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Thyroid hormone calorigenesis and mitochondrial redox signaling: upregulation of gene expression

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1. ABSTRACT

Thyroid hormone (TH, T_3) is required for the normal function of most tissues, with major effects on O_2 consumption and metabolic rate. These are due to transcriptional activation of respiratory genes through the interaction of T_3-liganded TH receptors with TH response elements or the activation of intermediate factors, with the consequent higher rates of mitochondrial oxidative phosphorylation and reactive O_2 species (ROS) generation and antioxidant depletion. The genomic effects of TH are accompanied by redox upregulation of the liver expression of cytokines (tumor necrosis factor-alpha [TNF-alpha]), enzymes (manganese superoxide dismutase), and anti-apoptotic proteins (Bcl-2), via a cascade initiated by TNF-alpha produced by Kupffer cells and involving inhibitor of kappa-B phosphorylation and nuclear factor-kappa-B activation. Thus, TH calorigenesis triggers non-genomic effects leading to an expression pattern that may represent an adaptive mechanism to re-establish redox homeostasis and promote cell survival under conditions of ROS toxicity secondary to TH-induced oxidative stress. Mechanisms of expression of respiratory and redox-sensitive genes may be functionally integrated, which could be of importance to understand the complexities of TH action and the outcome of thyroid gland dysfunction.

2. INTRODUCTION

Thyroid hormones (TH) are required for the normal function of most tissues of the body, playing essential roles in growth, development, differentiation, and metabolism, with major effects on O_2 consumption (QO_2) and metabolic rate leading to stimulation of basal thermogenesis. Several biochemical processes have been suggested to explain the mechanism by which THs enhance thermogenesis. These include (i) a short-term nongenomic mechanism involving the direct allosteric activation of cytochrome-c oxidase by 3,5-diiodothyronine and 3,3',5-triiodothyronine (T_3), as a rapid response to sudden variations in energy requirements (1), and (ii) a long-term pathway upregulating nuclear and mitochondrial gene transcription through T_3 signaling (2).

2.1. Genomic actions of thyroid hormone

Activation of gene transcription by T_3 involves its binding to different thyroid hormone receptor (TR) isoforms that are ligand-regulable transcription factors having a similar domain organization. Liganded TR isoforms can bind to TH response elements (TRE) in DNA, mainly in the form of TR/retinoic acid receptor (RXR) heterodimers, with variable orientation, spacing, and sequences for TRE half-sites. In addition, liganded

TR/RXR heterodimers can form complexes with specific co-activators, which regulate histone acetylation and interact with the basal transcriptional apparatus, thus determining gene transcription. In the absence of T_3, TR/RXRs exist in the transcriptionally inactive state that is stabilized by the binding of co-repressor proteins, thus diminishing basal transcription of positively regulated TREs (2). Alternatively, T_3-responsive genes that do not interact with TR may involve an indirect induction mechanism via the activation of intermediate factors, such as nuclear respiratory factor-1 or the peroxisome proliferator-activated receptor gamma coactivator 1 (3). These T_3-dependent signaling mechanisms induce the synthesis of the enzymes involved in energy metabolism leading to enhanced oxidative phosphorylation and higher ATP production (4,5), which is partially balanced by intrinsic uncoupling afforded through induction of uncoupling proteins (UCP) by T_3 (6). T_3-induced cellular respiration may be contributed by alternate processes, namely, (i) energy expenditure due to higher active cation transport or from futile cycles coupled to increased catabolic and anabolic pathways, (ii) higher activity of membrane-bound enzymes involved in electron transport and metabolite carriers due to changes in the lipid composition of mitochondrial membranes, and (iii) O_2 utilization related to oxidative stress induced by TH calorigenesis (4,5).

2.2. Nongenomic actions of thyroid hormone

In addition to genomic pathways, actions of THs that are nongenomic or extranuclear in mechanism have been recognized recently, being independent on the formation of a nuclear complex between T_3 and its TRs (7). The simplest mechanism of nongenomic action of THs is their direct interaction with effector proteins, as reported for pyruvate kinase M2 (8) and subunit Va of cytochrome-c oxidase (1). Additional nongenomic mechanisms of THs appear to involve their interaction with specific cell surface G protein-coupled receptors, leading to the activation of signal transducing kinases such as mitogen-activated protein kinase, protein kinase A and C, and protein tyrosine kinase. TH-induced kinase activation may influence several cellular processes, such as activation of signal transducer and activation of transcription proteins that mediate certain cytokine and growth factor signals (7), the interferon-γ-induced HLA-DR expression (9), or the enhancement in the respiratory burst activity of human neutrophils (10). Nongenomic effects of THs have been observed in cells containing nuclear TR or which are devoid of functional TR, and may be related to genomic mechanisms by promoting serine phosphorylation of nuclear TRs that alters their transcriptional activity (7).

3. THYROID HORMONE CALORIGENESIS AND OXIDATIVE STRESS

Normal aerobic life is characterized by a steady-state level of reactive oxygen (ROS) and nitrogen (RNS) species, balanced by a similar rate of production of the reactive species and of their consumption by antioxidants. The imbalance in the pro-oxidant/antioxidant equilibrium in favor of the pro-oxidants constitutes the oxidative stress phenomenon, which may determine different cellular events (11). The relation between TH calorigenesis and oxidative stress has been studied extensively (5) in line with the significant correlation established for the basal metabolic rate and the lipid peroxidative potential of tissues from several mammalian species (12).

Experimental animals made hyperthyroid by T_3 administration exhibit a thermogenic response that coincides with increases in the rate of O_2 consumption by the liver (Figure 1A), involving a progressive accumulation of products of hepatic lipid peroxidation and protein oxidation (Figure 1B), thus evidencing the attainment of significant oxidative stress in the liver (13,14). Acceleration of hepatic respiration during thyroid calorigenesis leads to a marked elevation in the rate of superoxide (O_2^-) production by liver submitochondrial particles in the presence of succinate (152%; Figure 1C), with higher rates of hydrogen peroxide (H_2O_2) generation, either under basal conditions or in the succinate-supported process (Figure 1C), both in the absence and presence of antimycin (15). Higher rates of liver mitochondrial O_2^- production by T_3 are also observed in the presence of NADH (15). In addition, enhancement in liver mitochondrial H_2O_2 production occurs in the transition from hypothyroid to hyperthyroid state as a function of the content of autoxidisable electron carriers (16), an effect that is mimicked by cold-induced hyperthyroidism (17). Mitochondria are the most important physiological source of O_2^- and H_2O_2, accounting for about 2% of the total O_2 consumption of perfused rat liver (18). O_2^- is not permeable through the inner mitochondrial membrane and is confined in the matrix where nitric oxide (NO) and manganese-superoxide dismutase (Mn-SOD) are the O_2^- co-reactants to produce peroxynitrite and H_2O_2 (19). Thus, considering that ROS are able to act as signal mediators, TH-induced mitochondrial H_2O_2 production may contribute to alter cell redox state, affecting mitochondria-to-nucleus signaling pathways (20).

In addition to T_3-induced liver mitochondrial O_2^- and H_2O_2 production (Figure 1C), ROS generation is also enhanced at microsomal (13) and cytosolic (21) subcellular sites, as well as that of NO by NO synthase (NOS)(22), changes that are presumed to occur at the parenchymal cell level. Furthermore, T_3 also leads to hyperplasia and hypertrophy of Kupffer cells with the resulting enhancement in the respiratory burst activity (23). The latter process is mainly due to the activity of the O_2^-/H_2O_2 generating enzyme NADPH oxidase, with a smaller but important contribution by NOS, being T_3-induced respiratory burst significantly reduced by the Kupffer cell inactivator gadolinium chloride ($GdCl_3$)(23). Thus, a higher pro-oxidant activity is developed in the liver as result of the functional interdependence established between TH calorigenesis, liver QO_2, and generation of ROS and RNS, which accounts for 16-25% of the net increase in total QO_2 (24), including O_2 utilization in polyunsaturated fatty acid, protein, and DNA oxidation (5,13,14,41-44). Furthermore, T_3-induced free radical activity decreases the cellular antioxidant defenses, leading to oxidative stress in liver and in extrahepatic tissues exhibiting a calorigenic response (5).

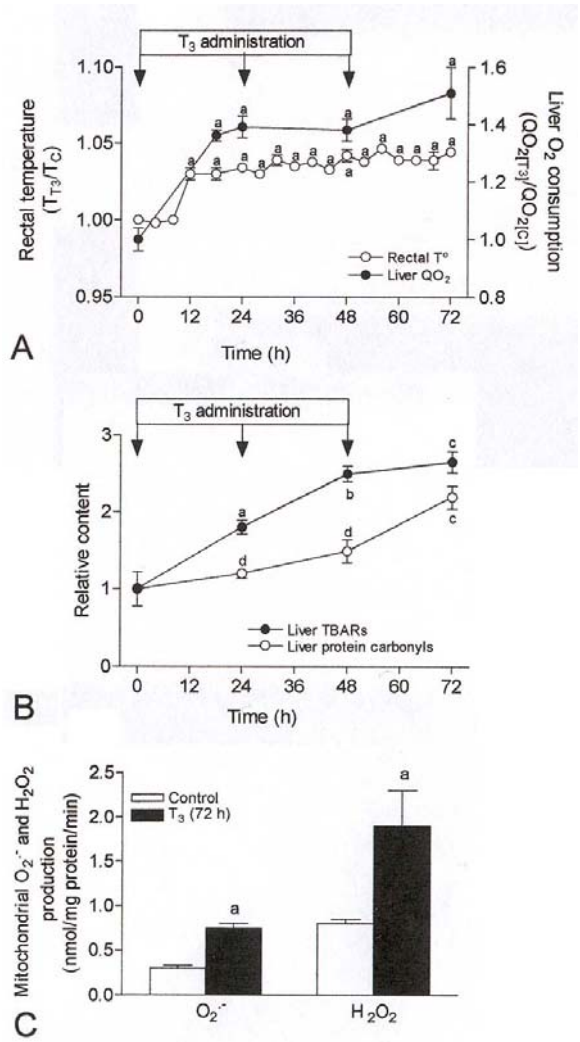

Figure 1. Influence of T_3 administration on (A) the rectal temperature of the animals and liver O_2 consumption rates (QO_2), (B) liver thiobarbituric acid reactants (TBARs) and protein carbonyl contents, and (C) the mitochondrial production of superoxide radical (O_2^{-}) and hydrogen peroxide (H_2O_2). Sprague-Dawley rats weighing 200-300 g fed *ad libitum* received either daily doses of 0.1 mg T_3/kg (ip) for three consecutive days (arrows) or equivalent volumes of hormone vehicle (0.1 N NaOH, controls) and studies were performed at the indicated times as previously described (15,31,36). In panels A and B, data from control rats at zero time were set to unity, and values at other time points were normalized to this. Each data point represents the mean ± SEM for three to fifteen different animals. Significance studies (one-way ANOVA and the Newman-Keuls' test): [a]$p<0.05$ versus controls (at time zero); [b]$p<0.05$ versus controls and T_3-treated rats at 24 h; [c]$p<0.05$ versus controls and T_3-treated rats at 24 and 48 h; [d]$p<0.05$ versus controls and T_3-treated rats at 72 h.

4. REDOX REGULATION OF GENE TRANSCRIPTION BY THYROID HORMONE

At the cellular level, oxidative stress leads to a wide spectrum of responses, depending on the cell type, the level of ROS achieved, and the duration of the exposure. Under normal conditions, ROS and RNS occur at relatively low steady-state levels. The regulated and moderate increase in ROS and RNS production can lead to a temporary imbalance capable of redox regulation. However, persistent generation of large amounts of ROS and RNS may induce substantial oxidation of biomolecules and persistent changes in signal transduction and gene expression, resulting in cell death via either necrotic or apoptotic mechanisms (25,26). Thus, transient fluctuations in ROS and RNS levels may represent important regulatory signals regulating either protein function, through reversible oxidation and/or nitrosation of protein sulfhydryls (27), or gene expression, through ROS and lipid oxidation products of ROS-dependent reactivity that modulate the activity of kinases, phosphatases, and redox-sensitive transcription factors (28,29).

T_3-induced calorigenesis involving increases in liver O_2 consumption and ROS production (Figure 1) results in transient elevations in the serum levels of tumor necrosis factor-alpha (TNF-alpha) (Figure 2A, left panel). The latter response is determined by actions exerted at the Kupffer cell level and these are related to the oxidative stress status achieved, as it is virtually abolished by pretreatment with (i) $GdCl_3$ (30), (ii) the antioxidants alpha-tocopherol and N-acetylcysteine (NAC)(Figure 2A, right panel), and (iii) an antisense oligonucleotide targeting the primary RNA transcript of TNF-alpha, prior to hormone administration (30). These pretreatments also markedly reduced liver glutathione (GSH) depletion and the enhancement in biliary glutathione disulfide (GSSG) efflux by T_3, supporting the involvement of oxidative stress in the effects elicited by T_3 (30). T_3-induced TNF-alpha response coincided with induced mRNA expression of TNF-alpha and interleukin- (IL-) 10 through an NF-kappa-B-associated mechanism, which correlates with increases in the serum levels of the cytokines (31). Upregulation of the IL-1-alpha gene also occurred after T_3 administration, a response that may be due to TNF-alpha induction (31). The latter changes could play a role in the onset of TH calorigenesis (30), as TNF- alpha and IL-1-alpha are considered endogenous pyrogens due to their direct effects on the hypothalamus, leading to activation of responses that decrease heat loss and increase heat production (32). Interestingly, liver TNF- alpha mRNA expression by T_3 levels off before that of IL-10 (31), suggesting that late expression of IL-10 may contribute to limit that of pro-inflammatory cytokines, probably through IL-10-induced NF-kappa-B deactivation due to preserved expression of the inhibitory I-kappa-B protein (33).

TNF-alpha released from Kupffer cells exhibits autocrine and paracrine actions in the liver through interactions with two surface receptors in target cells, TNF-alpha receptor 1 (TNFR-1) and TNFR-2, in order to mediate TNF-alpha-dependent signals from cell membrane to nucleus (34). Signal cascades operating after TNF-alpha-TNFR-1 coupling are important in the homeostatic response of the liver to oxidative stress, triggering defense and reparative processes against injury under conditions of moderate pro-oxidant status and low levels of transient

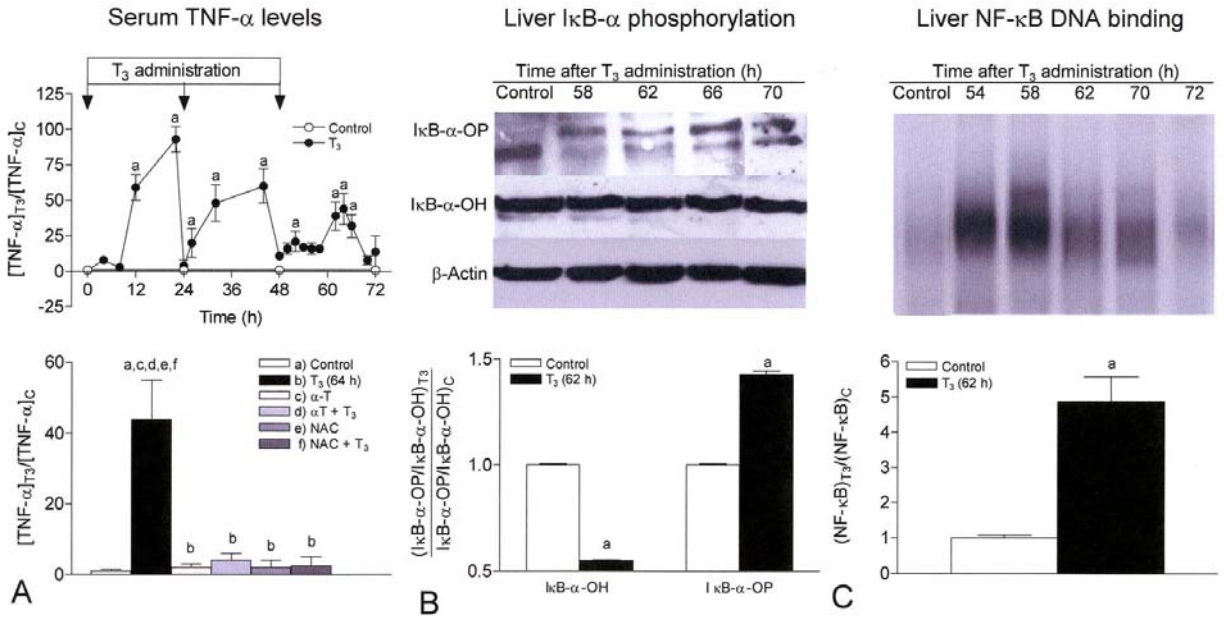

Figure 2. Influence of T_3 administration on (A) the tumor necrosis factor-alpha (TNF-alpha) levels in serum (enzyme-linked immunoabsorbent assay), (B) liver inhibitor of kappa-B-alpha (I - kappa-B-alpha) phosphorylation (Western blot), and (C) liver nuclear factor-kappa-B (NF-kappa-B) DNA binding (electromobility shift assay) in the rat. Hormone administration was performed as shown in Figure 1 and studies were carried out at the indicated times as previously described (30,36,37). Data from control rats were set to unity, and values at other time points were normalized to this. Each data point represents the mean ± SEM for three to seven different animals. Significance studies (one-way ANOVA and the Newman-Keuls' test): (A, right panel), $p<0.05$ as shown by the letters identifying each experimental group; (A, left panel), (B), and (C), $^{a}p<0.05$ versus controls. Reproduced with permission from Society for Endocrinology (37).

TNF-alpha expression (35). In agreement with these views, the transient TNF-alpha response induced by T_3 (Figure 2A) correlates with the enhancement in either liver IκB-alpha serine 32 phosphorylation (Figure 2B), the NF-kappa-B DNA binding (Figure 2C), or in the mRNA expression of the NF-kappa-B-responsive genes encoding inducible NOS (iNOS)(36), manganese superoxide dismutase (Mn-SOD)(Figure 3A), and Bcl-2 (Figure 3B). These changes (Figure 3) and the increase in the hepatic activity of NOS (36) and Mn-SOD (Figure 3A) induced by T_3 are abrogated by the administration of alpha-tocopherol prior to T_3, which achieved significantly higher levels of the antioxidant in serum (37). Interestingly, mRNA expression of the mitochondrial glicerol-3-phosphate dehydrogenase (mGPDH) and the adenine nucleotide translocator 2 (ANT2) is not modified by pretreatment with alpha-tocopherol or NAC prior to T_3 administration (Figure 4). mGPDH and ANT2 are target proteins of TH action (38) and regulation of gene expression occurs either directly through binding of liganded TR to functional TRE (39) or indirectly via the activation of intermediate regulators (3), respectively (Figure 5). These findings support the contention that the redox regulation of gene transcription by T_3 is a nongenomic secondary mechanism to those triggered by genomic pathways, which upregulates cytokine-encoding genes in Kupffer cells, with the consequent TNF-alpha response and concomitant I-kappa-B-alpha phosphorylation, suggesting the activation of the I-kappa-B kinase (IKK) complex, although the participation of other signaling kinases cannot be discarded. The process requires the recruitment of several adaptor molecules causing the activation of NF-kappa-B-inducing kinase, which in turn associates and activates the IKK complex, leading to a higher activating potential of NF-kappa-B and transcription of NF-kappa-B-responsive genes (34,35). Suppression of T_3-induced gene expression by alpha-tocopherol and NAC, antioxidants having different mechanisms of action, strengthens the contention that the underlying mechanisms are oxidant dependent. NAC exerts antioxidation by preventing ROS formation or through a ROS scavenging mechanism, either directly or via GSH replenishment, whereas alpha-tocopherol reacts with lipid-derived radicals formed in cellular membranes and ROS that gain access to this environment (40). In agreement with these views, oxidative stress-related parameters induced in hyperthyroid state are normalized or reduced in response to alpha-tocopherol (30,41), NAC (30), and ascorbic acid (42) supplementation, as well as by antithyroid therapy alone (43,44) or combined with alpha-tocopherol (43). In addition, non-antioxidant ligand-induced effects on specific proteins have been proposed to mediate cell signaling and regulation of gene expression by alpha-tocopherol (45). However, this non-antioxidant mechanism is not imitated by structurally related (gamma-tocopherol) or unrelated (NAC) antioxidants (45) and its relationship with the redox activation of signaling cascades has not been established.

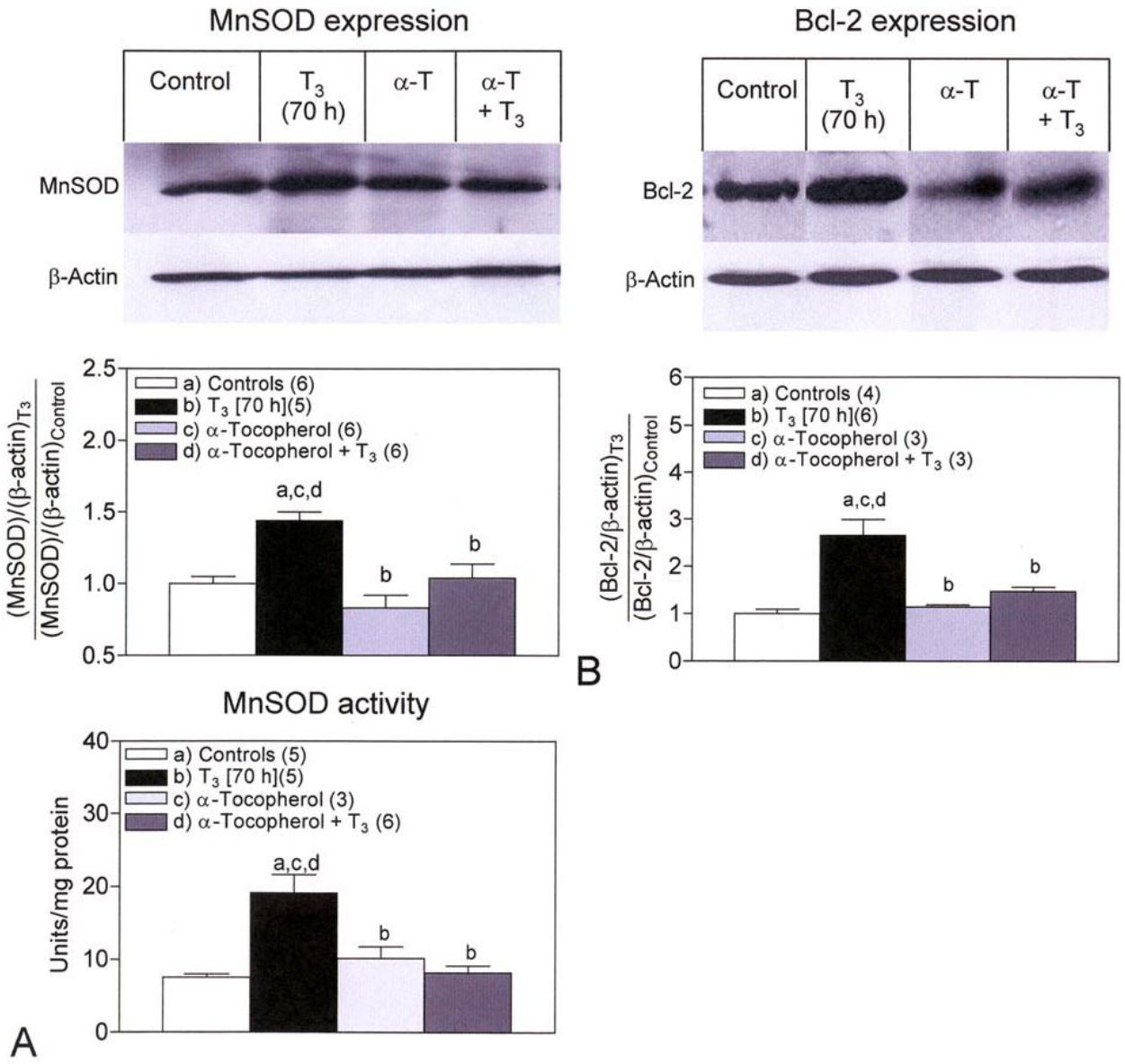

Figure 3. Influence of T_3 administration on liver (A) manganese superoxide dismutase (MnSOD) expression and activity and (B) Bcl-2 expression (Western blot) in the rat. Hormone administration was performed as shown in Figure 1 and studies were carried out at the indicated times as previously described (37). Data from control rats were set to unity, and values for T_3-treated rats were normalized to this. Each data point represents the mean ± SEM for the number of different animals shown in parentheses. Significance studies (one-way ANOVA and the Newman-Keuls test): $p<0.05$ as indicated by the different letters identifying each experimental group. Reproduced with permission from Society for Endocrinology (37).

5. CONCLUSIONS AND PERSPECTIVES

Recent data suggest that T_3 elicits the redox upregulation of gene transcription as a secondary mechanism of ROS induced by TH calorigenesis triggered by redox independent signal transduction pathways, namely, direct T_3-liganded TR interactions with TREs in DNA and/or indirect induction through activation of intermediate factors (Figure 5). Redox regulation of gene transcription by T_3 represents an additional nongenomic pathway to those proposed for the stimulation of plasma membrane transport and for the modulation of enzyme activities, mitochondrial processes, and signal transduction cascades (1-3, 7-10). Specifically, upregulation of hepatic iNOS, Mn-SOD, and Bcl-2 expression by T_3 may represent a defense mechanism by protecting the liver from cytokine-mediated lethality and ROS/RNS toxicity (Figure 5), which can be accomplished through different actions. (i) High levels of NO that are expected upon iNOS expression can scavenge O_2^-, to reduce the oxidation potential that damages biomolecules and activates NF-kappa-B, and reduce NF-kappa-B DNA binding by nitrosylation of NF-

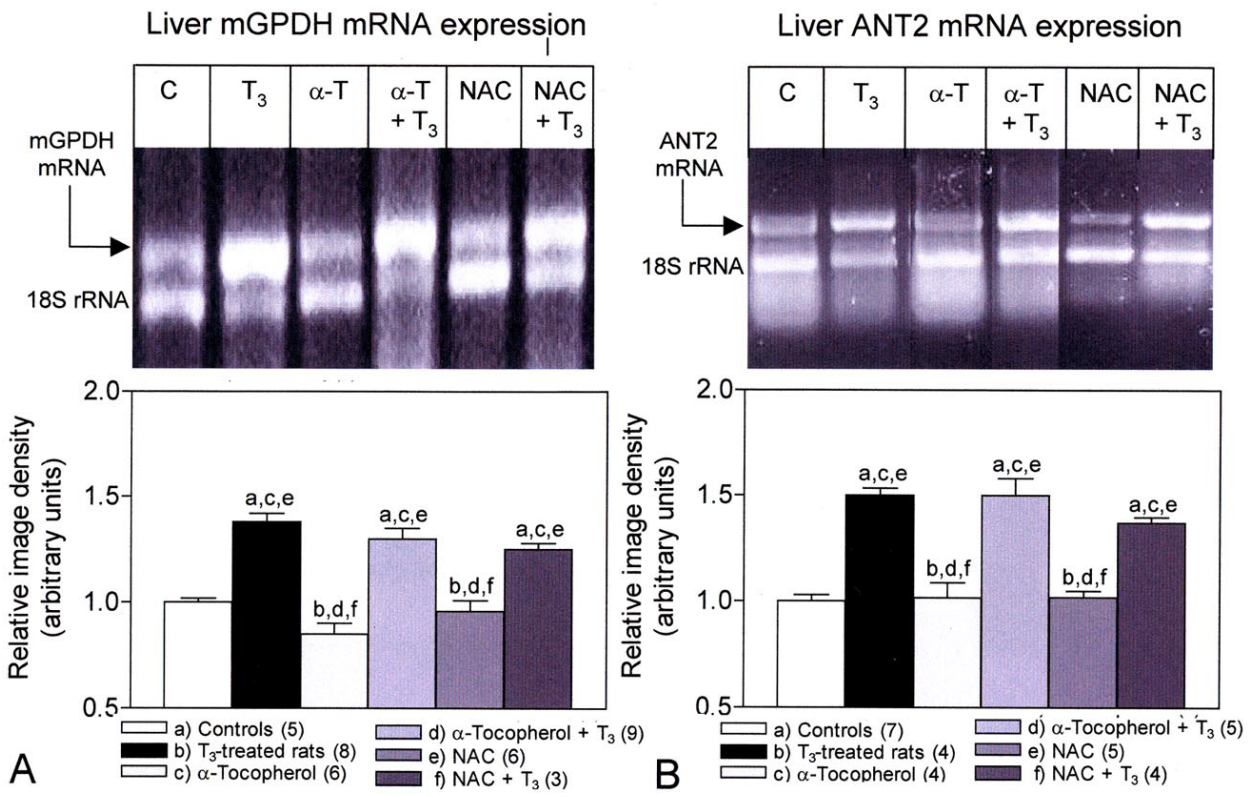

Figure 4. Rat liver mitochondrial glycerol-3-phosphate dehydrogenase mGPDH)(A) and adenine nucleotide translocator 2 (ANT2)(B) mRNA expression induced by T_3 administration under the influence of alpha-tocopherol (alpha-T) or N-acetylcysteine (NAC) pretreatment. Left panels show representative agarose gel electrophoresis of the reverse transcription-polymerase chain reaction (RT-PCR) products for mGPDH mRNA (604 bp) and 18S rRNA (489 bp) or ANT2 mRNA (600 bp) and 18S rRNA (324 bp) after ethidium bromide staining in total hepatic RNA samples from control rats (C), T_3-treated animals (0.1 mg T_3/kg) at 12 h (mGPDH) and 72 h (ANT2) after treatment, and separate groups of rats subjected to alpha-T (100 mg/kg 17 h prior to T_3) or NAC (1 g/kg 30 min prior to T_3) pretreatment. Right panels show the respective densitometric quantification of RT-PCR products of the mGPDH mRNA and ANT2 mRNA expressed as mGPDH/18S rRNA and ANT2 mRNA/18S rRNA ratios to compare lane-to-lane equivalency in total RNA content. Average data from control rats were set to unity, and values for the other groups were normalized to this. Data are means ± SEM for number of different animals shown in parentheses. Statistical studies ($p<0.05$ by one-way ANOVA and the Newman-Keuls test) are shown by the letters identifying each experimental group.

appa-B p50 and/or induction of the synthesis or stabilization of I-kappa-B (46); (ii) upregulation of Mn-SOD will increase O_2^- removal from mitochondria and the cytosol, whose production is enhanced by T_3 in liver mitochondria, microsomes, and cytosol (13, 15-17, 21), thus minimizing its reaction with NO and favoring the maintenance of high NO levels due to iNOS induction; (iii) upregulation of hepatic Bcl-2 will diminish apoptosis commitment and increase the antioxidant potential of the liver, the latter effect being ascribed to a higher intracellular availability of GSH (47), endogenous antioxidant that is substantially depleted by T_3 administration (5). Re-establishment of cellular redox homeostasis may also involve the upregulation of the T_3-responsive nuclear genes for UCP. Firstly, mild uncoupling by UCP decreases the mitochondrial membrane potential below a critical level, thus increasing QO_2 and reducing O_2^-/H_2O_2 generation (6); secondly, it was hypothesized that UCP may transport peroxidized insaturated fatty acid anions, in addition to native fatty acid anions, from the inner to outer side of the inner mitochondrial membrane, with the consequent diminution in the oxidative damage to mitochondrial proteins and DNA (48). Cellular defense mechanisms induced by TH also include the enhancement in O_2^- generation (10,49,50) and myeloperoxidase activity (10) in rat and human neutrophils, which are mediated by cell surface G protein-coupled TH receptors and signal transduction kinase activation.

The above observations, and the finding that the CBP/p300 complex activating liganded TR (Figure 5) can function as co-activator for various transcription factors including the redox-sensitive NF-kappa-B (2), suggest the integration of different genomic and nongenomic TH-signaling inputs to achieve redox balance under calorigenic conditions. These aspects may be assessed in the future along with the development of modern technologies such as

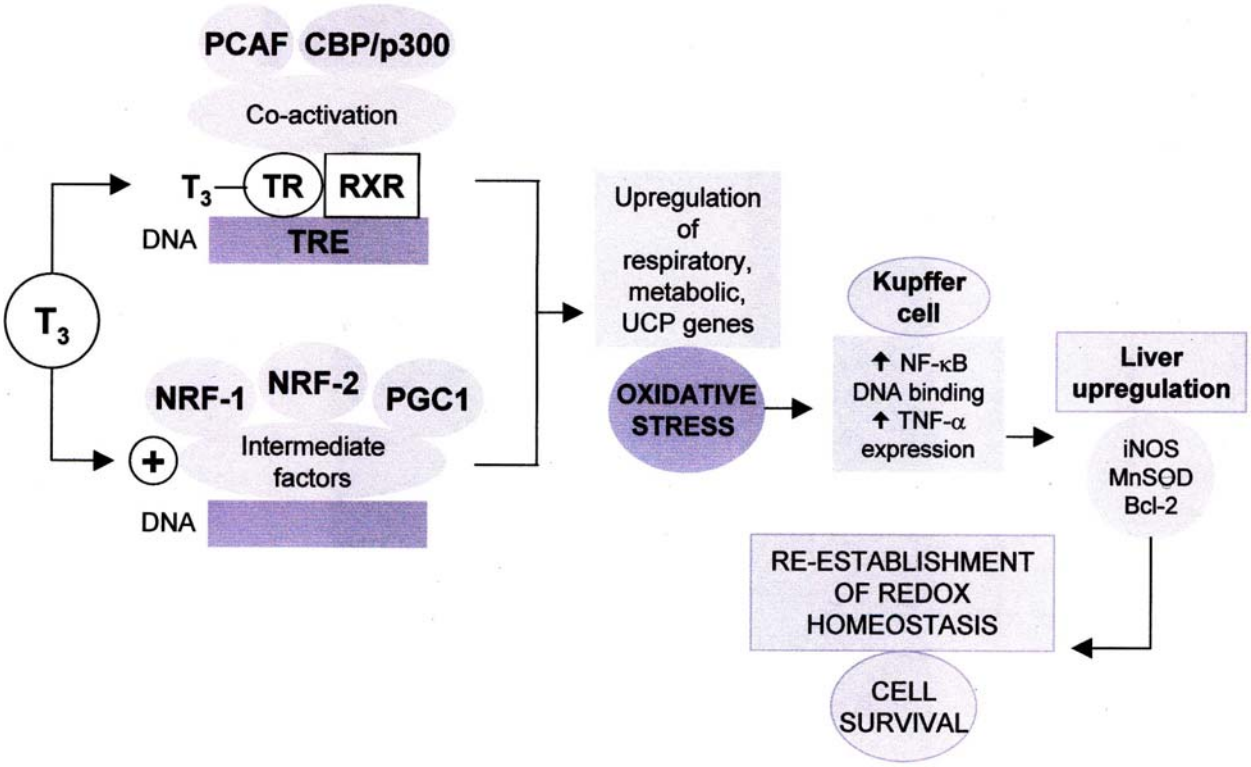

Figure 5. Relationship between T_3-dependent genomic mechanisms of transcriptional activation involving liganded thyroid hormone receptors and intermediate factors, O_2 metabolism, oxidative stress, and the redox regulation of gene transcription. Abbreviations: CBP, CREB binding protein; iNOS, inducible nitric oxide synthase; Mn-SOD, manganese superoxide dismutase; NF-kappa-B, nuclear factor-kappa-B; NRF-1(2), nuclear respiratory factor-1(2); p300, CBP related protein; PCAF, p300/CBP-associated factor; PGC1, peroxisome proliferator-activated receptor gamma coactivator-1; RXR, retinoic acid receptor; T_3, L-3,3',5-triiodothyronine; TNF-alpha, tumor necrosis factor-alpha; TR, thyroid hormone receptor; TRE, thyroid hormone response elements; UCP, uncoupling proteins.

microarrays, proteomics, and genetically engineered animal models.

In the scenario of the oxidative stress phenomenon, numerous important cellular processes and signaling cascades are activated through regulation of the function of a variety of enzymes and transcription factors determining transcriptional activation. Thus, the influence of TH on these regulatory processes merits further investigation to get a deeper understanding of the complexities of TH action and the outcome of thyroid gland dysfunction.

6. ACKNOWLEDGMENTS

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