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Review Article

Ovarian dysfunction due to thyroid hormone imbalances and stress: Rescue by melatonin

Shruti R. Hansda[1], Jayita Pal Chowdhury[1], Chandana Haldar[1]

[1]Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

***Corresponding author:**
Chandana Haldar,
Department of Zoology,
Institute of Science, Banaras
Hindu University, Varanasi,
Uttar Pradesh, India.

chaldar2001@yahoo.com

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ABSTRACT

Reproduction is essential and the essence of life, but it is clouded by infertility-related issues, and most of them are endocrine in origin/nature. The prevalence of disorders due to thyroid hormone imbalances (hyperthyroidism and hypothyroidism) and stress due to adrenal hormones is a common scenario in women of reproductive age. Thyroid disease has been linked to a variety of negative impacts on female reproductive capability. Melatonin is best described as a pineal hormone and a bioactive amine with cellular targets in selected tissues. Melatonin is produced mainly in the oocyte and ovarian follicular cells. Furthermore, oxidative stress is reduced in all female reproductive organ cells, including the oocytes, due to the free radical scavenging activity of melatonin and its metabolites, ensuring appropriate function. The present review deals with the role of melatonin in female reproductive alterations due to thyroid dysfunction and various other related factors, such as oxidative stress and lifestyle disorders. At the same time, we have proposed the effective role of melatonin in rescue or managing above female anomalies since melatonin, being a multi-potent molecule, has numerous possibilities in therapeutics. This is due to the ameliorative properties of melatonin as anti-oxidative, anti-inflammatory, and also a regulator of certain metabolism which can appear in the above pathological conditions.

Keywords: Melatonin, Ovary, Stress, Thyroid

INTRODUCTION

The metabolic and developmental process of ovarian, uterine, and placental tissues needs thyroid hormones for their proper functioning. In females, thyroid hormone disorders (hypo- and hyperthyroidism) are often associated with altered folliculogenesis and adverse pregnancy outcome, whereas hyperthyroidism is mostly leading to infertility.[1] Thyroid disease has been linked to a variety of negative impacts on female reproductive capabilities. Both hypo- and hyperthyroidism can cause menstrual irregularities and ovulation in case of thyrotoxicosis. Thyroid hormone receptors (TR) have been found in female reproductive organs such as the ovary, uterus, and oviduct, not only in humans but also in rodents and primate. In animals, the effects of thyroid hormones on female reproductive capability are, however, related with a variety of factors (climatic and toxicological) that may play a role alone or in combination.[2]

IMPACT OF THYROID GLAND ON FEMALE REPRODUCTION

The metabolic and developmental process of ovarian, uterine, and placental tissues needs thyroid hormones for their proper functioning. TRs are present and expressed in all reproductive cells of both males and females, suggesting a direct action. It is located on ovarian granulosa and

stromal cells during follicular development, along with its expression in the endometrium. In females, thyroid hormone disorders (hypo- and hyperthyroidism) are often associated with altered folliculogenesis and adverse pregnancy outcome, whereas hyperthyroidism mostly leads to infertility.[1]

Thyroid disease has been linked to a variety of negative impacts on female reproductive capabilities. Both hypo- and hyperthyroidism can cause menstrual irregularities and ovulation impairment in case of thyrotoxicosis. TRs have been found in female reproductive organs such as the ovary, uterus, and oviduct, not only in humans but also in rodents and primates.[3] Therefore, oxidative stress plays much significant role in the normal functioning of the female reproductive system.

IMPACT OF MELATONIN

Melatonin functions in the follicular fluid by removing free radicals, increasing antioxidant enzymes, and encouraging granulosa cell production of sex steroid hormones.[4] The role of melatonin in female reproductive alterations [e.g., polycystic ovary syndrome (PCOS) and premature ovarian failure] due to thyroid dysfunction and various other related factors, such as oxidative stress and lifestyle disorders, are still poorly understood. At the same time, the effective role of melatonin in rescuing or managing female anomalies is experimentally proposed since melatonin, being a multi-potent molecule has numerous possibilities in therapeutics. This is due to the ameliorative properties of melatonin as anti-oxidative, anti-inflammatory, and also being a regulator of certain metabolism which can appear in the above pathology/conditions. The main activity of melatonin includes promoting oocyte maturation and preserving oocyte quality, at least as reported for the *in vitro* fertilization (IVF) procedure. Furthermore, oxidative stress in the ovary under *in vivo* conditions gets reduced in oocytes/cells due to the free radical scavenging capacity/activity of melatonin and its metabolites, ensuring appropriate healthy function.[5] Melatonin protects the oocyte from harmful oxygen species as these cells have membrane receptors (MT1) for the melatonin.[6] Major metabolic effects, along with the irregularities in ovarian functions due to thyroid dysfunction get ameliorated by melatonin due to its direct action through its receptor MT1.

HYPO-/HYPER-THYROIDISM IN FEMALES: ROLE OF MELATONIN

The hypothyroidism and its impact on female reproduction have widely been investigated, influencing fertility. Hyperthyroidism is a well-known endocrine disorder in females due to excess secretion of thyroid hormone causes reproductive alteration, including infertility. Induced hypo- and hyperthyroidism causes a decrease in serum levels of gonadotropin, thereby also gonadal steroids. Melatonin is a hormone known to modulate the estrous/menstrual cycle and pregnancy. Studies have shown that the exogenous melatonin increased T4 levels in female rats and controlled the decrease in serum T3 levels, thus reverting the signs of hypothyroidism.[7] Melatonin treatment is known to increase the thyroid hormone concentration in case of hyperthyroidism.[8]

IMPACT OF ADRENAL GLAND AND STRESS

The sequential activation of the hypothalamic corticotrophin releasing hormone (CRH), the pituitary adrenocorticotropic hormone (ACTH), and adrenal steroids [glucocorticoids (GCs) and mineralocorticoids] is involved in stress response. The stress response shows a strong sexual dimorphism, and it is more noticeable in females by the presence of estrogen-responsive elements in the *CRH* gene. In the case of humans, the stress-induced disruptive changes make the females more vulnerable. The hypothalamo–pituitary–adrenal axis, when activated by stress, exerts an inhibitory effect on the female reproductive system. This process involves suppression of HPA-O/U axis at the hypothalamic, pituitary, ovarian, and uterine levels. The CRH inhibits gonadotropin-releasing hormone (GnRH) secretion, whereas GCs suppress GnRH and luteinizing hormone (LH) secretion as well as inhibit ovarian estrogen and progesterone biosynthesis and thereby reduce the action of estrogen at target tissues.[9] These may lead to preterm birth of offspring with low birth weight and the development of adult diseases ranging from metabolic syndrome.[10]

The GC-mediated inhibition of the ovarian axis is through the generation of free radicals, mainly reactive oxygen species (ROS). Acute and chronic elevation of the level of GC may lead to oxidative stress.[11] GCs impair mitochondrial quality and might be involved in chronic stress conditions leading to neurodegenerative diseases.[12] Hypothyroidism is associated with several menstrual abnormalities, anovulation, and hyperprolactinemia, resulting in a high rate of abortions, premature births, placental rupture, and weight-related neonatal deficits. In addition, there are studies showing that hypothyroidism can affect ovarian morphology (number of ovarian follicles).

OVARY WITH THE ADRENAL GLAND/HPA AXIS: THE STRESS RESPONSE

There is proof that the HPA axis's components, which are normally antagonistic, have a conversation with the female reproductive center.[12] Remarkably, there is a strong response in females, and the response is more pronounced due to the presence of estrogen responsive elements in the *CRH* gene,[10] which renders females more susceptible to disruptive change brought on by stress. Free radical production, particularly that of ROS, is another potential mechanism by which GC

mediated regulation of the ovarian axis operates. According to studies, oxidative stress can occur in tissue, including the ovary, as a result of both acute and chronic rise of GC levels.[11] In addition, it is possible that GC receptors contribute to the stress response[13] by affecting the production of ROS and adenosine triphosphate (ATP);[14] this is supported by the finding that GC receptor exists in mitochondria.

OXIDATIVE STRESS AND OVULATION: THE ROLE OF GOOD ROS

Although it might have negative consequences, the biological system will always produce ROS[10] conducted a thorough investigation of the role of ROS in the follicular fluid environment, folliculogenesis, and steroidogenesis. Although locally generated ROS affect the expression of genes that control oocyte maturation and are necessary for follicle rupture, they also function as second messengers.[15,16] A follicle's granulosa cells and oocytes may suffer harm from oxidative stress brought on by an excess of ROS. Apoptosis of granulose cells induced by oxidative stress has been shown to substantially affect antral follicles, while data regarding the impact of oxidative damage on primordial follicles are conflicting. According to,[17] there may be a complex interaction between ROS and antioxidants in the ovary. Especially in oocytes of dominant follicles, an increase in ROS triggers the resumption of meiosis I, which is inhibited by antioxidants, whereby antioxidants promote the progression of meiosis II.

STRESS-INDUCED ROS PRODUCTION IN FEMALE

ROS are chemically reactive molecules containing oxygen, and while they are naturally produced during cellular metabolism, excessive levels due to stress can cause oxidative damage. The oxidative and antioxidant system suggests that the oxidative stress, infertility, and certain reproductive diseases such as endometriosis and hydrosalpinx are caused.[18] The contact of the ovary and the fallopian tubes with the peritoneal fluid maximizes the risk of oxidative damage caused by the ROS present. Melatonin in this fluid inhibits the death of preovulatory follicles to fully develop and delivers mature oocytes for ovulation.[19] An increase in follicular fluid melatonin content in the maturing human follicle is thought to play a significant role in preventing atresia.[19] Furthermore, during the follicular dominance stage, melatonin inhibits CYP11A, a particular gene for progesterone synthesis, which enhances progesterone secretion through negative feedback,[20] which is required for follicular maturation and the ovulation process.[21]

Further, increased ROS and reactive nitrogen species (RNS) production, together with oxidative stress, has tens oocyte aging and degrades oocyte quality under pathologic circumstances.[22] Numerous investigations have found that melatonin can protect the oocyte from deoxyribonucleic acid (DNA) fragmentation and modulate cytochrome c release, most likely due to its action on mitochondria.[23] Melatonin modulates mitochondrial uncoupling protein, which reduces electron leakage from respiratory chain enzymes.[24] It also decreases electron leakage from the respiratory chain in the inner mitochondrial membrane.[25] Melatonin concentrations in follicular fluid have been linked to oocyte quality, and melatonin in this fluid permits a preovulatory follicle to fully mature and provide an oocyte for fertilization.[26] The release of oocytes from a Graafian follicle involves processes comparable to a local inflammatory response in the follicular wall, where melatonin again exhibits its protective effects during ovulation.[27] As a result, local inflammatory cells produce an overabundance of reactive species, increasing the chance of oxidative damage to the oocyte. Given that melatonin and its metabolites effectively minimize molecular damage caused by ROS and RNS,[28] high endogenous melatonin concentrations in the follicular fluid may protect both the oocytes and the steroid-secreting granulosa cells from damaging oxygen and nitrogen-based by-products.[21]

DISCUSSION

Thyroid hormone receptors (TR) are present and expressed in all reproductive cells of both male and female suggesting a direct action. The hypothalamic–pituitary–gonadal (HPG) axis is the humoral component of an intercommunicating neural and endocrine system that functions in the regulation of female fertility.[29] Melatonin is a principal product of the pineal gland, is secreted mainly during the dark phase of the circadian cycle. It plays a crucial role in the regulation of circadian and seasonal changes in various aspects neuroendocrine functions. In mammals, melatonin can influence sexual maturation and reproductive functions via activation of its receptors and binding sites in the HPG axis.[30] The stress system induced by HPA axis is having suppressive effects on female reproduction involving suppression of the hypothalamic pituitary ovarian (HPO) axis at the uterine level as well.[31] The major hormonal systems that mediate the stress response are the CRH and AVP synergistically stimulating pituitary ACTH secretion and, subsequently, glucocorticoid secretion by the adrenal cortex. An increased glucocorticoid activity is the hallmark of stress. Glucocorticoids have a wide range of effects in multiple systems involved in growth, maintenance, and reproduction. The HPA axis, when activated by stress, exerts an inhibitory effect on the female reproductive system. This process involves suppression of HPO axis at the hypothalamic, pituitary, ovarian, and uterine level.[32] CRH inhibits GnRH secretion whereas glucocorticoids suppress

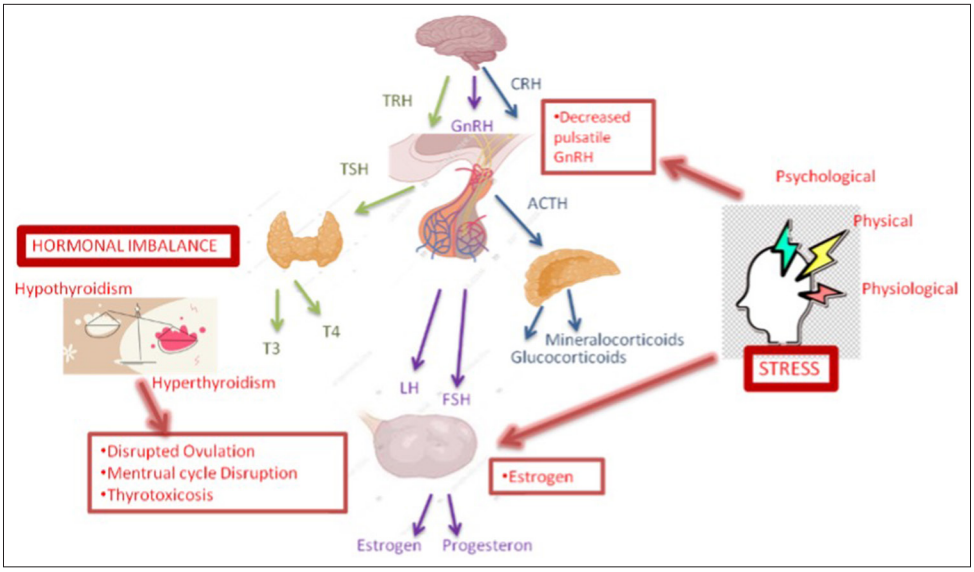

Figure 1: Schematic representation of the interactions between the hypothalamic–pituitary–adrenal axis and the reproductive axes. CRH: Corticotropin-releasing hormone, GnRH: Gonadotropin-releasing hormone, ACTH: Adrenocorticotropic hormone (corticotrophin), LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, TSH: Thyroid stimulating hormone, TRH: Tyrotrophin releasing hormone. Activation is represented by solid green lines and inhibition by red lines.

GnRH and LH secretion, as well as inhibit ovarian estrogen and progesterone biosynthesis and estrogen actions at target tissues [Figure 1]. Any dysfunction in thyroid or adrenal gland may lead to many ovarian and uterine anomalies including preterm birth of the offspring, low birth weight, and the development of adult diseases ranging from the metabolic to several reproductive disorders.[10]

CONCLUSION

Thyroid imbalances and stress are key regulators of female reproduction leading to infertility. Both may lead to oxidative stress in the ovarian tissue. Therefore, an early management of thyroid or adrenal disorder is required where neuro hormone melatonin having antioxidant and anti-inflammatory properties plays an important role and hence may be a therapeutic agent.

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