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INVITED REVIEW

Redox signaling associated with thyroid hormone action: perspectives in medical sciences

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ABSTRACT

Redox signaling, as a consequence of thyroid hormone (TH)-induced energy metabolism, triggers adaptive cellular changes to resume homeostasis. In the liver, this is associated with the activation of redox-sensitive transcription factors promoting cell protection and survival, including the upregulation of antioxidant, anti-apoptotic, anti-inflammatory, and cell proliferation responses, with concomitant higher energy supply and detoxification potentials.

Beneficial effects of THs are also observed in extrahepatic tissues against different types of noxious stimuli evidenced in preclinical studies, as well as in several clinical conditions after restoration of the normal levels of THs. Future additional preclinical and clinical studies are needed in order to validate diagnostic biomarkers and the suitable endpoints to be endorsed, and to solve discrepancies concerning the low number of patients studied and the type of trial and TH protocol employed.

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MECHANISMS OF THYROID HORMONE ACTION

Thyroid hormones (THs; thyroxin, T_4; triiodothyronine, T_3) regulate metabolic processes that are essential for fetal development, post-natal growth, and maintenance of cellular functions in adulthood [1]. These TH-mediated functions are executed through direct and indirect control of target gene expression, involving direct, genomic actions and indirect, nongenomic mechanisms [1, 2]. In the former case, T_3 interacts with nuclear TH receptors (nTRs) and heterodimerizes with retinoid X receptor to initiate transcription, through binding to TH response elements (TREs) in the promoter regions of positively regulated genes [1], whereas alternative mechanisms are proposed for control of genes negatively regulated by T_3 [3, 4]. In addition, TH regulation of gene expression may be exerted through changes in mRNA abundance by acting on the induction of specific microRNAs (5, 6). Nongenomic mechanisms of TH action are triggered without the participation of nTRs, involve cell surface receptors, extranuclear TR_β, or TR_α derivatives, which trigger complex nuclear and cellular effects [2]. These include cell proliferation [7], angiogenesis [8], intracellular protein trafficking [2], activation of enzymes such as mitochondrial cytochrome-c oxidase [9] and plasma membrane Na^+K^+-ATPase [10], and the activation of transcription factors and enzymes by low levels of reactive oxygen species (ROS) [11], leading to redox-modulated cell signaling [12, 13].

Current concepts indicate that development of oxidative stress may lead to disruption of redox signaling achieving either control or molecular damage, hormetic responses being attained when nonlethal ROS levels trigger adaptive changes to resume homeostasis [12-14]. Under these conditions, hydrogen peroxide (H_2O_2) is considered to represent a suitable second messenger for redox signaling, providing specificity for reversible cysteine oxidation in key regulatory proteins such as kinases, phosphatases, and transcription factors [12, 15].

T_3-INDUCED REDOX SIGNALING AND LIVER PRECONDITIONING

Activation of Redox-Sensitive Transcription Factors

Enhancement in ROS generation induced in the liver by T_3 administration (24 h after 0.1 mg/kg, i.p.) is associated with **(i)** the T_3-dependent genomic signaling increasing the expression of catabolic enzymes and uncoupling proteins [16]; and **(ii)** the nongenomic pathway involving 3,5-diiodothyronine (T_2)- and/or T_3-dependent allosteric activation of mitochondrial cytochrome-c oxidase [9] (Figure 1). T_3-induced liver ROS production primarily occurs at the mitochondrial level, due to the central role of mitochondria in energy-transduction pathway [17]. The mechanisms involve enhancement in T_3-induced mitochondrial biogenesis [18] and in the nongenomic cytochrome-c oxidase activation [9] and mRNA expression [19], with concomitant induction of ATP synthase [20], the glycerol phosphate dehydrogenase shuttle directly associated with H_2O_2 production [21], and other respiratory components increasing the respiratory activity. In addition, the generation of ROS also occurs at microsomal, cytosolic and peroxisomal levels in hepatocytes, with Kupffer cell-dependent respiratory burst activity playing a contributory role [22].

This T_3-induced pro-oxidant state is characterized by **(i)** its occurrence in the absence of morphological changes in liver parenchyma [23]; **(ii)** the activation of redox-sensitive transcription factors nuclear factor-κB (NF-κB) [24], signal transducer and activator of transcription 3 (STAT3) [25], activating protein 1 (AP-1) [26], and nuclear factor erythroid 2-related factor2 (Nrf2) [27], an effect that is abolished by pre-treatment with the antioxidants N-acetylcysteine (NAC; 0.5 g/kg i.p., 0.5 h before T_3) or α-tocopherol (α-TP; 100 mg/kg i.p., 17 h prior to T_3) [11, 22]; and **(iii)** its ability to protect the liver against the injury produced by ischemia/reperfusion (IR; 1 h/20 h) [23].

As shown in Figure 1, the preconditioning (PC) action of T_3 against IR injury involves upregulation of the expression of antioxidant proteins (NF-κB, Nrf2), anti-apoptotic and acute phase proteins (NF-κB, STAT3), phase II enzymes and phase III transporters of the xenobiotic biotransformation system (Nrf2), and cell proliferation (AP-1, STAT3). It is important to note that T_3-induced Kupffer cell activity plays a key role in the PC effect of T_3, as evidenced by the re-establishment of liver IR injury after Kupffer cell elimination by gadolinium chloride ($GdCl_3$) administration (10 mg/kg i.v., 24 h prior to T_3) [28]. Mechanistically, Kupffer cell involvement in T_3 liver PC can be visualized in terms of the enhanced release of tumor necrosis factor α (TNF-α) [28], which upon coupling with TNF-α receptor 1 in hepatocytes may lead to **(i)** inhibition of mitochondrial electron transport with increased ROS production [29], thus contributing to T_3-dependent redox signaling; and **(ii)** further NF-κB activation [30] (Figure 1).

The operation of the T_3-dependent genomic signaling includes alternate hormetic responses leading to cell protection. Among them, induction of respiratory and metabolic enzymes (Figure 1) may accelerate substrate cycles such as ATP and NADPH cycling, with higher ATP supply and cellular antioxidants reduction, thus preventing excessive ROS generation [31]. The latter feature is also related to the upregulation of UCP expression lowering mitochondrial ROS generation [32] and the lipoperoxidative status, by exporting peroxidized fatty acid anions from inner to outer membranes [33]. Recently, T_3 was reported to induce hepatic autophagy by a TR-dependent mechanism that is coupled to fatty acid β-oxidation enhancement to support ATP production, which with the simultaneous increase in amino acid availability for protein synthesis, may favor cell survival [34]. In this respect, recent studies by our group discussed bellow indicate that T_3 triggers the unfolded protein response (UPR) in the liver [35], which may constitute an essential mechanism for autophagy induction [36].

Upregulation of AMP-Activated Protein Kinase Signaling

The PC action of T_3 against IR injury requires a significant supply of energy to cope with the underlying protective mechanisms. These comprise ATP requirements for the induction of proteins related to defensive functions outlined in Figure 1, cellular processes repairing oxidized DNA and unsaturated fatty acids in phospholipids, hepatocyte and Kupffer cell proliferation to compensate IR-induced necrosis, and repletion of ATP levels lost in the ischemic phase [11]. Energy requirements for T_3-induced liver PC are associated with upregulation of AMP-activated protein kinase (AMPK) [37], an ATP sensor regulating physiological energy dynamics by limiting anabolism and stimulating catabolism to increase ATP availability [38].

T_3 administration upregulates liver AMPK due to **(i)** significant increases in AMPK mRNA expression; **(ii)** higher AMPK Thr-172 phosphorylation coupled to the activation of the upstream kinases Ca^{2+}-calmodulin-dependent protein kinase kinase-β (CaMKKβ) and transforming growth factor-β-activated kinase-1 (TAK1); **(iii)** enhancement in the AMP/ATP ratios leading to the allosteric activation of AMPK [39]; and **(iv)** ROS-dependent activation evidenced by suppression of AMPK upregulation by NAC treatment prior to T_3 [40] (Figure 1). The latter feature of T_3 is supported by previous studies showing AMPK activation by either *in vitro* H_2O_2 addition to cell cultures [41, 42] or by *in vitro* and *in vivo* conditions involving ROS production in hepatocytes and heart [43, 44]. Consequently, the higher phosphorylation potential underlying AMPK activation by T_3 is associated with elevations in the levels the AMPK phosphorylated targets acetyl-CoA carboxylase (pACC) and cyclic AMP response element binding protein (pCREB) triggering fatty acid oxidation (FAO), as evidenced by the ketogenic response observed [40].

In agreement with these views, T_3 upregulated the expression of the FAO-related enzymes carnitine palmitoyl transferase-1α, acyl-CoA oxidase-1, and acyl-CoA thioesterase, thus sustaining higher FAO and ATP supply to comply with high energy requiring processes such as liver PC [39, 40] (Figure 1). This contention is supported by the lost of the PC effect of T_3 against IR injury observed in animals subjected to treatment with compound C (10 mg/kg i.p. along with T_3) [11] (Figure 1), a selective inhibitor of AMPK [45].

Redox Activation of the Endoplasmic Reticulum Unfolded Protein Response

Previous studies by our group revealed that T_3 administration induces a significant increase in liver ROS-dependent protein oxidation [46], a process involving partial protein unfolding resulting in proteome instability and endoplasmic reticulum (ER) stress, with activation of the UPR program to promote cell survival [47, 48]. Recently, T_3-induced protein oxidation was reported to upregulate the ER-localized signal transducer protein kinase RNA-like ER kinase (PERK) and its downstream components in a NAC-sensitive fashion [35] (Figure 1). The activation of the PERK regulatory axis of the UPR involves the release of PERK bound to the ER chaperone binding immunoglobulin

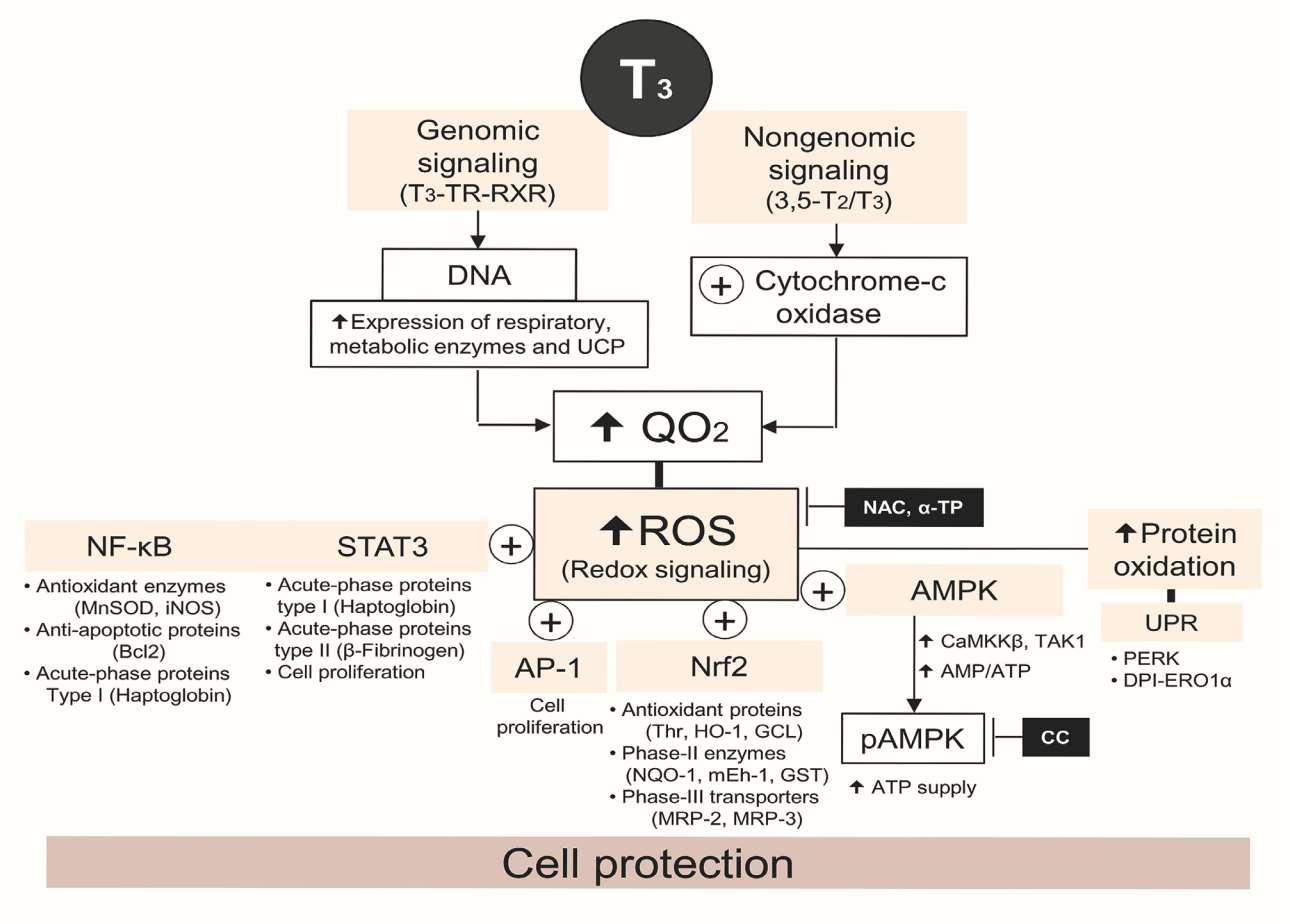

Figure 1. Genomic and nongenomic mechanisms in the calorigenic action of thyroid hormone (T_3) and consequent redox signaling upregulating genes that afford cytoprotection. **AMPK**, AMP-activated protein kinase; **AP-1**, activating protein-1; **CaMKKβ**, calcium-calmodulin-dependent kinase kinase-β; **CC**, compound C; **ERO1α**, endoplasmic reticulum oxidoreductin-1α; **HO-1**, heme-oxygenase 1; **GCL**, glutamate cysteine ligase; **GST**, glutathione-S-transferases; **iNOS**, inducible nitric oxide synthase; **mEH-1**, microsomal epoxide hydrolase-1; **MnSOD**, manganese superoxide dismutase; **MRP-2(3)**, multidrug resistance protein 2(3); **NAC**, N-acetylcysteine; **NF-κB**, nuclear factor-κB; **NQO-1**, NADPH-quinone oxidoreductase; **Nrf2**, nuclear factor erythroid 2-related factor 2; **PDI**, protein disulfide isomerase; **PERK**, protein kinase RNA-like ER kinase; **QO_2**, oxygen consumption; **ROS**, reactive oxygen species; **RXR**, retinoid X receptor; **3,5-T_2**, 3,5-diiodothyronine; **TAK1**, transforming growth factor-β-activated kinase 1; **STAT3**, signal transducer and activator of transcription-3; **Thr**, thioredoxin; **α-TP**, α-tocopherol; **TR**, thyroid hormone receptor; **UCP**, uncoupling protein; **UPR**, unfolded protein response; ⊢, inhibition.

protein (BiP), to achieve PERK dimerization and autophosphorylation for maximal activity [47, 49], in agreement with the enhanced BiP levels and pPARK/PERK ratios elicited by T_3 [35].

In addition, T_3-induced PERK activation is related to the augmented phosphorylation of its target eukaryotic translation initiator factor 2α (eIF2α) [35], with attenuation of global mRNA translation, but allowing selective translation of specific mRNAs [47, 49], such as that for activating transcription factor 4 (ATF4) leading to higher ATF4 protein levels [35]. As a transcriptional activator induced by different forms of metabolic stress, ATF4 upregulates the expression of autophagy genes, chaperones, proteins involved in mitochondrial functions, amino acid metabolism, and redox processes [50, 51]. The latter case includes heterodimerization with Nrf2 that results in the induction of antioxidant enzymes [52], a pathway that may contribute to T_3-induced redox activation of Nrf2 in the liver [27] (Fig. 1). T_3-induced liver UPR favoring the transition from unfolded polypeptide to adequate tertiary structure also includes disulfide bond formation [35, 53]. This is accomplished through the NAC-sensitive induction of hepatic protein disulfide isomerase (PDI) that increases the potential of the liver for oxidative protein folding, a process that requires the assistance of endoplasmic reticulum oxidoreductin-1α (ERO1α) [35] (Figure 1), to recover the oxidant functional status of PDI [54].

PROTECTIVE EFFECTS OF THYROID HORMONES ON LIVER INJURY INDUCED BY NOXIOUS STIMULI OTHER THAN ISCHEMIA-REPERFUSION

The beneficial effects of THs are not only exerted against IR injury [11, 19], but also on other stressful conditions evidenced in preclinical studies. In this respect, liver tissue regeneration after 70% hepatectomy was favored by pretreatment with T_3 combined with methylprednisolone, with concomitant reductions

in ALT serum levels, liver oxidized protein content, inflammation and necrosis foci being observed over control values [55], which are in agreement with the upregulation of the proteins involved in the control of cell cycle by T_3 [56]. In addition, brain-dead rats pretreated with T_3 and exhibiting lower circulating levels of ALT and AST, showed diminished Bax gene expression and cleaved Caspase-3 activation compared to control animals, supporting the protective and anti-apoptotic PC action of T_3 in the liver of brain-dead rats [57]. Interestingly, T_3 supplementation in rats substantially recovered hypothyroidism-induced liver apoptosis [58], an effect that may involve the redox signaling-dependent activation of NF-κB (Figure 1).

THYROID HORMONE-DEPENDENT PROTECTION OF EXTRAHEPATIC TISSUES AGAISNT DELETERIOUS STIMULI

Protection against Ischemia-Reperfusion Injury in Heart, Kidney and Brain

Cardioprotection against IR by THs reducing myocardial infarct size [59] and recovering heart function [60] underlie several molecular mechanisms of action that may involve redox signaling. These include **(i)** reduction in ROS levels [61]; **(ii)** upregulation of heat shock protein 70 [62] and AMPK [63, 64]; **(iii)** inhibition of the mitochondrial permeability pore opening during reperfusion [59]; and **(iv)** reduced p38 and enhanced protein kinase Cδ levels mediating cardioprotection [60]. Furthermore, T_3 induces microRNAs 30a and 29 having antiapoptotic and antifibrotic actions, respectively [65], an aspect that requires further investigation under IR conditions. Redox signaling by TH also operates in kidney PC against IR injury as it improves renal function by increasing inulin clearance [66] and diminishing serum creatinine and urea levels [67] and proteinuria [68].

Redox-dependent mechanisms such as oxidative stress suppression [67-69] and HO-1 induction [67] (Figure 1) are accompanied by improvement in renal ATP levels [66] and anti-inflammatory responses [67]. Besides heart and kidney PC by THs, T_4 administration to rats significantly diminished brain injury caused by middle cerebral artery occlusion, which was associated with downregulation of the expression of the inflammatory-related pro-oxidant enzymes inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2), while restoring that of neurotrophins [70]. Interestingly, both THs and TH analogs can exert neuroprotective effects through alternate defense mechanisms that may be of importance in brain damage settings [71].

Organ Defense Against Injuring Stimuli other than Ischemia-Reperfusion

T_3 exerts beneficial effects in several non-IR models of cell injury, comprising **(i)** Akt activation preventing serum starvation-dependent cell death in cardiac cardiomyocytes [72]; **(ii)** preservation of coronary microvasculature and attenuation of cardiac dysfunction in experimental diabetes mellitus [73]; **(iii)** preservation of ovarian granulose cells from chemotherapy-induced apoptosis [74]; **(iv)** keratinocyte proliferation affording optimal wound healing [75]; **(v)** stimulation of alveolar fluid clearance coupled to enhanced Na^+K^+-ATPase activity in hyperoxia-injured lungs [76]; and **(vi)** enhancement in the restoration of neuromuscular junction structure and improvement of synaptic transmission following rat sciatic nerve transection [77].

BENEFICIAL EFFECTS OF THYROID HORMONE RESTORATION TO NORMAL LEVELS IN CLINICAL CONDITIONS

Reinstatement of the normal serum levels of THs, depressed by alterations in their synthesis, transport, and/or processing, is a major achievement in medical sciences restoring cellular T_3-dependent signaling and function. In the case of primary hypothyroidism, which is characterized by a derangement of the normal negative feedback control in the hypothalamic-pituitary-thyroid (HPT) axis, serum levels of T_3 and T_4 are low whereas those of thyroid stimulating hormone (TSH) are enhanced, and patients may require TH replacement therapy to attain a euthyroid status [78].

Besides primary hypothyroidism, restoring normal TH levels with beneficial effects has been reported in prematurity and in bipolar disorders. In the former case, levels of THs in premature infants are lower than in term-born infants due to thyroid system immaturities [79], in association with enhanced mortality and morbidity, with a higher risk of impaired neurodevelopmental outcome [80]. In this respect, the results of the post-hoc subgroup analyses by van Wassenaer *et al* [80] indicate that the effects of TH supplementation are dependent on the gestational age, since T_4 improved mental, motor and neurological outcomes in infants of less of 28 weeks gestation, but was detrimental in those of 29 weeks gestation. The positive gestational age-dependent effects observed were ascribed to processes in brain maturation induced by T_4, with continuous TH administration being more effective than bolus administration in attaining tissue euthyroidism [80].

Lithium and electroconvulsive therapy for the treatment of bipolar disorders are also associated with transient diminutions in T_4 and T_3 levels in serum with enhancement in those of TSH, which are related to inhibition of TH synthesis and metabolism, with the adjunctive administration of TH having the potential to diminish the associated cognitive side-effects [81]. This feature that is also observed after T_4 treatment combined with antidepressants and mood stabilizers in patients with resistant bipolar depression, with the concomitant improvement in the abnormal function of prefrontal and limbic brain areas assessed by positron emission tomography using [^{18}F]fluorodeoxyglucose [82].

Brain-dead potential organ donors [83] or critically ill patients [79] have also been studied in relation to the attainment of a euthyroid status, which is altered in association with a derangement in the HPT axis, in order to improve organ procurement or to obtain positive endpoints, respectively. In these cases, however, no conclusive evidence has been published; a controversy

that may be due to differences in the TH protocol, the outcome measures, and/or the type of trial employed [79, 84]. Recently, a report based on a large data availability provided by the Unites Network of Organ Sharing (UNOS) showed that TH therapy significantly enhanced the procurement/transplantation rate of the heart, lung, kidney, and pancreas, excepting the liver [85]. Interestingly, TH therapy was not detrimental to the liver, it was associated with a greater outcome after transplantation, and exhibited a better procurement rate (>80%) independently of TH treatment, compare to other organs [85]. The latter observation suggests that the liver is more resistant to brain-death related injury than other organs, which is probably related to its greater protective capacity and adaptability to noxious stimuli such as IR injury (Figure 1) [11].

CONCLUDING REMARKS

Acceleration of energy metabolism by THs involves production of low levels of ROS that trigger redox signaling mechanisms upregulating cytoprotective processes. The data regarding preclinical research constitute the basis for TH-induced organ preconditioning against damaging stimuli allowing functional recovery, which deserve application in clinical practice [11]. This would require that conditions in animal research can be reproduced in the clinical setting, using validated diagnostic biomarkers and suitable endpoint assessments [86]. Redox signaling by TH may also be beneficial upon restoration of normal TH levels that are depressed in several clinical conditions, provided that additional large-scale, prospective, multicentre, double-blind and placebo-controlled studies are carried out, in order to solve discrepancies concerning the low number of patients studied and the type of trial and TH protocol employed.

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