# Amino acid metabolism II

## Metabolism of individual amino acids

Biochemistry I
Lecture 7

2009 (J.S.)

**The degradation of amino acids usually begins with deamination**.

However, transamination or oxidative deamination is not the first reaction in catabolism of eight amino acids:

**Serine** and **threonine** are deaminated by dehydration, and **histidine** undergoes deamination by desaturation (both reactions were mentioned previously).

The five remaining amino acids are deaminated later on, after partial transformation:

**Arginine** – deamination occurs after transfomation to ornithin,
**lysine** – transamination follows the transformation to α-aminoadipate,
**methionine** – deamination of homoserine,
**proline** – deamination after conversion to glutamate,
**tryptophan** – after its transformation to kynurenine, alanine is released.

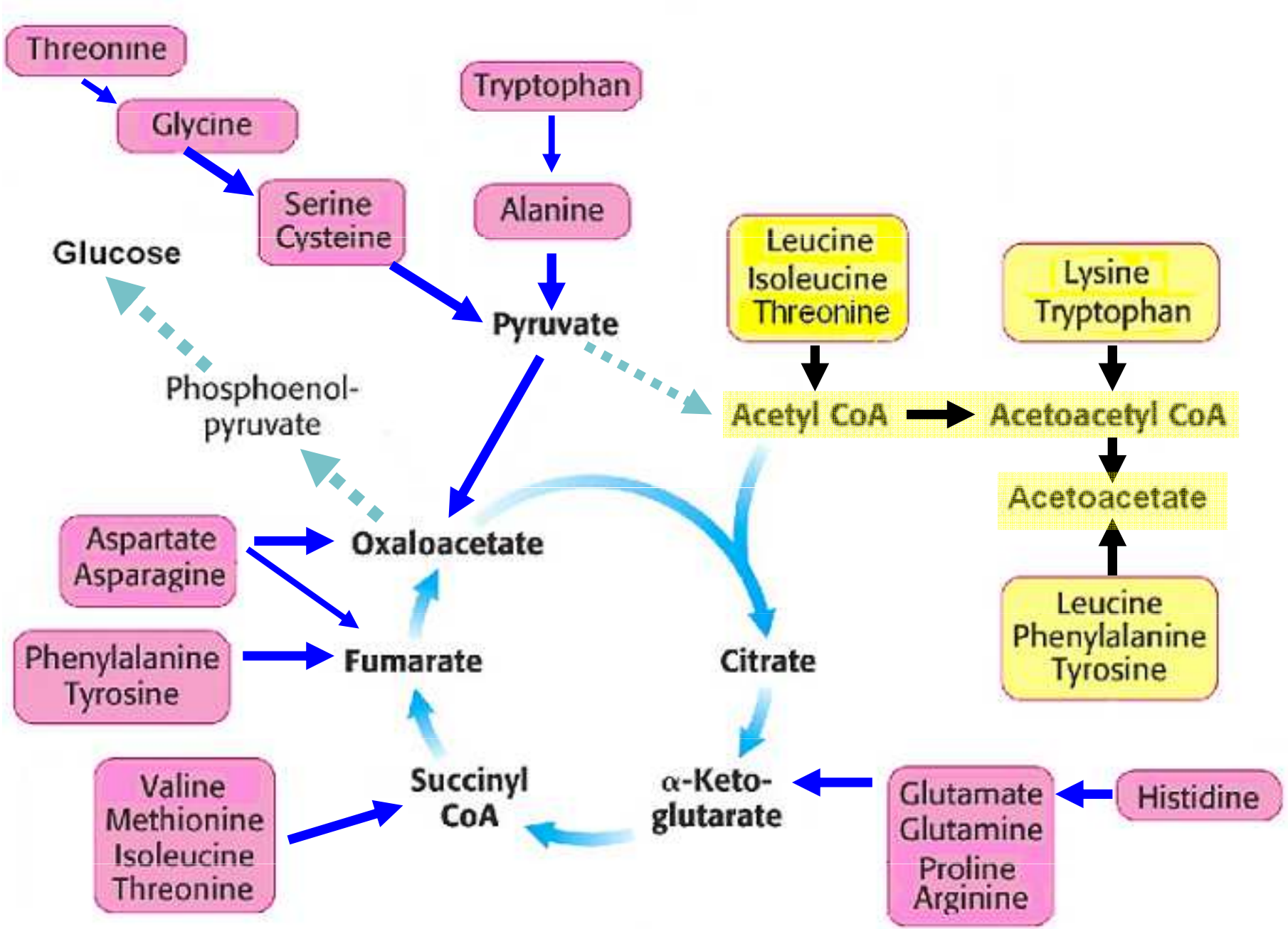
Each **carbon skeleton** of deaminated amino acids follows a unique metabolic pathway to compounds , which can be **completely oxidized by way of the citrate cycle** to $CO_2$ and water.

In spite of this common fate, amino acids are classified as **glucogenic** and **ketogenic** according to the type of their intermediate metabolites.

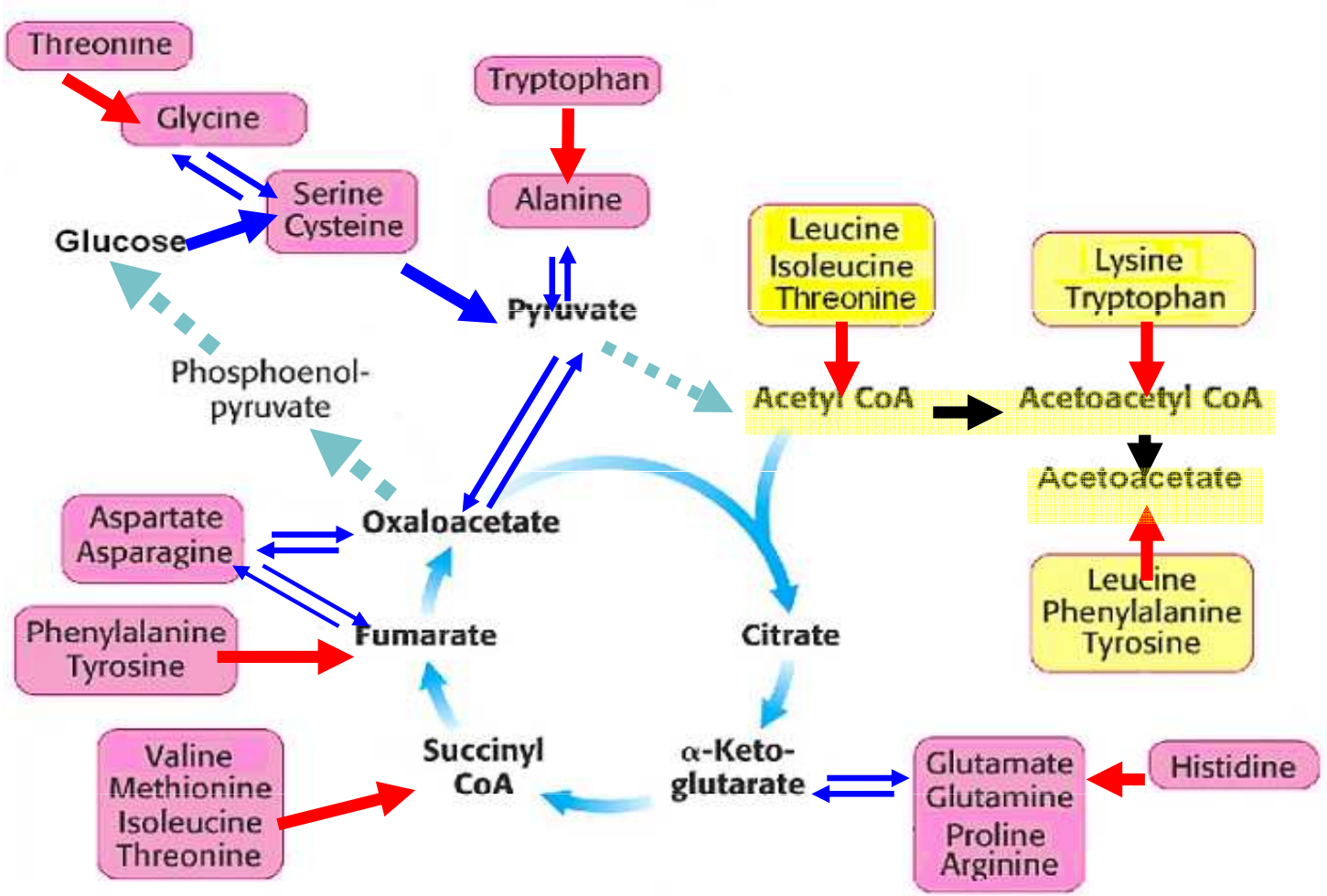
**The glucogenic amino acids** give rise to pyruvate or some of the intermediate of the citrate cycle, which can serve as **substrates for gluconeogenesis**.

**The ketogenic amino acids** give rise to acetoacetate or acetyl-CoA (from which acetoacetate can be synthesized) that **cannot be transformed to glucose**.

# Glucogenic and ketogenic amino acids



**Irreversible conversions** in the metabolism of amino acids show which proteinogenic amino acids are essential:



## Nonessential amino acids

Glycine
Alanine
Serine
Cysteine
Aspartate
Asparagine
Glutamate
Glutamine
Proline
Arginine
Tyrosine

## Essential amino acids:

**Threonine**
**Methionine**
**Lysine**
Valine
Leucine
Isoleucine
**Histidine**
**Phenylanine**
**Tryptophan**

**The metabolism of amino acids will be described in the following sequence:**

1 The most simple AA that give pyruvate – Ala, Ser, Gly, Thr
2 Amino acids containing sulfur – Met, Cys
3 Sources of one-carbon units and use of those units in syntheses
4 Aspartic acid
5 Glutamic acid and its relation to Arg, Pro, His
6 Branched-chain amino acids – Val, Ile, Leu
7 Lysine
8 Aromatic amino acids – Phe, Tyr, and Trp

# 1 Amino acids that are converted to pyruvate:

**Alanine** - by transamination.

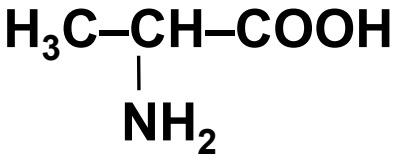
**Serine** - by deamination catalyzed of dehydratase (hydrolyase).

**Glycine** - by accepting one-carbon group gives **serine**.

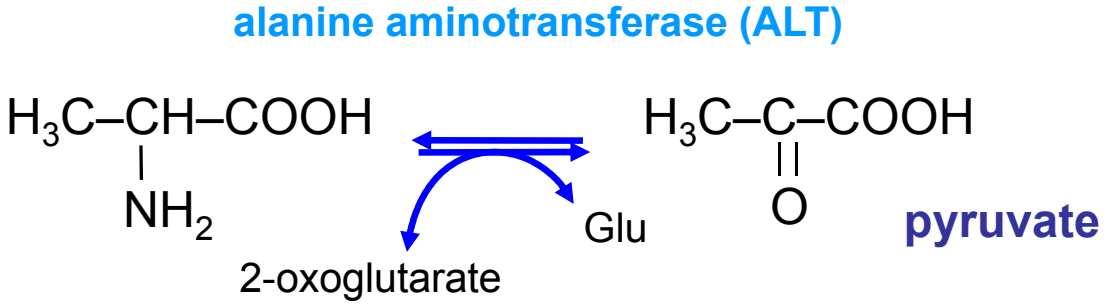
**Threonine** - by splitting gives **glycine** that may give **serine**.

**Cysteine** also gives pyruvate by deamination and desulfuration (see "Amino acids containing sulfur"), as well as **tryptophan** that after transformation to kynurenin releases alanine (see "Aromatic amino acids").

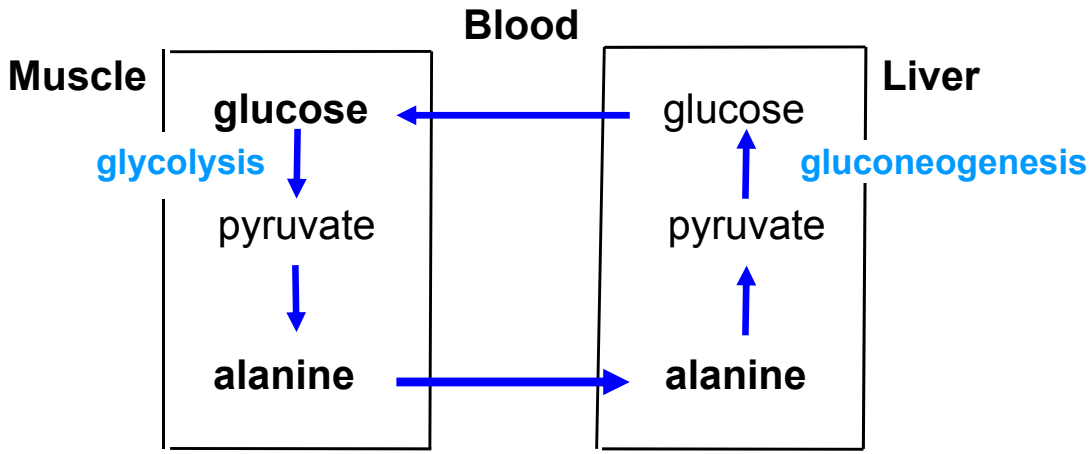
# Alanine



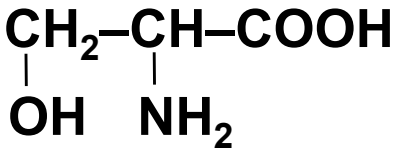

is nonessential and glucogenic;
it undergoes **transamination to pyruvate** readily:




Concentrations of alanine in blood plasma are 300 – 400 μmol/l (the second highest next to glutamine). Alanine is released from muscle tissue and serves both as the vehicle for $NH_3$ transport from muscle to liver and a substrate for liver gluconeogenesis. This bidirectional transport is called **the alanine cycle** (or glucose-alanine cycle).



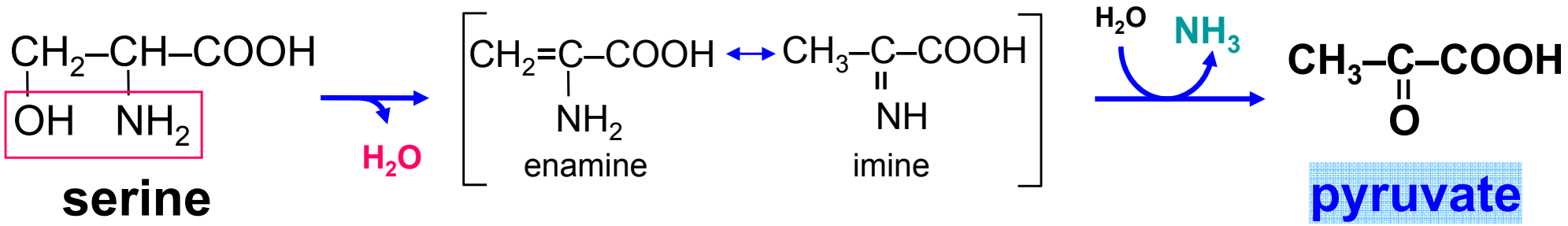
# Serine



is nonessential and glucogenic;

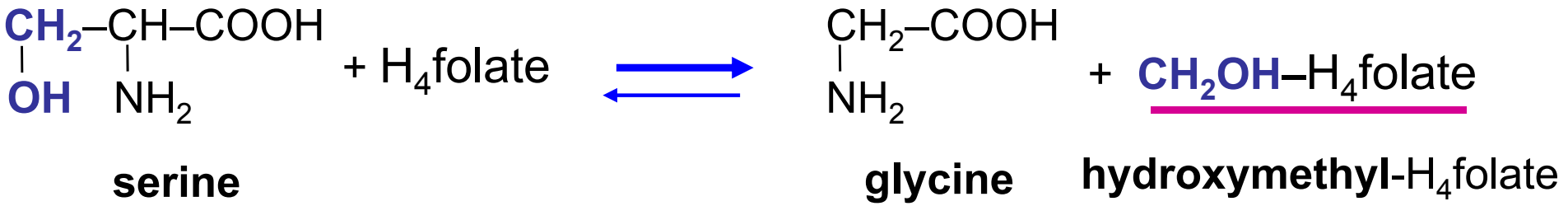
– nonessential – synthesis of the carbon skeleton from 3-phosphoglycerate
– glucogenic – direct deamination by *serine dehydratase* to pyruvate

Serine does not take part in transamination,
but it is **directly deaminated by dehydration**:

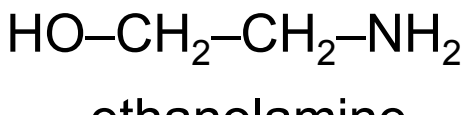


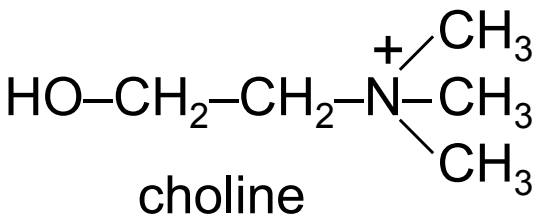
Serine is a **substantial source of one-carbon groups**:
its -$CH_2$-OH group is readily transferred to tetrahydrofolate (coenzyme of $C_1$-group transferase), the product is **glycine** that is able to yield the second $C_1$-group.

The reaction is reversible, but the synthesis of serine from glycine and a $C_1$-group is not an advantage.

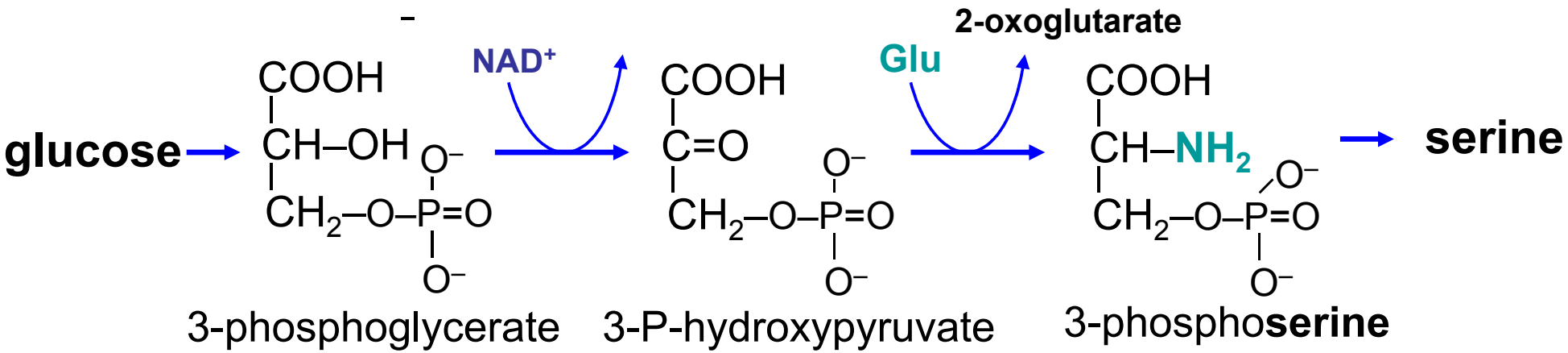


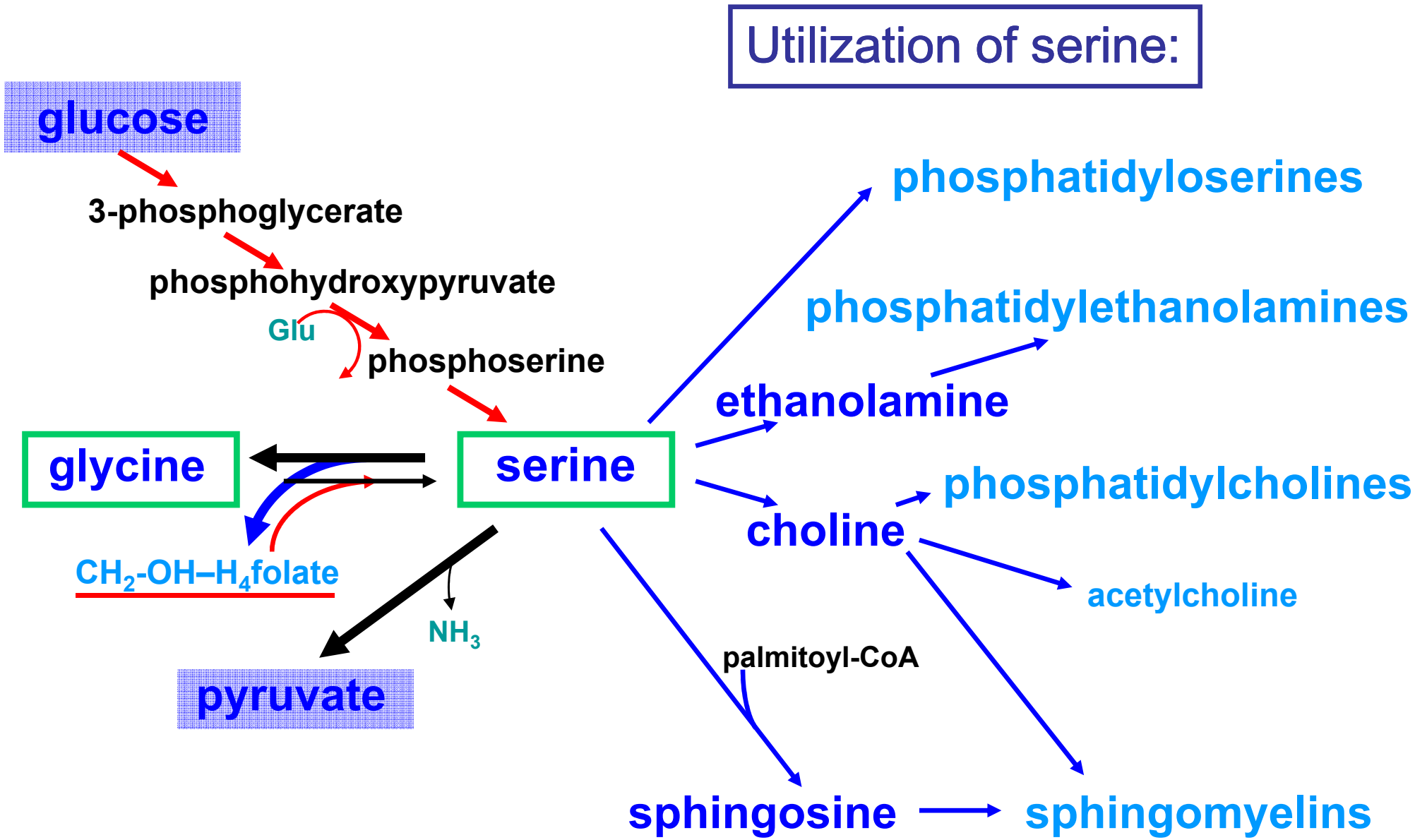

**Decarboxylation** of serine results in **ethanolamine** (a constituent of phospholipids) that gives **choline** by methylation.



Demands for serine in the body are great – both one-carbon groups and substrates for the synthesis of complex lipids have to be supplied.
Therefore, the **synthesis of carbon skeleton from glucose** is of great significance:




Utilization of serine:
glucose
3-phosphoglycerate
phosphohydroxypyruvate
Glu
phosphoserine
glycine
serine
CH2-OH–H4folate
NH3
pyruvate
phosphatidyloserines
phosphatidylethanolamines
ethanolamine
phosphatidylcholines
choline
acetylcholine
palmitoyl-CoA
sphingosine
sphingomyelins

# Glycine

$CH_2$–COOH
|
$NH_2$

is <u>nonessential</u> and <u>glucogenic</u>;

– nonessential – **originates from serine** or from $CO_2$, $NH_3$, and $C_1$-group
– glycogenic (weakly) – may accept $C_1$-group and give serine

Reversible reaction

**glycine** + **$CH_2OH$**–$H_4$folate ⇌ **serine** + $H_4$folate

(described as an important source of $C_1$-groups) is not a useful way of glycine catabolism, because it consumpts one $C_1$-group.

**Transamination** of glycine with pyruvate

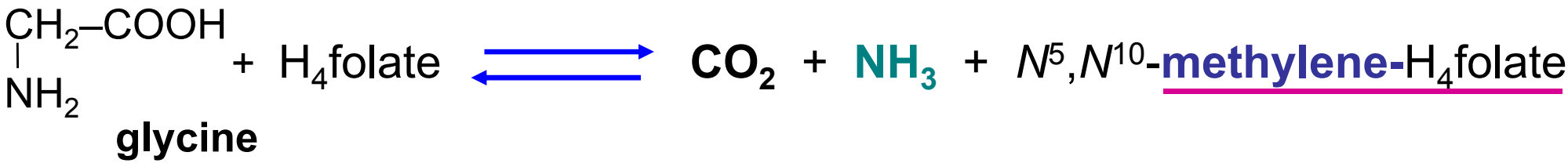
glycine + pyruvate ⇌ **glyoxylate** + alanine

as well as **oxidative deamination** of glycine

glycine + FAD → **glyoxylate** + $FADH_2$

are possible, although limited; the enzymes catalyzing those reactions have sufficient activity only in <u>peroxisomes</u>. It is worth mentioning that glyoxylate formed in those minor pathways gives small amounts of unwanted **oxalate.** High production of oxalate is dangerous.

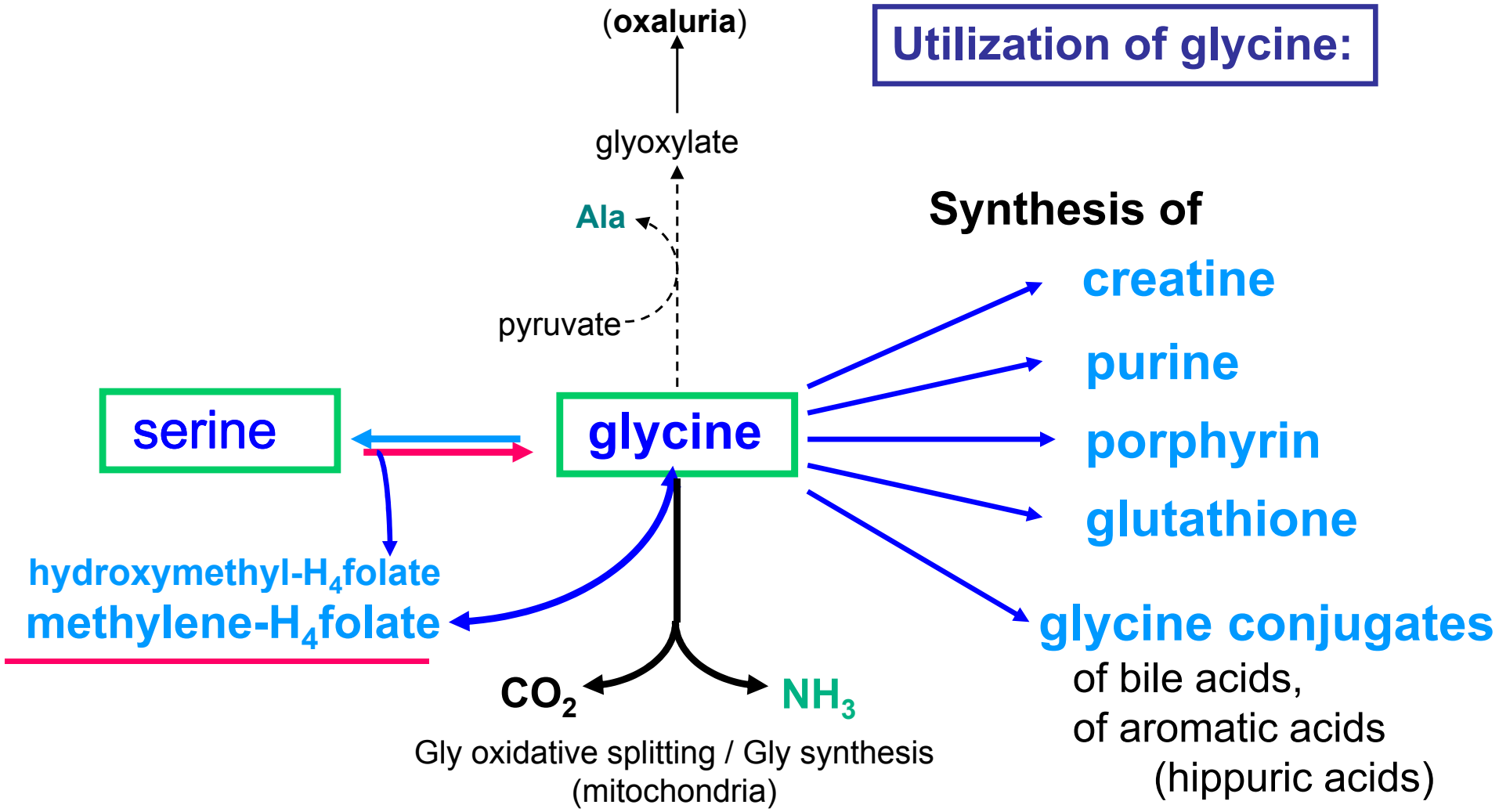
The major pathway of glycine catabolism is **oxidative cleavage of glycine** in mitochondria:




The reaction is reversible and catalyzed by *glycine synthase* and controlled by respiration and energetic charge of the cell. For the synthesis of glycine, **3 molecules of ATP are lost**.

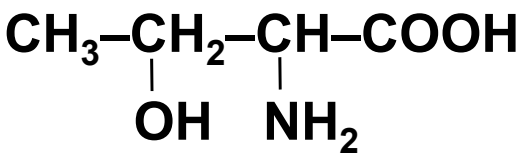
Molecule of glycine is the **substrate required for the syntheses** of several very important compounds, e.g.

purine bases of nucleic acids, porphyrins of haemoproteins, phosphocreatine of skeletal muscles (phosphagen), and tripeptide glutathione (intracellular antioxidant).


(oxaluria)
glyoxylate
Ala
pyruvate
serine
glycine
hydroxymethyl-H4folate
methylene-H4folate
CO2
NH3
Gly oxidative splitting / Gly synthesis
(mitochondria)
Utilization of glycine:
Synthesis of
creatine
purine
porphyrin
glutathione
glycine conjugates
of bile acids,
of aromatic acids
(hippuric acids)

# Threonine

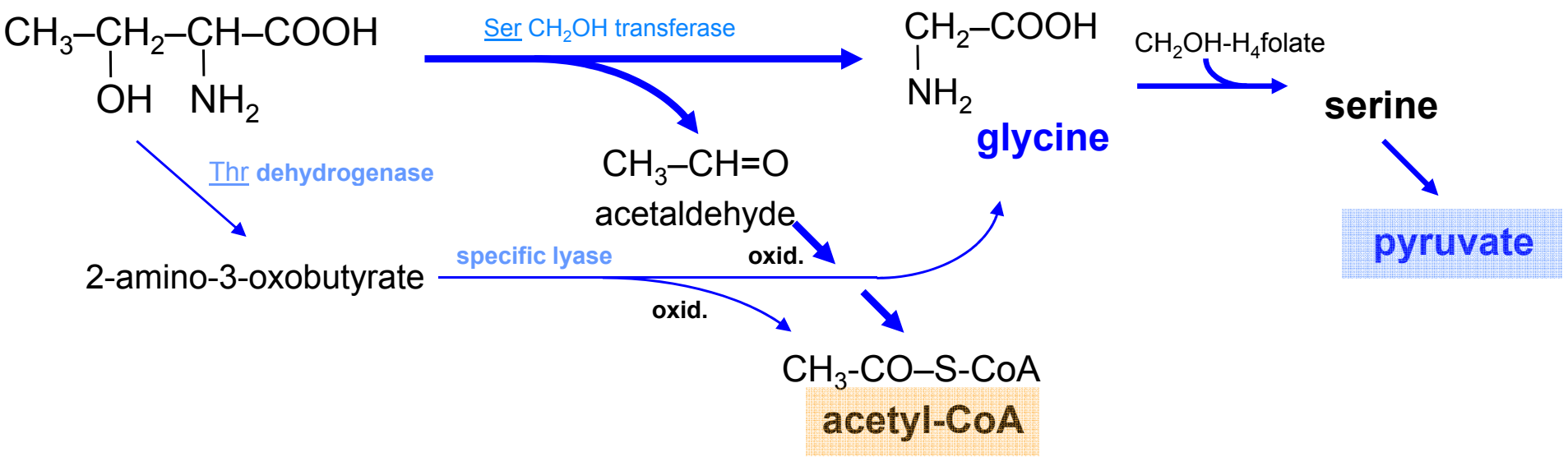
is **essential** and both glucogenic and ketogenic



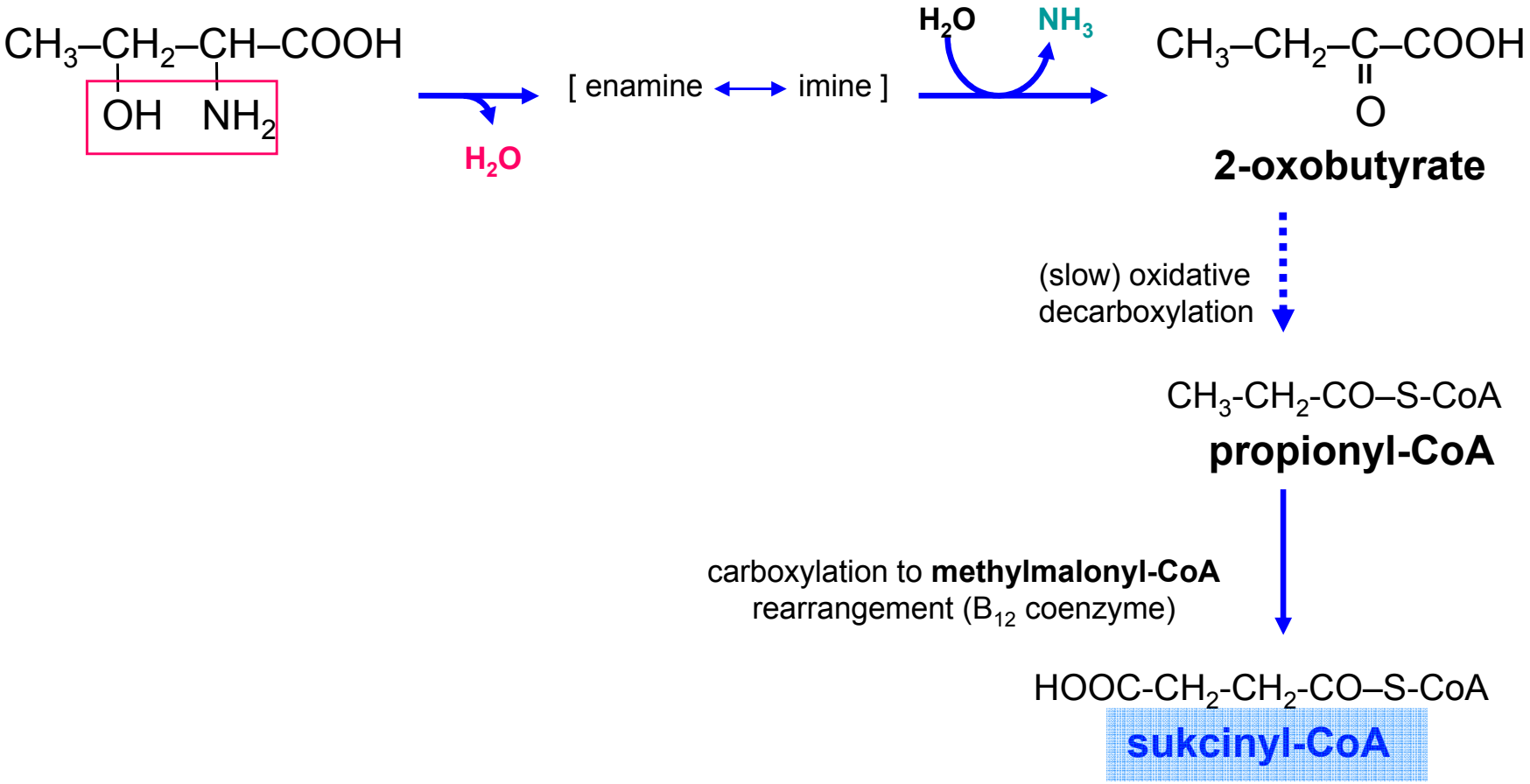

It **does not undergo transamination**

– glucogenic – gives glycine by splitting
or succinyl-CoA (by dehydratation and
and oxid. decarboxylation to propionyl-CoA)
– ketogenic – by splitting to glycine gives acetyl-CoA

## Splitting of threonine to glycine

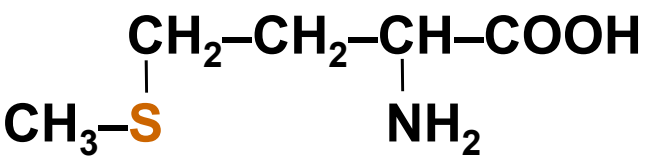


An alternative pathway is
the direct deamination of threonine by dehydration:



# 2 Sulfur containing amino acids

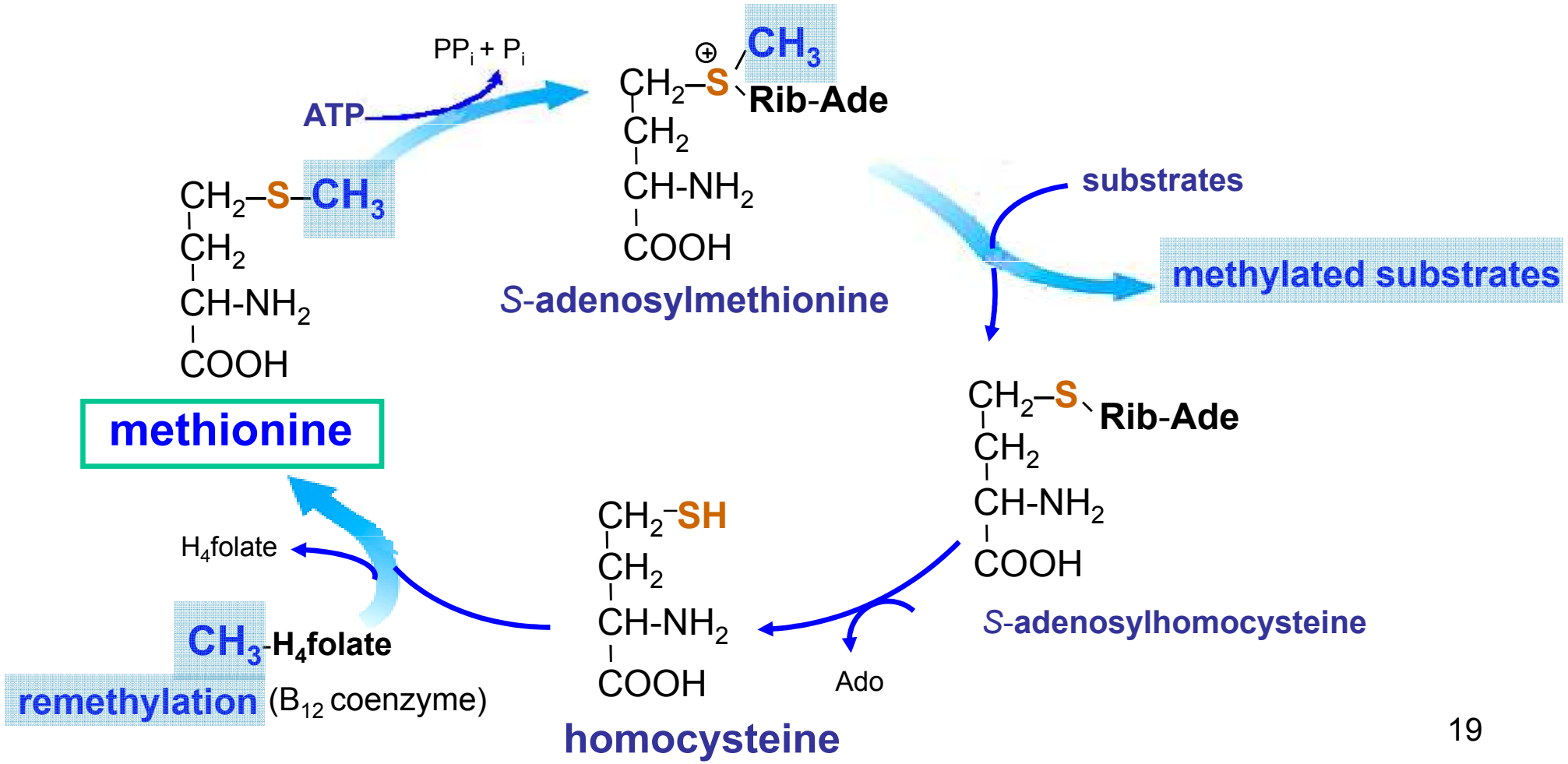
**Methionine**



is **essential** and glucogenic

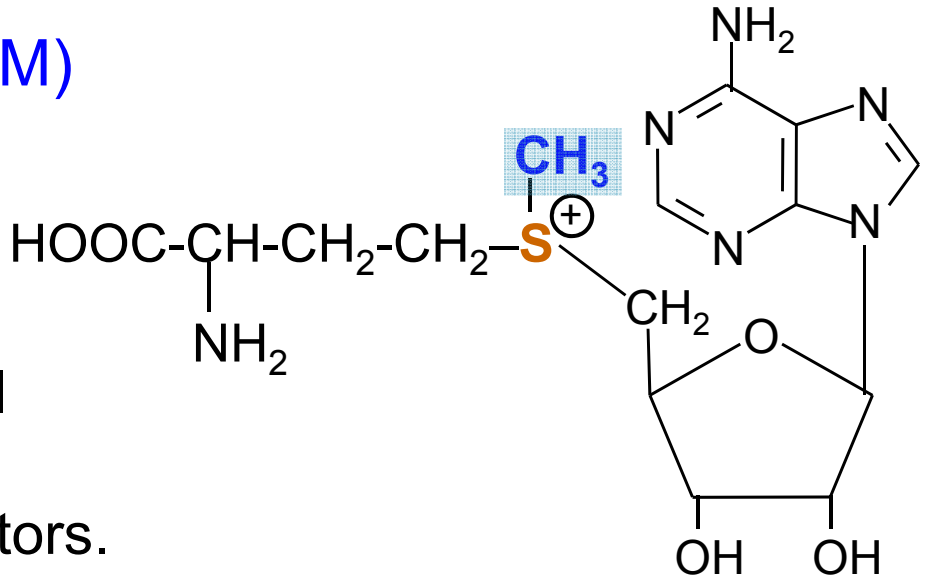
– glucogenic (it yields succinyl-CoA)

**Methionine is a common methyl donor in the cell:**



Activated methionine

**S-adenosylmethionine** (*S*-AM)



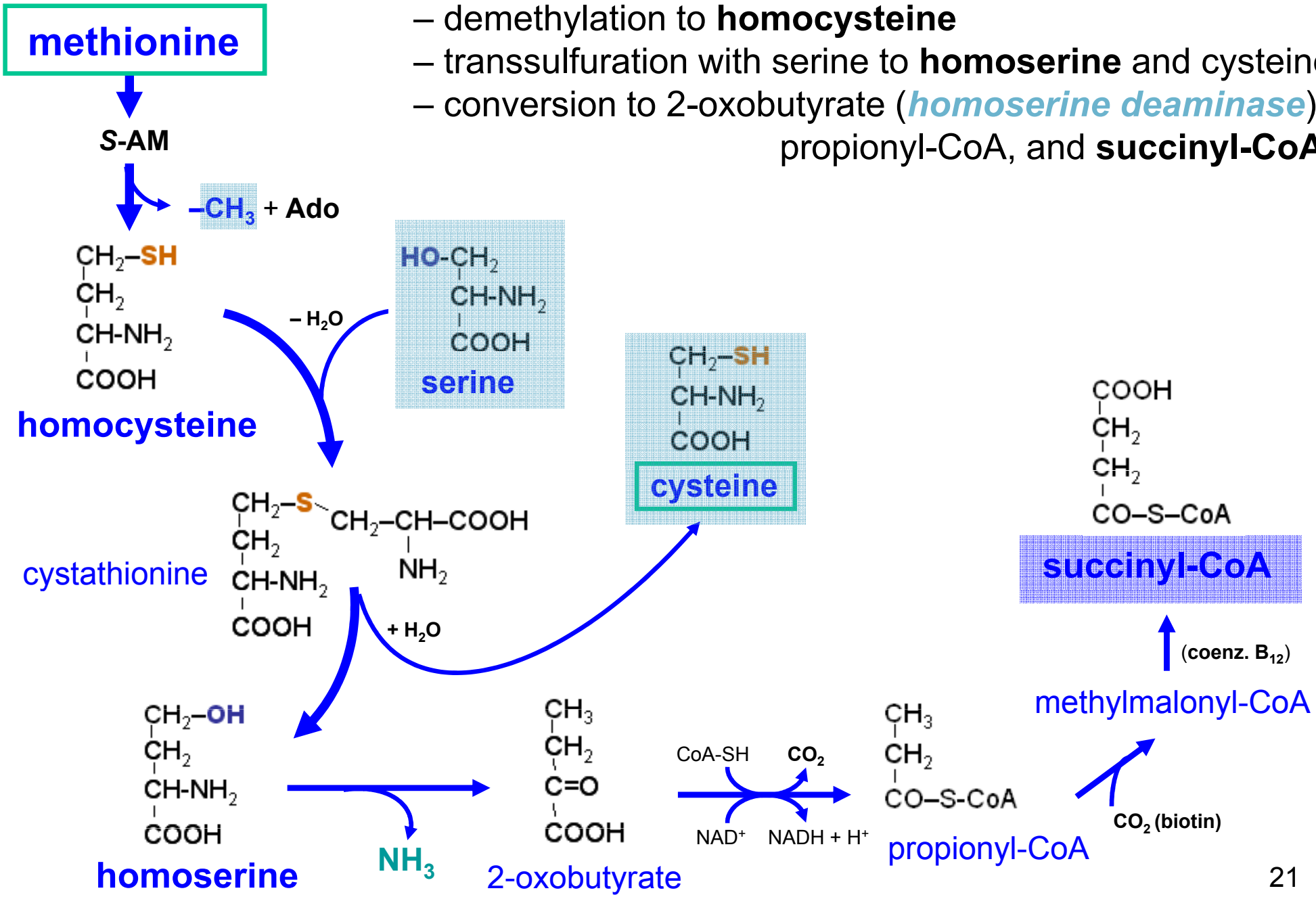

is the **methyl donor**. The methyl group may be transferred from a sulfonium ion to various acceptors.

**Examples:**

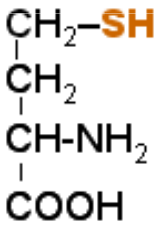
synthesis of choline from phosphatidylethanolamine,
synthesis of creatine (by methylation of guanidinoacetate),
methylation of noradrenaline to adrenaline,
inactivation of catecholamines by catechol-*O*-methyl transferase,
methylation of histones, etc.

# Catabolism of methionine

– demethylation to **homocysteine**
– transsulfuration with serine to **homoserine** and cysteine
– conversion to 2-oxobutyrate (***homoserine deaminase***), propionyl-CoA, and **succinyl-CoA**.



**Homocysteine** is an important intermediate in metabolism of methionine;



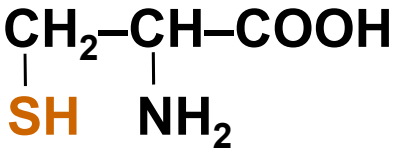

it is readily transformed, either **remethylated to methionine**
(the reaction requires tetrahydrofolate and cobalamin)
or **decomposed to homoserine** by transsulfuration with serine,
(vitamin $B_6$ dependent).

If those mechanisms are not sufficient and the concentration of homocysteine in biological fluids increases, injury of endothelial cells by homocysteine (e.g., high production of reactive oxygen species, lipoperoxidation) and decreased vitality of blood platelets may appear.

At present, high concentration of homocysteine in blood plasma is included among other biochemical markers of cardiovascular diseases – as a **risk factor for atherosclerosis** that is quite independent on the concentration of cholesterol.

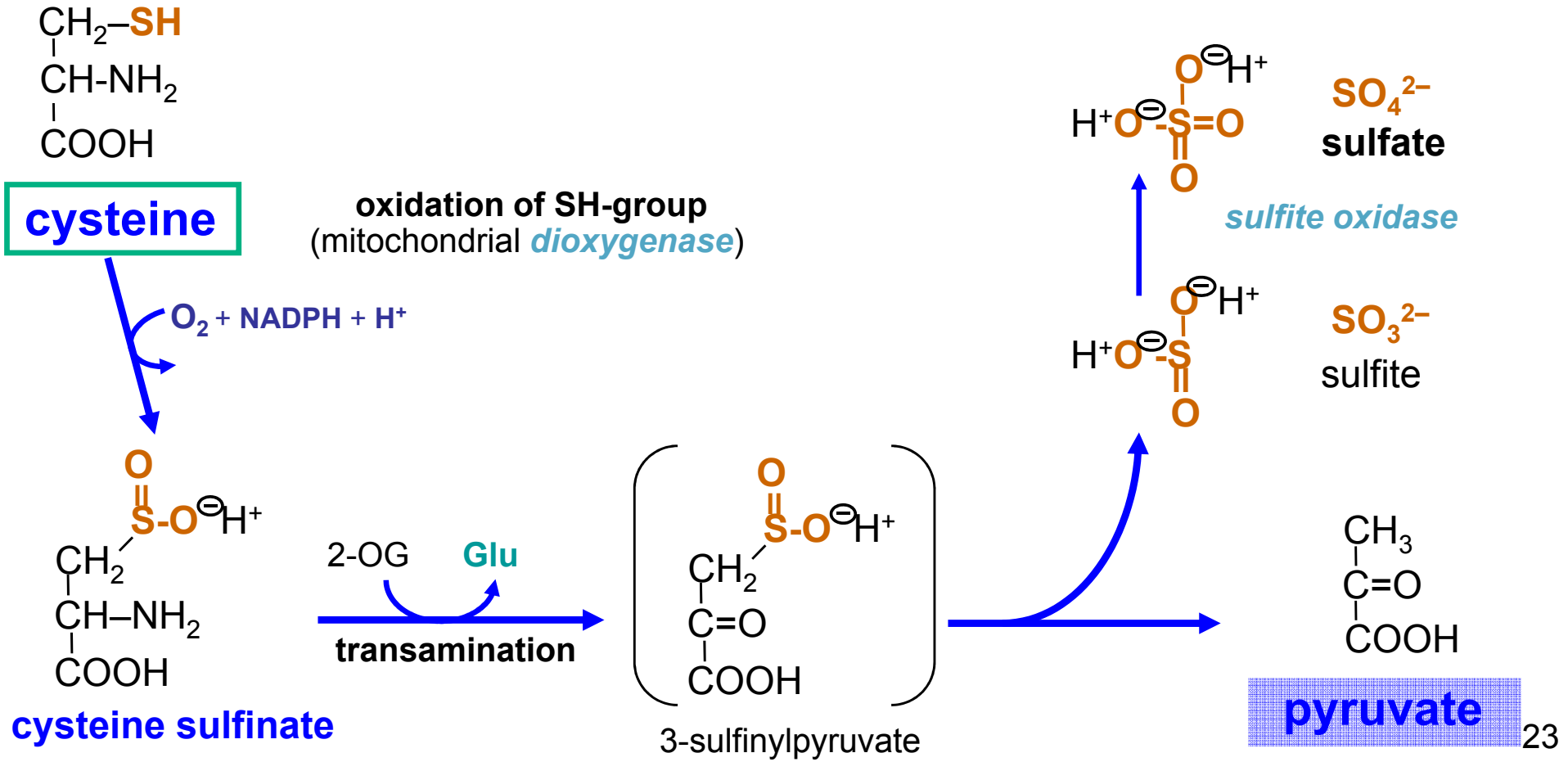
# Cysteine

is nonessential and glucogenic



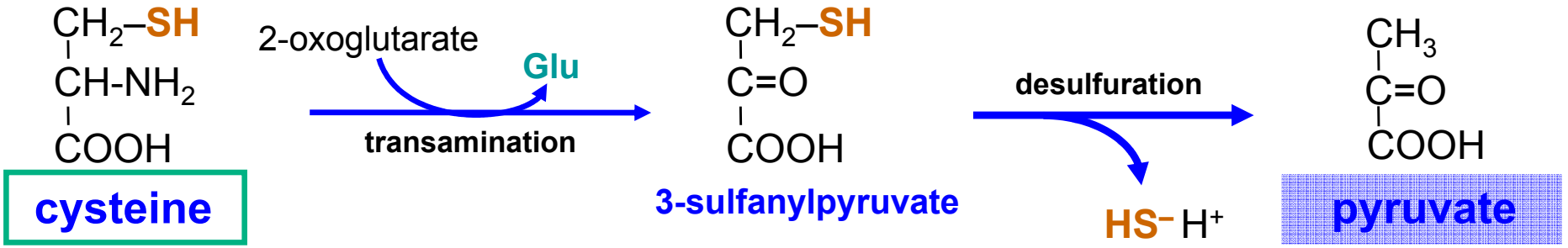
– nonessential – synthesis from serine
(methionine supplies the sulfur atom)
– glucogenic – cysteine is converted into pyruvate
(sulfur atom is released as $SO_3^{2-}$, $HS^-$, or $SCN^-$)

**The major catabolic pathway is the direct oxidation of SH-group:**



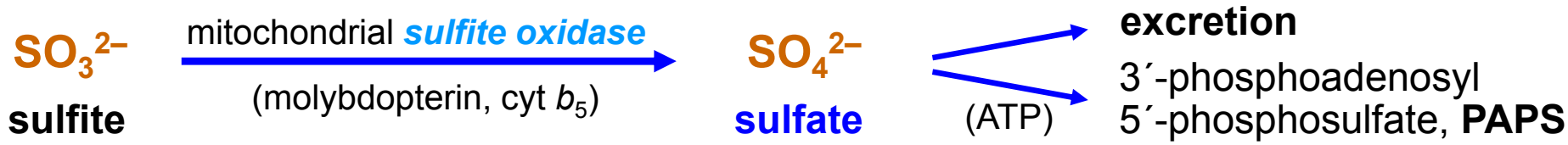
Oxidation of $S^{-II}$ to $S^{IV}$ or $S^{VI}$ (sulfinate, sulfite, sulfate) is a **proton-producing process**, nonvolatile acids are formed from non-ionized groups. The catabolism of sulfur-containing amino acids slightly acidifies the body.

**An alternative catabolic pathway of cysteine is transamination :**



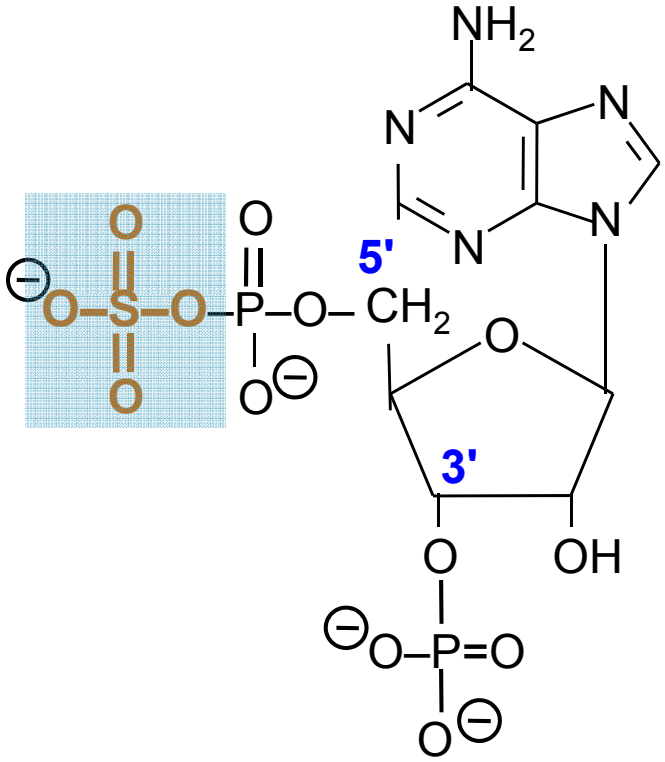

Hydrogen sulfide $HS^-$ ion is mostly oxidized to **sulfite** $SO_3^{2-}$ or, if cyanide ion $CN^-$ is present (e.g. tobacco smokers), hydrogen sulfide gives thiocyanate $SCN^-$.

**Sulfite anion** is oxidized to **sulfate anion**, which is either excreted into the urine (approx. 20 – 30 mmol/d) or utilized for sulfations after activation:



# 3‘-Phosphoadenosyl-5‘-phosphosulfate (PAPS)

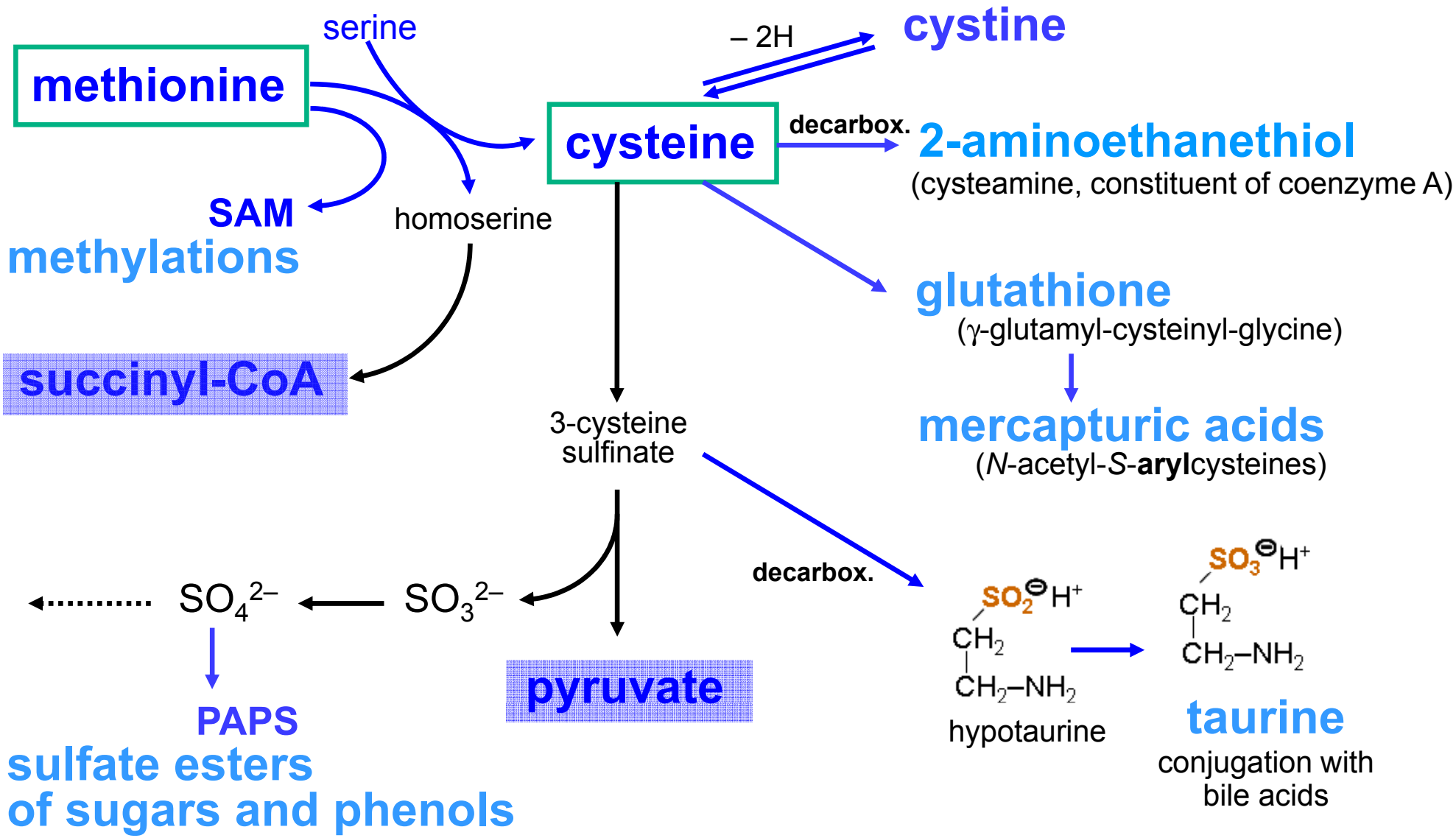
is the mixed anhydride of sulfuric and phosphoric acid called "active sulfate"; it serves as the **sulfate donor** in forming of sulfate esters (or *N*-sulfates).



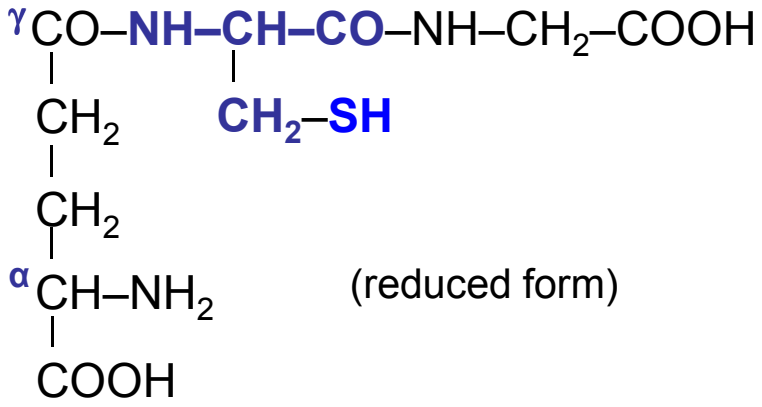

**Examples** of sulfations by means of PAPS:

synthesis of proteoglycans (sulfation of glycosaminoglycans),
sulfation of saccharidic components in glycolipids and glycoproteins,
formation of sulfate esters in inactivation of steroid hormones, catecholamines, and in the phase II of biotransformation of phenols.

# Utilization of methionine and cysteine

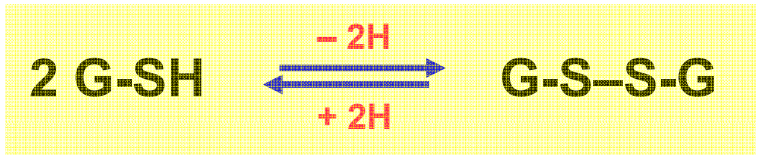


# Glutathione (GSH, γ-glutamyl-**cysteinyl**-glycine)




(reduced form)

is a tripeptide with a free sulfanyl group, required to maintain the normal reduced state in the cell:




**Functions:**

**1** Reduced G-SH confronts oxidative stress,
it **reduces peroxides** (lipid hydroperoxides and hydrogen peroxide) in the reaction catalyzed by a selenoprotein ***glutathione peroxidase***, and (non-enzymatically) **methaemoglobin** ($Fe^{III}$, hemiglobin) to haemoglobin ($Fe^{II}$) and **disulfides** to thiols:

$$\text{L-OOH} + 2\ \text{G-SH} \longrightarrow \text{L-OH} + \text{G-S–S-G} + H_2O$$

$$\text{R-S–S-R} + 2\ \text{G-SH} \longrightarrow 2\ \text{R-SH} + \text{G-S–S-G}$$

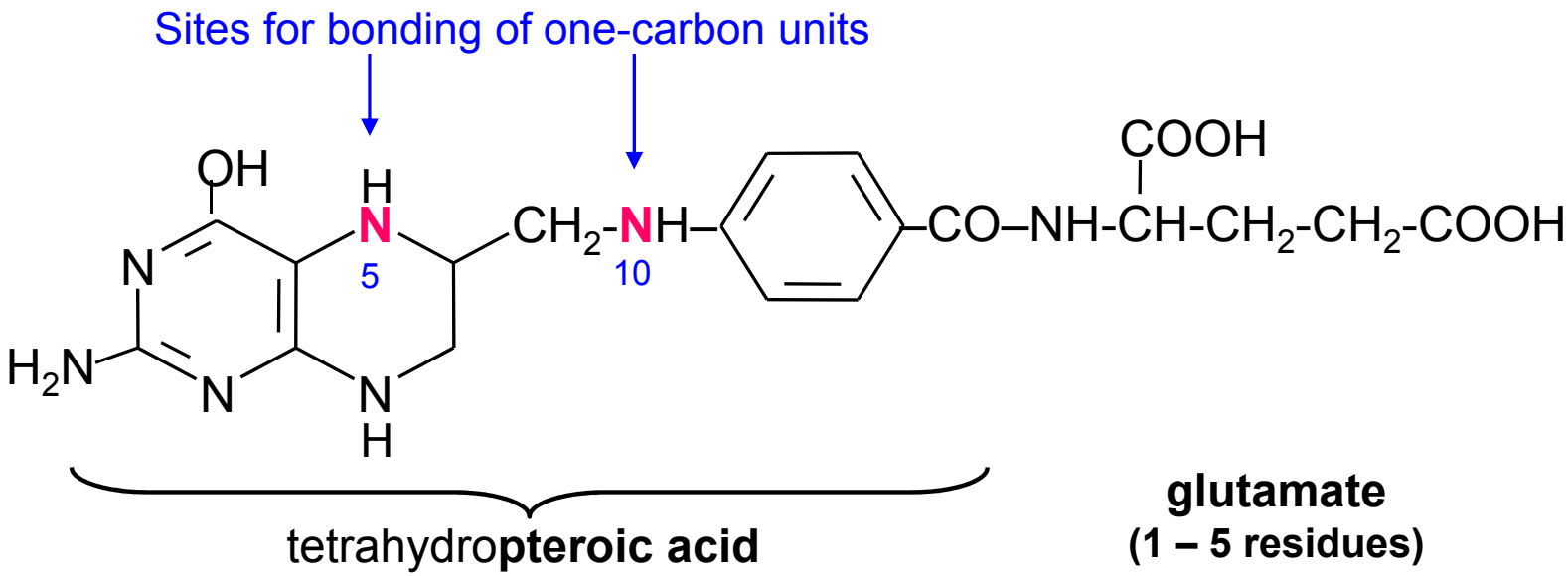
reduced G-SH can be regenerated by ***glutathione reductase*** and NADPH + $H^+$.

**2** Conjugation to lipophilic compounds (detoxification of reactive electrophiles).

**3** Transport of amino acids into cells with concomitant attachment of γ-glutamyl (group translocation, γ-glutamyl cycle).

# 3 Sources of one-carbon groups and utilization of those groups in syntheses

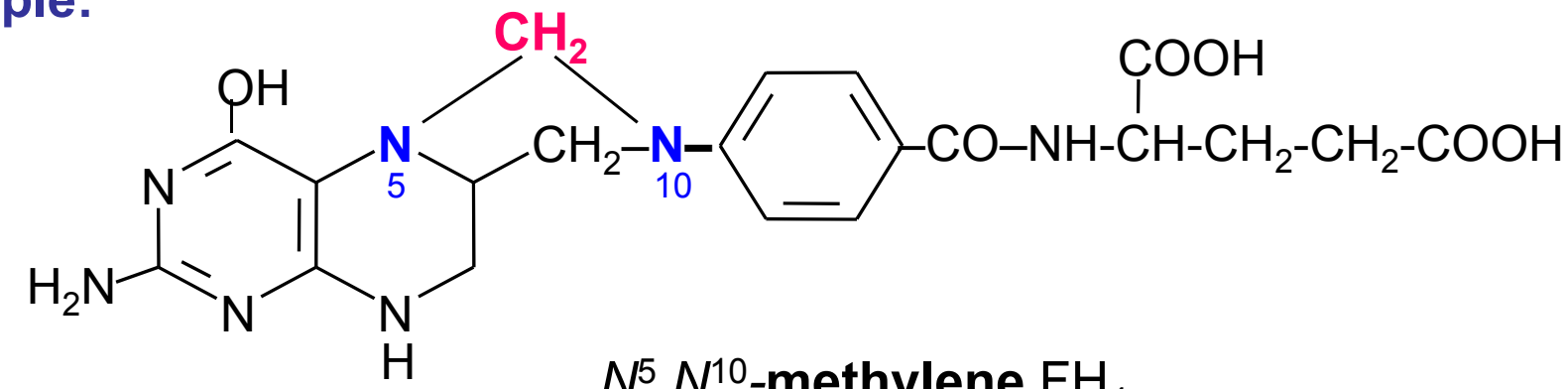
One-carbon groups are transferred by **tetrahydrofolate** (**$H_4$folate, $FH_4$,** tetrahydropteroylglutamate).
Mammals can synthesize the pteridine ring, but they are unable to conjugate it to the other two units. They obtain folate from diets or from microorganisms in their intestinal tracts.



**The one-carbon groups transferred by $H_4$folate exist in three oxidation states:**

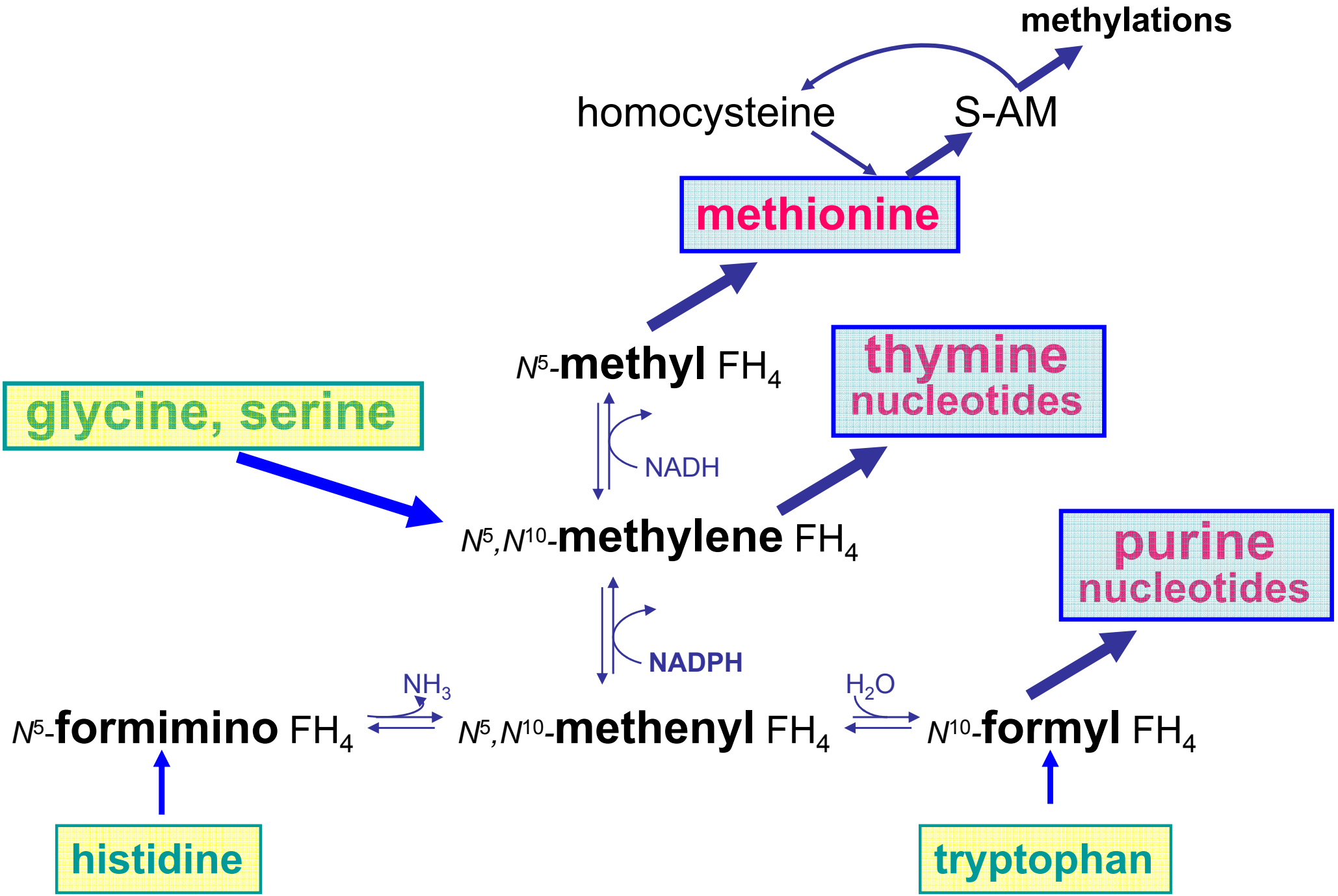
| Oxidation state | Group | |
|---|---|---|
| Most reduced ( = methanol) | $-CH_3$ | Methyl |
| Intermediate ( = formaldehyde) | $-CH_2-$ | Methylene |
| Most oxidized ( = formic acid) | $-CHO$ | Formyl |
| | $-CHNH$ | Formimino |
| | $-CH=$ | Methenyl |

**Example:**




$N^5$,$N^{10}$-**methylene** $FH_4$

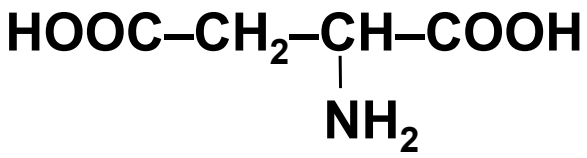
(The fully oxidized one-carbon group is **$CO_2$**, but $CO_2$ is **transferred by biotin**, not by $H_4$folate.)


methylations
homocysteine
S-AM
methionine
$N^5$-methyl $FH_4$
thymine
nucleotides
glycine, serine
NADH
$N^5,N^{10}$-methylene $FH_4$
purine
nucleotides
NADPH
$NH_3$
$H_2O$
$N^5$-formimino $FH_4$
$N^5,N^{10}$-methenyl $FH_4$
$N^{10}$-formyl $FH_4$
histidine
tryptophan

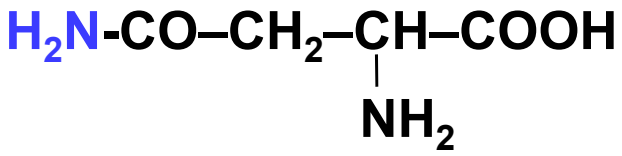
# 4 Aspartic acid and asparagine

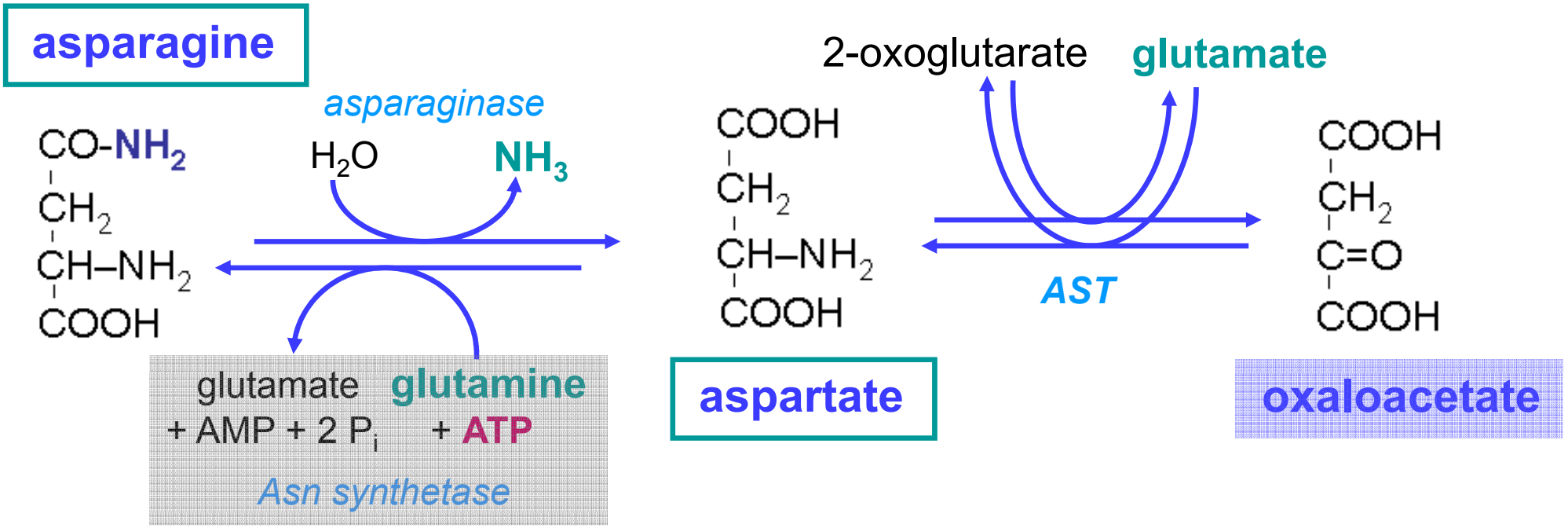
**Aspartate** is nonessential and glucogenic

– it gives oxaloacetate by transamination

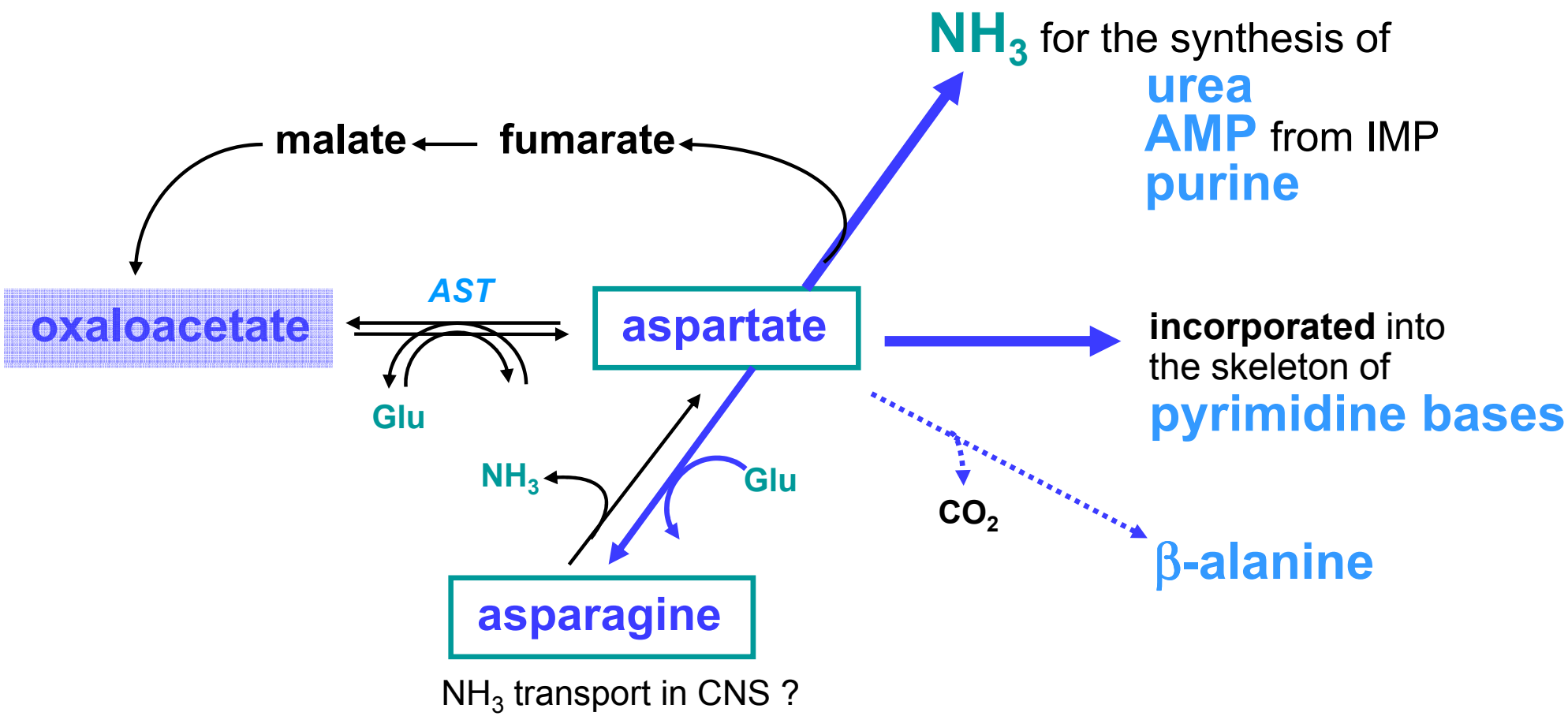



**Asparagine** is the amide of aspartate



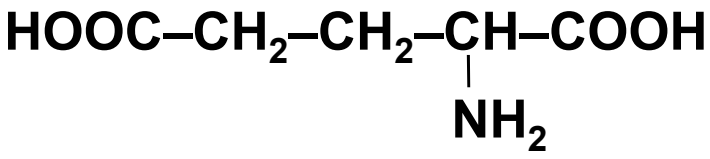



# Utilization of aspartate and asparagine



# 5 Glutamic acid, glutamine, and the relationship to proline, arginine, and histidine

## Glutamate

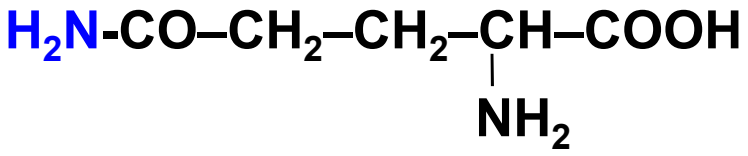



is nonessential and glucogenic

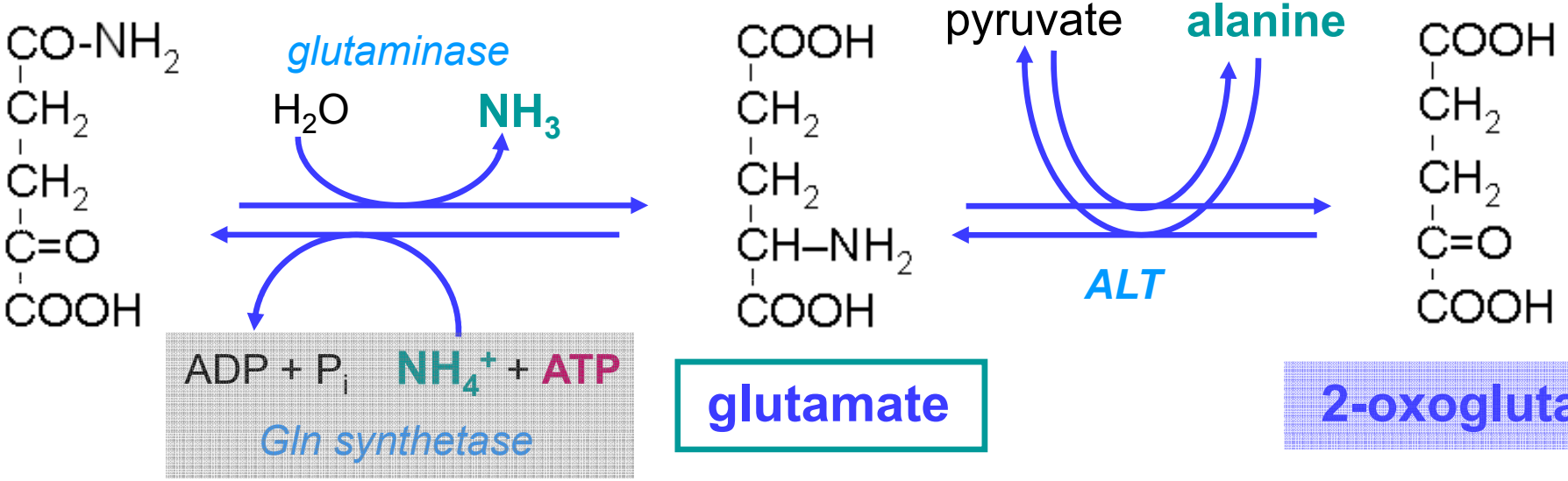
– it gives oxaloacetate readily by oxidative deamination or transamination

## Glutamine

is an amide of glutamate




**glutamine**

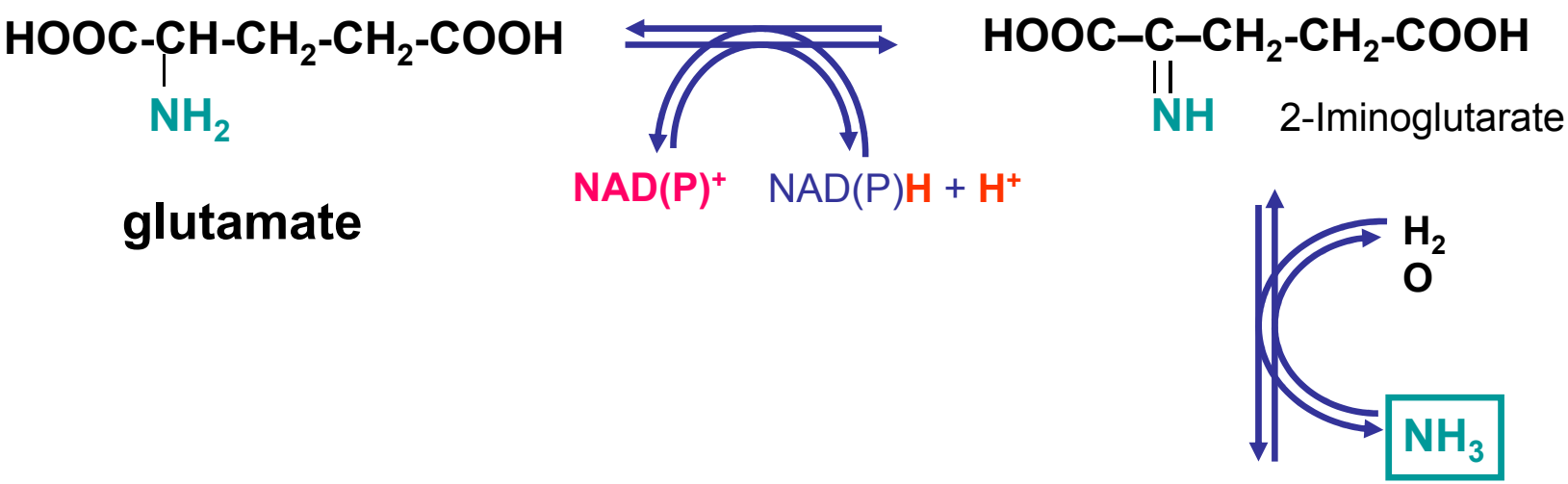



**glutamate**

**2-oxoglutarate**

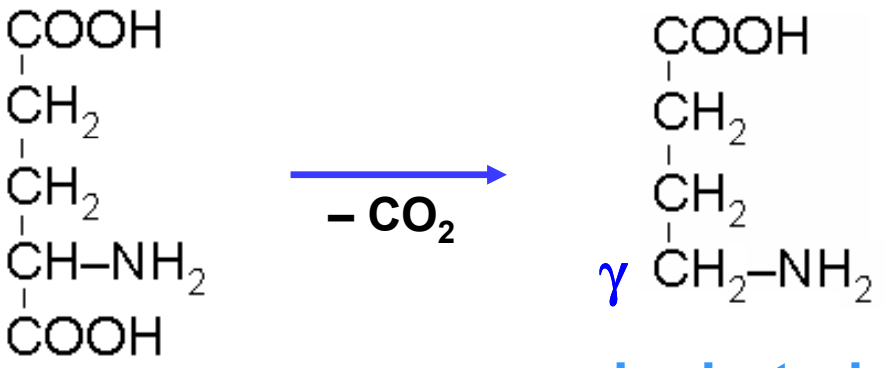
# Direct oxidative deamination of glutamate by dehydrogenation

The reaction is catalysed by the **mitochondrial** enzyme ***glutamate dehydrogenase*** (***GLD***). It requires either $NAD^+$ or $NADP^+$ as coenzyme, and its activity in mitochondria is high.




The equilibrium favours glutamate synthesis, but it is pulled in the direction od deamination by the continuous removal of $NH_3/NH_4^+$.

## Decarboxylation of glutamate (very active in brain)

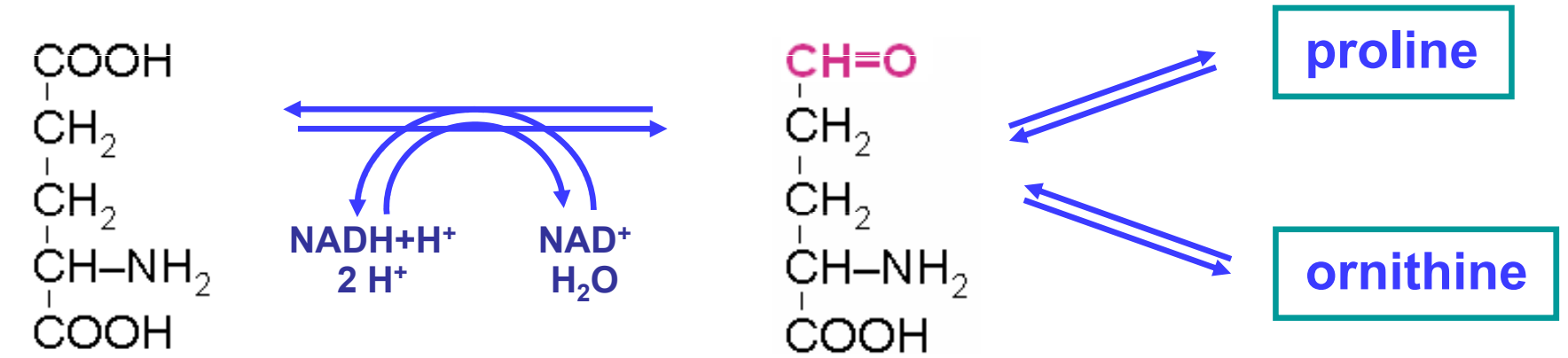



**glutamate**

**γ-aminobutyric acid (GABA)**

an inhibitory neurotransmitter in CNS

## Reversible reduction of glutamate

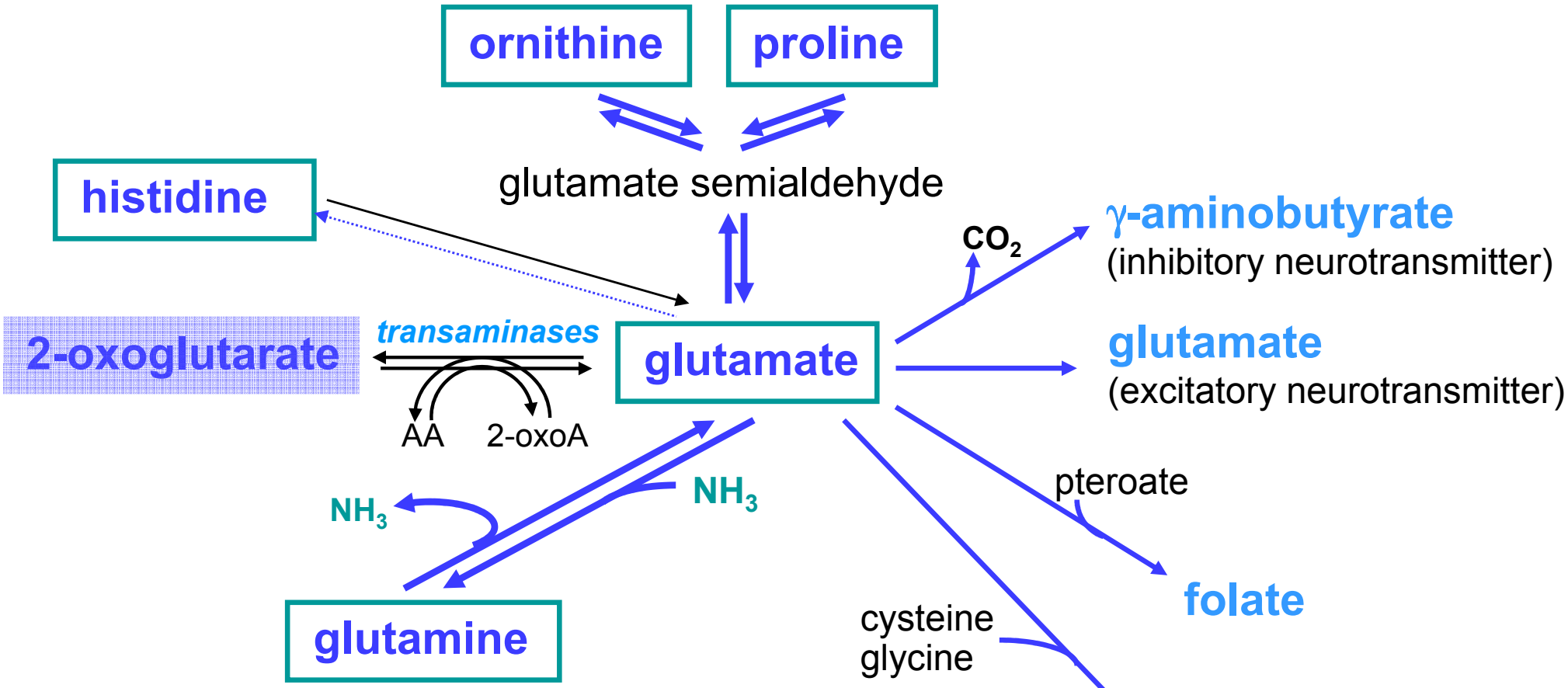



**glutamate**

**glutamate 5-semialdehyde**

– **intermediate** in the synthesis and degradation of **proline** and **arginine**

# Utilization of glutamate and glutamine




**transport** of $NH_3$ to the liver and kidney

**donor** of $NH_3$ for the syntheses of

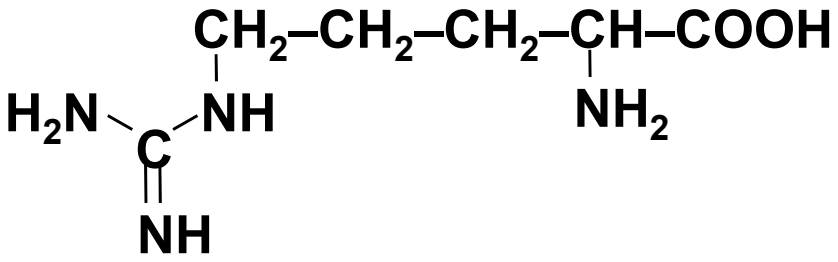
carbamoyl phosphate

purine

amino sugars

Glutamate is widely used as a **food additive** to enhance flavour of dishes, particularly in Chinese cookery in high amounts.
Excess in the diet (1 – 5 g of glutamate in one dose, e.g. in the form of "Von-Ton“ soup) can cause unpleasant feelings in sensitive persons – the **Chinese restaurant syndrome**.

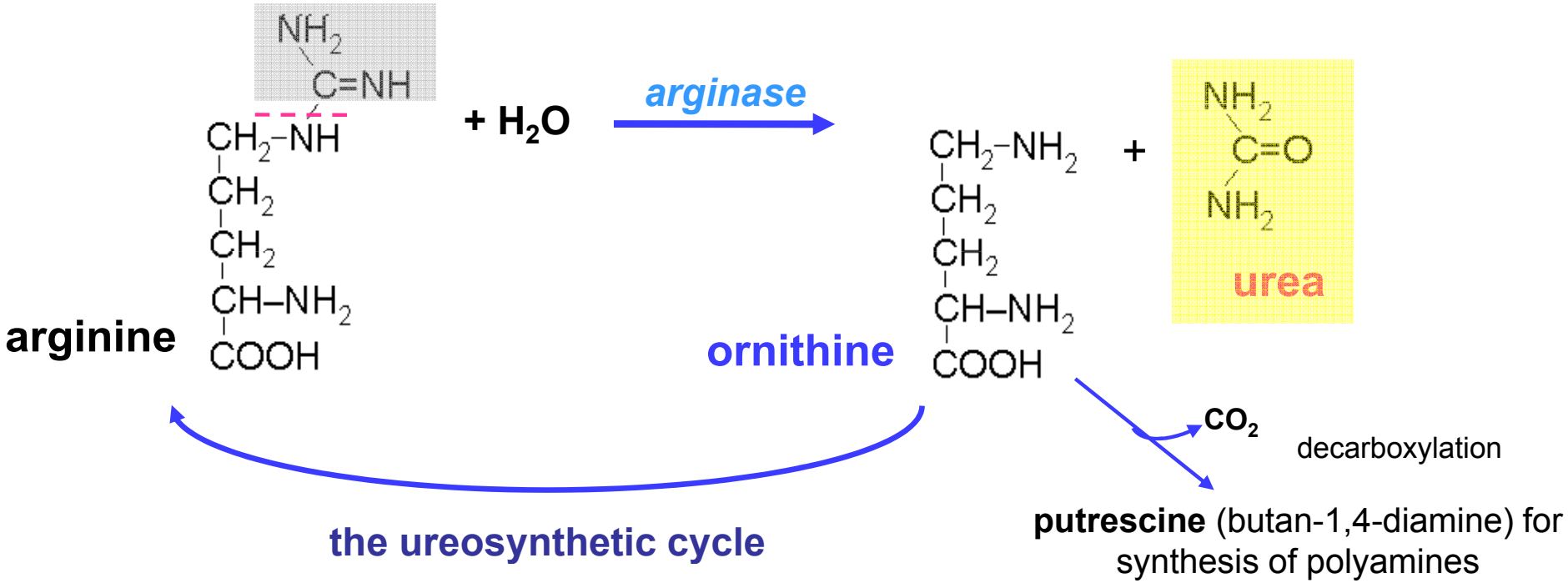
# Arginine



is <u>nonessential</u> and <u>glucogenic</u>

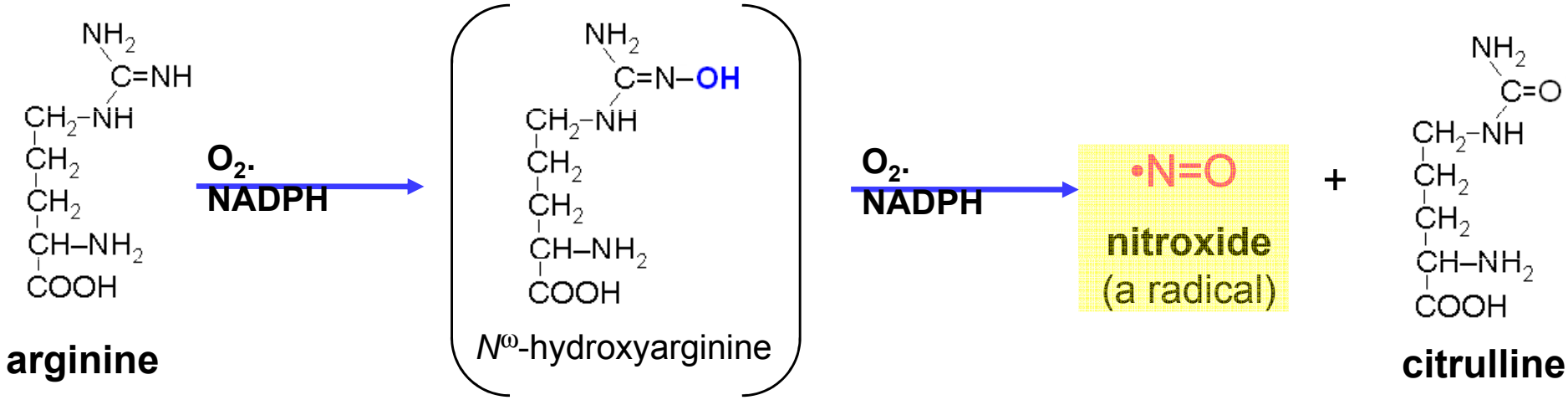
- nonessential in adult man (required in the diet during the growth)
- degraded to 2-oxoglutarate

**In the liver**, arginine is hydrolyzed to ornithine and urea. Ornithine serves as the substrate for ureosynthetic cycle:



After hydrolysis of arginine to ornithine,
**ornithine is degraded** by **transamination of the 5-amino group** to glutamate 5-semialdehyde that gives glutamate and **2-oxoglutarate**.

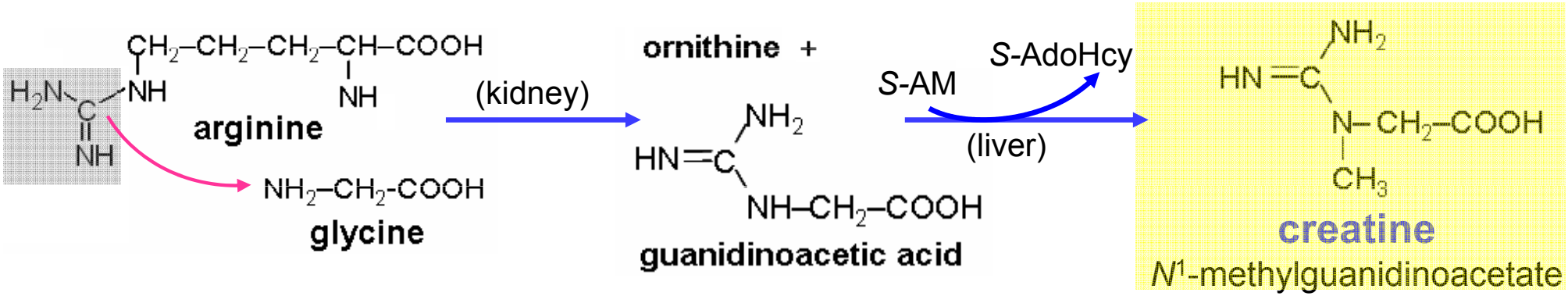
## Nitroxide (nitrogen monoxide, NO) originates from arginine:



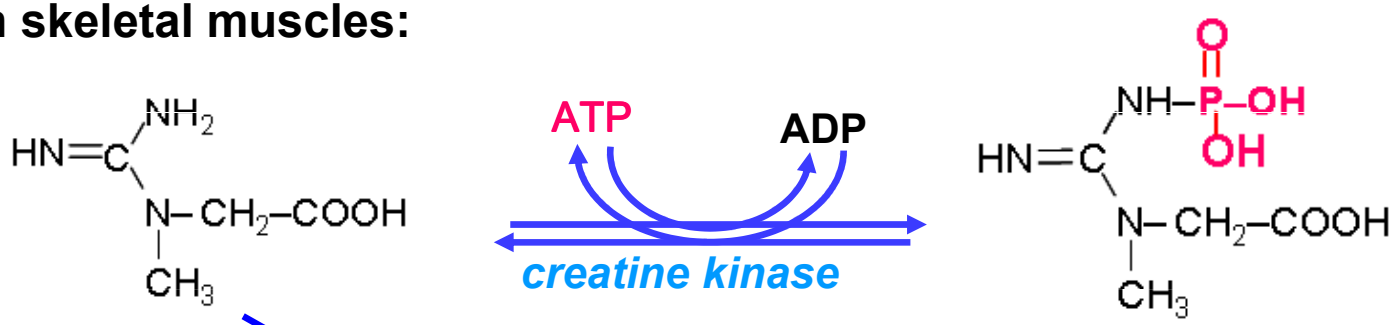

The reaction is a five-electron oxidation catalyzed by ***nitroxide synthase*** (**NOS**), employing five redox cofactors (NADPH, FAD, FMN, cytochrome, $H_4$biopterin). There are three isoenzymes of NOS: **endothelial** NOS responsible for vasodilation and inhibition of platelet aggregation, **neuronal** NOS modulation events on synapses (both are $Ca^{2+}$-dependent), and NOS in **phagocytes** (NO gives bactericidal peroxynitrite $ONOO^-$).

# Synthesis of creatine

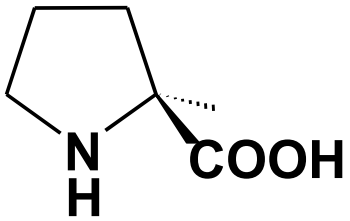
Arginine is the **donor of amidino group** for the synthesis of creatine:




**Creatine in skeletal muscles:**

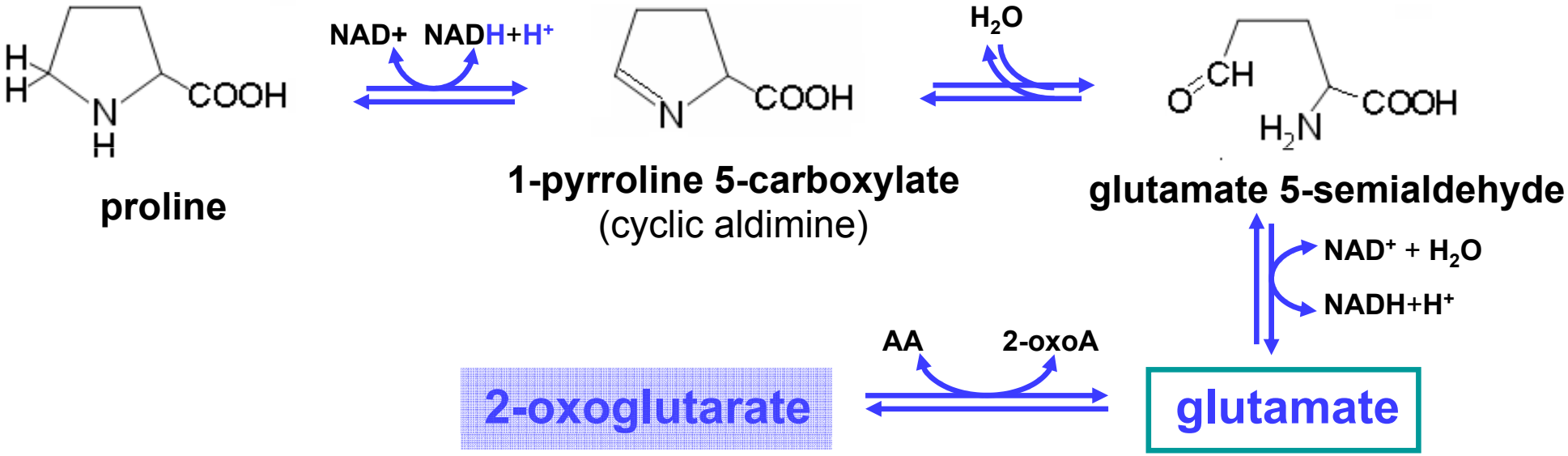


# Proline (pyrrolidine-2-carboxylic acid)

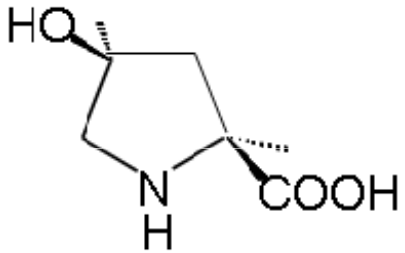



is nonessential and glucogenic

– nonessential – originates from glutamate
– glucogenic – it gives 2-oxoglutarate

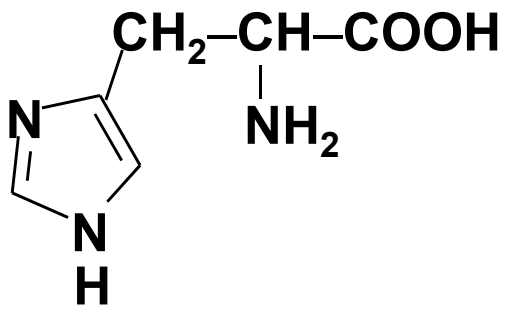



## 4-Hydroxyproline




occurs only in collagen, and is formed by posttranslational hydroxylation of prolyl residues in procollagen polypeptide chains. Similarly to proline, 4-hydroxyproline is degraded to 4-hydroxyglutamate, which is cleft to **pyruvate** and **glyoxylate**.

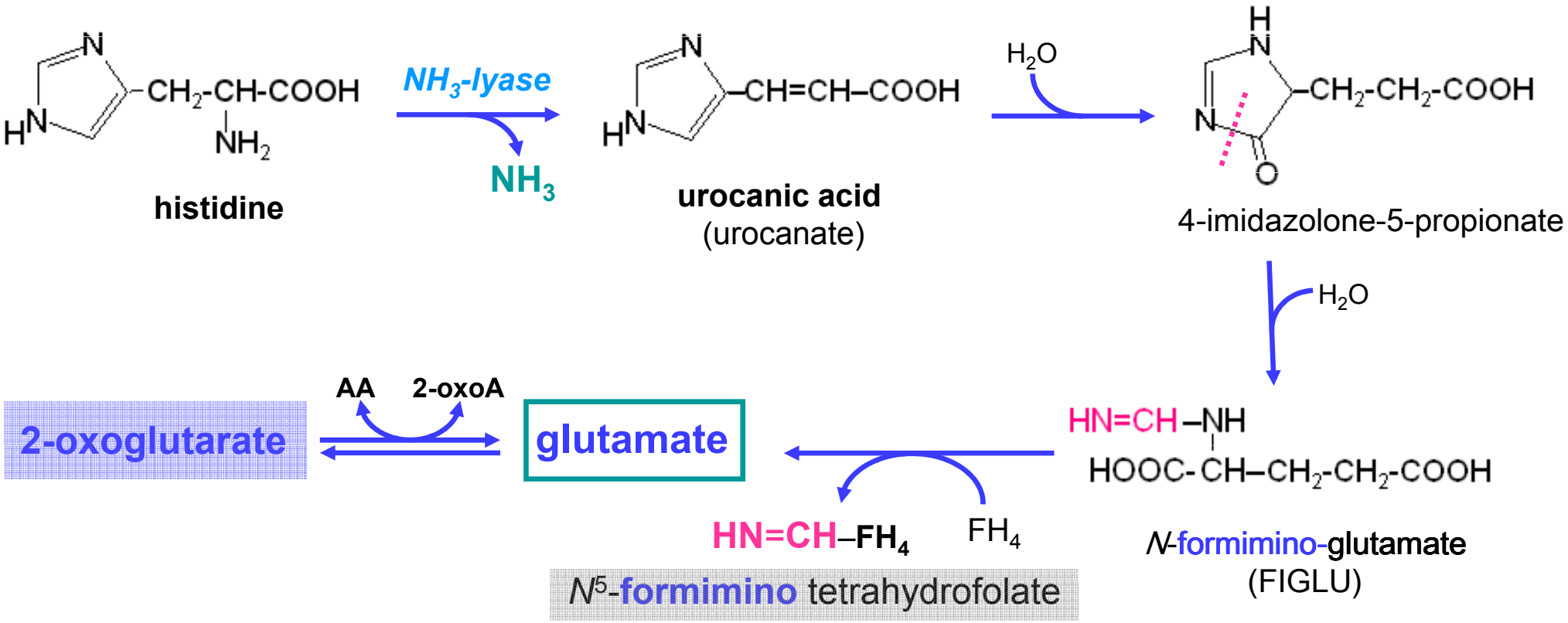
# Histidine



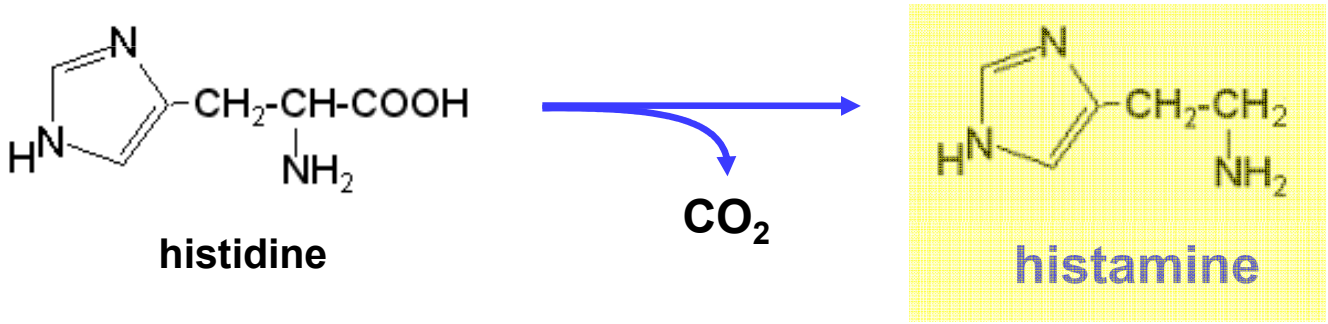

is nonessential and glucogenic

– nonessential for adults (essential for children)
– glucogenic - it gives glutamate and 2-oxoglutarate

Histidine mostly **does not undergo transamination**, it is deaminated **directly by elimination** (desaturation):



**Histamine is the product of histidine decarboxylation** catalyzed by specific *histidine decarboxylase*:



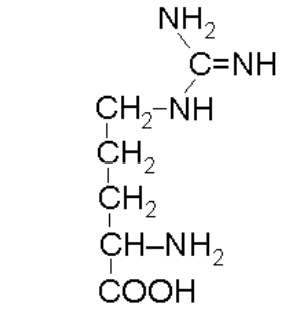

Histamine is a biogenic amine stored within granules of **basophils and mast cells** (more than 90 % body stores) and within synaptosomes of certain CNS neurons.

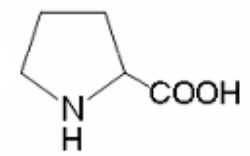
When released, histamine induces complex physiological and pathological effects, including **immunological reactions** (symptoms of allergic conditions of the skin and airways), **gastric acid secretion**, smooth muscle contractions (e.g. **bronchoconstriction**), and profound **vasodilatation**. Histamine exerts its action via at least four distinct histamine receptor subtypes.

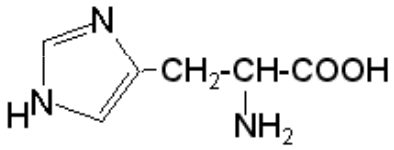
Released histamine is metabolized by oxidation (to imidazolylacetic acid) or methylation (to *tele-N*-methylhistamine and *tele-N*-methylimidazolylacetic acid).

**Antihistaminics** – drugs which antagonize the effects of histamine.

# Amino acids metabolized to 2-oxoglutarate – relationships:




arginine

urea

proline

histidine

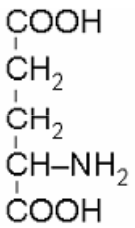
ornithine

1-pyrroline-5-carboxylate

urocanate

glutamate semialdehyde

*N*-formiminoglutamate




glutamate

2-oxoA

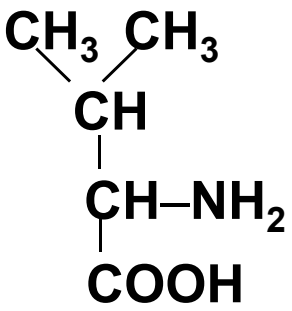
AA

2-oxoglutarate

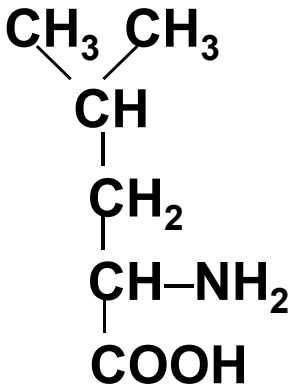
glutamine

# 6 Branched-chain amino acids

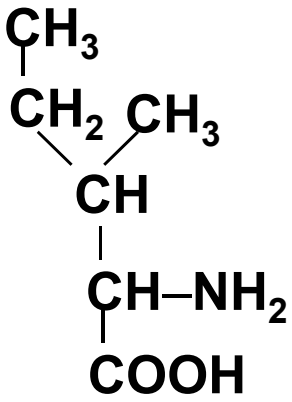
**Valine**



**Leucine**



**Isoleucine**



are all <u>essential</u>, their final metabolites are different:

valine is <u>glucogenic</u>,

leucine is <u>ketogenic</u>,

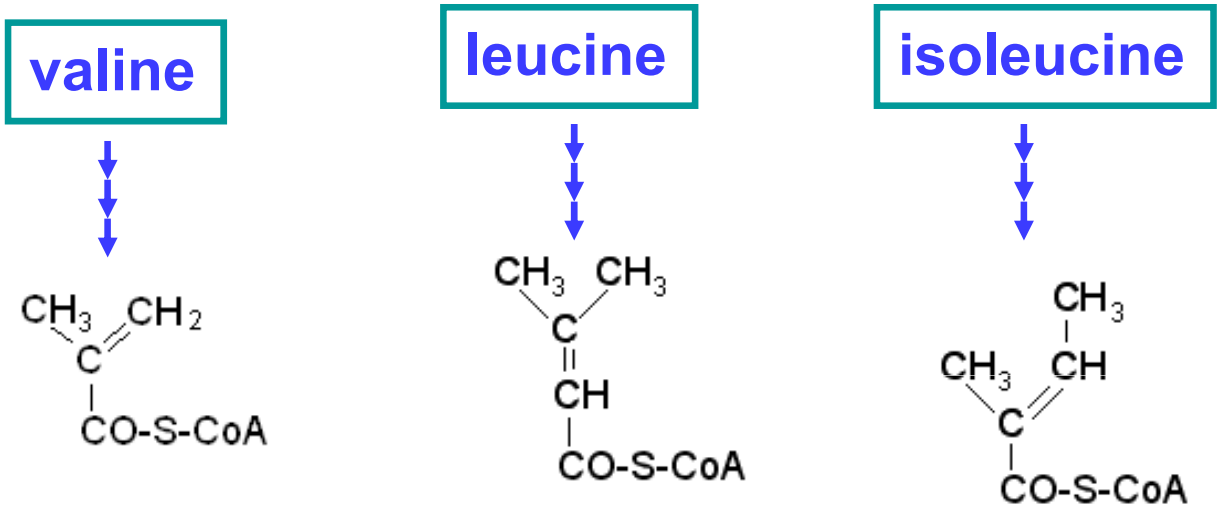
isoleucine <u>both gluco- and ketogenic</u>.

These amino acids are taken up from the blood predominantly by skeletal muscles and their catabolism (transamination) begins there.

The **three initial catabolic reactions are common** to all three branched-chain amino acids:

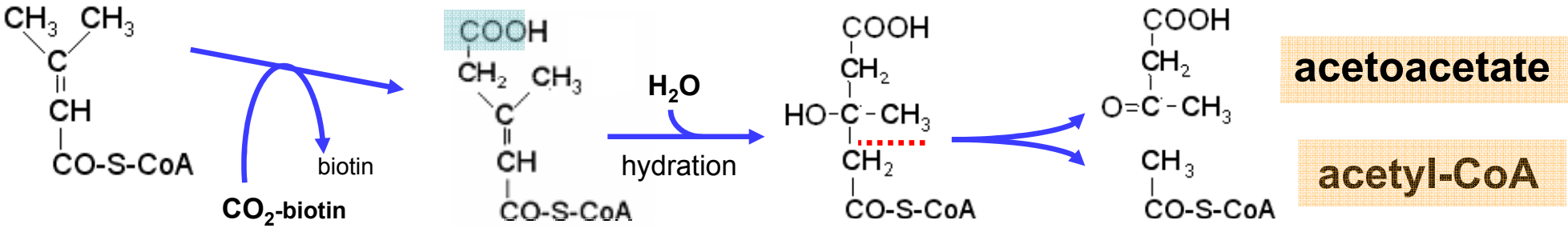
- **transamination** to corresponding **2-oxoacids**,
- **oxidative decarboxylation** catalyzed by 2-oxoacid dehydrogenase producing corresponding **acyl-CoA thioesters**, and
- the **second dehydrogenation** between carbons α and β catalyzed by flavin dehydrogenase resulting in corresponding **2-alkenoyl-CoA thioesters**:

The **resulting 2-alkenoyl-CoAs** after three initial reactions:

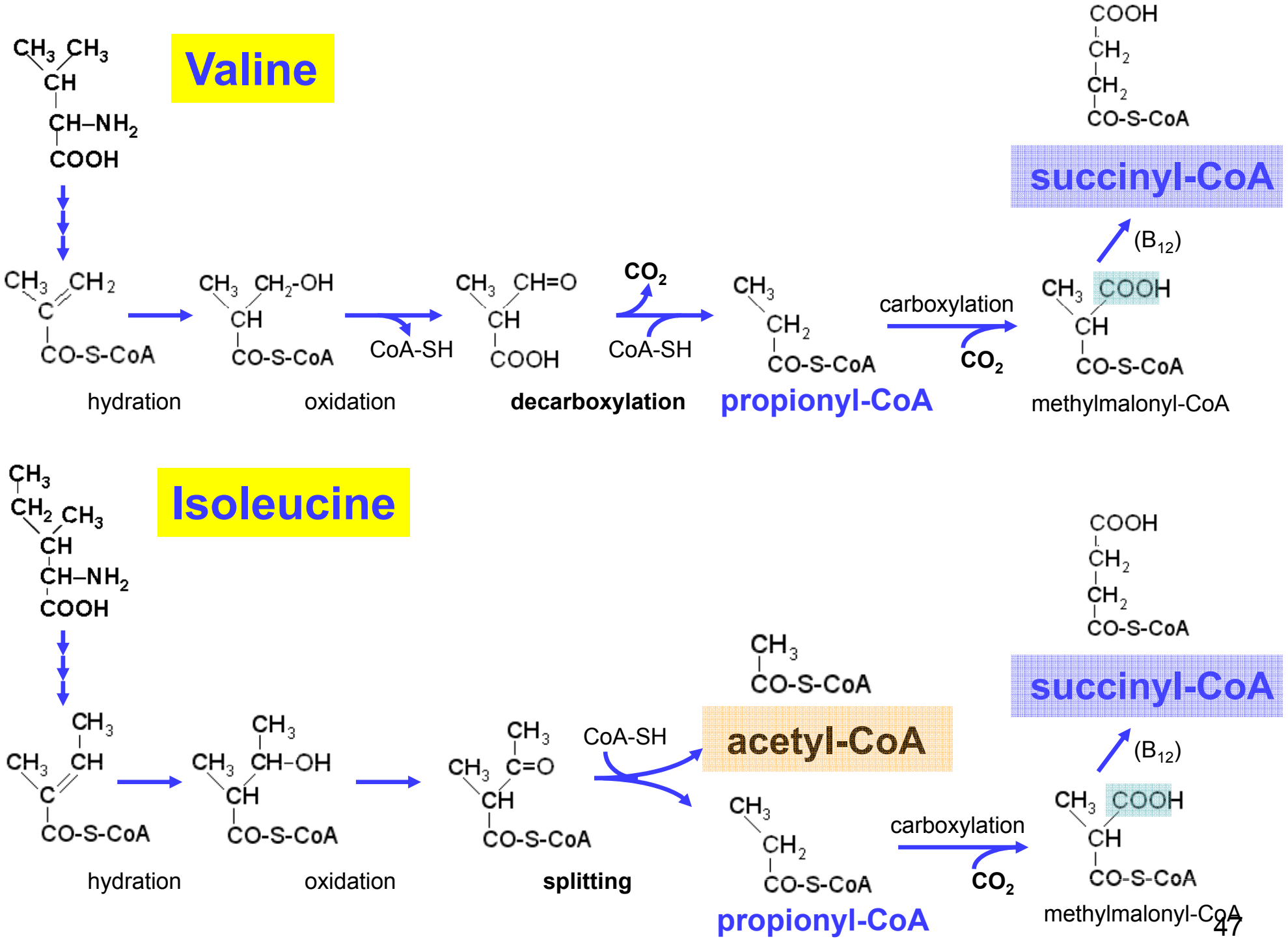



The following reactions differ (expected addition of water, hydration, occurs as the next reaction only in the case of valine and isoleucine).

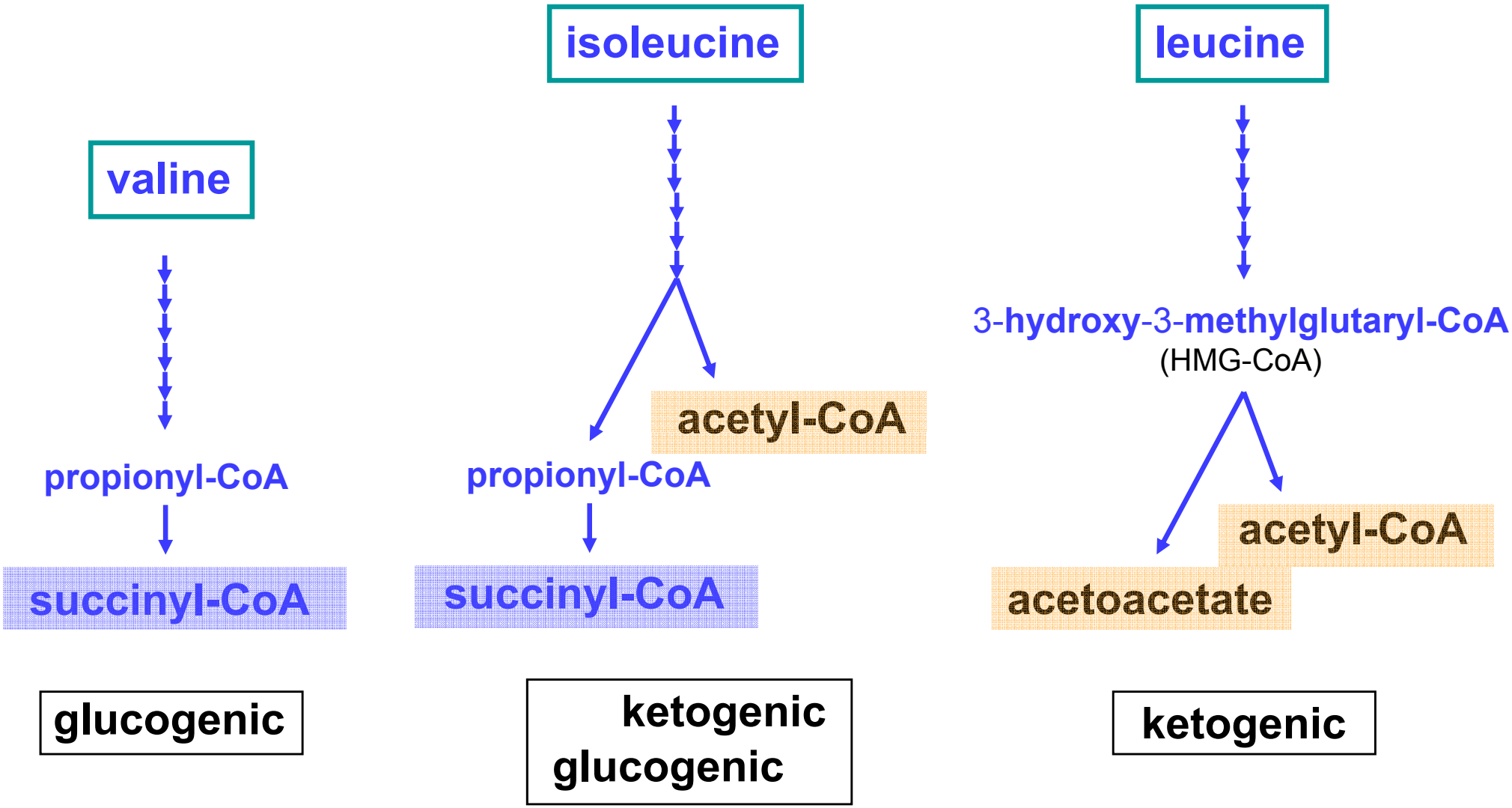
**Leucine** is <u>ketogenic</u>. The alkenoyl-CoA is carboxylated ($CO_2$ donor is carboxy-biotin) and the product hydrated to HMG-CoA that splits to free acetoacetate and acetyl CoA:.




3-**hydroxy**-3-**methylglutaryl-CoA**
(HMG-CoA)

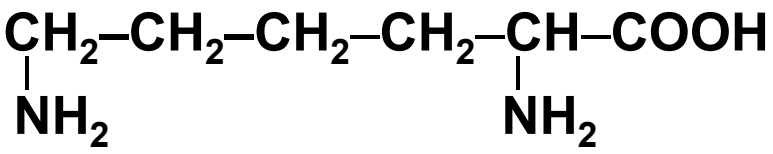

Valine
succinyl-CoA
(B12)
CO2
CoA-SH
CoA-SH
carboxylation
CO2
hydration
oxidation
decarboxylation
propionyl-CoA
methylmalonyl-CoA
Isoleucine
succinyl-CoA
(B12)
CoA-SH
acetyl-CoA
carboxylation
CO2
hydration
oxidation
splitting
propionyl-CoA
methylmalonyl-CoA

## Branched-chain amino acids – summary:

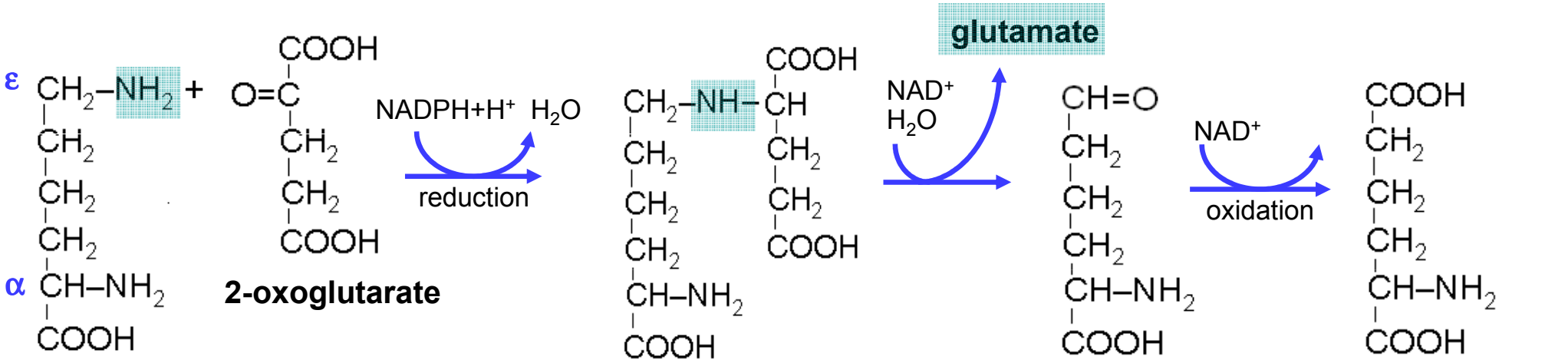


# 7 Lysine

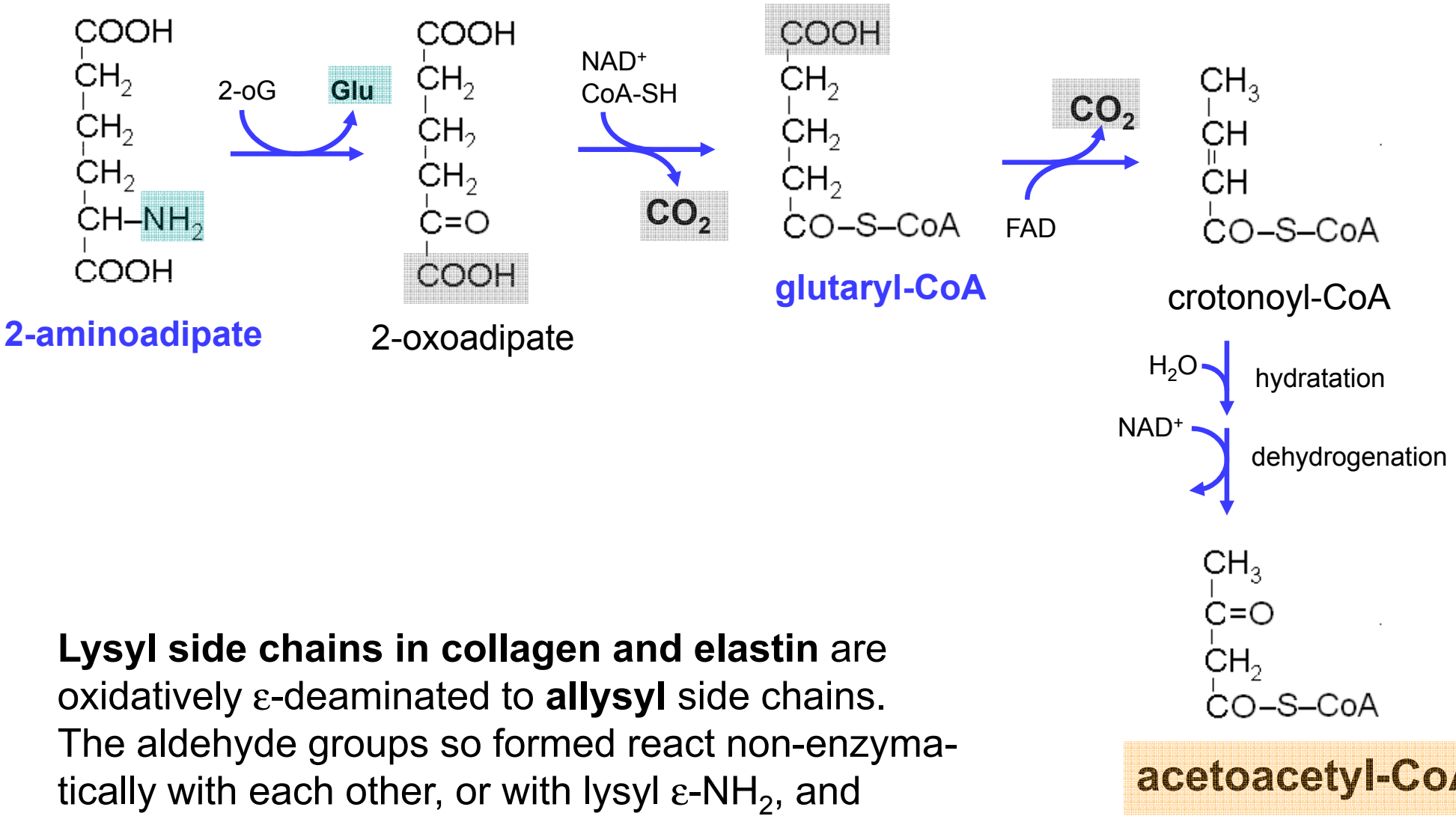
is essential and ketogenic
– it gives acetoacetyl-CoA



Lysine **does not undergo transamination**.
Primarily, **ε-deamination** occurs through the formation of saccharopine:

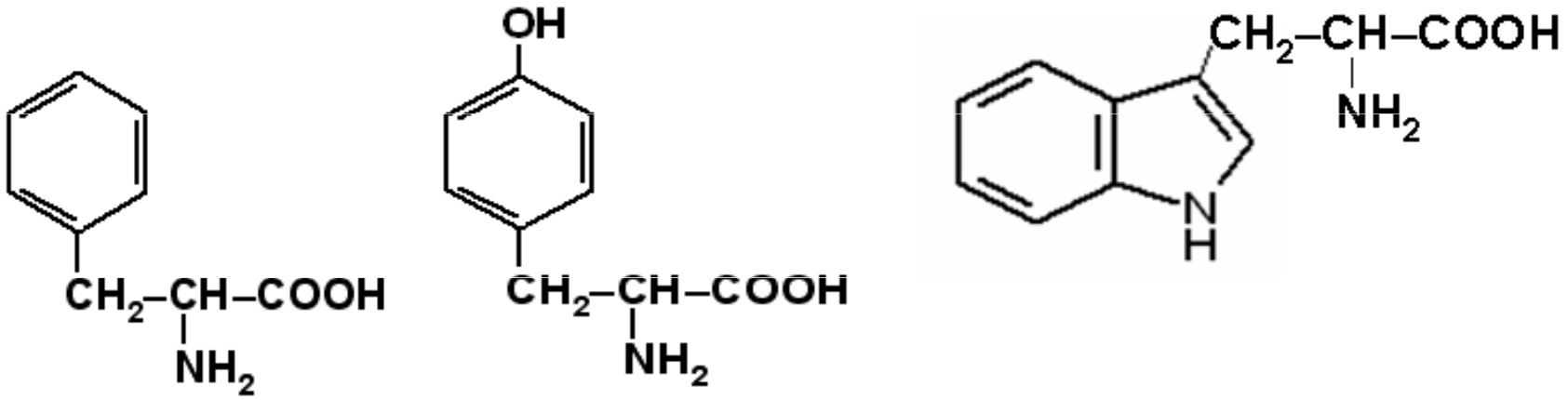



Transamination of α-amino group in 2-aminoadipate follows:




**Lysyl side chains in collagen and elastin** are oxidatively ε-deaminated to **allysyl** side chains. The aldehyde groups so formed react non-enzymatically with each other, or with lysyl ε-$NH_2$, and **form covalent crosslinks** (pyridinoline type in collagen, isodesmosine in elastin).

# 8 Aromatic amino acids
## phenylalanine, tyrosine, and tryptophan



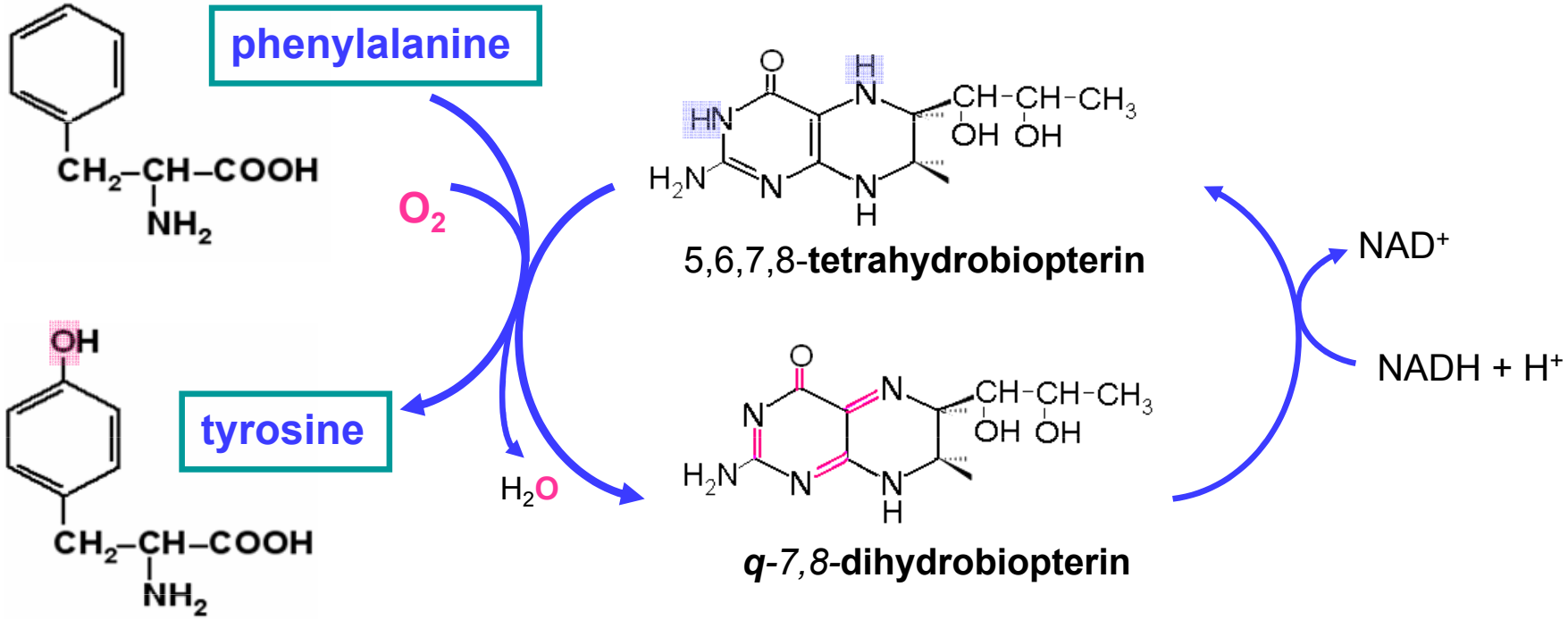

All three amino acids are <u>essential</u> (though tyrosine is also formed by hydroxylation of phenylalanine), and both <u>glucogenic and ketogenic</u>,

- phenylalanine and tyrosine give fumarate and acetoacetate,
- tryptophan gives alanine and acetoacetyl-CoA.

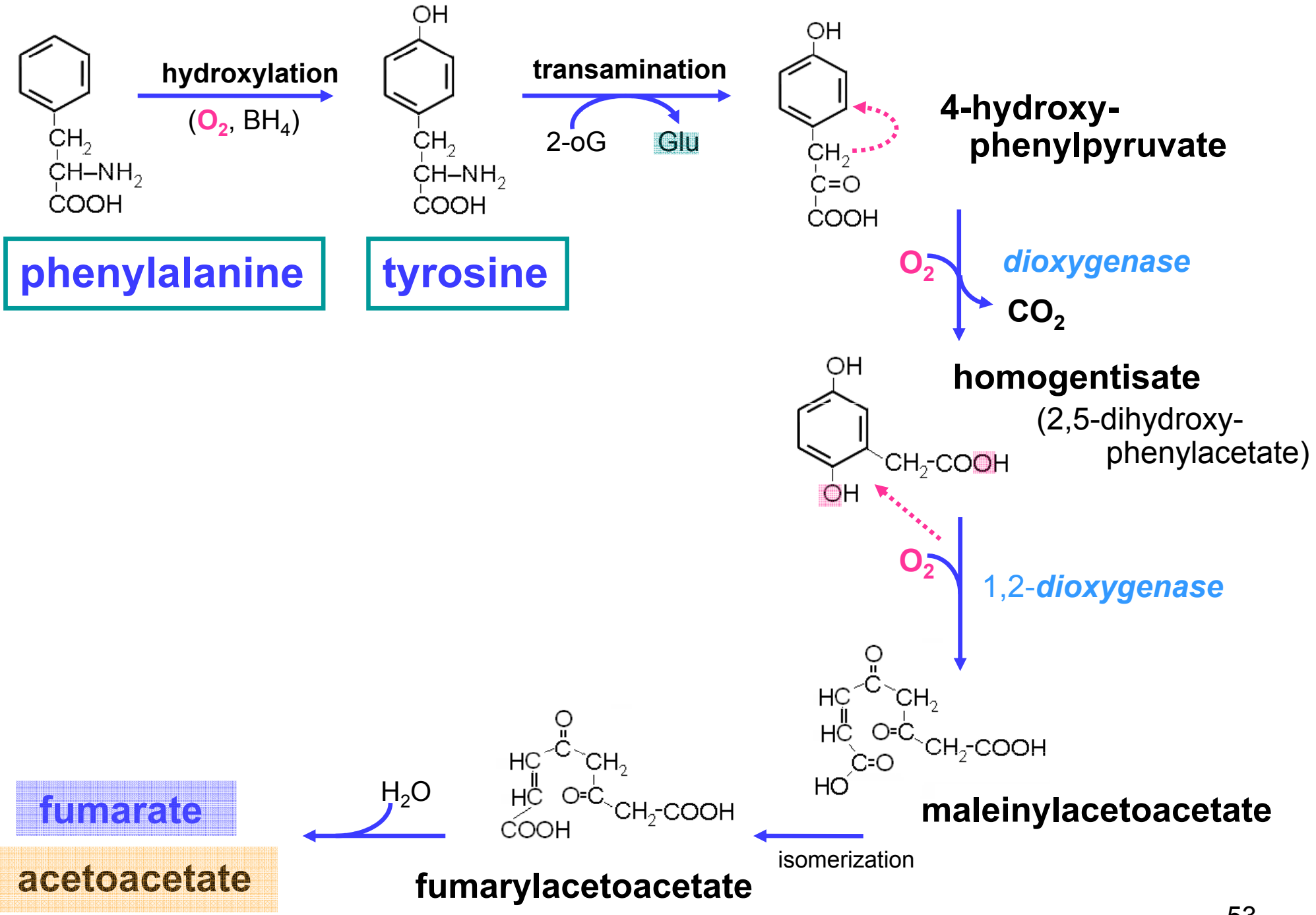
# Phenylalanine and tyrosine

## Hydroxylation of phenylalanine to tyrosine

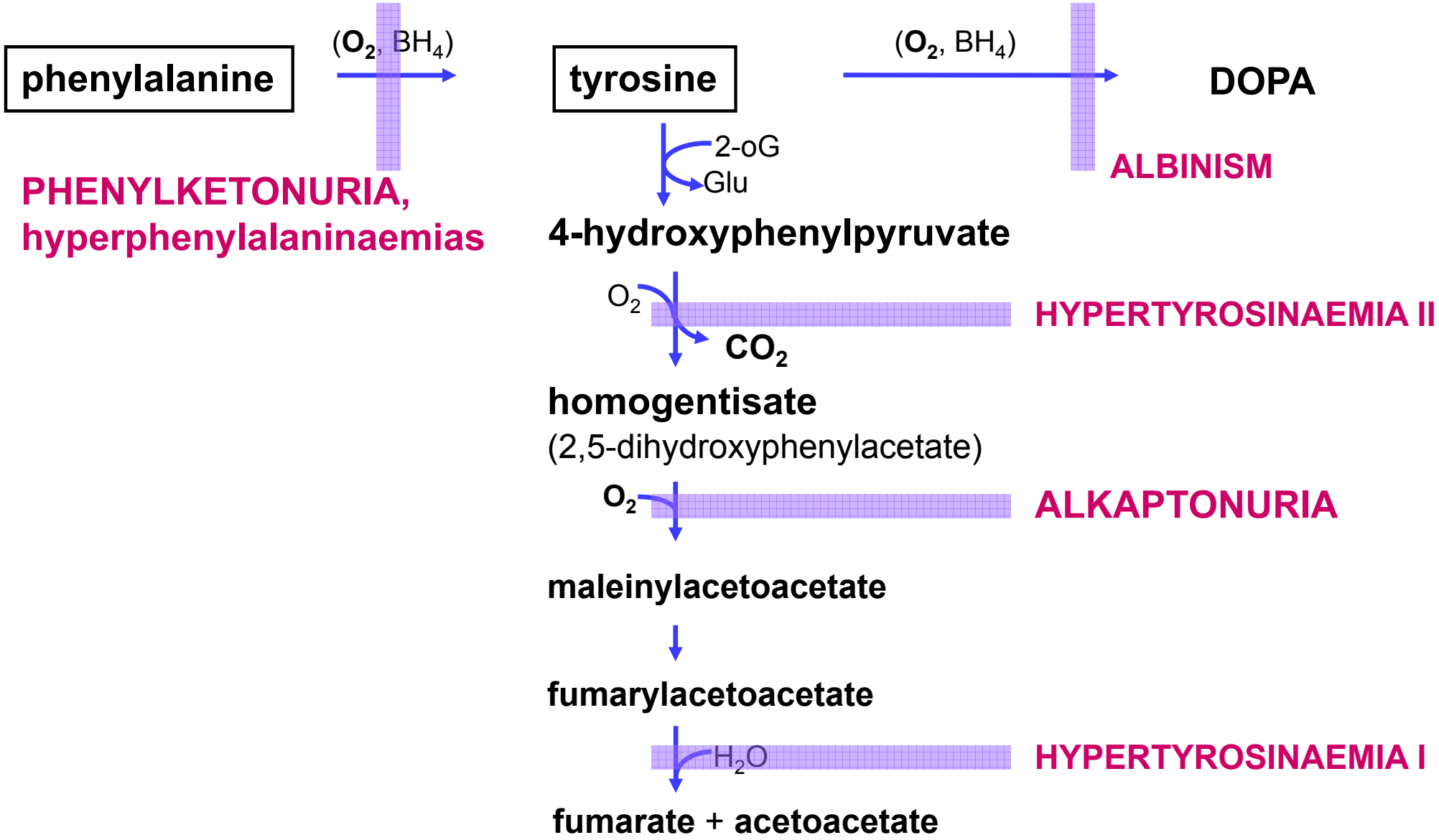
is catalyzed by a monooxygenase – ***phenylalanine hydroxylase***, for which the reducing coenzyme is **tetrahydrobiopterin** (**$BH_4$**):




Similarly, **tyrosine** is hydroxylated to **DOPA** by ***tyrosine 3-hydroxylase***, and **tryptophan** to **5-hydroxytryptophan** by ***tryptophan 5-hydroxylase***.


hydroxylation
($O_2$, $BH_4$)
transamination
2-oG
Glu
4-hydroxy-
phenylpyruvate
phenylalanine
tyrosine
$O_2$
dioxygenase
$CO_2$
homogentisate
(2,5-dihydroxy-
phenylacetate)
$O_2$
1,2-dioxygenase
maleinylacetoacetate
isomerization
fumarylacetoacetate
$H_2O$
fumarate
acetoacetate

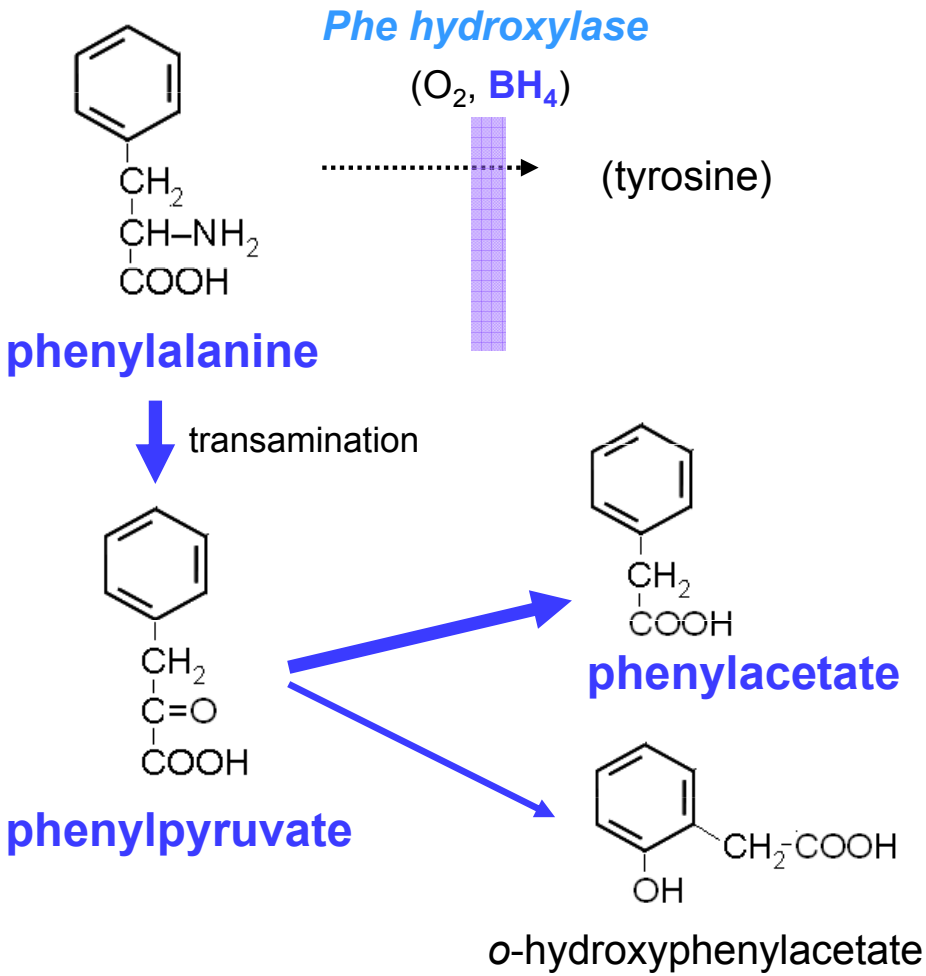
# Inborn metabolic disorders of phenylalanine catabolism



# **Hyperphenylalaninaemia** type **I** (**classic phenylketonuria, PKU**)

is a defect in **phenylalanine hydroxylase**, the ability to convert Phe to tyrosine is considerably impaired.
PKU have to be recognized through the compulsory screening of newborn infants and treated by a **low-phenylalanine diet** till the age of 8 – 10 years.

The consequence of untreated PKU is **mental retardation** (oligophrenia phenylpyruvica). Besides high levels of blood Phe, alternative catabolites are produced and excreted in high amounts (a "mousy" odour of the urine) :




## **Malignant hyperphenylalaninaemias** type **IV** and **V**

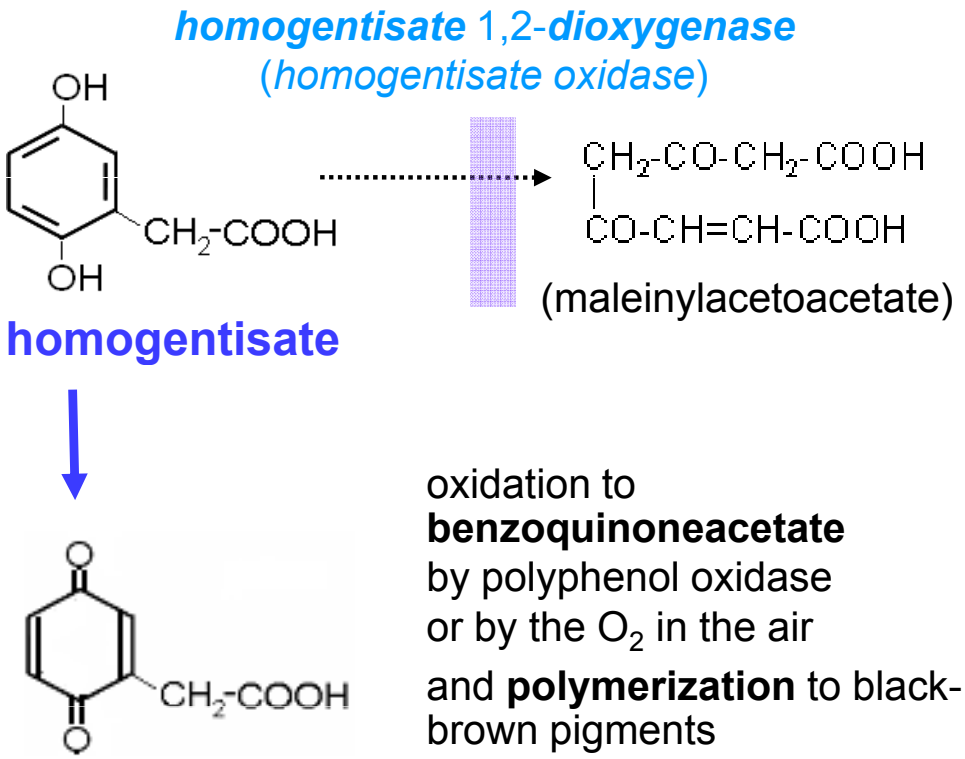
**$BH_4$** (**tetrahydrobiopterin**) **is lacking** due to the defective dihydrobiopterin biosynthesis from guanylate, or an ineffective reduction of $BH_2$ to $BH_4$.

## Hypertyrosinaemias

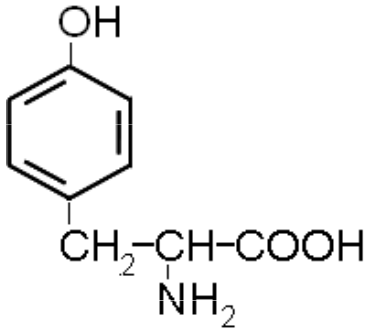
occur in several forms. They may be caused by a deficit of enzymes which catalyze either the transamination of tyrosine, or oxidation of *p*-hydroxyphenylpyruvate and hydrolysis of fumarylacetoacetate. A low-tyrosine diet may be very useful. Plasma levels of tyrosine are elevated, and large amounts of tyrosine, *p*-hydroxyphenylpyruvate, –lactate, and –acetate are excreted into the urine (tyrosyluria).

# Alkaptonuria

is an inborn deficit of **homogentisate oxidase** characterized by the excretion of homogentisate in the urine. Except for the **darkening of the urine on the air**, there are no clinical manifestations in youth until the second or third decade, when **deposits of pigments** in the connective tissue begins to appear (ochronosis – bluish colouring of the scleras, the ear and nasal cartilages, etc.) which are the cause of deforming arthritis.



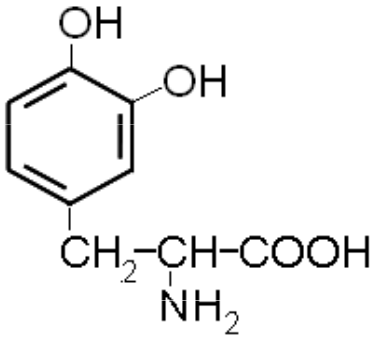
# Biosynthesis of catecholamines




**tyrosine**

3-hydroxylation

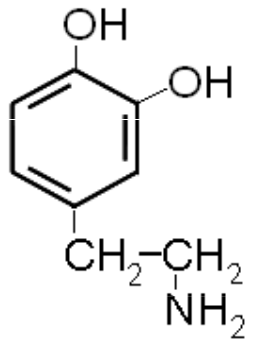
($O_2$, $BH_4$)




**DOPA**
(3,4-dihydroxyphenylalanine)

decarboxylation

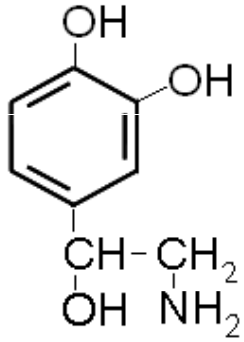
**- $CO_2$**




**dopamine**

β-hydroxylation

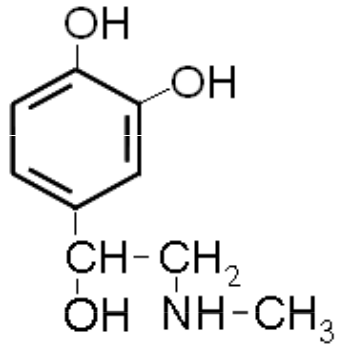
($O_2$, L-ascorbate)




**noradrenaline**
(norepinephrine)

*N*-methylation

(*S*-AM)

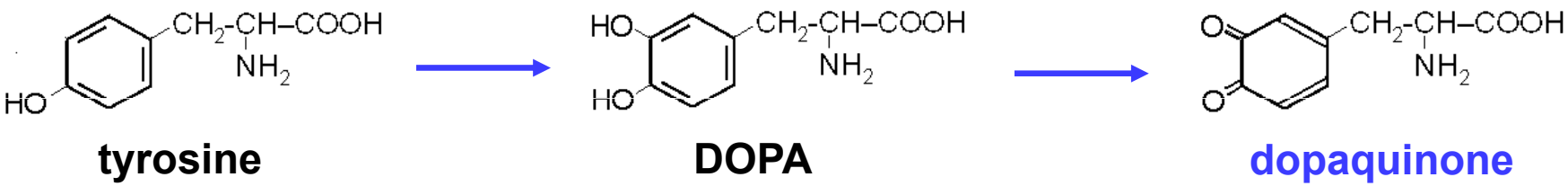


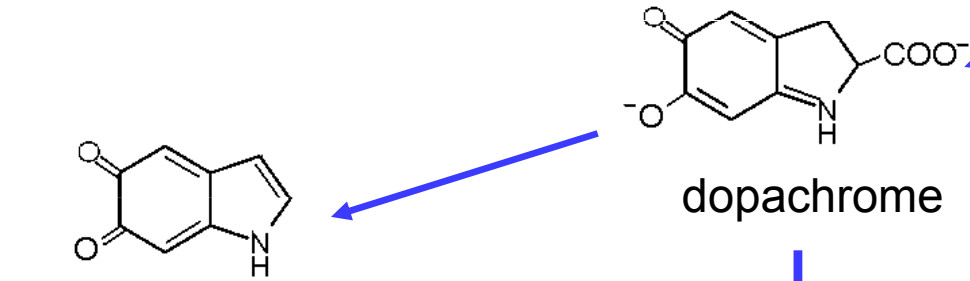

**adrenaline**
(epinephrine)

Inactivation of catecholamines occurs by means both **oxidative deamination** (*monoamine oxidase*, MAO) to acidic metabolites and 3-***O*-methylation** (*catechol-O-methyl transferase*, COMT) to metanephrines.

# Intermediates in the melanin biosynthesis

Pigments melanins occurs in the eye, skin, and hair. The initial steps are a hydroxylation of tyrosine to DOPA and oxidation of DOPA to **dopaquinone** – both reaction in the pigment-forming cells are catalyzed by the copper-containing enzyme ***tyrosinase***. The products of oxidation readily and spontaneously **undergo polymerization** resulting in insoluble dark pigments.



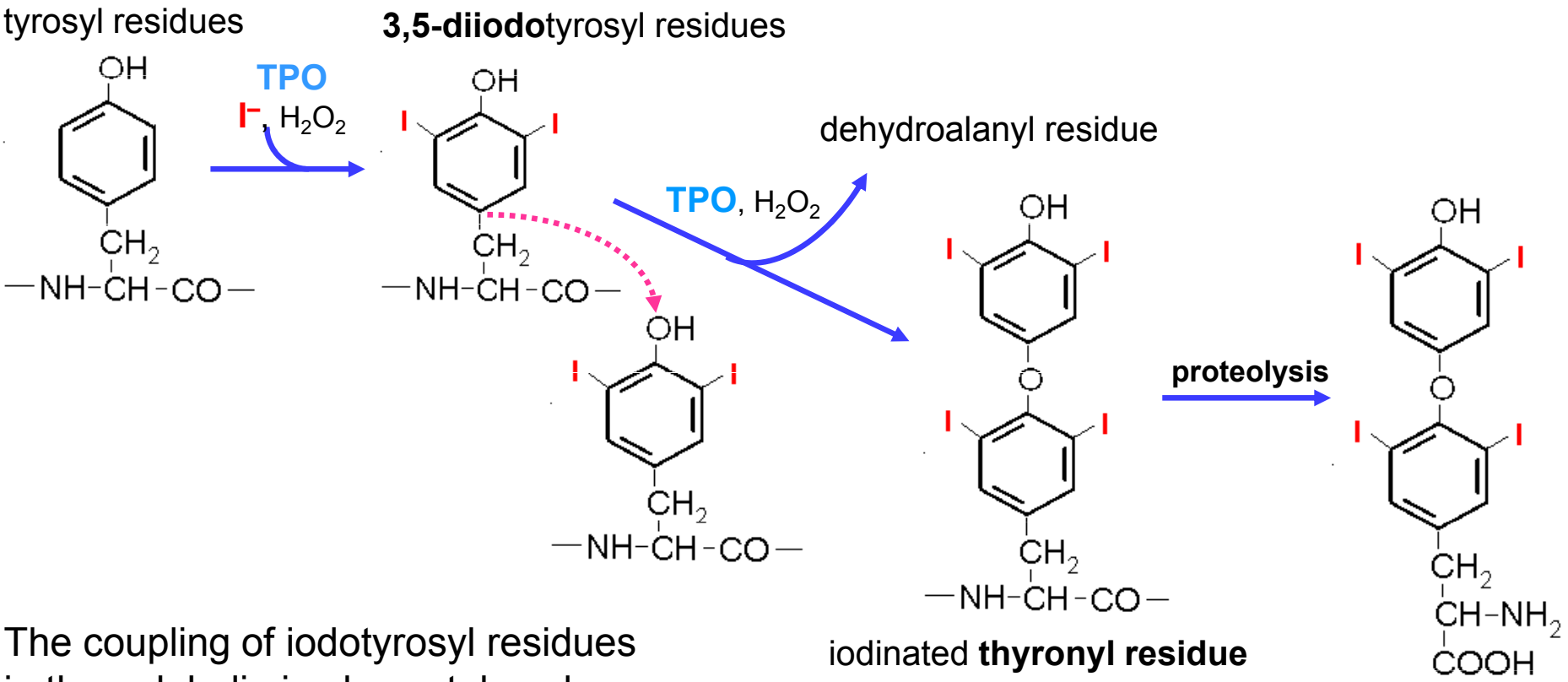




black **eumelanins**

ochre pheomelanins

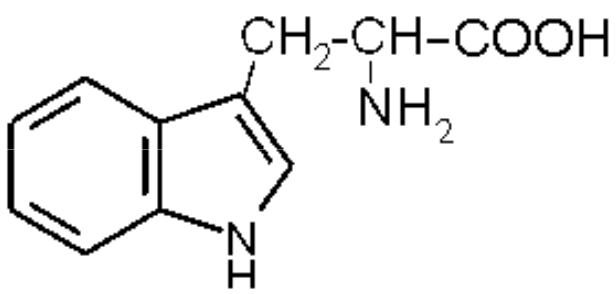
# Biosynthesis of the thyroid hormones

Within the thyroid cell, at the cell-colloid interface, iodide anions are oxidized (to $I^+$, $IO^-$, or •I ?) by ***thyroperoxidase*** (**TPO**) and incorporated into tyrosyl residues of thyroglobulin:




The coupling of iodotyrosyl residues in thyroglobulin is also catalyzed by thyroperoxidase. Proteolysis of thyroglobulin follows in lysosomes and thyroxine (or 3,3´,5´-$T_3$) is secreted.

# Tryptophan

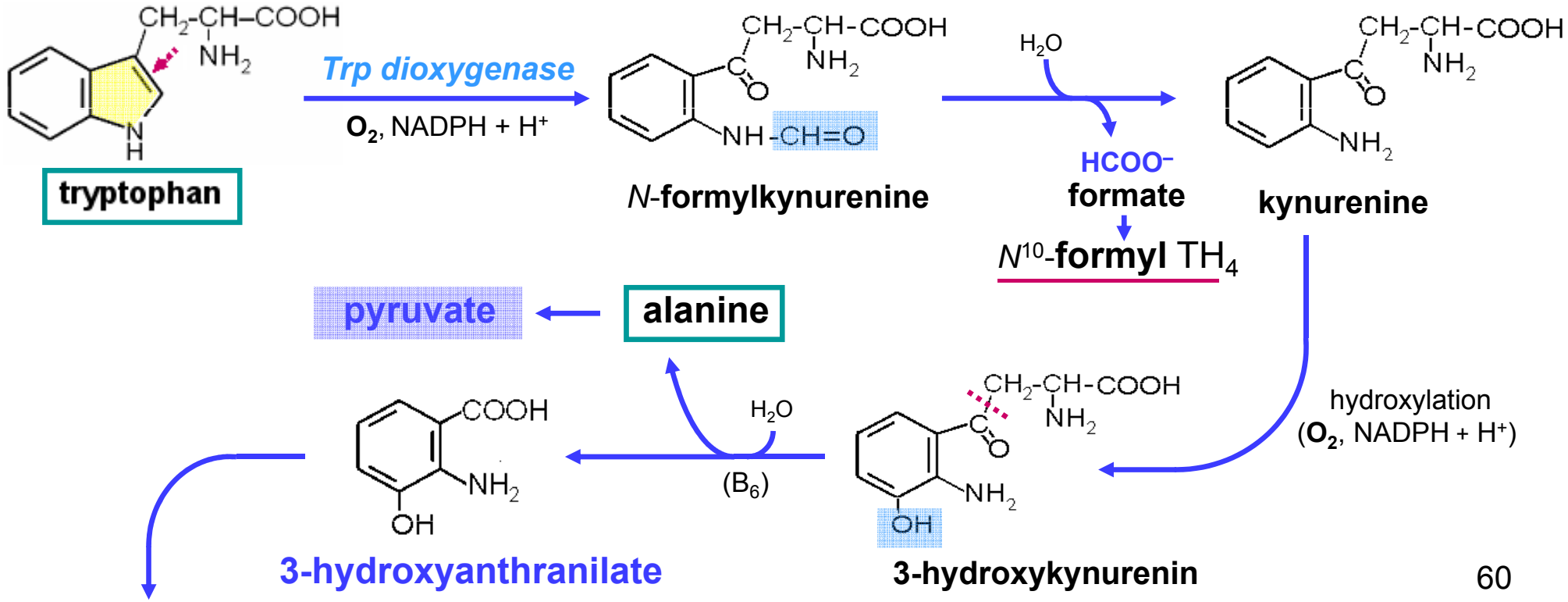


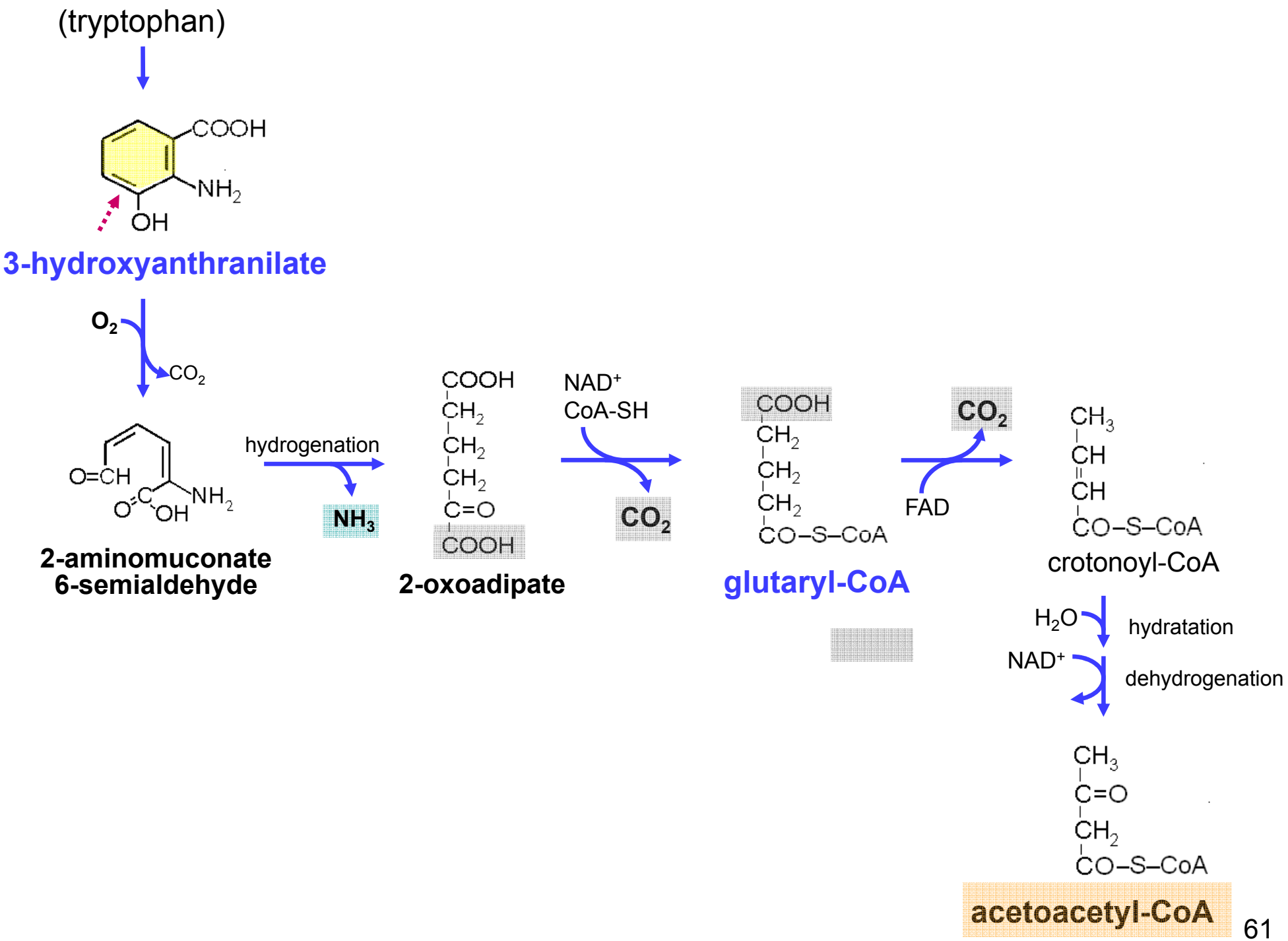
is <u>essential</u> and both <u>glucogenic</u> and <u>ketogenic</u>

– after opening of the indole pyrrole ring, it releases alanine, the carbon atoms of aromatic ring give acetoacetate.

Tryptophan mostly **<u>does not undergo transamination</u>**.

Catabolism of tryptophan is usually initiated by cleavage of the pyrrole ring of indole by ***tryptophan dioxygenase*** (*tryptophan pyrrolase*):

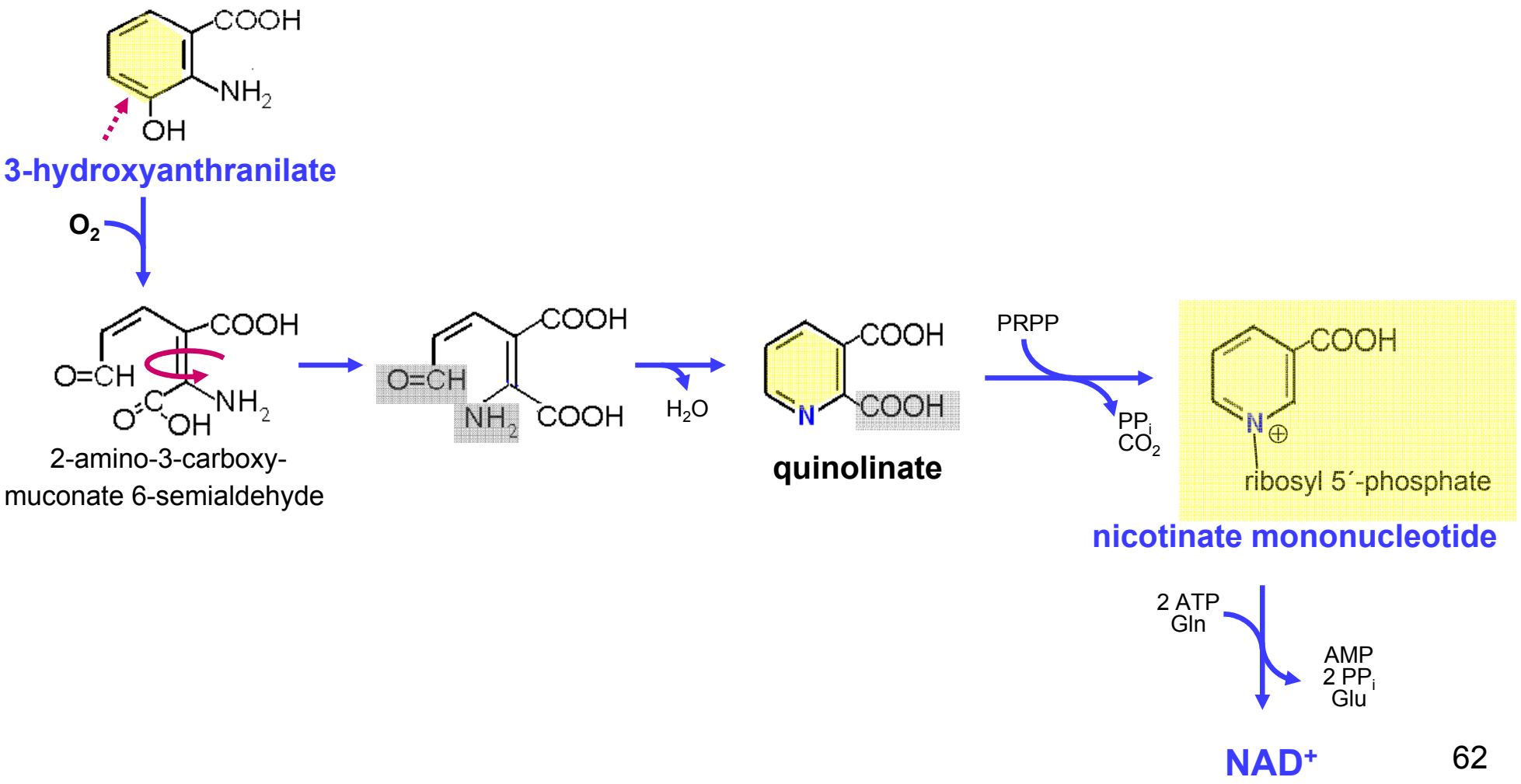


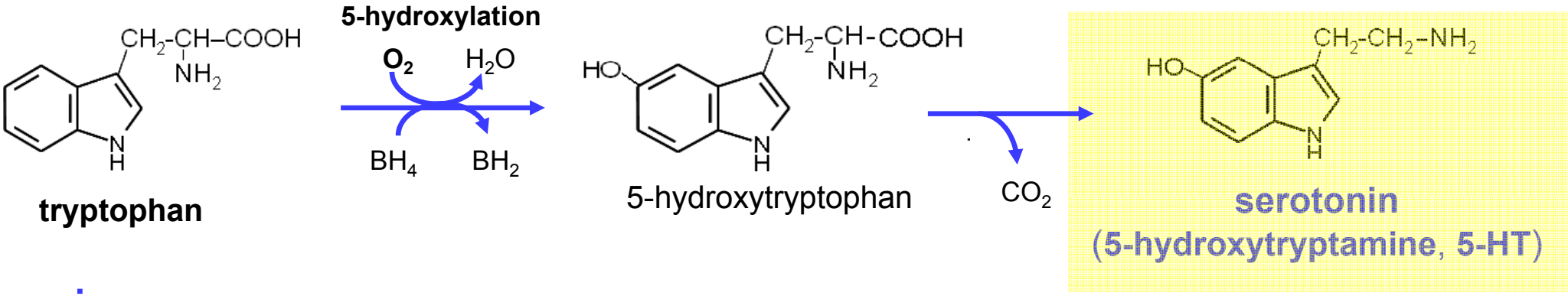

(tryptophan)
COOH
NH2
OH
3-hydroxyanthranilate
O2
CO2
O=CH
NH2
OH
2-aminomuconate
6-semialdehyde
hydrogenation
NH3
COOH
CH2
CH2
CH2
C=O
COOH
2-oxoadipate
NAD+
CoA-SH
CO2
COOH
CH2
CH2
CH2
CH2
CO–S–CoA
glutaryl-CoA
FAD
CO2
CH3
CH
CH
CO–S–CoA
crotonoyl-CoA
H2O
hydratation
NAD+
dehydrogenation
CH3
C=O
CH2
CO–S–CoA
acetoacetyl-CoA

# Utilization of tryptophan

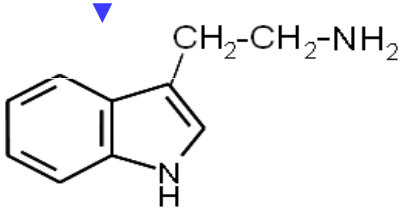
## Nicotinate ring synthesis for NAD(P)$^+$:

Humans can provide nearly all of their nicotinamide requirement from tryptophan, if there is a sufficient amount of tryptophan in the diet. Normally, about two-thirds comes from this source:

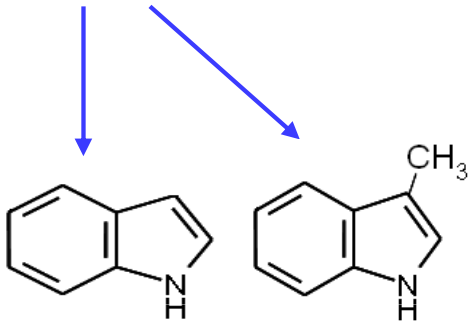





**large intestine**
decarboxylation

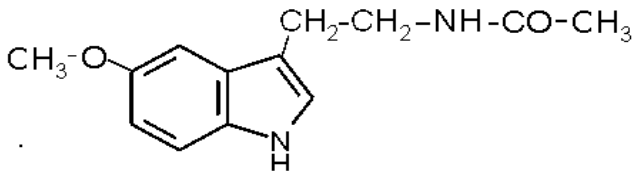


**tryptamine**




Serotonin is a neurotransmitter in CNS and a local hormone of argentaffin cells of the intestinal mucosa. It is degraded to 5-hydroxyindoleacetic acid (5-HIAA).

**pineal gland**
(*N*--acetylation
5-*O*-methylation)



**melatonin**
(*N*-acetyl-5-methoxytryptamine)

Secretion of melatonin from the pineal gland is increased in darkness. Its physiologic roles remains to be elucidated, but they involve **chronobiologic rhythms**.
(In frogs, melatonin is an antagonist of the melanocyte-stimulating hormone, MSH.)

# The fate of the carbon skeleton of amino acids – summary: