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# Effects of thyroid hormone on testicular functions and antioxidant defence status

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## ABSTRACT

Thyroid hormone plays a vital role in regulating differentiation, growth, cognitive development, metabolism and physiological functions of virtually all tissues of vertebrates. Mammalian testis is a target of thyroid hormone action and altered thyroid status is well known to modify testicular functions. Hyper-metabolic state resulted in hyperthyroidism consequences in increase in free radical production. As, testis is very rich in polyunsaturated fatty acids with poor antioxidant defense system, it is much more vulnerable to oxidative damage in compared to other tissues. Altered testicular antioxidant defence system by hyper- and hypothyroidism keeps testis under oxidative stress in consequence influencing its physiology.



## KEYWORDS

Thyroid hormones;
Testes;
Antioxidant defence system;
Oxidative stress.

## INTRODUCTION

In recent years, there has been a growing concern regarding the progressive decline in male fertility. Male fertility markers have been scrutinized in order to understand the molecular events that can direct sub-fertility or infertility and permit an accurate diagnosis and design of therapeutic protocols. Among these markers, oxidative stress and antioxidant defence status in testis as well as semen has emerged as a promising field[1-8]. Thyroid hormones are well known to regulate steroidogenesis and spermatogenesis, thereby, affecting male fertility[9, 10]. Hence, its role in regulating testicular antioxidant defence system and thereby influencing the testicular physiology can not be ruled out.

## THYROID HORMONES AND TESTIS

Thyroid hormones play a vital role in regulating differentiation, growth, cognitive development, metabolism and physiological functions of virtually all tissues of vertebrates[11, 12]. Most vertebrates are unable to grow and reach their normal adult form without the hormone[13, 14]. The normal thyroid gland produces about 80% thyroxine ($T_4$) and about 20% triiodothyronine ($T_3$), however, $T_3$ possesses about four times the hormone "strength" as $T_4$. This is the biologically active form of the hormone[15]. In adults, the most vital effect attributed to thyroid hormones, is their influence on metabolic rate and the oxygen consumption of nearly all tissues[16].

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The testis was considered for years to be a thyroid hormone (TH) unresponsive tissue[17]. However, various subsequent studies revealed that TH plays an important role in rat testis development. Thyroid hormone is very much essential for the functional development of the reproductive tract[18]. It plays an important role in the regulation of growth and differentiation of the somatic cells of the seminiferous epithelium[19] that in turn influences gametogenesis[20]. Thyroid hormone is associated with abnormal sexual function and infertility[9, 21-25]. Testicular 5'-deiodinase (5'-D) is suggested to be a key factor in regulating local supply of biologically active $T_3$, and an essential factor in testicular paracrine function in growing piglets[26].

Mammalian testis is a target of thyroid hormone action and altered thyroid function is known to modify testicular functions[9, 25]. Triiodothyronine receptors (TRs) have been identified in sperm, developing germ cells, Sertoli, Leydig, and peritubular cells[27]. However, receptors for $T_3$ are highly expressed in rat Sertoli and Leydig cells before puberty[28, 29] indicating that thyroid hormones appear to have an inhibitory effect on the proliferation of Sertoli cells but stimulate their differentiation[30-33]. Responsiveness of adult rat testis to $T_3$ has been confirmed by the presence of TR-α1 mRNA and a protein that not only affects the differentiation and development, but also modulates the metabolism of tubular cells[34]. Thyroid hormone is known to modulate cyclin-dependent kinase inhibitors (CDKI) p27(Kip1) and p21(Cip1) which plays a critical role in establishing Sertoli cell number, testis weight, and daily sperm production[35, 36].

Earlier studies have shown that thyroid hormone plays an important role in rat testis development by inducing Sertoli cell differentiation[37] and also regulates the differentiation of Leydig cells in neonatal rat testis[38]. Morphological and functional development of the testis has also been shown to be dependent upon thyroid hormone by various workers[9, 19, 39].

Gonad-specific transporter GST-1 and GST-2 molecules for transporting thyroid hormones ($T_3$ and $T_4$) are highly expressed in the rat testis; especially in Sertoli cells, spermatogonia, and Leydig cells as revealed by Northern blot analyses and *in situ* hybridization[40]. Thyroid hormone is also known to regulate connexin 43 (Cx43)-dependent gap junctional communication in the testis and epididymis[41]. Thyroid hormone is responsible for triggering the onset of mesenchymal precursor cell differentiation into Leydig progenitor cells, proliferation of mesenchymal precursors, acceleration of the differentiation of mesenchymal cells into Leydig cell progenitors, and enhances the proliferation of newly formed Leydig cells in the neonatal rat testes[42]. TRα1 is expressed in proliferating Sertoli cell nuclei and the decrease in its expression coincides with the cessation of proliferation[43]. TRα1 is also expressed in germ cells from intermediate spermatogonia to mid-cycle pachytene spermatocytes. The demonstration of TR expression in germ cells undergoing spermatogenic differentiation suggests a possible role for thyroid hormones in the adult testis[43].

## HYPERTHYROIDISM ON TESTICULAR FUNCTIONS

Hyperthyroidism affects both the male reproductive function and testicular development. Hyperthyroid condition leads to a reduced sperm number[4, 6, 7] and motility[9] that improves under euthyroid condition[44]. Administration of $T_3$ to hypothyroid rats improves body and testis growth and restores both cytochrome oxidase activity and ATP content[25]. Other effect of hyperthyroid condition includes gynecomastia, decrease in libido, reduction in testicular volume and abnormalities in metabolism of androgen and estrogen leading to an increased concentration of testosterone, dihydrotestosterone and estradiol[45]. Hyperthyroidism in male modifies the hypothalmo-hypophyseal-testicular axis and affects steriodogenesis[46, 47]. It has also been reported that under hyperthyroid state there is an alteration in the glycoprotein metabolism in the accessory sex glands that might be linked to impaired fertility[48].

## HYPERTHYROIDISM ALTERS SERTOLI CELL POPULATION AND PHYSIOLOGY

Triiodothyronine regulates Sertoli cell proliferation and differentiation in the neonatal testis[49]. Thyroid hormone directly affects the regulation of follicle-stimulating hormone receptor (FSH-R) and an-

drogen binding protein (ABP) gene expression in Sertoli cells[50]. Thyroid hormone is known to stimulate glucose transport as well as erythrocyte/brain glucose transporter isoform (GLUT1) mRNA level in rat Sertoli cells[51]. Although, glucose transporters GLUT1 and GLUT8 both are expressed in prepubertal testis, only GLUT1 is regulated by $T_3$[52]. Hyperthyroidism induces premature cessation of Sertoli cell proliferation[53]. The $T_3$ inhibition of neonatal Sertoli cell proliferation may be through Cx43 (connexin 43), a constitutive protein of gap junctions[49]. Effects of exogenous manipulation of $T_3$ on neonatal Sertoli cell development are predominately mediated through TRα1[53]. The human testis exclusively expresses TRα, which is localized in Sertoli cells whereas TRβ is always undetectable. Fetal and prepubertal ages represent the period of maximal expression of TRα1 and TRα2 and the α2/α1 ratio rises dramatically after development[54]. $T_4$ and $T_3$ stimulate amino acid accumulation and protein synthesis in Sertoli cells through eliciting a hyperpolarization of the Sertoli cell membrane potential involving K(+) channels[55, 56]. Down-regulation of neural cell adhesion molecule (NCAM)-based intercellular adhesion during postnatal maturation is important for differentiation of testicular cells and $T_3$ is identified as a regulator of NCAM expression in neonatal testicular cells and as a modifier of gonocyte/Sertoli cell adhesion in vitro[57]. Tri-iodothyronine stimulates Sertoli cell mRNA expression of inhibin-alpha, androgen receptor, IGF-I, IGFBP-4, protein synthesis (+55%) and lactate (+50%) production, while it inhibits mRNA expression of Mullerian inhibiting substance (MIS), estradiol receptor, ABP, ABP secretion, DNA synthesis (-30/35%) and aromatase activity (-45/50%)[20, 27]. The binding of the thyroid hormone/thyroid receptor alpha1 complex to the steroidogenic factor-1 (SF-1) motif is the molecular mechanism by which $T_3$ exerts an inhibitory effect on aromatase gene expression[58].

Short-term experimental hyperthyroidism induces Sertoli cell differentiation[37]. Further it has been observed that $T_3$ up-regulates androgen receptors in peripuberal Sertoli cells and has a role in influencing the androgen responsiveness of the Sertoli cells during spermatogenesis[59].

## HYPERTHYROIDISM ALTERS LEYDIG CELL AND STEROIDOGENESIS

A direct stimulatory effect of $T_3$ on basal production of testosterone and estradiol by Leydig cells is reported[60]. $T_3$ directly increases Leydig cell LH receptor numbers and mRNA levels of steroidogenic enzymes and steroidogenic acute regulatory protein[50]. $T_3$ also stimulates basal and LH-induced secretion of progesterone, testosterone, and estradiol by Leydig cells and steroidogenic factor-1 acts as a mediator for $T_3$-induced Leydig cell steroidogenesis[27]. Thyroid hormones cause proliferation of the cytoplasmic organelle peroxisome, stimulate the production of steroidogenic acute regulatory protein (StAR) and StAR mRNA expression in Leydig cells. Both peroxisomes and StAR are linked with the transport of cholesterol, the obligatory intermediate in steroid hormone biosynthesis, into mitochondria[10, 61]. Hyperthyroidism stimulates premature hypotrophy of fetal Leydig cells (FLCs) and early differentiation of increased numbers of mesenchymal cells (MCs) to adult Leydig cells (ALCs) in the prepubertal rat testis[62]. Out of all cell types in the testis, the thyrotropin releasing hormone (TRH), TRH mRNA and TRH receptor are present exclusively in Leydig cells[10, 63].

## HYPOTHYROIDISM ON TESTICULAR GERM CELLS AND FUNCTIONS

Alteration in thyroid activity is frequently associated with changes in male reproduction and hypothyroidism hinders the sexual maturation and development. The structural organization of testis as well as testicular physiology alters in response to different durations of hypothyroid condition. Hypothyroidism has been known to affect various parameters like size and weight of testes[8, 24, 64], germ cell population[5, 8, 32], growth and maturity of the testis[22, 65], serum testosterone level, morphology and anatomy of the organ[8, 19, 66-67]. Thyroid deficiency during development affects testis growth and maturation deleteriously marked by reduction in seminiferous tubule diameter, germ cell number per tubule, increased degeneration and arrested maturation of germ cells[8, 65]. Neonatal hypothyroidism causes arrest of germ cell proliferation and differentiation and

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reduction of germ cell number and levels of plasma testosterone, estradiol and sex hormone binding globulin (SHBG) in rat[68]. Juvenile hypothyroidism/neonatal transient hypothyroidism causes a delayed differentiation of Sertoli cells, an increase in Sertoli, Leydig, and germ cell number resulting in enlargement of adult rat testis and an elevation of daily sperm production[8, 27, 30]. Moderate neonatal hypothyroidism stimulates the proliferation of Leydig cells and increases their number to almost double with normal testicular weight[69]. However, congenital hypothyroidism causes infertility and enlarged testes in adulthood demonstrating that a sufficient circulating thyroid hormone level from the immature stage plays a pivotal role in restoring mating activity, probably through FSH-mediated action towards adulthood[70]. Thyroidectomy (permanent lack of thyroid hormones) causes a depression in seminiferous tubule growth marked by reduced outer and luminal diameters and area occupied by the seminiferous epithelium due to both the inability of Sertoli cells to support spermatogenic cells and the diminished levels of GH and FSH[71]. Severe neonatal hypothyroidism impairs the development and function of the testes marked by decreased testis weight, Leydig cell number reduction and only a single layer of spermatogonia due to spermatogenic arrest[69, 72]. Persistent hypothyroidism diminishes the bioavailability of androgens and oestrogens, while transient hypothyroidism enhances the same, indicating the importance of euthyroidism during foetal and neonatal period towards the maintenance of optimal hormonal status in the epididymis required for its maturation[73]. Hypothyroidism induces type-2 iodothyronine deiodinase expression in mouse testis[74].

Hypothyroidism induces atrophy of testes and reduced testosterone levels[9, 25, 75]. The neonatal hypothyroidism-induced changes in rat testis size, is also temperature dependent[76]. The transient neonatal hypothyroid rats maintained at $34^0$C temperature show lower testis mass, increased germ cell degeneration, and reduced tubular size, germ cell numbers and sperm density. In contrast, the transient neonatal hypothyroid rats (maintained under $21^0$C temperature) have higher testis mass, lower body mass, increased tubular diameters, germ cell numbers and sperm density[76]. There have been varied reports on the level of LH and FSH in male rats under hypothyroid condition. While it was found to decrease in hypothyroid male rats with intact gonads[77-79], it was recorded to be elevated in castrated male rats[78]. Further treatment of hypothyroid rats with thyroxine either restored[78] the LH level to normal or failed to do so[77]. On the contrary, it has been reported that the serum LH and testosterone level decreases after thyroxine treatment[46].

## HYPOTHYROIDISM ALTERS LEYDIG CELL POPULATION AND STEROIDOGENESIS

Onset of neonatal hypothyroidism adversely affects Leydig cell proliferation, differentiation along with impaired steroidogenesis[38, 80]. *In vitro* studies of Leydig cells from hypothyroid rats suggest less production of testosterone, both spontaneously as well as in response to cAMP and non-cAMP-mediated stimuli[81]. The serum and intratesticular testosterone, the specific activities of Leydig cell 3 beta- and 17 beta-hydroxysteroid dehydrogenases and cAMP diminish in hypothyroid rats[82]. The inhibitory mechanism of hypothyroidism on testosterone production involves a decreased activity of 17beta-hydroxysteroid dehydrogenase (17beta-HSD) and post-cAMP pathways in testicular interstitial cells[83] or by inhibiting mRNA expression of the steroidogenic acute regulatory protein and cytochrome P450 side chain cleavage enzyme (P450scc) function[84]. The decreased plasma testosterone concentration in hypothyroid condition may point towards a decrease in the binding affinity of testosterone binding protein, increase in the metabolic clearance rate and an increased conversion to androstenedione[45].

## HYPOTHYROIDISM ALTERS SERTOLI CELL POPULATION AND ITS PHYSIOLOGY

Neonatal hypothyroidism increases adult Sertoli cell populations by extending Sertoli cell proliferation[53, 72] while continuous hypothyroidism from birth reduces Sertoli cell number[72]. TH modifies nucleoside triphosphate diphosphohydrolase (NTPDase) activities in hypothyroid Sertoli cells, probably via nongenomic mechanisms marked by unaltered Sertoli cell NTPDase 1, 2 and 3 expressions in hypothyroidism. Sertoli cell culture studies from congenital hypothyroid rats show a decrease in extracellular ATP and ADP hydrolysis with-

out effecting AMP hydrolysis[85].

## THYROID HORMONES, OXIDATIVE STRESS AND TESTES

Thyroid hormones play a crucial role in increasing the basal metabolic rate and the energy metabolism of tissues in several mammalian species[86]. Hypermetabolic state in hyperthyroidism results in increase in free radical production[87-90]. Testis is very rich in polyunsaturated fatty acids and has poor antioxidant defense system[91]. Hence, it is much more vulnerable to oxidative damage than other tissues.

## ANTIOXIDANT DEFENCE SYSTEM

Aerobes protect themselves from the oxidative stress generated due to the ROS by neutralizing them by their well-evolved antioxidant defences[92]. Testicular cells are well equipped with both small molecular weight antioxidants (reduced glutathione, ascorbic acid, vitamin E, uric acid, ubiquinone and carotenoids etc) and antioxidant enzymes (superoxide dismutase (SOD); catalase (CAT); glutathione peroxidase (GPx); glutathione reductase (GR); glutathione S-transferase (GST) etc), that efficiently neutralize ROS (Figure 1). Superoxide dismutase (SOD) dismutates superoxide radicals into hydrogen peroxide ($H_2O_2$), which in turn is efficiently neutralized by catalase (CAT) and glutathione peroxidase (GPx). GSH is the major non-enzymatic antioxidant and the most abundant non-protein thiol source of cell[93, 94] and serves as the substrate for glutathione peroxidase (GPx) as well as glutathione S-transferase (GST). Glutathione peroxidase (GPx) oxidizes GSH to GSSG and GSSG is reduced back to GSH by glutathione reductase (GR)[92] (Figure 1). Cells with high level of intracellular GSH are protected against oxidative damage caused by ROS. GSH either non-enzymatically reacts with ROS[95] or directly scavenges them by neutralizing OH[96].

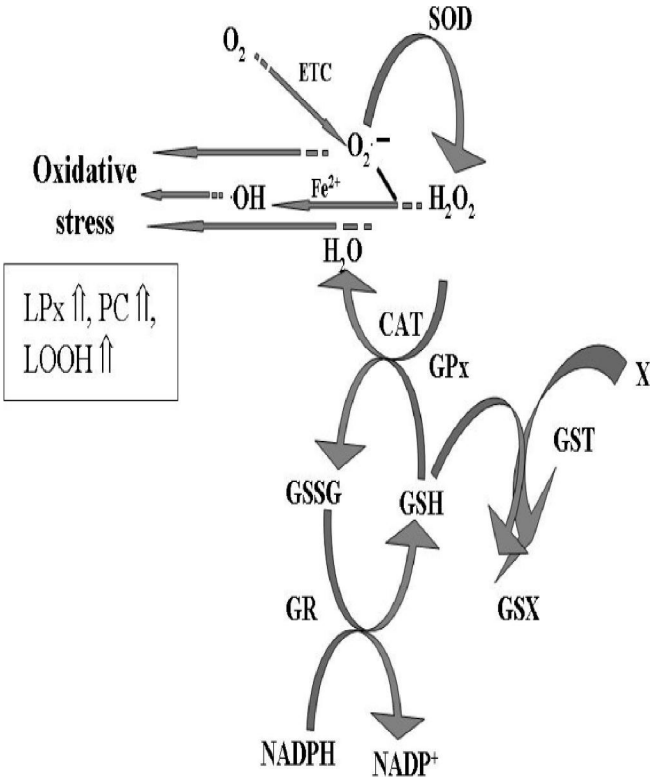


**Figure 1 : Antioxidant defence system and oxidative stress parameters. LPx, lipid peroxide; PC, protein carbonyl; $H_2O_2$, hydrogen peroxide; LOOH, lipid hydroperoxide; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; GSH, reduced glutathione; GSSG, oxidized glutathione, $O_2^{\cdot-}$, superoxide radical, X, Xenobiotics; GSX, Glutathione-Xenobiotics Conjugate; ⇑, arrows indicating elevation.**

## ALTERATION OF TESTICULAR AODS BY HYPERTHYROIDISM

Tissues in hyperthyroid rats exhibit high vulnerability to oxidative challenge[87, 90]. L-thyroxine[7, 97, 98] or tri-iodothyronine[2, 4, 6] was administered in rats to induce hyperthyroidism experimentally and oxidative stress parameters as well as antioxidant defence profile were measured.

### a) Oxidative stress parameters

Most of these studies confirm the increase of testicular oxidative stress as marked by elevated MDA levels[97], TBARS, lipid hydroperoxide, hydrogen peroxide or protein carbonyl contents[2, 4, 6, 7] (Figure 2 and TABLE 1). However, hyperthyroid rats fed with vitamin E and or curcumin results in decreased oxidative stress marked by reduced lipid peroxide and protein carbonyl contents[7].

### b) Antioxidant defence parameters

Interestingly while short-term thyroxine administration to hypothyroid rats causes an increased testicular

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**TABLE 1 : Different thyroid states i.e. hypo-and hyperthyroidism regulating testicular antioxidant defence status. $T_3$, tri-iodothyronine; LPx, lipid peroxide; PC, protein carbonyl; $H_2O_2$, hydrogen peroxide; LOOH, lipid hydroperoxide; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; GSH, reduced glutathione; ⇑, indicating elevation; ⇓, indicating decline; ⇔, denoting no change; —, not reported.**

| | | Hypothyroid | | Hyperthyroidism | |
|---|---|---|---|---|---|
| | | Persistent | Transient | L-thyroxine induced | $T_3$ induced |
| Oxidative stress parameters | LPx | ⇑ | ⇔ | ⇑ | ⇑ |
| | PC | ⇑ | ⇔ | ⇑ | ⇑ |
| | $H_2O_2$ | — | — | ⇑ | ⇑ |
| | LOOH | — | — | — | ⇑ |
| Antioxidant defence parameters | SOD | ⇑ | ⇓ | ⇓ | ⇓ |
| | CAT | ⇑ | ⇓ | ⇓ | ⇑ |
| | GPx | ⇓ | ⇓ | ⇑ | ⇔ |
| | GR | ⇓ | ⇓ | ⇑ | ⇑ |
| | GST | ⇓ | ⇔ | ⇑ | ⇓ |
| | GSH | ⇓ | ⇔ | ⇓ | ⇑ |
| | Ascorbic acid | — | — | — | ⇑ |

GSH contents[98], $T_3$ treatment for three days to hypothyroid rats causes an elevation of oxidized (GSSG) and a decline in reduced (GSH) glutathione contents resulting in a decreased reduced to oxidized glutathione ratio[2]. Furthermore, $T_3$ injection to PTU-treated rats elevates catalase and decreases glutathione peroxidase activity in post-mitochondrial fraction without altering superoxide dismutase and glutathione reductase activities in testicular post-mitochondrial fractions[2]. In contrast, during acute hyperthyroid state, testis exhibits lower SOD activity and higher activities of CAT, GPx, GR, G6PD and GSH[4, 6]. Moreover, L-thyroxine induced hyperthyroid rats also exhibit decreased testicular SOD, CAT activities with elevated GPx activity[7]. Hyperthyroid rats given with vitamin E and/ or curcumin show elevated testicular SOD and CAT activities. However, curcumin or vitamin E is unable to change testicular GPx activity alone but in together they elevate the GPx activity in L-thyroxine treated rats[7]. Similarly, it has been shown that, melatonin; an antioxidant decreases hyperthyroid induced testicular oxidative stress to some extent with increasing testicular glutathione contents[97].

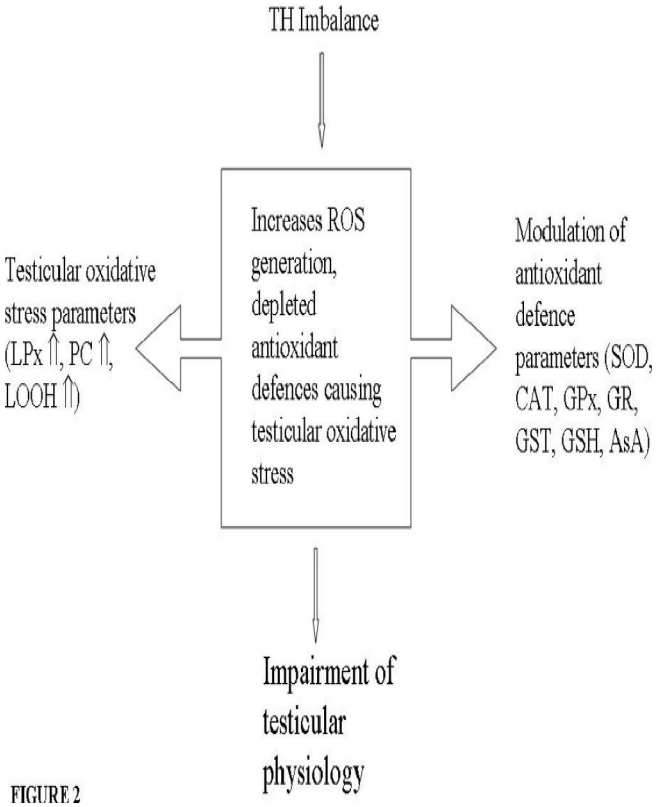


FIGURE 2

**Figure 2 : Altered thyroid status influencing testicular antioxidant status and physiology. TH, thyroid hormones; ROS, Reactive Oxygen Species; LPx, lipid peroxide; PC, protein carbonyl; LOOH, lipid hydroperoxide; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; GSH: reduced glutathione; AsA, ascorbic acid; ⇑, arrows indicating elevation.**

## ALTERATION OF TESTICULAR AODS BY HYPOTHYROIDISM

Hypothyroidism alters the oxidant generation and testicular antioxidant defence system as it is linked to a hypo-metabolic state. Effect of persistent and transient hypothyroidism on testicular antioxidant defence system during development and maturation has been evaluated[8] (TABLE 1).

### a) Oxidative stress parameters

Oxidative stress parameters such as malondialdehyde (MDA) level decreases[98] in hypothyroid rat testes, however the levels of hydrogen peroxide and protein carbonyl contents increase in the crude homogenate of testis of hypothyroid rats[2]. However, another study shows a decreased mitochon-

drial LPx in transient hypothyroidism but elevated mitochondrial LPx and protein carbonylation in persistent hypothyroidism in the testis[8]. The extent of oxidative damage marked by elevation in mitochondrial membrane protein carbonylation was also reported in hypothyroid rat testis[99]. It has been further shown that germ cells of transient hypothyroid rats exhibit higher LPx contents[5].

**b) Antioxidant defence parameters**

Rat testicular reduced glutathione (GSH) levels are lower in testicular tissues of the hypothyroid rats[98]. On the other hand, oxidized glutathione (GSSG) content remains elevated as a result of which reduced to oxidized glutathione ratio of testis decreases during hypothyroidism. Reduced activities of superoxide dismutase and catalase and elevated activity of glutathione peroxidase in the PMF of testis in the hypothyroid rats have also been reported[2]. Hypothyroidism also reduces the rat testicular GST levels[100]. Transient hypothyroidism is associated with reduced testicular SOD, CAT, GR and GPx activities. In contrast, persistent hypothyroidism causes elevation of SOD and CAT activities with decreased GPx and GR activities[8]. Further study shows that germ cells of transient hypothyroid rats exhibit lower GSH, CAT and SOD activities[5]. In a recent study, it has been reported that hypothyroid rat testis mitochondrial matrix exhibits lower glutathione and ascorbate contents that is not nullified with $T_3$ treatment[99]. However, in the case of hypothyroid immature rat testis, an altered antioxidant defence system marked by elevated SOD, CAT and GR activities with decreased GPx and GST activities were observed[101].

Thus thyroid hormone always plays a key role not only in regulating the testicular physiology but also by modulating its antioxidant defense status.

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