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Review article

Energy metabolism, thyroid calorigenesis, and oxidative stress: functional and cytotoxic consequences

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INTRODUCTION

The energy demands of animal cells and tissues are met primarily by the combustion of glucose and fatty acids. This is accomplished in the catabolic phase of the intermediary metabolism by the transfer of hydrogen atoms from the dietary fuels to O_2 in a stepwise fashion through a number of enzyme-catalyzed oxidation-reduction reactions. The process involves the initial transfer of electrons from the fuels to primary acceptors, namely, nicotinamide adenine and flavin adenine dinucleotides, and then to O_2 through a series of respiratory complexes located in the inner mitochondrial membrane.[1] The energy released in the latter process is used in part to pump H^+ across the inner membrane, thus establishing an electrochemical proton gradient ($\Delta\mu_{H+}$) that allows ATP production by the adenosine 5`-triphosphate synthase complex.[2]

Since most of the energy required to perform cellular functions in animal tissues is generated by mitochondrial respiration,[3] the control of oxidative phosphorylation is a central issue for the maintenance of an energy balance, a phenomenon initially considered to be exerted by the extramitochondrial ADP concentration.[4,5] This concept was later expanded to include not only ADP concentration but also that of ATP and P_i, and respiration was suggested to be a function of the extramitochondrial phosphate potential ([ATP]/[ADP] [P_i]).[6,7] These conclusions were supported by studies carried out in isolated mitochondria; however, control of respiration in the intact cell may be distributed between several steps such as the adenine nucleotide translocator, the dicarboxylate carrier, and/or cytochrome c oxidase.[8] This latter enzyme complex represents the irreversible step of the respiratory chain, having a quaternary structure consisting of three mitochondrial-encoded subunits (I–III) surrounded by ten nuclear-encoded subunits.[9] Under physiological conditions, the activity of cytochrome c oxidase is controlled by several factors including substrate availability, O_2 concentration, the $\Delta\mu_{H+}$, and the [ATP]/[ADP] ratio prevailing in the mitochondrial matrix through allosteric feedback inhibition.[10] Binding of ATP either to subunit IV or to subunit VIaH leads to a 50% reduction in the activity or in the efficiency of H^+ pumping of the isolated cytochrome c oxidase, respectively.[11,12] Furthermore, the hyperbolic kinetics of cytochrome c oxidase in the presence of ADP changes into sigmoidal kinetics in the presence of both ADP and ATP,[10] due to the exchange of bound ADP by ATP at the matrix domain of subunit IV.[11] These data, obtained in isolated or reconstituted cytochrome c oxidase, support the mechanism of respiratory control by the intramitochondrial [ATP]/[ADP] ratio through allosteric regulation of the enzyme activity.[13] In line with this proposal, Jeneson *et al.*[14] observed a sigmoidal relation between the specific rate of mitochondrial oxidative phosphorylation and the concentration of cytosolic ADP in human skeletal muscle *in vivo*, a kinetic response that agrees with data found in canine heart muscle *in vivo*[15] and in the *ex situ* perfused mouse liver.[16] It is important to point out that the regulation of cytochrome c oxidase by the [ATP]/[ADP] ratio is, in turn, under the influence of thyroid hormones, since 3,5-diiodothyronine (3,5-T_2) completely eliminates the allosteric inhibition of the oxidase by ATP, an effect mimicked by 3,5,3`-triiodothyronine (T_3) to a small extent, but not by thyroxine (T_4).[17] This is exerted through binding of 3,5-T_2 to subunit Va of cytochrome c oxidase,[17] which is located on the matrix side adjacent to the ADP–ATP binding matrix domain of subunit IV.[9] In agreement with these data, obtained with reconstituted cytochrome c oxidase, diiodothyronines were shown to stimulate both cytochrome c oxidase

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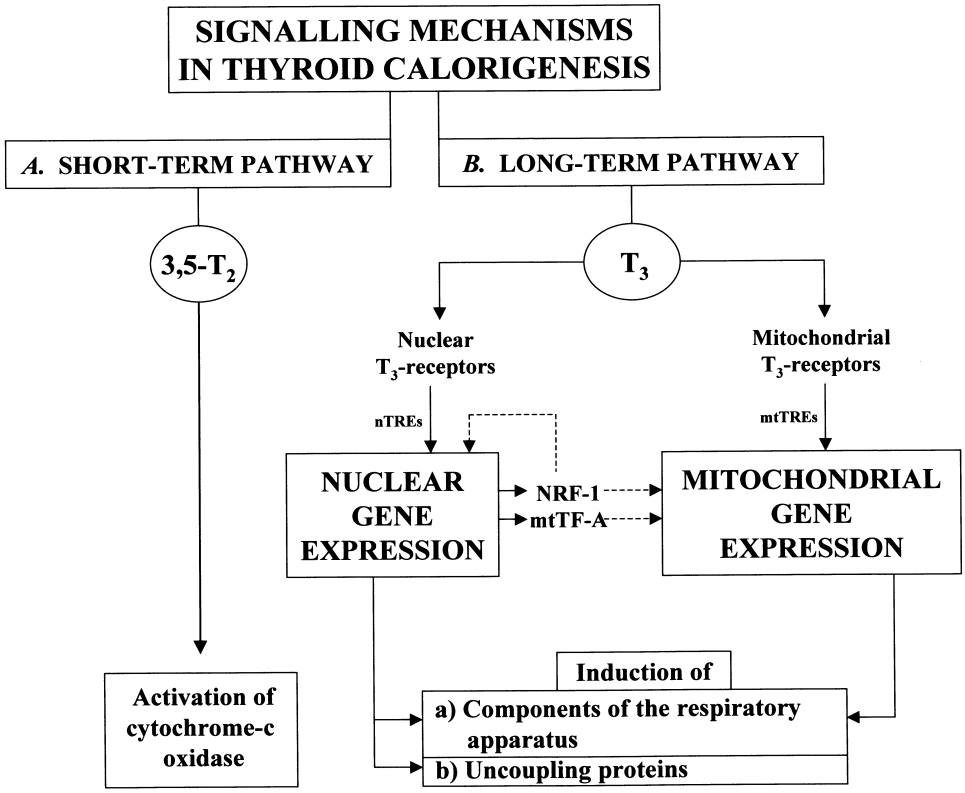

Fig. 1. A general scheme of the proposed molecular mechanisms involved in thyroid calorigenesis. Abbreviations: 3,5-T_2, 3,5-diiodothyronine; T_3, 3,5,3′-triiodothyronine; nTREs, nuclear thyroid hormone response elements; mtTREs, mitochondrial thyroid hormone response elements; NRF-1, nuclear respiratory factor-1; mtTF-A, mitochondrial transcription factor-A.

activity in rat liver homogenate[18] and energy metabolism *in vivo*.[19]

THYROID CALORIGENESIS

Normal thyroid gland activity is concerned primarily with energy metabolism in most tissues of the body. The development of a hyperthyroid state in vertebrates involves an enhancement in their basal metabolic rate (BMR) due to increments in the rate of O_2 consumption in nearly all tissues with the exception of spleen, testis, and adult brain.[20] Although the molecular circuitry underlying thyroid calorigenesis is not completely understood,[21] there is consensus that regulation of energy metabolism by thyroid hormones is accomplished by both short-term and long-term signalling pathways (Fig. 1).[22,23] Physiological variations in energy requirements are dealt with by a short-term mechanism activating cytochrome c oxidase through 3,5-T_2 signalling,[17,22,23] whereas long-term effects of thyroid hormones or states modulating thyroid gland activity (cold exposure, aging, dietary changes)[23] are transduced through T_3-induced changes in both nuclear and mitochondrial gene expression (Fig. 1). Biogenesis of the mitochondrial respiratory apparatus requires about 100 gene products, with 13 components being encoded in the mitochondrial DNA, while the rest are encoded in the nuclear genome.

Activation of nuclear gene transcription by T_3 may involve a direct interaction of T_3 with nuclear T_3 receptors (TR), which behave as transcription factors, followed by binding of T_3-TR complexes to specific sites in DNA, the nuclear thyroid hormone response elements (nTREs; Fig. 1).[21–23] In addition, T_3 may lead to the stimulation of trans-acting factors such as nuclear respiratory factor-1 (NRF-1; Fig. 1), able to bind to consensus sequences of various nuclear-encoded and mitochondrial-encoded respiratory genes.[23,24] Stimulation of these nuclear pathways by T_3 leads to the induction of electron transport chain components, the ADP/ATP carrier, the βF_1-ATPase subunit, and mitochondrial enzymes (*i.e.* α-glycerophosphate dehydrogenase, succinate dehydrogenase),[22] thus stimulating mitochondrial respiration by enhancement in mitochondrial ATP synthesis and transport for the cellular biosynthetic output and other ATP-dependent processes. The interaction of T_3 with the nuclear genome also stimulates the expression of uncoupling proteins (UCP; Fig. 1), which are present in the inner mitochondrial membrane, allowing H^+ re-entry into the mitochondrial matrix, thus dissipating the $\Delta\mu_{H+}$ as heat.[22,23] In rodents and humans,

UCP-2 mRNA levels are increased by T_3 in brown and white adipose tissue,[25] skeletal muscle,[25–27] and heart,[26] with moderate[27] or no effect[26] in liver. Furthermore, T_3 strongly increases the expression of UCP-3 (5–6-fold) in skeletal muscle,[27–29] an effect that partially explains the T_3-induced enhancement in resting metabolic rate.[27] Interestingly, UCP-3 expression also is stimulated by β_3-adrenergic agonists in white adipose tissue and by leptin in muscle and brown adipose tissue, suggesting that UCP-3 is an important factor in thermogenesis.[28]

T_3-induced protein synthesis in mitochondria seems to be regulated at the transcriptional level and may involve the interaction of T_3 with a mitochondrial T_3 receptor, acting as a T_3-dependent transcription factor,[30] and activation of the expression of mitochondrial transcription factor-A (mtTF-A; Fig. 1).[31] This action of T_3 leads to the induction of subunits I, II, and III of cytochrome c oxidase,[31–33] subunits 1, 4, and 5 of NADH dehydrogenase, and of cytochrome b.[33]

In summary, thyroid calorigenesis involves: (i) a short-term mechanism mediated by diiodothyronines such as 3,5-T_2 leading to the allosteric activation of cytochrome c oxidase; and (ii) a long–term pathway responding to prolonged thermogenic stimuli. This latter mechanism is mediated by T_3 through stimulation of both nuclear and mitochondrial gene expression, exerted at the transcriptional level (Fig. 1). Induction of the components of the respiratory apparatus will result in a higher capacity of oxidative phosphorylation in the hyperthyroid state, with the consequent enhancement in ATP supply being partially compensated by a parallel decrease in the efficiency of ATP synthesis due to intrinsic uncoupling.[22] These adaptive changes make a significant contribution to the increased BMR induced by the hyperthyroid state; however, other factors also are involved. These include: (i) the enhancement in extramitochondrial energy expenditure due to acceleration of active cation transport and of both catabolic and anabolic pathways of intermediary metabolism, resulting in a loss of energy from futile cycles; and (ii) alteration of the lipid composition of mitochondrial membranes, thus increasing the activity of membrane-bound proteins associated with the electron transport chain and metabolite carrier.[22]

THYROID HORMONE-INDUCED OXIDATIVE STRESS

Normal aerobic life is characterized by a steady-state generation of both reactive oxygen (ROS) and nitrogen (RNS) species, known as pro-oxidants, balanced by a similar rate of their consumption by antioxidants.[34] To maintain homeostasis, there is a requirement for the continuous regeneration of antioxidant capacity. If this is not met, oxidative stress occurs, a redox phenomenon involving an imbalance in the pro-oxidant/antioxidant equilibrium in favor of the pro-oxidants that may lead to pathophysiological events, either directly[34] or by alteration of the redox-sensitive expression of genes involved in the genesis of some diseases.[35] Cellular protection against oxidative stress is organized at multiple levels including prevention and/or interception of reactive species, and replacement and/or repair of essential biomolecules altered by reactive species.[34,36] These mechanisms are coupled to the intermediary metabolism for a continuous supply of energy, reducing equivalents, and precursors, and depend on the dietary supply of metabolic fuels and essential molecules to allow optimal cellular functioning.[36]

Thyroid hormone-induced liver oxidative stress

The relationship between hyperthyroidism and oxidative stress has been studied extensively in line with the significant direct correlation between the BMR and the lipid peroxidative potential of tissues established for different mammalian species.[37] Experimental animals made hyperthyroid by T_3 administration exhibit a thermogenic response, evidenced by an increase in body temperature, that coincides with an enhancement in the rate of O_2 consumption by the liver (Fig. 2).[38,39] Acceleration of hepatic respiration by hyperthyroidism is primarily determined through increased mitochondrial respiratory chain activity (see above) involving a greater mitochondrial size and content of the components of the respiratory apparatus (Fig. 1),[40] which is known to generate $O_2^{\bullet-}$.[41] In fact, liver submitochondrial particles from hyperthyroid rats exhibit a marked elevation in the rate of $O_2^{\bullet-}$ production, both in the presence of NADH or succinate, and in that of H_2O_2, both under basal conditions and in the succinate-supported process, in the absence and presence of antimycin-A.[42] The antimycin-A-insensitive respiration is presumed to represent O_2 equivalents used in microsomal electron transfer involved in xenobiotic biotransformation.[43] Development of a hyperthyroid state involving higher rates of hepatic O_2 uptake results in the proliferation of the smooth endoplasmic reticulum, with higher activities of glucose-6-phosphatase,[40] NADPH–cytochrome P-450 reductase,[40,44–46] and NADPH oxidase,[38] the latter enzymatic activity representing the oxidase activity of cytochrome P-450 responsible for microsomal $O_2^{\bullet-}$ and H_2O_2 production.[47] In agreement with this view, T_3 treatment increases the rate of microsomal NADPH-dependent $O_2^{\bullet-}$ production (Fig. 2)[38] and the NADPH-dependent O_2 uptake, the latter effect being completely abolished by the antioxidant (+)-cyanidanol-3.[48] In addition, thyroid hormones enhance the number of liver peroxisomes[49] and their oxidative capacity,[49,50] with a 5-fold increase in the rate of urate-supported antimycin-A-insensitive H_2O_2 generation by liver submitochondrial

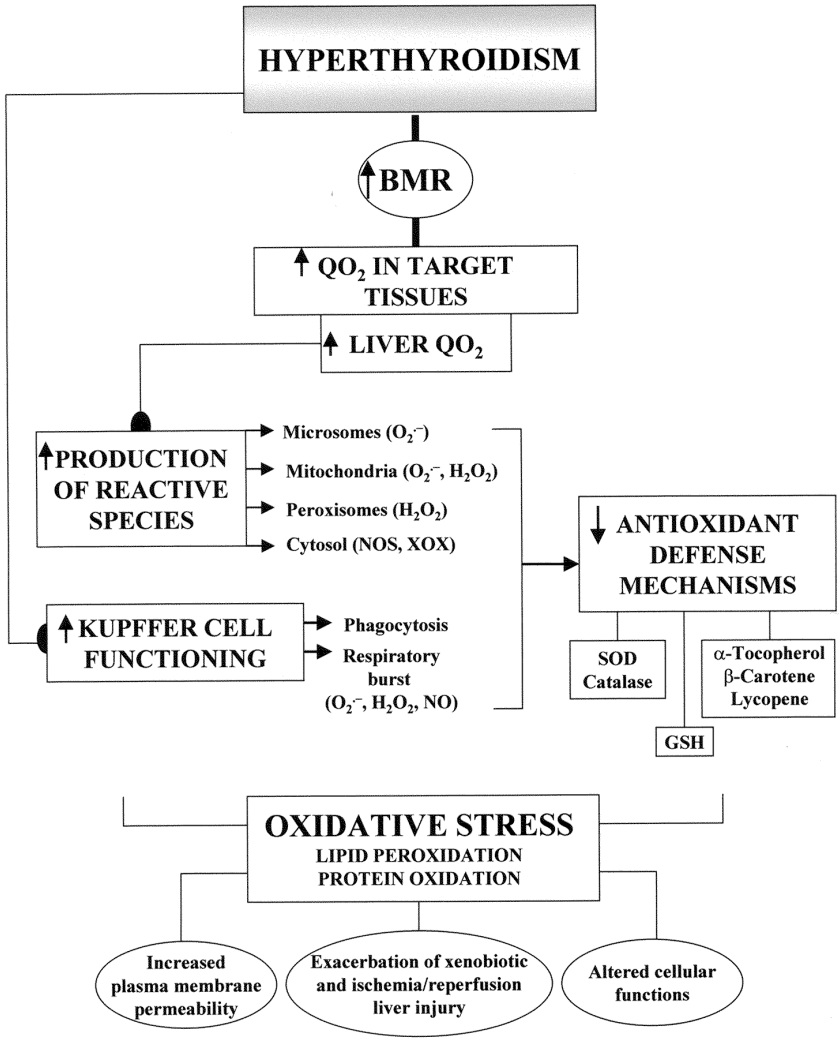

Fig. 2. Relationship between thyroid calorigenesis, liver oxidative stress, and its functional and cytotoxic consequences. Abbreviations: BMR, basal metabolic rate; QO_2, rate of oxygen consumption; $O_2^{\bullet-}$, superoxide radical; H_2O_2, hydrogen peroxide; NOS, nitric oxide synthase; XOX, xanthine oxidase; SOD, superoxide dismutase; GSH, reduced glutathione.

particles,[42] suggesting a role for peroxisomal oxidation in the enhancement in liver ROS production by hyperthyroidism (Fig. 2). Recently, rats subjected to comthyroid treatment (T_3:T_4 = 1:4) were found to exhibit increased xanthine oxidase activity in the liver, a well known generator of ROS.[51] Thus, thyroid calorigenesis in the rat leads to an enhanced rate of O_2 consumption in the liver, associated with increased ROS production at mitochondrial, microsomal, and peroxisomal sites, as well as that of RNS, as evidenced by the significant and reversible enhancement in the activity of hepatic nitric oxide synthase (NOS; Fig. 2).[52] These changes are presumed to occur at the parenchymal cell level. However, hyperthyroidism also leads to hyperplasia and hypertrophy of Kupffer cells, with a consequent elevation in the rate of colloidal carbon phagocytosis and in the carbon-induced O_2 uptake as assessed in the intact liver.[53] The latter findings indicate that enhancement of Kupffer cell function by thyroid hormone may represent an alternate source of ROS ($O_2^{\bullet-}$ and H_2O_2)[53] and RNS (NO)[52] to that induced in parenchymal cells, thus contributing to the pro-oxidant activity developed in the liver which accounts for 16–25% of the net increase in total respiration (Fig. 2).[39] In support of this view, a significant portion of T_3-induced enhancement in liver lipid peroxidation and NOS activity is abolished by Kupffer cell inactivation *in vivo* elicited by gadolinium chloride ($GdCl_3$) pretreatment.[52,53]

Thyroid hormone-induced liver free radical activity is paralleled by a diminution in antioxidant defenses, leading to enhanced oxidative stress in the liver (Fig. 2). In fact, the activity of hepatic superoxide dismutase (either total SOD[48] or CuZnSOD[54]) and catalase[48,54] are decreased

by T_3, probably due to enzyme inactivation by the ROS produced,[55–57] whereas the content of the water-soluble antioxidant glutathione (GSH)[48,51,58] and those of the lipid-soluble antioxidants α-tocopherol, β-carotene, and lycopene[59] are drastically diminished due to increased consumption. GSH depletion is a major hepatic alteration induced by hyperthyroidism in experimental animals[48,51,58,60] and in man,[61] due to loss of GSH into the blood and enhanced intracellular catabolism of the tripeptide.[58] In this condition, the rate of GSH synthesis is increased[62] as is GSH turnover rate in the liver.[58,62] However, the magnitude of the former effect is insufficient to sustain the basal levels of the tripeptide thus establishing a low steady-state concentration of GSH in the tissue. Conversion of the hyperthyroid state to the euthyroid condition occurs in conjunction with the recovery of hepatic GSH levels, coinciding with a substantial elevation in sinusoidal γ-glutamyltransferase ectoactivity[63] and in removal of circulating GSH by the liver.[64] This was proposed to represent an adaptive response to recover hepatic GSH levels, after depletion by the initial T_3-induced oxidative stress, by supplying the precursors for intracellular synthesis of the tripeptide.[63,64] Interestingly, hyperthyroidism substantially enhances the hepatic content of ubiquinone (coenzyme-Q),[65,66] the well known electron and proton carrier in the mitochondrial respiratory chain with antioxidant activity.[67] However, this effect occurs after the increment in BMR and, therefore, in free radical production,[66] suggesting an adaptive response of the liver to oxidative stress involving a derangement of other antioxidant mechanisms.

As a consequence of the increased oxidative stress imposed on the liver by thyroid calorigenesis, hepatic lipid peroxidation indicators are enhanced (Fig. 2), as measured by hepatic production of thiobarbituric acid reactants (TBARs) in liver homogenates,[38,51,68,69] biliary release of TBARs in the anesthetized rat,[70] chemiluminescence by rat liver homogenates[38] and rabbit liver mitochondria,[71] light emission of the *in situ* rat liver,[48] and microsomal hydroperoxide formation.[72,73] In addition to lipid peroxidation, hyperthyroidism promotes hepatic protein oxidation (Fig. 2), as evidenced by enhanced content of protein hydrazone derivatives,[68] possibly reflecting the increased susceptibility of the liver to *in vitro* oxidative challenge.[69] Maximal rates of lipid peroxidation occur at 1 day after T_3 treatment, whereas those of protein oxidation are attained after three daily doses of T_3.[68] These differential time courses of changes may represent differences in the susceptibility of target molecules to free radical attack and/or in the efficiency of repair or replacement mechanisms. Interestingly, prolonged T_4 administration (4–5 weeks) decreases membrane fatty acid unsaturation indices in mouse liver, possibly representing an adaptive change to maintain membrane functional integrity and to protect membranes from oxidative damage.[74]

Oxidative stress induced by thyroid hormone in extrahepatic tissues

Thyroid hormone-induced energy metabolism[20] and the consequent increase in cellular oxidative stress status is not restricted to the liver. In fact, heart[54] and skeletal muscles such as soleus[54,75] from hyperthyroid rats exhibit increased lipid peroxidation over that in euthyroid animals, whereas muscles such as extensor digitorum longus[54] and gastrocnemius-white portion[75] do not. This lipid peroxidation implies an enhanced free radical activity, coupled to the increased oxidative metabolism, that may be facilitated by the significant diminution in the activity of glutathione peroxidase[54,75,76] and catalase[54,75] which occurs despite enhanced activity of MnSOD[54,75] or total SOD.[76] In agreement with this view, the content of ubiquinol-9 (coenzyme-Q9) shows a 31% decrease in the heart of hyperthyroid rats over euthyroid values;[76] however, that of α-tocopherol has revealed conflicting results.[77] Furthermore, rats supplemented with α-tocopherol exhibit protection against lipid peroxidation in hyperthyroid heart and soleus muscles, independent of the changes in oxidative metabolism and antioxidant enzymes.[78] These overall data provide evidence that mitochondrial function and the enzymatic systems handling H_2O_2 are important for the maintenance of the structural and functional integrity of muscles, and that thyroid hormone-induced oxidative stress may predispose muscular tissues to free radical-mediated injury.[77] Thyroid hormones also provoke oxidative stress in lymphoid organs such as mesenteric lymph nodes and thymus, without major effects in the spleen,[75] a tissue devoid of a calorigenic response.[20]

Thyroid hormones play a key role in the normal development, growth, and maturation of the central nervous system.[79] Newborn rats made hyperthyroid by T_3 administration show a marked increase in brain chemiluminescence *in vivo*, assessed either after removal of the parietal bones or through the translucid parietal bones, coupled with an enhanced rate of O_2 consumption.[80] These findings point to the development of oxidative stress in the hyperthyroid brain, involving an incomplete compensatory increase in antioxidant enzyme activities (SOD, GPx, and catalase).[80]

Thyroid hormone-induced oxidative stress in man

Early studies by our group revealed that hyperthyroidism in man is associated with a pro-oxidant condition characterized by enhanced levels of circulating and urinary TBARs,[81] and spontaneous chemiluminescence in urine samples,[82] which are suppressed by propylthiouracil (PTU) treatment.[81,82] This contention is supported by subsequent studies showing reduced levels of thiols,[83,84] ascorbic acid,[85,86] α-tocopherol,[86,87] and coenzyme-Q10[87] in plasma samples of hyperthyroid patients over control values, with a parallel increase in those of TBARs.[84–88] These changes

are either normalized or reduced by carbimazole, PTU, and ^{131}I treatments,[83,84,87] or in response to ascorbic acid supplementation[85] and PTU therapy combined with propranolol and/or α-tocopherol.[84] However, values reported for other oxidative stress-related parameters in blood plasma or erythrocytes are controversial.[83,85] Erythrocytes from hyperthyroid patients exposed to *t*-butyl hydroperoxide (*t*-BHP) exhibit a lower induction time preceding the onset of O_2 uptake (reflective of cellular antioxidant capacity), in conjunction with enhanced rates of O_2 consumption and light emission (indicative of free radical-mediated processes), effects also abolished by PTU.[81] These data indicate that erythrocytes from hyperthyroid patients are more susceptible to *t*-BHP-induced oxidative stress than those of euthyroid subjects, a condition that might result in shortened half-lives of red blood cells[89] and associated stimulation of erythropoiesis.[90]

Polymorphonuclear leukocytes (PMNs), phagocytes known to possess saturable nuclear binding sites for T_3[91] and to display a calorigenic response in thyrotoxic patients,[92] show enhanced respiratory burst activity in a hyperthyroid state, as assessed by the zymosan-induced luminol-amplified chemiluminescent response.[93] The effect is observed in hyperthyroid patients or in rats after T_3 treatment, and it is characterized as being: (i) produced in the absence of changes in the opsonic capacity of plasma; (ii) reduced to euthyroid values by PTU treatment; and (iii) drastically diminished by azide, a potent inhibitor of phagocyte myeloperoxidase activity.[93] Furthermore, thyroid hormone-induced respiratory burst activity of PMNs is not due to a direct action of the hormones,[93] which exhibit phenolic structures suitable for free radical interactions, in agreement with the lack of pro-oxidant or antioxidant behaviour of T_3 or thyroxine assayed in biological systems at nanomolar concentrations.[94] Complementary studies carried out in rat PMNs revealed that T_3-induced respiratory burst activity occurs independently of changes in NOS activity,[95] being primarily related to an enhancement in NADPH oxidase activity, with the observed higher myeloperoxidase activity playing a contributory role.[96] Under these conditions, hyperthyroidism causes a net increment in the pro-oxidant capacity of PMNs, as the increased rate of $O_2^{\bullet-}$ generation occurs in the absence of changes in the activity of SOD.[96] Collectively, these data provide evidence for the presence of oxidative stress in hyperthyroid patients, and suggest that nutritional support with antioxidants in addition to thyrostatic therapy might be useful in preventing oxidative damage.[84,85,87]

Functional and Cytotoxic Consequences of Thyroid Hormone-Induced Oxidative Stress

Thyrotoxicosis, the clinical syndrome of hypermetabolism due to high serum levels of thyroid hormones, may lead to clinical and biochemical disease.[97] Underlying this condition is oxidative stress, known to represent a major mechanism of cell dysfunction and injury,[34] which correlates with a significant shortening of life-span.[80] Circumstantial evidence shows that thyroid hormone-induced oxidative stress in muscular tissues may be related to injury,[77] as the effects of T_3 on the electrophysiological properties of the heart[98] and myocardial damage[99] are partly mediated through a membrane modification associated with increased lipid peroxidation.

Before the advent of effective treatment for hyperthyroidism, serious hepatobiliary complications were associated with the disease, including fatty changes, centrilobular hepatic necrosis, and cirrhosis.[100] This association may involve: (i) liver damage secondary to the systemic actions of thyroid hormone excess; (ii) thyroid hormone effects through autoimmune mechanisms; (iii) subclinical effects of thyroid hormones on liver functions; and (iv) direct toxic effects of thyroid hormones on the liver.[101] At present, only mild non-specific histological changes have been described,[102] in addition to abnormalities in liver function tests such as elevated serum alkaline phosphatase,[103,104] glutathione-S-transferase,[104] γ-glutamyltransferase,[104,105] aspartate aminotransferase,[105] and bilirubin,[103] and decreased prothrombin time,[103] found in a significant proportion of hyperthyroid patients. In the rat, T_3-induced liver oxidative stress is paralleled by significant increases in the efflux of GSH, lactate dehydrogenase (LDH), and protein from the liver into the sinusoidal space.[58] These observations support the contention that the hyperthyroid state in man and in experimental animals may destabilize hepatic plasma membranes, possibly via substantial enhancement in lipid[38,51,68,69] and protein[68] oxidation (Fig. 2).

It is important to point out that the hepatic oxidative stress underlying thyroid calorigenesis may exacerbate hepatic injury caused by other agents (Fig. 2). In fact, hyperthyroidism enhances the hepatotoxicity of low doses of lindane, leading to extensive hepatic necrosis and the presence of granulomas containing lymphocytes, Kupffer cells, and PMNs.[106] In this condition, potentiation of the oxidative stress status of the liver by hyperthyroidism[59,106] seems to be associated with an enhanced phagocytic and respiratory burst activity due to the observed Kupffer cell hyperplasia and PMN infiltration, in addition to the increased generation of ROS in parenchymal cells.[106] A similar situation is encountered in livers from hyperthyroid rats subjected to ischemia-reperfusion, which exhibit a more pronounced liver injury than euthyroid animals.[107,108] In the case of acute iron overload in hyperthyroid animals, the enhanced hepatotoxicity observed also is associated with the severe oxidative stress status established in the tissue, that is related to an impairment of Kupffer cell phagocytosis and particle-induced respiratory burst activity.[109] In agreement with

these studies, thyroid hormone-induced sensitization to hepatotoxicity also has been reported for halothane,[110–112] isoflurane and enflurane,[111] carbon tetrachloride,[113] thioacetamide,[114] 1,1-dichloroethylene,[115,116] and chloroform.[117] Moreover, a hypothyroid state induced by methimazole or PTU administration and thyroidectomy substantially reduces the development of liver injury associated with thioacetamide intoxication,[114] cold organ storage in liver transplantation,[108] or that produced by the exposure of rats chronically treated with ethanol to low O_2 tensions.[118] These observations support the contention that thyroid status is an important factor in the development and progression of various types of liver diseases or in their prevention (Fig. 2). In line with this view, hyperthyroidism has been found to increase the oxidative stress status of the rat eye, involving an enhancement of lipid peroxidation and reduction in glutathione peroxidase activity, in association with endotoxin-induced acute anterior uveitis.[119]

As depicted in Figure 2, thyroid hormone-induced liver oxidative stress also is related to the alteration of cellular functions. Among them, increased sulphobromophthalein retention was reported in hyperthyroid patients,[61,120] a finding that may be related to the liver GSH depletion observed in these patients[61] and to the diminished activity of hepatic glutathione-S-transferases catalyzing this reaction, as reported in hyperthyroid rats.[58] Secondly, thyroid hormone-induced liver oxidative stress involves an enhancement in hepatic protein oxidation,[68] the biological relevance of which can be visualized at two levels, namely: (i) loss of protein function, *i.e.* reduction in enzyme activity due to inactivation[121] by the high ROS and RNS input established by thyroid calorigenesis;[48,57] and (ii) increased protein degradation,[122] as the oxidative modification of proteins by oxidative stress renders them highly susceptible to proteolytic attack.[121,123] Thirdly, thyroid hormone regulates the expression of NADPH–cytochrome P-450 reductase in liver and extrahepatic tissues,[46] causing substantial increases in its activity.[40,44,45,59] These observations, and the enhanced activity of the NADPH-generating enzyme glucose-6-phosphate dehydrogenase by T_3 treatment,[59] may accelerate cytochrome P-450 reduction and xenobiotic biotransformation. In agreement with this suggestion, thyroid hormone administration increases the biotransformation of aminopyrine,[124] hexobarbital,[124] aniline,[125] and zoxazolamine[125] in female euthyroid rats, as well as that of ethylmorphine, benzo(a)pyrene, and aniline in thyroidectomized rats,[126] the microsomal reduction of Δ^4-3-ketosteroids,[127] and activity of the microsomal ethanol-oxidizing system.[128] Hyperthyroidism also may enhance the biotransformation of lindane, as suggested by the significantly lower levels of the insecticide found in the serum, liver, and adipose tissue of hyperthyroid rats compared to those in euthyroid animals.[106] In man, hypothyroidism caused an increase, and hyperthyroidism a decrease, of antipyrine half-life over that in the same patients after normalization of thyroid status,[129] whereas hyperthyroid patients metabolize ethanol twice as rapidly as euthyroid subjects.[130] Discrepancies in the enhancing effect of hyperthyroidism on xenobiotic biotransformation may be related to alterations in the hepatic content or isoform pattern of cytochrome P-450, which in turn seems to be related to the dose of hormone given and the period of treatment,[131] in addition to possible changes in cardiac, hepatic, and renal function.[132]

Concluding remarks

Thyroid hormones exert significant actions on energy metabolism, with mitochondria being a major target for their calorigenic effects. This seems to be achieved by: (i) allosteric activation of cytochrome c oxidase by 3,5-T_2; and/or (ii) stimulation of nuclear and mitochondrial gene expression by T_3 with the consequent induction of components of the respiratory apparatus and of uncoupling proteins, thus increasing the respiratory rate (Fig. 1). Acceleration of energy metabolism by thyroid hormones involves an enhanced generation of ROS and RNS in target tissues, which determines a higher consumption of cellular antioxidants and inactivation of enzymatic mechanisms affording antioxidant protection, thus inducing oxidative stress (Fig. 2). This pro-oxidant condition has been shown both in experimental animals and in man, and it has been associated with cellular dysfunctions in several target tissues. In the liver, thyroid hormone-induced oxidative stress leads to cell injury by increasing plasma membrane permeability, exacerbates ischemia-reperfusion and xenobiotic-induced liver injury, and induces significant changes in several hepatic functions. Furthermore, T_3-induced respiratory burst activity in Kupffer cells could have deleterious consequences,[52,53] as gene expression in liver macrophages may be stimulated by the enhanced free radical activity. This latter action can be accomplished through activation of specific transcription factors (i.e. NF-κB, AP-1),[35,133,134] thus inducing the synthesis of toxic cytokines including tumor necrosis factor-α, various interleukins, and adhesive molecules involved in inflammatory processes.[135] These aspects, however, remain to be studied.

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