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**COURSE: MEDICAL BIOCHEMISTRY: BCH 302**

**DEPARTMENT: PHYSIOLOGY DEPARTMENT**

**QUESTION:** Discuss the synthesis of any two neurotransmitter

**ANSWER**

* **NITRIC OXIDE (NO):** Nitric oxide is produced by a group of enzymes call nitric oxide synthases. These enzyme convert arginine into citrulline, producing NO in the process. Oxygen, tetrahydrobiopterin (BH4) and NADPH are necessary cofactors. There are three isoforms of nitric oxide synthase (NOS) named according to their activity or tissue type which they were first described. The isoforms of NOS are:
* Neuronal NOS (nNOS) or NOS1
* Endothelial NOS (eNOS) or NOS2
* Inducible NOS (iNOS) or NOS3

Two of the enzymes (nNOS and eNOS) are constitutively expressed in mammalian cells NO in response to increases in intracellular calcium levels. In some cases, however, they are able to increase NO production independently of calcium levels in response to stimuli such as shear stress. iNOS activity is independent of the level of calcium in the cell, however its activity like all of the NOS isoforms is dependent on the binding of calmodulin. Increase in celluar calcium leads to increase in calmodulin and the increased binding of calmodulin to eNOS and nNOS leads to a transient increase in NO production by these enzymes. By contrast iNOS is able to bind tightly to calomodulin even at very low cellular concentration of calcium. Consequently iNOS activity does not respond to changes in calcium levels in the cell. As a result the production of NO by iNOS lasts much longr than from the other isoforms of NOS, and tends to produce much higher concentration of NO in the cell. The production of NO by iNOS can, however, be controlled through transcription. In most cell type iNOS protein levels are either very low or undetectable. However, stimulation of these cells with, cytokines or growth factors, can lead to increased transcription of the iNOS gene, with subsequent production of NO.

* **DOPAMINE:** Dopamine is synthesized from the amino acid tyrosine; majority of circulating tyrosine originates from dietary source, but small amount are derived from hydroxylation of phenylalanine by the liver enzyme phenylalanine hydroxylase. Blood-borne tyrosine is taken up into the brain by a low-affinity amino acid transport system and subsequently from brain extracellular fluid into dopaminergic neurons by high and low affinity amino acid transporters. Tyrosine is converted to dopamine by the enzymes tyrosine hydroxylase (TH) and dihydroxypheneylalaine (DOPA) decarboxylase (DDC). TH is the rate limited step for the biosynthetic pathway; Th gene is localized to chromosome 11p in humans and encodes a single form of TH that can be alternatively spliced. The mRNA expressed of TH is abundant throughout the human mesencephalon. The mature enzyme is a soluble cytosolic protein composed of four subunits of approximately 60kDa each. TH activity is the most critical factor that controls dopamine synthesis, and considerable efforts have been devoted to understanding activation of the enzyme. DOPA is the second terminal enzyme in dopamine biosynthesis. The enzyme useds pyridoxal phosphate as a cofactor and convert DOPA to dopamine and 5-hydroxytryptophan to serotonin [5-hydroxytryptamine (5-HT)].

L-dopa formation, L-tyrosine, tetrahydrofolic acid (THFA), and ferrous iron are essential and for dopamine biosynthesis from L-dopa, pyridoxal phosphate is essential. The activity of the enzyme rises and falls according to how much pyridoxal phosphate there is. There are two enzymes that are required for the formation of dopamine from L-tyrosine, three coenzymes are also required. They are they are: THFA (for L-tyrosine to L-dopa), pyridoxal phosphate (for L-dopa to dopamine), and NADH (for formation of THFA and Pyriodoxal phosphate). The cofactor tetrahydrobiopterin (BH4) donates the hydrogen atom needed for hydroxylation of tyrosine to DOPA. Pterin also serve as a cofactor for other monoxygenases as well as nitric oxide synthease, its availability is a determining factor in the control of TH activity.

L-tyrosine + THFA +O2 + Fe2 → L-dopa + DHFA + H2O + Fe2+

L-dopa + pyridoxal phosphate → dopamine +pyridoxal phosphate +Co2