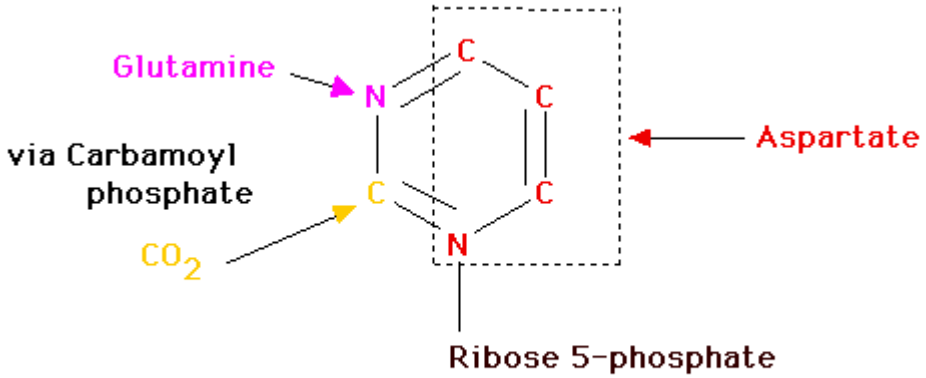
* pyrimidine Synthesis & Degradation :

- pyrimidine ring is synthesize before being attatched to ribose 5-phosphate (not like purine) (MCQ)



Generic pyrimidine base

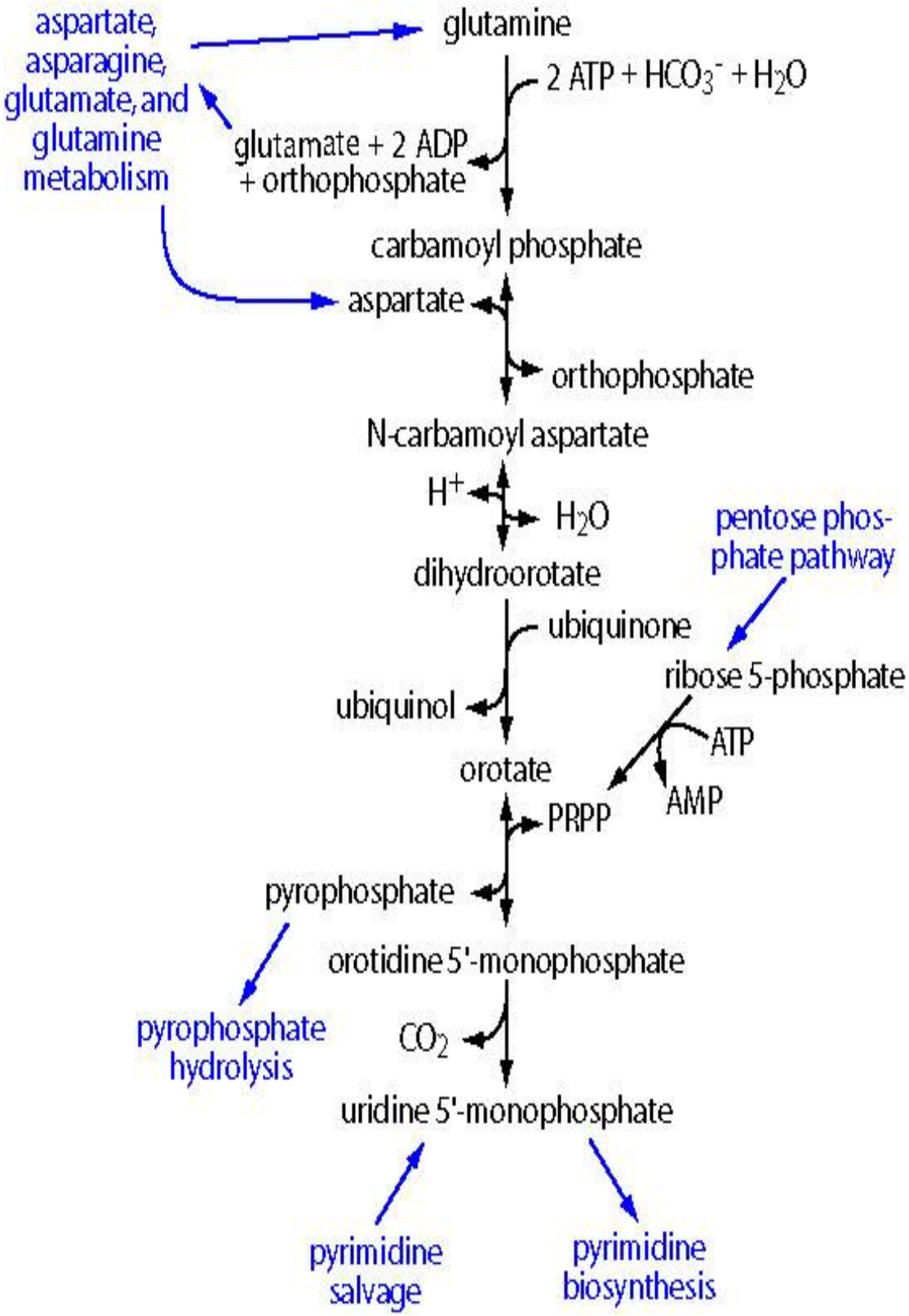
- aspartate for { (C4,5,6),(N1)} (MCQ) (IMPORTANT)
  Aspartate donate C in both purine & pyrimidine (F)
  Aspartate donate N in both purine & pyrimidine (T)
- Glutamine for (N3)
- CO2 for C2
- So only glutamine & aspartate required for both purine & pyrimidine .

Now we will begin (all the reaction are irreversible)

* synthesis of carbamoyl phosphate : (MCQ)

2ATP + CO2 + glutamine ----- (CPS11)-→ carbamoyl phosphate

* carbamoyl phosphate synthase 11 :
  a) in cytosol .
  b) source of N: amide group of glutamine
  c) activator : ATP & PRPP .
  d) inhibitor : UTP .
  e) no need for biotin .


aspartate, asparagine, glutamate, and glutamine metabolism
glutamine
2 ATP + HCO_3^- + H_2O
glutamate + 2 ADP + orthophosphate
carbamoyl phosphate
aspartate
orthophosphate
N-carbamoyl aspartate
H^+
H_2O
dihydroorotate
pentose phosphate pathway
ubiquinone
ribose 5-phosphate
ubiquinol
ATP
orotate
AMP
PRPP
pyrophosphate
orotidine 5'-monophosphate
pyrophosphate hydrolysis
CO_2
uridine 5'-monophosphate
pyrimidine salvage
pyrimidine biosynthesis

* synthesis of orotic acid : (see figure 22.21 page 301)

-Pyrimidine ring is closed by dihydroorotase .
-first 3 enzyme :
(CPS 11 , aspartate transcarbamoylase , dihydrooratase)
a) in cytosol
b)are all domain of the same polypeptide chain (multicatalytic) (MCQ)

- Dihydrooratate dehydrogenase : (MCQ)
a) convert dihydroorotate to orotate .
b) in mitochondria .
c) use NAD --------→ NADH

* synthesis of a Pyrimidine nucleotide :

- orotate is the first Pyrimidine ring . (MCQ) (IMPORTANT)
- orotidine 5-monophosphate (OMP) is the parent Pyrimidine mononucleotide . (MCQ)

- **orotate phosphoribosyl transferase :**
a) convert orotate to OMP .
b) irreversible (release pyrophosphate)
c) here we add ribose 5-phosphate that come from PRPP (not from pentose phosphate pathway like purine)(MCQ)

NOTE : (**both purine & pyrimidine synthesis require glutamine & PRPP)**

***** (OMP) is converted to Uridine 5-monophosphate (UMP) by :**
OMP decarboxylase (which remove acidic carboxyl group)

- UMP synthase : (MCQ) (very important)
- a single polypeptide contain both :
1) **orotate phosphoribosyl transferase**
2) orotidylate decarboxylase

*OROTIC ACIDURIA :

a) deficiency of UMP synthase .(MCQ)
b)rare genetic defect , cause abnormal growth , megaloblastic anemia , large amount **of orotate** in urine (MCQ)
c) **treatment** : uridine diet (improvement of anemia & decreased orotate excretion)

Carbamoyl phosphate synthetase:

a) is inhibited by ATP.
b) requires biotin as a coenzyme.
c) is inhibited by PRPP.
d) is present in the mitochondria.
e) is present in one of the domains of the same polypeptide chain. (answer)

*Which of the following statements about nucleotide metabolism is **incorrect**?*

a) sulfonamides competitively inhibit purine synthesis in human. (answer)(bacteria)
b) IMP and OMP are parent purine and pyrimidine nucleotides, respectively.
c) the synthesis of AMP requires GTP.
d) AMP inhibits de novo purine synthesis.
e) folic acid analogs are competitive inhibitors of dihydrofolate reductase.

*All the following statements about PRPP are correct **except**:*

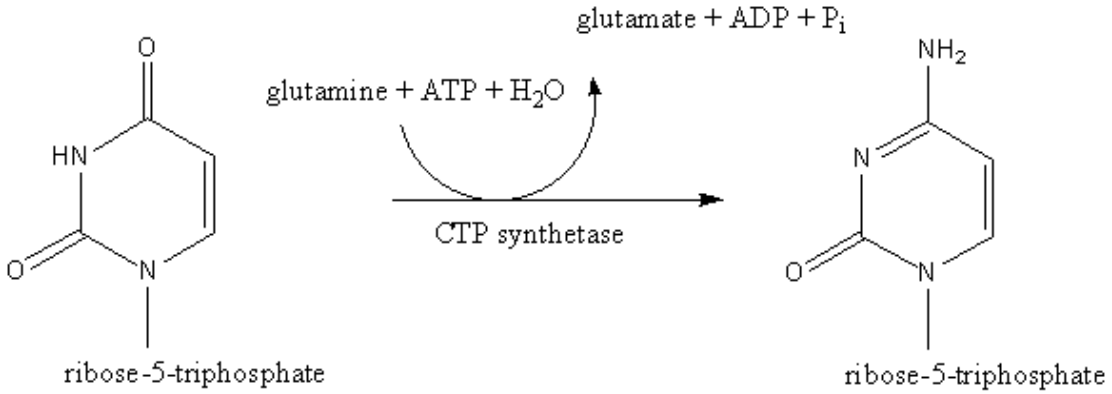
a) it participates in purine and pyrimidine nucleotide synthesis.
b) PRPP synthetase is inhibited by Pi and stimulated by ATP. (answer) (activated by Pi)
c) its tissue levels increase in Lesch–Nyhan syndrome.
d) it participates in the salavage reactions of uracil base.
e) an intact HMP pathway is important for its synthesis.

Regarding de novo purine & pyrimidine nucleotide biosyntheses:
a. The committed-step in purine synthesis is catalyzed by PRPP synthetase.
b. The committed-step in pyrimidine synthesis is catalyzed by CPS 1.
c. The rate of purine & pyrimidine syntheses is controlled by the intracellular concentration of PRPP (answer)
d. A deoxyribose is required for adenine nucleotide synthesis whereas a ribose is required for uracil nucleotide synthesis.
e. The end product of purine synthesis is dATP.

Carbamoyl phosphate synthase II:
a. Is a mitochondrial enzyme.
b. Requires biotin as a co-enzyme.
c. Is activated by ATP. _
d. Is a bifunctional enzyme.
e. Deficiency leads to orotic aciduria.

A one year old female patient is anemic. Her urine contain as elevated level of orotic acid. The intake of which one of the following compounds is most likely to control her
condition:
a. Thymidine.
b. Hypoxanthine.
c. Uridine. (answer)
d. Allopurinol.
e. Adenine

* Synthesis of uridine triphosphate (UTP) & Cytidine triphosphate (CTP) :



UTP **CTP**

Note: the nitrogen is provided by glutamine

OMP-------UMP-----UDP-------UDP---------UTP---------CTP

*Synthesis of thymidine monophosphate (dTMP) from (dUMP) :

- SEE FIGURE (22.23) (MCQ) (important)

OMP------UMP------UDP------dUDP------dUMP—(thymidylate synthase)----dTMP

*thymidylate synthase :
- convert dUMP to dTMP .
- methyl group source : N5,N10-methylene tetrahydrofolate .
- tetrahydrofolate contribute for C & 2H .
- inhibitor : 5-flurouracil (thymine analogs) which convert to 5-FdUMP . (MCQ) (important)

*** dihydrofolate reductase :**

- Convert dihydrofolate to THF
- inhibitor : methotrexate (folate analogus) (MCQ) .
- methotrexate by inhibiting this enzyme it decrease THF (MCQ)
- so methotrexate inhibit both :
  a) purine synthesis .
  b) preventing methylation of dUMP to d TMP .
  c) inhibit DNA synthesis & cell growth .
  e) slow growth rate of cancer cell .

*Salvage of Pyrimidine :

- salvage pyrimidine bases (FEW) (MCQ)
- salvage pyrimidine nucleoside (more) (MCQ)

* e.g :
- Uridine & Cytidine >>>> uridine cytidine kinase .
- deoxycytidine >>>>>>> deoxycytidine kinase
- Thymidine >>>>>>>>> thymidine kinase

NOTE : all of these reaction use ATP and form :
UMP , CMP , dCMP , TMP

* (MCQ) Acyclovir : a substrate for thimidine kinase (not synthase be careful) (MCQ) .
-Herpes simplex virus encodes a virus specific thymidine kinase which phosphorylate the nucleoside analog acyclovir (acycloguanosine).
- **Acycloguanosine triphosphate** incorporated by the viral DNA polymerase into viral DNA causing **chain termination** . (MCQ) .

Acyclovir is:
a. Thymine analog.
b. A substrate for thymidine kinase (answer)
c. Folic acid analog.
d. PABA analog.
e. An inhibitor of thymidylate synthase.

* Degradation of pyrimidine nucleotide :

- purine rings are not cleaved in human cell .
- pyrimidine rings are cleaved & opened TO HIGHLY SOLUBLE STRUCTURE : (MCQ) :
- a) B-alanin : precursor of Acetyle CoA
  b) B –aminoisobutyrate : precursor of succinyl CoA

The least soluble degradation product of purine or pyrimidine bases is:
a. Uric acid. (answer)
b. ®-aminoisobuturic.
c. Allatoin.
d. Xanthine.
e. ®-alanine.

تمت المحاضرة الرابعة

DONE BY:

مجهول