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◉Sheet ○Slides

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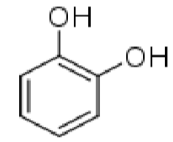
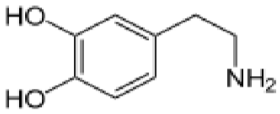
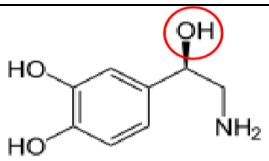
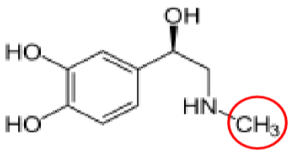
♠ NITROGEN-CONTAINING COMPOUNDS:

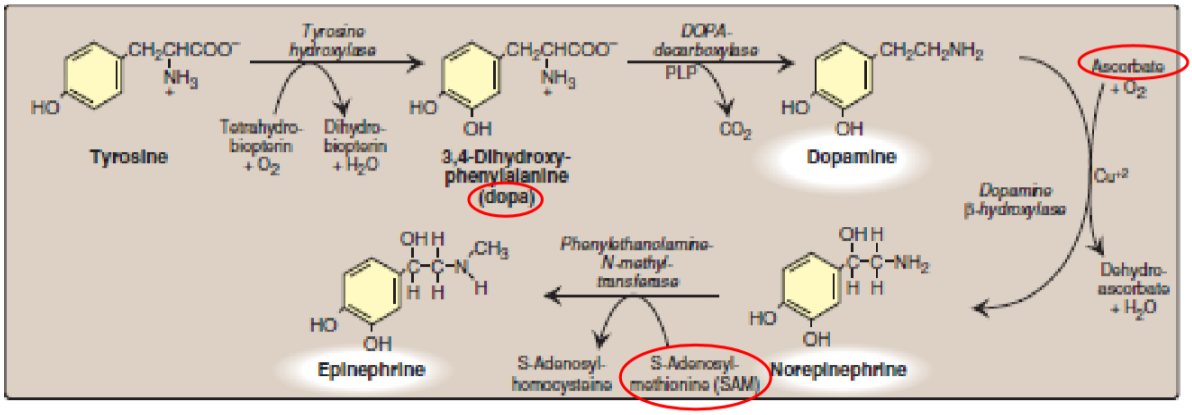
- **Catecholamine synthesis.**
- First of all, we should define the word **Catechol** (catechol is a benzene ring with two hydroxyl groups attached to two adjacent carbons).
- Catecholamines are compounds that have a catechol ring and a side-chain amine.

 Catechol	 Dopamine	 Norepinephrine	 Epinephrine
Simple catechol. benzene with two hydroxyl side groups next to each other.	**Dopamine** is a catechol with amine-containing side chain (catecholamine).	Hydroxylation of Dopamine produces **NE,** which acts as both a **neurotransmitter** and a **hormone**.	Methylation of NE produces **epinephrine,** a **hormone** that is secreted by the adrenal gland.

- ♠ Dopamine and norepinephrine are synthesized in the brain and function as **neurotransmitters**.
- ♠ Norepinephrine and epinephrine are synthesized in the adrenal medulla, outside the nervous system, norepinephrine and epinephrine, are **hormone regulators** of carbohydrate and lipid metabolism.
- ♠ Norepinephrine and epinephrine are released from storage vesicles in the adrenal medulla in response to fright, exercise, cold, and low levels of blood glucose to increase the degradation of glycogen and TAG, and increase blood pressure and the output of the heart (to prepare for **"fight-or-flight"** reactions).

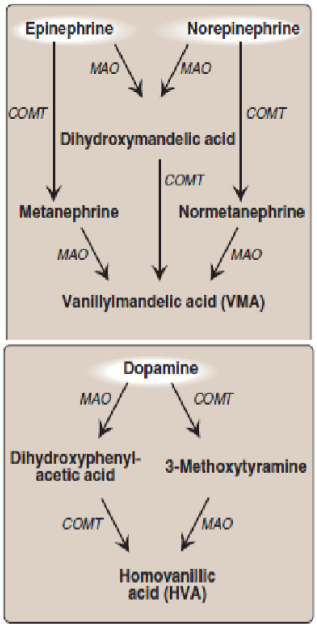
♠ Synthesis of catecholamines:

1. **Tyrosine** (phenol) is hydroxylated by the enzyme **Tyrosine Hydroxylase (tetrahydrobiopterin (BH4)-requiring enzyme)** to form **DOPA** (catechol).
2. **DOPA** is decarboxylated by **DOPA decarboxylase** which requires **PLP** to form **Dopamine**, this step is required to convert the amino acid into amine.
3. **Dopamine** is hydroxylated to yield **Norepinephrine** by **Dopamine β-hydroxylase** which requires **ascorbate (vitamin C and copper).**
4. **Methylation** of **NE** produces **epinephrine** in the adrenal medulla, this reaction is catalyzed by the enzyme **phenylethanolamine N-methyltransferase (PNMT)** which utilizes **S-adenosyl methionine (SAM) as the methyl donor.**



- ♠ Parkinson's disease, a neurodegenerative movement disorder, is due to insufficient dopamine production due to an idiopathic loss of dopamine-producing cells in the brain.
- ♠ Administration of L-DOPA (levodopa) is the most common treatment.
- ♠ **Degradation of catecholamines:**
  - There are two enzymes mainly involved in the breakdown of catecholamines, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).
  - The two enzymes can work in either order, that is COMT catalyzes the first step in catabolism and MAO completes the degradation and vice versa, intermediates differ with the order but the final metabolite is the same in both cases.

- Dopamine metabolic product is **homovanillic acid (HVA)**. Norepinephrine and epinephrine are degraded to form a metabolite known as **vanillylmandelic acid (VMA).**
- Oxidative deamination is catalyzed by monoamine oxidase (MAO).
- O-methylation is catalyzed by catechol-O-methyltransferase (COMT) using SAM as the methyl donor.
- The aldehyde products of the MAO reaction are oxidized to the corresponding acids.
- The metabolic products of these reactions (VMA, HVA) are excreted in the urine
- **VMA** is increased with **pheochromocytomas** (adrenal tumor with increased catecholamine production).



♠ MAO inhibitors:

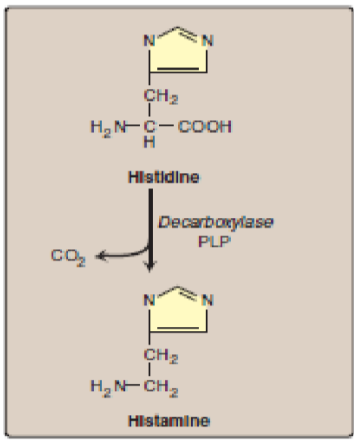
- MAO is found in neural and other tissues, such as the intestine and liver.

Neuron	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.
MAO inhibitors	**Irreversible or reversible MAO inactivation** Neurotransmitter molecules escape degradation, accumulate within the presynaptic neuron and leak into the synaptic space. ⬇ Activation of norepinephrine and serotonin receptors leads to the **antidepressant action** of MAO inhibitors

♠ Histamine:

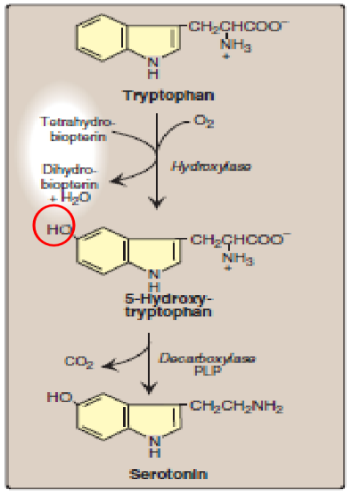
- Histamine is formed by **decarboxylation** of histidine in a reaction requiring **PLP.**
- Histamine is a chemical messenger that mediates a wide range of cellular responses.

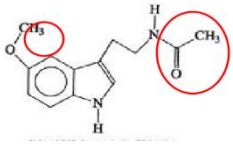
- Roles include mediation of:
  1. Allergic and inflammatory reactions.
  2. Gastric acid secretion.
  3. Neurotransmission in parts of the brain.
- It is secreted by mast cells and basophils as a result of allergic reactions or trauma.
- Histamine is a vasodilator and it increases vascular permeability.



♠ **Serotonin, or 5-hydroxytryptamine (5HT):**

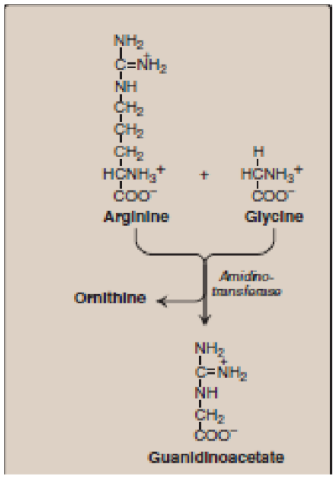
- **Serotonin** is synthesized from tryptophan, which is **hydroxylated** by a **BH4-requiring enzyme** followed by decarboxylation by a **decarboxylase** that requires **PLP** producing **Serotonin,** hence the name (5-hydroxytryptamine).
- Serotonin is synthesized and stored at several sites in the body, mostly in intestinal mucosal cells.
- Smaller amounts in the CNS (functions as a **neurotransmitter**), and in platelets.
- Physiological roles are pain perception, regulation of sleep, appetite, temperature, blood pressure, cognitive functions, and mood (**causes a feeling of well-being**).
- Serotonin is converted to **melatonin** in the **pineal gland** via **acetylation** and **methylation**.





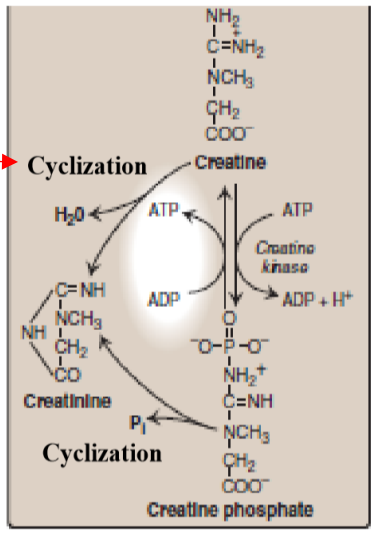
Melatonin is a hormone made by the pineal gland. It helps your body know when it's time to sleep and wake up.
Normally, our bodies make more melatonin at night (sleeping time).
You can use melatonin supplements, it's used to treat or prevent jet lag (the tired, run-down feeling some get when they're traveling across time zones).

♠ Creatine:



- Creatine is synthesized from **Glycine** and the **guanidino** group of **Arginine** and a **methyl group** from SAM. Creatine is reversible phosphorylated to creatine phosphate by creatine kinase.
- Creatine phosphate or phosphocreatine is a high-energy compound found in muscle and provides a small but rapidly mobilized reserve of high-energy phosphates.
- The amount of creatine phosphate in the body is proportional to the muscle mass.
- The presence of creatine kinase in the plasma indicates heart damage, and is used in the diagnosis of MI.

♠ Creatine Degradation:



- Creatine and creatine phosphate cyclize to form creatinine, which 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 decreases (paralysis or muscular dystrophy), the creatinine content of the urine falls.
- Rise in blood creatinine is a sensitive indicator of kidney malfunction, because normally it is rapidly removed from the blood and excreted.
- A typical adult male excretes ~15 mmol of creatinine per day.

♠ Melanin:

- 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.
- **Melanin formation:**

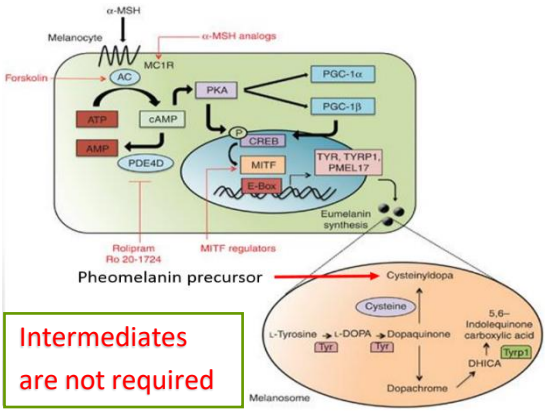
Tyrosine → **DOPA** → **dopaquinone**

1.Pheomelanin

Or

2.Eumelanin

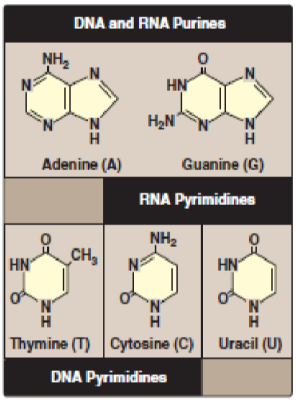
- **Eumelanin** (Brown and black).
- **Pheomelanin** (responsible for the color of **red hair**).
- A defect in melanin production results in albinism (the most common form is due to defects in copper-containing tyrosinase).



Nucleotide metabolism

♠ Purine and pyrimidine structures and roles:

- Essential for RNA and DNA synthesis.
- They serve as carriers of activated intermediates in the synthesis of some carbohydrates, lipids, and conjugated proteins, such as, UDP-glucose and CDP-choline
- They are structural components of several essential coenzymes, such as coenzyme A, FAD, NAD+, and NADP+.
- They serve as second messengers in signal transduction pathways, such as cAMP and cGMP
- They are "energy currency" in the cell, nucleotides are needed for energy transfer. Nucleoside triphosphates (ATP and GTP) provide energy for reactions that would otherwise be extremely unfavorable in the cell.
- They act as regulatory compounds for many metabolic pathways by inhibiting or activating key enzymes.
- Nucleotides are composed of a nitrogenous base, pentose sugar and one, two, or three phosphate group.
- Purines are larger than pyrimidines because they have a two-ring structure (six and five membered rings) while pyrimidines only have a single ring (six membered ring).
- If you can't distinguish between purines and pyrimidines, please refer to Bashar's post.

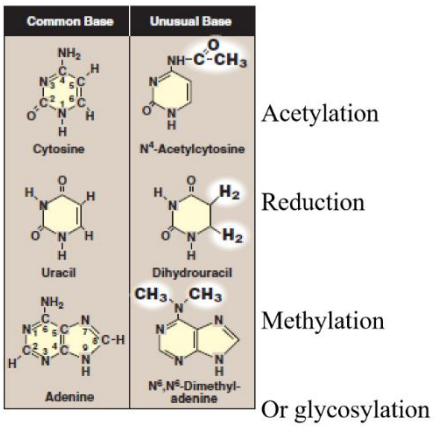


♠ Purine and pyrimidine synthesis:

- The purine and pyrimidine bases can be synthesized de novo (from scratch).
- Or can be obtained through salvage pathways (reuse of the preformed bases resulting from normal cell turnover).
- In many cells the capacity for de novo synthesis to supply purines and pyrimidines is insufficient, and salvage pathway is essential for adequate nucleotide synthesis.
- Little of the purines and pyrimidines supplied by diet are utilized, and are degraded instead

♠ Base modifications:

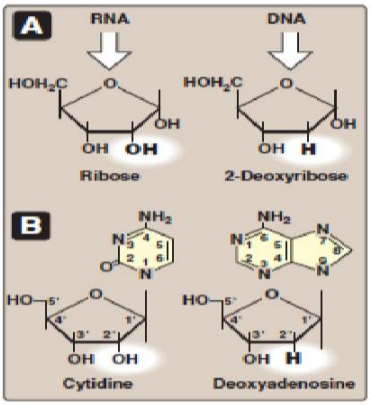
- Base modifications include methylation, glycosylation, acetylation and reduction.
- DNA methylation is associated with gene silencing and inactivation of chromosome X, while acetylation is associated with gene activation.
- Epigenetic changes (base modification) play an important role in the aging process and are responsible for some human diseases.



- The presence of an unusual base in a nucleotide sequence may aid in its recognition by specific enzymes, or protect it from being degraded by nucleases.

♠ Nucleosides:

Nucleoside= Pentose sugar + Base
Ribose + base = Ribonucleoside

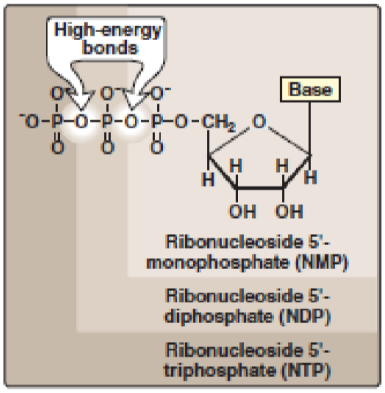


- The ribonucleosides of A, G, C, and U are named adenosine, guanosine, cytidine, and uridine, respectively.
- 2-deoxyribose + base = deoxyribonucleoside.
- The deoxyribonucleosides of A, G, C, and T are named deoxyadenosine, deoxyguanosine, deoxycytidine, and deoxythymidine, respectively.

- Numbering is separate and different (prime and on prime)

♠ **Nucleotides:**

- Nucleoside + one or more phosphate groups= Nucleotide
- The first P group is attached by an ester linkage to the 5'-OH of the pentose forming a nucleoside 5'-phosphate or a 5'-nucleotide.
- The type of pentose is denoted by the prefix in the names “5'-ribonucleotide” and “5'-deoxyribonucleotide.”



- The second and third phosphates are each connected to the nucleotide by a “high-energy” bond.
- The phosphate groups are negatively charged causing DNA and RNA to be nucleic acids.

GOOD LUCK