**\*Biochemistry \*Heme synthesis \* Lec.31**

* **Introduction:**🡪 **Conversion of amino acids to specialized products:** - The **bases** of nucleotides forming DNA and RNA are made from: **Amino Acids
 -** Amino acids and their role in synthesizing other products:1. **Tryptophan**:
 🡪 some of tryptophan can be metabolized to form: 1. **Melatonine** “small amount”
 2. **Serotonine** “neurotransmitters”

 🡪 Melatonine an serotonine can be fond in the GI in bacteria

 2. **Histidine:** 🡪 Histidine can be metabolized to form: the chemical messenger “**Histamine**”

 3. **Glutamate :**
 🡪 Glutamate can be metabolized to form : **gamma amino butyrate**

 4. **Serine:**
 🡪 Serine involve in the synthesis of **acetyl choline “later on”** 5. **Arginin & Glycine**:
 🡪 Aginine and glycine can be metabolized to form **creatine** 6. **Glycine:**
 🡪Glycine involve in the synthesis of **Heme “our lec.”

 7. Cystine, Glutamic acid, Glycine**:
 🡪 These three amino acids involve in the synthesis of **Glutathione** “Tripeptide”

 8. **Lysine, Methionine:**
 🡪 These two amino acids involve in the synthesis of **Carnitine transporter**

 9. **Spermine, spermidine:**
🡪 These two amino acids involve in the **regulation** of gene expression.

🡪 **Note:**
 - Spermine and spermedine are made from the amino acid “**ornithine**” metabolism
 - so, ornithine is converted to these amino acids because it can’t be involved in protein structure.

* **Catecholamines:** 1. Epinephrin
 2. Norepeniphrin
 3. Dopamine
* **Catecholamines synthesis:**1. **Dopamine**: - It’s synthesized in the central nervous system "brain”
 - It’s made from the amino acid **Tyrosine**
 - Tyrosine is converted to Dopamine by 2-step reactions:
 🡪 Hydroxylation
 🡪 Decaboxylation
 - The enzyme requires **tetra hydrobiopterin**

 **Tyrosine DOPA Dopamine**2. **Norepinephrin:** - It’s synthesized in the central nervous system”brain” & **medulla** of adrenal gland
 - Dopamine is converted to noepinephrin by hydroxylation reaction

  **Dopamine Norepinephrin**3. **Epinephrin:** - Synthesized in the adrenal gland from norepinephrin by **Methylation
 -** In the **adrenal gland,** Norepinephrin undergoesmethylation by the methyl donner SAM “S- adinosyl methionine”.

 **Norepinephrine** **Epinephrine

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🡪 Note:
 - Epinephrine & norepinephrine:** 🡪found in the circulatory system
 🡪 contribute in regulation of: 1. Glycogen metabolism
 2. Fat metabolism
 🡪 They enhance their HYDROLYSIS for energy purposes

 - **Norepinephrin & Dopamine are found in the CNS as “neurotransmitters”**

 **SAM**

**Phenylethanolamine-N-methyl transferase**

**Dopamine B- hydroxylase hydroxylase**

**DOPA decarboxylase**

 **BH4**

**Tyrosine hydroxylase**

* **Role of “tyrosine” in melanocytes:**- Note: melanocytes are the cells the make the “melanine” pigment.
- Tyrosine in the melanocyte can make melanine
- “**Tyrosinase amine 🡪**” is the most important enzyme in melanine metabolism
 from tyrosine clinically
- A deficiency in “tyrosinase” cause 🡪 **Albinism.**
* **Metablism of catecholamines “briefly”:
-** Catecholamines are degraded by 2-enzymatic systems:
 1. Mono amine oxidase
 2. Catechol-O-methyl transferase 🡪 “COMT”.

- Degradation of catecholamines gives these products:
 1. Vanillylmandelic acid 🡪 “VMA”
 2. Homovanillic acid 🡪 “HVA”
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* **Serotinin synthesis**:
 - It’s made from the amino acid “Tryptophan”
 - synthesis catalyzed by the enzyme “tryptophan hydroxylase
 - Like “tyrosine hydroxylase”, “tryptophan hydroxylase” requires BH4
 “**tetra hydrobiopterin**” and O2.
- So, serotonin is synthesized from tryptophan by 2-step reactions”
 🡪 Hydroxylation
 🡪 Decarboxylation

 Tryptophan 5-Hydroxy-tryptophan **Serotonin**

🡪 Note:
 - **serotonin is synthesized in several tissue, specifically in the intestinal mucosal cells
 - Serotonin is degraded by “Mono amine oxidase”🡪 MAO
 - serotonin is involved in a hormone formation 🡪 Melatonin
 - To sum up: tryptophan involve in synthesis of serotonin and a hormone “melatonin”**

**Decarboxylase PLP**

**Tryptophan hydroxylase**

* **Histamine synthesis:**- It’s synthesized from Histidine by **decarboxylation**
- Histamine is a chemical messenger that mediates: 🡪 many allergic reactions
 🡪 inflammatory reactions
 🡪 gastric secretion
 🡪 act as vasodilator
- Histamine has no clinical applications, but agents that interfere with the action of
 histamine “**inhibition** of it” have wide spectrum of therapeutic applications.

 Histidine **Histamine**------------------------------------------------------------------------------------------------------------

**Decarboxylase PLP**

* **Creatine synthesis:مهم**- creatine is found in the **muscles
-** It’s involved in energy metabolism
- creatine phosphate is a temporart storage form of energy for emergency!
 🡪 **When we do muscular activity and ATP is depleted, creatine phosphate compensate
 for that loss “temporarily” till the factory of the ATP becomes quick.
-** creatine is made from: 🡪 Arginine “has **Guanidine** group”

 
 🡪 Glycine

- **Synthesis mechanism of Creatine:**
 1. The guanidine group of arginine is transferred to the glycine by **amidino transferase**,
 a step associated with releasing of **ornithine** and forming of **Guanidinoacetate** “product”.

 2. **Guanidinoacetate** undergoes methylation by “SAM” resulting in formation of **Creatine** 3. There is **interconversion** between creatine and creatine-phosphate that is catalyzed
 by **Creatine kinase “using ATP”** 4.Creatine undergoes cyclization to give **Creatinine.

 

🡪 Notes:
 -** Creatinine is removed slowly and at constant rate is released immediately in the urine
 - Creatinine level in the blood is one of the most important marker of **kidney** functions
 - Creatinine and Urea are very important to indicate the efficiency of kidney function
 “by chemical test”.
 - The amount of **creatinine** that is **excreted** depends on the **muscle mass** of the body,
 because there is proportionality between creatine, creatinine, and muscle mass.

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* **Glutathione:** - Is an important antioxidant
 - It’s made from three amino acids: 1. Glutamate
 2. Cysteine
 3. Glycine
 - It’s synthesis is through ATP requiring anabolism mechanism, meaning that 2 a.a. are
 attached using ATP and the third one comes to be attached to them also using ATP,
 forming a “**Tripeptide**”.

 - Structure:
 🡪It has 2 carboxylates terminals, because the “glutamate” isn’t linked to the alpha
 carboxylate, it’s attached to the gamma one.


**α**

**β**

**ɣ**

* **Role of glutathione:**
1. major antioxidant compound “REDUCTANT”
2. Include “SH” group 🡪 scavenger group
 🡪 undergoes oxidation so as to protect other homoxidation
 🡪 the protection occurs through “**glutathione peroxidase**”
 \* inorganic peroxide is neutralized with glutathione
 🡪 when oxidized, a disulfide bridge is formed, resulting in
 oxidized glutathione
 🡪 oxidized glutathione has to be **regenerated** :
 - by “glutathione reductase”
 - requiring “NADPH”
* Glutathione can conjugate many drugs
* It’s used in some transport of amino acids
* It’s a cofactor
* It’s used for rearrangement of proteins 🡪 changing the aarrangement/angle of disulfide bond.
* **Heme synthesis:**- Heme is a cofactor for several heme protins, mostly in **hemoglobin:
 🡪** 85% of the heme is associated with hemoglobin
 🡪 the rest 15% is distributed between myoglobin and seversl other enzymes:
 1. Myoglobin
 2. Cytochrome
 3. Enzyme catalase
 4. Pyrolase
 5. Nitric oxide sythase
* The isomer of heme that found in our body is “heme III”
* There are many isomers of heme that are refered to the relative distribution of specific
groups🡪 4 pyrrole rings 🡪 tetra pyrrol rings
* Tetr pyrroel rings are attached to each other by “**methenyl bridge**”
* Discrimination of isomer III:
- refer to figure 21.2
- type III porphyrins contain an asymmetric substitution on ring D
* Notes:
- Heme = Ferro-proto porphyrin
- protoporphyrin is withot iron

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* **Heme synthesis:**- It’s made from 2 precursors:
 1. Glycine 🡪 small amino acid
 2. Succinyl COA 🡪 Krebs cycle intermediate “in mitochondria”
- the synthesis **starts** in mitochondria, because succinyl COA is an intermediate of TCA that occurs in the mitochondria.
- we need **8** of these precursors to make one heme
- daily, our body make 7g of hemoglobin to substitute turnover
* **Pathway:**
- **First reaction** (2 Steps):
 🡪 Glycine and Succinyl COA condense by an enzyme “delta-aminolivulinate synthase/ ALAS”
 \*Most important enzyme 🡪 rate limiting enzyme “under regulation”
 🡪 after they are condensed by synthase, they will undergo decarboxylation forming
 “ delta amino levulinic acid (ALA).

 - Glycine
 - Succinyl COA

**ALA**

**Decarboxylation**

**ALAS**

* **Note: فاصل
-** these steps occur in all tissue because all tissues contain heme proteins, but mooostly occur
 in : 1. **Bone** **marrow** “erythrocyte precursors”🡪 mostly
 2. Liver
- the enzyme that is responsible for these steps of first reaction is:
 1. ALAS “II” 🡪 in bone marrow “regulated by a hormone erythropiotein and presence of iron”
 2. ALAS “I” 🡪 in liver

- Difference between these 2 enzymes:
 🡪 ALAS “I” in liver: is feedback regulated by “**Heme**”

 🡪 synthesis of the globin and heme in the **bone marrow”erythrocyte precursors”** always goes parallel, then they join to form hemoglobin.

 🡪 this synthesis in the **liver** is under regulation:
 - When synthesis of heme increase and there is **no** globin, it will be oxidized
 “ferrus 🡪 ferric”
 - As we know that, heme in hemoglobin structure is buried in a pocket that is hydrophobic “to prevent it’s oxidation”
 - if the iron in the heme becomes ferric, it won’t bind to other oxygen🡪 PROBLEM

 - **REGULATION**:خلاصة الموضوع
 1. Excess heme
 2. Iron within heme is oxidized to be ferric forming 🡪 *HEMIN*
 3. Hemin makes feedback regulation through :
 🡪 **inhibition** of enzyme
 🡪 **suppressing** it’s level “**less of the enzyme is being made**”
* **ALAS “I” is inducible enzyme**:بصم والتم ساكت
 1. Administration of ALAS “I” to a large # of drugs “**xenobiotic compounds**” results in significant
 increase hepatic ALAS “I” activity.

 2. These drugs “xenbiotic compounds” are metabolized by the microsomal cytochrome P450 monoxygynase system.

 3. This cytochrome P450 monoxygynase system is a hemeprotein oxidase system found in the liver.

 4. In response to these drugs, the synthesis of cytochrome P450 proteins increases,leading to an
 enhanced consumpotion of **heme**” a componenet of cytochrome P450 proteins.

 5. This is in turn, causes a decrese “reduction” in the concentration of heme in liver cells

 6. The lower intracellular heme concentration leads to an increase in synthesis of ALAS “I“ “DEREPRESSION”, and prompts a corresponding increase in ALA synthesis.
* **Refer to the reaction**:
- the product of the first reaction is : “delta amino livulinic acid”
- 85% of all heme is made in the body in the **erythroid tissue** for making HEMOGLOBIN of the
 erythrocytes
* **Second reaction: “1 step”
-** Delta amino livulinic acid that has been in the first reaction is transferred from mitochondria to the cytosol
- In the **cytosol**, it’s acted on by an enzyme “delta amino livulinic acid dehydratase/ ALAD” 🡪 which make the **FIRST pyrrole ring derivative.
- Delta amino livulinic acid dehydratase:** 🡪other name: **porphobilinogen synthase**”
 🡪 Zinc containing enzyme
🡪 abbreviated as “ALAD”
 🡪 cytosolic enzyme
 🡪 condenses 2 molecules, a step associated with releasing 2H2O
 🡪 aims to for the first pyrrole ring derivative: “**Porphobilinogen”
 🡪** MW = 218 KD
 🡪 consists of “A” subunit which is a sulfhydral enzyme, so it’s sensitive to heavy metal ions,
 specifically 🡪 **LEAD:
 \*\* lead replaces the zinc of this enzyme 🡪 causing:** 1. Inhibition of ALAD enzyme
 2. Elevation in ALA
 3. Anemia seen in lead poisoning

 \*\* **these cases are seen in persons who work in Factories dealing with lead, so they are monitored with heavu metals, specially the “lead”.
🡪 Note:
 - Anemia** is dangerous , because it can be progress to affect other enzymes involved in energy metabolism.
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* **Third reaction: “2 steps”**- complicated step
- 4 molecules of **porphobilinogin** are condensed
- 2 enzymatic system works on this step:
 🡪 **porphbilinogen deaminase “hydroxymethyl-bilane synthase”:** - make the four rings by catalyzing the head to tail condensation of four [porphobilinogen](http://en.wikipedia.org/wiki/Porphobilinogen%22%20%5Co%20%22Porphobilinogen) molecules into the **linear**[**hydroxymethylbilane**](http://en.wikipedia.org/wiki/Hydroxymethylbilane) while releasing **four** [**ammonia**](http://en.wikipedia.org/wiki/Ammonia) molecules.

 🡪 **Co-synthase “uroporphyrinogen III synthase”**:
 - gives isomer III **(AP,AP,AP,PA)** and small quantities of isomer I**(AP,AP,AP,AP).**
 - Note: linear hydroxymethylbilane undergoes ring closure and isomerization by this enzyme forming isomer “III”.
* **Fourth reaction: “1 step”**- these 2 isomers “uroporphyrinogen I&III” undergo decarboxylation
- by “uroporphyrinogen **decarboxylase**”, 4 co2 are released.
- All “A” subunits undergo decarboxylation, resulting in releasing **methyl group** and 4 co2
- giving🡪 **coproporphyrinogen III**
* **Sixth reaction: “2 steps”**-coproporphyrinogen III enters the mitochondria
- In the mitochondria, coproporphyrinogen III undergo “**oxidative decarboxylation”,** that involve only 2 **propionate**🡪 forming **vinyl groups**, the other 2 propionates remain. “refer to figure 21.4”
- At all, oxidative decarboxylation of coproporphyrinogen forms 🡪 **Protoporphyrinogen**- **Protoporphyrinogen is the only tetra pyrrole intermediate that undergoes enzymatic oxidation forming** 🡪 **protoporphyrine** 🡪 **next step can occur non enzymatically but it’s slow** 🡪 **It’s facilitated by an enzyme called “ferro chelatase”** 🡪 **ferro chelatase binds the iron with protopophyrin forming** 🡪 **ferro proto porphyrin** 🡪 **ferro proto porphyrin = HEME** 🡪 **ferro chelatase is seneitive to lead inhibtion**

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🡪 Note:
 - you have to differentiate between copropophyrinogen & coproporphyrine:
 \* coproporphyrine:
 1. is an oxidizing product
 2. Colored
 3. In certain disorder, theyir color transform from red to blue, when expose to light

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