Metabolism of nitrogen containing molecules

Amino acids

Nucleotides

Overview

- The nitrogen cycle
- Metabolic turnover of nitrogen
- Metabolic fate of amino acids
- Proteolysis
- Fate of amino group
- Fate of carbon chain of amino acids
- Biosynthesis of amino acids
- Biosynthesis of nucleotides
- Degradation of nucleotides

Bacterial

Nitrogen turnover in eukaryotes

Fate of the carbon chain of AAs

N_2

Denitrification

NO_3^-

Fix

Anammox bacteria

Nitrification

Air bags

NO_2^-

synthesis

degradation

Amino acids

NH_4^+

protein synthesis

Protein

Nucleotide

Uric acid

proteases

nucleotide synthesis

Urea cycle

Urea

Amino acids

Ribose-5-P

Glucose

Pyruvate

Ketone bodies

TCA

$ATP + CO_2 + H_2O$

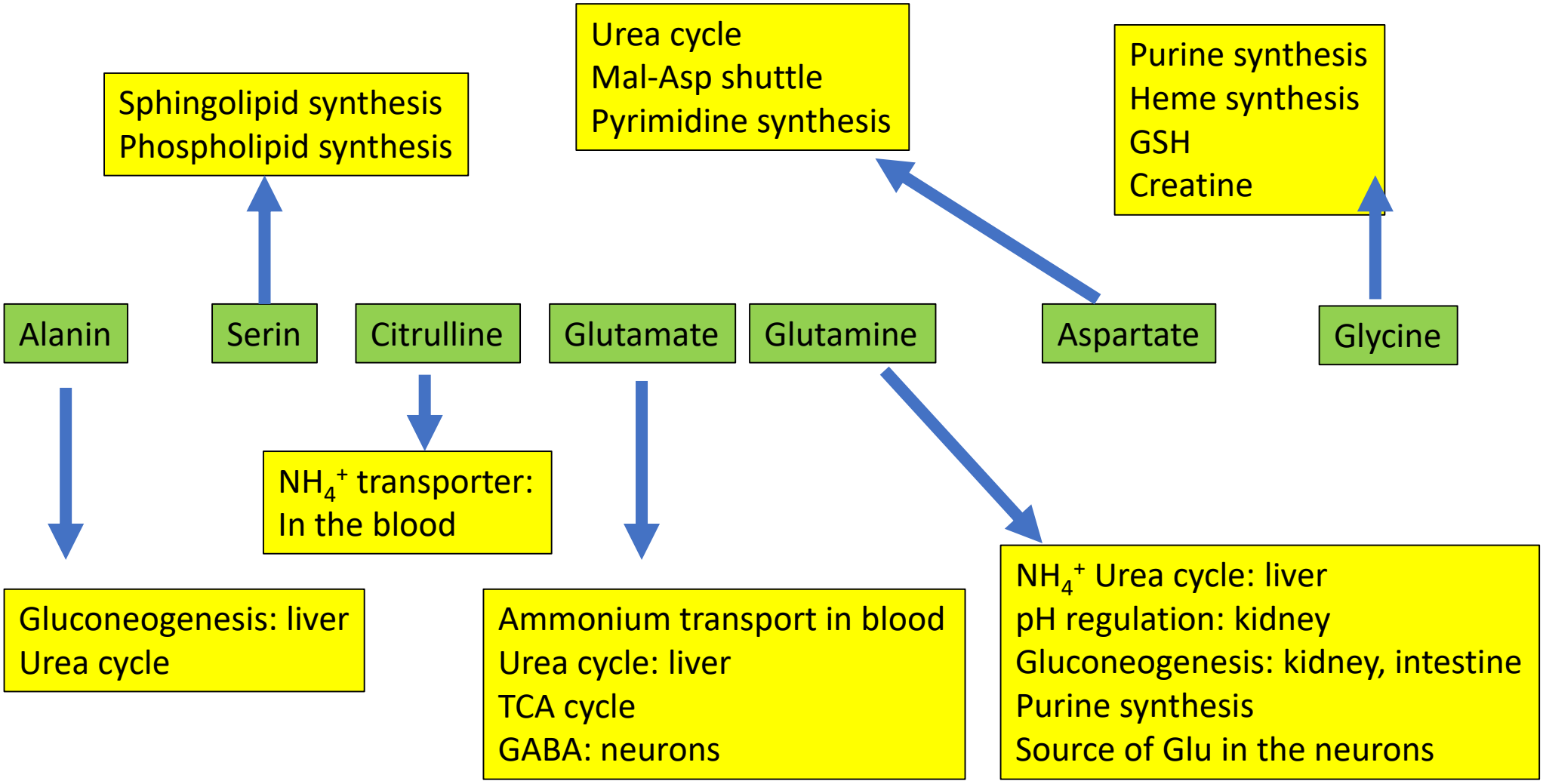
Amino acid

$2\ NaN_3 \rightarrow 2\ Na + 3\ N_2\ (g)$

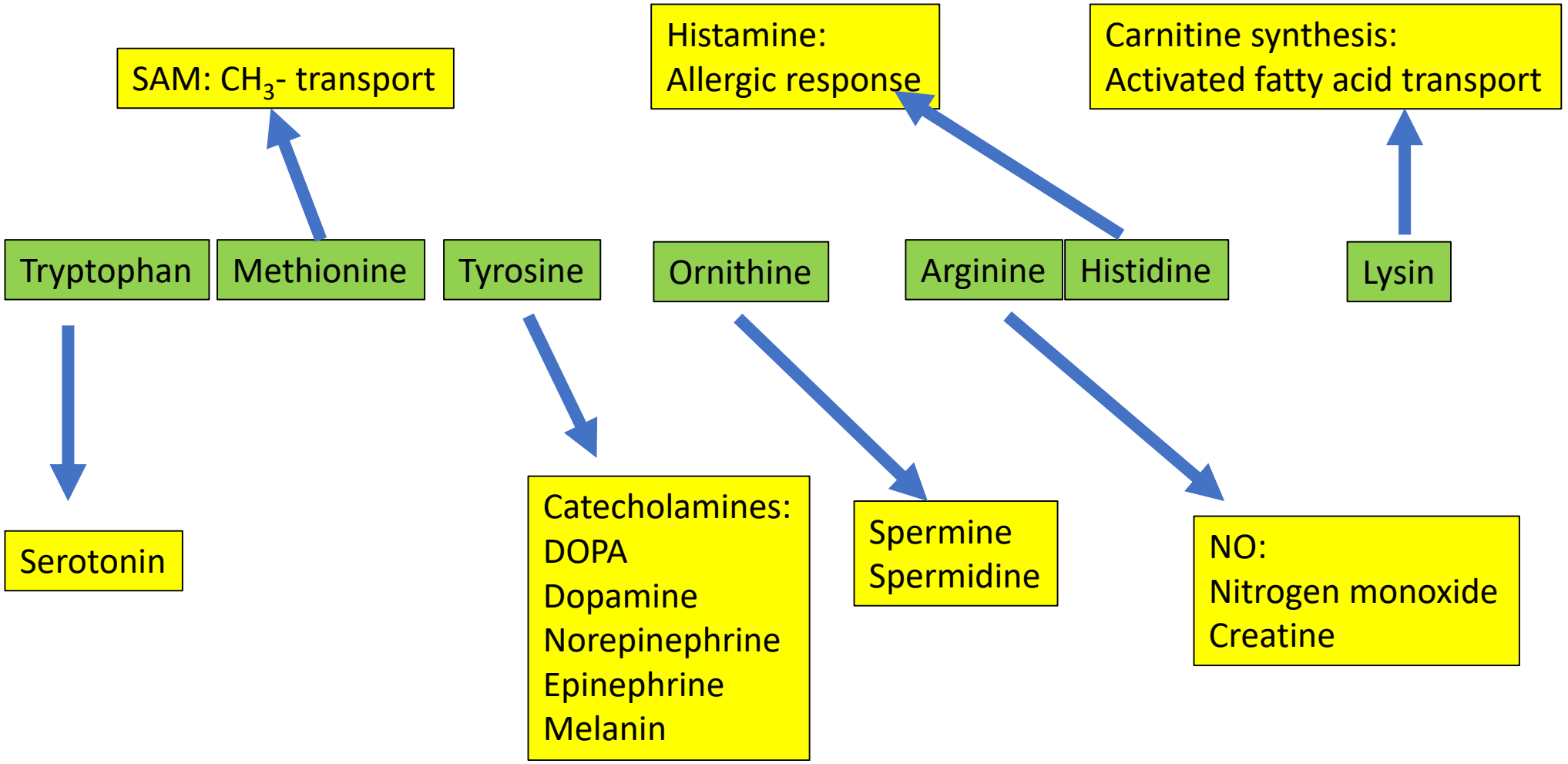
$10\ Na + 2\ KNO_3 \rightarrow K_2O + 5\ Na_2O + N_2\ (g)$

$K_2O + Na_2O + 2\ SiO_2 \rightarrow K_2SiO_3 + Na_2SiO_3$

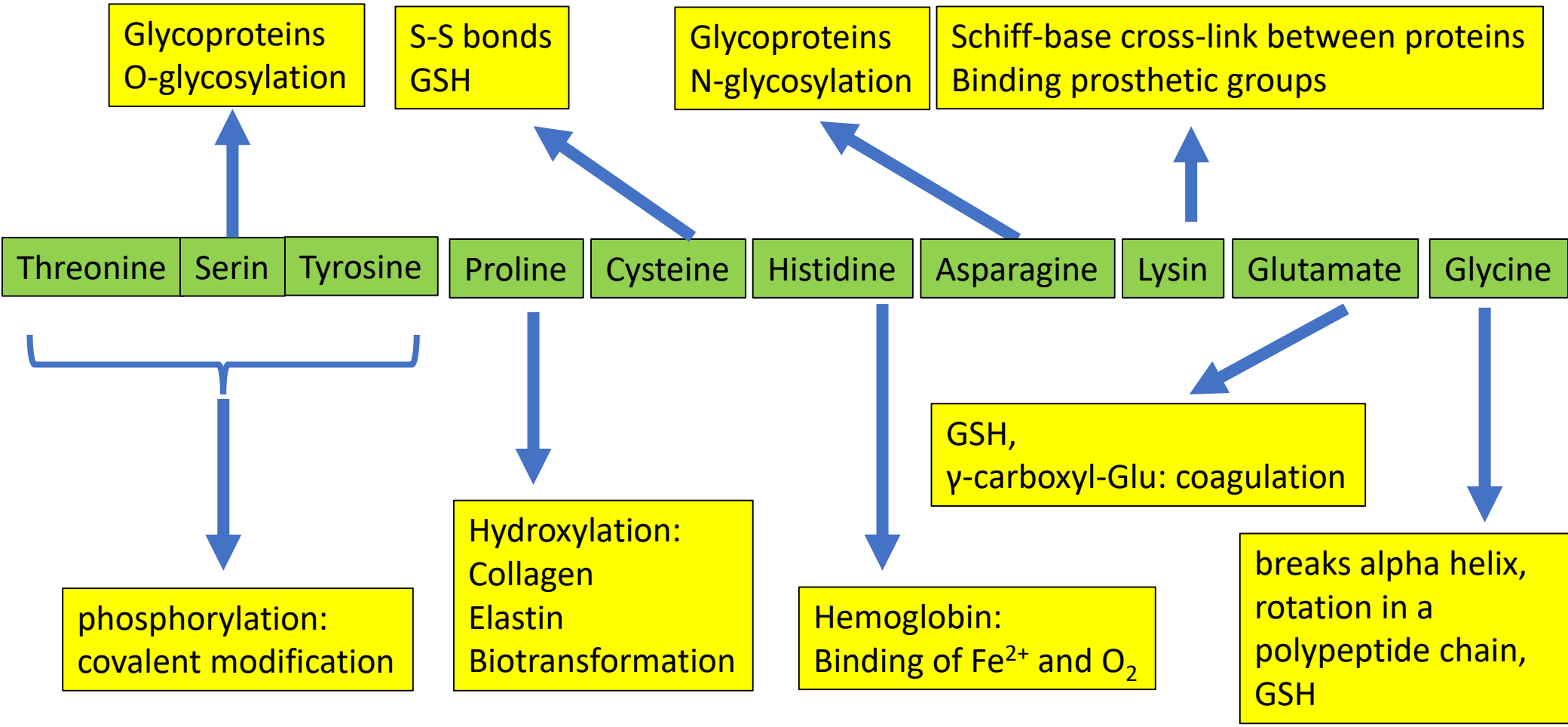
Metabolic fates of amino acids I



Metabolic fates of amino acids II



Role of the amino acids inside of a polypeptide chain



Proteolysis

- **Digestion**:
- Intestinal proteases
- Zymogens
- P-H^+ pump
- Resorption: Na^+ -amino acid cotransport

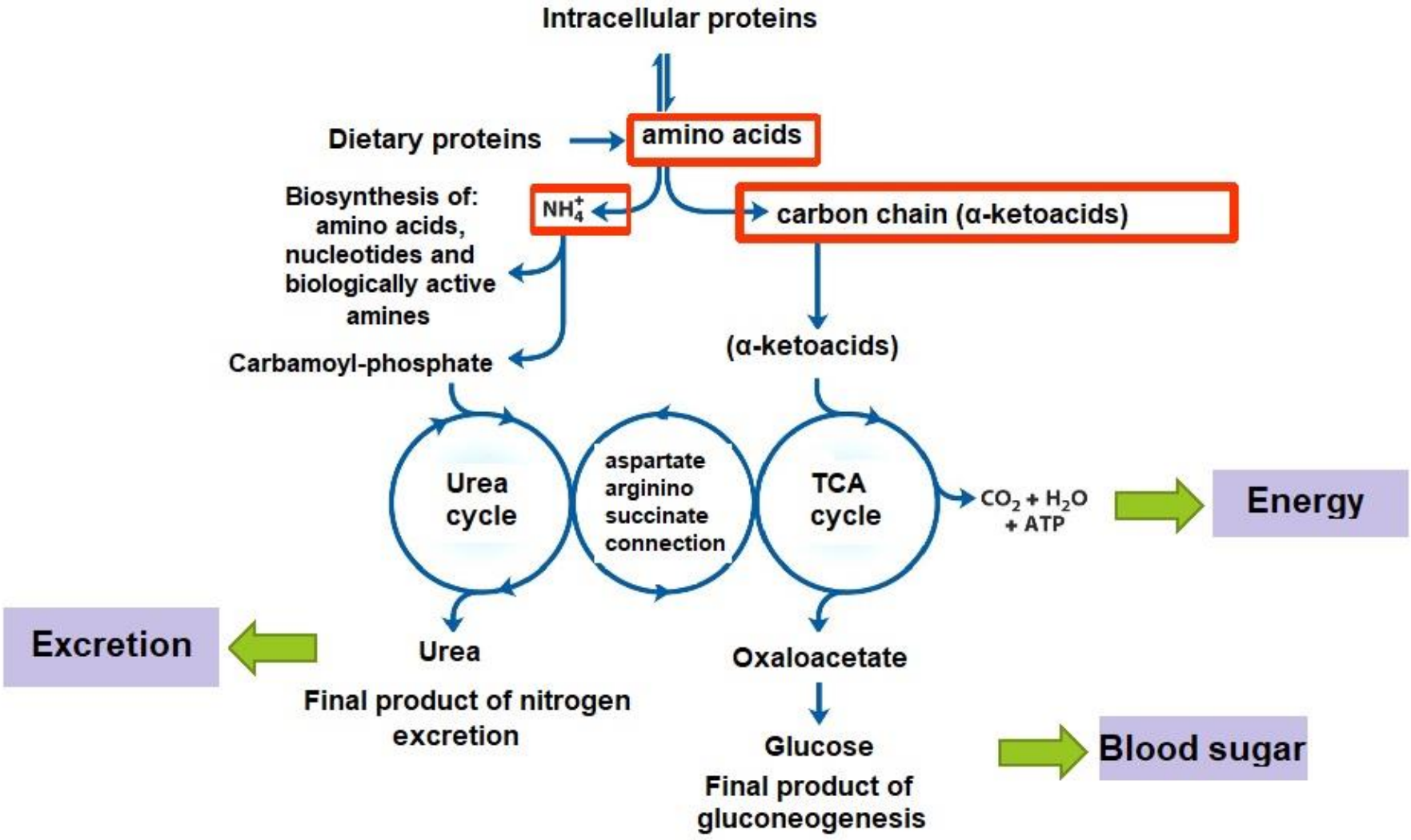
- **Intracellular:**
- Proteosome
- Lysosome: V-H^+ pump
- Autophagy
- Caspases

Proteolysis

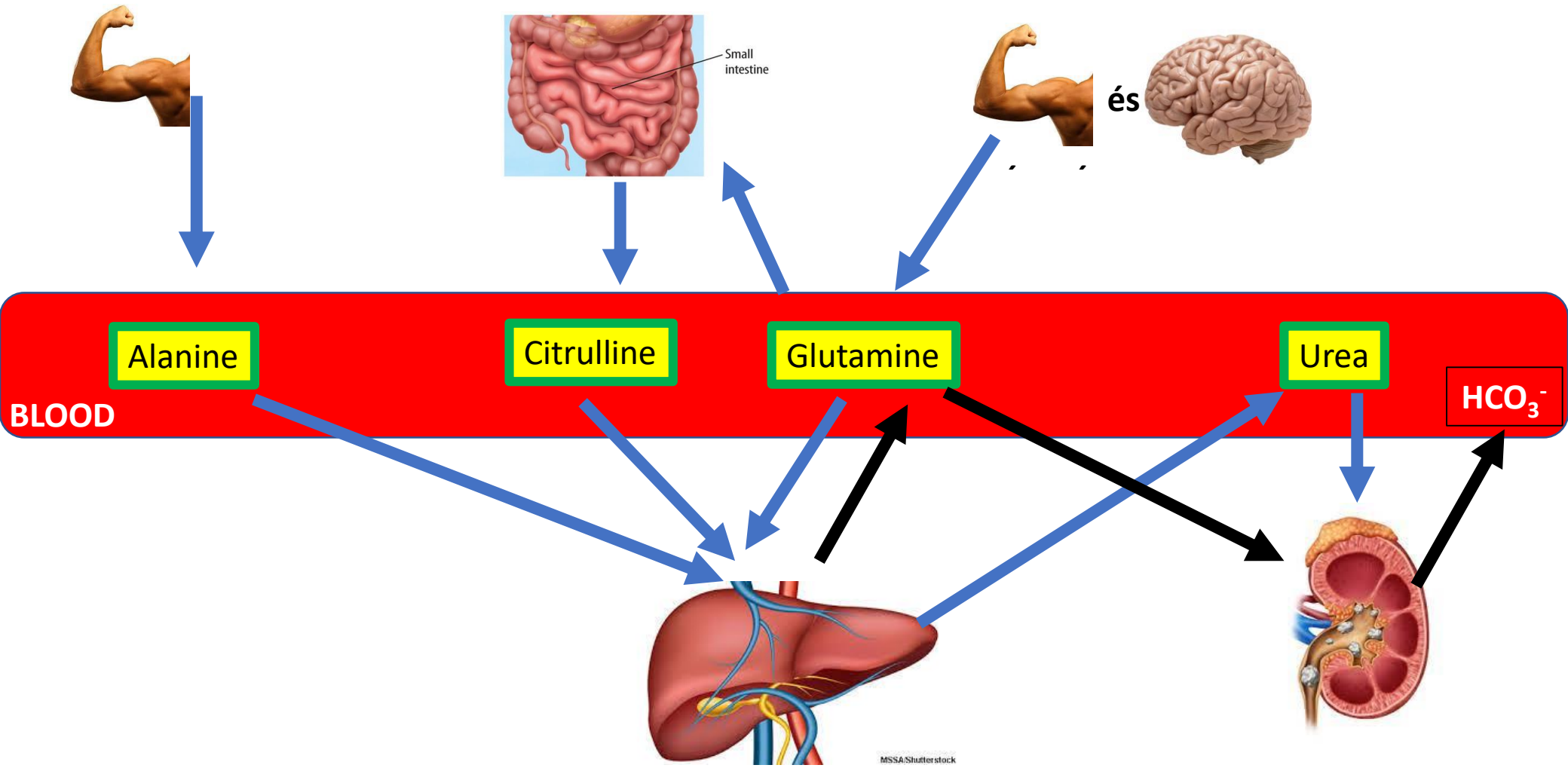
- **ECM**
- MMP (Matrix Metalloproteinases)
- Damaged tissue, wound healing
- Metastasis
- Virus and bacterial infection

- **Blood proteinases**
- Coagulation factors:
  - Serin proteinases

Fate of the amino group



Transport of toxic ammonia: transport of the amino group of amino acids



The converting of amino acids

Amino acid → α-Keto acid → Glucose, Ketone body, ATP

Amino acid → NH_4^+ → Urea

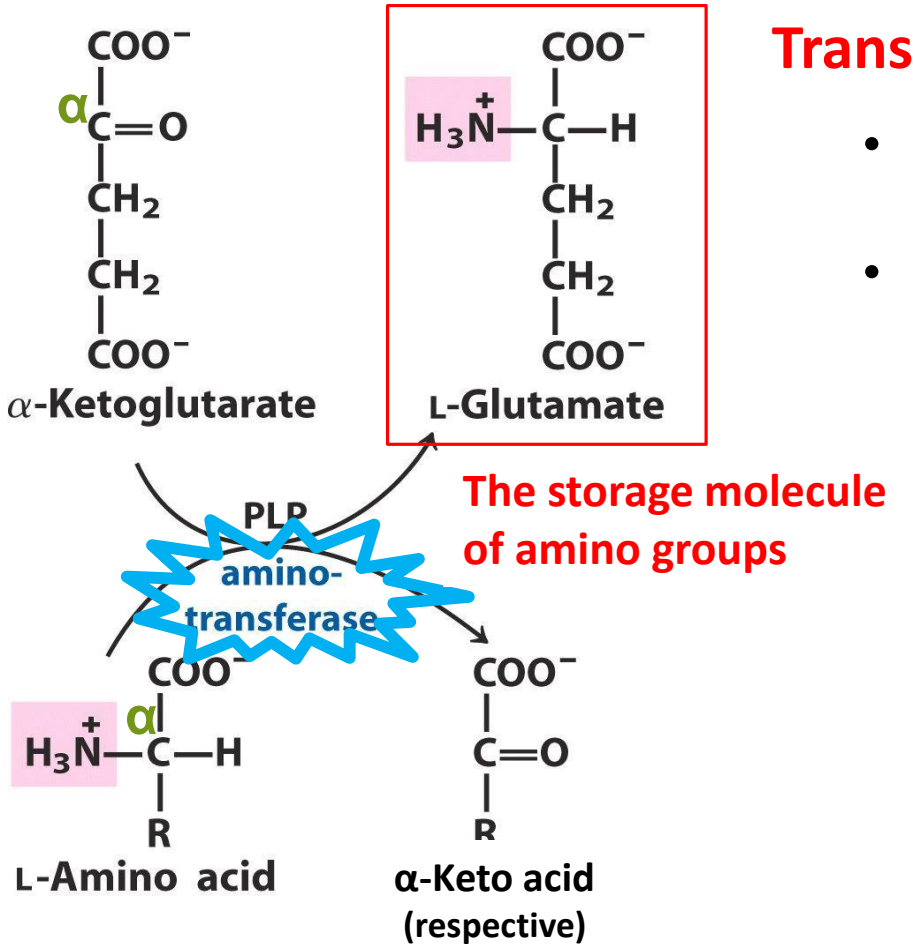
- TRANSAMINATION
- DEAMINATION

- DECARBOXYLATION

Amino acid → GABA, Serotonin, Histamine, Dopamine

UNDER RECONSTRUCTION

Aminotransferases
(Transaminases)



The storage molecule of amino groups

Transamination:

- The amino group will not be lost, ammonia will not be released
- Different aminotransferases

  ✓ Identical amino group acceptor (α-ketoglutarate)

  ✓ Different amino group donor (respective amino acids)

  ✓ Identical reaction mechanism, identical prosthetic group (PLP)

Deamination

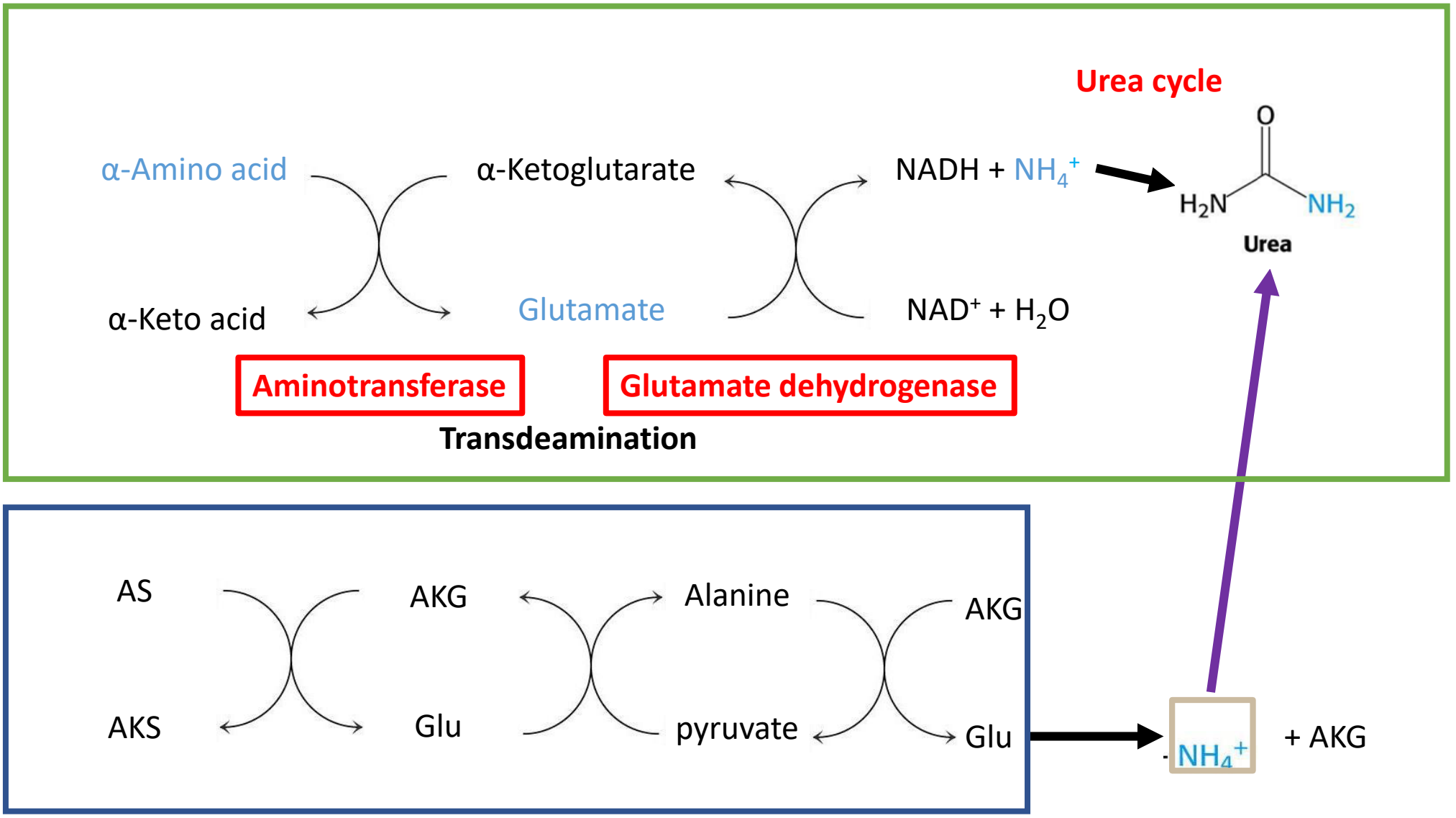
In the liver the amino groups originate finally from glutamate!

How does the liver gets rid of the glutamate's amino group in order to prepare it for excretion?

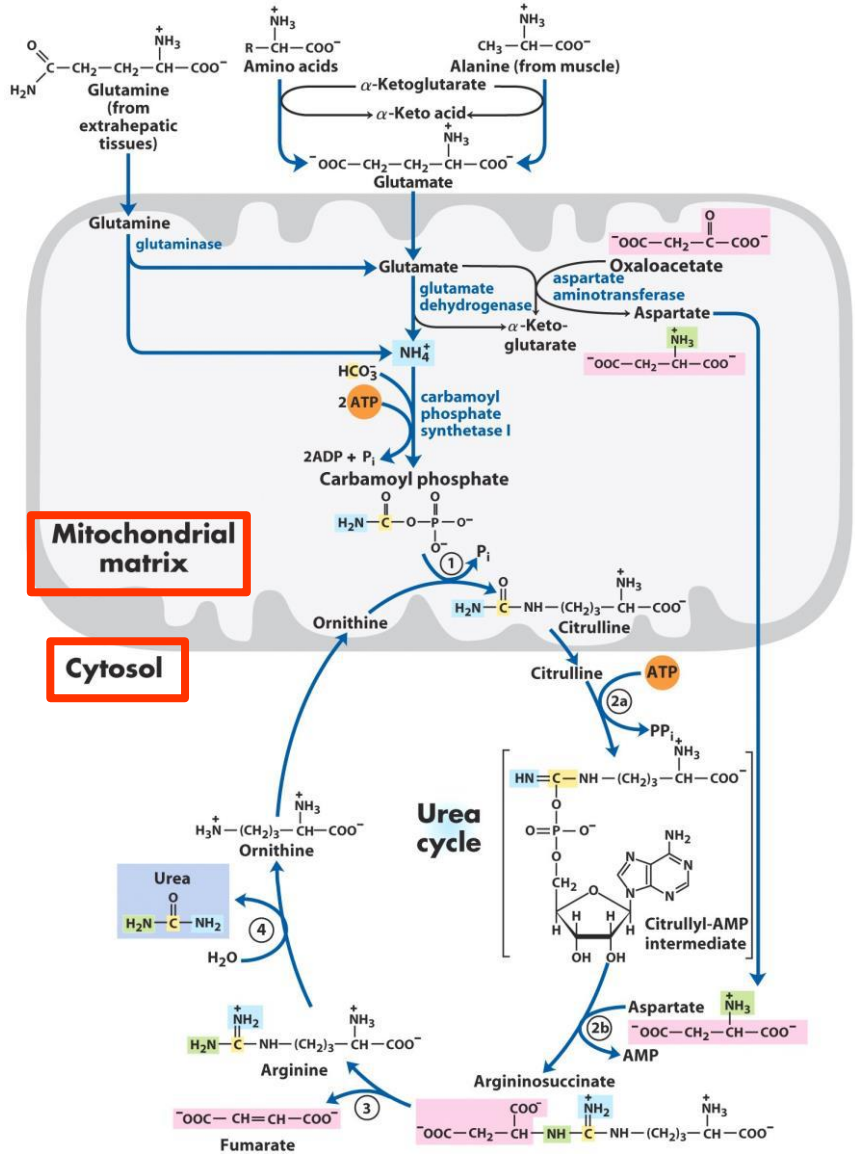
Oxidative deamination:

- The glutamate-dehydrogenase is located in the mitochondrial matrix, and uses **NAD^+** or **$NADP^+$** as proton acceptor during reduction.
- Free ammonia is released.
- The combined activity of **glutamate-dehydrogenase** and the **aminotransferases** are called transdeamination.

Transdeamination



The fate of the amino group

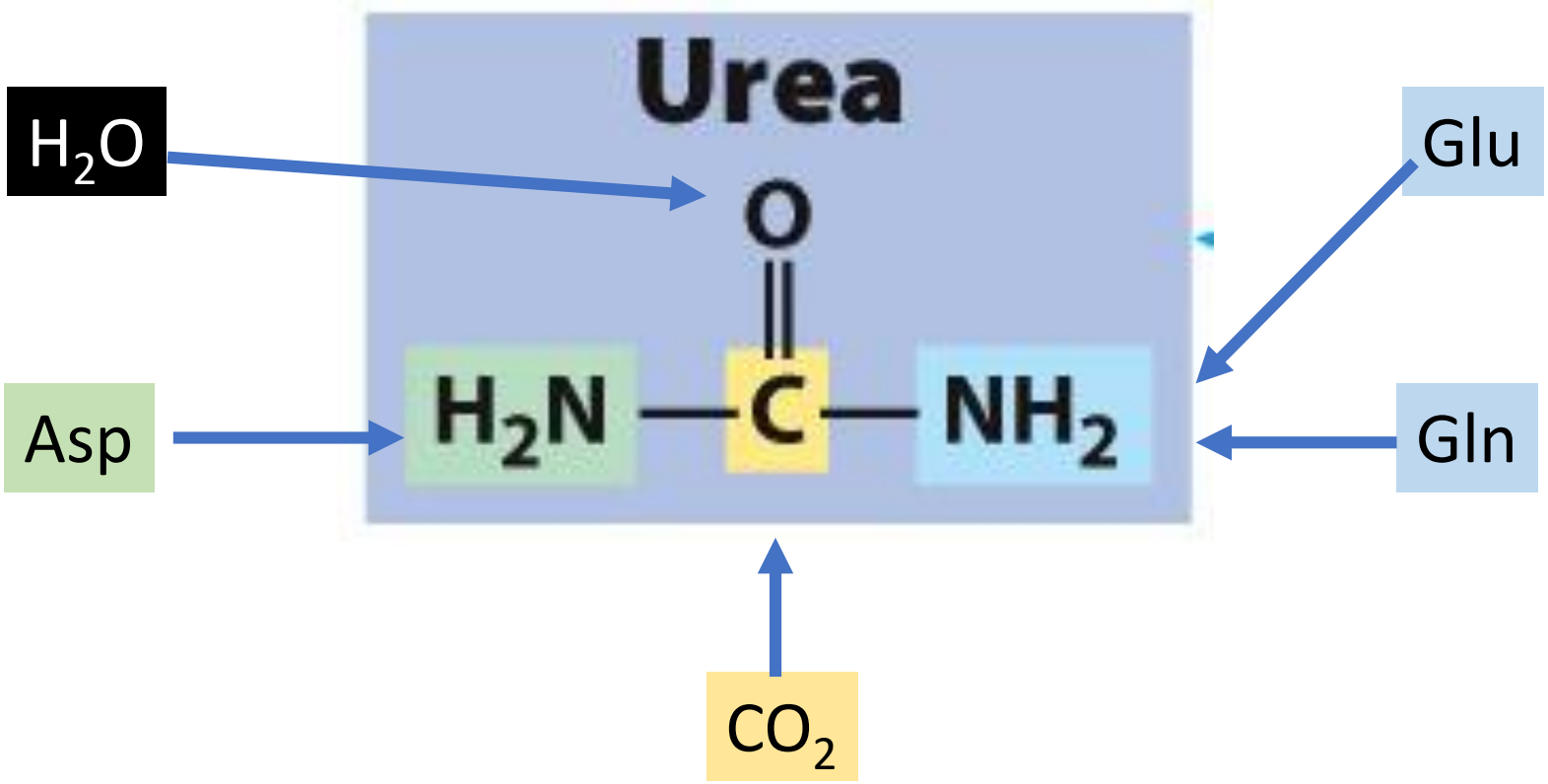


How does the liver detoxify the excess ammonia and how will it be excreted?

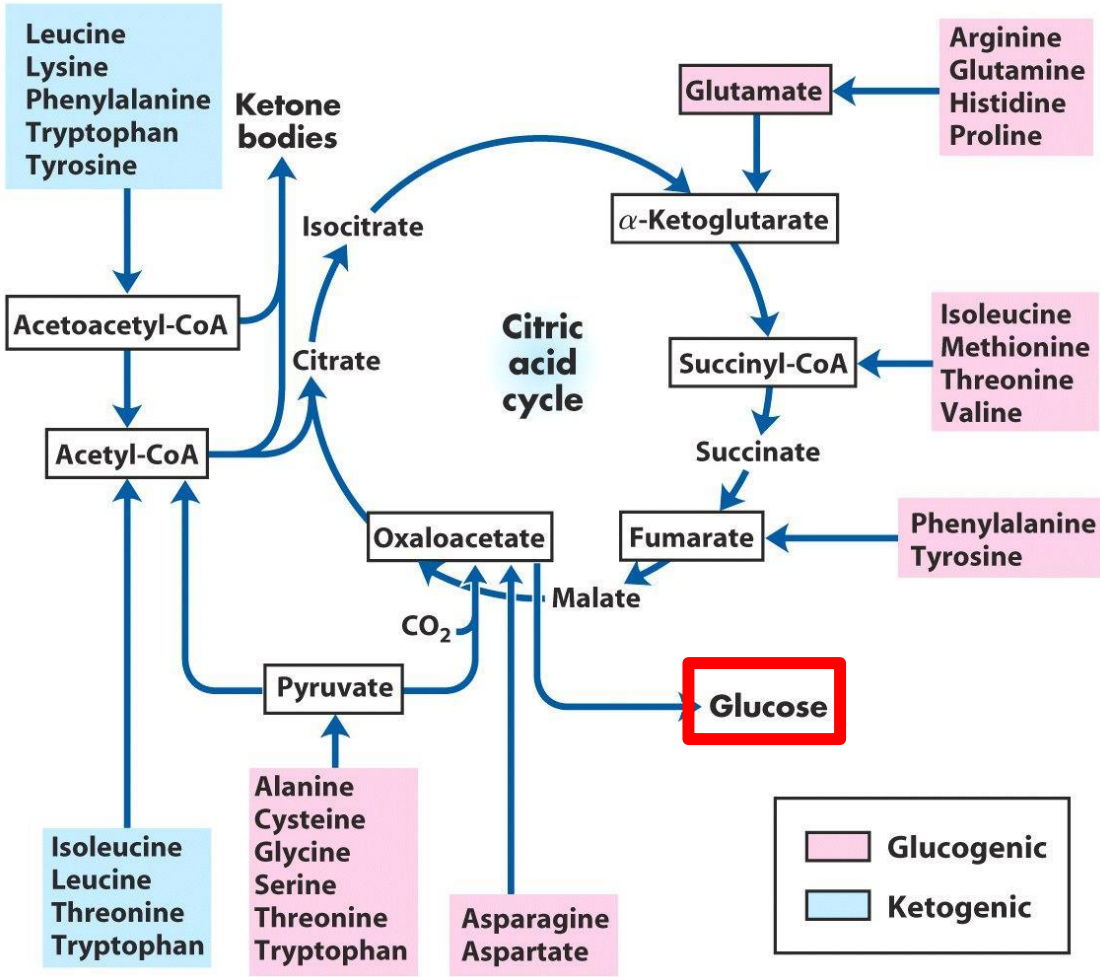
Urea cycle

What are the precursors of urea?

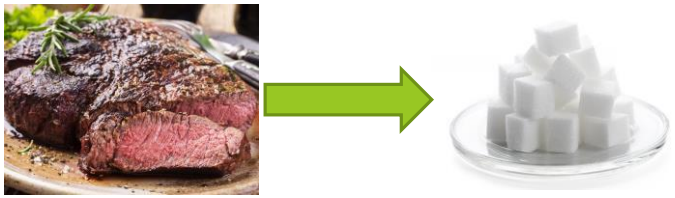
3 ATP or 4 makroerg phosphate + 2 x NH_4^+ + CO_2 + H_2O



The fate of the carbon chain

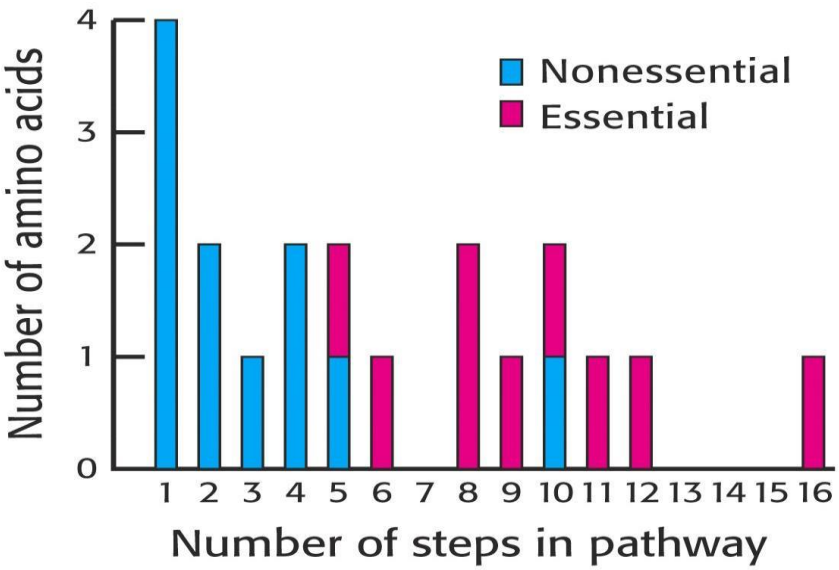


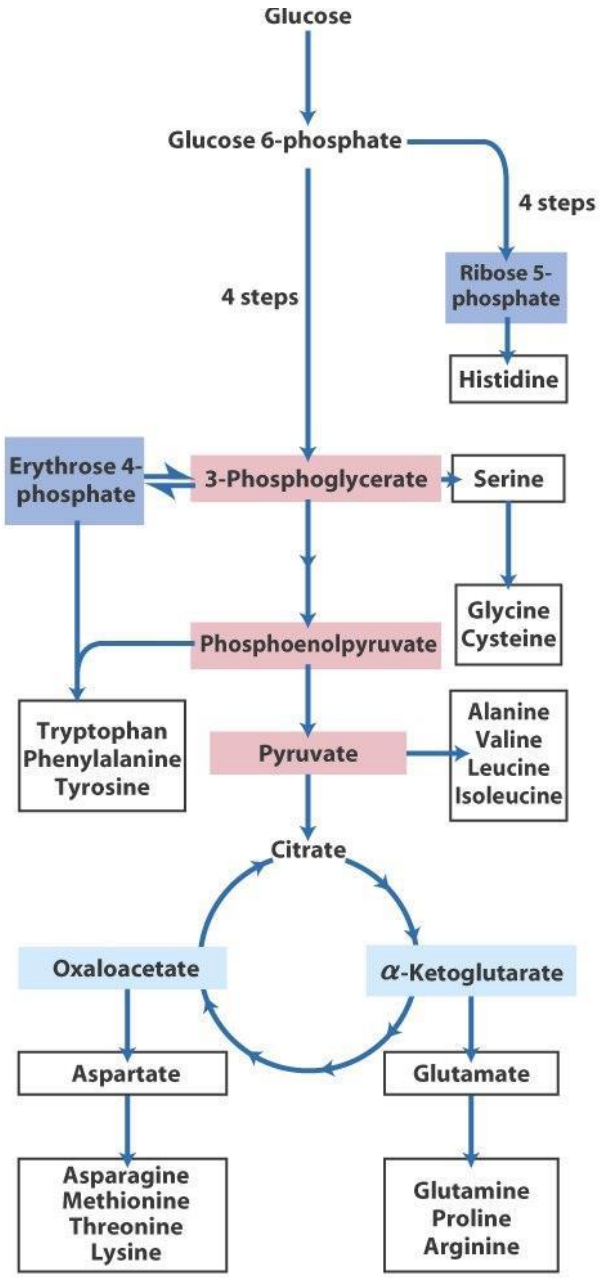
- The products of the amino acid degradation are intermediates in the urea cycle
- The carbon chain is either being oxidized to CO_2 and H_2O or being transferred to form C3-, C4-intermediate products, from which via gluconeogenesis glucose forms!
- This is meat becoming sugar!



Biosynthetic reactions of amino acids

- Glycolysis
- TCA cycle
- Pentose phosphate pathway





Classification of amino acids according to their metabolic precursors

TABLE 22–1 Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

α-Ketoglutarate
Glutamate
Glutamine
Proline
Arginine[a]

3-Phosphoglycerate
Serine
Glycine
Cysteine

Oxaloacetate
Aspartate
Asparagine
Methionine*
Threonine*
Lysine*

Pyruvate
Alanine
Valine*
Leucine*
Isoleucine*

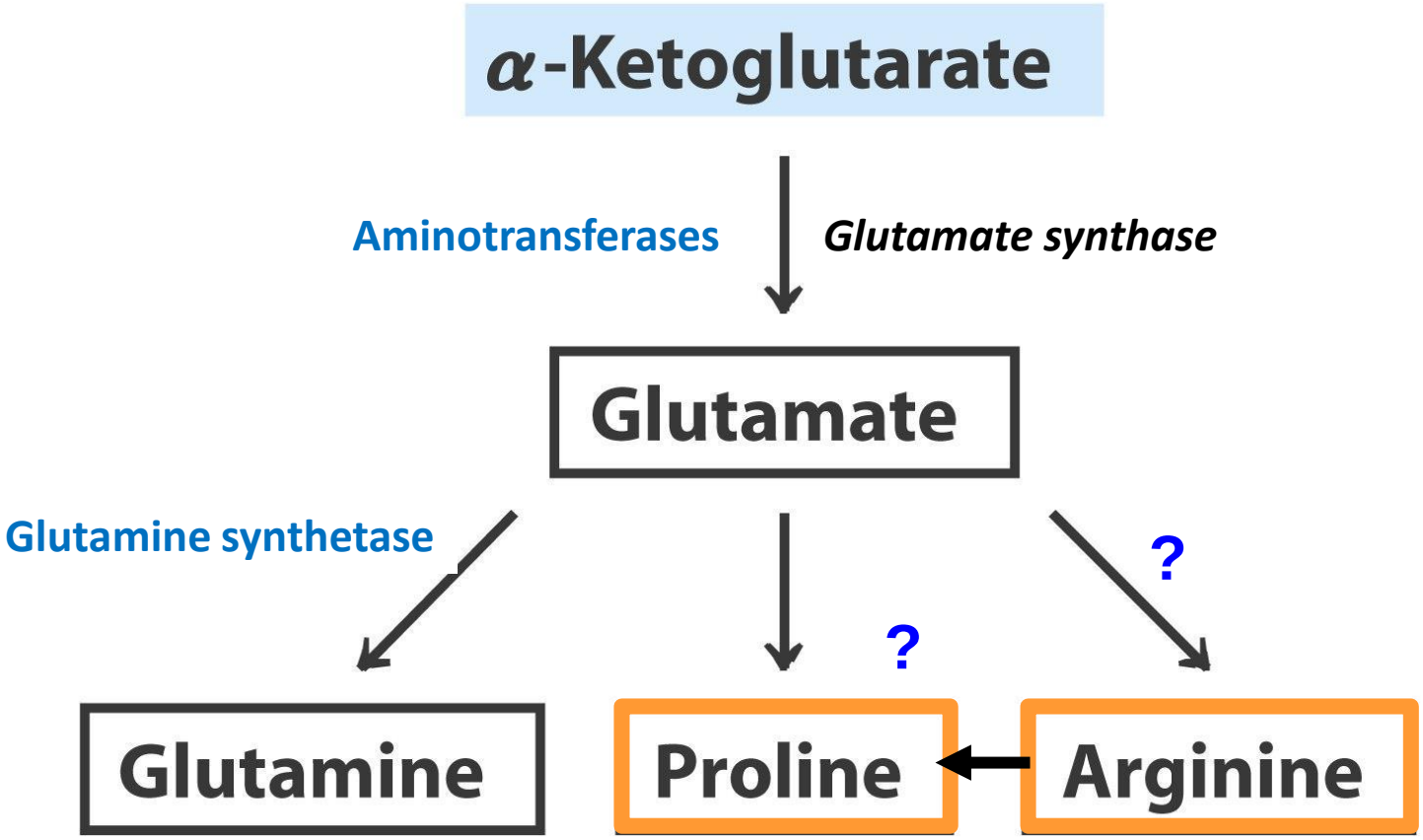
Phosphoenolpyruvate and erythrose 4-phosphate
Tryptophan*
Phenylalanine*
Tyrosine†

Ribose 5-phosphate
Histidine*

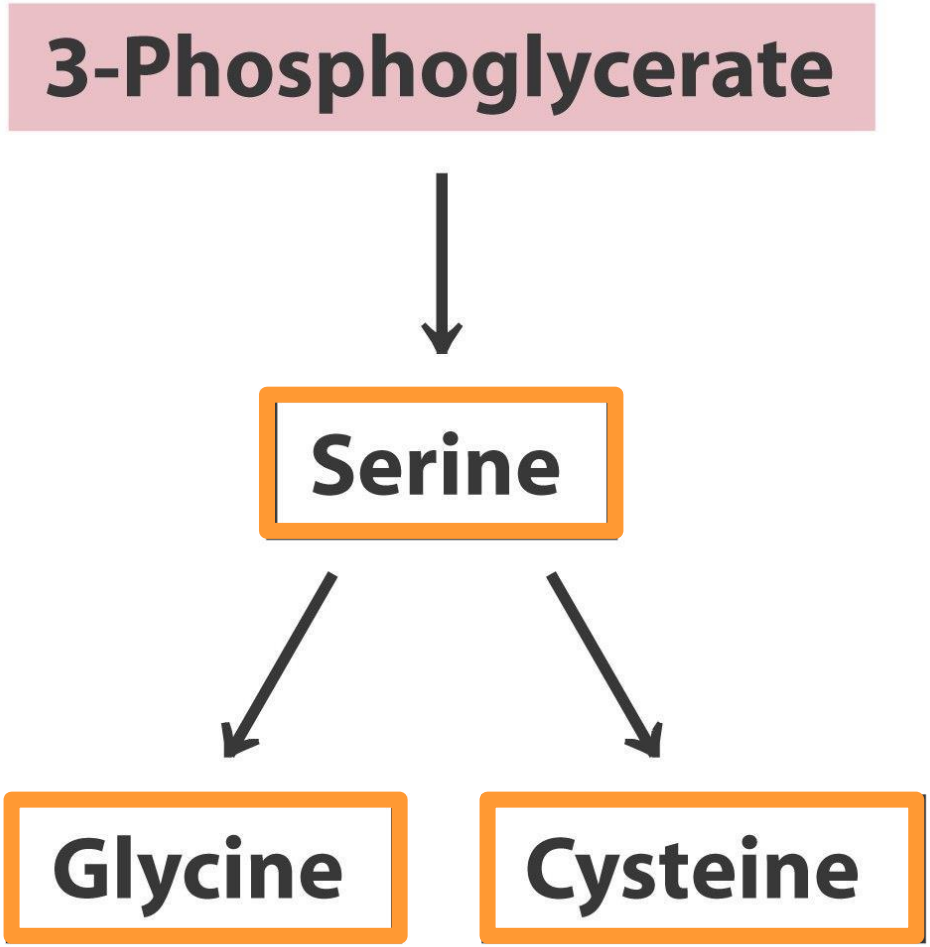
*Essential amino acids.
†Derived from phenylalanine in mammals.

[a] Esszenciális a fiatal állatokban

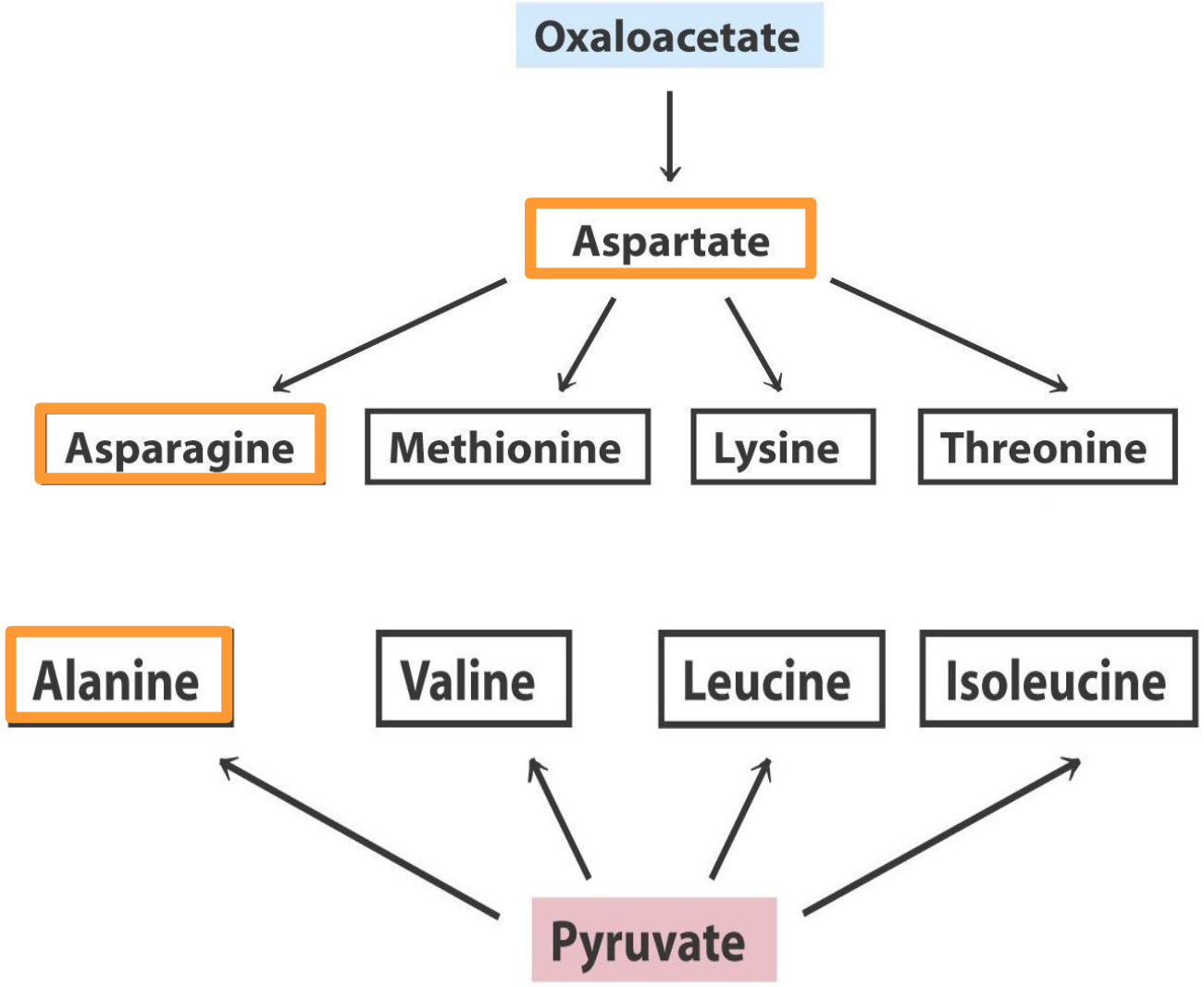
Amino acid synthesis from α-ketoglutarate



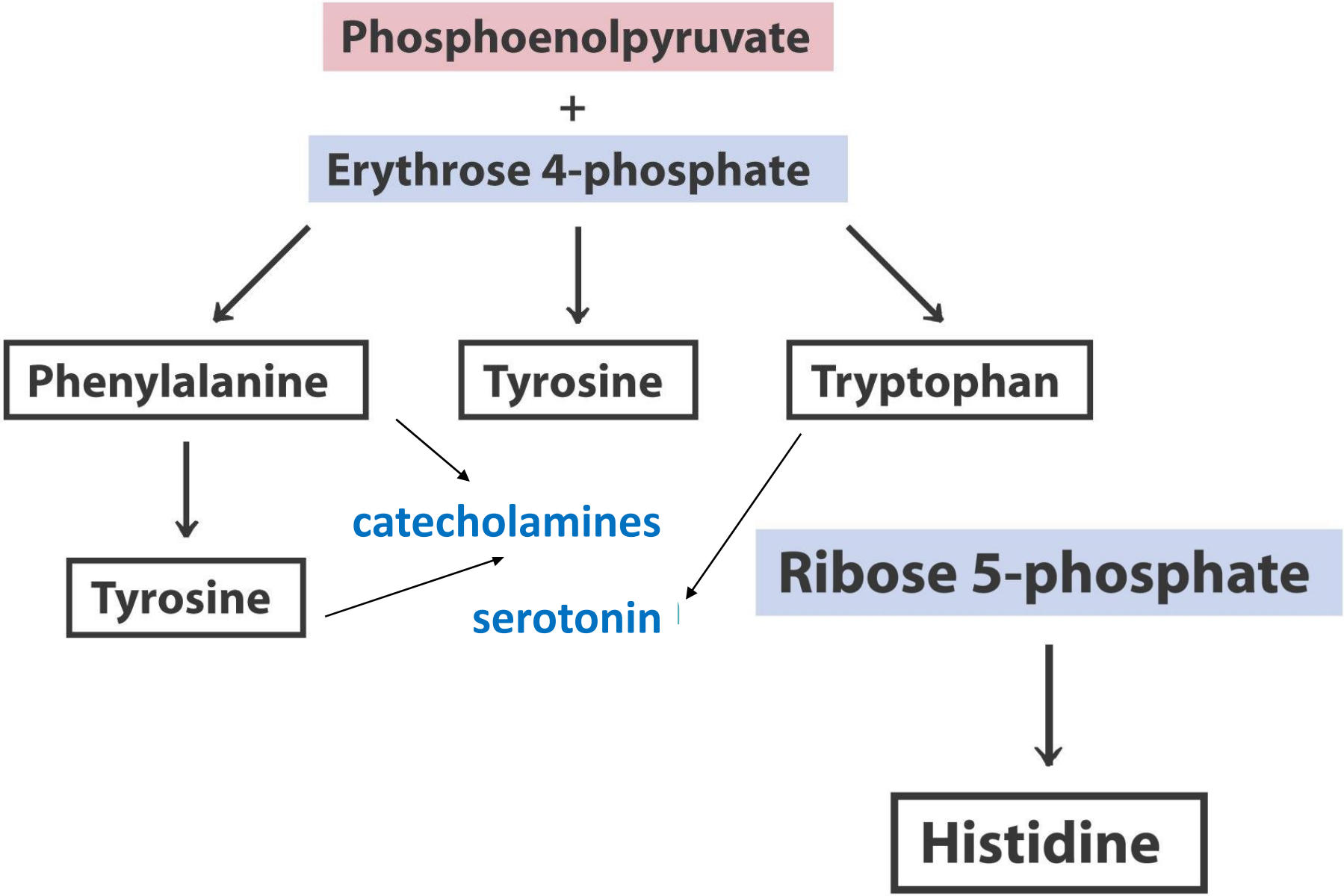
Amino acid synthesis from 3-phosphoglycerate



Amino acids synthesis from oxaloacetate and pyruvate

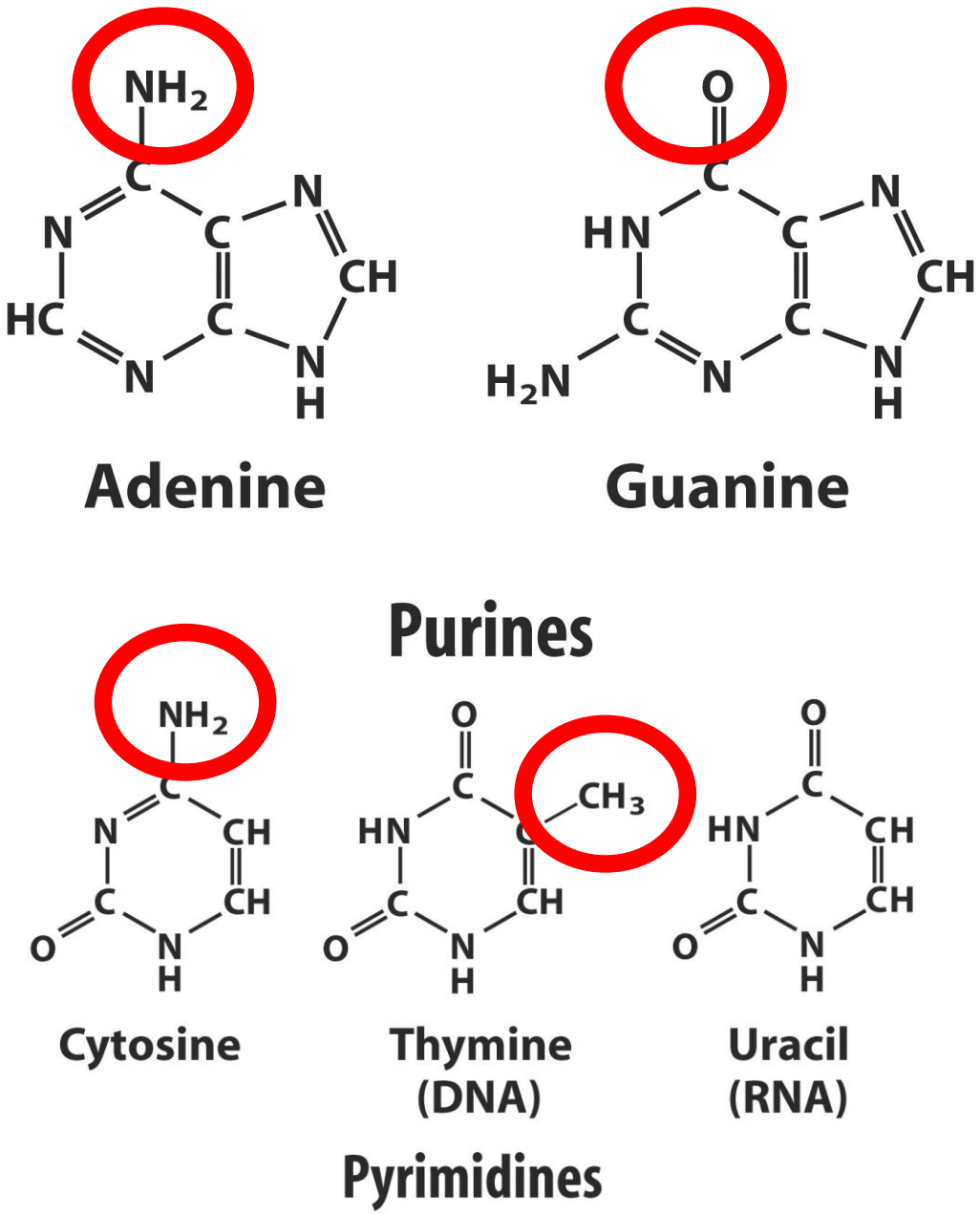


Amino acid synthesis from PEP, E4-P and ribose 5-P



Nucleotide metabolism

- No nucleotide storage! DNA and RNA metabolism depends on nucleotide synthesis
- Absorption:
  - Max. 5% reaches blood stream
  - 95% utilized locally in enterocytes
- Intracellular localization: cytoplasm
  - Even the ATP production of the mitochondria depends on the cytosolic ADP synthesis and transport.



Modifications of the bases

- Methylation
  - Replication, DAM
  - Gene expression:
  - GC rich promoters
  - Alkylation
- Amination
- Deamination
  - RNA “editing”

Occurrence of nucleotides

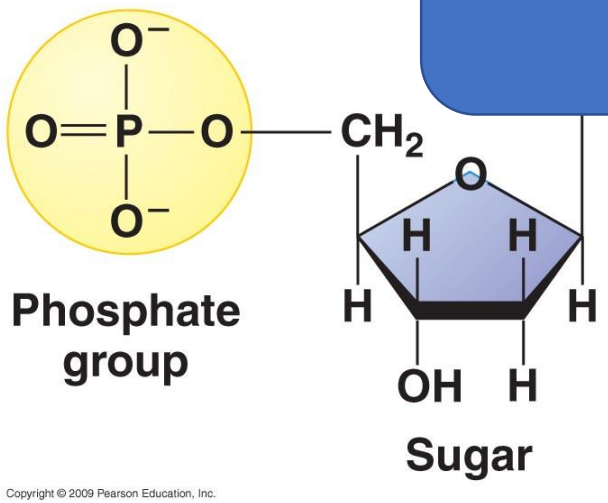
- DNA, RNA
- Coenzymes
  - NAD, FAD, FMN, CoA, SAM
- Second messenger
  - cAMP, cGMP
- Monosaccharide activator
  - UDP-Glc, UDP-Gal, CDP-Fuc
- Phospholipid activator
  - CDP-DAG
- Adenylation
  - Amino acid activator, ligase activator
- Biotransformation
  - UDP-Glucuronic acid
- Energy storage
  - ATP, GTP
- Pharmaceuticals:
  - 5-Fluoro-uracil, Allopurinol, Azido-timidine, AICAR
- PTM
  - ADP-ribosylation
- Substrate
  - NAD: PARP, Ligase
- Regulator
  - Allosteric: AMP, ADP, ATP, GTP

Nucleotide synthesis

"De novo" synthesis

Base

Recycling: Salvage



Pentose-phosphate pathway

Salvage reactions: Recycling

Adenine + PRPP → AMP + PP_i

Guanin + PRPP → GMP + PP_i

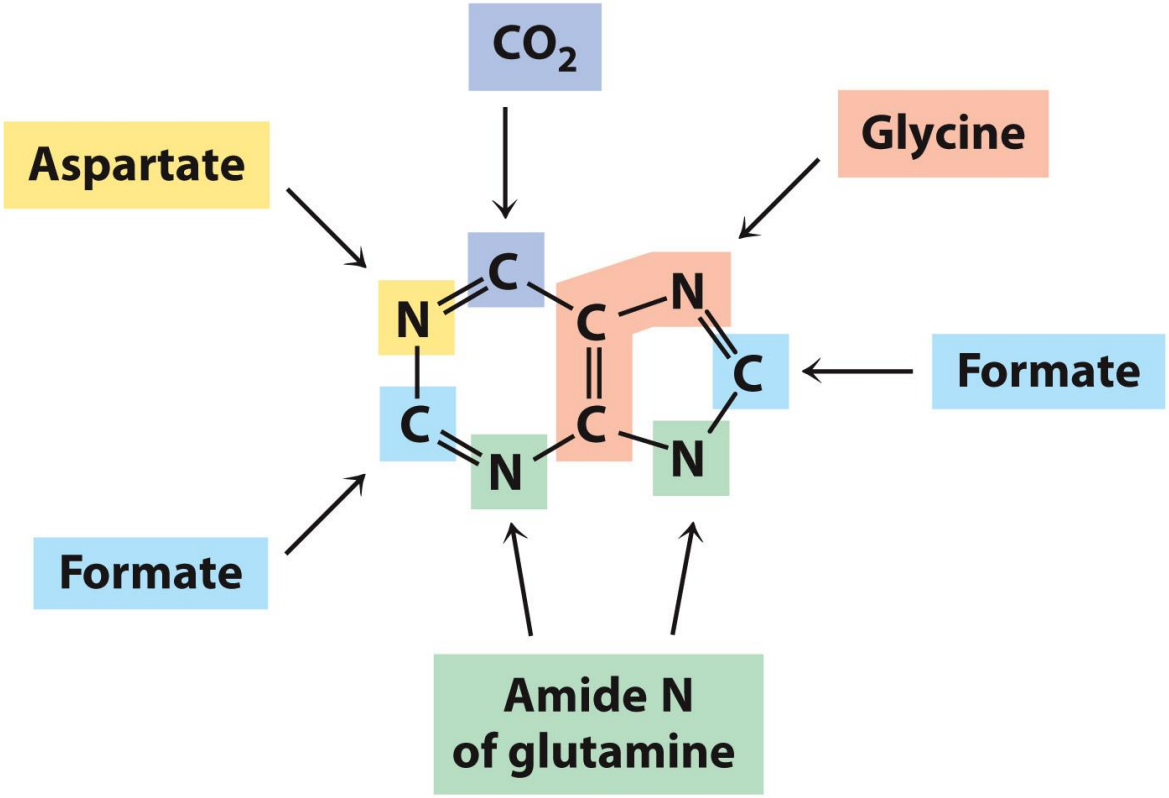
Hypoxanthine + PRPP → IMP + PP_i

Uracil + PRPP → UMP + PP_i

Uridine + ATP → UMP + ADP

Cytidine + ATP → CMP + ADP

C and N sources of purine and pyrimidine bases: “de novo”



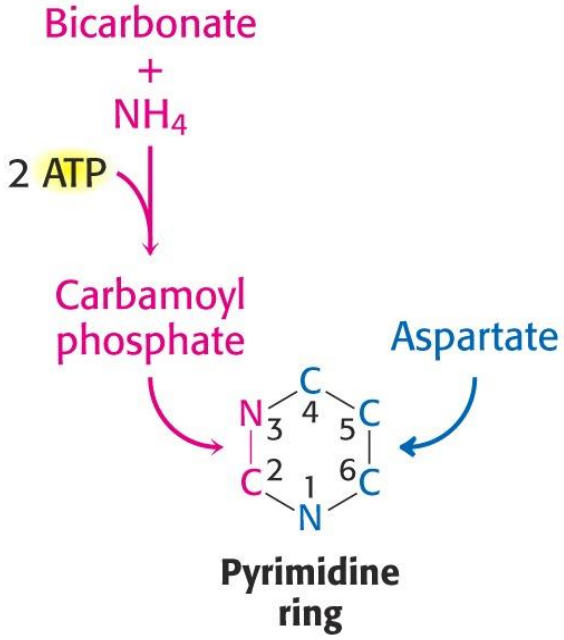


Figure 22-34
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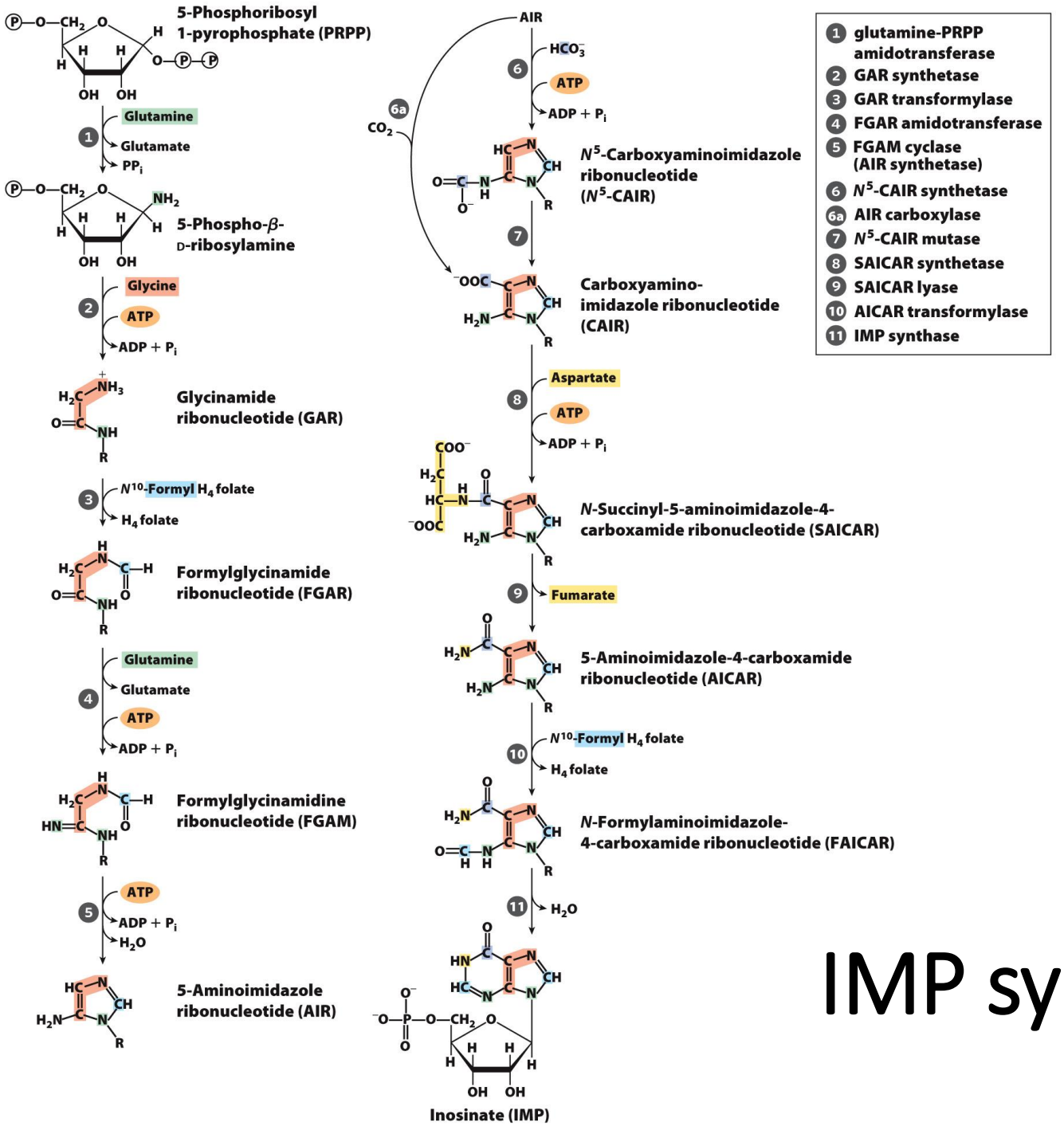

IMP synthesis

AMP and GMP synthesis

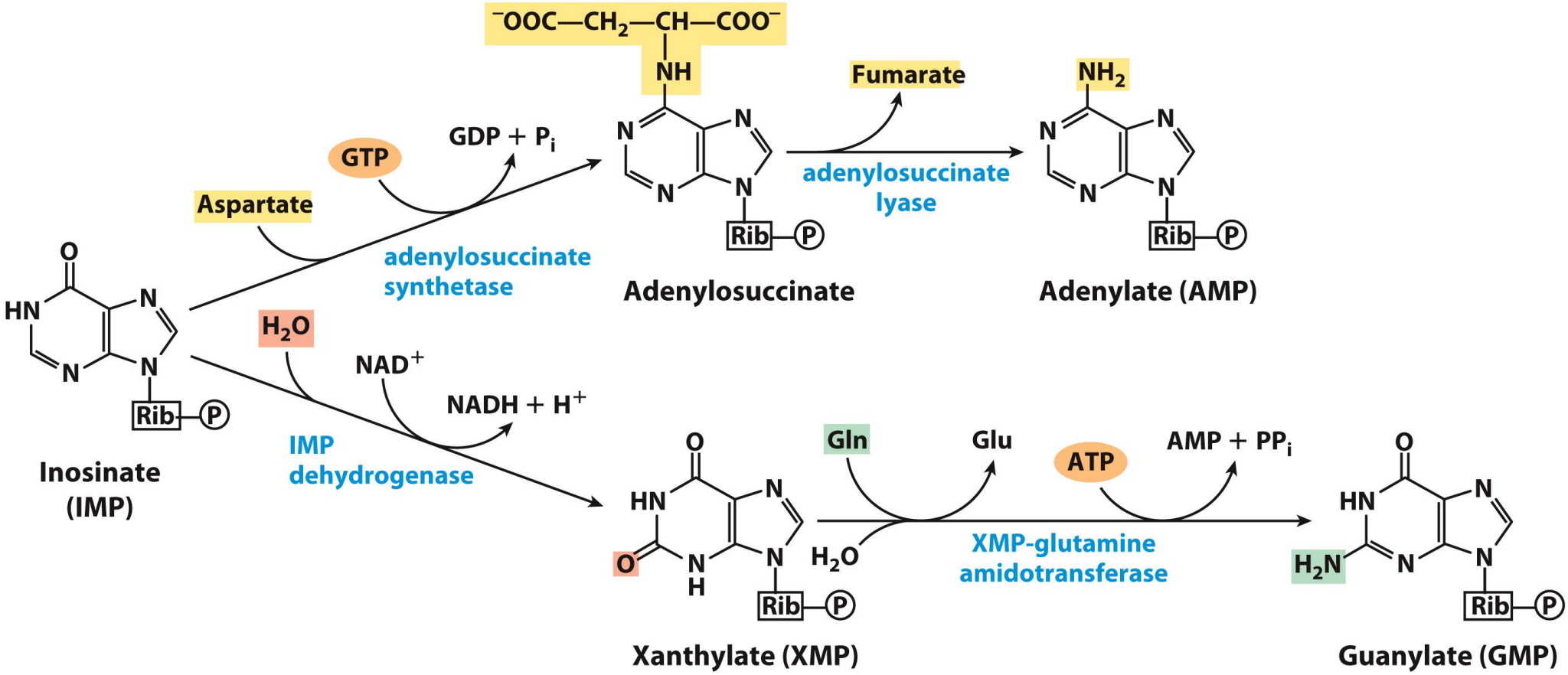

Figure 22-36
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Synthesis of pyrimidine bases

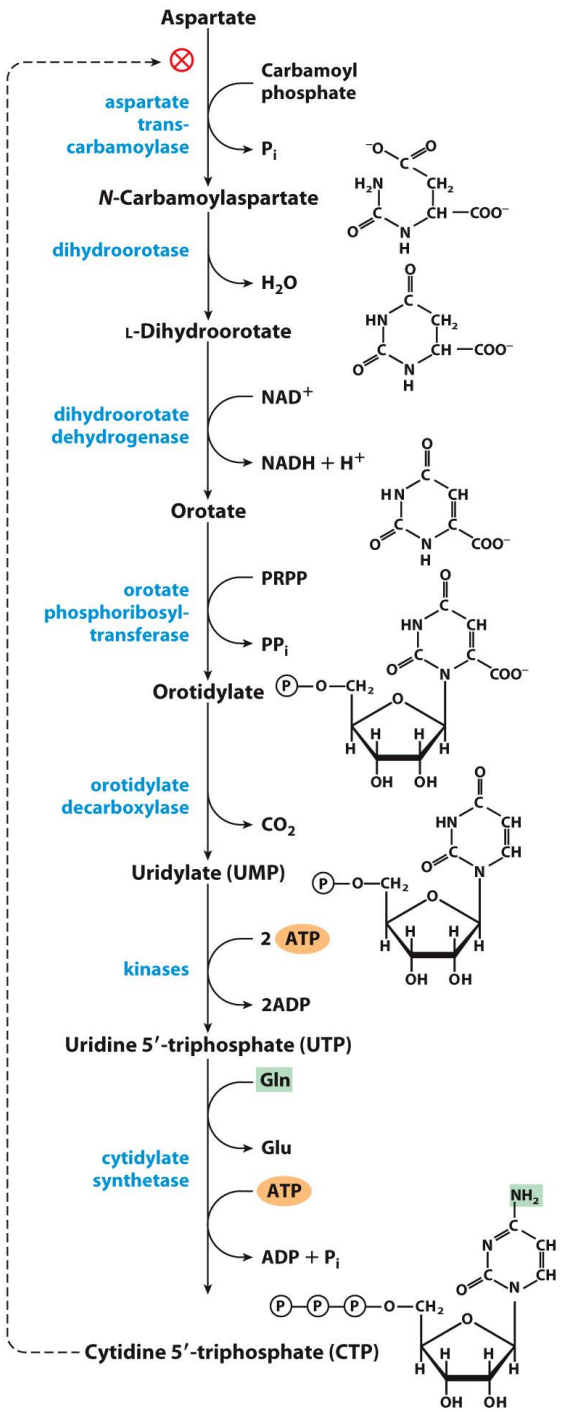
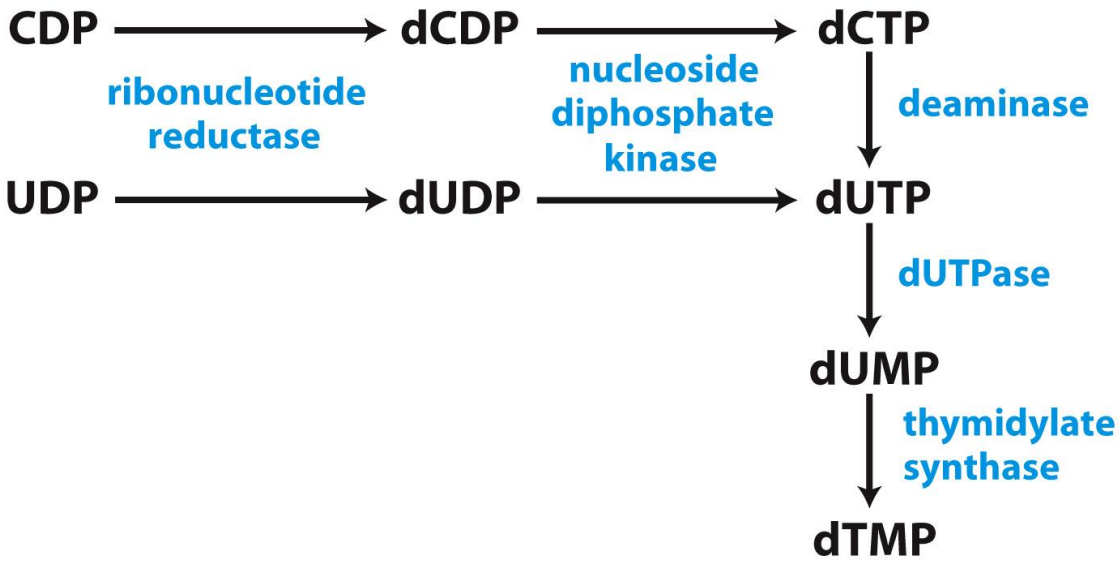


Figure 22-38



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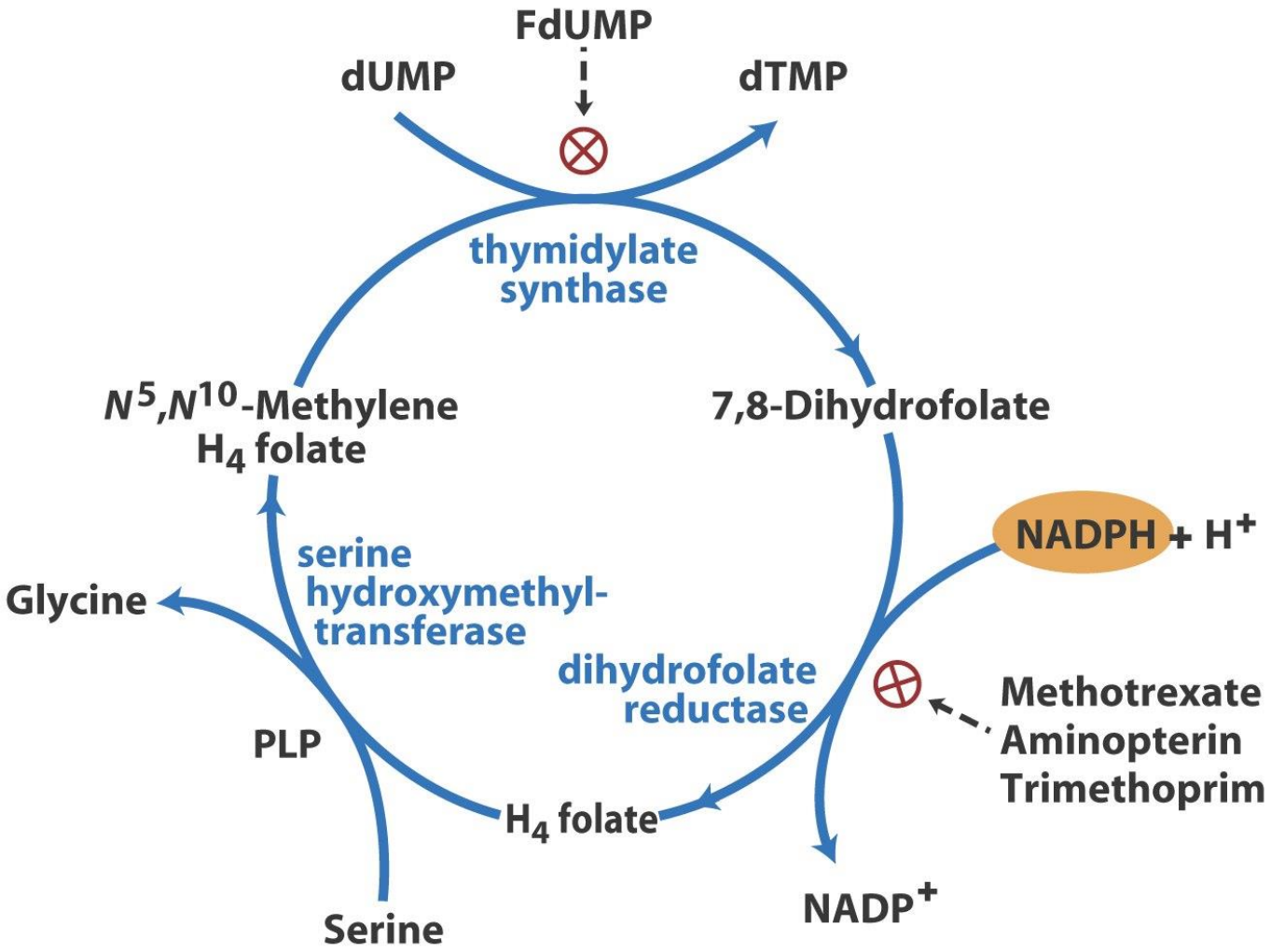
Chemotherapy



- Formation of deoxyribonucleotides is catalysed by ribonucleotide reductase
- The NADPH serves as electron donor
- Connected by glutathione (a) or thioredoxin (b) pathways

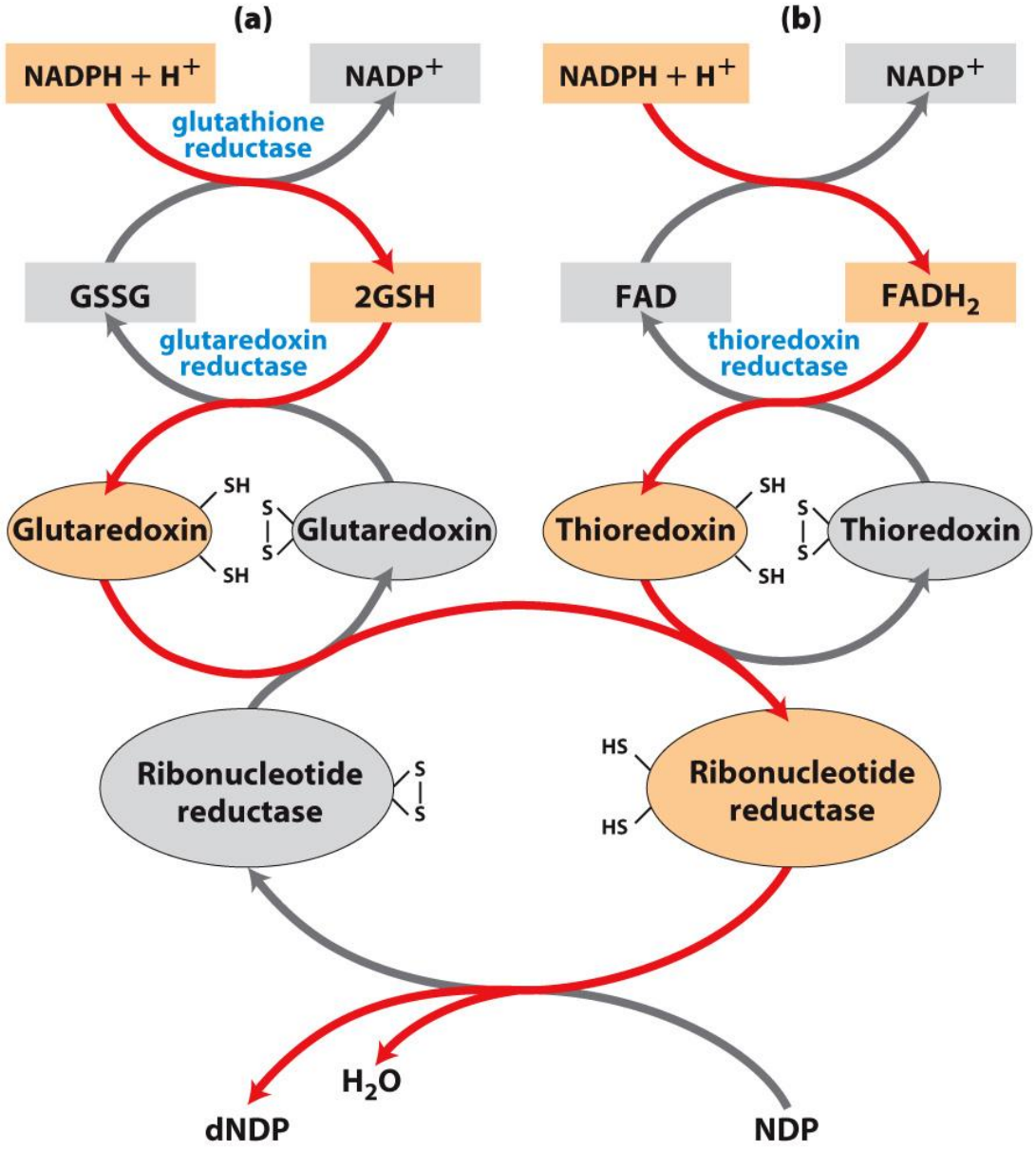


Figure 22-41
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Nucleotide degradation