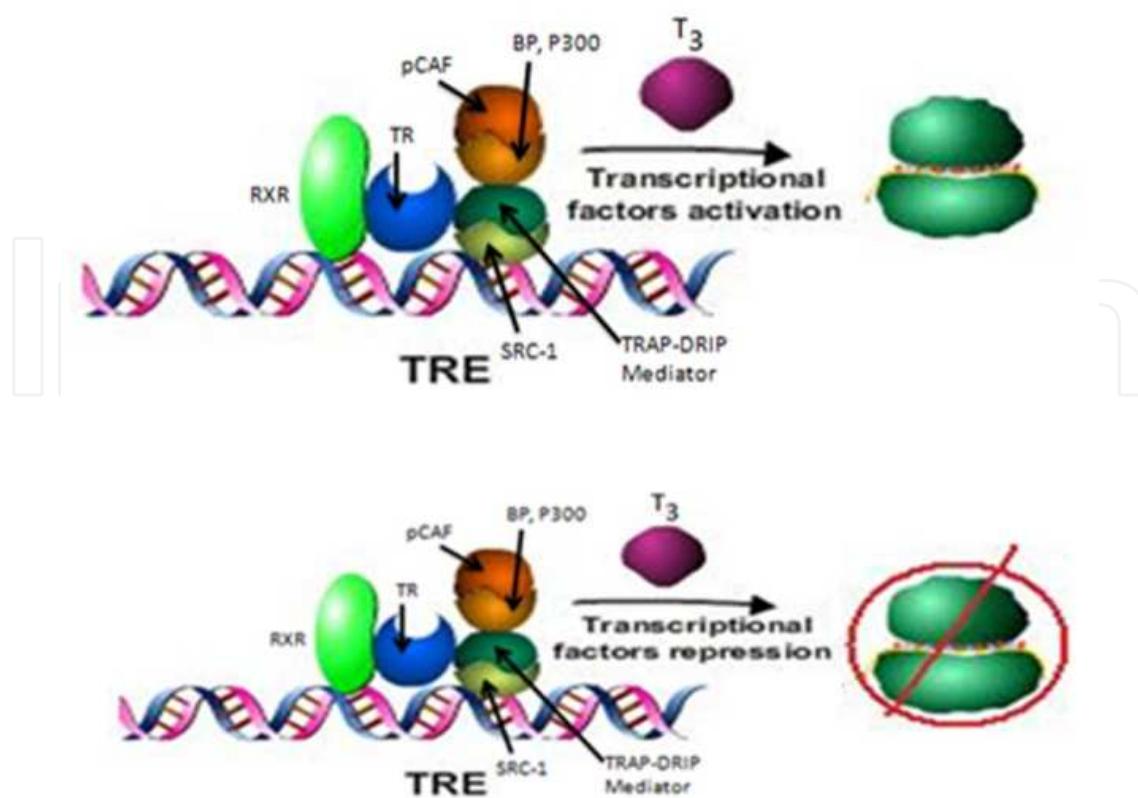


Fig. 4. Nuclear gene expressions by T_3 to the thyroid hormone receptors $TR\alpha$ and $TR\beta$. Heterodimers must bind to specific thyroid response elements (TREs) in the promoters of T_3 -target genes and activate or repress transcription in response to hormone.

The existence of cell-surface receptors for thyroid hormones has been acknowledged. The presence of binding sites for thyroid hormones on the cell surface has been known for many years in the red blood-cell membrane (Davis et al., 1983) and in the synaptosome (Giguere et al., 1996; Giguere et al., 1992). The identity of the proteins involved in membrane binding of hormones was not established in these studies and there has been a reluctance to believe that integrin av β 3, containing a binding site for the thyroid hormones, is an initiation site for complex hormone-directed cellular events, such as cell division and angiogenesis (Davis et al., 2005).

Integrins are ubiquitous heterodimeric structural proteins of the cell membrane that convey signals from the cell interior to the extracellular matrix (ECM) (inside-out) and from the ECM to the cell (outside-in). The integrin purified from the plasma membrane bound radiolabeled thyroid hormones and with high affinity. This integrin contains a binding site for thyroid hormones caused by the functional consequences of the binding activation of MAPK (figure 5). The receptor has been located at the Arg-Gly-Asp (RGD) recognition site on the integrin that is important to the binding of a number of extracellular-matrix proteins and growth factors. From this site, the thyroid hormone signals are transduced by MAPK (ERK1-2) in angiogenesis in endothelial cells and the cell proliferation of tumor cell lines. The T_4 in concentrations that are physiological (10^{-10} M free T_4) and T_3 in supraphysiological concentrations cause ERK-dependent cell proliferation. It is now clear that the hormone receptor domain on the integrin is more complex than initially thought. There is a T_3 -specific

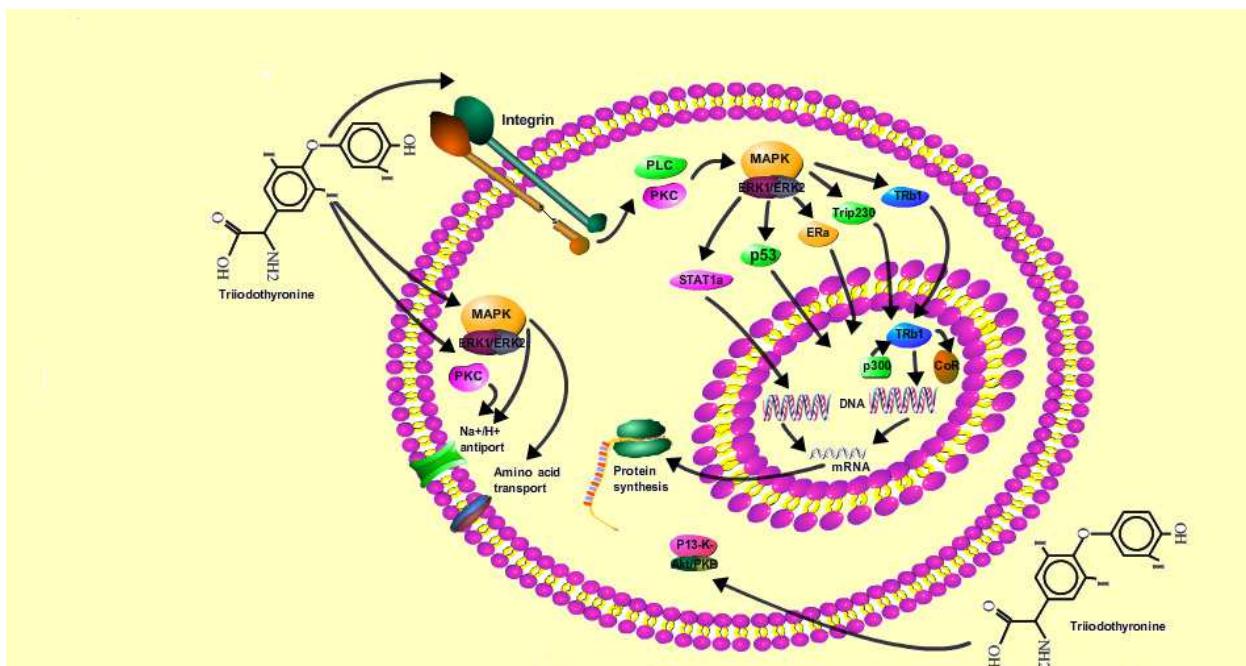


Fig. 5. Nongenomic mechanisms of action of thyroid hormones mediated by integrine-type membranal receptors.

site in the domain and a site at which both T₄ and T₃ may act. The T₃-specific site activates PI3K and is linked not to cell proliferation, but to trafficking of certain intracellular proteins such as shuttling of TRs from the cytoplasm to nucleus and to the transcription of specific genes, such as hypoxia-inducible factor-1 (HIF-1). T₄ is unable to activate PI3K (Cheng et al., 2010).

2.3 Thyroid hormone actions

The T₃ is recognized as a key metabolic hormone of the body. It has many physiological actions and it modulates all metabolic pathways through alterations in oxygen consumption and changes in protein, lipid, carbohydrate, and vitamin metabolism. Through its direct manipulation of protein expression associated with such pathways, T₃ affects the synthesis and degradation of many other hormones and growth factors and indirectly influences additional endocrine signaling. To see more details of the thyroid hormone action, check the review of Hulbert (Hulbert, 2000).

2.4 Abnormalities of the thyroid function

Abnormalities of the thyroid function are among the most common of all endocrine disorders. They fall into two categories, hypothyroidism and hyperthyroidism, reflecting deficient and excess thyroid hormone secretion. There are many causes that generate these conditions. Whatever the cause, the consequences of too little or too much thyroid hormone secretion are largely predictable, given the knowledge of the functions of the thyroid hormones.

3. Relationship between alterations of the thyroid hormones and the ROS-steady state

It has been proposed that the thyroid hormones influence the ROS steady-state and REDOX environment in the cell. The most common idea is that hyperthyroidism enhances the ROS production that perturbs the ROS steady-state and changes the REDOX environment to facilitate cell damage. A hypometabolic state caused by hypothyroidism could be a protective state. In the next part of this chapter we show the evidence for this.

3.1 Hyperthyroidism and the ROS-steady state

Because thyroid hormones modulate many functions, if thyroid hormone levels change, many cellular processes could be altered, including modifications in the REDOX environment. Related to this issue we can ask what happens in a hyperthyroid condition?. Because one of the most studied effects of the thyroid hormone is the control of the basal metabolic rate, a hypermetabolic state produces a modification of the REDOX environment (Venditti & Di Meo, 2006). It is well-known that a higher T₃ level, a hypermetabolic state, causes calorigenesis in two ways. The first is a short-term signaling mechanism with the allosteric activation of cytochrome-C oxidase and the second is a long-term pathway producing nuclear and mitochondrial gene transcription through T₃ signaling, thus stimulating basal thermogenesis (Oppenheimer et al., 1994). This last mechanism causes the synthesis of the enzymes involved in energy metabolism and the components of the respiratory-chain apparatus, leading to a higher capacity of oxidative phosphorylation (Videla, 2000; Soboll, 1993). These short- and long-term pathways are mainly responsible for the increased cellular respiration caused by the hyperthyroid state. Other processes may also play a role, namely 1) energy expenditure caused by a higher active cation transport, 2) loss of energy from futile cycles caused by increases in catabolic and anabolic pathways of intermediary metabolism, 3) higher activity of membrane-bound enzymes associated with electron transfer and metabolite carriers caused by changes in the lipid composition of mitochondrial membranes (Soboll, 1993), and 4) O₂ equivalents related to oxidative stress (Videla, 2000), a REDOX imbalance that leads to various pathological events in several organs as the liver (Jaeschke et al., 2002). In these pathologies, the cellular damage occurs when the balance between oxidant and antioxidants is disturbed and the antioxidant system does not balance the oxidants, thus altering the ROS steady-state level (Lushchak, 2011). An enhanced ROS causes lipid peroxidation, enhancement of reactive oxygen species, nitration, carbonylation, or glutathionylation of proteins, and fragmentation of DNA.

Fernandez et al. found that thyroid calorigenesis is a hormonal stimulus for the REDOX activation of NFκB, a response that is triggered in Kupffer cells having higher respiratory-burst activities (Fernandez et al., 2006). These findings are in agreement with studies showing that the NFκB activation can be achieved by physiological levels of the ROS, which are produced during the respiratory burst after stimulation of isolated or cultured macrophages (Kaul & Forman, 1996) and in carbon-stimulated Kupffer cells in the isolated, perfused rat liver (Romanque et al., 2003). This may be caused by the damage produced by the oxidative stress generated by an excess of thyroid hormones. There are data indicating that excess thyroid hormones act at multiple levels to cause apoptosis, because this higher level enhances the expression of several death receptors and their ligands, such as TNF-α,

FasL, proNGF, and proBDNF, resulting in activation of apical caspase-8, which is further amplified through the activation of the p75NRT-mediated pathways (Kumar et al., 2007). Hyperthyroid animals appear to have a shorter lifespan and, at an advanced age, have a myelin deficit (Carageorgiou et al., 2005). It is known that hyperthyroidism increases hepatic protein oxidation, as evidenced by a significant 88% increase in the content of protein hydrazone derivatives 3 days after a T₃ treatment. This effect may be caused by the increased generation of ROS generated by T₃ (Fernández et al., 1985; Fernandez & Videla, 1993) leading to the formation of carbonyl derivatives mainly occurring at the arginyl, prolyl, lysyl, and histidyl residues in proteins (Stadtman, 1990; Reznick & Packer, 1994). The T₃-caused ROS formation can cause the conversion of cysteinyl residues to protein-protein disulfide conjugates or to mixed-disulfide derivatives (Stadtman, 1990), whereas T₃-caused NO generation (Fernandez et al., 1997) may lead to protein oxidation or nitration through peroxynitrite formation (Alvarez & Radi, 2001). The biological significance of the oxidative modification of proteins in T₃-caused liver oxidative stress can be visualized on two levels; 1) loss of protein function and 2) increased protein degradation. Under high rates of ROS and RNS input, the oxidative modification of enzymes can occur with the consequent reduction in enzyme activity (Stadtman, 1990; Lissi et al., 1991). The inactivation of hepatic antioxidant enzymes has been described in several conditions *in vivo* involving oxidative stress in the tissue, including hyperthyroidism (Lissi et al., 1991), which determines a decrease in the activity of superoxide dismutase and catalase (Fernandez et al., 1988) and in the content of cytochrome P450 (Fernández et al., 1985). In agreement with this contention, inactivation of superoxide dismutase by H₂O₂ (Bray et al., 1974) and of catalase by O₂^{·-} (Kono & Fridovich, 1982) has been reported in conditions *in vitro*. In addition to enzyme inactivation, thyrotoxicosis in mammals results in the stimulation of both synthesis and degradation of protein, with a predominance of degradation, as shown by the increase in protein catabolism, negative nitrogen balance, and the loss of protein from muscle and other body stores (Loeb, 1996). These findings are in accordance with those of Tapia et al. who found a higher oxidation of the liver protein and an increase in lipid peroxidation levels in hyperthyroid rats (Tapia et al., 2010).

Interestingly, the activities of both GPx-1 and GR are decreased in hyperthyroid rats. It is remarkable that both enzymatic activities are strongly GSH-dependent. The GPx-1 catalyzes the reduction of H₂O₂ and lipid hydroperoxides coupled with oxidation of GSH into GSSG whereas the GR replenishes the GSH pool with the help of NADPH principally provided by the pentose-phosphate pathway. The intracellular GSH status appears to be a sensitive indicator of the cellular ability to resist ROS. Furthermore, it has been found that total GSH equivalents and the GSH and GSSG pools were increasingly depleted by T₃ over time (Chattopadhyay et al., 2007). The liver is especially rich in GST that metabolizes xenobiotics by conjugating with GSH. In fact, the GST-catalyzed conjugation of GSH with exogenous compounds and endogenous metabolites such as 4-hydroxynonenal is regarded as a major cellular-defense mechanism against toxicity (Cheng et al., 2001). The activities of GST were considerably impaired with the progression of the T₃ treatment (Chattopadhyay et al., 2007). Because recycling of oxidized glutathione consumes NADPH, the cellular levels of NADPH and its synthesis represent the rate limiting factors of H₂O₂ consumption by catalase-deficient tissues (Ho et al., 2004). Moreover, prolonged hyperthyroidism diminishes GR but

elevated G6PD activity indicates that severe hyperthyroidism may compromise the cellular ability to maintain the redox state. Lombardi et al. have demonstrated that injection of T₃ into hypothyroid rats caused an increase in both enzyme activity and mRNA expression of G6PD in the liver. Nevertheless, the reduced activities of GPx, GR, and GST in the hyperthyroid liver prevent optimum GSH use and recycling. Accumulation of GSSG can lead to protein modifications because of interactions with -SH groups (Reed, 1990). Though the T₃ exerted a positive stimulatory effect on the NADPH supply, it was not sufficient to compensate for the massive GSH depletion and this probably explains the negative regulatory impact of T₃ on activities of GSH-dependent enzymes such as GPx and GR in the rat liver. Under such conditions, the cellular redox-status is disturbed, as reflected in the high oxidative-stress index of hyperthyroid rats.

In brief, thyroid calorigenesis resulting from acceleration of energy metabolism and secondary electron-transfer processes lead to a higher generation of ROS in the target tissue. This prooxidant condition enhances the oxidative-stress status of the organs when the decrease in the antioxidant potential is not adequately compensated for, leading to

a) substantial oxidative deterioration of biomolecules, with loss of their functions that may compromise cell viability, b) activities of GPx, GR, GST, catalase, and superoxide dismutase are considerably impaired, c) total GSH equivalents and GSH and GSSG pools were increasingly depleted, d) a higher susceptibility of the liver to toxic stimuli that exacerbate liver injury, e) upregulation of gene expression, f) apoptosis, g) shorter lifespan, and h) myelin deficit.

3.2 Hypothyroidism and the ROS-steady state

Hypothyroidism has been related to some diseases because it causes a hypometabolic state. This condition can be beneficial. Why can we make this assertion? There are many findings to support this suggestion. It is well-known that a deficiency of the thyroid hormones results in decreased metabolism and lowering of the basal metabolic rate (BMR). There is evidence that supports the lower cell stress in the hypothyroidism condition. Tenorio-Velázquez et al. have demonstrated that hypothyroidism attenuates oxidative stress and renal injury caused by ischemia-reperfusion, produced by an increase in the ROS and reactive nitrogen species (Tenorio-Velásquez et al., 2005). Most research has been done in the kidney and liver models of ischemia (Swaroop & Ramasarma, 1985; Paller, 1986). The postulated mechanism in such organs has been either a decrease in the general metabolic rate or a reduced free radical scavenging response after ischemia. The lipid peroxidation in hypothyroid animals with renal ischemia was decreased (Paller, 1986). The content of malondialdehyde, which is an indirect measure of the generation of oxygen free radicals, was decreased and the cortical content of glutathione, a free radical scavenger, was increased in the hypothyroid, ischemic animals. Similarly, in the liver model of hypothyroid-ischemic injury, lipid peroxidation and free-radical generation were decreased in the hypothyroid animals (Swaroop & Ramasarma, 1985). These investigators have shown a significant decrease in hydrogen peroxide, a measure of the oxygen free-radical status, in the liver mitochondrion in the hypothyroid animals. Hypothyroidism attenuates not only renal but also cardiac damage caused by ischemia and reperfusion. Bobadilla et al. have shown that hypothyroidism conferred protection against reperfusion arrhythmias and the cardiac release of creatine kinase and

aspartate amino transferase and preserved the normal structure of the myocardial tissue (Bobadilla et al., 2002). It has been proposed that hypothyroidism protects against pore opening and heart reperfusion (Chávez et al., 1998). This may be relevant to the protective effect of hypothyroidism in ischemia and reperfusion because it has been recognized that the mitochondria play a key role in cell-death pathways by activating the mitochondrial-permeability transition pore and causing the release of cytochrome C, proapoptotic factors, and the Ca^{2+} overload that causes a nonselective permeability of the inner membrane. The prolonged opening of the membrane-permeability transition pore during the first few minutes of reperfusion is a critical determinant of cell death, and pharmacological inhibition of the pore at the time of reperfusion protects the cell (Halestrap et al., 2004). It has been found that there is a decreased glutamate release during hypothyroidism and this is correlated to a protection in cerebral ischemia (Shuaib et al., 1994). The reason why hypothyroidism results in a decreased release of glutamate is as yet unknown. It is possible that the hypothyroidism affects the release mechanisms in the presynaptic receptors. It is also possible that the hypothyroid state results in an increase in the reuptake mechanism for glutamate.

We have noted the protector effect of hypothyroidism, but many investigators use methimazole to cause it. There are some indications that antithyroid-caused hypothyroidism can produce cellular damage. Although, some results indicate that this drug causes cellular protection because of its chemical structure (Bruck et al., 2007; Tutuncu et al., 2007). In addition, there is evidence of extrathyroidal effects of antithyroid drugs, such as thionamides, in humans and animals (Bandyopadhyay et al., 2002). One of the effects of thionamides is the contribution to oxidative stress and cellular damage. These effects can produce an increase of oxidant species that causes lipid peroxidation, nitration, carbonylation, or glutathionylation of proteins, and fragmentation of DNA (Halliwell & Gutteridge, 2007; Valko et al., 2007). Because of this, we determined if methimazole or hypothyroidism causes cellular damage in several organs. After producing a hypothyroid animal caused by thyroidectomy or methimazole administration, the spleen, heart, liver, lung, and kidney were obtained. A portion of these tissues was processed for histological study and another portion was used for the biochemical assay for determining oxidative stress. Histologically, we demonstrated that only methimazole-caused hypothyroidism causes cellular damage in the kidney, lung, liver, heart, and spleen. Animals with methimazole and with T_4 supplementation showed cellular damage in the lung, spleen, and renal medulla with lesser damage in the liver, renal cortex, and heart. Hypothyroidism did not produce cellular damage in any organs except the lung. The thyroidectomy group showed no other tissue alterations (Cano-Europa et al., 2011). These results are in accordance with what others have observed in animals and humans. Five percent of patients with hyperthyroidism treated with antithyroid drugs, including methimazole, are reported to have liver (Casallo Blanco et al., 2007; Woeber, 2002), lung (Tsai et al., 2001) and kidney damage (Calañas-Continente et al., 2005). The methimazole-caused hypothyroidism in animals has tumorigenic effects (Jemec, 1977) and modifies the pulmonary function (Liu & Ng, 1991). No tissue damage was seen in a model of hypothyroidism caused by a thyroidectomy (Tenorio-Velásquez et al., 2005). We also compared, over a time-course, markers of oxidative stress, the REDOX environment, and the antioxidant enzymatic system in the liver and the spleen of rats with methimazole- or thyroidectomy-caused hypothyroidism. We found that the cell damage was related with an increase of oxidative

stress markers (ROS and lipid peroxidation) that were not compensated for by the antioxidant system. The catalase activity is reduced in hepatic tissue and this allows H₂O₂-caused hepatic damage (Cano-Europa et al., 2010). The increase of the glutathione-cycle enzymes was insufficient to prevent oxidative-stress markers (Ortiz-Butron et al., 2011). All these findings together pointed out that methimazole and not the hypothyroidism is responsible for the cell damage. The tissues evaluated, especially the kidney and liver, have a high metabolic activity that generates ROS. Under physiological conditions the presence of antioxidant enzymes, in particular peroxidases and dismutases, prevent oxidative stress and tissue damage (Halliwell & Gutteridge, 2007; Angermuller et al., 2009). Some drugs, such as methimazole, disturb the physiological steady state. Methimazole alters the intracellular REDOX environment and causes cellular damage because of oxidant generation and ROS, and consequently the lipid peroxidation is not completely neutralized by the antioxidant system. We suggest that the central mechanism of the methimazole-caused cell damage is based on the reduction of catalase activity caused by a methimazole-inactivated catalytic center (Bandyopadhyay et al., 1995; Bandyopadhyay et al., 2002).

Other investigators, like Bergman and Brittebo, have demonstrated this anthytiroid-caused damage in other models, i.e. an olfactory mucosa model. They found that this drug covalently binds to the tissue, and pretreatment with the cytochrome-P450 inhibitor metyrapone prevented both the covalent binding and the toxicity of methimazole in this tissue. They suggest a cytochrome P450-dependent metabolic activation of methimazole to a reactive and toxic intermediate at this site (Bergman & Brittebo, 1999). The pretreatment with thyroxin did not protect against the methimazole-caused necrosis, suggesting that this lesion is not related to a transient decrease in thyroid hormone levels. The covalent binding shown by methimazole in this tissue has been found in other tissues, such as the bronchial epithelium and the centrilobular parts of the liver. It is possible that methimazole suffers activation at these sites. Further, this drug is metabolized stepwise to the corresponding sulfenic and sulfinic acids with a concurrent formation of reactive intermediates (Poulsen et al., 1974). It is known that methimazole produces a decrease of P450 at the hepatic level (Decker & Doerge, 1992). In rodents given the methimazole analogs 1-methy-imidazole, 4-methylimidazol, or methyl pyrrole, which are devoid of a thiol group, no morphological changes were observed in the olfactory mucosa (Brittebo, 1995). The thiol group in methimazole seems to be important for the methimazole-caused toxicity, suggesting that enzyme-catalyzed changes of the thiol group will give rise to an intermediate toxin in the tissue.

Other methimazole-caused damage mechanisms are associated with its chemical structure and its biotransformation. Some investigators suggest that this drug binds covalently to the hepatocytes, mainly those next to the hepatic triad (Decker & Doerge, 1992; Lee & Neal, 1978). For biotransformation, methimazole may be oxidized by the P450 enzymes to form the 4,5-epoxide. The enzymatic or nonenzymatic hydrolysis of the epoxide formed would produce an unstable hemiketal-like intermediate, which it is expected to undergo spontaneous ring cleavage to form glyoxal and N-methylthiourea. The metabolism of N-methylthiourea is complex, but it is believed that sulfur oxidation, mediated mainly by flavin-monooxygenase (FMO, EC.1.14.13.8), proceeds primarily to the sulfenic acids and then possibly to the sulfinic acids. It is known that this step is necessary in the bioactivation of thioureas resulting in protein binding, enzyme inactivation, and organ toxicity (Mizutani et al., 1994; Neal & Halpert, 1982).

The thyroidectomy group examinee showed no other tissue alterations, except for the lung. There is some evidence that demonstrates molecular mechanisms by which hypothyroidism itself may produce a protected state of the tissues, such as reducing the enzyme activity associated with the mitochondrial-respiratory chain (Paradies et al., 1994), the decrease in adenine nucleotide translocase (Schonfeld et al., 1997), reduced activity of cytochrome-C oxidase (Paradies et al., 1997), and the resistance to forming the permeability transition-pore formation of the inner mitochondrial membrane (Chávez et al., 1998).

With all this evidence it is important to develop other therapies or antithyroid drugs with fewer side effects. We suggest that hypothyroidism is a protective state against toxic agents and it is related to an increase of reduced glutathione or γ -L-glutamyl- cysteinyl-glycine (GSH) synthesis and a mild immunosuppression.

3.3 Enhanced GSH synthesis in the hypothyroid state, a mechanism of cell protection

Before we show evidence of the relationship between hypothyroidism and high γ -L-glutamyl- cysteinyl-glycine (GSH) concentration, we need to know more about GSH. The synthesis of reduced glutathione or GSH involves two ATP-dependent enzymatic steps made in the cell cytoplasm. Figure 6 shows the cycle of GSH.

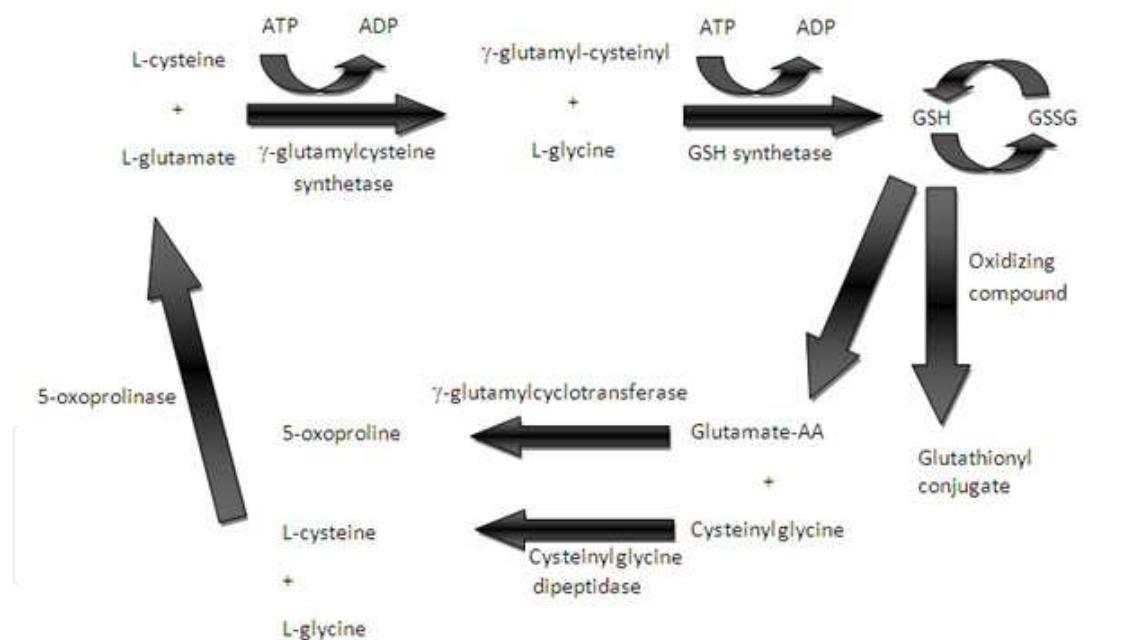


Fig. 6. GSH cycle. GR is glutathione reductase; GST glutathione S-transferase, and GSSG oxidized glutathione.

The synthesis of GSH starts with the entry into the cells of its amino acid precursors: glutamate, cysteine, and glycine. Glutamate and glycine can enter the cell by secondary active transport. Some of the glutamate cotransport carriers transfer cysteine. For the cysteine, entry into the cell may also be caused by the transporters of the neutral amino acid system. It is believed that cysteine is the limiting amino acid for the synthesis of GSH

because it occurs in lower concentrations in plasma and has a lower Km (Aoyama et al., 2008). Once the amino acids have entered the cell, the g-glutamylcysteine synthetase (γ -GCS, EC 6.3.2.2) forms the g-glutamylcysteine. The formation of the product involves two steps. The first is the interaction between glutamate and ATP in the presence of Mg^{+2} to form g-glutamylphosphate and the second involves the interaction of this intermediate with the cysteine and with ADP release (Griffith & Mulcahy, 1999; Griffith, 1999). This first step is the most important in the formation of GSH because γ -GCS is the limiting enzyme in the synthesis of GSH. The γ -GCS is an heterodimeric enzyme composed of a catalytic subunit known as the heavy subunit (γ -GCS_H Mr, \approx 73 kDa) and a regulatory or light subunit (γ -GCS_L Mr, \approx 31 kDa). The γ -GCS activity depends primarily on the substrates and is inhibited by GSH. The γ -GCS_L activity is under the control of kinases such as protein kinase A (PKA) and PKC (Griffith, 1999).

Two processes can occur thermodynamically once γ -glutamyl-cysteinyl is formed. The compound may be used by the GSH synthetase (GS, EC 6.3.2.3) to form GSH when conjugated with glycine or it may interact with g-glutamyl cyclotransferase to form 5-oxo-L-proline and L-cysteine. The pathway that prevails depends of the Km of each enzyme. Under physiological conditions the Km of GS is 12 times greater than the γ -glutamyl cyclotransferase so it favors the formation of GSH in more than 95% (Weber, 1999). Once GSH has been synthesized there are different processes in which it participates;

1. In the hydrolysis of plasma GSH to synthesize GSH de novo for another cell. For example, if a hepatocyte secretes GSH, another cell can hydrolyze such a compound into its precursors (cysteinylglycine and glutamate) by the g-glutamyl transpeptidase (γ -GT, EC 2.3.2.2) expressed on the outside of the plasmatic membrane. The cysteinylglycine compounds or their S-conjugates can be hydrolyzed by dipeptidases to yield free amino acids that can be introduced into the cell and start the formation of GSH (Weber, 1999).
2. In the detoxification of electrophiles by conjugating these with α -carbonyls and by β -unsaturation by glutathion-S transferase (GST, EC. 2.5.1.18). This reaction results in the elimination of the electrophile by the consequent metabolism of the glutathione S-conjugate by the γ -GT enzymes and the cysteinylglycine dypeptidase. This process is not always in the favor for the cell, because it can sometimes create more toxic species (Weber, 1999).
3. In the detoxification of hydrogen peroxide by the action of the glutathione peroxidase enzymes (GPX, EC 1.11.1.19) (Beckett & Arthur, 2005).
4. In maintaining ascorbic acid and vitamin E (Van Acker et al., 1993).
5. In intracellular communication processes as a modulator of diverse signaling pathways (Cruz et al., 2003).
6. In the modulation of membrane receptors as for NMDA receptors in the central nervous system (Oja et al., 2000).
7. In the transport of metals such as Cu^{+2} , Hg^{+2} , Pb^{+2} , and Zn^{+2} (Filomeni et al., 2002).

The mitochondrial concentration of GSH is approximately 11-15 mM. The entry of GSH into the mitochondria depends on the electroneutral transporters, such as the tricarboxylic or dicarboxylic acids (Lash, 2006). In general, the ratio GSH/GSSG is greater than 10 for the cells and organelles, such as mitochondria and nucleus, whereas the endoplasmic reticulum

has the lowest GSH/GSSG ratio of 1 to 3. The best indicator of the REDOX environment is the GSH²/GSSG ratio because the REDOX environment involves the transfer of electrons, for which the theoretical model of Schafer and Buettner uses the Nernst equation (Schafer & Buettner, 2001). These authors proposed that other REDOX couples can participate in the REDOX environment maintaining the ratios of NADPH/NADP⁺, reduced thioredoxin/oxidized thioredoxin (TrxSH₂/TrxSS), and GSH²/GSSG. These REDOX couples could participate in the maintaining of the REDOX environment because their pKas are above the physiological pH and the ratio of the reduced pair to its oxidized counterpart is 1:100, 1:1000, or greater. The GSH²/GSSG ratio is the most important couple in the REDOX environment because their chemical structures are not susceptible to any peptidase and their use is in the cell, particularly for cell antioxidant protection, and not in essential biosynthetic pathways. Also, the GSH²/GSSG ratio has the highest concentration of the three REDOX ratios mentioned, and this one best buffers the REDOX potential changes between -300 and -100 mV, despite varying the concentration of the GSH. The change in the half-cell reduction potential of this REDOX couple is related to the processes such as cell proliferation, differentiation, apoptosis, and necrosis in biological experiments (Cai & Jones, 1998; Cai et al., 2000; Hwang et al., 1992; Jones et al., 1995; Kirlin et al., 1999).

In our group we are studying the effect of the hypothyroid state and the GSH synthesis in various organs, with special interest in the liver and kidney. For that we used thyroidectomized rats with a parathyroid gland reimplant (only to affect thyroid hormone system). Two weeks postsurgery we determined the GSH content by a fluorometric method and the γ -GCS by a spectrophotometric method as described (Cano-Europa et al., 2010; Ortiz-Butron et al., 2011). Figure 7 shows that hypothyroid animals have a higher GSH content than euthyroid animals because they have an enhanced γ -GCS activity.

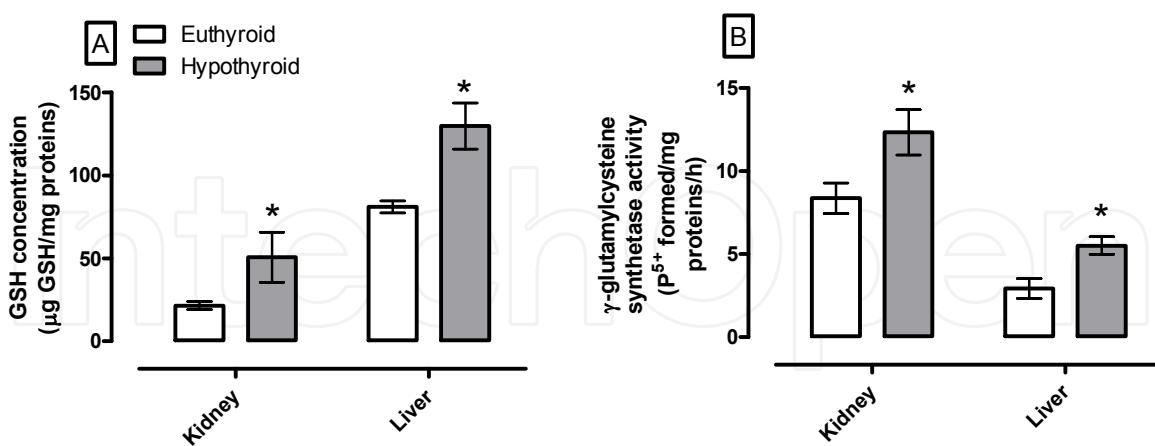


Fig. 7. Effect of hypothyroidism on GSH content (A) and γ -GCS activity in liver and kidney. Values are the mean \pm SE. (*) $P < 0.05$ vs. euthyroid ($n = 5$ for each group).

It is possible that some intracellular signals modify the γ -GCS activity. It is also probable that the thyroid hormone-receptor complex acts as a negative regulator for γ -GCS because the putative thyroid-hormone response-element sequences in the promoter regions of both the

catalytic and modulator subunit of γ -GCS genes have been seen. However, we need to do further experiments to demonstrate this. If this does occur then hypothyroidism could be a protective state against chemical- or physical-caused oxidative stress and cell damage. At present, we are evaluated if the hypothyroid state protects against ethylene glycol-caused oxidative stress and renal damage. At this respect, the results are in accordance with the idea that the hypothyroidism-enhanced REDOX environment (unpublished data).

3.4 Thyroid hormone alteration levels and the immune response

There is evidence of the thyroid hormones and immune systems and their development and function from amphibious animals to mammals (Rollins-Smith & Blair, 1990; Lam et al., 2005; Watanabe et al., 1995; Nakamura et al., 2007).

In zebra fish the thyroid state participates in thymus development and lymphopoiesis (Lam et al., 2005). In humans and other mammals, clinical hyperthyroidism increased the size and cellularity of the thymus, particularly a larger number of thymus nurse cells, Thy1⁺ thymocytes, and the CD4-CD8- and CD44-positive cells (Villa-Verde et al., 1993; Scheiff et al., 1977). Hyperthyroidism increases T cells in the spleen and thymus with high levels of NK cells only in the spleen (Watanabe et al., 1995). Hypothyroidism reduces the cellularity in the spleen and thymus (Bendyug et al., 2003). In neonatal hypothyroidism, it has been observed that the NK cells and regulatory T cells (CD4⁺CD25⁺) are enhanced in thymus, spleen, and peripheral blood. The dendritic cells integrate signals from several pathways and receptors, including those arising from engagement of uptake and pattern recognition receptors, proinflammatory and antiinflammatory cytokines, chemokines, and hormones like THs. The T₃ promotes the dendritic-cell maturation and Th1-type cytokine secretion (Mascanfroni et al., 2008). The dendritic cells are modulated by the THs because the T₃-TR β 1 causes Akt signaling-pathway activation and NF κ B-dependence, but a PI3K-independent pathway (Mascanfroni et al., 2010).

There are reports that hypothyroidism decreases immune system activity and increases infection in humans (Schoenfeld et al., 1995; Amadi et al., 2008).

All this evidence suggests the proposal that the hypothyroid condition decreases the immune response. This could be protective in the case of toxicant-caused oxidative stress and cell damage caused by the immune system activation by a substance like aniline. Aniline is a toxic, aromatic amine and it is an extensively used industrial chemical. Exposure to aniline is known to cause toxicity to the hematopoietic system. Aniline toxicity is generally characterized by methemoglobinemia, hemolysis, and hemolytic anemia and by the development of splenic hyperplasia, fibrosis, and a variety of primary sarcomas after chronic exposure in rats. The immunological system participates actively in aniline-caused oxidative stress and spleen damage (Wang et al., 2011; Wang et al., 2010; Wang et al., 2008).

In our laboratory, we evaluated the participation of hypothyroidism and aniline-caused oxidative stress and spleen damage. We used male Wistar rats weighing 240 to 260 g divided into four groups; 1) euthyroid, 2) euthyroid + aniline, 3) hypothyroid, and 4) hypothyroid + aniline. The hypothyroidism was produced by thyroidectomy with implantation of the parathyroid gland. Two weeks after surgery, the animals were treated with 1 mmol/kg/d ig aniline for five days. On the fifth day, the animals were killed, the

blood obtained to determine the lymphocyte count and the spleen was dissected to assess lipid peroxidation and the quantification of reactive oxygen species as preliminary results. In figure 8 are the results. It was shown that hypothyroid rats had decreased ROS concentration, lipid peroxidation, and the lymphocyte counts in aniline-treated rats compared with euthyroid rats.

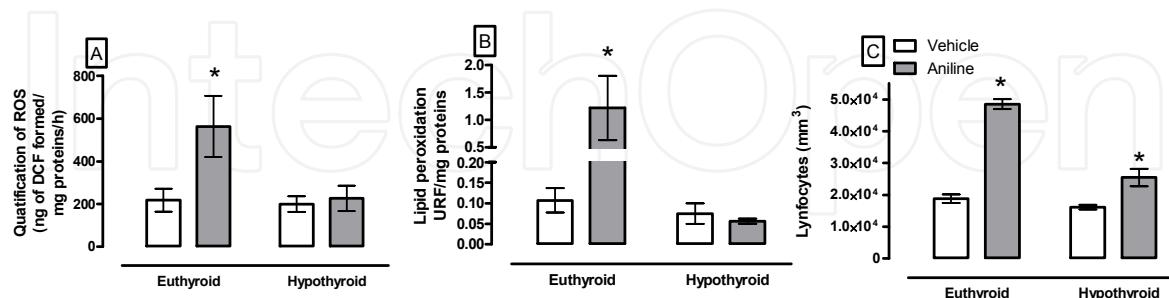


Fig. 8. Effect of hypothyroidism on ROS concentration (A), lipid peroxidation (B), and lymphocyte count (C) in the spleen of rats treated with aniline. Values are the mean \pm SE. (*) $P < 0.05$ vs. euthyroid ($n = 5$ for each group).

The hypothyroid state can be protective in this situation because it decreased the ROS production, increased the GSH, and decreased the lymphocyte count. Although we need to do more experiments to demonstrate the idea of a mild immunosuppression participating in cell protection, these preliminary results suggest it.

4. Final remarks

In earlier years it was believed that the hypo- and hyperthyroid conditions modifying the ROS steady state caused cell damage. Presently, there is much evidence that only hyperthyroidism does this. Hypothyroidism is believed to be a protective state because scientists did not believe the drug-caused hypothyroidism modified the ROS steady state. On this point, by studying hypothyroidism in animal models that modify only TH concentrations, such as thyroidectomy, we can observe cell protection against chemical- and physical-caused oxidative stress. Right now, we can describe two different pathways by which the hypothyroid state can protect: GSH synthesis and mild immunosuppression. This is now an open field in which to study these possibilities.

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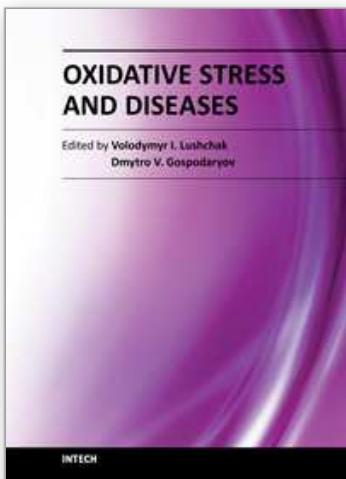
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The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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