Overview and Integration of Cellular Metabolism

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Lecture 38: Tyrosine Metabolism – II (Catecholamines)

Hello everyone. So, we were in the discussions of the NPTEL lecture series, the subject Overview and Integration of Cellular Metabolism. In the last class, we have discussed regarding the tyrosine amino acid metabolism, how tyrosine is catabolized as well as different inborn disorders of tyrosine catabolism, tyrosinemias and alcaptonurias. Now, here we are going to discuss different important products which are synthesized from tyrosine and their related disorders. In this class, we are going to discuss catecholamine. The important catecholamines are epinephrine, norepinephrine and dopamine.

So, how these catecholamines are synthesized and how they are catabolized, how what are the different physiological functions they impart as well as the related clinical condition. Apart from that apart from these catecholamines which are synthesized from tyrosine, there are few other important products very important that is thyroid hormone, thyroxine and triiodothyronine and also one pigment melanin. So, in this class, we are going to discuss about the catecholamines. Now, catecholamines as I told you there these are the catecholamines most important epinephrine and norepinephrine, dopamine is the important neurotransmitter we are aware of.

Now, catecholamines are synthesized in adrenal medulla and sympathetic ganglions. This is the region where catecholamines are synthesized. So, catecholamines are synthesized as I told you in the adrenal medulla and sympathetic ganglions. Now, in those cells of adrenal medulla, pheochromocytes and also neuro glial cells, they are catecholamines, they uptake tyrosine and those tyrosines are converted to different catecholamine. Now, there are four major step of catecholamine formation.

So, tyrosine is first forming dopa, this is dopa not dopamine. Remember the first step is formation of dopa from where there is formation of dopamine. So, here you can see the first one is formed, then dopamine is converted to norepinephrine and norepinephrine finally, is producing epinephrine. So, this is how catecholamines are formed, but remember the reaction occurs in the cell, the reaction occurs in different regions. Now,

let us see the first one is formation of dopa, this step occurs in mitochondria.

Within mitochondria tyrosine is hydroxylated to form dihydroxy phenylalanine. So, tyrosine was the in the tyrosine, we we were having the hydroxyl group at para position. Another hydroxyl group is basically added to form dihydroxy phenylalanine and the enzyme is tyrosine hydroxylase. Now, remember these enzyme for catecholamine synthesis, this is the rate limiting enzyme and the coenzyme here is tetrahydrobiopterin and NADPH is also required in this pathway here, you can see NADPH is also required. Now, from dopa there is formation of dopamine with the help of the enzyme dopa decarboxylase.

So, basically there you can see one carbon is less in dopamine fine. So, there is decarboxylation and like all other decarboxylation here the cofactor is pyridoxal phosphate. Now, remember these step is important for dopamine formation which is one very important neurotransmitter. Now, why important this is a very common disease parkinsonism parkinsonism manifest because there is reduced dopamine in brain. So, this step is very important the dopa decarboxylase enzyme this is responsible for formation of dopamine from dopa.

So, dopamine is now forming the another catecholamine norepinephrine with the help of the enzyme dopamine hydroxylase. Now, dopamine hydroxylase this hydroxylation occurs I remember for the dopamine was formed in cytosol. Now, from cytosol dopamine enters chromaffin granules and that chromaffin granules are basically located mainly in pheochromocytes or the granulated vesicles of the brain cells or nerve endings like that. So, first the reaction was in mitochondria from mitochondria it comes out to cytosol from cytosol it enters the chromaffin granules for hydroxylation where dopamine is hydroxylated to form norepinephrine with the help of the enzyme dopamine beta hydroxylase and remember this enzyme is a vitamin C as well as copper ion dependent enzyme. Now, from norepinephrine there is formation of epinephrine once again the norepinephrine comes out of the chromaffin granules in the cytosol in cytosol there is formation of epinephrine the reaction is basically methylation reaction and you all know the methyl group donor is S adenosyl methionine which when gives up its methyl group forms S adenosyl homocysteine.

So, there is formation of epinephrine in cytosol after formation in cytosol epinephrine goes back to the chromaffin granules where it is stored. So, basically catecholamines are stored in chromaffin granules, but the synthesis of epinephrine from norepinephrine it occurs norepinephrine comes out of the chromaffin granules to cytosol there is the enzyme n methyl transferase n methyl transferase causes the trans methylation reaction forms epinephrine epinephrine goes back to the chromaffin granules and there it is stored

with norepinephrine. Now, the actions of epinephrine basically it increases the blood pressure as well as the heart rate myocardial contraction rate force of myocardial contraction, but it has also relaxation effect on the smooth muscles of bronchi also it imparts anti insulin effect basically it causes glycogenolysis glycogen breakdown lipid breakdown stimulates lipolysis and also you all know adrenaline is the hormone of flight and fight response. So, adrenaline is released in response to flight fight exercise hypoglycemia different stress this causes release of adrenaline or epinephrine. Then how the degradation of epinephrine or norepinephrine occurs? So, norepinephrine is basically converted to epinephrine via methyl transferase enzyme.

Now, the half life of epinephrine is very short around 2 to 5 minutes only once the action is over either it is restored in the chromaffin granules or it is degraded and degraded mostly by the enzyme catechol o methyl transferase comped where by this enzyme epinephrine is converted to one metabolite metanephrine and then metanephrine via monoamine oxidase undergoes degradation to form vinyl mandelic acid and this vinyl mandelic acid is basically excreted in urine. So, this is the degradation of epinephrine. So, the products are metanephrine and vinyl mandelic acid. Now, there are disorders related to this catecholamines epinephrine or epinephrine or dopamine. So, as I told you very common disease we all know Parkinson's disease is related to dopamine deficiency.

Now, why dopamine deficiency? Because there is degeneration of the dopaminergic neuron in brain the most the very I mean the most important region in brain is substantia nigra where the dopaminergic degeneration of neuron occurs. Now, what happens because there is dopaminergic neuronal degeneration there is dopamine deficiency due to decreased production. Now, dopamine is important for its role in different types of voluntary movement as well as , award response reflex and it is also important for inhibiting the production of prolactin synthesis , then there are different coordination in the movement. So, basically when this dopamine is absent the manifestation is hypo or bradykinetia. So, basically movement is slowed down as well as there is rigidity of muscle also because there is the coordination and in the voluntary movement is lost.

So, there is repeated involuntary movement which is known as tremors you know the tremors are manifested as the uncontrolled involuntary repetitive movements. Then patients are having a mask spaces mask faces where the face is expression less , the blinking of eye is decreased then the heads are flexed to pinc posture like that. So, this is a very typical posture of parkinsonism with which the patients present. Associated with that there is sleep disturbances mood or behavioral disorder there is depression dementia like that and now this you all know this is one very debilitating condition because finally, the patients the patients are actually the movement disorder are so, aggravated that they are totally bedridden their movements are totally restricted. So, these are the

manifestations of Parkinson's disease.

So, what is the tip treatment there is dopamine deficiency. So, supplementation with dopamine is the main mode of treatment. Now the problem is if you directly gives dopamine it cannot cross the blood brain barrier. So, which is the I mean dopa is the molecule which can cross the blood brain barrier. So, dopa is given in the form of carbidopa or levodopa .

These are the drugs which are given as dopa supplement and when it crosses the blood brain barrier it forms dopamine. Apart from that there is also mau inhibitors and comp inhibitors these are the enzymes which are actually responsible for the degradation of dopamine. So, we are here by these drugs mau inhibitors like selegiline, comp inhibitors like entacapone, tolcapone these enzymes sorry these drugs they inhibits the degradation of enzyme. So, they augment the actions of levodopa or carbidopa. Now there are different drugs which induces Parkinsonism we call it drug induced Parkinsonism.

Now there is antiemetic metoclopramide then lithium carbonate which is given in manic repressive psychosis antihypertensives like reserpin, methyl dopa they basically mimic the manifestations of rather induces the manifestations of Parkinsonism by mimicking dopamine deficiency. Now we are moving on to pheochromocytoma. Now pheochromocytoma is the disorder related to catecholamines epinephrine and norepinephrine there is excess synthesis of catecholamines. Now pheochromocytoma is basically a disorder of adrenal medulla, adrenal medulla is the site where catecholamines are synthesized. So, tumor of adrenal medulla causes excess synthesis of catecholamines.

Now excess amount of catecholamines causes severe hypertension, hot flushes, excessive sweating, diarrhea. Now how it is detected by definitely excess amount of catecholamines produced causes excess catabolism forming vinyl mandelic acid and those are excreted in urine. So, the normal vinyl mandelic acid excretion is around 2 to 6 milligram in 24 hours based on that if there is urinary VMA high it is diagnosed as pheochromocytoma and the treatment is just the surgical removal of the tumors to dissipate the excess function of catecholamines. So, these are the key points which we have discussed in today's class that is catecholamine, epinephrine, norepinephrine as well as dopamine synthesis and their catabolism final and then the related disorders dopamine related disorder Parkinson's disease one of the important then pheochromocytoma related to excess production of catecholamines. So, these are my references and see you in the next class.