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## Testicular Protection From Thyroid Hormone Mediated Oxidative Stress

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# Testicular Protection From Thyroid Hormone Mediated Oxidative Stress

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## Abstract

Testis is very rich in unsaturated fatty acids with poor antioxidant defense system and due to presence of a potential reactive oxygen species (ROS)-generating systems, it is much more vulnerable to oxidative damage than other tissues. Thyroid hormones are well known to regulate steroidogenesis and spermatogenesis, thereby, affecting male fertility. In the presence of disturbed thyroid conditions, in hyperthyroidism as well as hypothyroidism testis is much more susceptible to oxidative stress. The increase of testicular oxidative stress marked by elevated MDA or TBARS levels, lipid hydroperoxide, hydrogen peroxide or protein carbonyl contents along with disturbed antioxidant enzyme levels happens during L-thyroxine or tri-iodothyronine induced hyperthyroidism. The reduction of testicular oxidative stress can be achieved either by increasing glutathione contents through administration of melatonin or by vitamin E and/or curcumin or by elevating of levels of antioxidant defence enzymes like SOD, CAT or GPx through administration of vitamin E and/or curcumin. In contrast, during hypothyroidism, the extent of testicular oxidative stress is marked by elevation in rat testicular mitochondrial membrane protein carbonylation, lower GSH contents and decreased antioxidant enzyme levels. Hypothyroidism-induced oxidative stress condition could not be reversed with T<sub>3</sub> treatment. Furthermore, such oxidative stress condition is not nullified still after withdrawal of reversible goitrogen PTU. Besides, in case of transient hypothyroidism, the oxidative stress condition is prevailed as marked by decreased antioxidant enzymes like SOD, CAT, GPx and GR levels and that might be responsible for triggering germ cell apoptosis in transient hypothyroid rats results in reduction in sperm count.

## Introduction

For the last few years infertility rates have increased exponentially in both men and women where at least the central cause of infertility is attributable to biological reasons and only 10% is attributed to psychological and emotional reasons. Infertility

statistics 2011 and 2012 indicate that at least over 90 million people across the world are unable to conceive children for one reason or another (<http://www.breathingtherightway.com/infertility/infertility-statistics-2011-and-2012>). Male fertility markers have been identified and studied extensively in order to understand the molecular mechanisms that can direct sub-fertility or infertility and permit an accurate diagnosis and design of therapeutic protocols. Among these markers, oxidative stress and poor antioxidant defence status in testis as well as in semen has emerged as a promising field (Sanocka et al., 1997; Choudhury et al., 2003; Agarwal et al., 2003). High concentrations of ROS play an important role in the pathophysiology of damage to human spermatozoa (Sharma and Agarwal, 1996). Thyroid hormones are well known to regulate steroidogenesis and spermatogenesis, thereby, affecting male fertility (Sahoo, 2011; Jannini et al., 1995; Mendis-Handagama and Ariyaratne, 2005). Hence, thyroid hormones have a vital role in regulating testicular antioxidant defence system and thereby influencing the testicular physiology (Sahoo, 2011).

## Testicular Antioxidant defence system

Aerobes protect themselves from the oxidative stress generated due to the ROS (reactive oxygen species) by neutralizing them by their well-evolved antioxidant defences (Halliwell and Gutteridge, 2001). Testicular cells are well equipped with both small molecular weight antioxidants like reduced glutathione, ascorbic acid, vitamin E, uric acid, ubiquinone and carotenoids; and antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), that efficiently neutralize ROS (Figure-1; Sahoo, 2011). Spermatozoa and seminal plasma contain a battery of ROS scavengers, including enzymes such as SOD and catalase, and also a variety of substances with antioxidant activities (Dandekar et al, 2002; Sheweita et al, 2005).

### Reduced glutathione (GSH)

Reduced glutathione (GSH) is the major non-enzymatic antioxidant and the most abundant

non-protein thiol source of cell (Irvine, 1996; Sies, 1999) and it plays an important role in many biological processes of cells, including synthesis of proteins, DNA and protection against oxidative damage (Sies, 1999). The testis has high concentration of GSH, which plays an important role in spermatogenesis (Meister and Anderson, 1983; Knapen et al., 1999; Sahoo et al., 2007). A glutathione deficiency can lead to instability of the mid-piece, resulting in defective sperm motility (Hansen *et al*, 1996; Ursini et al., 1999). Cells with high level of intracellular GSH are protected against oxidative damage caused by ROS. GSH either non-enzymatically reacts with ROS (Anderson, 1998) or directly scavenges them by neutralizing OH<sup>·</sup> (Sies, 1986). Thiols such as thioredoxins (small disulphide-containing proteins) and reduced glutathione (GSH) can neutralize a hydroxyl radical or a vitamin C radical (Sahoo et al., 2007).

### Vitamin E

Vitamin E specifies a group of lipid soluble compounds, tocopherols and tocotrienols that act as antioxidants defending the organism against lipid oxidation.  $\alpha$ -Tocopherol, the most abundant and active vitamin E family member is a chain-breaking antioxidant that prevents the propagation of free radical reactions (Mardones et al., 2002). Vitamin E as a lipid soluble plays a major protective role against oxidative stress and prevents the production of lipid peroxides by scavenging free radicals (particularly strong scavenger of hydroxyl radicals) in biological membranes (Sundararajan et al., 2006). Vitamin E also plays a vital role in protecting the sperm from morphological damage by binding endoperoxides, hence affecting the percentage of normal and motile sperm cells (Marin-Guzman et al., 1997; Sonmez et al., 2007). Vitamin E deficiencies cause testicular degeneration in chickens, rats, hamsters, dogs, cats, pigs, boars and monkeys and resulted in a reduction in sperm production (Marin-Guzman et al., 1997). Brzezinska-Slebodzinska et al. (1995) suggested that dietary vitamin E serves as an antioxidant in boar semen. In vitro studies also show that vitamin E is a major chain-breaking antioxidant in the sperm membrane and it appears to have a dose-dependent protective effect (Hull *et al*, 2000).

### Vitamin C

Vitamin C (ascorbic acid) is another important chain-breaking antioxidant contributing up to 65% of the antioxidant capacity of the seminal plasma. Vitamin C also contributes to the support of spermatogenesis at least in part through its capacity to reduce  $\alpha$ -tocopherol and maintain this antioxidant in an active state. Vitamin C is itself maintained in a

reduced state by a GSH-dependent dehydroascorbate reductase, which is abundant in the testes (Paolicchi *et al*, 1996). Deficiency of vitamins C leads to a state of oxidative stress in the testes that disrupts both spermatogenesis and the production of testosterone.

### Superoxide dismutase (SOD)

Superoxide dismutase (SOD) dismutates superoxide radicals into hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Mammals have three isozymes of SOD namely, SOD1 which encodes mostly cytosolic CuZnSOD having Cu and Zn metal cofactors; SOD2 encodes mitochondrial isoform MnSOD containing Mn, while SOD3, encodes the extracellular form, ECSOD (structurally similar to CuZnSOD containing Cu and Zn as metal cofactors) (Fujii et al, 2003). A key role of SOD in protection of testicular cells against heat stress-induced apoptosis has been demonstrated in vivo and in vitro (Ikeda et al, 1999; Kumagai et al, 2002). SOD also prevents premature hyper-activation and capacitation induced by superoxide radicals before ejaculation (Lamirande et al, 1995). On the contrary, transgenic male mice expressing higher levels of MnSOD are infertile, but the mechanism for this is unknown. Since SOD only dismutates superoxide anion to hydrogen peroxide, the resulting hydrogen peroxide may also cause a toxic effect in testicular cells (Fujii et al., 2003). ECSOD is present at high levels in the epididymis (Mruk et al. 2002) as well as is localized in the nuclei in the seminiferous tubules of testis (Ookawara et al. 2002). Erectile function is improved by transferring the SOD3 gene to the penis in aged rats (Bivalacqua et al. 2003).

### Hydrogen peroxide metabolizing enzymes

Hydrogen peroxide produced from superoxide radicals in turn is efficiently neutralized by catalase (CAT) and glutathione peroxidase (GPx). Catalase is also known to activate nitrous oxide (NO)-induced sperm capacitation, in a complex mechanism involving H<sub>2</sub>O<sub>2</sub> (Lamirande et al, 1997). GSH 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) (Halliwell and Gutteridge, 2001). GPx may be of Selenium dependent or Selenium independent types. Selenium dependent glutathione peroxidases (Se-D GPxs) are the foremost selenoprotein-containing gene family in mammals (Esworthy et al., 2001). Among the different types of selenium dependent hydroperoxide reducing isozymes, phospholipids hydroperoxide glutathione peroxidase (PH-GPx/ GPx-4; EC1.11.1.12) and classic cellular glutathione peroxidase (cGPX/GPx-1; EC 1.11.1.9) are mainly found in testis (Sahoo and Roy,

2012). PHGPx is a monomeric seleno-enzyme present in different mammalian tissues in soluble and bound form (Tramer et al., 2002). The GPX4 protein represents about 50 % of the capsule material, that embeds the helix of mitochondria in the mid-piece of spermatozoa (Ursini et al., 1999). A correlation between male infertility and a GPX4 defect has actually been reported (Imai et al., 2001). Selenium-dependent glutathione peroxidases contribute to a part of the total GPx activity. Other GPx activities in mammalian systems are selenium-independent and the Se-independent GPx (Se-I GPx) component of GST alpha class (Accession: IPR003080GST\_alpha) is accountable for GPx activity in testis (Sahoo and Roy, 2012; Doyen et al., 2006; Instoris et al., 1995). GPX5 is a non-selenium enzyme under the non-selenium dependent GPX group and is found to be highly associated with the male reproductive system. GPX5 is expressed exclusively in the epididymis and is secreted and present in the caput and cauda epididymis lumens (Rejaji et al., 2002). It constitutes 6% of the secretory epididymal proteins (Fouchecourt et al., 2000). The binding of GPX5 to sperm membrane has also been reported. Thus, the protection of the sperm membrane against peroxidation is a possible function of this epididymis-specific isoform (Vernet et al., 1999).

## Alteration of testicular antioxidant parameters by hyperthyroidism

Tissues in hyperthyroid rats exhibit high vulnerability to oxidative challenge (Venditti et al., 1997; Sahoo and Chainy, 2007). L-thyroxine (Mogulkoc et al., 2005a; 2005b; Sahoo et al., 2008b) or tri-iodothyronine (Choudhury et al., 2003; Sahoo et al., 2005; 2007) was administered in rats to induce hyperthyroidism experimentally and oxidative stress parameters as well as antioxidant defence profile were measured. Since thyroid hormones in general activate all the systems in the body, hyperthyroidism inevitably causes lipid peroxidation in different tissues depending on its severity (Sahoo and Chainy, 2007; Chattopadhyay et al., 2007; 2010; Sahoo, 2011; Venditti et al., 1997). Hyper-metabolic state in hyperthyroidism results in increase in free radical production (Venditti et al., 1997; Das and Chainy, 2001; 2004). Testis is very rich in unsaturated fatty acids (particularly 20:4 and 22:6) with poor antioxidant defense system (Sahoo et al., 2008c; Peltola, 1992) and due to presence of a potential reactive oxygen species (ROS)-generating

systems, it is much more vulnerable to oxidative damage than other tissues.

### Changes in oxidative stress parameters

It was reported that different thyroid hormone isomers used in induced hyperthyroidism led to different degrees of oxidative stress. Most of the studies confirm the increase of testicular oxidative stress as marked by elevated MDA levels during L-thyroxine induced hyperthyroidism (Mogulkoc et al., 2005a) or by increased TBARS, lipid hydroperoxide, hydrogen peroxide or protein carbonyl contents during L-thyroxine or tri-iodothyronine induced hyperthyroidism (Choudhury et al., 2003; Sahoo et al., 2005; 2007; Sahoo et al., 2008b).

### Changes in antioxidant defence parameters

#### Small antioxidant molecules

Interestingly while short-term L-thyroxine administration to hypothyroid rats causes an increased testicular GSH contents (Mogulkoc, 2005b), T<sub>3</sub> 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 (Choudhury et al., 2003). However, T<sub>3</sub> treatment for five days enhances testicular GSH contents both in both mitochondrial (MF) and post-mitochondrial (PMF) fractions (Sahoo et al., 2007). The reduced to oxidized glutathione ratio (GSH: GSSG) remains higher in both MF and PMF fractions during L-thyroxine or tri-iodothyronine induced hyperthyroidism (Sahoo et al., 2007; Sahoo et al., 2008b). Ascorbic content is also elevated in crude homogenate of hyperthyroid rat testis by one to five days T<sub>3</sub> treatment (Sahoo et al., 2007).

#### Antioxidant Enzymes

During acute hyperthyroid state, testis exhibits lower SOD activity and higher activities of CAT, GPx, GR and G6PD enzymes (Sahoo et al., 2005; 2007). Moreover, L-thyroxine induced hyperthyroid rats also exhibit decreased testicular SOD, CAT activities with elevated GPx activity (Sahoo et al., 2008b). In testicular PMF and MF, both Se-dependent and Se-independent GPx are enhanced, respectively by around 20% and 30% in response to L-thyroxine (Sahoo, 2012). Se-I-GPx activity is elevated only in MF due to triiodothyronine treatment in rat testis (Sahoo et al., 2007). Increase in both Se-D and Se-I-GPx levels in response to L-thyroxine induced hyperthyroidism (Sahoo, 2012) and Se-I-GPx elevation in response to triiodothyronine treatment (Sahoo et al., 2007) may be an adaptive response to neutralize toxic hydrogen peroxides generated due to

impairment of normo-oxidant status of the organ. Such type of altered testicular antioxidant defence parameters and oxidative stress conditions by hyperthyroidism hampers fertility as evidenced by reduced viable and total sperm counts (Sahoo et al., 2005; 2007; 2008b).

### Treatments

#### By curcumin treatment

Curcumin (1,7-bis [4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is the principal curcuminoid found in turmeric, and is generally considered as its most active constituent (Sharma et al., 2005). Both phenolic and -diketone functional groups of curcumin have remarkable free radical scavenging activities (Cohly et al., 1998, Reddy and Lokesh, 1994) and it was reported to inhibit superoxide anion and hydroxyl radical generation by preventing oxidation of Fe<sup>2+</sup> to Fe<sup>3+</sup> through Fenton reaction (Reddy and Lokesh, 1994). The elevated LPx and PC of the testis in response to T4 get reduced to the normal level by curcumin (Sahoo et al., 2008b). Treatment of curcumin to T4-treated rats results in elevation of SOD level in post-mitochondrial fraction (PMF) and mitochondrial fraction (MF) and CAT in PMF. However, curcumin is unable to change GPx activity alone but together with vitamin E it elevates the GPx in PMF of T4-treated rat testis (Sahoo et al., 2008b). Curcumin decreases the increased Se-D-GPx (GPx-1 and GPx-4) in MF and Se-I-GPx in PMF of hyperthyroid rats to normal level like untreated control rats that might happen in response to less oxidative stress condition after curcumin treatment (Sahoo, 2012). The less oxidative stress condition is also due to the increased levels of GSH contents in testes of curcumin fed rats (Sahoo et al., 2008b). This may be because of the triggered GSH biosynthesis as studies in cell culture suggest that curcumin can increase cellular glutathione levels by enhancing the transcription of the two Gcl genes, i.e. Gclc and Gclm for glutamate cysteine ligase, the rate-limiting enzyme in glutathione synthesis (Dickinson et al., 2004).

#### By vitamin E treatment

Treatment of vitamin E to T4-treated rats results in elevation of SOD level in post-mitochondrial fraction (PMF) and mitochondrial fraction (MF) and CAT in PMF. Vitamin E does not change GPx activity alone but in together with curcumin increases the GPx in PMF of T4-treated rat testis (Sahoo et al., 2008b). Vitamin E treatment causes reduction of increased Se-D-GPx (GPx-1 and GPx-4) in MF and Se-I-GPx in PMF of hyperthyroid rats to normal levels as a result of decreased oxidative stress due to vitamin E treatment

(Sahoo, 2012). Vitamin E also elevates GSH to GSSG ratio (GSH:GSSG) when given to T4-treated rats (Sahoo et al., 2008b).

#### By melatonin treatment

Melatonin, which is mainly secreted from the pineal gland in the body, reduces oxidative stress by its free radical eliminating and direct antioxidant effects (Akbulut et al., 1999; Reiter et al., 2003). Due to hyperthyroidism, the significant increased level of MDA in testis is inhibited to a large extent by the increase in levels of GSH (an indicator of antioxidant system activity) as a result of melatonin administration (Mogulkoc et al., 2005a). Such result demonstrates that the oxidative stress brought about by hyperthyroidism was hindered to a great degree by melatonin's increasing antioxidant system activities. Exogenous melatonin administration in addition to endogenous melatonin secretion strengthens effectively the antioxidant defense system of the body (Mogulkoc et al., 2005a).

## Alteration of testicular antioxidant parameters by hypothyroidism

Hypothyroidism also 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 (Sahoo et al., 2008a)

#### Changes in oxidative stress parameters

Oxidative stress parameters such as malondialdehyde (MDA) level decreases (Mogulkoc et al., 2005b) in hypothyroid rat testes, however the levels of hydrogen peroxide and protein carbonyl contents remain increased in the crude homogenate (Choudhury et al., 2003). In addition, the mitochondrial LPx and protein carbonylation contents remain elevated in the testis during persistent hypothyroidism (Choudhury et al., 2003). The extent of oxidative damage marked by elevation in mitochondrial membrane protein carbonylation was also reported in hypothyroid rat testis (Chattopadhyay et al., 2010). Marked increased protein carbonylation in hypothyroid immature rat testis also states about the prevalence of oxidative stress during hypothyroidism (Sahoo and Roy, 2012).

#### Changes in Antioxidant defence parameters

##### Small antioxidant molecules

Rat testicular reduced glutathione (GSH) levels are

lower in testicular tissues of the hypothyroid rats (Mogulkoc et al., 2005b). On the other hand, oxidized glutathione (GSSG) content remains elevated as a result of which reduced to oxidized glutathione ratio (GSH: GSSG) of testis decreases during hypothyroidism (Choudhury et al., 2003). Moreover, persistent hypothyroidism causes disturbed redox status in immature rat testis (Sahoo and Roy, 2012).

### **Antioxidant Enzymes**

SOD and CAT activities get reduced and GPX activity gets elevated in the PMF of testis in the hypothyroid rats (Choudhury et al., 2003). Hypothyroidism also reduces the rat testicular GST levels (Choudhury et al., 1992-2003). In contrast, persistent hypothyroidism causes elevation in SOD and CAT activities with decreased GPx and GR activities (Sahoo et al., 2008a). Persistent hypothyroidism reduces both Se-D-GPx and Se-I-GPx in testicular MF and PMF fractions (Sahoo, 2012). The decrease in Se-D GPx (GPx-1 and GPx-4) as well as Se-I-GPx in the testis suggests that antioxidant enzymes like SOD and CAT have predominant role to combat oxidative stress than GPx in hypothyroid rats as indicated by elevated SOD and CAT levels (Sahoo et al., 2008a). An altered antioxidant defence system marked by elevated SOD, CAT, and GR activities, with decreased GPx and GST activities occurs in hypothyroid immature rat testis (Sahoo and Roy, 2012). GPx is primarily responsible for H<sub>2</sub>O<sub>2</sub> removal in testicular mitochondria that does not contain catalase. The metabolic pathway of testosterone biosynthesis requires protection against peroxidation and will be affected by a decrease in the GPx activity (Chandra et al., 2000). The lower serum testosterone level in hypothyroid rats (Sahoo et al., 2008a; Sahoo and Roy, 2012) also corroborates the fact. This compromised testicular antioxidant status contributes to poor growth and development by affecting the spermatogenesis and steroidogenesis in rats before puberty as indicated by reduced germ cell number due to increased apoptosis (Sahoo, 2013), complete absence of round spermatids, decreased seminiferous tubule diameter, and decreased testosterone level (Sahoo and Roy, 2012). Such type of altered testicular physiology by hypothyroidism is reflected in adulthood with hampered fertility as evidenced by reduced total viable germ cells (Sahoo et al., 2006) and sperm counts (Sahoo et al., 2008a).

### **Treatment**

#### **Withdrawal of hypothyroid state/ transient hypothyroid condition**

In spite of decreased mitochondrial LPx in transient hypothyroidism, it is associated with reduced testicular

SOD, CAT, GR and GPx activities (Sahoo et al., 2008a). In transient hypothyroidism, the declined GPx in MF is found to be due to the reduction in Se-D-GPx activity only (Sahoo, 2012). The significant decrease in Se-D-GPx and Se-I GPx in PMF of testis suggests the prevailed oxidative stress in hypothyroid rats (Sahoo, 2012). Studies on germ cells of transient hypothyroid rats also further demonstrate that the germ cells are under oxidative stress as exhibited by lower GSH contents, decreased CAT and SOD activities (Sahoo et al., 2006) and higher LPx contents (Sahoo et al., 2006). Such prevalence of oxidative stress marked by decreased antioxidant enzymes such as SOD, CAT, GPx and GR levels in both mitochondrial as well as post-mitochondrial fractions (Sahoo et al. 2008a; Sahoo and Roy, 2012) might be responsible for triggering germ cell apoptosis in transient hypothyroid rats (Sahoo, 2013) that results in reduction in sperm count (Sahoo et al. 2008a).

#### **Treatment with T<sub>3</sub> (tri-iodothyronine) administration**

When PTU induced hypothyroid rats are treated with T<sub>3</sub> (tri-iodothyronine) hormone, it causes elevation in catalase and decline in glutathione peroxidase activity without altering superoxide dismutase and glutathione reductase activities in testicular post-mitochondrial fractions (Choudhury et al., 2003). Increased pro-oxidant level and reduced antioxidant capacity renders the hypothyroid mitochondria susceptible to oxidative injury and the extent of damage is more evident in the membrane fraction, reflected in higher degree of oxidative damages inflicted upon membrane lipids and proteins (Chattopadhyay et al., 2010). While membrane proteins were more susceptible to carbonylation, thiol residue damage is evident in matrix fraction. Reduced levels of glutathione and ascorbate further weaken the antioxidant defenses and impair testicular functions (Chattopadhyay et al., 2010). Such hypothyroid condition disturbed intra-mitochondrial thiol redox status leads to testicular dysfunction. Hypothyroid rat testis mitochondrial matrix exhibiting lower glutathione and ascorbate contents is not nullified with the T<sub>3</sub> treatment (Chattopadhyay et al., 2010).

## **Conclusion**

Both the compounds curcumin and vitamin E are known as efficient scavenger of reactive oxygen species (Inano et al., 2000; Aydilek, et al., 2004). However, their effects on antioxidant enzymes are quite different. Both these antioxidants are reported to decrease L-thyroxine induced oxidative stress as shown by reduced lipid peroxide and protein carbonyl

contents in the testis (Sahoo et al., 2008b). Both vitamin E and curcumin are efficient in protecting testis from oxidative stress generated by T<sub>4</sub> mainly by restoring antioxidant enzymes to the level of euthyroid animals up to some extent; however, vitamin E is more efficient than curcumin as it restores the normal testicular physiology by elevating total sperm count and increasing percentage of live sperm impaired by hyperthyroid state (Sahoo et al., 2008b). Similarly, melatonin decreases hyperthyroid induced testicular oxidative stress to some extent with increasing testicular glutathione contents (Mogulkoc et al., 2005a).

The reduction of testicular oxidative stress is either by increasing glutathione contents through administration of melatonin (Mogulkoc et al., 2005a) or by vitamin E and/or curcumin (Sahoo et al., 2008b) or by elevating levels of antioxidant defence enzymes like SOD, CAT or GPx through administration of vitamin E and/or curcumin (Sahoo et al., 2008b).

Hypothyroidism-induced oxidative stress condition could not be reversed with T<sub>3</sub> treatment (Chattopadhyay et al., 2010). Furthermore, the oxidative stress condition is not nullified still after withdrawal of reversible goitrogen PTU and in case of transient hypothyroidism the prevalence of oxidative stress marked by decreased antioxidant enzymes like SOD, CAT, GPx and GR levels (Sahoo et al. 2008; Sahoo and Roy, 2012) might be responsible for triggering germ cell apoptosis (Sahoo, 2013) that results in reduction in sperm count. Further, more studies are needed to find out the role of different antioxidants for protecting testis from oxidative stress caused by hypothyroidism.

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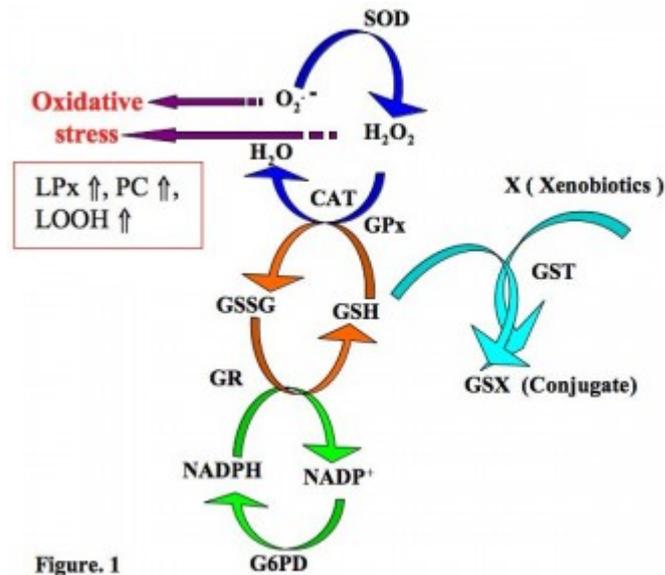
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## Illustrations

### Illustration 1

Figure 1 Testicular antioxidant defence system and oxidative stress parameters (Sahoo, 2011).



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