

**Human Physiology**  
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**Week - 05**  
**Lecture - 04**

Hello everyone, welcome to another new class on human physiology. In this class, we will discuss the thyroid and how the thyroid hormones are synthesized. So, if you remember in the last few classes, we have been discussing different endocrine glands, and some of the endocrine glands we covered in detail, for example, the pancreas. This class will cover our thyroid gland, and we will see how the thyroid gland synthesizes different types of endocrine hormones and what their specific roles are in our body. So, let us stay with it. So, what different content will be covered in this class? As we said, we will first discuss the thyroid gland, and then we will see how the synthesis of different thyroid hormones happens in our body.

Furthermore, we will also see the effects of thyroid on the body, and we will briefly discuss hypothyroidism and hyperthyroidism. In the next class, we will thoroughly discuss different endocrine diseases, and it will be covered in detail. So, as you see, the thyroid gland is shaped like a butterfly and is located in the anterior neck, just inferior to the larynx. And as you know, the function of the thyroid gland is to synthesize thyroid hormones, which play a very crucial role in our metabolic activity.

So, in terms of thyroid hormone synthesis, there are different roles of other hormone cells. So, let us see what the different types of steps involved in the synthesis of the thyroid hormone are. So, in this table, you can see in the first step the hormone that is secreted from the hypothalamus, which is called thyroid-releasing hormone. This TRH, or thyroid-releasing hormone, eventually stimulates the anterior pituitary gland to secrete thyroid-stimulating hormone. Once the thyroid-stimulating hormone is secreted by the anterior pituitary, it enters our blood circulation and eventually reaches the thyroid gland.

In the thyroid gland, certain steps happen sequentially. So, you can see that the first step occurs, which is thyroglobulin production in the thyroid follicular cells. After that, the sodium iodide symporter causes iodide uptake. After the iodide uptake, iodine oxidation happens by the function of the thyroid peroxidase enzyme. After the iodine oxidation, thyroglobulin iodination happens, followed by MIT and DIT coupling, and eventually thyroglobulin proteolysis happens.

So, this entire step, starting from thyroglobulin production to thyroglobulin proteolysis, is part of thyroid hormone synthesis. And this happens in various cells and compartments of the thyroid gland. And eventually, once the thyroid hormones are produced, the thyroxine binding globulin protein, or the TBG protein, eventually binds with the T3 and T4 enzymes, and they get circulated throughout the body. In terms of thyroid hormone synthesis, there is this specific organ that plays a crucial role, and we have to know why and how. So, the first one, which is mostly like the first major component of the organ involved in thyroid hormone synthesis, is the hypothalamus, because in the last slide we also said that the hypothalamus produces the TRH, or the thyroid-releasing hormone.

Once this TRH is produced, it comes and stimulates the anterior pituitary gland. So, TRH, once produced by the hypothalamus, comes out and stimulates the anterior pituitary gland, and eventually, it stimulates the production of TSH, which is the thyroid-stimulating hormone. Again, in the same way, thyroid-stimulating hormone comes into the bloodstream and goes to the thyroid gland for the following cascades. So, in general, the hypothalamus, anterior pituitary gland, and thyroid gland together are called the hypothalamic-pituitary-thyroid axis or HPT axis. So, it is very important to know that the hypothalamic-pituitary-thyroid axis, or the HPT axis, is an important and crucial component for the synthesis and development of our different thyroid hormones.

Now, let us see how this step-by-step synthesis of thyroid hormones occurs, right? So, the first step, as we said, is that the hypothalamus, which is present in our brain, has a very specific type of cell, for example, the paraventricular nuclei. So, this type of paraventricular nuclei cells in the hypothalamus secretes TRH, which is the thyroid-releasing hormone. Once this TRH is secreted from the paraventricular nucleus of the hypothalamus, it comes out through the hypophysial portal system, goes to the anterior pituitary, and stimulates the anterior pituitary. Once it stimulates the anterior pituitary, it secretes another hormone, which is TSH, or thyroid-stimulating hormone. So, once we said that once the thyroid-releasing hormone goes to the anterior pituitary, it secretes a peptide type of hormone, which is TSH or thyroid-stimulating hormone.

Nowadays, thyroid-stimulating hormone enters the bloodstream and goes to the thyroid gland. To start the synthesis of different thyroid hormones like triiodothyronine and thyroxine, which are T3 and T4. And then, once the T3 and T4 are synthesized in the thyroid, they eventually go out to the bloodstream and to the target tissue for different functions. It is important to highlight that TSH is a peptide type of hormone. Now, as we said, once TSH is secreted, it enters the circulation and eventually goes to the thyroid gland.

In the thyroid gland, there are different thyroid follicles or follicular cells. So, you can see here that in the thyroid gland, you will see specific circular types of thyroid cells or follicular cells. Sometimes, they are also called thyrocytes. And inside this cluster of thyroid cells or thyrocytes, there is a lumen space that is called colloid. So, there is this lumen space which is called colloid or which is filled with a substance called colloid.

And once TSH comes into circulation, in this type of thyrocytes or the thyroid cluster cells, there is a thyroid-stimulating hormone receptor. So, what is present here is a receptor for thyroid-stimulating hormone, and this TSH hormone eventually comes here and binds to this thyroid-stimulating hormone receptor. Once this is bound to the thyroid-stimulating hormone receptor, the TSH eventually enters the thyrocyte cell and starts the production of thyroglobulin, followed by the different thyroid hormones. So, let us see how this synthesis happens step by step. So, as we said, in this thyroid cluster of cells or thyrocytes, what do we have? We have the TSHR receptor, which is the thyroid-stimulating hormone receptor, and now this TSH hormone, or the thyroid-stimulating hormone, comes into circulation and binds to this thyroid-stimulating hormone receptor.

So, once thyroid stimulating hormone binds to the TSHR receptor, what it basically does is that TSH eventually promotes or stimulates the follicular cells to produce or synthesize a type of molecule called thyroglobulin. So, basically, this type of protein molecule, like thyroglobulin, is highly stimulated once TSH binds with the TSHR receptor. So, in the next step, this is one of the most important components for thyroid hormone synthesis,

thyroglobulin. Another important component for the thyroid hormone synthesis is iodide. So, together once the thyroglobulin and the iodide are combined, they produce the thyroid type of hormone.

So, where will we get the iodide? Basically, we consume different types of food, and iodine is one of the components of food nutrients. So, basically, we consume iodine from food, and eventually that iodine can get ionized into iodide ion, which is I minus. Now, this ion is basically going or is present in the bloodstream. Generally, iodide ions are highly concentrated inside the thyroid cells or the follicular cells, but they are generally low in amount in the bloodstream. That means the iodide ion, or the I<sup>-</sup> ion, has to go inside these thyroid cells against its concentration gradient.

So, what I am saying is that iodide ions are low in concentration in the blood and iodide ions are generally high in concentration inside the follicular cells. That means it needs to go against its concentration gradient. Now, who helps with that? Sodium ion. As you remember, sodium, when it goes inside, also helps the iodide ion in a secondary active co-transport mechanism. So, the sodium ion, in terms of a kind of piggyback, basically takes the iodine ion on top of it and helps the iodide ion cross the barrier and enter the follicular cells in a mechanism called the sodium iodide cotransport mechanism.

So, in a mechanism called sodium iodide cotransport mechanism. And this mechanism, if you remember our cellular transport class, we said that secondary active transport does not directly use ATP, but all secondary active transports are highly dependent on the primary sodium-potassium ATPase pump to initially build the sodium concentration gradient. So, this sodium iodide secondary active cotransport pump eventually uses ATP indirectly for this process. So, let us see what happens to the iodide then. So, in this way, iodide from the low concentration that is present in the blood, with the help of sodium, goes inside these follicular cells.

Now, there is another receptor which is called penguin receptor. So, this iodide ion moves against this concentration gradient because the iodide concentration here is much higher. In the colloidal space of this thyroid cluster of cells, iodide concentration is low. So, basically, like a protein-mediated diffusion or uptake, a penguin-type protein receptor or transporter facilitates the movement of iodine iodide ion from the follicular cells to the colloid space. So, in this way, in the colloid space of the cell, what do we have now? We have thyroglobulin, an abundant amount of thyroglobulin, and we also have an abundant amount of iodide ion.

Now, let us see what the next step is. So, once this iodide ion comes inside this colloidal part, this iodide ion gets oxidized to iodine. So, this iodide ion is oxidized to iodine by an enzyme called TPO, which is thyroid peroxidase. So, the enzyme that is present in those thyroid cells, or in the cuboid or the colloid part, which is the thyroid peroxidase, basically oxidizes the iodide ion to iodine or I<sub>2</sub>. This is called the iodide oxidation step.

Then let us see what happens in the next step. Once the oxidation happens, the iodide ion converts to iodine. So, after this oxidation step, the next step is the iodination of the tyrosine. So, what is tyrosine, basically? This is the thyroglobulin that was initially stimulated or overproduced by the effect of TSH, right? And this thyroglobulin protein eventually came out into the colloidal space. Now, thyroglobulin protein has different amino acids, and tyrosine is one of the most prominent and important amino acids present in thyroglobulin.

Now, once the iodine, which gets oxidized from the iodide, eventually what happens is that iodination occurs. So, iodine gets conjugated or bound with this tyrosine type of amino acid residues. Let us rehearse one more time. So, what we just said is that initially, TSH, which binds to the TSHR receptor, stimulates the production of thyroglobulin protein from the follicular cells, which eventually goes inside the colloid. In the same way, iodide enters the follicular cells through the sodium iodide secondary co-transport mechanism.

From there, using the penguin protein transporter, it goes to the colloid space; then this iodide ion gets oxidized and becomes iodine. Once the iodine forms, eventually on the thyroglobulin protein there are a lot of tyrosine amino acid residues, and those iodine molecules eventually get bound to this tyrosine molecule either in one number, then it will be called monoiodotyrosine. So, MIT, which is like mono-iodotyrosine, can also bind in pairs, meaning two molecules can bind to the tyrosine, which will be called diiodotyrosine. So, if one molecule of iodine binds to the tyrosine, it is called MIT or monoiodotyrosine, and if two molecules bind, it is called diiodotyrosine. So, this process is also called iodination.

Now, let us see what the next step is. So, once this DIT and MIT or the iodination happens, right? So, we now have DIT and MIT. In the case of DIT, how much iodine is there? 2. In the case of MIT, how much iodine is there? Only 1. After this step, what happens is that the TPO enzyme plays a role in all the other steps.

So, we just skip this thing that here also thyroid peroxidase, or the TPO enzyme, only reacts and actually triggers this step of iodination. So, what I mean to say is that the same enzyme, TPO, also affects this. So, in this step, when the DIT and MIT form, the coupling reaction happens between them. So, for example, what do we have? We have DIT, and we have MIT. Now, if two DITs get coupled, they will form T4 thyroid hormone or the thyroxine hormone.

And then, if one molecule of MIT and one molecule of DIT get coupled, we will get T3 or triiodothyronine hormone. And which enzyme again is helpful or triggered this conversion, the same way the TPA enzyme or the thyroid peroxidase enzyme, which is basically eventually triggering all these steps of iodine oxidation? Then, like iodination, followed by the coupling. So, eventually after the coupling by the activity of the TPO, what do we get? We get T3, which is a triiodothyronine hormone, and then we also get T4, which is a tetraiodothyronine hormone or the thyroxine hormone, okay. So, eventually T3 and T4 are the active thyroid hormones that are produced with the thyroglobulin inside the thyroglobulin colloid. But one thing, they are still attached to the thyroglobulin moiety, right? So, they are still attached to the thyroglobulin molecule.

So, T3 and T4, even though they are synthesized, are still attached to the thyroglobulin type of protein molecule. So, let us see, as we said, the T3 and T4 after the coupling reaction by the activity of the TPO. The T3 and T4 are still coupled with the thyroglobulin type of protein molecule. Now, the T3 and T4 need to basically come inside along with the thyroglobulin. So, what happens basically? Endocytosis happens.

So, endocytosis actually causes the T3 and T4 along with the thyroglobulin to basically be endocytosed or brought inside the follicular cell. And once it comes to the follicular cell proteolytic enzyme activity, it eventually breaks down the bond between the thyroglobulin and the T3 and T4, releasing the T3 and T4 from the thyroglobulin. So, what we just said is that initially after the coupling, T3 and T4 are still there with the thyroglobulin residue and the protein. Basically, the molecule, through the process of endocytosis, comes inside the follicular

cells from the colloidal part, and eventually, once it is inside the follicular cells, the proteolytic enzyme activity cleaves or degrades the bond between T3, T4, and thyroglobulin, releasing T3 and T4. So now what we have is that after the proteolytic enzyme activity, we have the T3 and T4 inside the follicular cells.

This T3 and T4 basically get released and enter the bloodstream. Where this thyroxine binding globulin protein, this thyroxine binding globulin protein, or the TBG eventually gets attached to or binds with the T3 and T4, and then basically it distributes and circulates to different types of organs. So, what happens eventually is that T3 and T4 bind with the thyroxine binding globulin protein, or TBG, and along with this binding condition, they get spread and distributed across various body organs. So, this is the whole mechanism. If we quickly rehearse what we said, first we have the hypothalamus, right? So, the hypothalamus secretes thyroid-releasing hormone that eventually stimulates the anterior pituitary, and once the anterior pituitary is stimulated, it releases TSH or thyroid-stimulating hormone.

This TSH eventually comes and binds with the receptor that is called TSH receptor, right? which is the TSHR receptor, and once it binds with the TSHR receptor, it basically stimulates the production of thyroglobulin from the follicular cells. Eventually, the thyroglobulin goes to the colloid cell. In the same way, we need one more important component for thyroid hormone production, which is iodide. Iodine, which we get as a nutrient from different foods, is ionized as iodide. By the action of the sodium iodide co-transport mechanism, which is a secondary active transport mechanism, iodide is internalized into the follicular cells, and using the pendrin-type protein transporter, it is pumped out into the colloid space.

And now, once we have both thyroglobulin and iodide, iodide at first, like with the activity of this enzyme, which is thyroid peroxidase or TPO, it converts iodide to iodine. Once it is converted to iodine, iodination happens. So, in the thyroglobulin, we said there is the amino acid, which is tyrosine. So, either iodination happens with one molecule of iodine, which is called MIT, or iodination can happen with two molecules of iodine, which is called DIT. So, once this DIT and MIT form, they can couple again by the action of TPA to form either T3, which is triiodothyronine, or T4, which is tetraiodothyronine or thyroxine.

Eventually, they are still together. So, what happens? They get endocytosed inside the follicular cells, where the proteolytic enzymes eventually cleave the bonds between T3, T4, and thyroglobulin. Now, this T3 and T4 come into the bloodstream and, with the help of thyroxine-binding globulin protein or TBG, eventually in this binding condition, they get distributed to various organs for their function. So, hopefully you understood the whole mechanism of thyroid hormone synthesis to eventually produce T3 and T4. Now, let us briefly discuss what the different effects of thyroid are in our body. So, at the cellular level, it basically increases protein synthesis and metabolic activity, and that is why we say thyroid hormones are highly important for our metabolic activity.

So, in this way, this increases the overall metabolism, and as you know, once the metabolism is increased, it produces heat, right? Because it is ATP, like, as you know, in that ion transport class, we also mentioned that it kind of stimulates the sodium-glucose pathway and other metabolic pathways that also further stimulate ATP production; overall, it generates a lot of heat. It increases the number and sensitivity of the beta-1 receptors. Beta-1 adrenergic receptors are found in the heart that can bind to epinephrine and norepinephrine. In this way, it is involved in a fight or flight type of sympathetic response. So, in our neurology class, we will discuss fight or flight in terms of sympathetic neurons.

There we will further discuss. So, in the same way that thyroid hormones increase the heart rate, they also increase stroke volume due to the increase in heart or cardiac contraction. Thus, it can increase cardiac output and blood pressure. In the GI system, thyroid hormones can increase the metabolic activity within the GI tract, which increases GI motility and secretion. In the CNS, or the central nervous system, it can increase neurogenesis, myelination, and dendritic formation. It can also increase the overall activity of the sympathetic nervous system.

It can help in terms of increasing subcutaneous blood flow and maintaining skin homeostasis and the proliferation of skin cells. It also stimulates the sweat glands and oil secretion. It also stimulates hair and other nail growth. As you can see, thyroid hormones have so many applications in terms of metabolic activity, and along with that, the nervous system and growth as well. So, let us think about it: which thyroid hormone is more active? What is the main role of T3 and T4? What does the thyroid gland need to produce hormones? So, you can read further about T3, T3 and T4 and find out their specific role in our body.

Hopefully, you like today's class. You can consult different textbooks, including Tortora and other books, and even medical physiology books by Guyton. So, you can refer to all these books. If you have any further questions, please discuss them with us during the live session. You can also send your questions via email.

Hopefully, you are enjoying the class. Today, we discussed in detail how thyroid synthesis occurs, and we also discussed briefly how thyroid hormones play an important role in different metabolic activities and growth in our body. So, thank you again; hopefully, we will meet with another new class of human physiology very soon. Thank you.