Thyroid hormone (T_3)-induced liver oxidative stress and redox regulation of gene expression.

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T_3 exerts significant actions on energy metabolism, with mitochondria being the major target for its calorigenic effect. Acceleration of O_2 uptake by T_3 leads to an increased generation of reactive O_2 and nitrogen species in the liver, with a higher consumption of cellular antioxidants and inactivation of antioxidant enzymes, thus inducing oxidative stress. This redox imbalance is further contributed by an enhanced respiratory burst activity in Kupffer cells, which may activate redox-sensitive transcription factors. T_3 elicited an 80-fold increase in the levels of TNF-α in serum, which is abolished by pretreatment with α-tocopherol and N-acetylcysteine, the Kupffer cell inactivator $GdCl_3$, or an antisense oligonucleotide against TNF-α. In addition, T_3 administration activates hepatic NF-κB, a response that is (i) inhibited by antioxidants and $GdCl_3$ and (ii) accompanied by induced expression of the NF-κB-responsive genes for TNF-α, IL-10, iNOS, MnSOD, and Bcl-2, through a cascade involving IκB-α phosphoryla-tion. In conclusion, T_3-induced oxidative stress triggers the redox upregulation of specific genes through a cascade initiated by TNF-α produced by Kupffer cells and involving IKK and NF-κB activation, a response that may represent a defense mechanism by protecting the liver from cytokine-mediated lethality and free-radical toxicity (Supported by grant 1030499 from FONDECYT, Chile).