Overview and Integration of Cellular Metabolism

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Lecture 39: Tyrosine Metabolism - III

Hello everyone, welcome back to the lecture series session of NPTEL platform. The topic is overview and integration of cellular metabolism. In the last class, in the last two classes rather we discussed we have started discussion for tyrosine metabolism. Then we have this have discussed the different properties of tyrosine, how what are the metabolic fats of tyrosine, roles of tyrosine. Then we have started to discuss the specialized product which are formed from tyrosine. In the previous class we have discussed about the catecholamines, catecholamines epinephrine, norepinephrine and dopamine.

In today's class we are going to discuss about other two very important products synthesized from tyrosine, thyroid hormone and a pigment melanin. Now thyroid hormone is a very vividly discussed hormone every day, every day we talk about thyroid level, thyroid hypothyroidism, hyperthyroidism, thyroid disorders. So, let us learn a few things about thyroid hormone and its synthesis. So, thyroid hormones are of two there are two molecules tyrosine which is T 4 tetra iodo thyronine and T 3 tri iodo thyronine.

Remember T 4 is the tetra iodo thyronine, T 3 is the tri iodo thyronine why we will discuss. Now this T 4 and T 3 these are the thyroid hormone and they are synthesized from a protein thyroglobulin is a large precursor protein and in those proteins there are tyrosine residues important from those tyrosine residues basically those are iodinated, iodinated by activated iodine. So, thyroglobulin the tyrosine residues of thyroglobulin and activated iodine they together form the thyroid hormone both T 4 and T 3. Now thyroglobulin the precursor protein is basically a large glycosylated and iodinated protein. Around 660 kilo Dalton is the molecular weight of this protein where the carbohydrate content is around 8 to 10 percent I told you this is a glycosylated protein.

So, the carbohydrate content is very high 8 to 10 percent and also the iodide that is 0.2 to 1 percent and remember this range is based on the dietary availability of iodine which decides how much iodination will be there in the thyroglobulin. Now, thyroglobulin has

2 large subunits around 115 tyrosine residues in the total around 500 amino acids there is 115 tyrosine residues. So, basically this is a very tyrosine rich protein and these tyrosine residues are basically the sites of iodination that is why tyro presence of tyrosine is important in thyroglobulin. Now in that thyroglobulin residues around 70 percent of the iodide exist in the inactive precursors that is mono iodide tyrosine and di iodide tyrosine and 30 percent are basically the iodothyronyl residues T 4 and T 3.

And these thyroglobulin along with mono iodide tyrosine di iodide tyrosine T 4 T 3 they all are stored in the colloid intracellular if this colloid is the storage of thyroglobulin as well as thyroid hormones. Now how the synthesis of thyroid hormone occurs? Basically this is iodination of the tyrosine which is present in the thyroglobulin residues. So, here you can see this is our tyrosine molecule which is you can see activated iodine is causing the iodination for once forming mono iodide tyrosine for twice iodination occurs twice forming di iodide tyrosine. So, this is our mono iodide tyrosine, this is our di iodide tyrosine then finally, thyronine formation. So, you can see when there is joining of mono iodide tyrosine with di iodide tyrosine that is forming triiodothyronine not tyrosine it forms triiodothyronine please concentrate on the name there is 3 iodinations, but there are 2 tyrosine residues.

So, that is forming triiodothyronine. Similarly, if 2 DIT's di iodotyrosines reacts they they form thyroxine or tetraiodothyronine. So, please concentrate on the name. Now these DIT, MIT, T3, T4 both basically are attached to the thyroglobulin residues and if there is proteolytic degradation it basically releases the T3, T4 from the stored thyroglobulin residues and T3, T4 is are they are released in the circulation. Now thyroid hormone synthesis is not this much simple.

Now, thyroid hormone synthesis is the is not this much simple because there are multiple other steps which has role in thyroid hormone synthesis. So, if you see thyroid gland there are different types of cells there are follicular cells, then colloids where the thyroglobulin along with the thyroid hormones are stored, then epithelial cell linings are there. So, they have different role in thyroid hormone synthesis. Now if we see a cell here this is our extracellular space and this is the follicular space facing the lumen where colloid is there. Now iodine is uptaken from the extracellular space by one transporter that is a sodium potassium ATPase dependent transporter that is thyroidal iodine transporter.

Here you can see the transporter now these transporter has the unique property of concentrating iodine from extracellular space within the thyroid cell against the concentration gradient. So, basically this transporter causes iodine uptake from the extracellular space. Now this iodine is utilized for iodine organification. Iodine

organification means it basically causes iodination of thyroglobulin. How now remember it enters the transporter is located.

In the extracellular sites of the cell it is uptaken inside the cell, but once again the iodine organification occurs in the luminal surface of the follicular cell here. Now iodine organification is basically iodination of thyroglobulin. Remember here is the very important enzyme thyroperoxidase also represented as TPO thyroperoxidase. Thyroperoxidase is one enzyme which contains heme and requires H2O2 as an oxidizing agent also requires NADPH for the organification. So, here you can see with the help of NADPH and oxygen iodine organification is there with the help of the peroxidase.

So, thyroglobulin is forming MIT, mono-iodotyrosine, DIT, di-iodotyrosine and then these mono MIT and DIT they undergoes coupling to form T3 as well as DIT and DIT they undergo coupling to form T4. So, here you can see the coupling reaction mono-iodotyrosine and di-iodotyrosine forms T3 and 2 di-iodotyrosine forms T4. So, these are our coupling reaction. But remember this DIT, MIT as you can see in this structure DIT, MIT, T3, T4 all are attached to thyroglobulin and they are these thyroglobulin as a whole is stored in colloid. So, colloid is the storage of thyroid hormone.

Now, for release of thyroid hormones T3, T4 in circulation the stimulus is TSH thyroid stimulating hormone. Now, when there is stimulation there is proteolytic activity which is induced by lysosome. So, you can see those thyroglobulins or the thyroglobulins in colloids are basically up taken by phagocytosis and pinocytosis forming endosome. Those endosomes are fused with the lysosomes forming endolysosomes. In the lysosome there are different proteolytic enzymes proteases peptideases they break the bonds between T3, T4 and thyroglobulin releases T3 and T4 in the extracellular space and T3, T4 comes out from the cell and comes to the circulation.

Now remember the most active form of thyroxine rather a thyroid hormone is basically T3. So, what happens T4 is also converted to T3 with the help of the enzyme deiodinase. So, there is peripheral deiodinase which converts T4 to T3 in different organs pituitary kidney these are the target organs, livers forming the potent or active form of thyroxine that is T3. Now, deiodinase is also present in the thyroid cell which causes the reutilization of iodine. So, here you can see T3-D4s are released in the circulation, but what remains is monoiodotyrosine and diiodotyrosine.

These are reutilized via deiodination tyrosine is released and those iodides are again reutilized for organification. So, that is the utilization of the available iodine inside our body. There are versatile metabolic role of thyroid hormones thyroid imparts thyroid

hormone imparts different metabolic role starting from carbohydrate metabolism, lipid metabolism to protein metabolism as well. Now the important function of thyroids are it regulates lipid homeostasis, influences the susceptibility of obesity and liver steatosis. It controls the lipid lipolysis or rather controls the lipid accumulation basically thyroid hormone actually enhances the mobilization of lipids.

Apart from that it also enhances the beta cellular beta cell in pancreas also pancreatic development then it controls the feeding behavior also controls the energy expenditure. Thyroid actually increases thyroid hormone increases the basal metabolic rates which causes expenditure of more energy. Then in skeletal muscle it determines the shift of type 1 to type 2 fiber. So, thyroid hormone switches different types of skeletal muscle fibers and via that it decides the steady contraction of skeletal muscle or fast contraction of skeletal muscle. Also regulates the regenerations in skeletal muscle and regulates the energy expenditure.

Then in adipose tissue BAT stands for brown adipose tissue, WAT stands for white adipose tissue. Remember in adults there is majority of the adipose tissues are actually basically white adipose tissue whereas, very small amount around 1 percent are brown adipose tissue which are scattered in white adipose tissues colony. Now in white adipose tissue thyroid hormone regulates their proliferation. Now brown adipose tissues are very important in terms of neonates and different hibernating animal. Remember in brown adipose tissue there is there is different uncoupling protein like thermogenin which causes heat degenerate heat dissipation.

So, this heat production or thermogenesis in brown adipose tissue is quite well regulated by thyroid hormone. So, these are the versatile metabolic role of thyroid hormone which are imparted in different tissues in our body. Now thyroid disorders are grossly here I am showing you they are divided as either high thyroid hormone level or low thyroid hormone level. So, when the thyroid hormone levels are low that is known as hypothyroidism. When the thyroid hormones level are high that is known as hyperthyroidism.

Now the manifestation of hypo and hyperthyroidism they shares few features in common like either due to excess activity or excess energy expenditure which occurs in hyperthyroidism there is fatigue as well as in hypothyroidism where the energy expenditure is very low available energy is low the person is fatigue. So, hypothyroidism the person is fatigue because the energy availability is low whereas, hyperthyroidism the energy expenditure is so high after that expenditure there is fatigue ability. Similarly there is muscle weakness menstrual irregularity as well as enlargement of the thyroid gland which is known as goiter. Apart from that the differential

manifestations are just like opposite to each other in case of hypothyroidism and hyperthyroidism like hypothyroidism there is weight gain whereas, hyperthyroidism there is weight loss. Remember all the metabolic activities are very much catabolic activities or energy expenditures are very much high in hyperthyroidism.

So, there is weight loss whereas, just the opposite occurs in hypothyroidism there is weight gain loss of appetite in hypothyroidism just the opposite increase appetite. Similarly cold sensitivity in hypothyroidism whereas, in hyperthyroidism there is excess perspiration in the patients of hyperthyroidism there is heat sensitivity. Hairs are thin in case of hypothyroidism whereas, in hyperthyroidism there is brittle hair skins are dry in hypothyroidism here the there is thinning of skin. Bowel movements are just opposite there is constipation low bowel movement whereas, in hyperthyroidism there is frequent bowel movement. Then in hyperthyroidism you will notice different neuronal disorders like tremor, uncontrolled repetitive movement, nervousness, anxiety, irritability.

In case of hypothyroidism you will see depression, memory impairment. Also in cardiac activity there is bradycardia or slow heart rate in case of hypothyroidism whereas, because you know the basal metabolic rate is very high there is rapid heart rate and palpitation in patients of hyperthyroidism. So, these are the gross details of thyroid hormone related disorder hypo and hyperthyroidism. Then we are moving on to the pigment melanin synthesis. Now, the melanin terms actually originated from the Greek word melan which stands for black, because melanin pigment gives the black color to our skin hair eye the all the black colors are basically due to the melanin pigment accumulation.

Now, the synthesis of melanin is from tyrosine occurs in melanosomes which is present in the cell melanocytes. So, these are the melanin synthesizing cells which is known as melanocytes. Definitely tyrosine is the precursor molecule and the enzyme important is known as tyrosinase. So, let us see how melanin is synthesized. Now, before that let us discuss different types of melanin in our body.

Mostly there are two types eumelanin and pheomelanins apart from there is other two trichochromes and neuromelanins. Now, eumelanin are of two types one is black another is brown based on their color. Now, eumelanin is insoluble and heterogeneous molecule heterogeneous why basically this is a cross linked product of dihydroxyindole and dihydroxyindole carboxylic acid. So, this these two compounds are cross linked to form the heterogeneous polymer of eumelanin. Coming to hypo sorry pheomelanin now pheomelanin it is most the color is mostly yellowish to reddish brown.

Remember eumelanin is insoluble whereas, pheomelanin is basically soluble contains

sulfur because there is cysteine residues. So, here the oligomers are having benzothiazine or benzothiazole. So, basically in eumelanin there were dihydroxyindole and dihydroxyindole carboxylic acid whereas, when there is cysteines present in melanin they form benzothiazine and benzothiazoles and they form a soluble oligomer containing sulfur. Now trichochromes these are low molecular weight compound remember eumelanin and pheomelanin they are high molecular weight compound whereas, trichochromes are low molecular weight compound, but the features are more like pheomelanin like in terms of solubility containing sulfur the features are like trichochromes. Now apart from that there is neudomelanin by name it is quite significant that it is produced in the noradrenergic cells of substantia nigra and also locus caruleas as a breakdown product of dopamine this is a dark and insoluble pigment.

So, once again eumelanin is insoluble, neuromelanin is insoluble, but pheomelanin is soluble and trichochrome which resembles pheomelanin is also soluble. So, these are the different types of melanin. Now coming to the synthesis of melanin now melanin synthesis the first step if you remember there is formation of dopa, dopa from dopa there is formation of quinone different quinone derivatives. Now those quinone can be of indole variety, indole carboxylic variety and finally, it can forms polymer these indoles from polymer to form melanin. Now if the L-dopa quinone undergoes cysteineylation it forms cysteineldopa it further undergoes to form pheomelanin.

So, remember the quinone product dopa quinone L-dopa quinone in absence of cysteine through a series of reactions which involves decarboxylation then oxidation it forms indole derivative indole 5 6 quinone as well as 5 5 6 dihydroxy indole carboxylic acid and these two undergoes these two undergoes polymerization to form eumelanin. Whereas, in presence of cysteine cysteineylation of L-dopa from cysteineldopa which forms the pheomelanin. So, melanogenesis or melanin synthesis is basically describing the eumelanin synthesis and that is a multistage chemical process and the pheomelanin synthesis the cysteine derivative is basically a defective variety of melanogenesis. Now the primary stimulus for the melanin synthesis is UV radiation. UV radiation what it does it up regulates the pro opioid melanocortin present in melanocytes which activates the downstream products alpha melanocytes stimulating hormone or alpha MSH and also adrenocorticotrophic hormone ACTH.

So, these are the stimulus for melanin synthesis. Then we are coming to different associated disorders associated with defective melanin synthesis the very common one is moles. Moles you can see in our bodies in the different part these moles are basically localized hyperactivity of melanocytes which causes excess melanin synthesis melanin synthesis and hyperpigmentation just the opposite is leucoderma decreased melanin synthesis. Now leucoderma is basically absence of either melanin there is degeneration

of the melanocytes or absence of the enzyme tyrosinase which causes localized absence of melanin in epidermis of skin which causes white patches. See you can you know this white patches appears in the skin that is localized absence of melanin in the epidermis.

Whereas if epi this melanin is absent in generalized throughout the body that causes albinism this this is we are going to discuss shortly. Then graying of hair due to the melanocyte disappearance in the hair root also as we have already discussed the enzyme tyrosinase is a copper containing enzyme copper deficiency is manifested as defective synthesis of melanin. Now this is very interesting thing when there is copper deficiency hair which is synthesized these are gray hairs, but in presence of copper tyrosinase act properly there is adequate melanin synthesis. Now assume the condition when there is intermittent deficiency of copper there is availability of copper after that there is copper depletion once again the copper is the copper concentration is restored in those case cases what happened there is alternate black and white regions in the hair which is known as flag type of hair. Then one malignancy is also associated with melanin synthesis which is the melanoblast proliferation causing malignant melanoma.

So, these are the disorders associated with melanin synthesis. Now we are going to discuss albinism in a bit detail. So, albinism is basically hypomelanosis melanosis in generalized term. So, what we say albino is basically the white. Now this is one inborn error of metabolism due to lack of synthesis of melanin the enzyme is tyrosinase.

Now tyrosinase can be partially absent or completely absent based on that manifestations are different. Now autosomal recessive pattern is there, but sometimes x linked variety of albinism is also present. What are the biochemical basis definitely there is tyrosinase enzyme function is loss as well as melanosomes of melanocytes are decreased polymerization of melanin is defective substrate tyrosin availability can be defective also the protein matrix in the melanosome can be defective. See in all the way the melanin synthesis can be hampered starting from the unavailability of the substrate to the suitable defect in the suitable environment in terms of melanocytes or melanosomes enzyme deficiency all these can cause to a generalized melanin deficiency. Now what are the different types of albinism? Albinism can manifest in eyes as well as skin.

So, that can be cutaneous albinism, ocular albinism, oculocutaneous both oculocutaneous albinism. Now based on the absence of tyrosinase complete absence of tyrosinase it causes tyrosinase negative albinose. So, if we want to detect the tyrosinase enzyme it is completely absent, but those are partially deficient in tyrosinase they causes tyrosinase positive albinose. Ocular albinism the manifestation in eye now remember ocular albinism can be autosomal recessive as well as X linked. So, here are the manifestation of albinism ocular albinism you can see also oculocutaneous albinism grey

hairs skins are white.

So, these are the manifestation of hypomelanosis. Now albinism predisposes to skin cancer why because this melanin pigment is basically very effective in dissipating the UV lights. It absorbs the UV lights very efficiently and dissipates whereas, in absence of melanin skins become sensitive to light. So, protection against UVB, UV arrays they are lost. So, there is radiation damage causing carcinogenesis. So, one such cancer we have already mentioned that is malignant melanoma which also presents with photophobia due to lack of melanin pigment in our eyes.

So, this is albinism we have discussed. So, these are the key points of this class we have discussed thyroid hormone synthesis its related disorders and also melanin synthesis its related disorder. So, we have discussed hypo and hyperthyroidism as well as albinism. These are my references see you in the next class. Thank you.