Subject: Biochemistry Lec 2 — موضوع الدرس

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Nucleotides: 1 building unit of nucleic acid
2 Synthesized in our body (non-essential nutrients)
3 digested in small intestine and the nucleotides in the intestinal mucosa cells degraded into nucleoside + 1) Pentose: is reabsorbed 2) phosphate 3) base: degraded + excreted

nucleic acid

base → G, A → Purine; Pyrimidine → C, U, T

are heterocyclic compounds.

- Pentose: Ribose ⇒ RNA Deoxy-ribose ⇒ DNA
  They ar in β-furanose form (closed 5-member ring)

Function of nucleotieds:
1- RNA + DNA
2- Coenzymes
3- Carries or synthesis (clio lipid protin)
4- CAMP, CGMP → 2nd massenger
5- energy currency (ATP)
6- Regulatory compounds for many pathways (inhibition or activation for key enzymes)

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Purine metabolism

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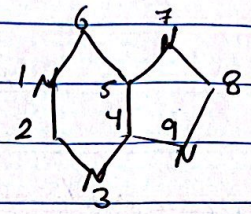
Purine synthesis 2 pathways.

main ← 1- denovo

in brain + bone marrow ← 2- salvage

Purine ring



- C_4 C_5 N_7 ← from glycine
- N_3 N_9 ← amide group of glutamine.
- C_2 C_8 ← N^{10} formyl THF
- N_1 ← amino group of Aspartate.
- C_6 ← directly from CO_2

* Purine built by the pre-existing R-5-P (sugar)
* Purine synthesis occur in liver.
* Purine synthesis can't occur in [erythrocyte, leukocyte, brain, Polymorphonuclear].

R-5-P (from CHO metabolism) is the starting material

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Ribose 5-phosphate (R-5-P)

ATP → PRPP Synthetase ← AMP

PRPP

addition of N: glutamine → glutamate; PPi; H_2O → PRPP Glutamyl amidotransferase

Controlled by a feedback mechanism

5-phospho ribosyl amine

addition of C5 and N: ATP → ADP + Pi; Glycine → Synthetase

Glycinamid ribosyl 5-phosphate

N^{10}-Formyl THF → THF; Formyl transferase

Formyl glycinamid R-5-P

ATP; glutamine → glutamate; Synthetase

Formyl glycinamidine R-5-P

ATP → ADP + Pi; H_2O →; Synthetase

Aminoimidazole R-5-P

CO_2 →; Carboxylase

Aminoimidazole carboxylated R-5-P

Aspartate → Synthase ← Aminoimidazol Succinyl Carboxy amid R-5-P

Fumarate ← arginosuccinase ← Aminoimidazole Carboxamid R-5-P

N^{10} Formyl THF → THF; Formyl Transferase; addition on C_2

Formimidoimidazole Carboxamide R-5-P

H_2O ← IMP cyclohydrolase; ring closure

Inosine monophosphate (IMP)

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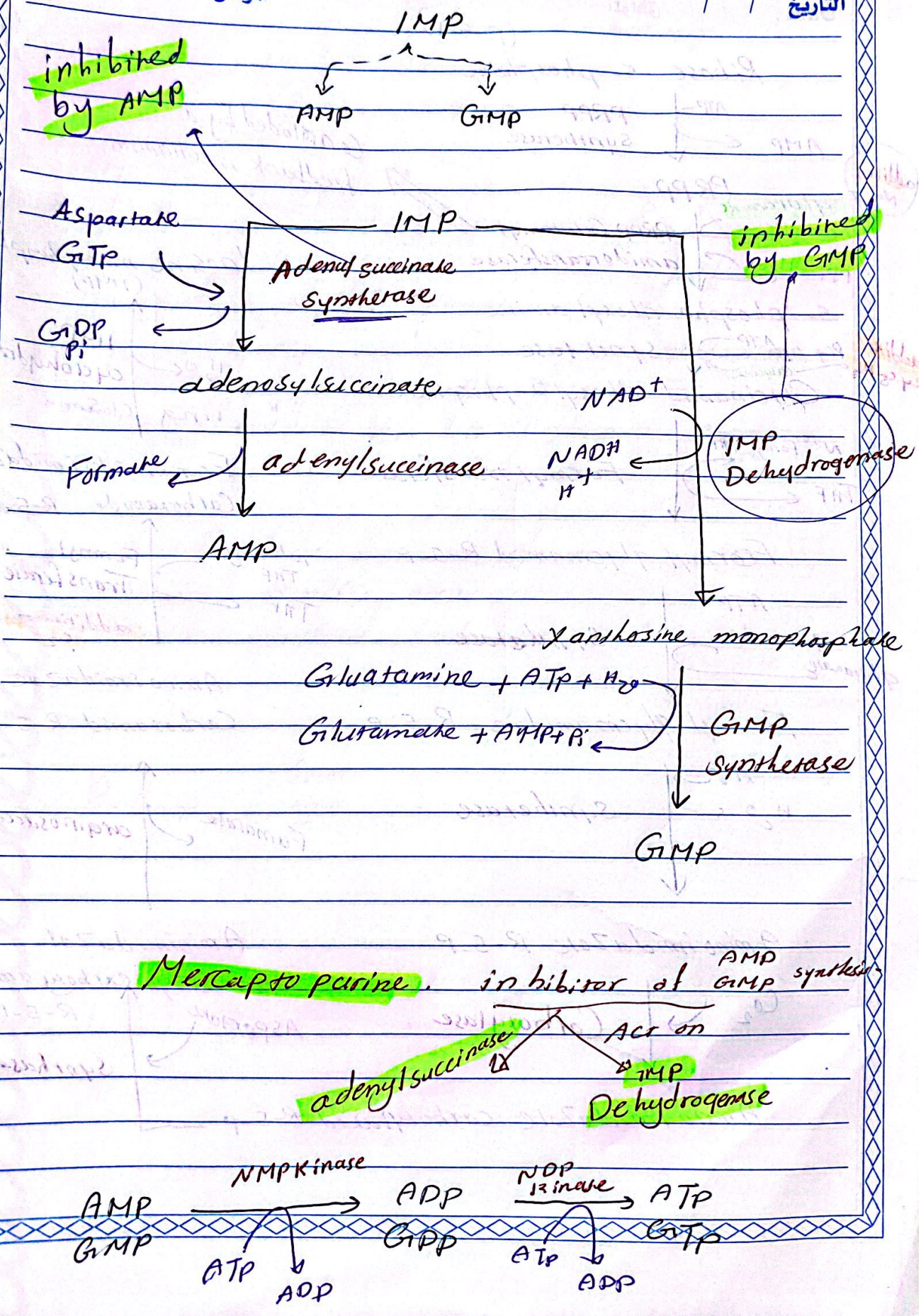
Date : / / الموافق / / التاريخ



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1) Sulf drugs as (sulfonamides) (structural analoges to PABA) inhibit the synthesis of folic acid → indirectly reduce the synthesis of DNA + RNA.

2) methotrexate (structural analoge to folic acid) used in control of cancer inhibits the synthesis of purine + nucleotied + nucleic acids.

3) Azaserine (diazo acetyl L-serine) is a glutamine antagonist. " stop glutamine " reactions.

4) the synthetic nucleotieds analoge used as anticancer agents (6-thio guanine + azaguanine) inhibitors for the purine synthesis.

energy saving ← Salvage pathway of purines. → bone marrow + brain

Adenin —adenine phosphoribosyl transferase (APRT)→ AMP + PPi

Guanin —HGPRT→ GMP + PPi

hypoxanthine —HGPRT→ IMP + PPi

its deficiency lead to Lesch Nyhan Syndrom

- PRPP is the starting
- recycling of purines of degenerated Nucleic acids
- PRPP is R-5-P donor

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The end product of purine synthesis is uric acid.

AMP, GMP, IMP] —nucleosidase→ Adenosine, Guanosine, Inosine

AMP —removal of amine group→ IMP / Adinosine —removal of amine group→ inosine

Inosine —nucleosid phosphorylase→ hypoxanthine

guanosine —n→ guanine

guanase (deamination)

hypoxanthine —[xanthine oxidase]→ xanthine

xanthine —[xanthine oxidase]→ uric acid

in liver + small intestine

contain FAD, Iron, Molybdenum

liberates $H_2O_2 \rightarrow H_2O + CO_2$

harmful

+ Uric acid in adult serum normally 3-7 mg/dL (women ↓ by 1 mg)

* daily uric acid excretion about 500-700 mg

↓ uric acid synthesis → ↑ Purine nucleosides + nucleotied

Subject: uric acid is non toxic to brain. موضوع الدرس

Date: / / الموافق hyperuricemia ⇒ XX any neurological syptoms. / التاريخ

↑ uric acid in serum ⇒ hyperuricemia.

↑ uric acid excretion ⇒ uricouria.

↑ uric acid production lead to Metabolic disorder which is Gout.

uric acid at normal pH found in more soluble form as Na urate → in sever hyperurecemia

crystal of it deposits in soft tissue as joints (Gout tophi)

Gout associated with alcohol high living overeating

deposion lead to painful gout arthitis.

first affect Toe metatarsophalangeal joint.

uric acid / Na urate → Play a role in renal damage or Stone formation

Lesch - Nyhan syndrom ① due to deficing in HGPRtase. (↑ more PRPP + ↓ IMP GMP)

② Sex - linked metabolic disorder. (HGPRtase gene in X - chromose)

③ affect males only.

④ ↑ uric acid produc (gout arthitis)

⑤ have mental retardation, agressive behavior, Learning disabily, self - mulitism.

↑ Synthesis + degradation of Purins.

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Gout

Primary

- inborn error of metabolism
- due to overproduction of uric acid and overproduction of purine nucleotides

[1] PRPP synthase (non subjected to feed back regulation)

[2] PRPP glutamylamidotransferase (Lack of feedback control)

[3] HGPRtase deficiency → Lesch Nyhan Syndrom → ↑ purine synthesis by 2 mechanisms

[A] ↓ utilization of Purin by Salvage pathway resulting in accumulation + diversion of PRPP for purine

[B] ↓ IMP GMP. Cause impairment in controlled feedback mechanism.

[4] G-6-phosphatase deficiency in (Von gierke's) type I glycogen storage disease

glucose 6-P ⟶ ✗ ⟶ glucose.

↓

↑ utilization of G-6-P in HMP shunt

↓

↑ PRPP + R-S-P

↓

↑ purine production

↑ glycolysis → lead to Lactic acidosis

Secondary

due to disease ↑ synthesis or ↓ excretion

↑ nucleic acid degeneration in

① Cancer.
- leukemia
- lymphomas
- Polycythemia

② Psoriasis
- ↑ tissue breakdown
- (trauma, starvation)

lead to

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reduced glutathion → play a role in cellular control of O_2 species

⑤ ↑ Glutathion reductase ⇒ generate more $NADP^+$ which utilized by HMP

↑ R5-P and PRPP synthesis

Gout treatment

① allopurinol → structural analog to hypoxanthine. Competitively inhibit Xanthine oxidase

allopurinol —(xanthine oxidase)→ oxypurinol

turn to more active inhibitor of xanthine oxidase

Suicide inhibition

inhibit xanthine oxidase

↓

accumulation of [xanthine + hypoxanthine] → more soluble + easily excreted

① Drugs + ② restriction of dietary intake of purine + alcohol is advised.

③ Consumption of plenty water

dGTP inhibit normal T development

* ADA deficiency → accumulation of dATP → inhibitor of ribonucleotide reductase → DNA synthesis + cell replication.

② deficiency of nucleoside phosphorylase

Lead to impairment in T cell function but No effect for B cell

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Pyrimidine metabolism (C U T)

1. heterocyclic ring
2. first synthesized then attached to RS-P
3. CO_2, Aspart + glutami → contribute to atoms in the ring formation

CO_2 + glutamine + ATP

↓ Carbamyl phosphate synthase II (CPS II)

Carbamoyl phosphate (CAP) → condenses with aspartate to form Carbamylaspartate

↓ Aspartate transcarbamylase

CO_2 + glutamine + ATP

↓ Carbamyl Phosphate synthase II (CPS II)

Carbamyl phosphate (CAP)

Aspartic acid → ↓ aspartate transcarbamylase ← Pi

Carbamyl Aspartic acid (CAA)

H_2O ← ↓ Dihydro orotase

Dihydroorotic acid (DHOA)

NAD+ → dihydroorotate dehydrogenase (mitochondrial enzyme) ← NADH + H

removing H from C5 + C6

orotic acid

PRPP → ↑ orotate phospho Ribosyl transferase ← Pi

orotate-phosphoribosyl transferase

↑ Decarboxylase ← CO_2

(OMP)

UMP

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* UMP is the first true pyrimide ribonucleotied.

UMP → (ATP → ADP, UMP kinase) → UDP → (ATP → ADP, DMP kinase) → UTP

UMP → CTP, TTP

UMP → UTP —(CTP synthase; H_2O, glutamine → glutamine; ATP → ADP+Pi)→ CTP

UDP → dTMP ?!

dUMP → UDP —(ribonucleotied reductase; thioredoxin (2SH) → Thioredoxin (S–S))→ dUDP → dUMP (dephosphorylated → substrate for TMP synthase)

dUMP —(Thymidylate synthase on C_5; N^5-N^{10} Methylen THF → THF)→ dTMP

Salvage ⇒ Pyrimidin + PRPP —(Pyrmdine phosphoribosyl transferase)→ Pyrmidine nucleotied + PPi

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① CPS II + aspartate transCarbonylase + dihydrootatase.

↓

Present as multienzymeComplex

② orotate phosphoribosyl transferase
OMP- deCarboxylase
] → single enzymes.

Degredation ⇒ U T C

↓ degraded into

[B-alanine
B-aminoisobutyrate] more soluble

↓ transamination + reaction

acetyl CoA
Succinyl CoA

C
↓ +O, -NH3

U
↓ NADPH+H → NADP

Dihydrouracil

↓

Carbonyl B-alanine ⇒ = Bera-ureido propionate

↓ -CO2, -NH3

B alanine

Carbonyl B-amino isobutyrate =

T
↓ NADPH+H → NADP

Dihydrothymine

↓

Bera ureido isobutyrate

↓ -CO2, -NH3

B-amino isobutyrate

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Disorders

① orotic aciduria = autosomal recessive

type 1 due to orotate phosphoribosyl transfera. OMP decarboxylase

type 2 due to deficiency of only OMP decarboxylase

Symptoms ↑ orotic acid and its excretion in urin by (1-1.5 g)

mental + Physical retardation

megaloblastic anemia

Drug (cause acido uria) allopurinol (Purin analog is a substra for orotate phospho ribosyl transfera)

Competes for phosphoribosylation with orotic acid

the resulting product inhibi OMP decarboxylase leading to → orotic aciduria, orotiduniria

Features

NO feed back inhibit (UMP inhibi OMP decarb) ⇒ ↑ product.

Rapidly growing cells affected → anemia

Retarded growth

urinary obstruction (due to crystals in urine)

Both response to uridine as it converse to UTP (feedback inhibits)

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Date : / / الموافق / / التاريخ

Reye's syndrom

1) 2° orotic aciduria

2) defect in ornithin transcarbomylase.

↓

accumulation of Carbomoyl Phosphate ↓ ↑ synthesis of orotic acid + ↑ excretion of orotic acid

* a child blood suger ↓ but amonia in blood ↑

* Liver may swell + fatty deposit-
* brain may swell → seizures
Convulsions
loss of consciousness

The end

12:40 Am
28/12/2022