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REVIEW ARTICLE

Thyroid Hormones and Oxidative Stress

Vikram Kesar

ABSTRACT

Thyroid hormones have a pro-oxidant effect and cause increased lipid peroxidation. Lipid peroxidation is an extremely damaging process implicated in many diseases and could be a causative factor, responsible for the varied systemic manifestations of hyperthyroidism, like myopathy and myocardial insufficiency. The activities of antioxidant scavenging enzymes like erythrocyte superoxide dismutase, catalase, and glutathione peroxidase, which prevent lipid peroxidation, are also significantly affected by hyperthyroidism and hypothyroidism. Further, it has been observed in various studies that hypothyroidism does induce changes in free radical scavenging enzymes opposite to those observed in hyperthyroidism. Oxidative injury, therefore, is an important mechanism in the pathophysiology of hyperthyroidism.

Keywords: Antioxidant enzymes, Hyperthyroidism, Hypothyroidism, Lipid peroxidation, Oxidative stress.

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INTRODUCTION

It is well established that thyroid hormones accelerate the basal metabolic rate and oxidative metabolism by causing an increase in the mitochondrial mass, cytochrome content, and respiratory rate, without an uncoupling effect on the oxidative phosphorylation, in the target tissues. One of the major effects of thyroid hormones is to increase mitochondrial respiration. The increased respiration is caused by many complex changes in the number and activity of mitochondrial respiratory components; such changes include increase in the concentration of electron transport components, such as ubiquinone.[1]

EFFECT OF THYROID HORMONES ON OXIDATIVE STATUS

Enhanced mitochondrial electron transport brought about by thyroid hormone induced hypermetabolic state results in the increased generation of superoxide at the site of ubiquinones. Mitochondrial ubiquinone serves as a coenzyme for the cytochrome b c complex and is an essential component of the electron transport chain. It functions as both an electron and a proton carrier and scavenges peroxy radicals and hydroxy radicals from the mitochondrial membrane. Thyroid hormones affect mitochondrial respiration by altering the concentration of the components of the electron transport chains as well as by altering the redox state of the components.[2]

Accumulating evidence has suggested that a hypermetabolic state in hyperthyroidism may accelerate free radical production in the mitochondria and induce changes in the antioxidant defense system. It has been demonstrated in experimental hyperthyroidism in rats that mitochondrial oxidative metabolism and level of lipid peroxide determined as thiobarbituric acid reactive substances are increased in a parallel manner in the heart and slow oxidative soleus muscle. Superoxide dismutase (SOD) was also increased in heart and soleus muscle. The activities of both glutathione peroxidase (GPX) and catalase (CAT) were found to be decreased in all the hyperthyroid tissues (heart, slow oxidative soleus muscle, liver, kidney, fast glycolytic extensor digitorum longus muscle).[3]

In another study it has been shown in rats that hyperthyroidism could enhance mitochondrial oxidative metabolism in slow oxidative muscle (soleus and heart). This was associated with increase in SOD and lipid peroxidation in these tissues. However, hypothyroidism suppressed oxidative metabolism in soleus, extensor digitorum longus, and heart and decreased SOD in soleus and heart. On the contrary, GPX was decreased in hyperthyroidism and was either normal or high in hypothyroidism in all tissues studied. Similarly, CAT tended to be low in hyperthyroidism and high in hypothyroidism in most of the tissues. Similarly, the changes in tissue levels of malondialdehyde (MDA) mimicked those in levels of the enzymes localized in mitochondrial matrix (SOD and fumarase).[1]

ln yet another study, levels of free radical scavengers (CAT, GPX, and SOD) were measured in the heart muscles of rats rendered hyper or hypothyroid. The GPX levels in the heart muscle were observed to be reduced in hyperthyroid rats but increased in hypothyroid rats. The concentration of SOD in heart muscle

Junior Specialist

Department of Biochemistry, Rao Tula Ram Memorial Hospital New Delhi, India

Corresponding Author: Vikram Kesar, Junior Specialist Department of Biochemistry, Rao Tula Ram Memorial Hospital New Delhi, India, Phone: +919650490014, e-mail: vikramkesar@hotmail.com

was increased in hyperthyroid rats and was unchanged in hypothyroid rats.[2]

One study examined the effect of experimental hyper- and hypothyroidism on the SOD, CAT, and GPX activities of rat lymphoid organs (mesenteric lymph nodes, spleen, and thymus) and muscle (soleus and gastrocnemius). Hyperthyroidism tended to enhance lipid peroxide content in all tissues. The activity of CAT was found to be reduced in the lymphoid organs and GPX was found decreased in the muscle. Hypothyroidism tended to diminish lipid peroxidation. Low levels of thyroid hormones tended to diminish SOD and GPX activities. The CAT activity was reduced in the lymphoid organs and increased in the gastrocnemius and soleus muscles when the rats were hyperthyroid, whereas hypothyroidism lowered CAT activity in the thymus.[4]

The GPX activity and MDA levels were measured in the homogenated anterior segment of rat eyes in euthyroid, hyperthyroid, and hypothyroid rats. The MDA concentrations were found to be increased and GPX activities decreased in the hyperthyroid group. The MDA concentrations of the hypothyroid rat eyes were higher than controls.[5]

The behavior of lipid peroxide and free radical scavengers was studied in the cerebral cortex of rats made hyper or hypothyroid. The concentration of MDA was decreased and concentrations of SOD, GPX, and CAT were increased in the cerebral cortex of hyperthyroid rats. The activities of SOD and GPX were increased in hypothyroid rats.[6]

In a study in humans, the levels of erythrocyte CAT have also been determined in patients with thyroid dysfunction. In hyperthyroid patients erythrocyte CAT activity was found to be higher than normal subjects.[7] These studies give sufficient evidence that a change in the thyroid status will affect the oxidative state by changing the balance between the pro-oxidants and antioxidants.

Thyrotoxic myopathy and myocardial insufficiency are well-known examples of tissue damage due to the direct action of thyroid hormones on target tissues. The pathophysiological basis of these abnormalities is not clear. It is possible that stimulation of mitochondrial respiration by thyroid hormones results in oxidative tissue injury secondary to increased production of active oxygen species. Various muscular injury models in which reactive oxygen species are found to play a role provide evidence that mitochondrial function and antioxidant systems are important for the maintenance of the structural and functional integrity of muscular tissues. Thyroid hormones accelerate mitochondrial oxidative metabolism and also lipid peroxidation, both of which are prevented by certain types of beta adrenoceptor blocking agents namely atenolol. Thus hyperthyroid muscles demonstrate similar biochemical derangements found in other oxidative muscular injury models and these are at least partially prevented by the suppression of oxidative metabolism and a chain breaking antioxidant vitamin E. Hyperthyroidism is associated with impaired functional cardiac reserve. The myocardial dysfunction can precipitate congestive heart failure. It is hypothesized that in hyperthyroidism increased lipid peroxidation occurring in mitochondria can reduce respiratory capacity and calcium transport and cause cardiac arrythmias.[1] Central nervous system dysfunctions, such as irritability, seizure, and pyramidal track dysfunction have been observed in hyperthyroidism while brain dysfunctions, such as coma, cerebellar ataxia, and dementia have been observed in hypothyroidism. Thyroid hormones are known to affect the activity of the mitochondrial enzyme monoamine oxidase present in the brain and also the oxidation the neurotransmitter dopamine.[8] Free radicals produced during the oxidation of dopamine might induce damage in the brain of hyper or hypothyroid patients, as reported in patients of Parkinson's disease.[9]

Thyroid hormones are known not only to promote the synthesis of certain specific proteins, such as mitochondrial enzymes but also enhance the protein degradation. The latter has been reported to occur via activation of lysosomal enzymes.[10] The changes in the level of antioxidant enzymes in hypo- and hyperthyroid state may be at least partially ascribable to the effect of thyroid hormones on protein synthesis and degradation. Thyroid hormones are known to increase the synthesis of myosin, a major structural protein. In experimental hyperthyroidism, certain organs (i.e., heart and kidneys) undergo hypertrophy due to increase in the rate of protein synthesis. There are studies implicating the role of thyroid hormones in bringing about changes in various enzyme system. Elevated activity of erythrocyte glucose-6-phosphate dehydrogenase in patients with thyrotoxicosis has been observed.[11] A decrease in the levels of human erythrocyte carbonic anhydrase has been reported in patients with hyperthyroidism.[12] Recent investigations point out the significant role of oxidative stress in the development of thyroid gland disease. A study designed to investigate the variation of oxidative state in women with non-autoimmunological subclinical hyperthyroidism found increased extracellular SOD plasma activity and parallel increase of MDA plasma concentration, indicating enhancement of lipid peroxidation in patients with subclinical hyperthyroidism that reflects disturbances of oxidative state in these patients.[13] A study evaluated and compared the oxidative profiles of three thyroid disorders: Graves' disease, Hashimoto's thyroiditis, and

papillary thyroid cancer by measuring MDA levels, GPX, SOD, and CAT activities in the plasma of 52 patients. The results clearly showed an oxidative profile that was highly disturbed for the papillary thyroid cancer patients as compared with those of autoimmune disorders.[14] Another study concluded that goiter is associated with increased oxidative stress; oxidative stress is a required condition for the growth of the thyroid gland.[15] A study aimed to elucidate the effect of 6-n-propylthiouracil (PTU)-induced hypothyroidism on oxidative stress parameters and expression of antioxidant enzymes in cerebral cortex of rat brain during postnatal development. It found a significant decrease in levels of lipid peroxidation in 7- and 30-day-old PTU-treated hypothyroid rats with respect to their controls. Significantly decreased activities of SOD and CAT were observed in 7, 15, and 30 day-old PTU-treated hypothyroid rats as compared with their respective controls. Glutathione peroxidase activity was decreased in 7-day-old and increased in 15-day-old PTU-treated hypothyroid rats with respect to their control groups.[16] A study determined the antioxidant status in overt hypothyroidism (OHT) and subclinical hypothyroidism. The MDA and GPX values were elevated, while GSH, SOD, and SOD/GPX ratio were decreased in both patient groups compared with controls. Thus, hypothyroid patients have a deficient antioxidant defense in the form of decreased activity of SOD, decreased GSH along with an increase in GPX activity, and the severity of the disease appeared to decide the degree of deficiency since the decrease in SOD and GSH was observed more in OHT than in subclinical hypothyroidism. Hormonal changes and increased lipid peroxidation, which also varied with the severity of disease, appeared to contribute to the antioxidant deficiency.[17] A study demonstrated substantial reduction in serum glutathione status in Hashimoto thyroiditis subjects. Data from this study supported the notion that serum glutathione diminution is a hallmark of the events leading to oxidative stress activation and the development of immunological intolerance in Hashimoto thyroiditis.[18] Another study elucidated the role of metabolic remodeling in cardiac dysfunction induced by hyperthyroidism. Cardiac hypertrophy, structural remodeling, and expression of the genes associated with fatty acid metabolism were examined in rats treated with triiodothyronine (T3). Ultrastructure of mitochondria was damaged in T3-treated rat heart and hyperthyroidism induced oxidative stress caused a reduction in cytochrome c oxidase activity and myocardial adenosine triphosphate concentration. Heart function studied at different time points during the course of T3 treatment showed an initial improvement and then a gradual but progressive decline with time. In summary, the results demonstrated that hyperthyroidism inflicts structural and functional damage to mitochondria, leading to energy depletion and cardiac dysfunction.[19]

CONCLUSION

It is possible that different regulation of antioxidant enzymes and different extent of lipid peroxidation observed in hypo- and hyperthyroid states is responsible for the different manifestations and varied pathophysiology of hypo- and hyperthyroidism seen in various thyroid disorders.

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