METABOLISM

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ARKAN ACADEMY

❖ Amino Acids

- Amino acids in humans are in L configuration
  - AAs are not stored in the body
  - The amino acid pool is in a steady state (constant amount)
- A.A sources: *endogenous* (body) protein degradation, *exogenous* (dietary) protein degradation or synthesis of non-essential
- AAs depleted (used) by 3 routes:
  - Synthesis of body protein
  - AAs consumed as precursors of nitrogen containing small molecules
  - Conversion of AAs to glucose, glycogen, fatty acids, ketone bodies, or $CO_2 + H_2O$
- **Protein turnover:** The rate of protein synthesis is sufficient to replace the degraded protein
  - In healthy adults, the total amount of protein in the body remains constant
  - Most proteins are long-lived proteins ($t_{½}$ days to weeks), ***structural proteins*** such as collagen, are metabolically stable (longer $t_{½}$ months or years)
  - Constitutively produced proteins (house-keeping genes), controlled by selective degradation
- Protein degradation:
  - ***ATP-dependent ubiquitin-proteasome:*** in the **cytosol**, and degrade endogenous proteins mainly
    - ✓ **Ubiquitin** is a small, globular, non-enzymic protein which tags proteins to be degraded forming a polyubiquitin chain
    - ✓ **Proteasome** is a large, barrel-shaped, proteolytic complex that recognizes Ub-protein
  - ***ATP-independent degradative enzyme*** system of the **lysosome** (acid hydrolases), degrade:
    - ✓ Extracellular proteins, such as plasma proteins, by endocytosis
    - ✓ Cell-surface membrane proteins by receptor-mediated endocytosis
- Protein digestion begins in the stomach, by the effect of:
  - *HCL (hydrochloric acid):* (pH 2-3) produced by parietal cells, kills bacteria and denature proteins
  - *Pepsin:* acid-stable endopeptidase, produced by chief cells as a zymogen (pepsinogen) and activated by **HCl** and other activated pepsin
- Protein digestion by pancreatic enzymes in the small intestine:
  - The release and activation of the pancreatic zymogens is mediated by the secretion of *cholecystokinin* and *secretin* (polypeptide hormones of the GIT)
  - Trypsinogen activation by ***Enteropeptidase*** (enterokinase) in the intestinal mucosal cells by the removal of a hexapeptide from the N-terminus of trypsinogen
    - ✓ Trypsin activates other peptidase (chymotrypsinogen, proelastase, procarboxypeptidase)
    - ✓ Trypsin, chymotrypsin, elastase are serine endopeptidases
    - ✓ Aminopeptidase at the luminal surface of the intestine, exopeptidase cleaves at the N-terminus

> Trypsin: cleaves after arginine and lysine
> Chymotrypsin: cleaves after tryptophan, tyrosine, phenylalanine, methionine and leucine
> Elastase: cleaves after alanine, glycine, serine
> A carboxypeptidase: cleaves before alanine, isoleucine, leucine and valine
> B carboxypeptidases: cleaves before arginine or lysine

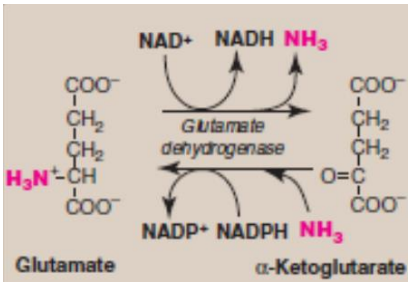
- Free AAs are absorbed by a *Na^+-linked secondary transport* system at the apical membrane
- Di- and tri- peptides are absorbed by a *H^+-linked transport* system
  - AAs are released into the portal system by facilitated diffusion, to be metabolized in the liver
  - ***Branched-chain amino acids*** are not metabolized by the liver, but are sent from the liver to **muscles**
  - AA uptake occurs by transporters such as *COAL transporter* (Cystine, Ornithine, Alanine, Leucine)

- **Celiac disease** caused by chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas
  - Abnormal appearance of lipids (steatorrhea), and undigested protein in the feces
- AA metabolism occurs by transamination, then oxidative deamination then production of intermediates

♦ **Transamination** by Aminotransferase

- The equilibrium constant of transamination reactions is near one
  - Alanine aminotransferase (***ALT***): Alanine + α-ketoglutarate → pyruvate + glutamate
  - Aspartate aminotransferase (***AST***): Oxaloacetate + Glutamate → Aspartate + α-ketoglutarate
    - ✓ Aspartate is used as a source of nitrogen in the urea cycle
- AST and ALT have a diagnostic value:
  - Liver disease: Plasma AST and ALT are elevated occurs in severe viral hepatitis, toxic injury, and prolonged circulatory collaps
    - ✓ **ALT is more specific** than AST for liver disease
    - ✓ **AST is more sensitive** because the liver contains larger amounts of AST
  - Non-hepatic disease: MI and muscle disorders

♦ **Oxidative deamination** by glutamate dehydrogenase



- ***Glutamate*** is the only amino acid that undergoes rapid oxidative deamination, producing free ammonia (NH_3) and α-keto acids
- Reactions occur primarily in the liver and kidney
- Inhibited by GTP (high energy state) and activated by ADP
- D-Amino acid oxidase (DAO): FAD-dependent peroxisomal enzyme
  - D-amino acids present in plants and cell walls of microorganisms, but absent in mammalian proteins
  - ***Increased DAO*** activity has been linked to increased susceptibility to ***schizophrenia***
    - ✓ Produces free ammonia, α-keto acids and H_2O_2
  - L-amino acid oxidases are components of several snake venoms
- Two mechanisms for ammonia transport (nontoxic methods):
  - ***Glutamine synthetase*** that combines NH_3 with Glu to form Gln
    - ✓ The major transport mechanism, which is ATP-dependent
  - Transamination of pyruvate to form ***alanine*** (glucose-alanine cycle)
    - ✓ Primarily in **muscles**
    - ✓ Pyruvate can be used in gluconeogenesis
- Sources of ammonia:
  - From ***glutamine***: Most of it is excreted into the urine as NH_4^+ (acid –base balance)
    - ✓ Glutamine serves as a safe carrier for transporting ammonia to the kidneys
  - From ***bacterial action in the intestine***: Ammonia is formed (from urea) by bacterial urease, which is absorbed from the intestine by the portal vein and is converted to urea by the liver
  - From ***amines*** in the diet and monoamines (hormones or neurotransmitters) by amine oxidase
  - From ***purines*** and ***pyrimidines***
- Urea accounts for about 90% of the N-containing components of urine
  - It consists of C and O (from **CO_2**), and 2 N (1 from free **ammonia**, 1 from **aspartate**)
  - Urea is produced by the **liver** by urea cycle which **consumes energy**, and all steps are **irreversible** with large negative ΔG
  - Occur in the mitochondria and cytosol, in 2 phases: building phase then breaking down phase

- Glutamate is the precursor of both ammonia
- Urea cycle steps:
  - *NH_3 + CO_2 + 2 ATP* produce *carbamoyl phosphate* by **CPS I**
  - *Carbamoyl Phosphate + L-ornithine = L-citrulline* by **ornithine trans carbamoylase (OTC)**
  - L-citrulline leaves mitochondria to cytosol
  - *L-citrulline + aspartate* = *Argininosuccinate* (the **largest** intermediate) by **Argininosuccinate** synthetase (ATP-dependent) through transferring **ATP to AMP**
  - Breaking down Argininosuccinate by **Argininosuccinatelyse** forming:
    - ✓ **Fumarate:** converted into malate, then OAA then aspartate
    - ✓ **L-arginine:** which degraded into L-ornithine and Urea by **arginase** where water is added
- Net formula: Aspartate + NH_3 + CO_2 + 3 ATP + H_2O → Urea + Fumarate + 2 ADP + AMP + 2 P*i* + PP*i*
- N-Acetyl glutamate is an essential activator for CPS I, the rate-limiting step in the urea cycle
  - N-acetylglutamate increases after a protein-rich meal, increased urea synthesis rate
- Arginine is an activator for N-Acetylglutamate synthesis
- ***Hyperammonemia:*** neurotoxic effect on the CNS (tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision), at high concentrations, ammonia can cause coma and death
  - *Acquired hyperammonemia:* Liver disease due to viral hepatitis, or to hepatotoxins such as alcohol
  - *Congenital hyperammonemia:* Genetic deficiencies of any of the five enzymes of the urea cycle leads to failure to synthesize urea
    - ✓ Ornithine transcarbamoylase deficiency is the most common
- Treatment: Restriction of dietary protein, administration of compounds that bind covalently to AAs
- Glucogenic and ketogenic amino acids:
  - **Glucogenic amino acids:** catabolism yields pyruvate or one of the TCA cycle intermediates
    - ✓ Oxaloacetate: Asparagine (converted into aspartate by asparaginase)
    - ✓ Pyruvate: Alanine, glycine, serine, threonine, cystine and cysteine (desulfuration)
      - Glycine can be oxidized into CO_2 and NH_3
      - Or converted into serine by serine hydroxymethyl transferase which requires ***N^5,N^{10} methylene tetrahydrofolate*** (methyl carrier) then serine converted into pyruvate
    - ✓ α-ketoglutarate: Glutamine, Proline, Arginine, Histidine
    - ✓ Fumarate: Phenylalanine, tyrosine
      - Phe is converted to tyrosine by phenylalanine hydroxylase (***tetrahydrobiopterin BH4*** is oxidized into dihydrobiopterin BH2)
      - Tyrosine can be converted into fumarate or acetoacetate
      - Phe hydroxylase deficiency causes *phenylketonuria, alkaptonuria* and *albinism*
    - ✓ Succinyl-CoA: Val, isoleucine, threonine, methionine
    - ✓ SAM (S-adenosyl methionine): methionine
  - **Ketogenic amino acids:** catabolism yields either acetoacetate or one of its precursors (acetyl CoA)
    - ✓ Phe, Tyr, Isoleucine, Leucine, Lysine, Tryptophan
- Branched chain amino-acids (Leu, Val, Ile) are essential amino acids, important for the synthesis of ***excitatory glutamate*** and ***inhibitory gammaaminobutyric acid (GABA)***

SAM synthesis, and activation of methyl group and it donation
Hydrolysis of SAH to adinosine and homocysteine
Homocysteine can be Remethylated into Met (by methionine synthase, require N5-methyltetrahydrofolate [Vit B9, B12]) or undergo transulfuration pathway to be converted to Cys (by adding serine, Cystathionine-β-synthase forming cystathionine which is broken down by cyatathionase into cysteine and alpha-ketobutyrate converted into propyonyl-CoA then succinyl CoA (require B6)

- They are metabolized primarily by the peripheral tissues (particularly muscle)
- High homocysteine promotes oxidative damage, inflammation, and endothelial dysfunction, and increases risk for occlusive vascular disease
  - Homocysteine levels are inversely related to levels of folate, B12, and B6
  - Elevated homocysteine or decreased folic acid levels during **pregnancy** increases the incidence of **neural tube defects** (improper closure, as in spina bifida) in the fetus
  - Women planning to get pregnant are given vitamin B9, B12, B6 supplements

❖ Amino acid synthesis

- **Essential:** Phe, Val, Thr, Trp, Met, Leu, Ile, Lys & His
- **Nonessential:** Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, Pro, Ser, tyrosin
- Synthesis from α-keto acids:
  - Alanine from pyruvate, aspartate from OAA, glutamate from α-ketoglutarate
- Synthesis by amidation (consume ATP)
  - Gln is formed from Glu by glutamine synthetase
  - Asn is formed from Asp by asparagine synthetase, using glutamine as the amide donor
- Glutamate is converted to proline by **cyclization** and reduction (**reduction**, **dehydration**, **reduction**)
- Serine can be synthesized by:
  - 3-phosphoglycerate → 3-phosphopyruvate → 3-phosphoserine then hydrolysis of the phosphate ester
  - Can be synthesized from glycine by transfer of a hydroxymethyl by serine hydroxymethyltransferase
    - ✓ N5 ,N10-methyleneTHF is the one carbon donor (methyl donor)
- Gly is synthesized from serine by removal of hydroxymethyl group by serine hydroxymethyl transferase
  - ✓ THF is the one carbon acceptor
- Cys is synthesized by two consecutive reactions:
  - ***Homocysteine*** combines with ***serine***, forming cystathionine that is hydrolyzed to α-ketobutyrate and Cys (Homocysteine is derived from **Met**)
- Tyr is formed from Phe by *phenylalanine hydroxylase*
  - It requires O_2 and tetrahydrobiopterin (BH4) which is oxidized to dihydrobiopterin (BH2)
  - BH4 is regenerated from BH2 by NADH-requiring dihydropteridine reductase
- **Phenylketonuria (PKU):** The most common inborn error of amino acid metabolism (prevalence 1:15,000) caused by ***phenylalanine hydroxylase deficiency*** causing the accumulation of phenylalanine and a deficiency of tyrosine (tyr becomes an essential amino acid)
  - Caused by any of 100 or more mutations in the gene that codes for phenylalanine hydroxylase (PAH)
  - It causes mental retardation, but if a newborn is diagnosed early before accumulation of phenylalanine it will not develop mental retardation (born normal)
  - Manifestations: Elevated phenylalanine in tissues, plasma and urine, musty (mousey) urine odor due to phenyllactate, phenylacetate, and phenylpyruvate, CNS symptoms including mental retardation (IQ < 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow and Hypopigmentation: fair hair, light skin color, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe
  - PKU is treatable by **dietary restriction** (natural foods low in Phe content (fruits, vegetables, certain cereals), and avoid aspartame)
  - It lacks neonatal symptoms, neonatal screening can be done **24-48 hrs** after expose to protein feeding
  - High blood Phe levels in the mother cause microcephaly (small head), mental retardation, and congenital heart abnormalities in the fetus
  - Phenlyalanine is a **teratogen** (causes malformation of embryo) so dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy
- **Hyperphenylalaninemia:** ***Dihydropteridine reductase deficiency***
  - Restricting dietary Phe does not reverse the CNS effects due to deficiencies in neurotransmitters
  - Replacement therapy with BH4 or L-DOPA and 5-hydroxytryptophan improves the clinical outcome
  - Tryptophan hydroxylase (serotonin synthesis) & tyrosine hydroxylase are affected (depend on BH4)

- **Albinism:** ***defect in Tyr metabolism*** results in a deficiency in the production of melanin
  - Partial or full absence of pigment from the skin, hair, and eyes
  - Inheritance modes: AR (primary mode), AD, or X-linked
  - **Complete albinism** (tyrosinase-negative oculocutaneous albinism) results from a deficiency of copper-requiring tyrosinase
    - ✓ The most severe due to total absence of pigment, cause photophobia & higher risk for skin cancer
- **Alkaptonuria (Alcaptonuria):** A rare metabolic condition, however, cases were found in Jordan
  - A ***deficiency in homogentisic acid oxidase***, resulting in the accumulation of homogentisic acid (a reaction that occurs in the degradative pathway of Tyr)
  - Characteristic symptoms: Not life-threatening, patients are usually asymptomatic until age 40 Homogentisic aciduria, Large joint arthritis, Black ochronotic pigmentation of cartilage and collagenoustissue, dark staining of the diapers can indicate the disease in infants
  - Treatment: diets low in protein especially in Phe and Tyr reduce homogentisic acid & pigment levels
- **Homocystinuria:** ***Defects in homocysteine metabolism***, mode of inheritance: AR (autosomal recessive)
  - High plasma and urinary levels of homocysteine and Met and low levels of Cys
  - The most common cause is a defect in cystathionine β-synthase that converts homocysteine to cystathionine, where vitamin B6 and B12 are given as supportive
- **Maple syrup urine disease (MSUD):** Rare (1:185,000), autosomal recessive (AR) disorder
  - Partial or complete ***deficiency in branched-chain α-keto acid dehydrogenase*** complex that decarboxylates Leu, Ile, and Val
  - Branched-chain amino acids are an important energy source in times of metabolic need
  - Symptoms: feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine, If untreated it leads to mental retardation, physical disabilities, death
  - Prenatal diagnosis and neonatal screening are available
  - Treatment: a synthetic formula that contains limited amounts of Leu, Ile, and Val to provide the branched chain amino acids necessary for normal growth and development without producing toxic levels. Early diagnosis and lifelong dietary treatment is essential for child normal development

❖ Conversion of Amino Acids to Specialized Products

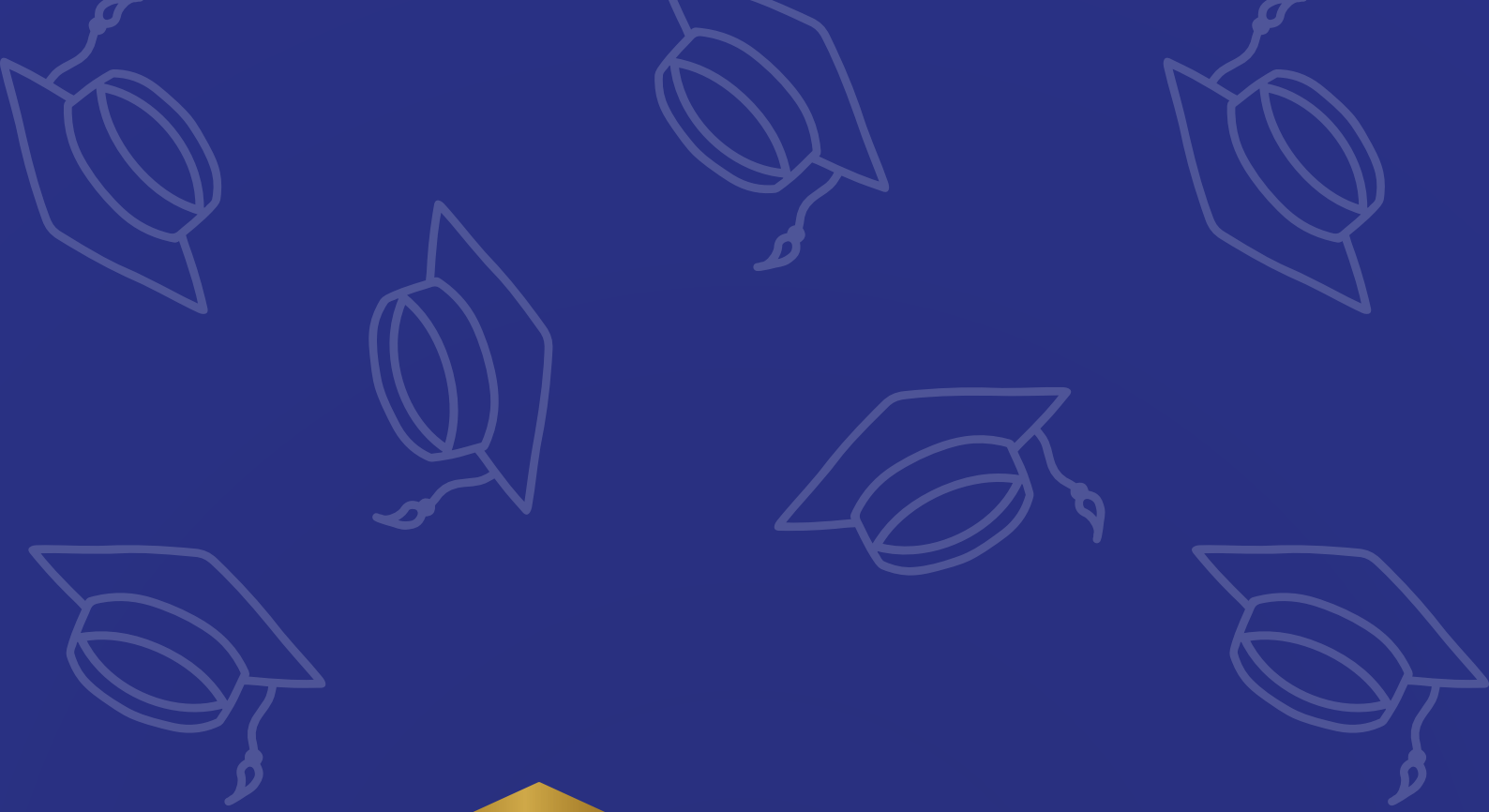
- **Porphyrin:** cyclic compounds that readily bind metal ions (Fe^{2+} or Fe^{3+})
  - The most prevalent metalloporphyrin in humans is **heme** found in hemoglobin, myoglobin, catalase, cytochrome, nitric oxide synthase, and peroxidase
  - Nature of the side chains that are attached to each of the four pyrrole rings, **uroporphyrin** contains **acetate** and **propionate**, **coproporphyrin** contains **methyl** and **propionate**, **Protoporphyrin IX** contains **vinyl**, **methyl**, and **propionate** groups
  - Distribution of side chains around the tetrapyrrole nucleus. Four different ways (I to IV)
    - ✓ Only Type III porphyrins (asymmetric on ring D) are physiologically important in humans
  - **Porphyrinogens** (porphyrin precursors) exist in a chemically reduced, colorless form, serve as intermediates between porphobilinogen and oxidized, colored protoporphyrins in heme biosynthesis
- Heme Biosynthesis: The major sites of heme biosynthesis are ***Liver*** (cytochrome P450) and ***Erythrocyte producing cells*** of the bone marrow (progenitor cells), more than 85% of all heme synthesis
  - The initial and last steps in porphyrins formation occur in **mitochondria** and the intermediate steps occur in the **cytosol**, so Mature RBCs lack mitochondria and are unable to synthesize heme
- Heme synthesis steps:
  - Conjugating Succinyl CoA with Glycine forming δ-aminolevulinic acid (ALA) [rate limiting step]
    - ✓ ALA is elevated in the ***anemia*** seen in ***lead poisoning***

- In the cytosol, 2 ALA are condensed to produce porphobilinogen
- Condensation of 4 porphobilinogen produces the linear tetra-pyrrole, hydroxymethylbilane which is isomerized and cyclized by uroporphyrinogen III synthase to produce the asymmetric uroporphyrinogen III, then decarboxylated generating coproporphyrinogen III
- In the mitochondria, 2 propionate are decarboxylated to **vinyl** groups generating ***protoporphyrin IX***
- Protoporphyrinogen IX is oxidized to protoporphyrin IX, and introduction of iron (Fe^{2+}) by **ferrochelatase** (an enzyme that is *inhibited by lead*)

- Heme Degradation:
  - RBCs are degraded by the reticuloendothelial system (liver and spleen) ~85% of degraded heme comes from senescent RBCs, and ~15% of degraded heme comes from immature RBCs turnover and cytochromes of nonerythroid tissues
- Steps:
  - Addition of an OH to the methenyl bridge between two pyrrole rings, and then a second oxidation by the same enzyme system to cleave the porphyrin ring, producing the ***green pigment biliverdin***, ferric iron (**Fe^{3+}**) and CO, then Biliverdin reduced to ***bilirubin*** (redorange)
  - Bilirubin and its derivatives are bile pigments function as an ***antioxidant*** (oxidized to biliverdin)
  - In the blood, bilirubin is transported by **albumin**
  - In hepatocytes, bilirubin binds to intracellular proteins, such as, **ligandin**
  - 2 glucuronic acid are added to increase solubility (conjugation) by ***bilirubin glucuronyl-transferase***, forming *bilirubin diglucuronide*
    - ✓ Deficiency of this enzyme results in Crigler-Najjar I and II and Gilbert syndrome
  - Secretion of conjugated **bilirubin into bile** [rate-limiting step] by active transport
    - ✓ Dubin-Johnson syndrome results from a deficiency in the transporter protein of conjugated bilirubin, unconjugated bilirubin is normally not secreted
  - Bilirubin diglucuronide is hydrolyzed and reduced by gut bacteria yield ***urobilinogen*** (***colorless***)
- Urobilinogen fates: Oxidation by intestinal bacteria to ***stercobilin*** (gives feces the brown color), reabsorption from the gut and entrance to the portal blood to participate in the enterohepatic urobilinogen cycle where it is taken up by the liver, and then resecreted into the bile then the remainder is transported by the blood to the kidney, where it is converted to ***yellow urobilin*** and excreted, giving urine its characteristic color

- **Jaundice** (or icterus) is the yellow color of skin, nail beds, and sclera due to bilirubin deposition secondary to hyperbilirubinemia
  - Jaundice is a symptom not a disease, related to the metabolism of heme group bilirubin specifically
  - ***Hemolytic jaundice:*** Sickle cell anemia, pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency
  - ***Hepatocellular jaundice:*** due to damage to **liver** cells, more unconjugated bilirubin levels in the blood and urobilinogen is increased in the urine resulting in **dark urine**
  - ***Obstructive jaundice:*** Obstruction of the bile duct (extrahepatic cholestasis) due to a tumor or bile stones, preventing bilirubin passage into the intestine, causing GI pain and nausea, ***pale clay color stool***, and ***urine that darkens upon standing***, Hyperbilirubinemia
- **Newborn infants**, particularly if premature, often **accumulate bilirubin**, because the activity of hepatic bilirubin glucuronyl transferase is low at birth It's not a problem it is just a matter of time
  - Enzyme adult levels are reached in ~4 weeks
  - High bilirubin above the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic ***encephalopathy (kernicterus)***
  - Treatment: Blue fluorescent light that converts bilirubin to more polar water-soluble isomers

- **Catecholamines** (Dopamine (2 OH), norepinephrine (3 OH), and epinephrine (3 OH + CH_3)
  - They are produced by hydroxylation of **tyrosine** into catechol then further modification
- Oxidative deamination of catecholamines is catalyzed by ***monoamine oxidase*** (MAO) and ***catechol-O-methyltransferase*** (COMPT) where the methyl donor is SAM
  - Epinephrine and norepinephrine metabolic product of degradation: Vanillylmandelic acid (VMA)
  - Dopamine metabolic product of degradation: Homovanillic acid (HVA)
- MAO oxidatively deaminates and inactivates any excess neurotransmitters (norepinephrine, dopamine, or serotonin) that may leak out of synaptic vesicles when the neuron is at rest. Irreversible or reversible MAO inactivation Neurotransmitter molecules escape degradation, accumulate within the presynaptic neuron and leak into the synaptic space. MAO inhibitors Activation of norepinephrine and serotonin receptors leads to the ***antidepressant action of MAO inhibitors***
- **Histamine** is a chemical messenger that mediates a wide range of cellular responses
  - Roles include mediation of *allergic and inflammatory* reactions, *gastric acid secretion*, *neurotransmission* in parts of the brain, *vasodilator*
  - It is secreted by **mast cells** as a result of allergic reactions or trauma
  - Histamine is formed by **decarboxylation of histidine** in a reaction requiring **PLP**
- **Serotonin, or 5-hydroxytryptamine (5HT):** Is synthesized and stored at several sites in the body, mostly in intestinal mucosal cells, smaller amounts in the CNS (functions as a neurotransmitter), platelet
  - Physiologic roles are pain perception, regulation of sleep, appetite, temperature, blood pressure, cognitive functions, and mood (causes a ***feeling of wellbeing***)
- **Melatonin Hormone (Sleep Hormone):** Regulation of *sleep wake cycle*, secreted in evening darkness
  - Serotonin is converted to melatonin in the pineal gland via acetylation and methylation
- The presence of ***creatine kinase in the plasma*** indicates heart damage, is used in the diagnosis of **MI**
  - The amount of creatine phosphate in the body is proportional to the muscle mass
  - Phosphocreatine a high-energy compound found in muscle and provides a small but rapidly mobilized reserve of high energy phosphates
- Creatinine is excreted in the urine, excreted *creatinine* amount is proportional to the total creatine phosphate content of the body, and thus can be used to *estimate muscle mass*
  - When muscle mass decrease (paralysis, muscular dystrophy), the creatinine content of the urine falls
  - Rise in ***blood creatinine*** is a sensitive indicator of **kidney** malfunction
  - A typical adult male excretes ~15 mmol of creatinine per day
- **Melanin Pigment:** A pigment in several tissues, particularly the eye, hair, and skin
  - It is synthesized from **tyrosine** in the epidermis by melanocytes
  - Melanin protects the underlying cells from the harmful effects of sunlight
  - *Pheomelanin precursor A defect* in melanin production results in **albinism** (the most common form is due to defects in copper-containing tyrosinase)



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