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Central Dogma in Thyroid Dysfunction: A Review on Structure Modification of TSH*R* as a Cornerstone for Thyroid Abnormalities

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Abstract: Thyroid stimulating hormone receptor (TSH*R*) is a vital thyrocyte membrane protein in the thyroid gland. Thyroid Stimulating Hormone (TSH) which is a pituitary hormone is the main stimulator of thyroid gland to produce thyroid hormones, it binds with high affinity to the TSHR through weak bonds including hydrophobic, ionic, hydrogen bonds and trigger the initial steps in thyroid gland stimulation to produce the related hormones. This study was carried out at department of biochemistry of Golestan university of medical sciences. All the related articles related to TSH*R* modification happened due to mutations and any other alterations which affect the level of TSH-TSH*R* complex were studied and the main points were extracted out of the pile of information and were organized as present review. TSH-TSH*R* is the initial and vital step of a long process of thyroid hormone production within the thyroid gland. Any alteration on the TSH-TSH*R* affinity which may happen due to the direct effect of TSH*R* modification eventually lead to the serious adverse effects of either hypothyroidism or hyperthyroidism if the TSH-TSHR level are suppressed or elevated, respectively. The prime cause of the thyroid disorders relay on the possible modification on the biochemical structure of TSH*R* with subsequent alteration on the level of TSH-TSH*R* complex. TSHR mutation accompanied by biochemical modification, unable it to bind properly to TSH. In some other conditions such mutation leave a TSHR with either of higher affinity towards to TSH or even TSH*R* which can be activated in the absence of TSH. The structural modification of TSH*R* and alteration in the level of TSH-TSH*R* in the thyroid gland eventually lead to thyroid disorders either of hypothyroidism or hyperthyroidism.

Key words: Receptor, mutation, alteration, hypothyroidism, hyperthyroidism

INTRODUCTION

The receptor to the thyroid stimulating hormone (TSH*R*) is a crucial protein located on the thyrocytes membrane of thyroid gland. The TSH*R* is critical mediator of thyroid stimulating hormone (TSH). The physical and mental growth during fetus life and early infancy directly related to the proper functioning of TSH*R* (Ando *et al*., 2005; Mansourian *et al*., 2010b; Mansourian and Ahmadi, 2010; Saber *et al*., 2009; Eftekhari *et al*., 2007; Vern *et al*., 2003; Zarei *et al*., 2009; Christensen and Davis, 2004). This receptor belong to the glycoprotein hormone receptor protein family with about 300-400 amino acids extra-cellulary (Tomer, 2010; Miyai *et al*., 2005; Morgenthaler *et al*., 2003; Moodley *et al*., 2010; Eschler *et al*., 2011).

There are extensive genetic studies, which evaluated the TSH*R* biochemical structures. On the base of these studies the TSH*R* extracellular domain consist of about 400 amino acids and as whole the TSH*R* contain about 800 amino acids, therefore it seems the TSH*R* ectodomain considered to occupy 50% of TSH*R* protein primary structure (Biebermann *et al*., 1997, 2001; Sanders *et al*., 2011). Extensive genetically, studies have been carried out on the biochemical structure of TSH*R*. It is found that TSH*R* is a member of glycoprotein receptors. TSHR is partly similar to Leutinizing hormone receptor (LH*R*), Follicule stimulating hormone receptor (FSH*R*) and human Chrionic gonadotropin receptor (HCG*R*). It should be also mentioned that FSH, LH and HCG bind to their specific receptors, but it seems the metabolic process, involve in the hormone message transduction look similar. The similarities of the above mentioned hormone receptors seem to be mostly on the section of receptors located on the membrane itself and in the cytoplasm region of target tissue of the hormones. In recent years, genome studies on TSH*R* provide detailed knowledge of this critically important protein (Nurwakagari *et al*., 2007; Lado-Abeal *et al*., 2010; Sanders *et al*., 2010; Sanders *et al*., 2011; Maiti *et al*., 2011; Li *et al*., 2011; Palos-Paz *et al*., 2008; Leitolf *et al*., 2000; Oda *et al*., 2000). In one study it is indicated that even stimulation of receptor cytoplasm site, in the absence of hormone may trigger the metabolic pathway initiated by the hormone

itself and some times such stimulation can lead to the various unwanted biochemical reactions and subsequent metabolic disorders of thyroid resulted due to the elevation of thyroid hormones originated from the undesired stimulation of thyroid gland. This latter observation is demonstrated by synthesized pathways leading to receptor stimulation in the absence of TSH itself (Hebrant *et al*., 2011; Van Sande *et al*., 1995a; Russo *et al*., 1997).

TSH*R* STRUCTURE

The information about the structure of TSH*R* derived mainly from a huge genome studies on the TSH receptor by stimulating gene mutation, accompanied by amino acid sequencing studies. Antibodies mediated receptor stimulation and other *in vivo* mechanisms eventually lead to stimulation of TSH*R* with subsequent thyroid activation (Sanders *et al*., 2007; Nunez Miguel *et al*., 2009; Sanders *et al*., 2010; Smith *et al*., 2007; Palos-Paz *et al*., 2008; Maiti *et al*., 2011; Lado-Abeal *et al*., 2010, 2011; Sanders *et al*., 2011; Neumann *et al*., 2010; Nurwakagari *et al*., 2007; Latif *et al*., 2010a; Mansourian 2010d,e). As it was mentioned earlier thyroid stimulating hormone, follicule-stimulating hormone, leutinizing hormone and human chrionic gonadotropin receptors have similarity among themselves. And these hormones are member of G-Protein-coupled receptor family (GPC*R*) which it is also abbreviated as (LG*R*) which stands for leucine-rich G-Protein receptor (Hebrant *et al*., 2011; Duprez *et al*., 1999; Kosugi *et al*., 1996). The TSH*R*, extracellular section is a region where TSH hormone binds with strong affinity (Chazenbalk and Rapoport, 1995; Osuga *et al*., 1997; Seetharamaiah *et al*., 1994; Latif *et al*., 2010a,b, 2007). The other studies in association with the above observation demonstrate that when ever the TSH binding to its receptor increased and in fact TSH-TSH*R* combination level is elevated the activity of thyroid gland is also increased accordingly (Kaczur *et al*., 2007; Kosugi, 2002; Grossmann *et al*., 1997; Leitolf *et al*., 2000; Mansourian, 2010e). But this is in contrast to the studies indicating that extra cellular domain of TSH*R*, is only the recognition sit of TSH and it is the cytoplasm region of TSH*R*, where it is responsible for the transmission of biological activity of TSH. Antibodies mediated receptor stimulation and other *In vivo* stimulation mechanism eventually is leading to the activation of TSH*R* with subsequent thyroid activation (Lado-Abeal *et al*., 2010, 2011; Palos-Paz *et al*., 2008; Maiti *et al*., 2011; Sanders *et al*., 2011; Sanders *et al*., 2010; Neumann *et al*., 2010; Nurwakagari *et al*., 2007; Latif *et al*., 2010a, b; Mansourian, 2010c-e).

TSH*R* IS A GLYCOPROTEIN IN NATURE

Also there are many similarities among, glycoprotein receptors family or for short GPC*R*, including an extended polypeptide region on extracellular region of thyrocytes, which is considered, the part of polypeptide backbone binding to the TSH (Chazenbalk and Rapoport, 1995; Osuga *et al*., 1997; Seetharamaiah *et al*., 1994). It should be mentioned that simultaneously there are other major difference which distinguish TSH*R* from other GPC*R* receptor family including the TSH*R* structure which is genetically more prone to be mutated compared to FSH*R*, LH*R* and HCG*R* (Van Sande *et al*., 1995a; Miyai *et al*., 2005). There are also some TSH*R* on the thyrocytes membrane which consist of two subunits (Tomer, 2010). It has also been reported that TSH*R* is a very sensitive type of receptor and easily can be stimulated. It can trigger the whole process of thyroid function even in the absence of TSH itself. But studies also indicated any biochemical modification on the extracellular region of TSH*R* eventually lead to the disruption of TSH*R* (Van Sandea *et al*., 1995a; Zhang *et al*., 1995). This observation seems contrary to leutinizing hormone receptor LH*R* (Richert and Ryan, 1997). It seems also some glycoprotein receptor, such as follicule stimulating hormone receptor (FSH*R*) can partly loose their activity by GTP analog, but it seems that TSH*R* activity is not altered under the same circumstances (Zhang *et al*., 1988; Palos-Paz *et al*., 2008; Akamizu *et al*., 1994) and it can be concluded that the differentiation between the recognition and activation domain of TSH*R* are negligible (Grossmann *et al*., 1997; Leitolf *et al*., 2000). TSH*R* is different from leutinizing hormone and follicle stimulating hormone receptors, regarding the positions of amino acids involved in the N-terminal of TSH*R*. There are some studies indicating that a section of TSHR on the N-terminal which contain about eight amino acid is a remarkable region for the attachment of TSH and most notably immunoglobulin (IgG) can bind with TSH*R* with high affinity on condition of autoimmunity to the thyroid gland (Kosugi and Mori, 1995; Wadsworth *et al*., 1990). This IgG-TSH*R* combination is behind, various type of thyroid disorders, staging from antibodies binding to the receptor and mimicking the TSH function. (Mansourian, 2010d, e). The other region of TSHR which contain about fifty amino acid on the extra -cellular region TSHR seems to have no biochemical activity. It can be stated that in extra -cellular region of TSH*R*, there are a group of amino acids presented to have the related physiological activity and bind TSH with high affinity; simultaneously there are a group of consecutive amino acids, with biological function most probably giving the back bone structural

characteristic of extra cellular TSH*R*. The other important aspect of TSH*R*, structure at outer membrane of thyrocyte is the cysteine the amino acid best known for producing strong disulfide bridges, which are chemically strong bond. These type of disulfide bridges are essential for unique conformation of TSH*R*

TSH*R* is a glycoprotein and the asparagine residues of TSH*R* is glycoloyated following TSH*R* translation, but it seems this post-translational modification of TSH*R* did not have a serious implication on the TSH*R* physiological function. Regarding what we expect from TSH-TSH*R* complex it is the eventual biosynthesis of cyclic Adenosin monophosphate (cAMP) synthesis which behave as second messenger for TSH biological function in the thyroid gland for thyroid hormones production. There are many studies on the TSH*R* biochemical structure and it also seems TSHR consist of two polypeptide chains but in real fact, TSH*R* is coded by a single gene. But the produced polypeptide chain cleaved post-transitionally (Lado-Abeal *et al*., 2010; Sanders *et al*., 2010; Sanders *et al*., 2011; Li *et al*., 2011; Nurwakagari *et al*., 2007; Loosfelt *et al*., 1992; Parma *et al*., 1995).

THE QUATERNARY STRUCTURE OF TSHR

Some workers disagree with the fact that TSH*R* consist of two units and believe TSH*R* is still a single polypeptide chain in natural thyrocyte cell and if *In vivo* study indicating that there are two subunits, it is due to artifact and possible, protease enzyme which can cleave the TSH*R* single polypeptide into two smaller peptide chains (Russo *et al*., 1991). On the other hand there are some disagreement and controversial discussions in this area of TSH*R* studies and some researcher believe the TSH*R* originally consist of two sub-units and this is the presentation of two polypeptide chain in thyrocyte of thyroid gland which is shown itself in laboratory study (Sanders *et al*., 2011; Misarhi *et al*., 1994; Fiedler and Simons, 1995). It should be emphasized this area of TSHR research is mixture area of black and white and there are various controversial argument about it whether TSH*R* is truly either single polypeptide or two polypeptide and even three polypeptide chains (Chazenbalk *et al*., 1997; Picchietti *et al*., 2009).

There are also some studies enlighten the true condition of research works in this area. These studies indicating if two polypeptides of *A* and *B* should be designated for TSH*R*, the *A* chain of TSH*R* (35 KDa) have been traced within the blood circulation and *B* chain (42 KDa) mostly collected from thyroid preparation (Picchietti *et al*., 2009; Couet *et al*., 1996; Hunt *et al*., 1992; Murakami *et al*., 1992; Couet *et al*., 1996; Chazenbalk *et al*., 1997). If the theory behind TSHR cleavage and *A* chain release into circulation is to be accepted, consequently the concept behind the auto-immunity to the thyroid gland can easily be documented. The idea behind TSHR cleavage in producing either of two fragments are the basis for extensive studies in this area of research. TSH binds with similar affinity either to intact cleaved TSH*R* (Russo *et al*., 1991) and in fact TSH does not require even a cleaved TSH*R* and therefore TSH can activate the TSHR, witch is not cleaved and it is reported that it is the trans-membrane section of TSH*R*, which in fact transmit the TSH signal through the membrane into thyrocyre cytoplasm region. The other characteristic of TSH*R* in contrary to other glycoprotein of GPC*R* group is that many fragments of TSH*R* exhibit the capacity to bind to TSH and activate the metabolic pathway of thyroid function to produce the hormones (Van Sande *et al*., 1995a, b).

Further studies, in the area of TSH*R* fragmentation and cleavage of even a single polypeptide chain in first place and converting to polypeptide chain post-transitionally into A and B and the connective polypeptide (C-Peptide) as postulated for insulin polypeptide, seems exhibit a very vital and interesting research topic on the presentation of thyroid autoantibody diseases arises from the raised antibody against the shed fragments of TSH*R* which are released into circulation, among the genetically susceptible subjects. (Couet *et al*., 1996; Hunt *et al*., 1992; Murakami *et al*., 1992). The sub-units *A* and *B* which can play an essential role in stabilizing the structure of TSH*R* through possible disulfide bridge, also the earlier four cysteines supposed to link the two sub-units of A and B as well (Kosugi and Mori, 1995).

THE ROLE OF CYSTEIN AS A CRUCIAL AMINO ACID IN THE BIOCHEMICAL STRUCTURE OF TSHR

The presence of four cysteine amino acid at extracellular region of TSH*R* provide a unique segment for he antibody attachment, which is seen particularly among subjects with auto-immunity with sever metabolic disorders (Palczewski *et al*., 2000; Palos-Paz *et al*., 2008; Mansourian, 2010d, e).

There are also studies on the possible mutation of TSH*R* gene and possible malformation of TSH*R* configuration. Furthermore it is postulated any disruption, misplacement or deletion of cystein residues, can have direct effect on the structure of TSH*R* polypeptide chain and even the TSH binding region on TSH*R*, can be manipulated. TSH*R* like other receptors in fact is a glycoprotein and carbohydrate play a vital role in TSH*R* structure and related biological function (Rudajev *et al*., 2005; Hamidi *et al*., 2011).

The other argument about TSH*R* comes from the tertiary and quaternary structure of TSH*R*. Whether single, double or triple sub-units of TSH*R* are present in any cases the disulfide bridges in the TSH*R* are critically importance for the proper structure of any configuration of TSH*R* polypeptide chain (Picchietti *et al*., 2009; Kajita *et al*., 1995).

There are extensive studies on the role of cysteine residues on the structure formation of any postulated type of TSH*R*. It is reported that eleven cysteines residues are participated in the TSH*R* chemical structure and probably arranged into four set of arrangements, which in real term are only it is a postulated pattern. It is argued that two disulfide bridges occurred between four cysteines residues in TSH*R* structure. It is reported that TSH*R* exhibit six glycosylation region within its structure and it seems that six-carbohydrate residue resided on the subunit of TSHR. (Guerra and Rodriguez, 2009; Da Costa and Johnstone, 1998; Fiedler and Simons, 1995).

CARBOHYDRATE PLAYS A VITAL ROLE ON THE TSH*R* BIOCHEMICAL FUNCTION

There are further evidence that all six sites on TSH*R* are glycosylated and further postulated that the carbohydrate residue on the TSHR are derived from mannose present within the endoplasmic reticulum (Russo *et al*., 1997). It is reported that the glycosylated segment TSH*R* play an important role in TSH and autoantibody binding to the TSH*R* (Amino *et al*., 1987). It is further reported the carbohydrate residue on the TSH*R* structure, converting the TSH*R* B-subunit into TSH*R* formation. In general TSH*R* dimerization are occurred when TSH binds to its receptor (Russo *et al*., 1991; Russo *et al*., 1992; Chazenbalk *et al*., 1997; Fiedler and Simons, 1995; Chazenbalk *et al*., 1996; Da costa and Johnstone, 1998).

THE EVENTUAL OUTCOME OF TSH*R* MUTATION

There are well-documented reports on the scale of eventuality of TSHR mutation. It is also argued that various TSH*R* mutations eventually correlated with a particular thyroid disease (Kosugi, 2002; Nebel *et al*., 1999; Paschke *et al*., 1996; Dias, 1996; Duprez *et al*., 1997; Hebrant *et al*., 2011).

The consequence of TSH*R* mutation is associated with failure of TSH being bind to TSH*R* as a result the thyroid gland either functions in very low scale or it may not function at all. TSH*R* mutation lead to conformational change of TSH*R* polypeptide unable to bind to TSH with eventual thyroid disorder of not producing a very low amount of thyroid hormone unacceptable for the well being and proper metabolic function. This subsequently leads the patient to get involved into primary hypothyroidism (Russo *et al*., 2000; Nebel *et al*., 1999; Paschke *et al*., 1996; Biebermann *et al*., 2001).

February 10, 2011The TSH*R* somatic mutations, which may be accompanied with TSHR over-activity, are also reported to stimulate the hyper activity of thyroid gland. It occurs due to genetic mutation at chromosomal level independent of autoimmunity to the TSH*R* with catastrophe adverse consequences (Farid *et al*., 2000; Sanders *et al*., 2010; Gruters *et al*., 1998; Kohler *et al*., 1996; Kopp *et al*., 1997a).

There are also some reports indicating that TSH*R* can become active, without TSH binds to TSH*R* or in some other cases TSH*R* show much more higher reactivity with TSH leading in both cases to hyperactivity of thyroid gland (Sanders *et al*., 2011; Nakabayashi *et al*., 2000). There are many suggestions in why TSH*R* should exhibit such over affinity or self-activity. In this later case, all arguments either additional or silent domains within the TSH*R* at some point that interfere with the routine process. It may also be some conformational change on the TSH*R* which may eventually lead to the over activity of thyroid gland due to extra production of TSH*R* and TSH binding and eventual signal which produce due hormone-reporter complex. There are also some studies indicating a mechanism is available in how TSH binds to the TSH*R* and in which way the signal is transmitted into the thyrocyte domain of thyroid. This area of research is not fully understood, but the main point behind this theory is that TSH binds to several section of TSH*R* with subsequent signal transduction. It is reported also that antibody raised against TSH*R* also follow the same mechanism, with ultimate thyroid activation through cAMP production (Oda *et al*., 2000; Morgenthaler *et al*., 2003; Hunt *et al*., 1992). It should be mentioned that various weak bonds including hydrophobic, ionic, hydrogen bond are involved in TSH*R* combination between TSH, antibody and TSH*R* to activate the thyroid gland (Fremont *et al*., 1997; Dias, 1996; Schreiber and Fersht, 1993; Lowman and Wells, 1993; Wang *et al*., 1997).

THE ROLE OF IODINE IN TSH*R MUTATION*

There are cases, in which iodine deficiency may eventually prepare the bases, to stimulate the mutation of TSH*R* and in majority of cases the solitary toxic adenoma is a direct consequence for the latter disorder

(Fuhrer *et al*., 1997a; Parma *et al*., 1997; Christensen and Davis, 2004). In contrary to the above result the activation of TSH*R* have been found among autonomous adenomas (Takeshita *et al*., 1995; Vanvooren *et al*., 2002). The receptor mutation and subsequent thyroid resistance to thyroid stimulating hormone the true stimulator of the gland result in thyroid hypo function some mutation in the TSHR gene may in some cases eventually lead to hypothyroidism (Mansourian, 2010a-e; Mansourian *et al*., 2007). There are also some reports indicating other types of mutation of TSH*R* was found in nodule and multinodular goiter (Hebrant *et al*., 2011; Duprez *et al*., 1997; Tonacchera *et al*., 1998a; Tonacchera *et al*., 1998b, 1996; Holzapfel *et al*., 1997; Maier *et al*., 2006).

TSH*R* STRUCTURAL MALFORMATION AND SUBSEQUENT TSH-TSH*R* MODIFICATION LEAD TO THE THYROID DISEASES HEREDITARY TOXIC HYPERPLASIA (NON-AUTOIMMUNITY)

TSH*R* abnormality in many ways leading to the thyroid diseases, as follow: at some point the TSH*R* can be activated in the absence of TSH, or there are situation where the TSH*R* is more sensitive to the present of TSH. TSH*R* can be modified in way that its specificity to TSH is expanded. Considering the above statements one can consider that the thyroid may enter into either a condition of autonomous thyroid hormone production, or the receptor require lower concentration of TSH to adjust itself to the new condition and finally in the third category the thyroid is not under the negative feed-back required for the control of thyroid hormone production. In any condition it is the cAMP pathway which is the mediator in responding to what thyroid has to do. One of the main reason for hyperactivity of thyroid gland is the autoimmunity of thyroid gland in Grave's disease, in which TSH*R* wrongly stimulated by the raised antibody against TSH*R* which is different from the TSH*R* mutation (Kraemer *et al*., 2009; Thomas *et al*., 1982; Hebrant *et al*., 2011; Tonacchera *et al*., 1996; Fuhrer *et al*., 1997b; Tonacchera *et al*., 2000; Biebermann *et al*., 2001; Alberti *et al*., 2001; Khoo *et al*., 1999; Lee *et al*., 2002; Fuhrer *et al*., 2000; Aoshima *et al*., 2000; Esapa *et al*., 1999; Kopp *et al*., 1995; Murakami *et al*., 1992; Van Sande *et al*., 1995a).

Toxic thyroid hyperplasia: The mutation of TSHR has been manifested among children with parents having no mutation of TSH*R*. Such disorders eventually causing congenital hyperthyroidism and the children require critical attention and therapeutic treatment which seems absolutely necessary (Kopp *et al*., 1995; Gruters *et al*., 1998; Kopp *et al*., 1997a; Holzapfel *et al*., 1997; Kopp *et al*., 1997b; Karges *et al*., 2005; Khoo *et al*., 1999).

Autonomous toxic adenoma: The adenoma to thyroid gland has been reported and the result was a type of hyperthyroidism which needed medical follow up and treatment. Toxic adenoma raised, due to somatic mutation and activated TSH*R*, eventually lead to adenomatous thyroid and follicular cancer. This all happened due to mutated TSH*R* (Lyons *et al*., 1990; Goretzki *et al*., 1992; Suarez *et al*., 1991; O'Sullivan *et al*., 1991; Fuhrer *et al*., 1997a; Kopp *et al*., 1997a; Lee *et al*., 2002; Russo *et al*., 1995).

Gestational hyperthyroidism: There are extensive studies indicating human chorionic gonadotropin (HCG) may bind to TSH*R* and stimulating the thyroid during pregnancy (Mansourain, 2010c; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2010b; Golinor, 1997; Burrow, 1993; Swaminathan *et al*., 1989; Zarei *et al*., 2009). In some pregnancy cases where the HCG concentration abnormally elevated it can subsequently trigger the TSH*R* to be activated. And eventually thyroid gland stimulated producing an elevated amount of thyroid hormones (Mansourian, 2010c; Goodwin *et al*., 1992; Swaminathan *et al*., 1989; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2010a; Burrow, 1993; Christensen and Davis, 2004; Saber *et al*., 2009; Eftekhari *et al*., 2007; Vern *et al*., 2003).

It is believed that the similarity of biochemical structure between TSH and HCG and the related receptor may be considered as a vital step in the thyroid stimulation during some pregnancy resulting in hyperthyroidism during this period of women life. It seems the sever hyperthyroidism during some pregnancies which is accompanied with serious complications and clinical manifestation of hyperemeis gravidarum directly related to thyroid gland stimulation by abnormally raised HCG (Shahmohammdi *et al*., 2008; Mansourian, 2010c; Mansourian *et al*., 2010b; Miyai *et al*., 2005; Vassart and Dumont, 1992; Kopp *et al*., 1995; Rodien *et al*., 1998).

There are controversial arguments in this area of research and some believe it is the mutation of TSH*R* in susceptible women, which make the thyrotoxicosis an overt pathway with related clinical manifestation. It is the amino acid misplacement within the structure of mutated TSH*R*, which cause the elevated HCG binds to TSH*R* and stimulate the thyroid to enter into thyrotoxicois in the absence of TSH, which is the true TSH*R* stimulator (Mansourian, 2010c; Rodien *et al*., 1998).

There are rare cases, in which the subjects are euthyroid, but with elevated TSH and there are arguments that the possible mutation within the receptor, make it difficult for the normal TSH concentration to bind properly to the TSH*R* and therefore an extra amount of TSH is required for the thyroid to be able to produce enough thyroid hormones. The sever hyperthyroidism during some pregnancies accompanied with serious complication with obvious clinical manifestation of hyperemeis gravidarum. It is said in addition to what was mentioned above the base behind this abnormality may come from the possibility that due to mutation of TSH*R* in one hand it can not bind properly to the thyrocyte membrane where it is originally located and the inability to bind to the TSH in other hand (Kajava *et al*., 1995; DE Roux *et al*., 1996; De Bernard *et al*., 1999). There are also other type of loss of function and mutation of TSH*R* also have been indicated in some other studies and the patients with above criteria demonstrat higher TSH level, with low thyroxine (Abramowicz *et al*., 1997; Biebermann *et al*., 1997; Gagne *et al*., 1998). Anatomically thyroid size looks smaller than normal. The other reason behind hypothyroidism in such subjects it is the inadequacy of iodine within the thyroid gland specifically due to the absence of activated TSH-TSH*R* pathways on thyrocyre to be able to concentrate iodine from blood circulation into the thyroid gland by the inactivity of Na/K pump. (Alberti *et al*., 2002; Calebiro *et al*., 2005). There are also rare cases, in which due to unidentified genetical abnormality the combination between the TSH and TSH*R* is prevented in proper manner leading to the hypothyroidism. It should be mentioned that in some cases mutation on either of TSH or TSH*R* may eventually lead to thyroid disorder leading to hypothyroidism, (Xie *et al*., 1997; Grasberger *et al*., 2005a,b).

Stimulation of thyroid takes place through following pathways*:*

- The mutations of TSH*R* which eventually stimulate the thyroid through the autonomous activation of thyroid gland without the need for TSH the true stimulator of thyroid gland
- The increased affinity of TSH*R* with TSH itself or any legend which many bind to TSH*R* with eventual stimulation of thyroid gland
- There are also mutation which enabling the TSH*R* to become more active due to expanded affinity to TSH
- The consequence of all of the above TSH*R* disorder lead to over production of thyroid hormones leading to hyperthyroidism with sever clinical manifestation and need urgent medical follow-up (Van Sande *et al*., 1995a; Lyons *et al*., 1990; Goretzki *et al*., 1992; Grasberger *et al*., 2005a; Suarez *et al*., 1991; Aoshima *et al*., 2000; Tonacchera *et al*., 2000; O'Sullivan *et al*., 1991; Mansourian, 2010e; Mansourian, 2010d)

Suppression of thyroid occurs through the following mechanism:

- The inactivation of TSH*R* and eventual loss of ability of receptor to bind to TSH
- Misplacement of some amino acids within the vital part of TSH*R* structure where TSH binds TSH*R* on thyrocyte membrane and consequently the proper TSH-TSHR complex is not formed
- The production of modified form of TSH*R* which can not bind to the thyrocyte membrane properly
- All of the above TSH*R* malfunctions can eventually lead to a weak linkage of TSH-TSH*R* complex which might be accompanied with sever hypothyroidism if the patient is left clinically unattended (Abramowicz *et al*., 1997; Alberti *et al*., 2002; Russo *et al*., 2000; Mansourian, 2010a; Mansourian *et al*., 2008; Marjani *et al*., 2008)

CONCLUSION

The outcome of TSH*R* mutation can be summarized as either of stimulation or suppression of thyroid gland leading to hyperthyroidism or hypothyroidism, respectively. Therefore the outcome of TSH*R* mutation eventually is left with two obvious scenarios of either increased or decreased production of T4 and T3.In either of cases it is accompanied with metabolic disorders of sever adverse effects if the thyroid is remained untreated.

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