**NAME: NWACHUKWU CHINAZA**

**MATRIC NUMBER: 17/MHS03/033**

**DEPARTMENT: ANATOMY**

**COURSE CODE: BCH308**

**SYNTHESIS OF NEUROTRANSMITTERS**

* GABA( gamma-Aminobutyric acid)
* Nitric Oxide

**SYNTHESIS OF NITRIC OXIDE**

Nitric oxide is produced by a group of enzymes called nitric oxide synthases. These enzymes convert arginine into citruline, producing NO in the process. Oxygen and NADPH are necessary co-factors. There are three isoforms of nitric oxide synthase(NOS) named according to their activity or the tissue type in which they were fisrt described. The isoforms of NOS are neuronal NOS or nNOS, endothelial NOS or eNOS and inducible NOS or iNOS. These enzymes are also sometimes referred to by number, so that nNOS is known as NOS1, iNOS is known as NOS2 and eNOS is known as NOS3. Despite the names of the enzymes, all three isoforms canbe found in a variety of tissues and cell types.

Two of the enzymes (nNOS and eNOS) are constitutively expressed in mammalian cells and synthesise 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. Increases in cellular calcium lead to increases in levels of calmodulin and the increased binding of calmodulin to eNOS and nNOS leads to a transient increase in NO production by these enzmes. By contrast iNOS is able to bind tightly to calmodulin even at very low cellular concentration of calcium. Consequently iNOS activity does not respond to chnages in calcium levels in the cell. AS a result the production of NO by iNOS lasts much longer than from the other isoforms of NOS, and tends to produce much higher concentrations of NO in the cell

The production of NO by iNOS can however, be controlled through transcription. In most cell types iNOS protein levels are either very low or undetectable. However stimulation of these cells with, e.g cytokines or growth factors can lead to the increased transcription of the iNOS gene, with subsequent production of NO.

**SYNTHESIS OF GABA**

GABA is primarily synthesized from glutamate through the enzyme glutamate decarboxylase(GAD) with pyridoxal phosphate( which is the active form of vitamin B6) as a cofactor. This process converts glutamate-the principal excitatory neurotransmitter into GABA-the principal inhibitory nerotransmitter.

The GABA shunt is a closed-loop process with the dual purpose of producing and conserving supply of GABA, GABA is present in high concentrations in man brain regions such as the hippocampus. These concentrations are about 1,000 times higher than concentrations of the monoamine transmitter in the same regions and this is in accord with the powerful and specific actions of GABAnergic neurons in these regions. Glucose is the principal precursor for GABA production, although pruvate and other amino acids can also act as precursors. The very first step in the GABA shunt is the transamination nof a-ketoglutarate, formed from glucose metabolism in the Krebs cycle by GABA a-oxoglutarate transaminase into I-glutamic acid. Glutamic acid decarboxylase catalyzes the decarboxylation of glutamic acid to form GABA, GAD appears to be expressed only in cells that use GABA as a neurotransmitter. GAD localized with antibiodies or mRNA hbridization probes serves as an excellent marker for GABAnergic neurons in the CNS.Two related but different genes for GAD have been cloned, suggesting independent regulation and properties or the two forms of GAD which are: GAD65 and GAD67.

Furthermore, expression of GAD and some GABA receptor subunits has been demonstrated in some non-neuronal tissues, indicating the likely function of GABA outside of the CNS. GABA is metabolized by GABA-T to form succinic semialdehyde. To conserve the available supply of GABA, this transamination generally occurs when the initial parent compound, a-ketoglutamate, is present to accept the amino group removed from GABA, reforming glutamic aid. Therefore, a molecule of GABA can be metabolized only if a molecule of precursor is formed. Succinuic semialdehyde can be oxidized by succinic semialdehyde dehydrogenase into succinic acid and can then reenter the Krebs cycle, completing the loop.

GABA release into the synaptic cleft is stimulated by depolarization of presnaptic neurons. GABA diffuses across the cleft to the target receptors on the postsnaptic surface. The action of GABA at the snapse is terminated by reuptake into both presynaptic nerve terminals and surrounding glial cells. The membrane transport systems mediating reuptake of GABA are both temperature and ion dependent processes. These transporters are capable of bidirectional neurottransmitter transport. The have an absolute requirement for extracellular Na positive ions with an additional dependence on cl negative ions. Under normal phsiological conditions, the ratio of internal to external GABA is 200. The driving force for this reuptake process is supplied by the movement of sodium ions down its concentration gradient. GABA taken back up to its nerve terminal is available rfor reutilization but GABA in glia is metabolized to succinic semialdehyde by GABA-T and cannot be resynthesized in this compartment since glia lacks GAD. Ultimately GABA can be recovered from this source by a circuitous route involving Krebs cycle; GABA in glia is converted by glutaminase to glutamate which re-enters the GABA shunt.