**\*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**

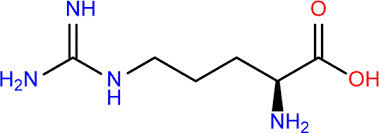
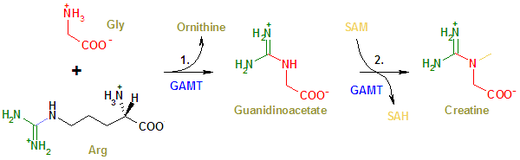
* **Role of “tyrosine” in melanocytes:**- Note: melanocytes are the cells the make the “melanine” pigment.  
  - Tyrosine in the melanocyte can make melanine  
  - “**Tyrosinase amine 🡪**” is the most important enzyme in melanine metabolism   
   from tyrosine clinically  
  - A deficiency in “tyrosinase” 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**

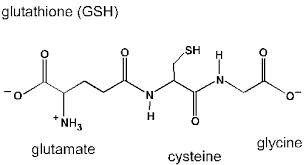
**Tryptophan hydroxylase**

* **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" \o "Porphobilinogen) 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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 Done by : Dana Ayman**