American Journal of Medicine Studies, 2014, Vol. 2, No. 2, 34-37
Available online at http://pubs.sciepub.com/ajms/2/2/2

DOI:10.12691/ajms-2-2-2

Effect of Anti-Thyroperoxidase on Thyroid Gland and Breast Tissue: A Comprehensive Review

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Received March 16, 2014; Revised April 22, 2014; Accepted April 27, 2014

Abstract Relationship between thyroid disease and breast tissue has long been debated as both the tissues have same embryological origin. Recent studies have implicated the possible role of thyroid dysfunction in the development and progression of breast related disorders. In view of increased prevalence of hypo and hyper thyroidism globally, there is a possibility of hormonal imbalance which may contribute to the initiation of tumor growth. Current literature has confirmed the role of sodium-iodide symporter (NIS) gene expression in breast cancers. Elevated anti-thyroperoxidase enzyme has been associated with increased risk of breast cancer. Activity of thyroid gland in post menopausal women, role of iodide levels and its relation to breast tissue and development of breast cancer needs extensive evaluation. In this comprehensive review we describe the role of NIS in thyroid gland functioning, thyroid hormone signaling mechanism.

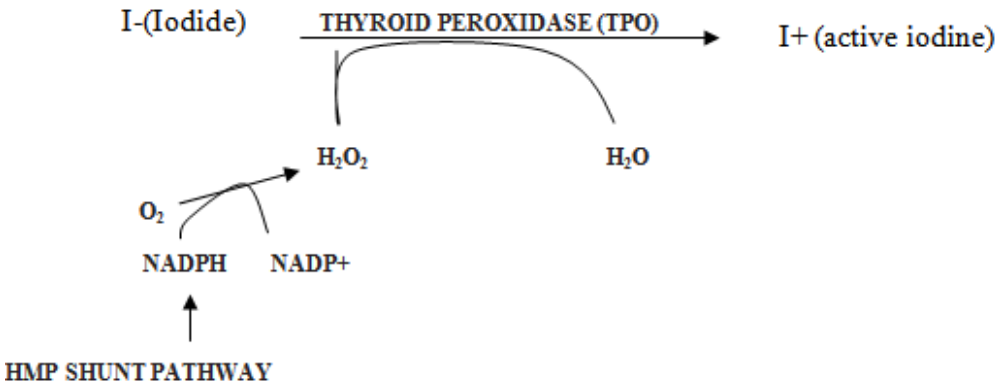
Keywords: *thyroid peroxidase (TPO), sodium-iodide symporter (NIS), thyroid disease, breast disease*

Cite This Article: Sabitha Kandi, Venkata Bharatkumar Pinnelli, Pragna Rao, and K V Ramana, "Effect of Anti-Thyroperoxidase on Thyroid Gland and Breast Tissue: A Comprehensive Review." *American Journal of Medicine Studies*, vol. 2, no. 2 (2014): 34-37. doi: 10.12691/ajms-2-2-2.

1. Introduction

Thyroid peroxidase (TPO) is a key enzyme in the synthesis of thyroid hormone. TPO is involved in the thyroid hormone synthesis (Organification and Coupling reactions). Iodide uptake is the critical step in thyroid hormone synthesis. Ingested iodine is bound to serum albumin and unbound iodine is excreted in urine. Iodide uptake is mediated by sodium iodide symporter(NIS), which is expressed at the basolateral region of thyroid follicular cells. NIS is expressed mostly in thyroid gland and leastly in salivary glands, lactating breast and placenta.

After iodide enters the thyroid, it is trapped and transported to the apical region of thyroid follicular cells. The oxidation of iodide to iodine is catalysed by the enzyme thyroid Peroxidase(TPO). This reaction requires H_2O_2 and NADPH, NADPH is from hexose mono phosphate(HMP) shunt pathway.



The reactive or active iodine atoms are added selectively to tyrosyl residues within thyroglobulin. The iodotyrosine residues of thyroglobulin are coupled via ether linkage catalysed by TPO. Further it leads to formation of T3 andT4, the thyroglobulin molecules are taken back into thyroid cell. The release of T3, T4 are by the action of lysosomal enzymes. Uncoupled Monoiodotyrosine (MIT) Diiodotyrosine(DIT) are deiodinated by dehalogenase or deiodinase, the iodine liberated is recycled for thyroid hormone synthesis (Figure 1).

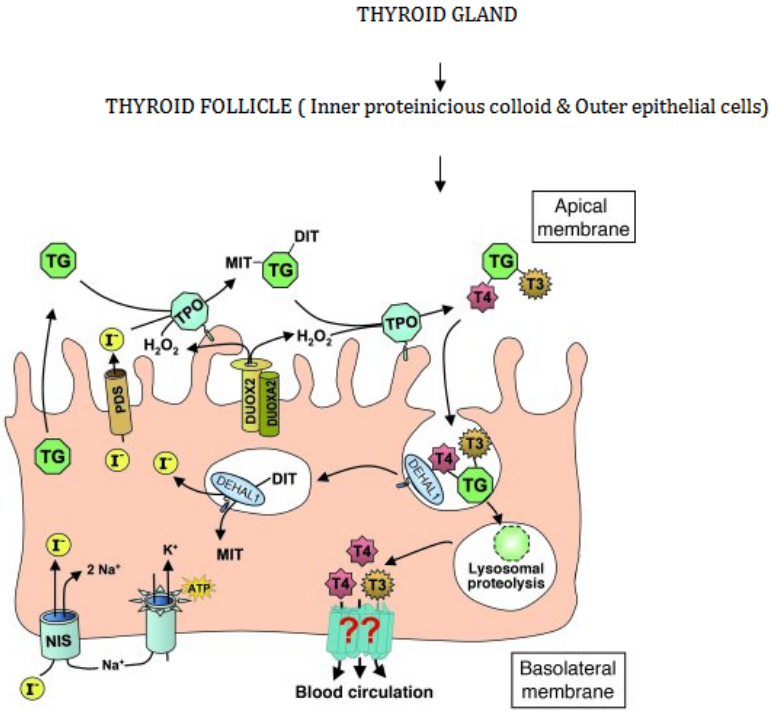


Figure 1. Diagramatic sketch of NIS and thyroid hormone synthesis

Thyroid hormone acts by binding to thyroid hormone receptors(TR) α andβ. The α andβ subunits of these receptors are expressed in most tissues. TR is coupled to α subunit of G protein activates adenylate cylase, Increases the production of cyclic AMP. The receptor contain a central DNA binding domain, they bind to specific DNA sequences termed as thyroid response elements(TRE) in the promoter region of target genes. The receptors mostly bind as homodimers stimulate gene transcription or inhibition [1] (Figure 2).

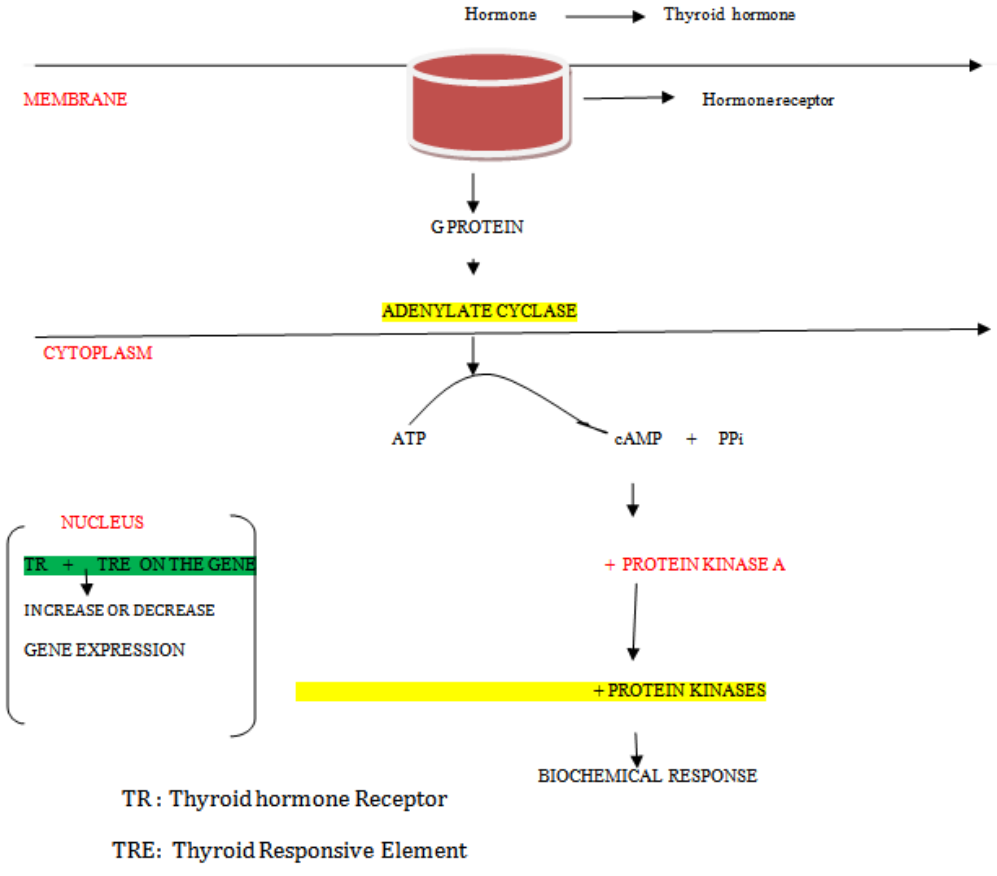


Figure 2. Mechanism of Thyroid hormone signaling pathway and Receptor action

A rise of 26% in breast cancer i.e., about 1.7 million women will be affected by breast cabncer in 2020, mostly in developing countries [2,3]. The progression of many human cancers including breast are known to be

influenced by steroid hormones [4,5]. The oestrogen hormone levels play an important role in growth and development of breast cancer [6,7].

The complex interaction between genetic and environmental factors may lead to autoimmune thyroid diseases. The genes identified are HLA – DR gene locus, non – MHC genes such as CTLA – 4, CD40, PTPN22, Thyroglobulin and TSH receptor gene. The environmental factors includes low iodine content, infections, smoking, various medications and also due to stress [8]. It is reported by several authors that stress influences immune system and thus there is a relation between stress and worsening of autoimmune thyroid disorders [9]. The environmental factors, pathological conditions and physiological agents and hormone levels of thyroid gland influence the development of breast cancer [10]. Martinez et.al., reported that addition of thyroid hormones at physiological concentrations effects the proliferation of epithelial cells of breast tissue [11].

Thyroid hormone and oestrogen share similar pathways in regulating growth and proliferation of the cells in the target tissues, including cancer cells. The evaluation of presence of the receptors of these hormones is important in understanding the progression of the cancer [12,13]. One of the recent study states that a change in the expression of the thyroid hormone receptors in breast cancer tissues, which says that these receptors are deregulated which in turn increases the risk for development of breast cancer [14,15,16].

A raise in serum anti –TPO levels is seen not only in breast cancer but also in goiter cases (8% diffuse 50% nodular). This findings show both increased goiter rates and increased thyroid enlargement by ultrasound in breast cancer patients [17,18,19]. Breast cancer and thyroid diseases predominantly affect females and that to post menopausal women which show an association between these two diseases [20,21]. The presence of circulating TPO antibodies shows an increased risk for future hypothyroidism [22].

2. Relation between Functioning of Thyroid and Breast Tissues

The uptake and utilization of iodide by thyroid and breast tissue is similar. In the thyroid Iodide is required for the formation of T_3 and T_4. Iodide of breast helps in neonatal nutrition. There is no other role of iodide in breast tissue except acting as a nutrient in breast milk. In these orgens, iodine undergoes Organification (oxidize Iodide to iodine) to foirm iodoprotiens [23,24]. This step requires the presence of H_2O_2 as an oxidizing agent catalyzed by TPO in the thyroid and by lactoperoxidases in the breast tissue. These iodoproteins / iodinated compounds inhibit the functions of thyroid gland by inhibiting the actions of adenylate cyclase, NADPH oxidase and TPO activities [25]. Thus, the inhibitory actions of these iodinated compounds play an important role in development of breast cancer [26,27]. The tissue iodine levels are low in breast cancer than in normal/benign breast tumors [28].

In a survey conducted, it is found that breast cancer proceed to thyroid tumor. The survey concludes that breast and thyroid cancer occur at almost sametime, but the growth of breast cancer might be faster than that of thyroid tumors [29].

3. Discussion

Acetylation / deacetylatio0n and other modifications of histones lead to genetic alterations to the genome which proved to have a role in breast carcinogenesis [30]. Epigenetic alterations to the genome occur when there is deregulation of hormone signaling [31]. Several research findings reveal the proapototic potential of the thyroid hormone [32,33,34].

T_3 levels in post menopausal women are positively associated with the risk of breast cancer. T_3 in the circulation binds to thyroxin binding globulin (TBG), transthyretin and albumin. Increase in TBG leads to raised T_3 levels. Increased TBG levels are seen in breast cancer, Hormone Replacement Therapy (HRT) and use of Oral Contraceptives (OC). Excluding HRT &OC also similar risk i.e., increase TBG levels are seen in breast cancer patients [35].

T_3 binds and stimulates the estrogen receptor, acts in association with estrogen on breast cancer cell lines, potentiates estrogenic effect and enhances cell proliferation [36]. The role of estrogen in breast carcinogenesis is known and this high T_3 levels would enhances the carcinogenic effect to breast tissue.

A study conducted by Cristofanilli et.al., reports that women with previous hypothyroid conditions are at increased risk for breast cancer.

Thyroid diseases such as Carcinoma, adenoma and adenomatous goitre have an influence on the carcinogenesis of breast [29]. The incidence of non – toxic goitre and thyroid swelling are high in breast cancer patients which supports the above said influence on breast tissue [37].

The raised anti TPO levels in autoimmune thyroid diseases are positively correlated with an increased risk for breast cancer. So, it is not clear whether the raised anti TPO antibodies is related to breast cancer or general autoimmune response of the body to malignancy [38].

The sodium / Iodide symporter (NIS) gene is expressed approximately $1/3^{rd}$ of human breast cancer tissue. Its expression is independent of the hormonal receptor status of the patient (TSH-R gene, ER / PR) [39]. The studies on breast cancer patients indicates, an increased thyroid disorders in breast cancer patients, most commonly Hashimotos thyroiditis accounts to an increased thyroid disorders in these patients. This is independent of hormonal receptor status of the patient. These findings suggest the usefulness of screening for thyroid disease in any patient with breast cancer [40]. Alterations to expression of thyroid hormone receptors are found in breast cancer by several studies [10]. It suggests a role of thyroid hormone receptor in the progression of breast cancer.

It was reported that most thyroid neoplastic and normal tissues were positive for mRNA of both P_{450} aromatase and estrogen receptor, shows that human thyroid gland has a role in both estrogen synthesis and intracrine / paracrine estrogen responsiveness [42]. This indicates a possible association between breast disease and thyroid cancers [43].

4. Conclusion

The raised serum anti TPO antibodies, increased goiter rates, increased thyroid enlargement in breast cancer patients shows an association between these two organs. The increased serum anti TPO levels whether it is due to autoimmune response of the body to malignancy still remains to be clarified.

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