BIOKIMIA
Metabolisme Asam Amino

DOSEN PENGAMPU

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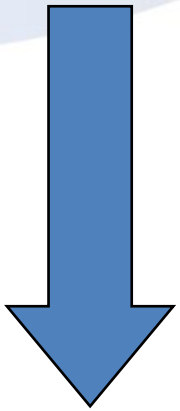
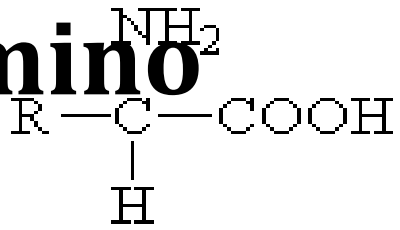
Protein



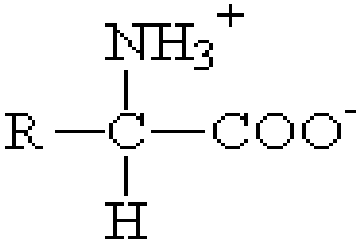
hidrolisis

asam amino

Asam amino



R is the functional group of the amino acid



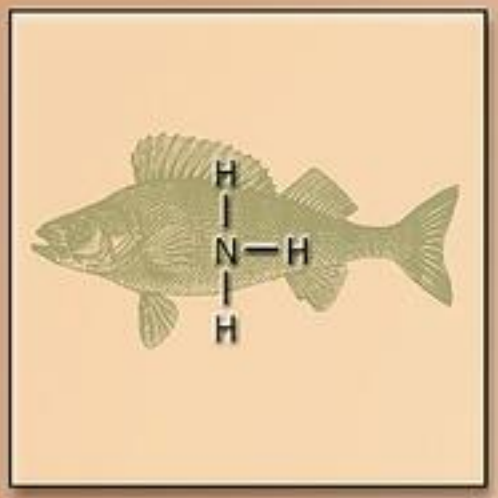
Ionization at physiological pH (7.4)

Katabolisme asam amino terdiri dari 2 bagian:

1. **Katabolisme nitrogen** asam amino
2. Katabolisme rantai/rangka **karbon**

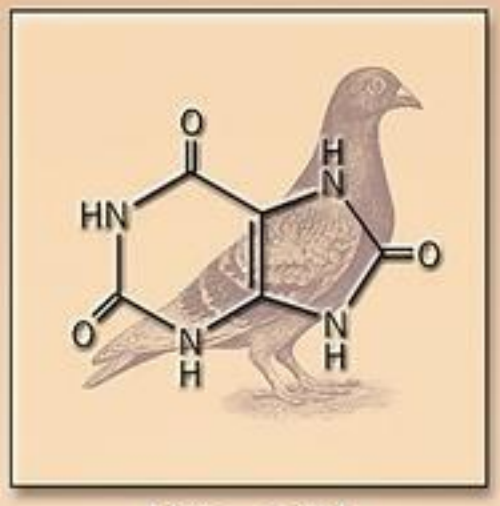
I. Katabolisme Nitrogen Asam Amin

- Tiap hari 1-2% dari total protein dipecah menjadi asam amino:
  - 75-80% dari asam amino untuk sintesis protein kembali
  - 20-25% dibuang nitrogennya dalam bentuk **urea** (pada manusia) → **biosintesis urea**



Ammonia

Urea



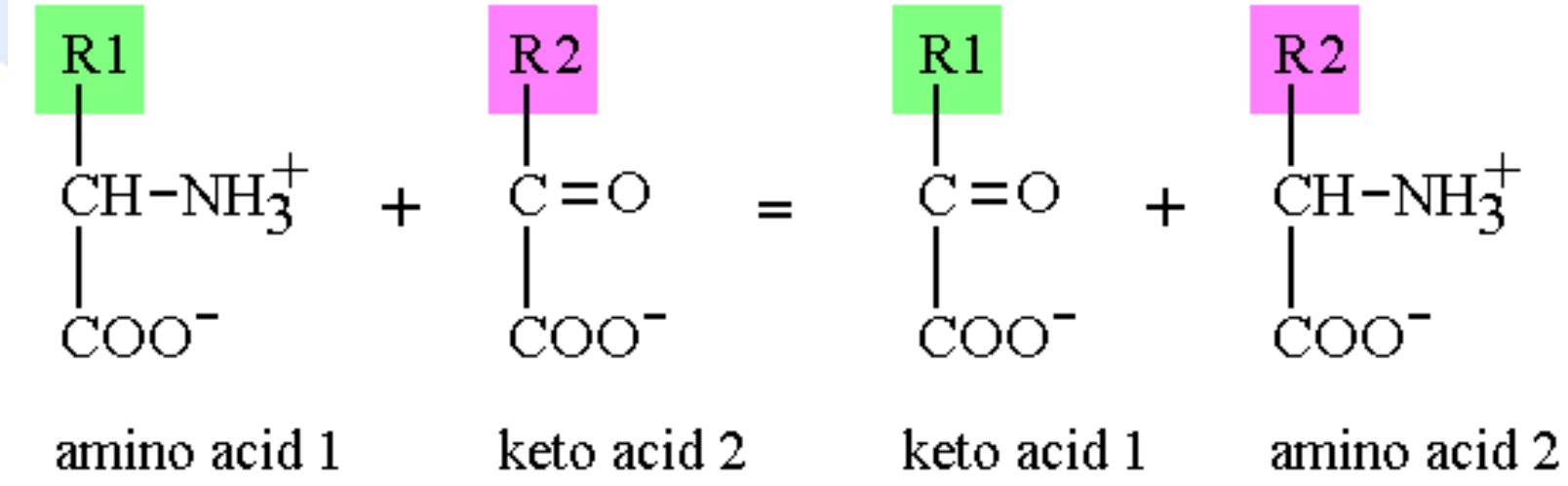
Uric acid

Excreted Forms of Nitrogen

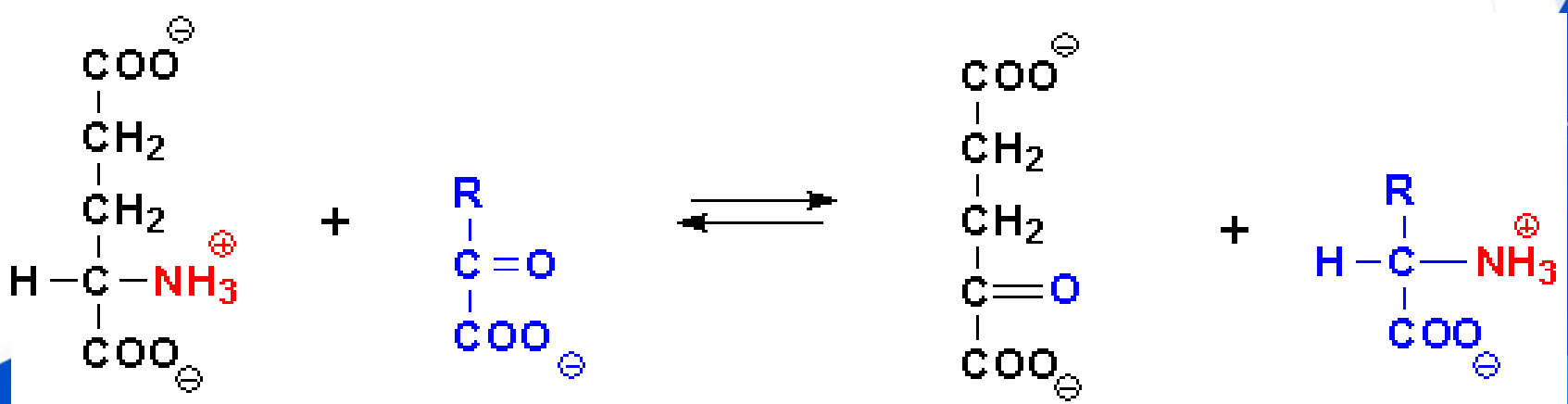
Biosintesis Urea

- Terjadi di **hepar**
- Terdiri dari 4 tahap reaksi:
  1. Reaksi **transaminasi** di jaringan
  2. Reaksi **deaminasi oksidatif** di jaringan
  3. **Transpor ammonia**
  4. **Reaksi2 siklus urea (sintesis urea)** di hati

1. Reaksi Transaminasi

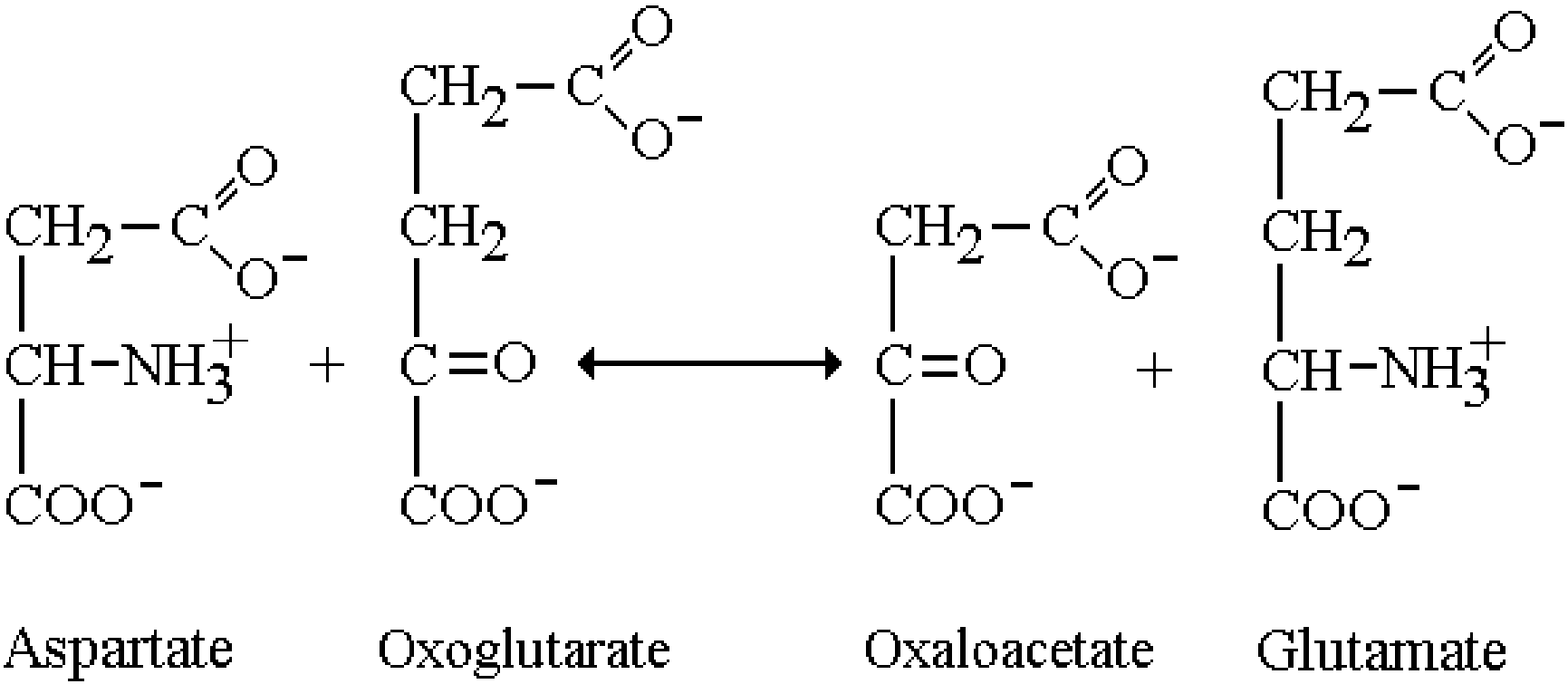


amino acid 1 | keto acid 2 | keto acid 1 | amino acid 2

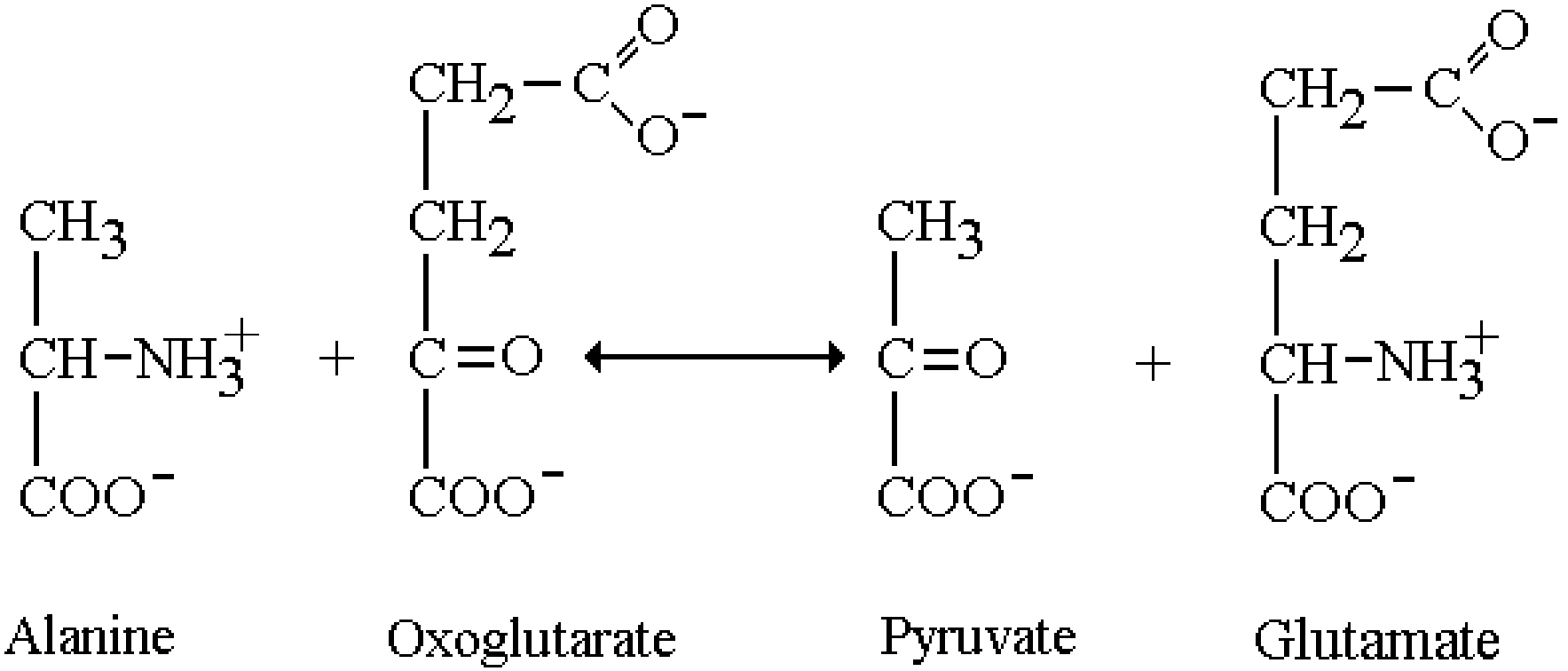


Glutamate | α-Keto acid | α-Ketoglutarate | α-Amino acid

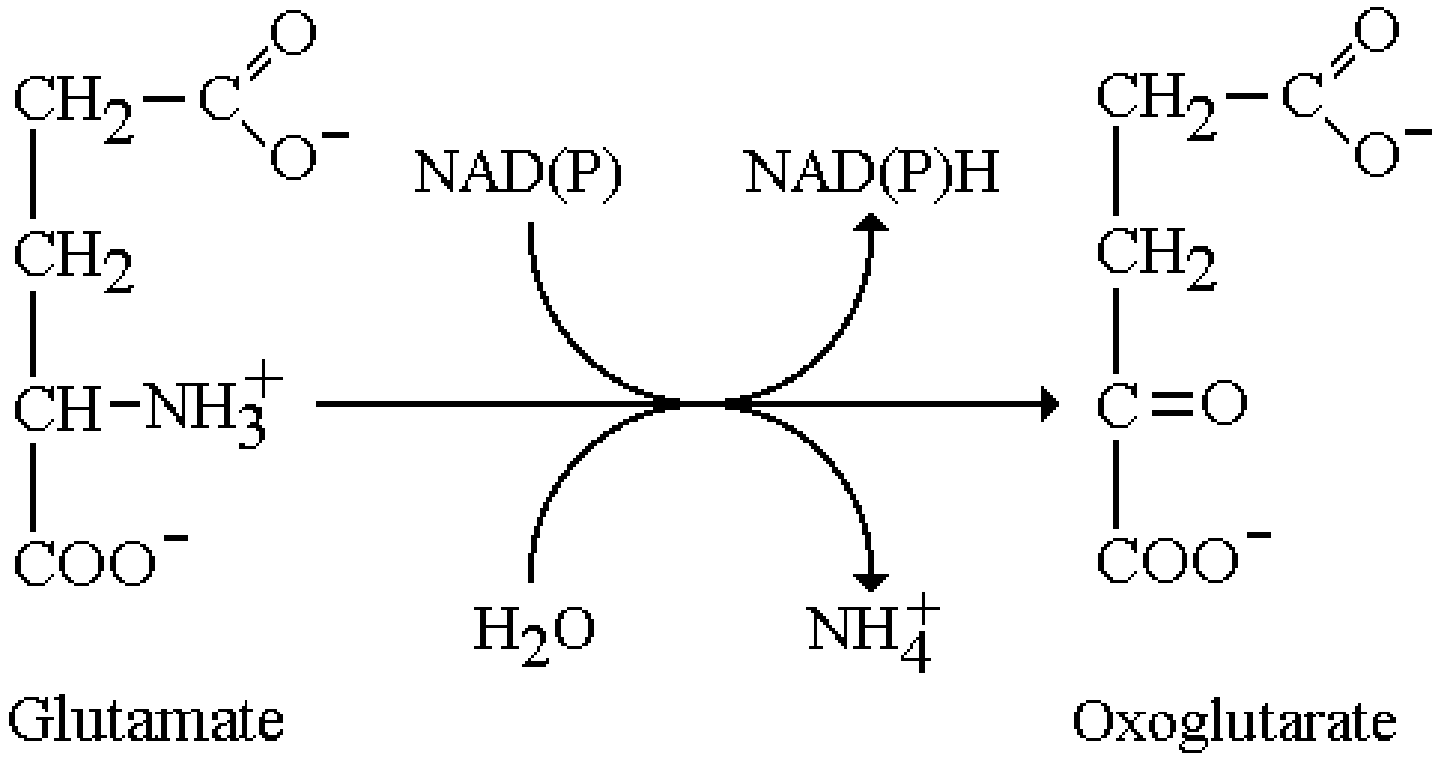
GOT = Glutamat Oksaloasetat Transaminase



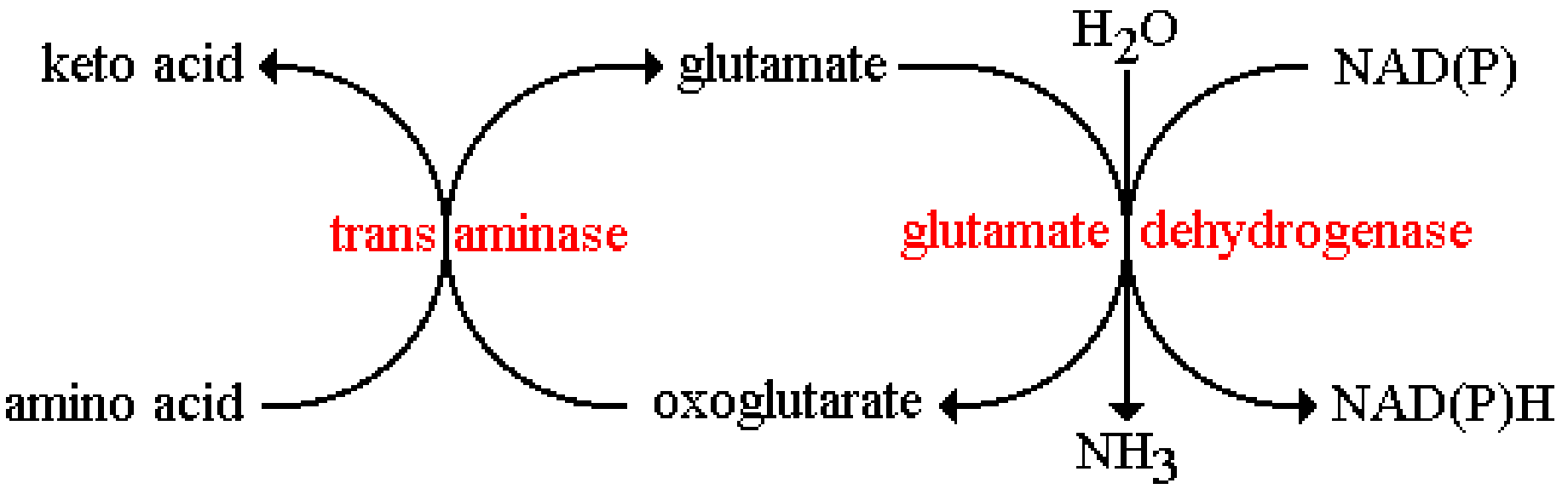
GPT = Glutamat Piruvat Transaminase



2. deaminasi oksidatif
GluDH = Glutamat Dehidrogenase



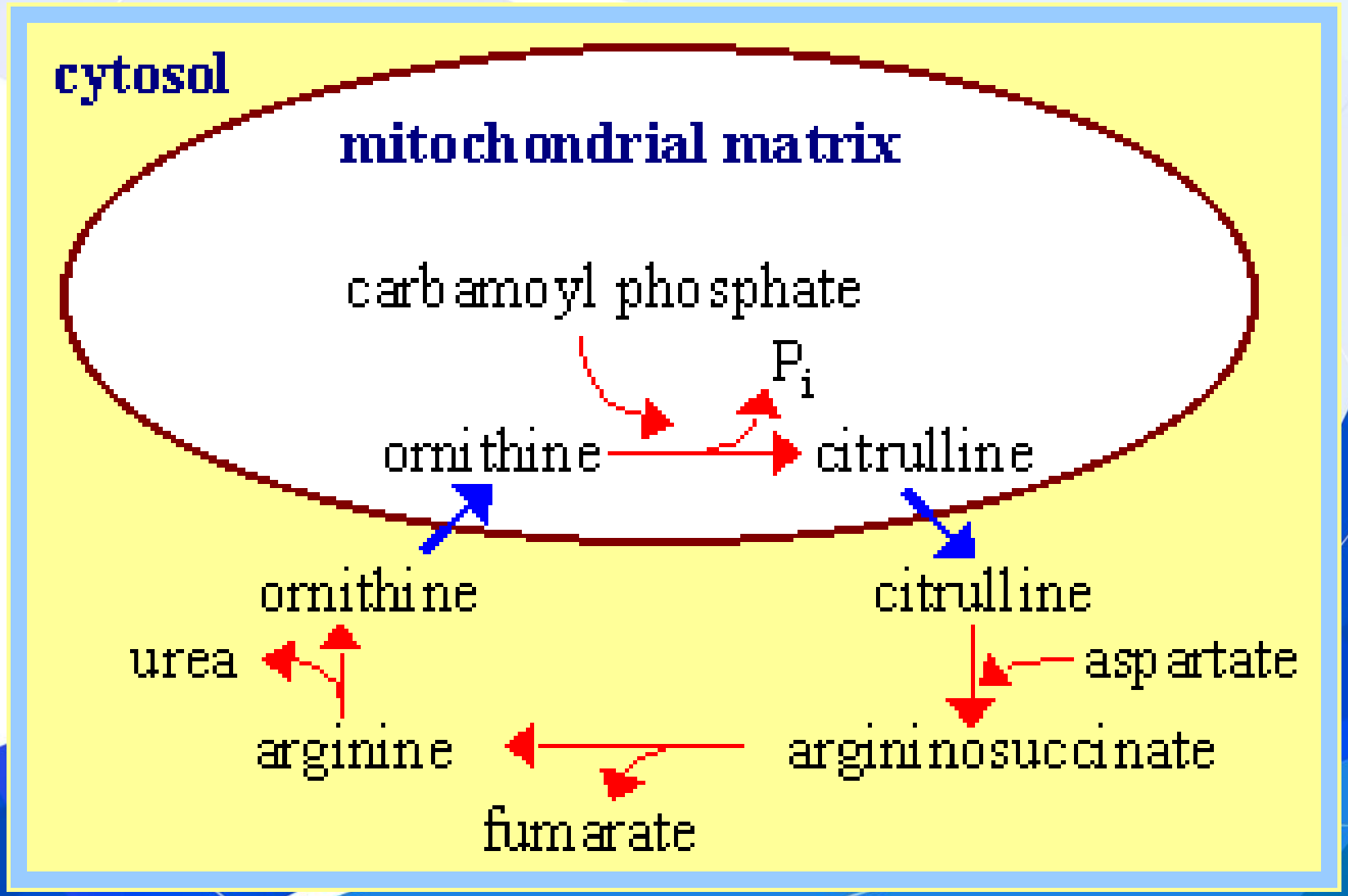
3. Transaminasi - Deaminasi

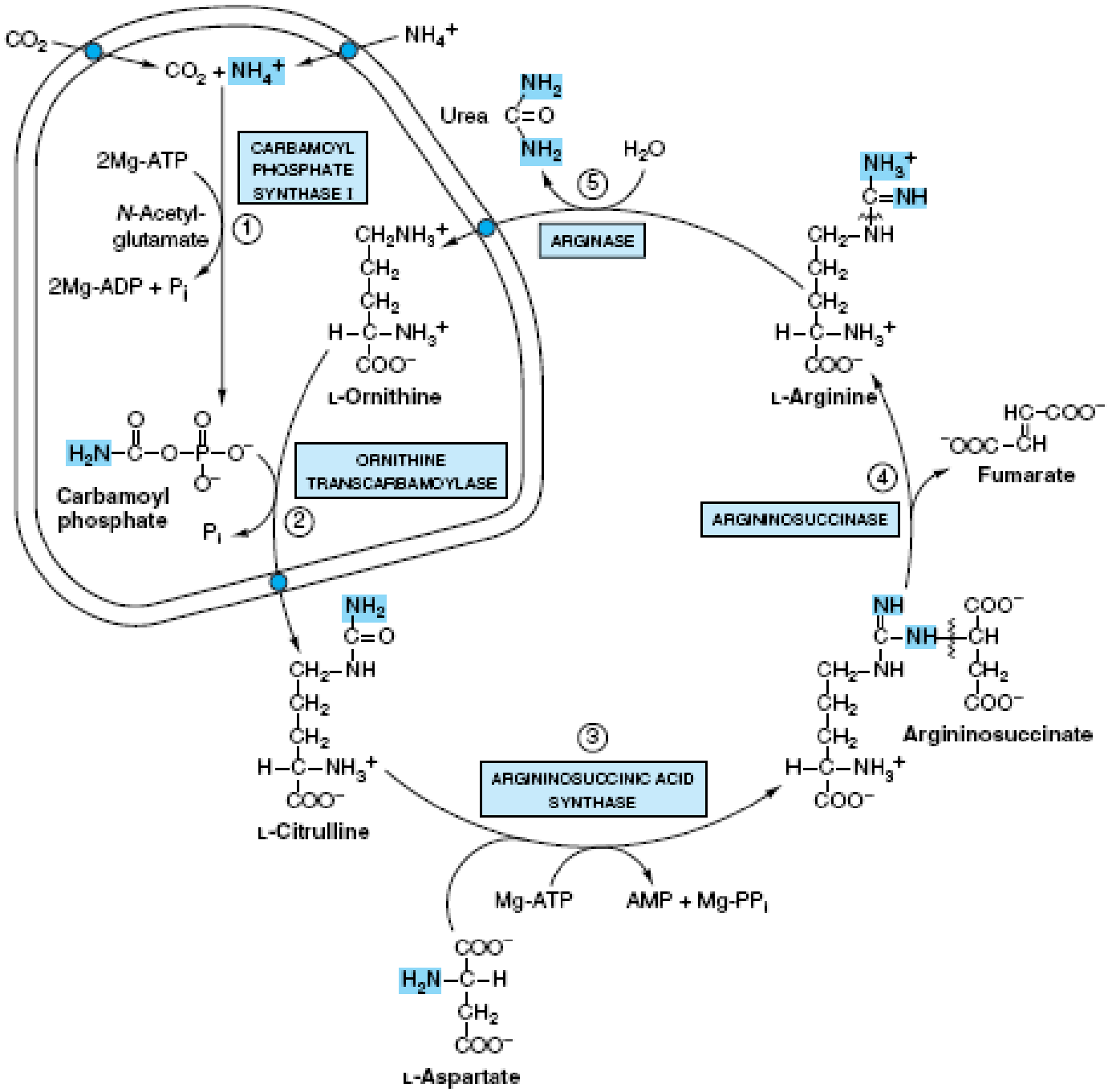


4. Siklus Urea

- Dikenal juga sebagai **ornithine cycle**
- Mengubah **ammonia → urea**
- Pada mamalia → hanya berlangsung di **hati**

Siklus Urea


cytosol
mitochondrial matrix
carbamoyl phosphate
P_i
ornithine
citrulline
ornithine
urea
arginine
citrulline
aspartate
argininosuccinate
fumarate


CO_2
NH_4^+
$CO_2 + NH_4^+$
2Mg-ATP
CARBAMOYL PHOSPHATE SYNTHASE I
N-Acetyl-glutamate
1
2Mg-ADP + P_i
Carbamoyl phosphate
P_i
2
ORNITHINE TRANSCARBAMOYLASE
L-Ornithine
Urea
NH_2
C=O
NH_2
H_2O
5
ARGINASE
L-Arginine
4
ARGININOSUCCINASE
Fumarate
Argininosuccinate
3
ARGININOSUCCINIC ACID SYNTHASE
L-Citrulline
Mg-ATP
AMP + Mg-PP_i
L-Aspartate

Reaksi Siklus Urea

Step	Reactant	Product	Catalyzed by	Location
1	2ATP + HCO_3^- + NH_4^+	carbamoyl phosphate + 2ADP + P_i	CPS1	mitochondrial
2	carbamoyl phosphate + ornithine	citrulline + P_i	OTC	mitochondrial
3	citrulline + aspartate + ATP	argininosuccinate + AMP + PP_i	ASS	cytosolic
4	argininosuccinate	Arg + fumarate	ASL	cytosolic
5	Arg + H_2O	ornithine + urea	ARG1	cytosolic

Summary reaction:

2 NH_3 + CO_2 + 4 ATP + aspartate → urea + fumarate + 4 ADP + 4 P_i

II. Katabolisme Rangka karbon asam amino

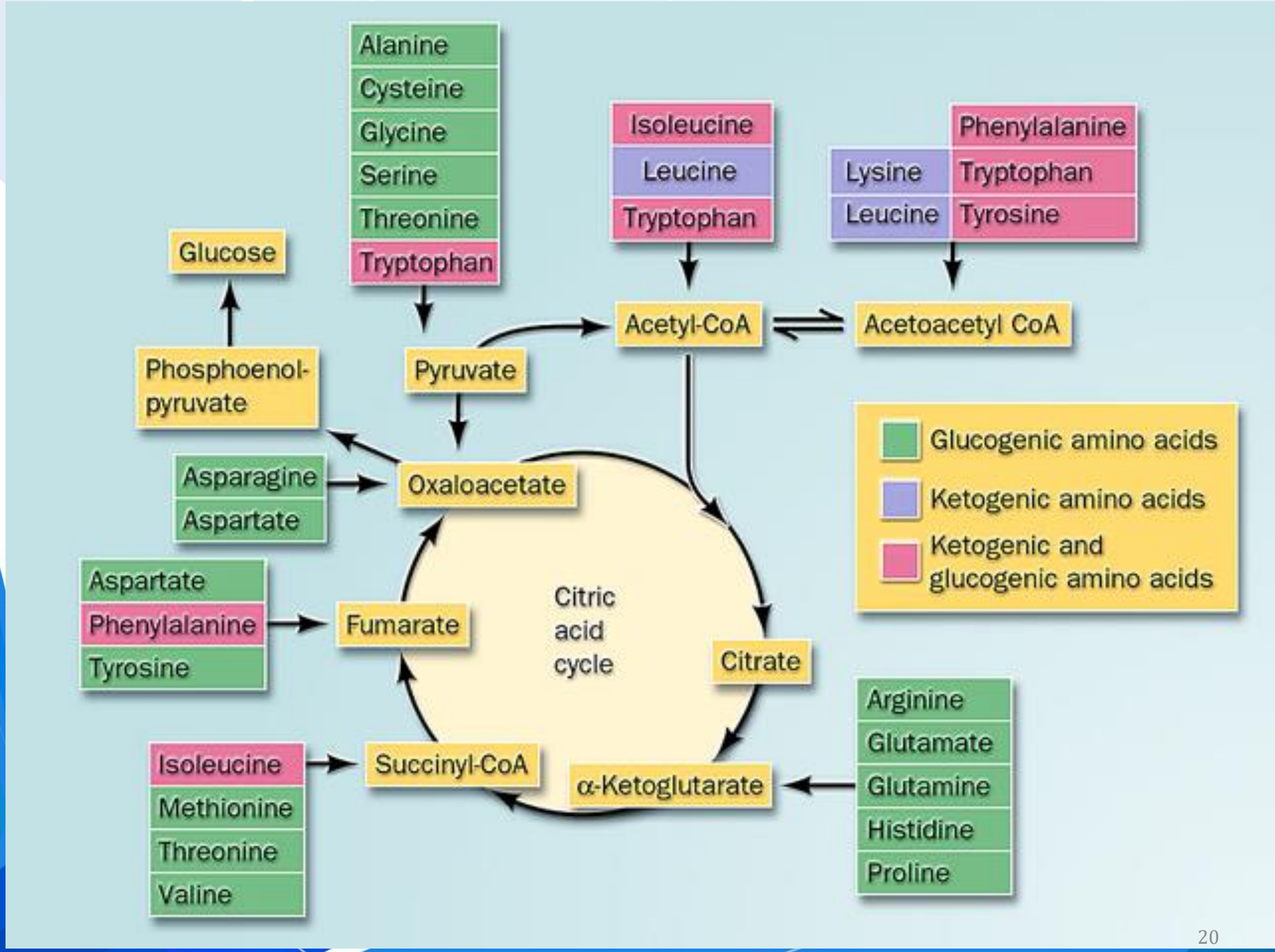
- conserved as carbohydrate, via **gluconeogenesis → glucogenic amino acids**
- conserved as fatty acid via fatty acid synthesis pathways **→ ketogenic amino acids**

Glucogenic amino acids

- Their carbon skeletons are degraded to **pyruvate**, or to one of the 4- or 5-carbon **intermediates of Krebs Cycle** that are precursors for gluconeogenesis.
- Glucogenic amino acids are the major carbon source for **gluconeogenesis** when glucose levels are low.
- They can also be catabolized for energy or **converted to glycogen or fatty acids for energy storage.**

Ketogenic amino acids

- Their carbon skeletons are degraded to **acetyl-CoA** or **acetoacetate**.
- Carbon skeletons of ketogenic amino acids can be catabolized for energy in **Krebs Cycle**, or converted to **ketone bodies or fatty acids**.
- They **cannot be converted to glucose**.


Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
Isoleucine
Leucine
Tryptophan
Phenylalanine
Lysine
Tryptophan
Leucine
Tyrosine
Glucose
Acetyl-CoA
Acetoacetyl CoA
Phosphoenol-pyruvate
Pyruvate
Glucogenic amino acids
Ketogenic amino acids
Ketogenic and glucogenic amino acids
Asparagine
Aspartate
Oxaloacetate
Aspartate
Phenylalanine
Tyrosine
Fumarate
Citric acid cycle
Citrate
Arginine
Glutamate
Glutamine
Histidine
Proline
Isoleucine
Methionine
Threonine
Valine
Succinyl-CoA
α-Ketoglutarate

Asam amino glikogenik:

- Aspartat
- Asparagin
- Glutamat
- Glutamin
- Alanine
- Glycine
- Serine
- Arginine
- Ornithine
- Prolin
- Cysteine
- Histidine

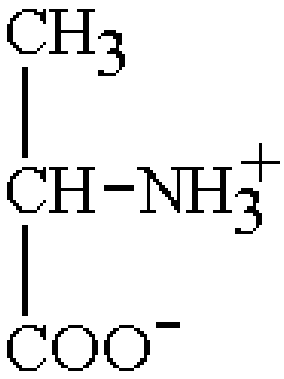
Asam Amino Ketogenik

- **Leusin**
- **Lisin**

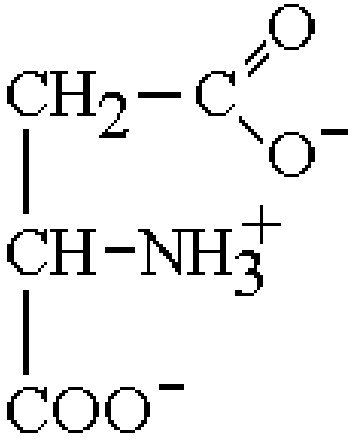
} **hanya ketogenik**

- Isoleusin
- Fenilalanin
- Triptofan
- Tirosin

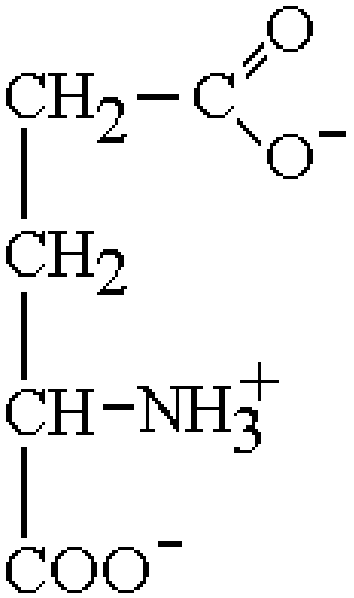
4 asam amino paling banyak di dalam tubuh



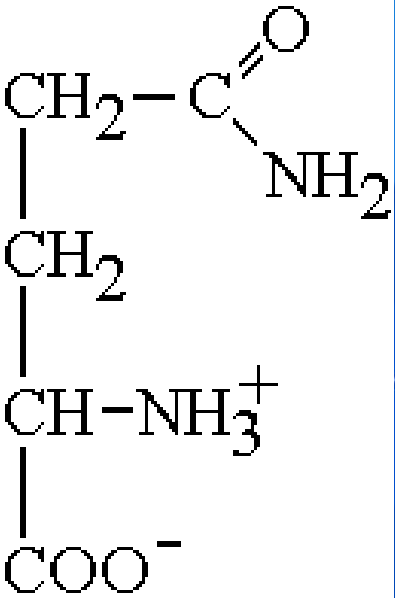
Alanine



Aspartate



Glutamate



Glutamine

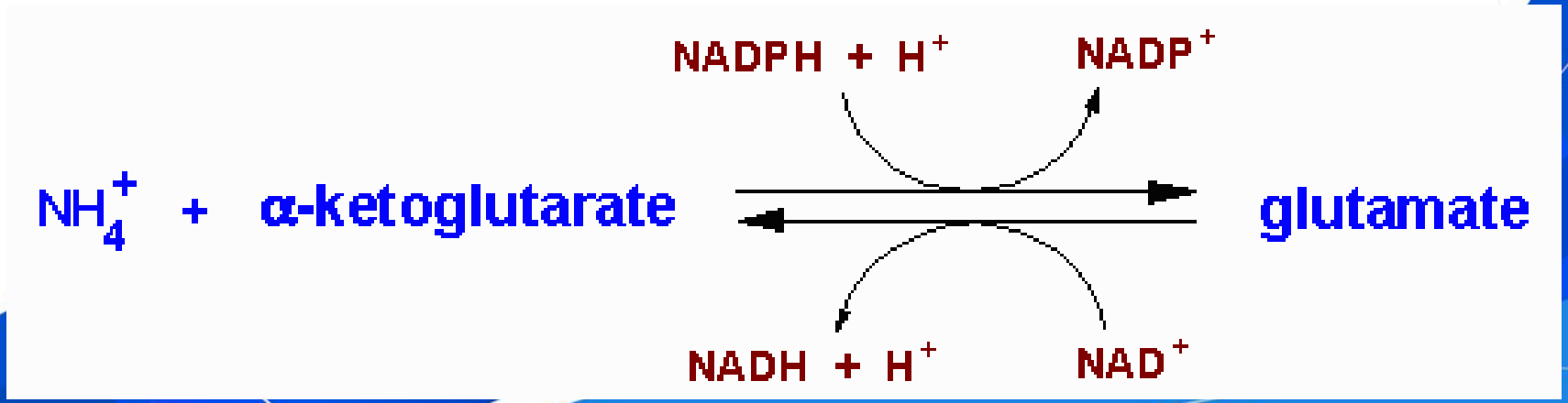
Katabolisme Glutamin/Glutamat

- **Glutaminase** is an important **kidney tubule** enzyme involved in converting glutamine (from liver and from other tissue) to glutamate and NH_3^+ with the NH_3^+ being excreted in the **urine**. Glutaminase activity is present in many other tissues as well, although its activity is not nearly as prominent as in the kidney.

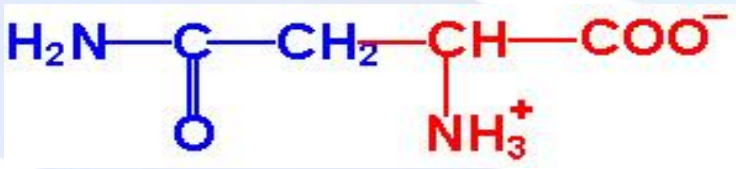
glutamine + H_2O -------> glutamat + NH_3^+

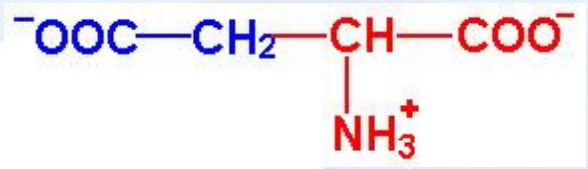
Katabolisme Glutamin/Glutamat

- The glutamate produced from glutamine is converted to **α-ketoglutarate** (by **glutamate dehydrogenase**), making glutamine a glucogenic amino acid.



Katabolisme Asparagin/Aspartat





- **Asparaginase** is also widely distributed within the body, where it converts asparagine into **ammonia** and **aspartate**.
- **Aspartate transaminates** to **oxaloacetate** , which follows the **gluconeogenic** pathway to glucose.

Katabolisme Glutamine/Glutamate dan Asparagine/Aspartate

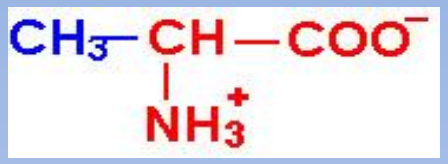
- Glutamate and aspartate are important in collecting and eliminating amino nitrogen via **glutamine synthetase** and the **urea cycle**, respectively.

- The catabolic path of the carbon skeletons involves simple 1-step **aminotransferase** reactions that directly produce net quantities of a **TCA cycle** intermediate.

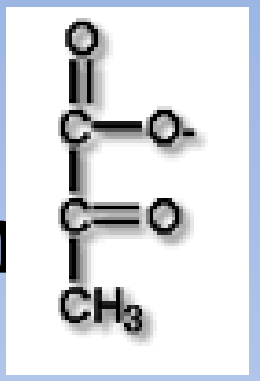
Glutamin sintetase & Glutaminase

glutamate + NH_4^+ + ATP -------> glutamine + ADP + Pi + H+

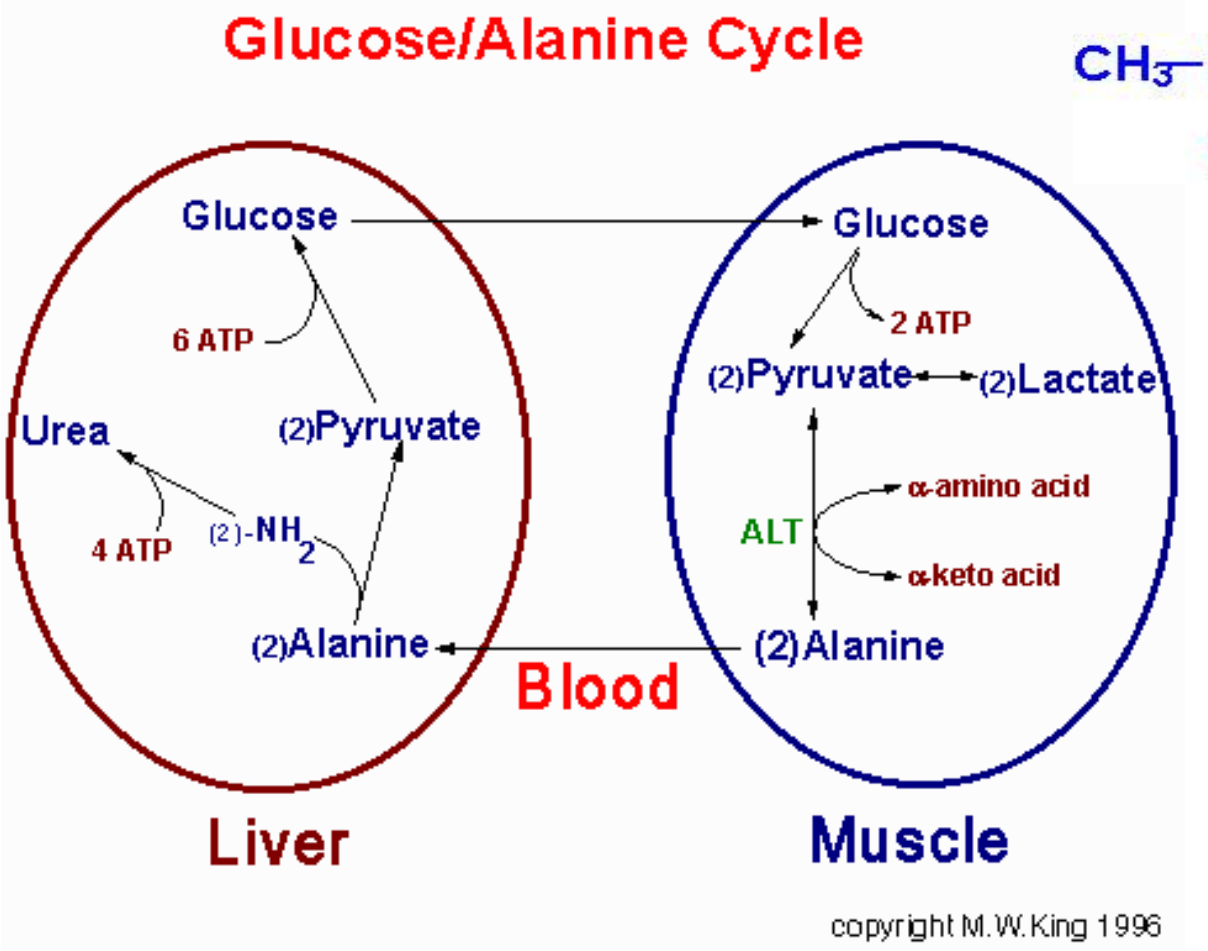
glutamine + H_2O -------> glutamate + NH_3



Katabolisme alanin

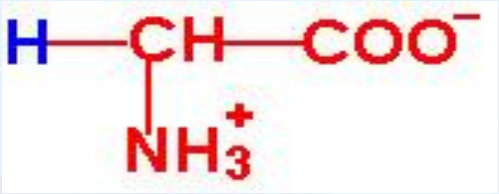


- Alanine is also important in **intertissue nitrogen transport** as part of the **glucose-alanine cycle**.
- Alanine's catabolic pathway involves a simple **aminotransferase** reaction that directly produces **pyruvate**.
- Generally pyruvate produced by this pathway will result in the formation of **oxaloacetate**, although when the energy charge of a cell is low the pyruvate will be oxidized to CO_2 and H_2O via the PDH complex (reaksi dekarboksilasi oksidatif piruvat) and the **TCA cycle**. This makes alanine a **glucogenic** amino acid.



The glucose-alanine cycle is used primarily as a **mechanism for skeletal muscle to eliminate nitrogen** while replenishing its energy supply. Glucose oxidation produces pyruvate which can undergo transamination to alanine. This reaction is catalyzed by alanine transaminase, ALT (**ALT** used to be called serum glutamate-pyruvate transaminase, **SGPT**). Additionally, during periods of fasting, skeletal muscle protein is degraded for the energy value of the amino acid carbons and alanine is a major amino acid in protein. The alanine then enters the blood stream and is transported to the liver. Within the liver alanine is converted back to pyruvate which is then a source of carbon atoms for gluconeogenesis. The newly formed glucose can then enter the blood for delivery back to the muscle. The amino group transported from the muscle to the liver in the form of alanine is converted to urea in the urea cycle and excreted.

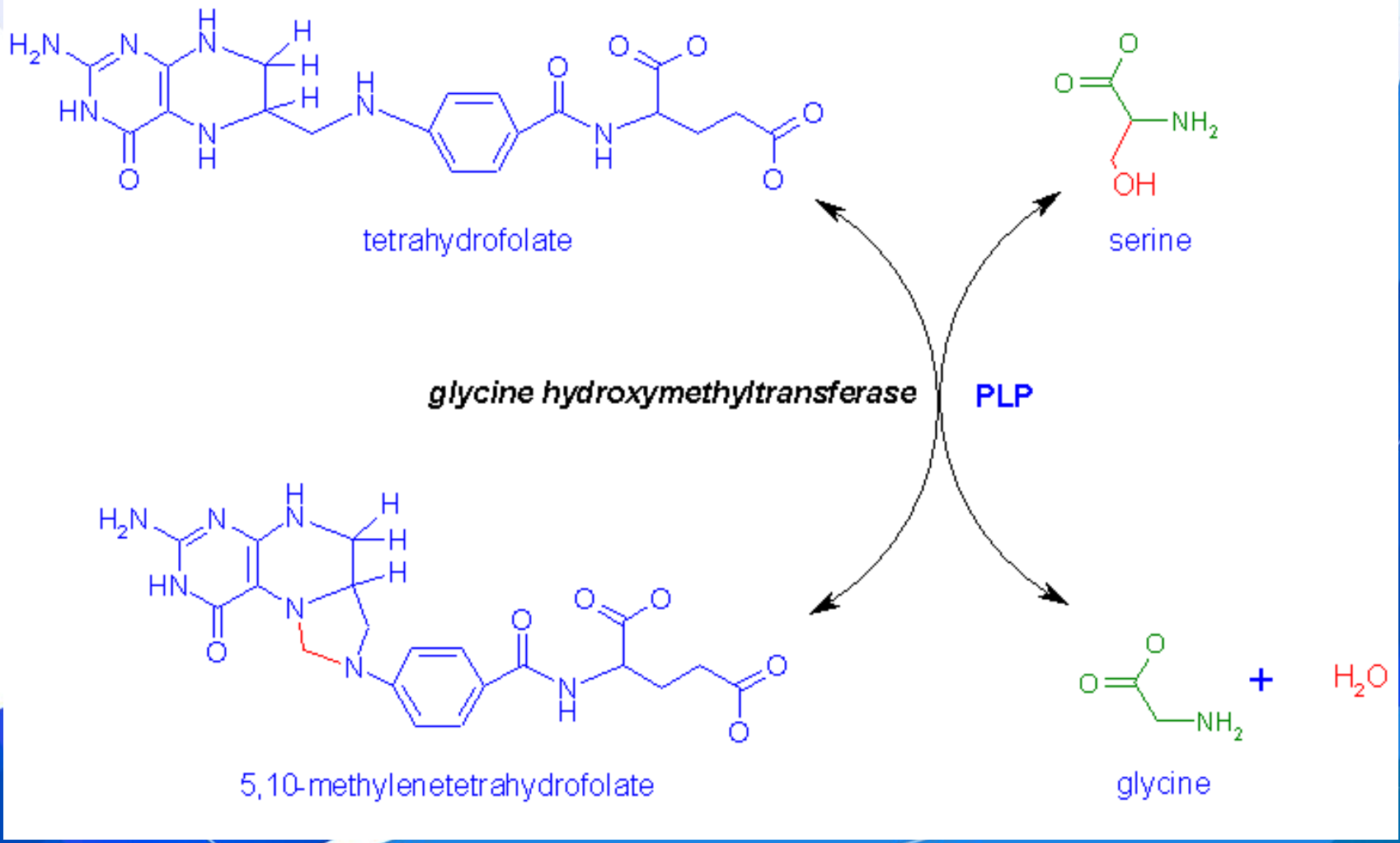
Katabolisme Glisin



- The main glycine catabolic pathway leads to the production of **CO_2**, **ammonia**, and one equivalent of ***N*5,*N*10-methyleneTHF** by the mitochondrial glycine cleavage complex.

  is classified as a **glucogenic amino acid**, since it can be converted to **serine** by serine hydroxymethyltransferase, and serine can be converted back to the glycolytic intermediate, **3-phosphoglycerate or to pyruvate** by serine/threonine dehydratase.

Konversi Glisin → Serin

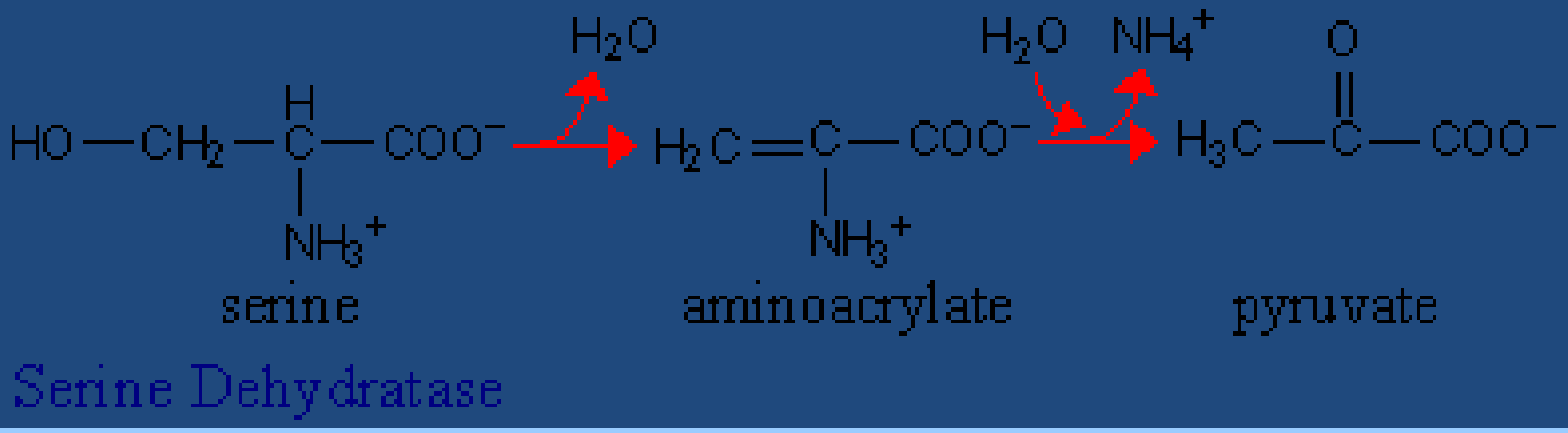


Katabolisme Serin

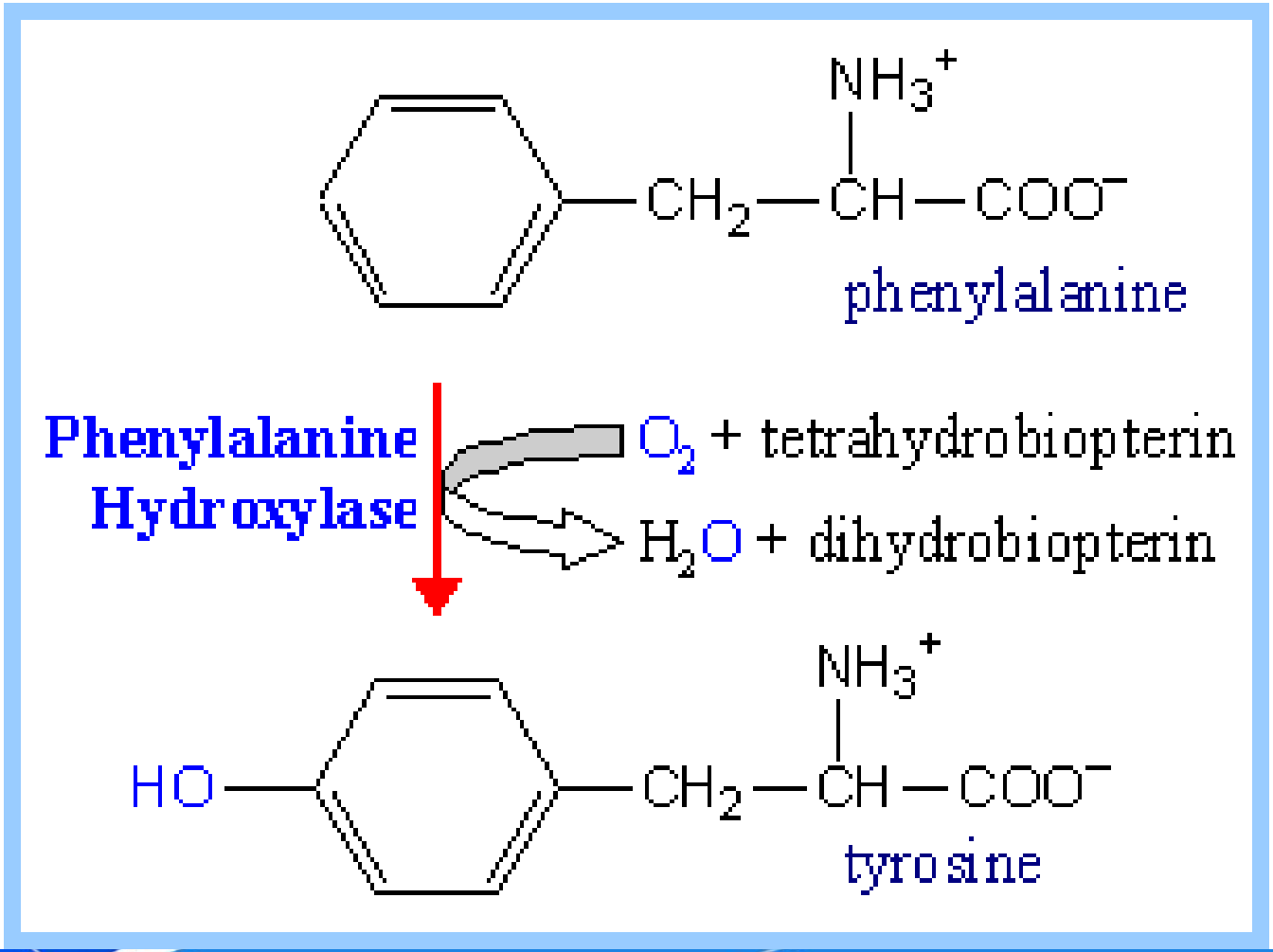
1. The conversion of serine to glycine and then glycine oxidation to CO_2 and NH_3, with the production of two equivalents of N5,N10-methyleneTHF.

   can be catabolized back to the glycolytic intermediate, **3-phosphoglycerate**, by a pathway that is essentially a reversal of serine biosynthesis. However, the enzymes are different.

3. Serine can also be converted to **pyruvate** through a **deamination** reaction catalyzed by **serine/threonine dehydratase**.

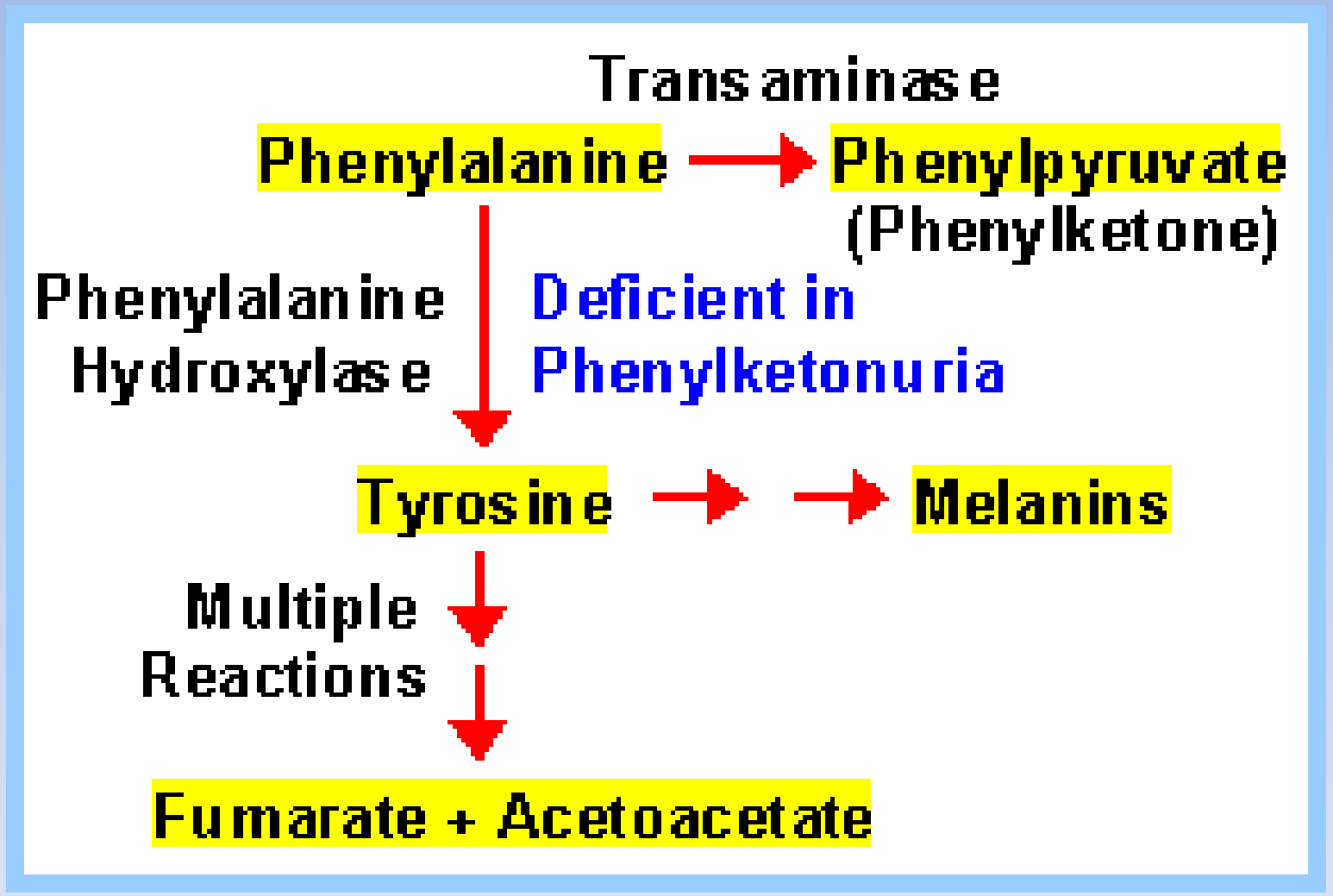

H2O
H2O
NH4+
HO—CH2—C(H)(NH3+)—COO−
H2C=C(NH3+)—COO−
H3C—C(=O)—COO−
serine
aminoacrylate
pyruvate
Serine Dehydratase

Katabolisme Fenilalanin → Tirosin



PKU (Phenylketonuria)

- Phenylketonuria (PKU) is a disorder that causes a build up of the amino acid phenylalanine, which is an **essential** amino acid that cannot be synthesized in the body but is present in food.
- Excess phenylalanine is normally converted to **tyrosine**, another amino acid, and eliminated from the body. Without the enzyme that converts it to tyrosine, phenylalanine builds up in the blood and is **toxic to the brain, causing mental retardation**.


Transaminase
Phenylalanine
Phenylpyruvate
(Phenylketone)
Phenylalanine
Hydroxylase
Deficient in
Phenylketonuria
Tyrosine
Melanins
Multiple
Reactions
Fumarate + Acetoacetate

Valine, Leucine and Isoleucine Catabolism

BCAAs ; essential amino acids

- The catabolism of all three compounds initiates in **muscle** and yields **NADH** and **$FADH_2$** which can be utilized for ATP generation.
- The catabolism of all three of these amino acids uses the same enzymes in the first two steps. The first step in each case is a transamination using a single **BCAA aminotransferase**, with α-ketoglutarate as amine acceptor. As a result, three different α-keto acids are produced and are oxidized using a common branched-chain **α-keto acid dehydrogenase**, yielding the three different **CoA derivatives**.

Valine, Leucine and Isoleucine Catabolism

- Subsequently the metabolic pathways diverge, producing many intermediates. The principal product from **valine is propionylCoA**, the glucogenic precursor of succinyl-CoA.
- **Isoleucine** catabolism terminates with production of **acetylCoA and propionylCoA**; thus isoleucine is both glucogenic and ketogenic.
- **Leucine** gives rise to **acetylCoA and acetoacetylCoA**, and is thus classified as strictly ketogenic.

Maple Syrup Disease

- Children with maple syrup urine disease are **unable to metabolize certain amino acids** (esp. BCAA).
- By-products of these amino acids build up, causing **neurologic changes**, including **seizures and mental retardation**. These by-products also cause body fluids, such as urine and sweat, to smell like maple syrup.

Maple syrup urine disease

- The most common defect is in the branched-chain α-keto acid dehydrogenase. Since there is only one dehydrogenase enzyme for all three amino acids, all three α-keto acids accumulate and are excreted in the urine. The disease is known as Maple syrup urine disease because of the characteristic **odor of the urine** in afflicted individuals. Mental retardation in these cases is extensive.
- Unfortunately, since these are essential amino acids, they cannot be heavily restricted in the diet; ultimately, the life of afflicted individuals is short and development is abnormal The main neurological problems are due to **poor formation of myelin in the CNS**.

BIOSINTESIS ASAM AMINO

Asam Amino Essensial

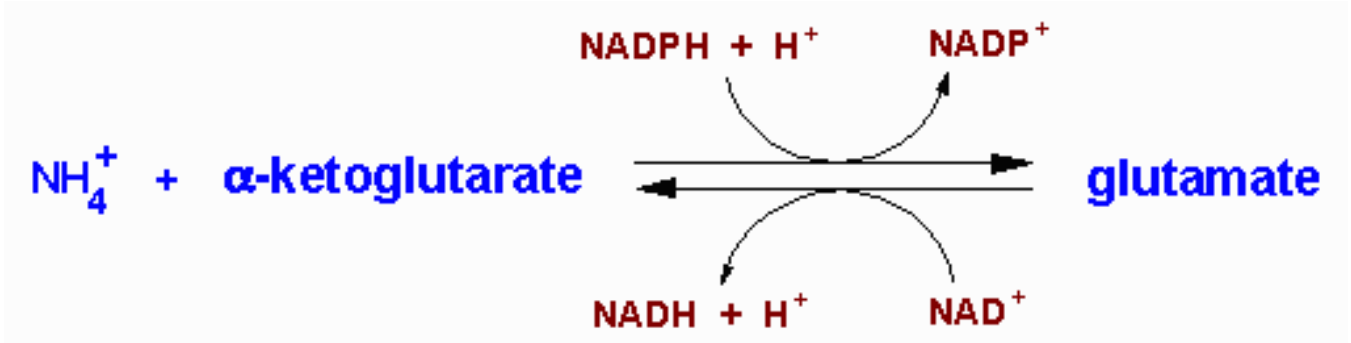
- Valin
- Leusin
- Isoleusin
- Lisin
- Fenilalanin
- Metionin
- Treonin
- Triptofan
- Arginin
- Histidin

Asam Amino Non Essensial

- Aspartat
- Asparagin
- Glutamat
- Glutamin
- Alanin
- Prolin
- Serin
- Tirosin
- Sistein
- Glisin

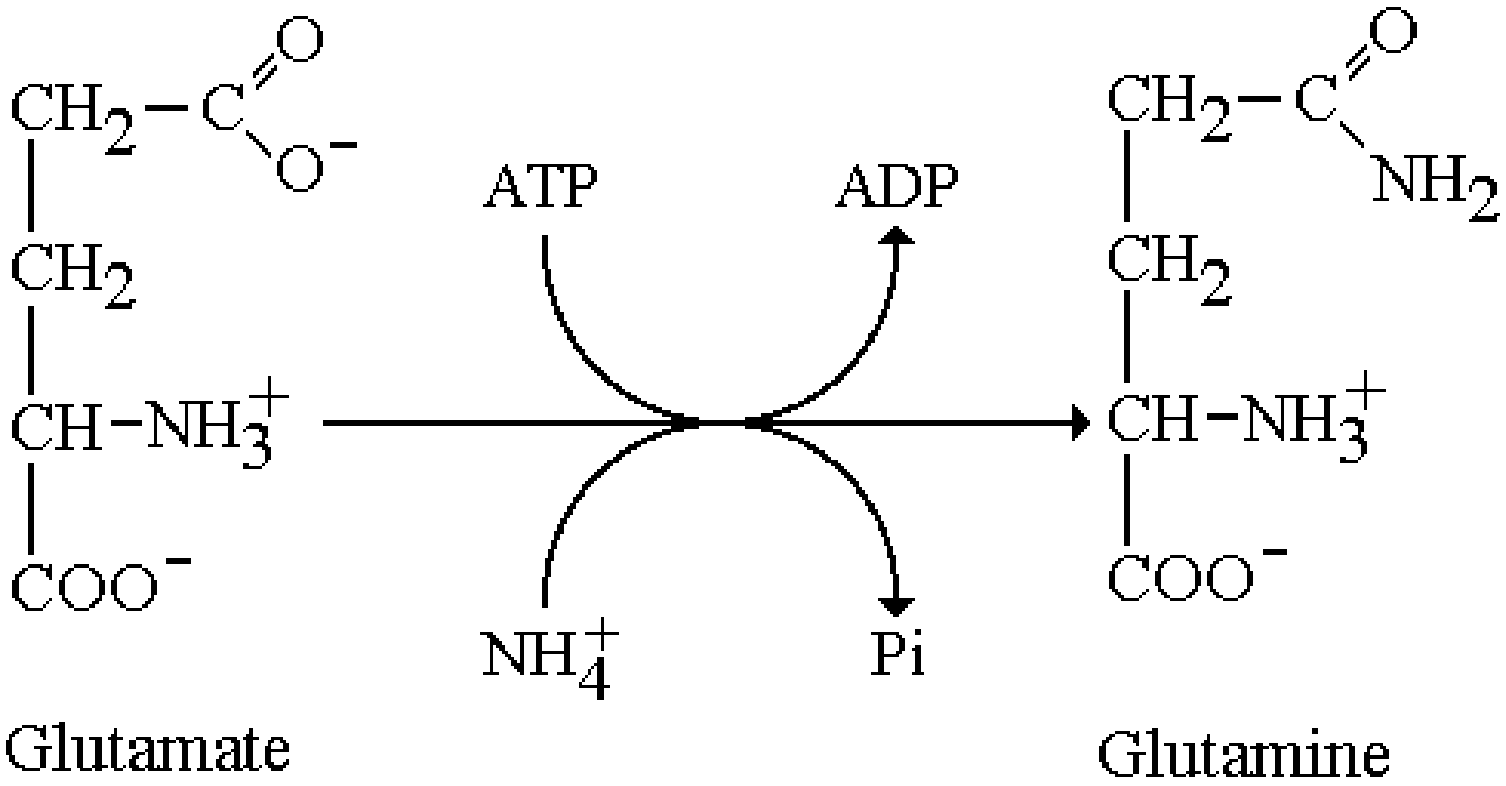
Biosintesis Aspartat dan Glutamat

- Glutamate and aspartate are synthesized from their widely distributed **α-keto acid precursors** (**α-ketoglutarat/ oksaloasetat**) by simple 1-step **transamination** reactions. The former catalyzed by **glutamate dehydrogenase** and the latter by **aspartate aminotransferase**, AST.
- Aspartate is also derived from **asparagine** through the action of asparaginase.



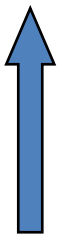
Reactions of *glutamate dehydrogenase*

Biosintesis Glutamin



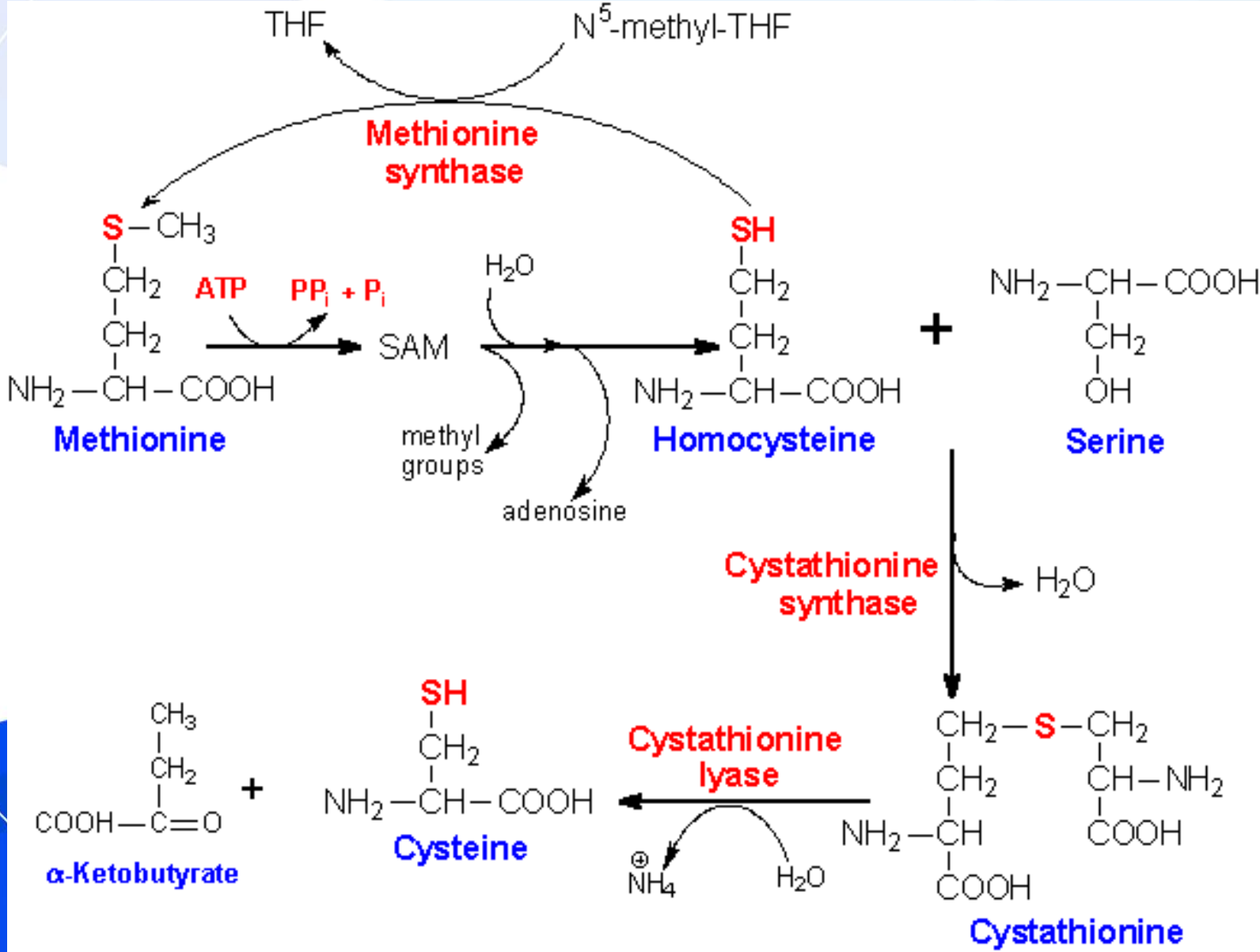
Biosintesis Alanin

glutamate + pyruvate <------> α-KG + alanine

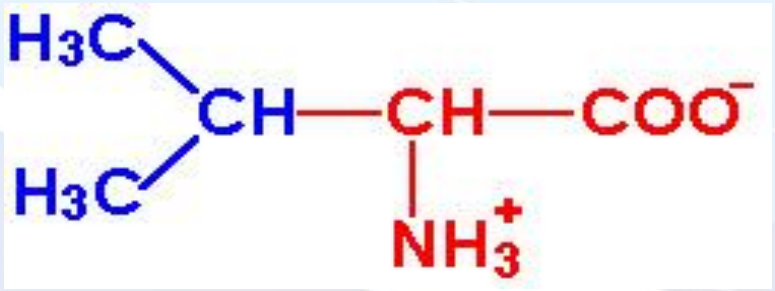


glutamate-pyruvate aminotransferase
(also called alanine transaminase, ALT).

Biosintesis Sistein



RESUME



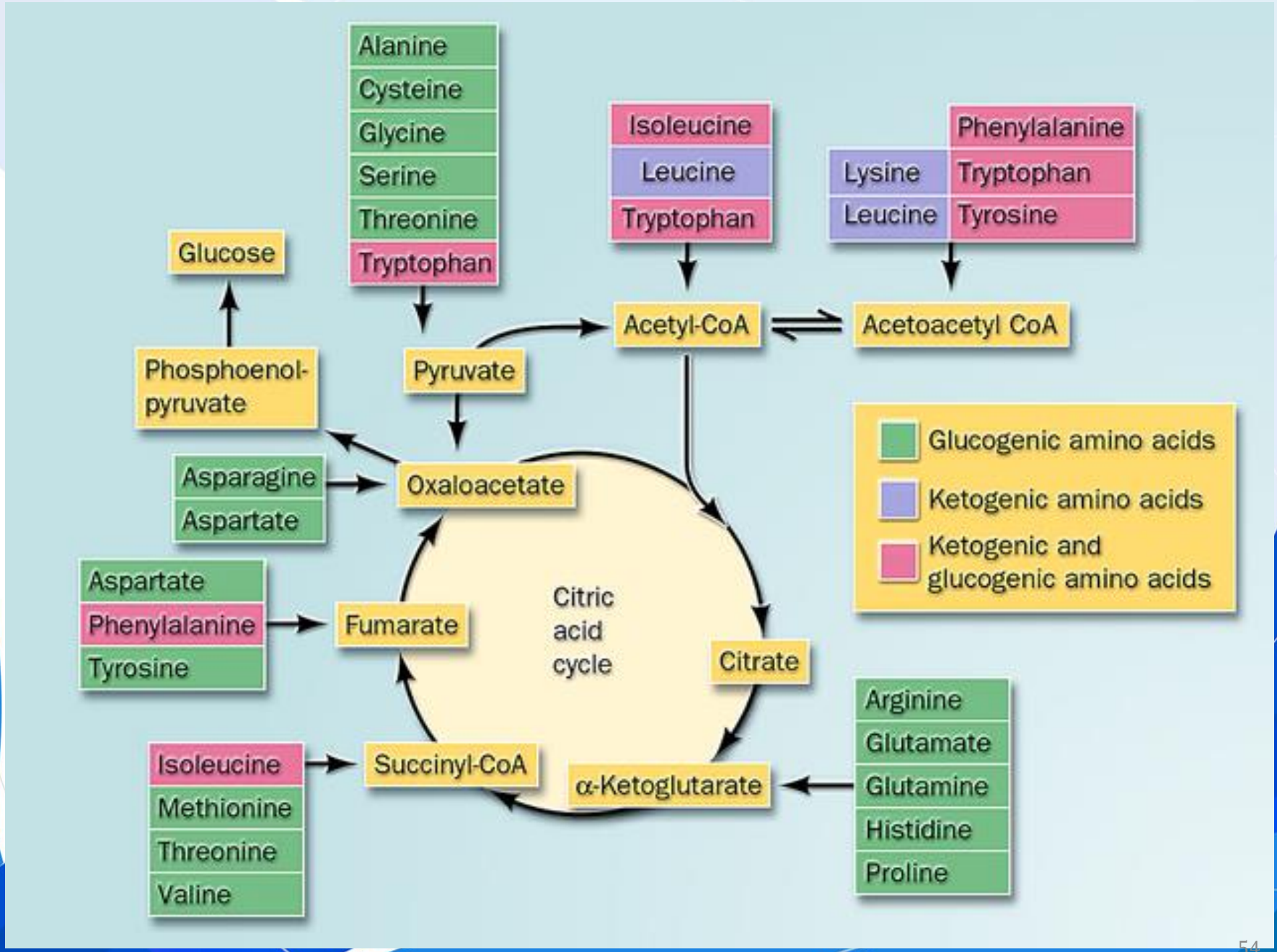
Deaminasi/Transaminasi

Rangka Karbon

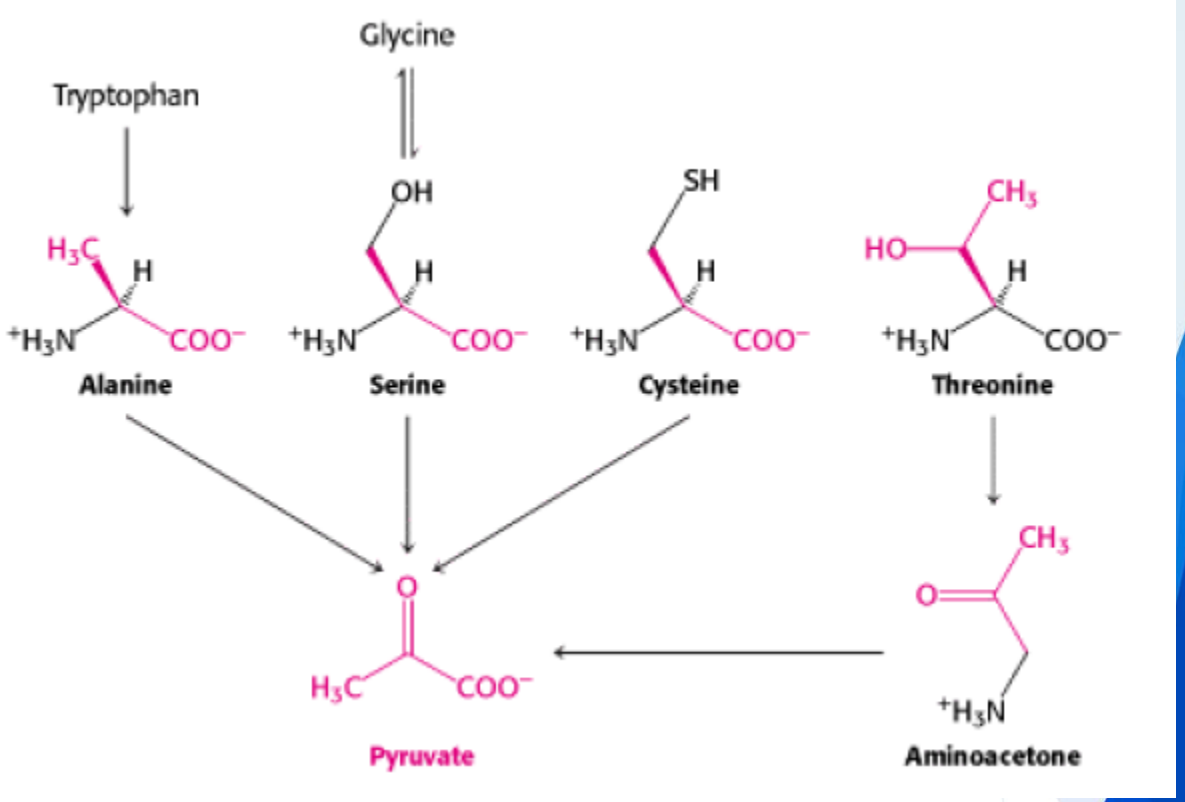
NH3

Siklus KREBS

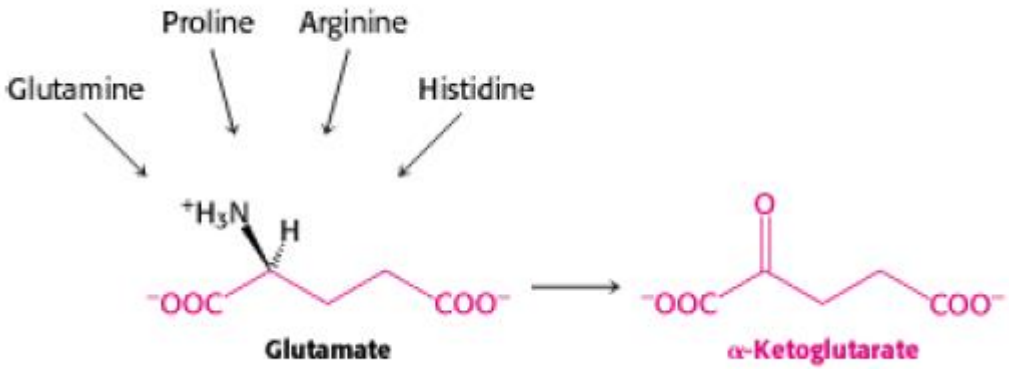
Siklus Urea


Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
Isoleucine
Leucine
Tryptophan
Phenylalanine
Lysine
Tryptophan
Leucine
Tyrosine
Glucose
Acetyl-CoA
Acetoacetyl CoA
Phosphoenol-pyruvate
Pyruvate
Glucogenic amino acids
Ketogenic amino acids
Ketogenic and glucogenic amino acids
Asparagine
Aspartate
Oxaloacetate
Aspartate
Phenylalanine
Tyrosine
Fumarate
Citric acid cycle
Citrate
Arginine
Glutamate
Glutamine
Histidine
Proline
Isoleucine
Methionine
Threonine
Valine
Succinyl-CoA
α-Ketoglutarate

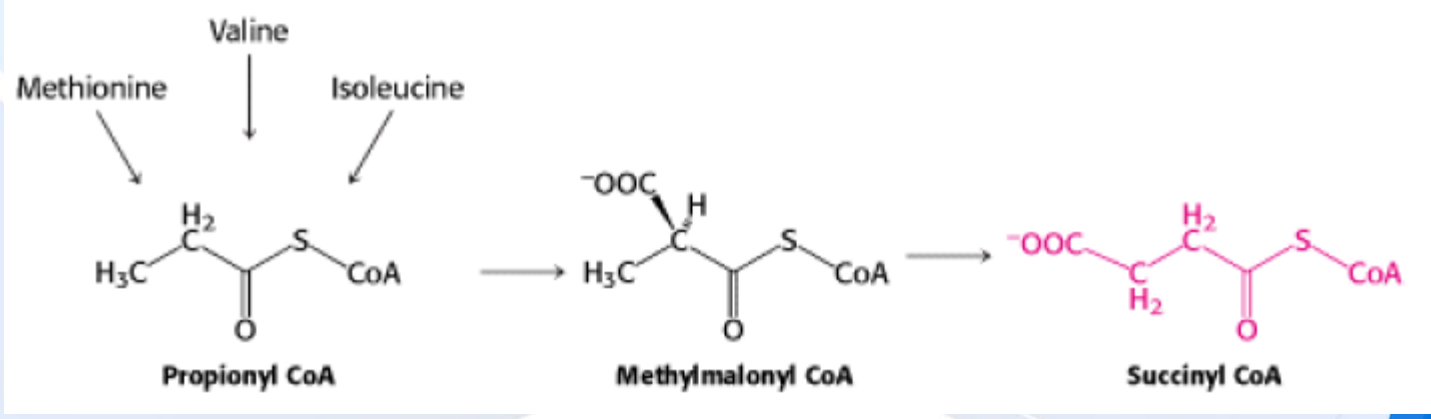
Degradasi asam amino menjadi **piruvat**



Degradasi asam amino menjadi **α-ketoglutarat**



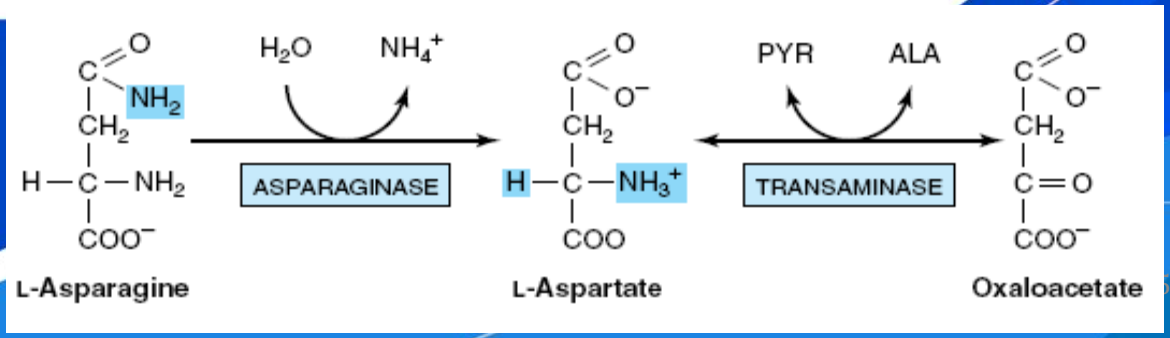
Degradasi asam amino menjadi suksinil-KoA



Degradasi asam amino menjadi fumarat

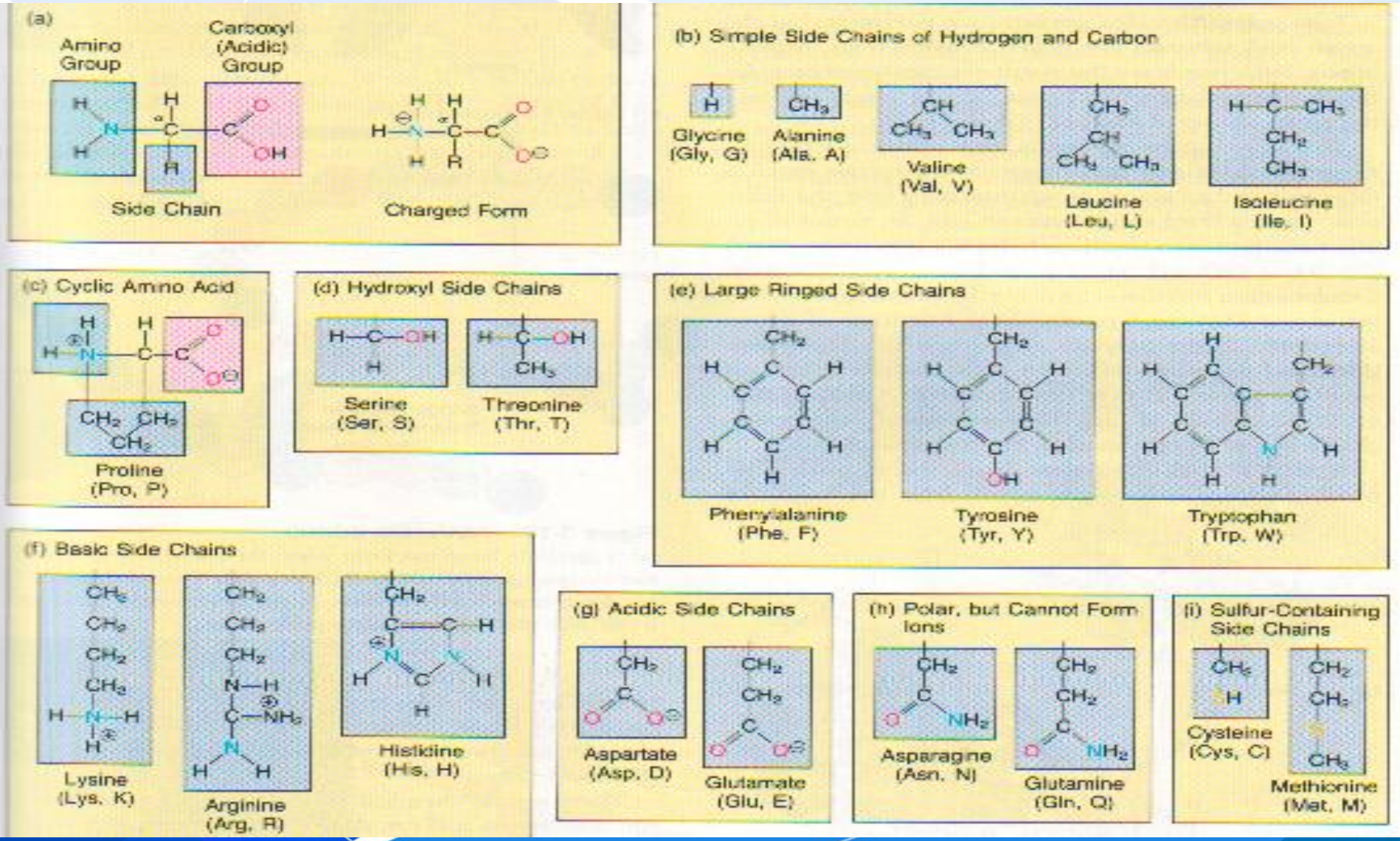
Phenylalanine → Tyrosine → P-Hydroxyphenylpyruvate → Homogentisate → Maleylacetoacetate → Fumarylacetoacetate → Acetoacetate + Fumarate

Degradasi asam amino menjadi oksaloasetat



BIOSINTESIS ASAM AMINO NONESSENSIAL

Asam-asam Amino Penyusun Protein



9. Bayi A berusia 10 bulan masuk UGD karena koma. Hasil pemeriksaan laboratorium menunjukkan kadar ammonia darah yang sangat tinggi. Kondisi ini menunjukkan adanya gangguan pada:

A. Siklus asam trikarboksilat
B. Siklus Krebs
C. Siklus Cory
D. Siklus Ornitin
E. Salvage Pathway

10. Valin, Leusin dan Isoleusin merupakan *Branched-chain amino acids* (BCAA). Pada proses metabolismenya, diperoleh tiga derivate CoA yang berbeda. Valin menghasilkan prekurson succinyl-CoA, Leusin menghasilkan Acetyl-CoA dan asetoacetyl-CoA, sedangkan Isoleusin menghasilkan acetyl-CoA dan precursor succinyl-CoA. Dengan demikian, Leusin termasuk:

A. Asam amino esensial
B. Asam amino non-esensial
C. Asam amino glikogenik
D. Asam amino glikogenik dan ketogenic
E. Asam amino ketogenic

11. *Maple syrup urine disease* merupakan penyakit yang dikarakerisasi dengan bau urin yang khas. Umumnya terjadi pada anak-anak akibat tubuhnya tidak dapat memetabolisme beberapa asam amino, yaitu:
    A. Fenilalanin
    B. Metionin
    C. Homosistein
    D. Asam amino rantai bercabang
    E. Triptofan

12. Pasien pasien anak Y dirujuk ke rumah sakit karena menunjukkan adanya retardasi mental pada proses tumbuh kembangnya dan diduga mengalami gangguan otak. Teridentifikasi bau tidak 'enak' pada nafas, urin, kulit dan rambut pasien. Diduga penyakit pasien akibat adanya gangguan metabolisme asam amino esensial, yaitu:
    A. Fenilalanin
    B. Tirosin
    C. Triptofan
    D. Serin
    E. Valin

3. Katabolisme asam amino terdiri dari dua bagian yaitu, katabolisme nitrogen dan rangka karbon.
   A. Biosintesis Urea merupakan katabolisme yang mana? (nilai maks. 2,5)
   B. Tuliskan 4 tahap reaksi biosintesis urea! (nilai maks. 2,5)
   C. Gambarkan reaksi-reaksi pada siklus urea! (nilai maks. 5)
   D. Katabolisme rangka karbon dapat mengklasifikasikan asam amino sebagai asam amino glukogenik dan ketogenic. Jelaskan asam amino tersebut beserta contohnya (nilai maks. 5)