Thyroid Stimulating Hormone

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In vertebrates, the endocrine system is comprised of a number of glands that release particular hormones into circulation. Many of these hormones are released along an axis, meaning that particular “releasing” hormones act on various receptors that induce the production and release of another hormone downstream. For example, the hypothalamic-pituitary thyroid axis works in this manner. Similar to the nervous system, the primary function of the endocrine system is to communicate and control various aspects of the body through the release of these hormones. Therefore, it is imperative that all systems in the body work in harmony with the endocrine system in order to maintain homeostatic ranges. This maintenance of homeostatic hormone levels is accomplished through various feedback mechanisms set in place along the particular axis. Similar to a system of checks and balances, the body’s hormone levels are constantly being monitored and altered accordingly.

The hypothalamic-pituitary thyroid axis is as it sounds, a direct functional relationship between the hypothalamus, anterior pituitary gland and thyroid gland which results in the releasing of thyroid hormones thyroxin (T4) and triidothyronine (T3) into circulation. Similarly, the hypothalamic–pituitary gonadal axis works in unison to produce estrogen and testosterone. Many other axis function in this same capacity using the hypothalamus and pituitary gland as intermediate messengers to a downstream target receptor.

As stated above, the body is constantly measuring levels of hormones in circulation. Within this particular axis, the measurement of T3 and T4 is done by the anterior pituitary gland. If the pituitary measures low levels of T3 and T4 in circulation, a signaling cascade is set forth which results in stimulated release of thyrotropic releasing horomone (TRH) from the hypothalamus. Thyrotrophic releasing hormone acts on the anterior pituitary which results in the release of thyroid stimulating hormone (TSH). TSH, the intermediate hormone, acts downstream
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on the thyroid causing a release of T3 and T4 into the blood. As this occurs, the anterior pituitary is measuring levels of T3 and T4 and halts the production of TRH and TSH when levels of T3 and T4 are homeostatic. Clearly, each hormone plays an important role in proper function of the axis; in particular to this writing, we will observe the structure, production, target receptor and various other topics pertaining to TSH.

The life of a thyroid stimulating hormone begins in the anterior pituitary. Located on specific basophilic like cells on the anterior pituitary are G coupled receptors which thyrotropic releasing hormone attaches to. This attachment induces the signaling cascade phospholipase C in which PIP2 or phosphatidylinositoldiphosphate is cleaved into IP3 (inositol triphophate) and DAG. The cleavage of PIP2 to DAG and IP3 is a common signaling pathway in the production of many cells within the human body including, immunologic T cells. As a result, the production of IP3 increases calcium release and results in activation of transcription factors. DAG, on the other hand, activates protein kinase C pathway which leads to activation of transcription factors as well within the nucleus. The activation of these transcription factors leads to the synthesis of TSH and release into circulation (Boron & Boulpaep, 2012).

Thyroid stimulating hormone is classified into the glycoprotein family along with follicle stimulating hormone and luteinizing hormone. These glycoprotein hormones are all stored within the basophilic like pituitary cells and consist of sugar moieties that are covalently bonded to asparagines on the adjacent polypeptide chain. All above hormones contain two peptide sub units, an alpha (a) subunit which is identical for each hormone and is produced by a gene located on chromosome six, and beta (b) subunit which is unique to the particular hormone. The gene which encodes for the beta subunit of TSH is located on chromosome one. Production of the various glycoproteins begins in the rough endoplasmic reticulum and Golgi apparatus where
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pairing of the two subunits occurs followed by unprompted folding till a stable hormone is
produced (Goodman, 2009).

After production and release of thyroid stimulating hormone from the anterior pituitary,
TSH travels through the circulatory system to the thyroid stimulating hormone receptor or,
TSHR located on thyroid epithelial cells. TSHR is classified in the family of G protein coupled
receptor (GPCR), class A, rhodopsin- like GPCR in the subfamily A7. Another receptor in this
subfamily is motilin receptor, used in stimulation of smooth muscle in the gut. G coupled
protein receptors are a very common type of hormone receptor also used for FSH and LH and is
classified as a transmembrane receptor. A large portion of GPCR is extracellular and is denoted
as the ligand binding domain and a small portion is intracellular and is the signal transduction
domain. The genes that code for TSHR are located on chromosome fourteen. An additional
name for the GPCR is the seven-transmembrane domain receptor because of the extracellular N-
terminus followed by these seven transmembrane receptors located in the cell membrane. These
receptors help increase affinity and communication between the hormone, target receptor and the
following signaling cascade (White & Porterfield, 2012). In comparison, the class of receptor
tyrosine kinase which insulin hormone binds to has a single transmembrane pathway.

Upon TSH adhering to G protein thyroid stimulating hormone receptor on thyroid
follicular cells, a series of events coined the second messenger concept occurs. This results in a
signal being passed down through the cell eventually leading to the nucleus where production of
thyroid hormone initializes. G coupled protein receptors have a variety of second messenger
pathways available to them. For thyroid stimulating hormone, this pathway is dubbed G(s) and
begins with the G(s) alpha protein subunit activating adenylyl cyclase and generating production
of cyclic AMP (cAMP). Cyclic AMP activates protein kinase A (PKA) which in turn
Thyroid Stimulating Hormone phosphorylates cytoplasmic and nuclear proteins CREB and phospholipase C among others. This results in activation of transcription factors and cell proliferation of TSH (Kondo, Ezzat & Asa, 2006). In comparison to the G(s) pathway, the G(q) secondary messenger pathway which is used for hormones such as oxytocin differs slightly in how the G subunit activates the signal cascade. Unlike G(s) messenger system where the alpha G(s) activates adenylyl cyclase which in turn produces cAMP, G(q) activates phospholipase C (PLC) and immediately generates IP3 and DAG from IPP2 without any cAMP mediator (Norris and Carr, 2013 pg 54-56). It is interesting to see how similar the varying communication methods are within the body. Communication for the production of hormones versus immunological cells is almost identical yet; the end results are completely different.

Unfortunately, TSHR is a common target for molecular mimicry through a wide variety of autoantibodies which can wreak havoc on thyroid hormone levels within the body. Examples of these various antibodies are thyroglobulin, thyroid peroxidase, sodium-iodide symporter and thyrotropin receptor autoantibody. In particular, thyrotropin receptor autoantibody or TSH-Ra acts in similar fashion to TSH and results in over production of T3 and T4 from the thyroid gland. The diagnosis of this autoimmune disease is called Graves’ Disease. TSH-Ra is an IgG class of antibody having two variable regions or binding regions and one constant region. Due to the two variable binding regions, one TSH-Ra is able to adhere to two different TSH receptors at once thus inducing a larger production of T3 and T4 (Yeung, 2009).

Once the TSH-Ra attaches to the receptors, activation of adenylyl cyclase and production of cAMP occurs in a similar manner to TSH. However, unlike TSH which activates phospholipase C (PLC) and in turn cleaves IP3 into PIP2 and DAG, TSH-Ra activates cAMP and immediately cleaves IP3 without activation of PLC (E Laurent & J Van Sande, 1991). Although
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TSH and the autoantibody differ in signaling, both induce production of T3 and T4. Due to the autoantibody causing increased T3 and T4 circulating, the body down regulates the production of TSH which can eventually cause complete dysfunction and loss of TSH hormones from the anterior pituitary. Lastly, TSH-Ra attaches to the follicular cell on the thyroid permanently thus causing constant release of T3 and T4 and results in hypertrophy of the follicular cells. This hypertrophy can cause an enlarged thyroid gland also known as a goiter (Yeung, 2009). There were no apparent medications which block TSH receptors on the thyroid. In order to reduce T3 and T4 production, methimazole is used which prevents the iodine and tyrosine from binding and creating T3 and T4. Other effective treatments include removal of the thyroid through surgery or radioactive iodine which down regulates the thyroid function. These individuals require daily T3 and T4 medication.

Thyroid stimulating hormone’s communication with the thyroid is important for the proper release and monitoring of thyroid hormone levels. This communication is constant and always playing a role in the serum levels of the hormone. This particular glycoprotein holds its own unique function yet, there are many similarities in how these classes of hormones and hormone receptors are constructed. These similarities are very beneficial in understanding why certain hormones function in certain ways. Additionally, this understanding helps identify medication applications as well as the understanding of disease which targets these areas of the endocrine system.
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Works Cited


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