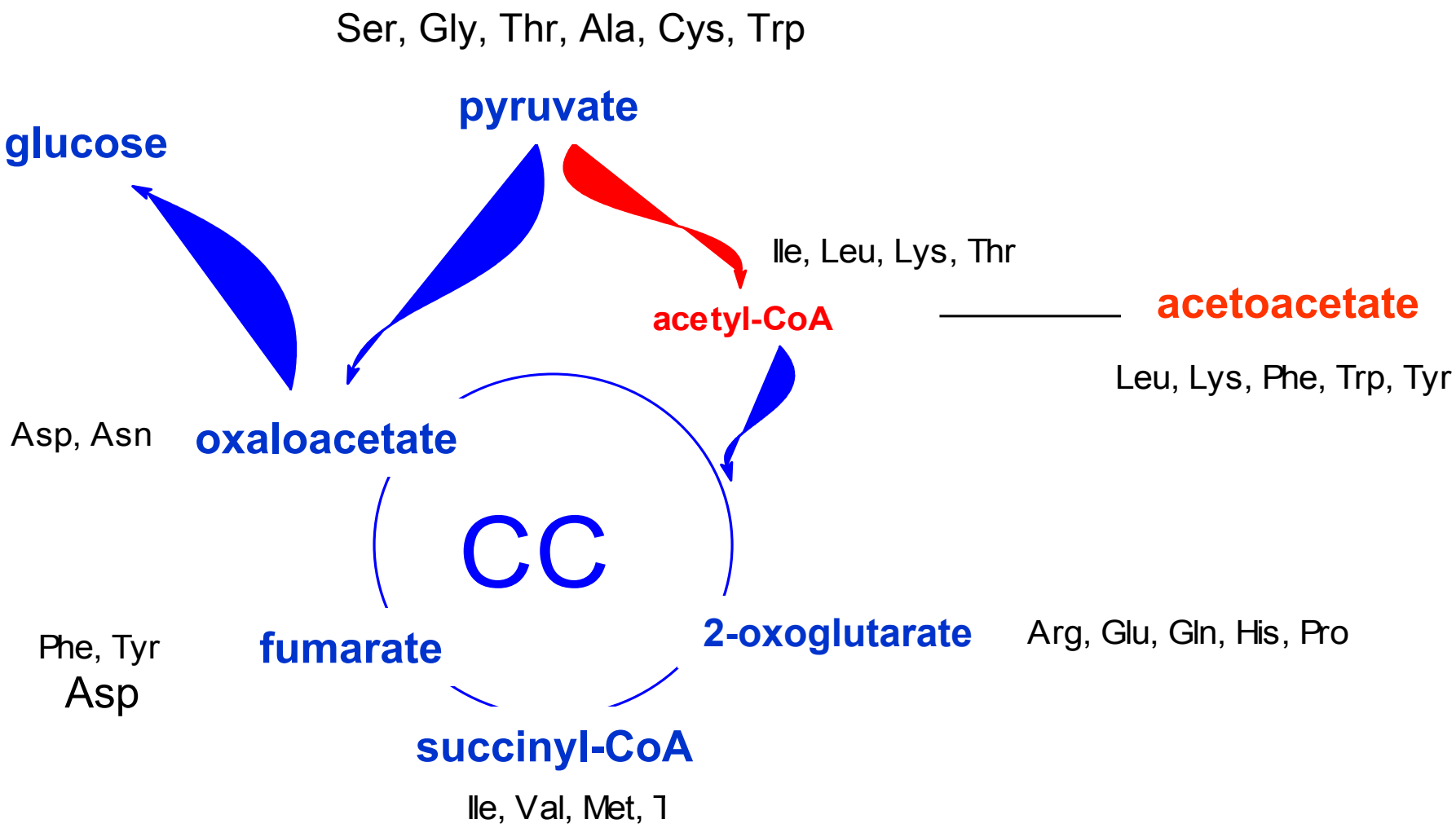
Metabolism of amino acids

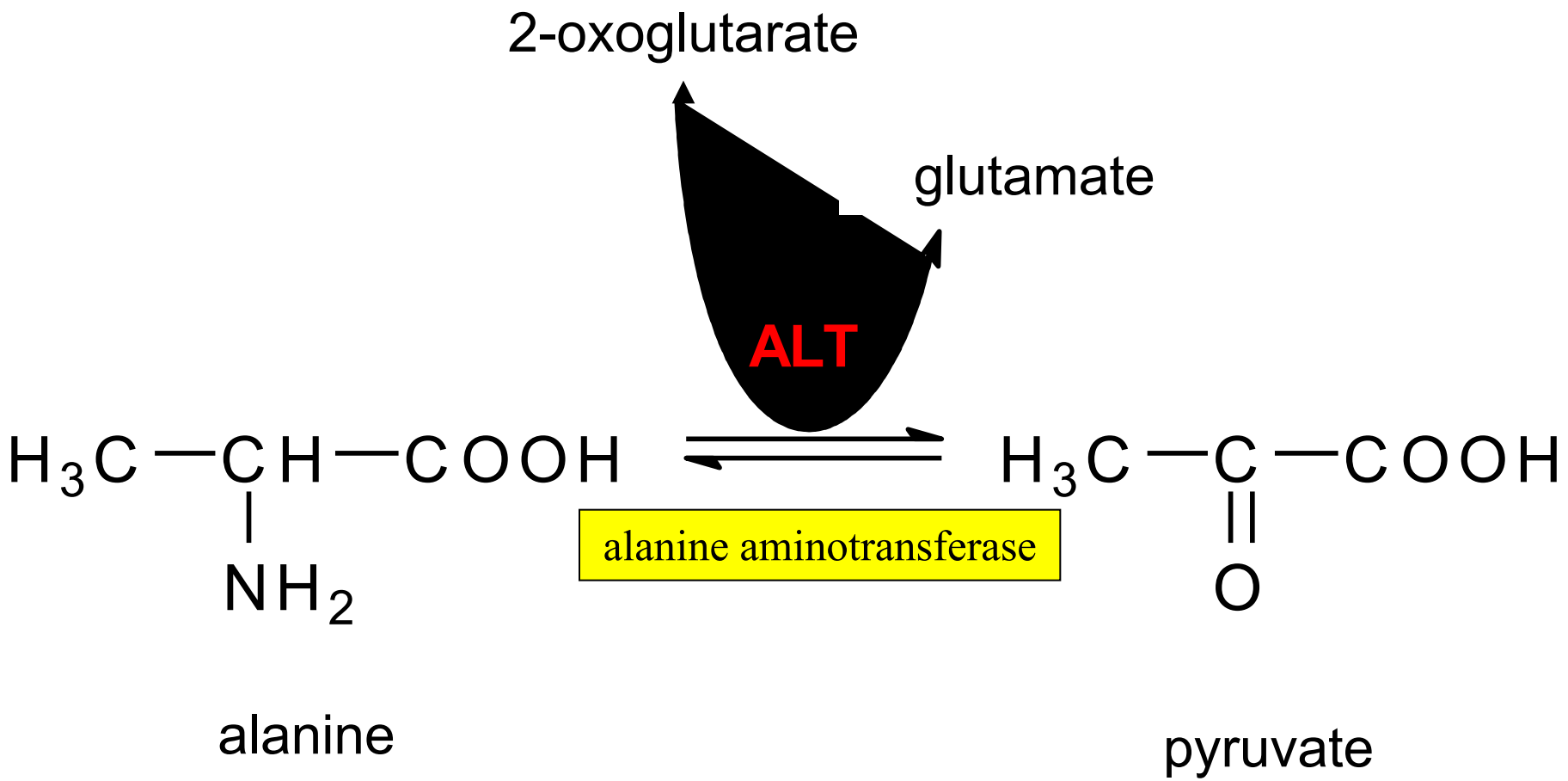
Intermediates of amino acid catabolism

- **Glucogenic (13)** → pyruvate and/or CAC intermediates
- **Ketogenic (2)** = Leu, Lys → acetyl-CoA + acetoacetate
- **Mixed (5)** = Thr, Ile, Phe, Tyr, Trp

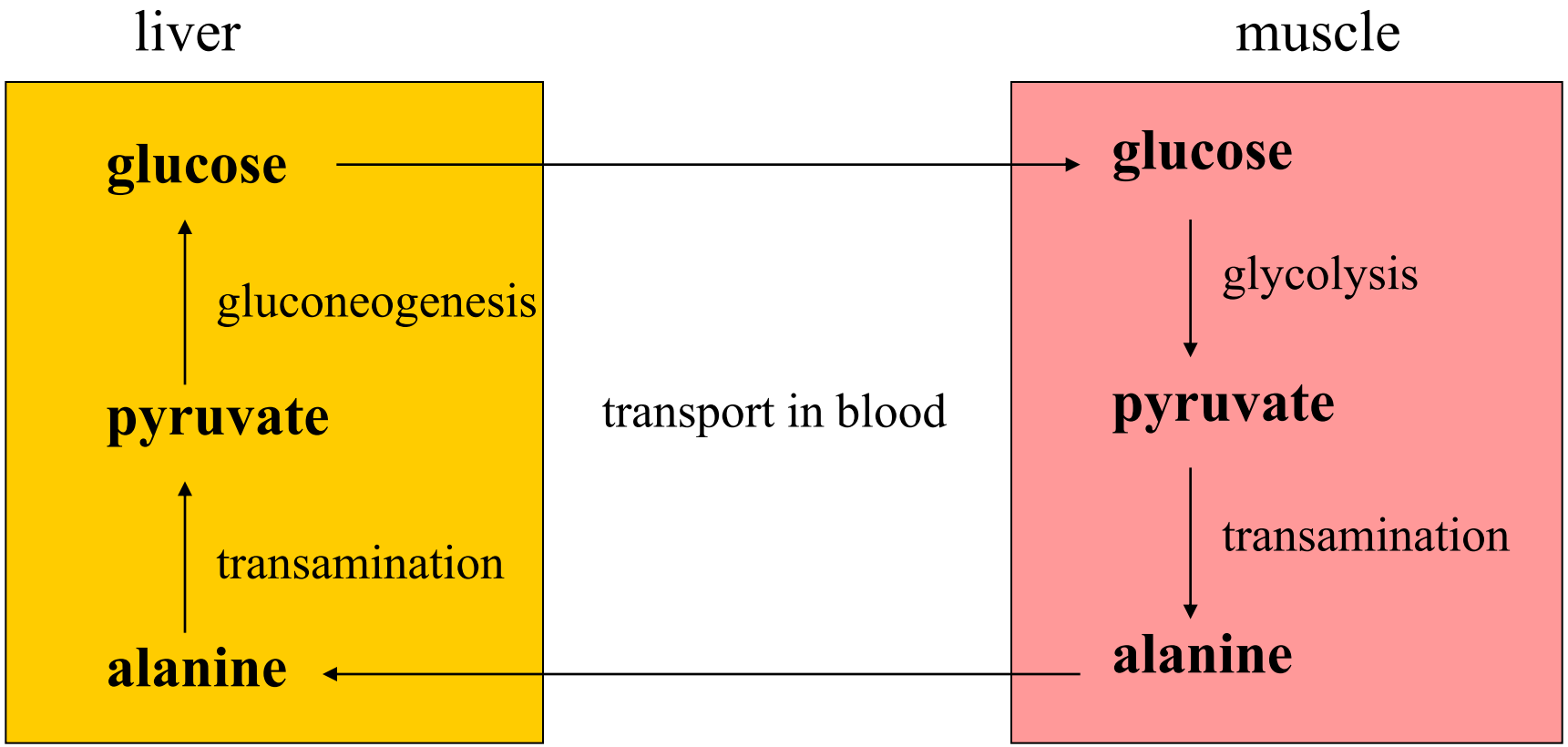
Intermediates of amino acid catabolism



Transamination of alanine



Glucose-alanine cycle



- alanine is non-toxic transport of ammonia from muscles to liver
- in the liver, alanine is the substrate for gluconeogenesis

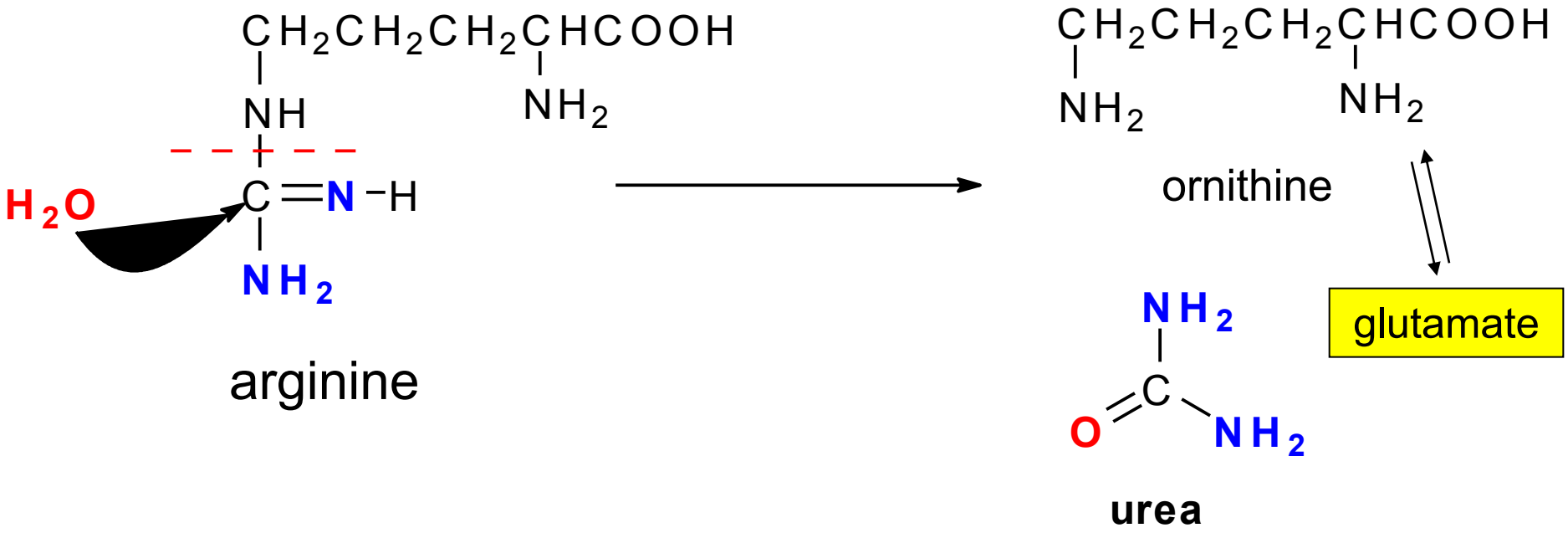
Alanine - summary

- readily made from pyruvate (transamination)
- ALT is clinically important enzyme, mainly in liver, elevated catalytic concentration in blood serum – liver diseases
- Ala is released to blood mainly from muscles, together with Gln (postresorption phase)
- semiessential AA (in metabolic stress) – important substrate for gluconeogenesis

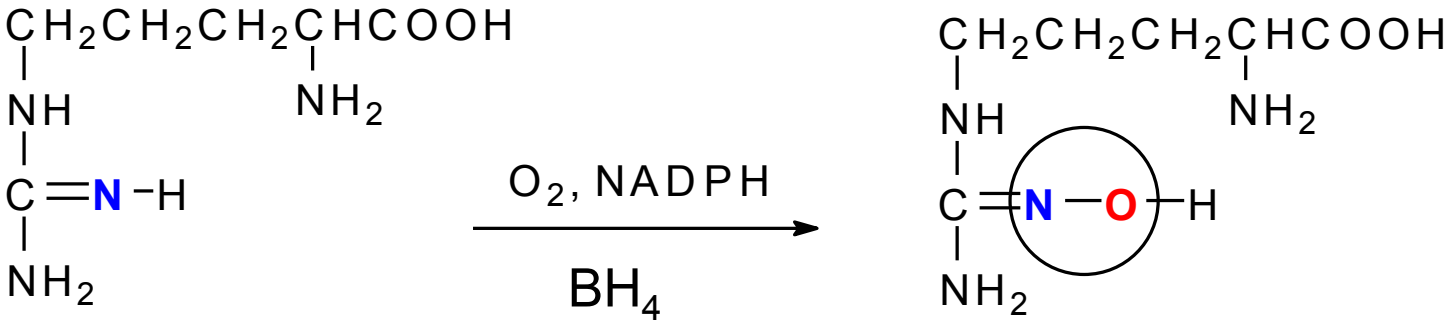
Arginine

no transamination

Hydrolysis of arginine → urea



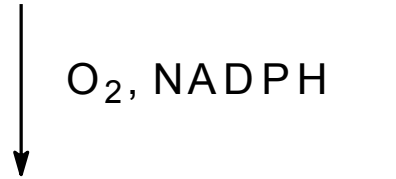
NO is signal molecule from arginine

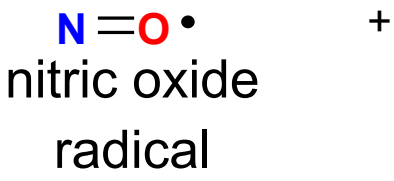


N-hydroxyarginine

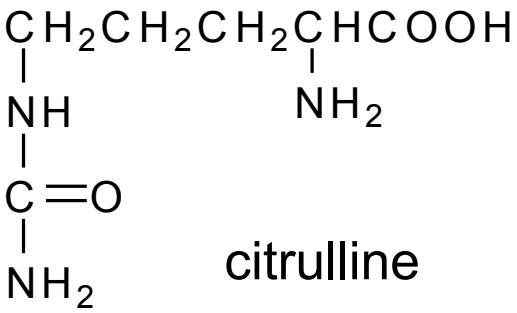
Exogenous NO sources

- glycerol trinitrate
- isosorbide dinitrate
- amyl nitrite
- isobutyl nitrite
- sodium nitroprusside





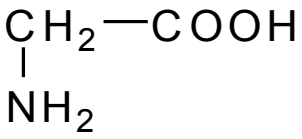
+



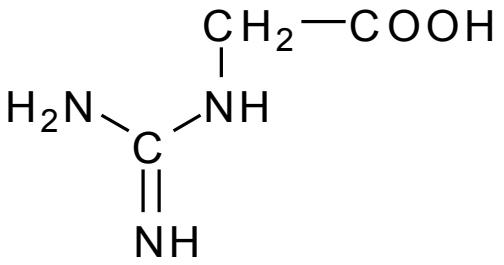
citrulline

Synthesis of creatine (1. part)

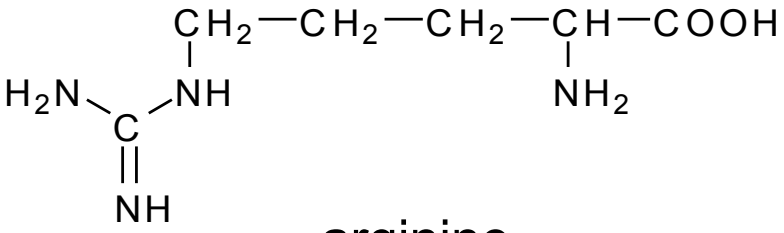
from Greek κρέας (meat)



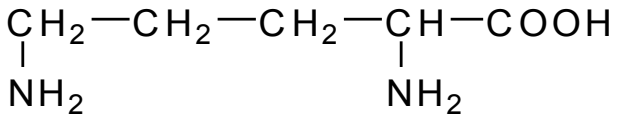
glycine



guanidinoacetate



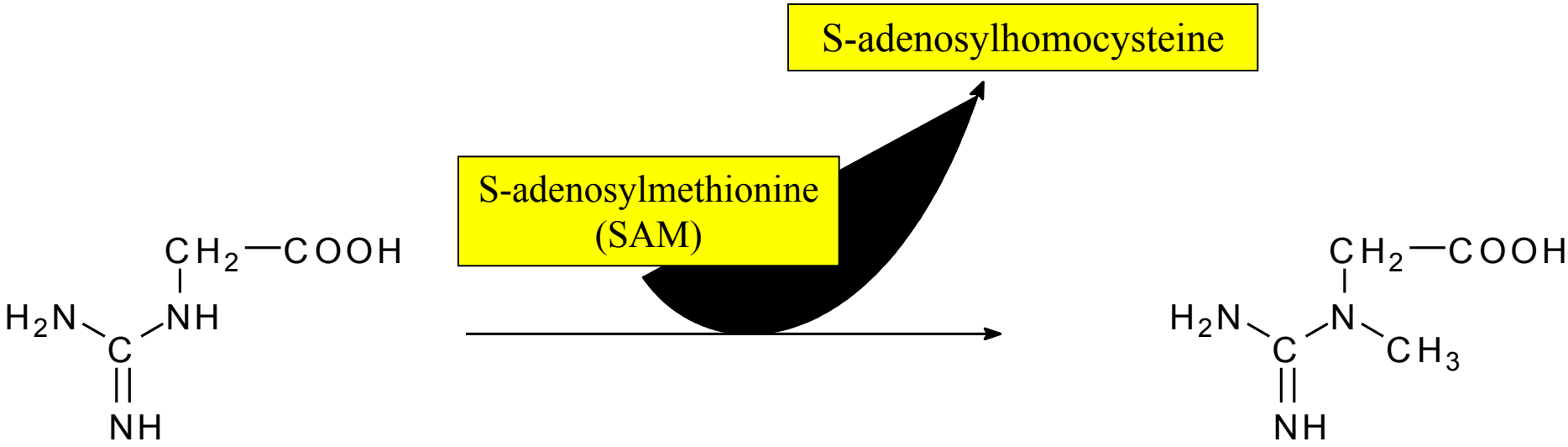
arginine



ornithine

Synthesis of creatine (2. part)

N^1-methylation of guanidinoacetate

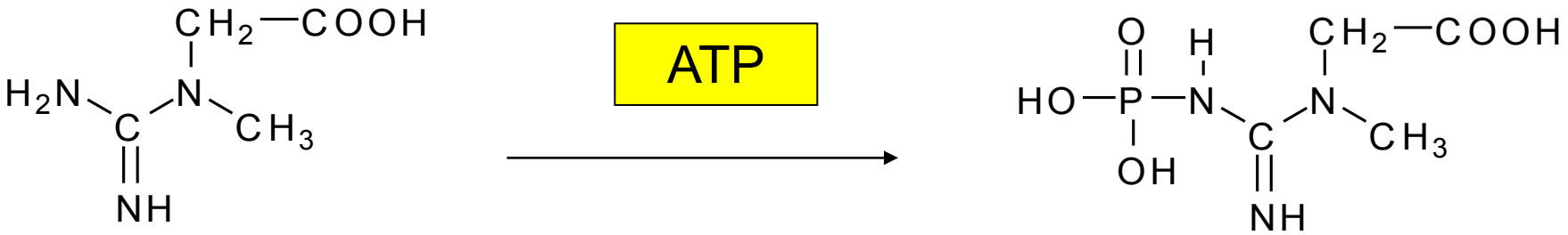


guanidinoacetate

creatine

N-methylguanidine-*N*-acetate

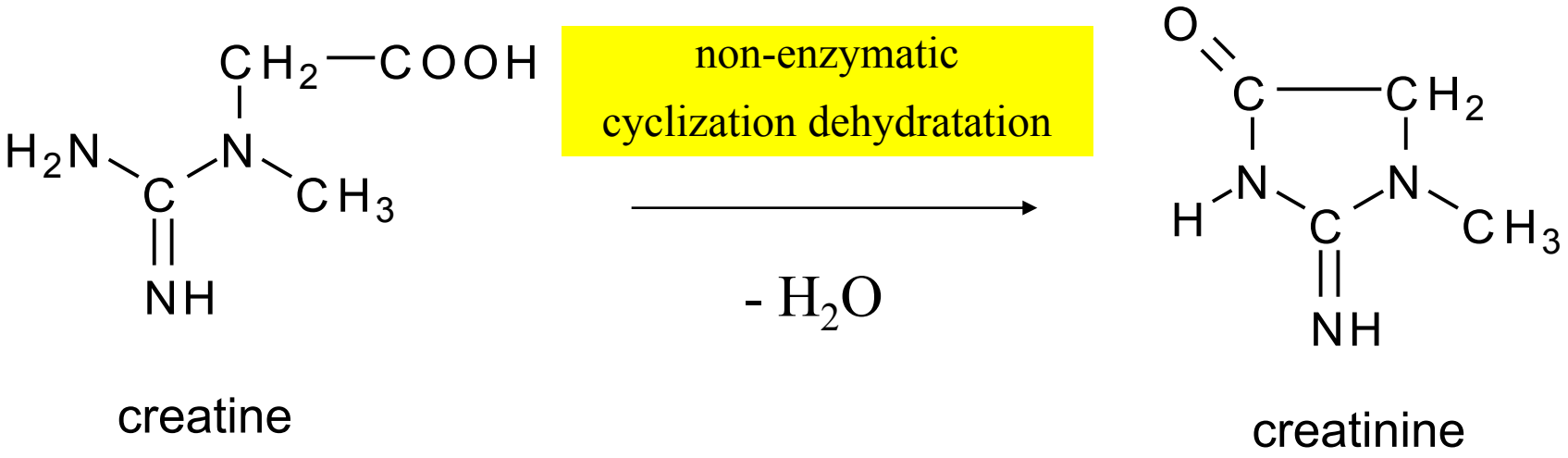
N^2-Phosforylation of creatine



creatine

creatine phosphate

Creatinine is a catabolite of creatine made in non-enzymatic reaction

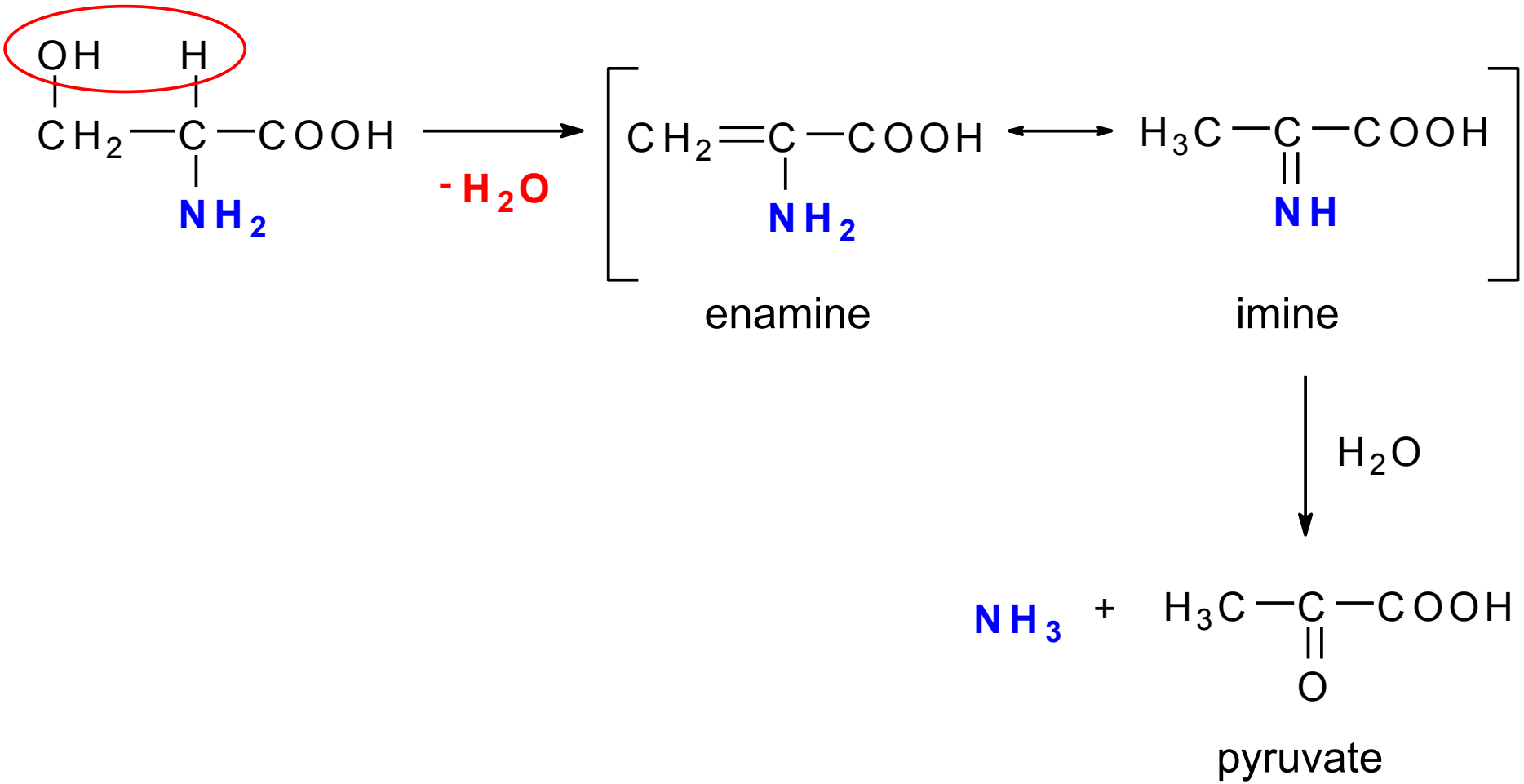


Arginine - summery

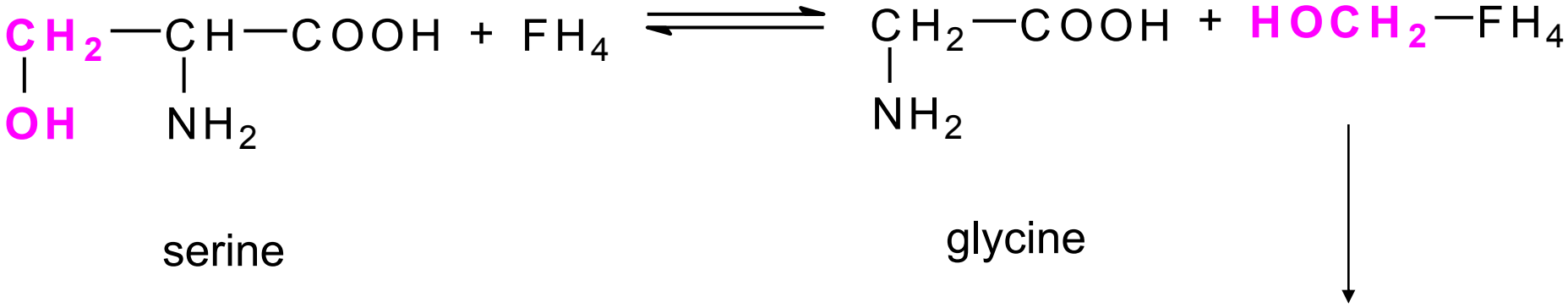
- semiessential AA (childhood)
- the most basic AA (guanidine, pK_B = 0.5)
- no transamination, Arg releases ornithine + urea
- Arg + Gly + Met $\rightarrow$ creatine
- releases NO (vasodilator)
- OTC (over-the-counter) preparations in pharmacy

Serine

Dehydratation + deamination of serine



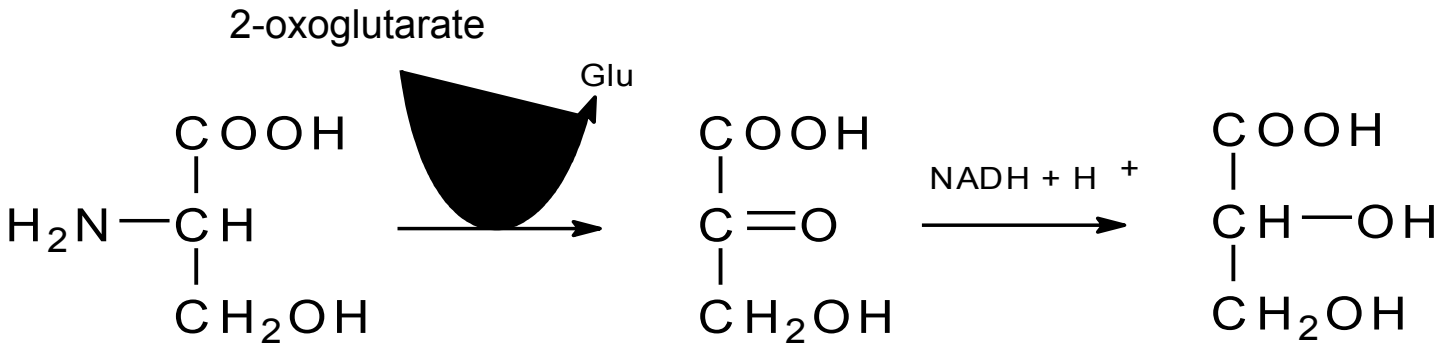
Conversion of serine to glycine



cofactor:

tetrahydrofolate (FH_4)

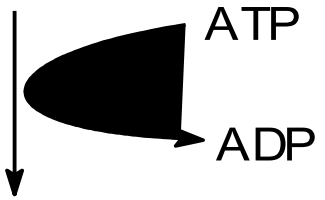
Transamination of serine and glucose formation

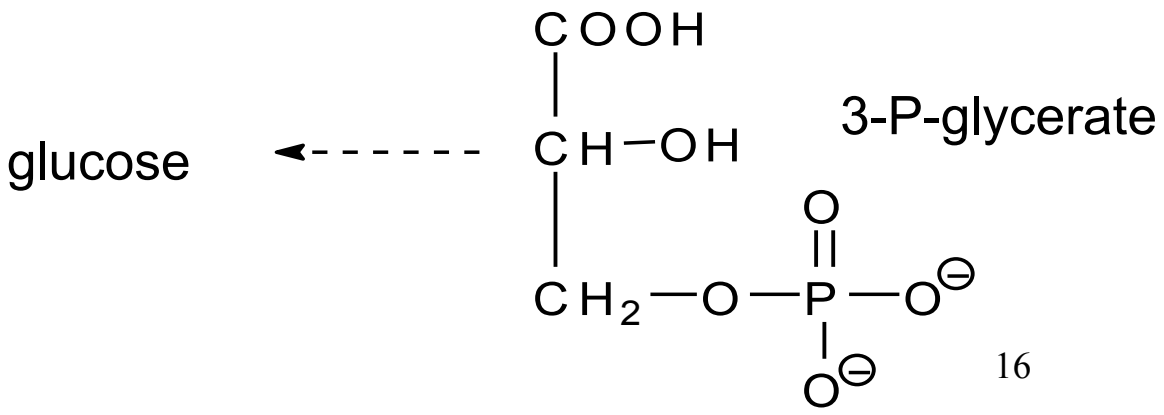


serine hydroxypyruvate glycerate

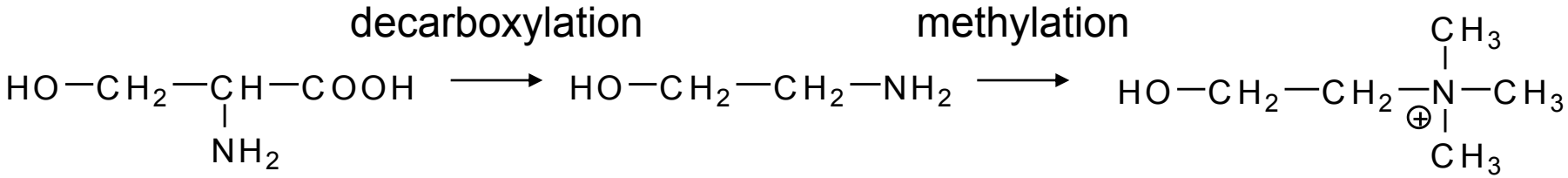
reverse reaction:
synthesis of serine

pathway is different -
through phosphoserine



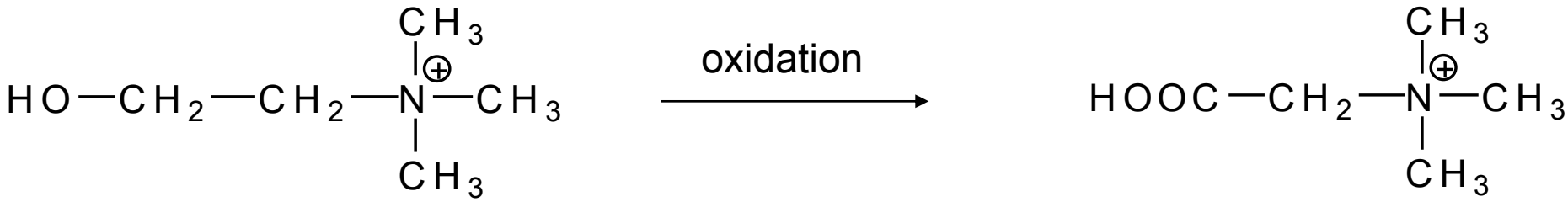


Decarboxylation of serine gives ethanolamine. Methylation of ethanolamine leads to choline



serine ethanolamine choline

Betaine is made by choline oxidation



choline betaine

Serine - summary

- non-essential glucogenic AA
- source of C1 fragments (attached to tetrahydrofolate)
- component of glycerophospholipids
- decarboxylation gives ethanolamine → choline
- carbon skeleton used for selenocysteine
- **serine side chain in proteins:**

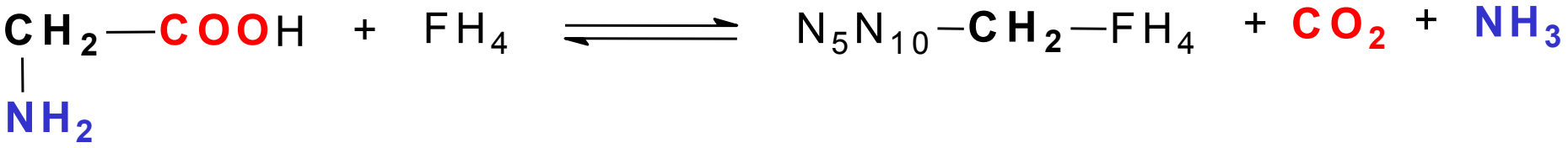
  the site of phosphorylation

  the linkage of oligosaccharides (*O*-glycoside bond)

  nucleophilic -OH group in active site of enzyme (serine proteases)

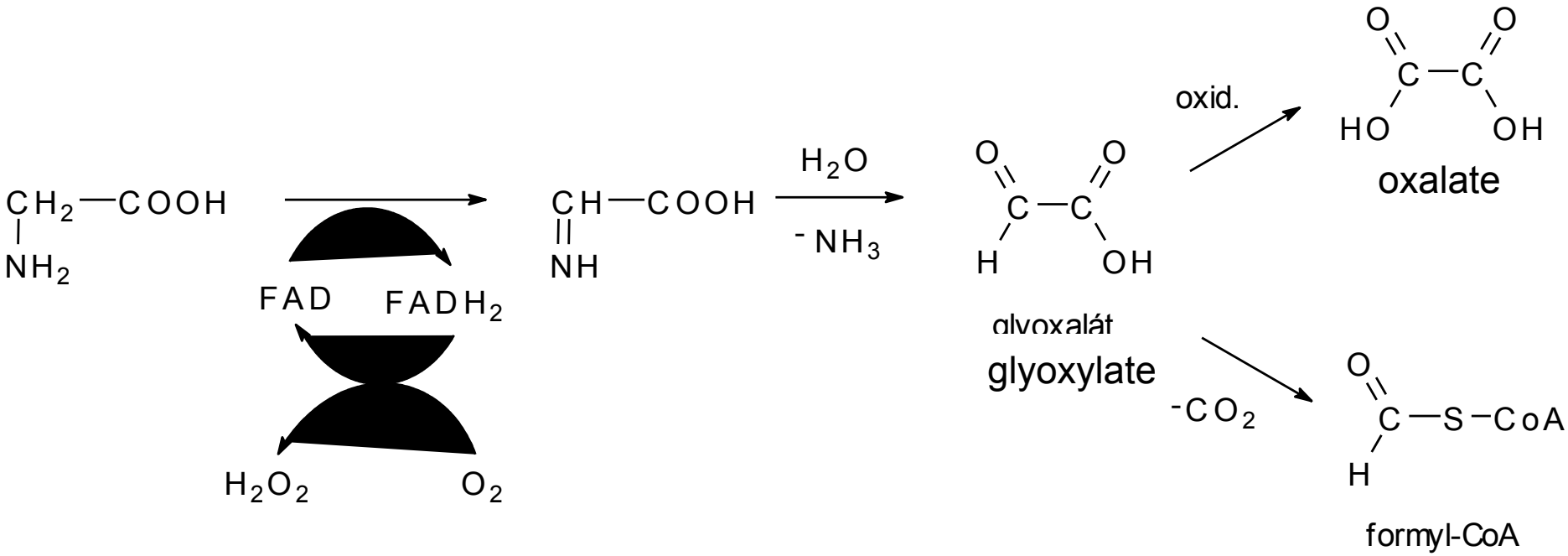
Glycine

The complete catabolism of glycine



C1 fragment (methylene) is transferred to tetrahydrofolate

Oxidative deamination of glycine



60 % catabolism of glycine and ethanolamine

30 % catabolism of vitamin C

10 % food (spinach, rhubarb, mangold, tea, cocoa)

Glycine - summary

Catabolism

- complete oxidation to $CO_2 + NH_3$
- oxidative deamination to oxalate

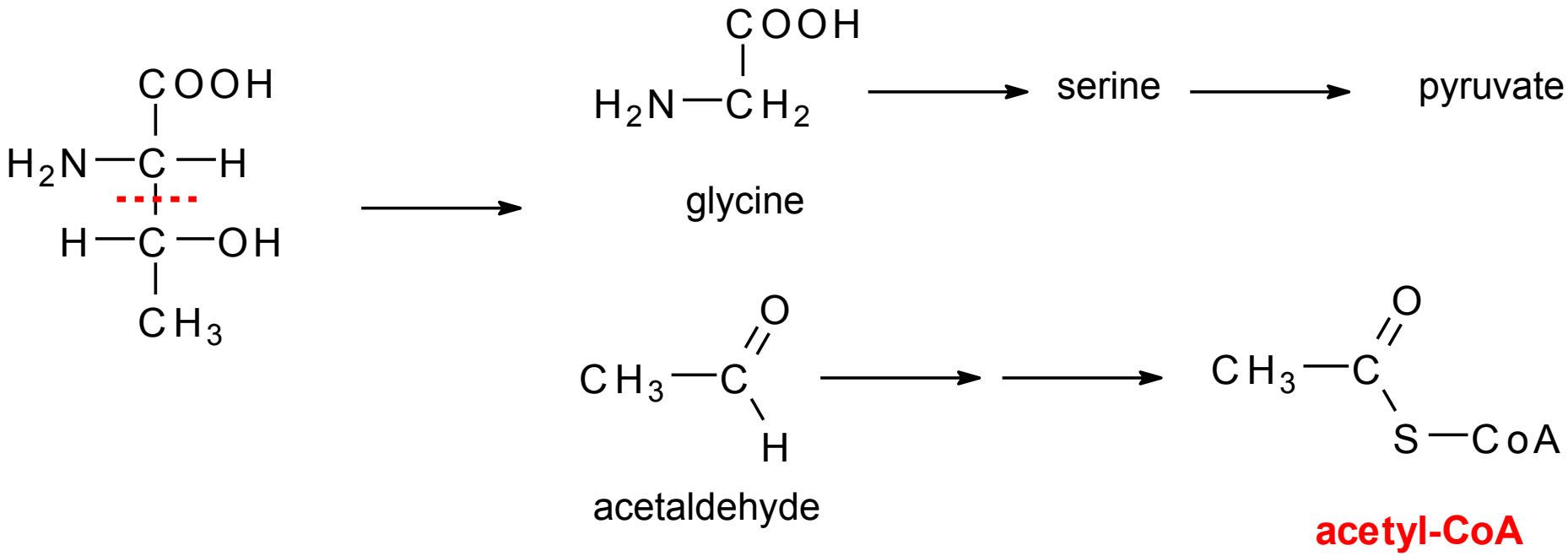
Anabolic conversions

- donor of C1 fragment
- serine
- porphyrines
- purine bases
- creatine
- glutathione (GSH)
- conjugation agent (bile acids, xenobiotics)

Threonine

no transamination

Threonine (4C) is split to glycine (2C) and acetaldehyde (2C)

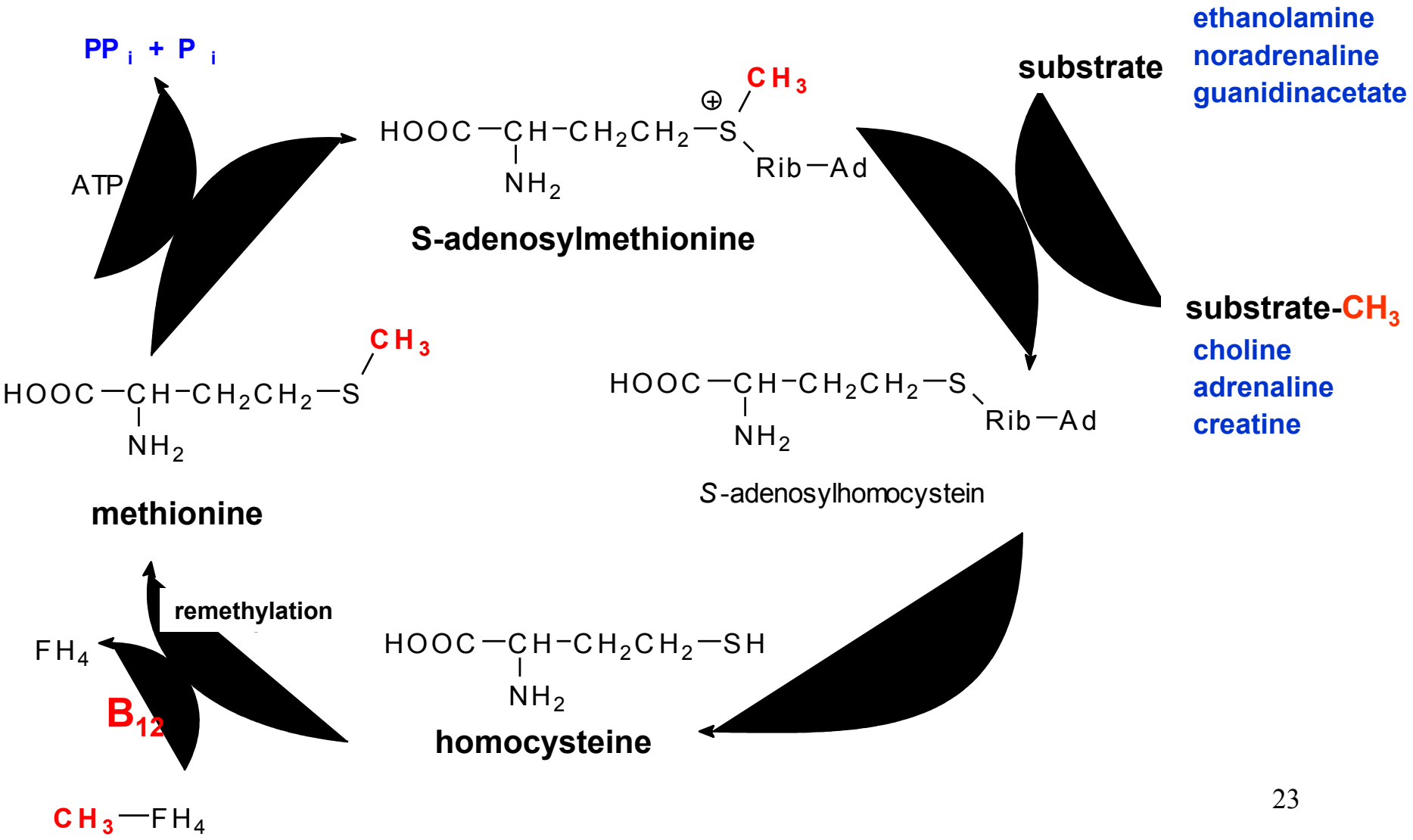


- essential AA
- two asymmetric C atoms
- the site of phosphorylation and glycosylation in proteins

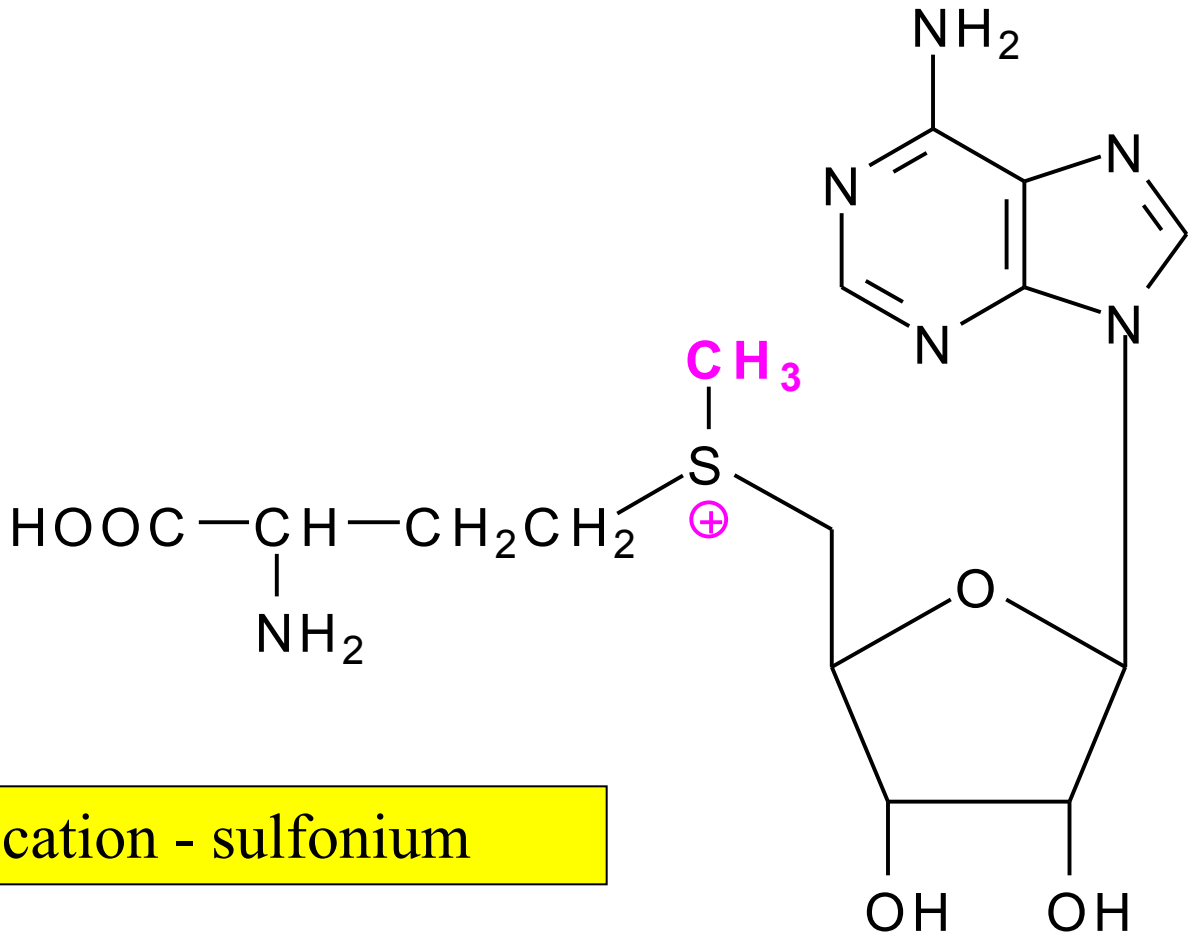
Methionine

no transamination

Methionine is methylation agent (homocysteine side product)

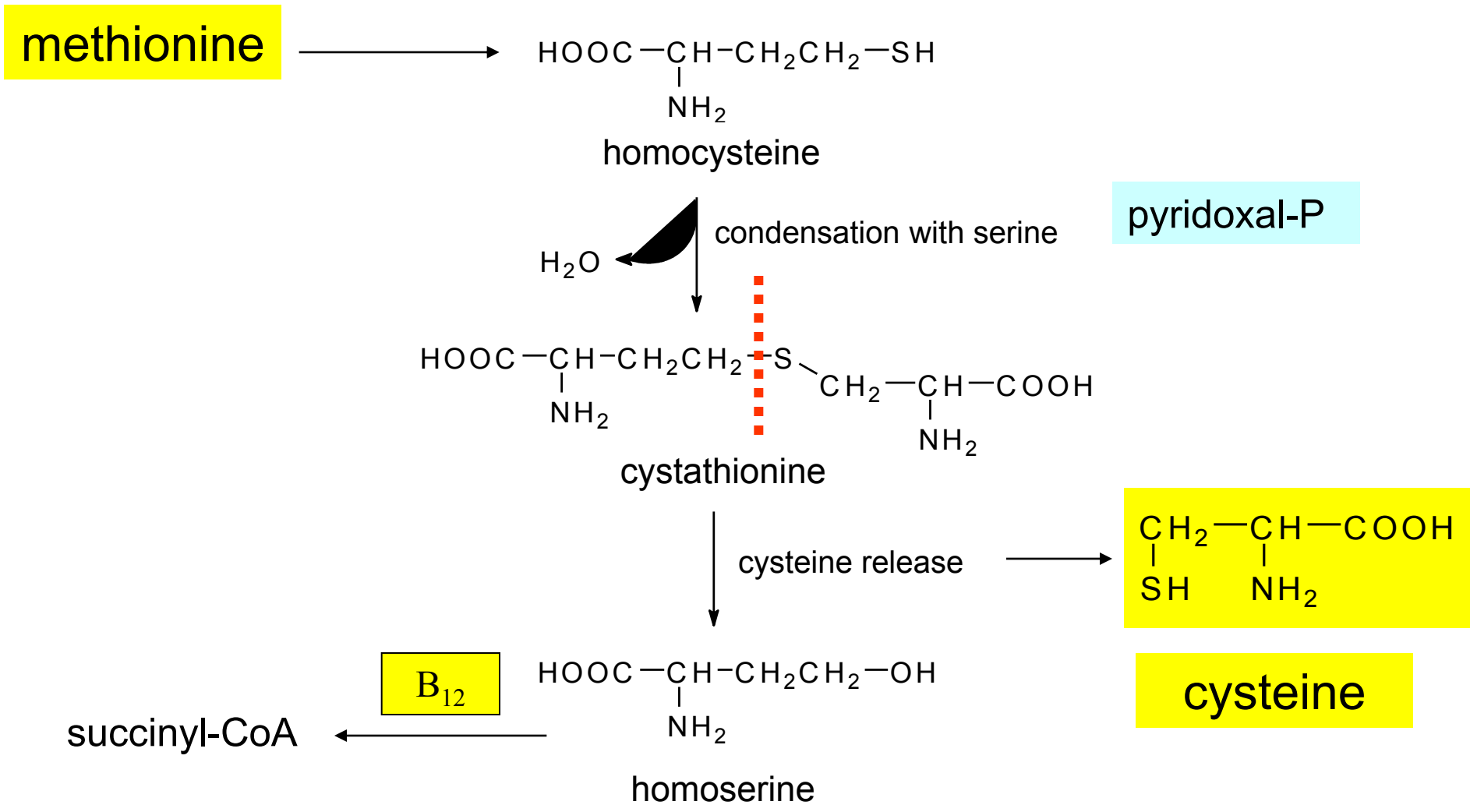


S-Adenosylmethionine (SAM) contains trivalent positively charged sulfur atom



cation - sulfonium

Cysteine is made from methionine



Methionine - summery

- essential AA, rather rare in foodstufs
- S-adenosylmethionine (SAM) is methylation agent
- metabolized to cysteine $\Rightarrow$ Cys is non-essential AA
- C-skeleton of cysteine comes from serine, sulfur atom from methionine
- final catabolite is succinyl-CoA (glucogenic)

Homocysteine is harmful

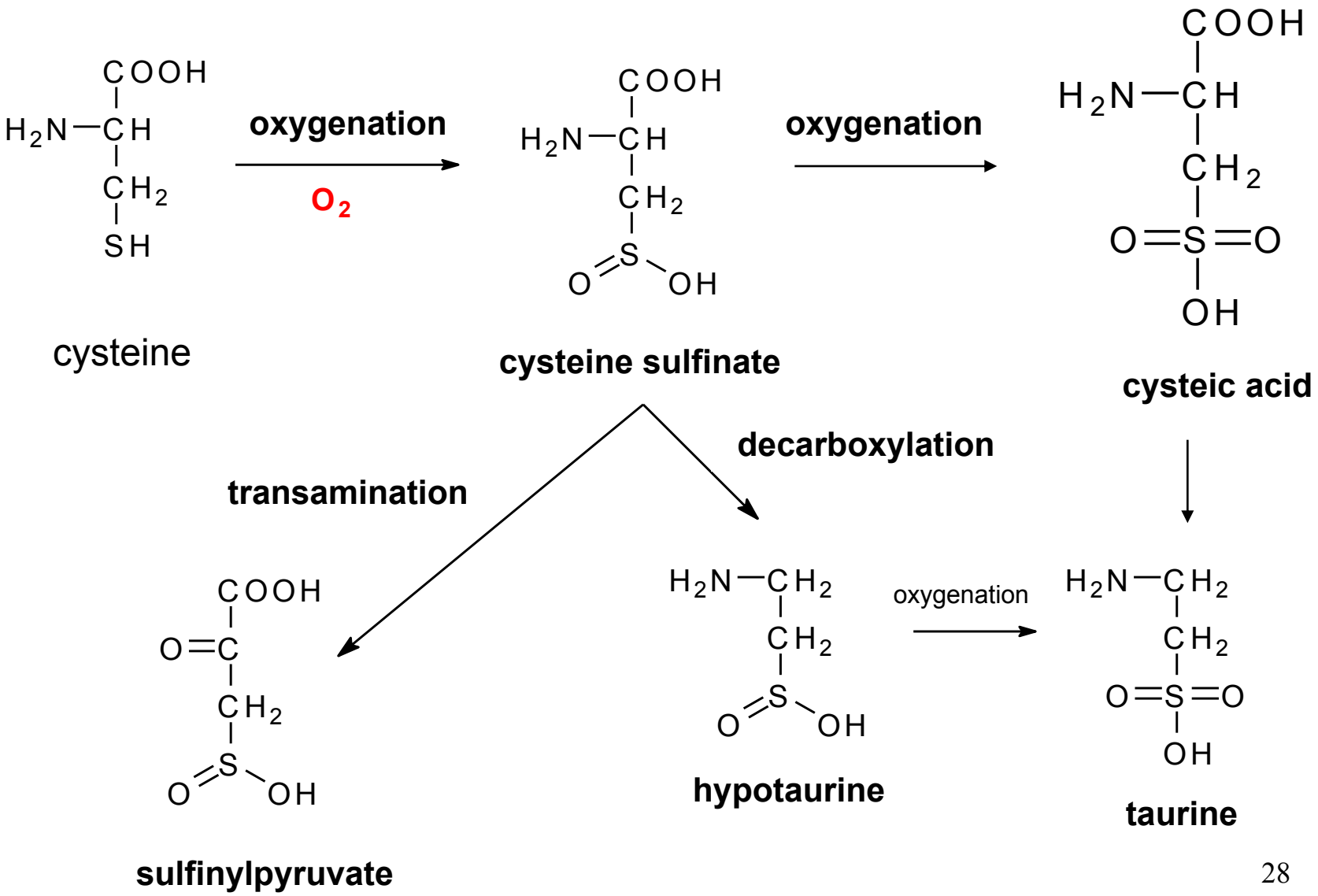
- mechanism of its action is not yet understood
- direct action on blood vessel epithelium
- decreases thrombocyte life and fibrinolysis
- supports formation of oxygen radicals – damage of vessel wall
- increases LDL lipoperoxidation
- elevated blood level of homocysteine is risk factor of cardiovascular diseases

to eliminate homocysteine - three vitamins are needed:

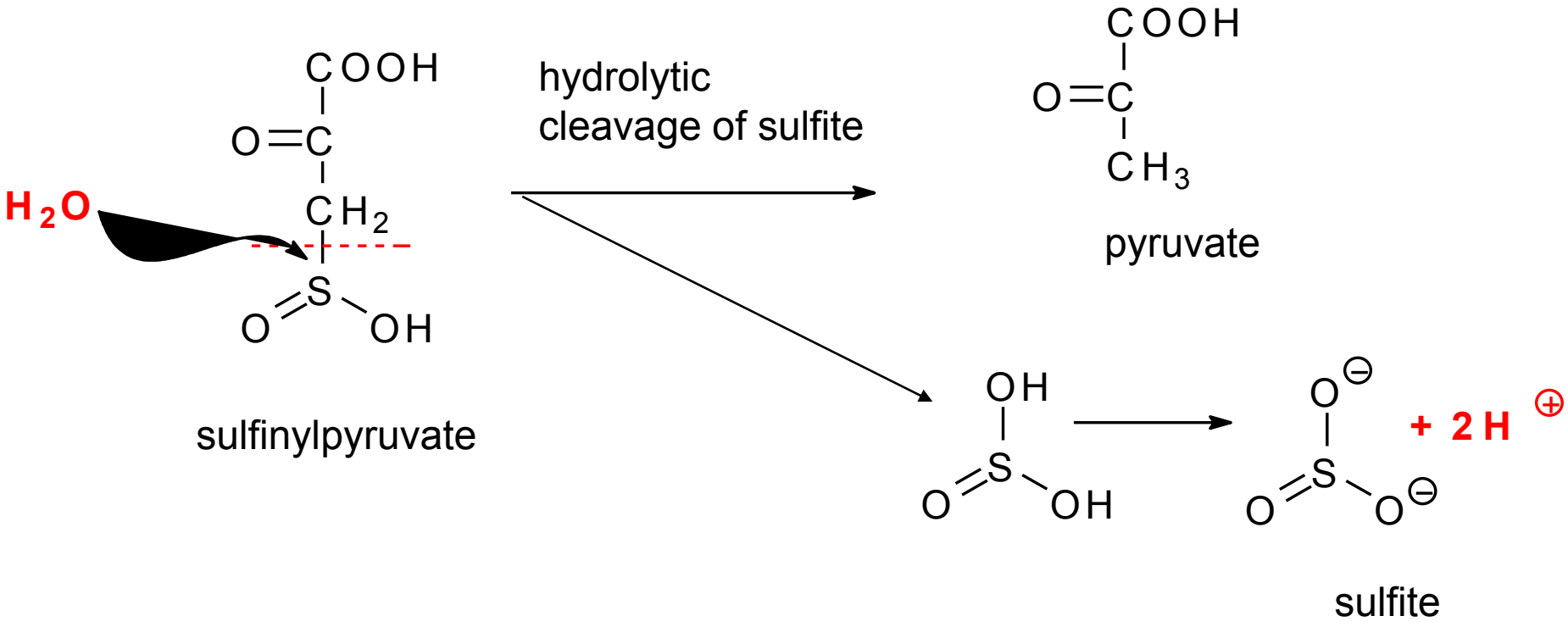
folate, cobalamine, pyridoxin

Cysteine

Cysteine catabolism: oxygenation of -SH group



The formation of sulfite

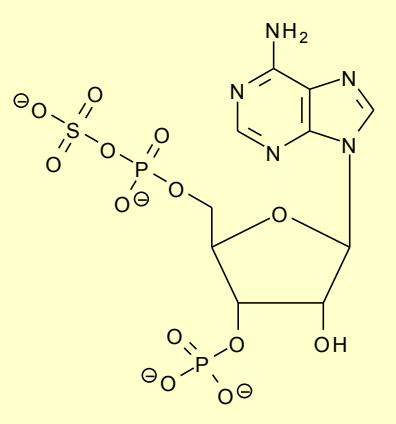


under physiol. pH – dissociation only to HSO_3^-

Sulfite oxidase catalyzes sulfate formation

cysteine

PAPS



$$HSO_3^- + H_2O \rightarrow SO_4^{2-} + 3H^+ + 2e^-$$

blood plasma
(0.5 mmol/l)

urine

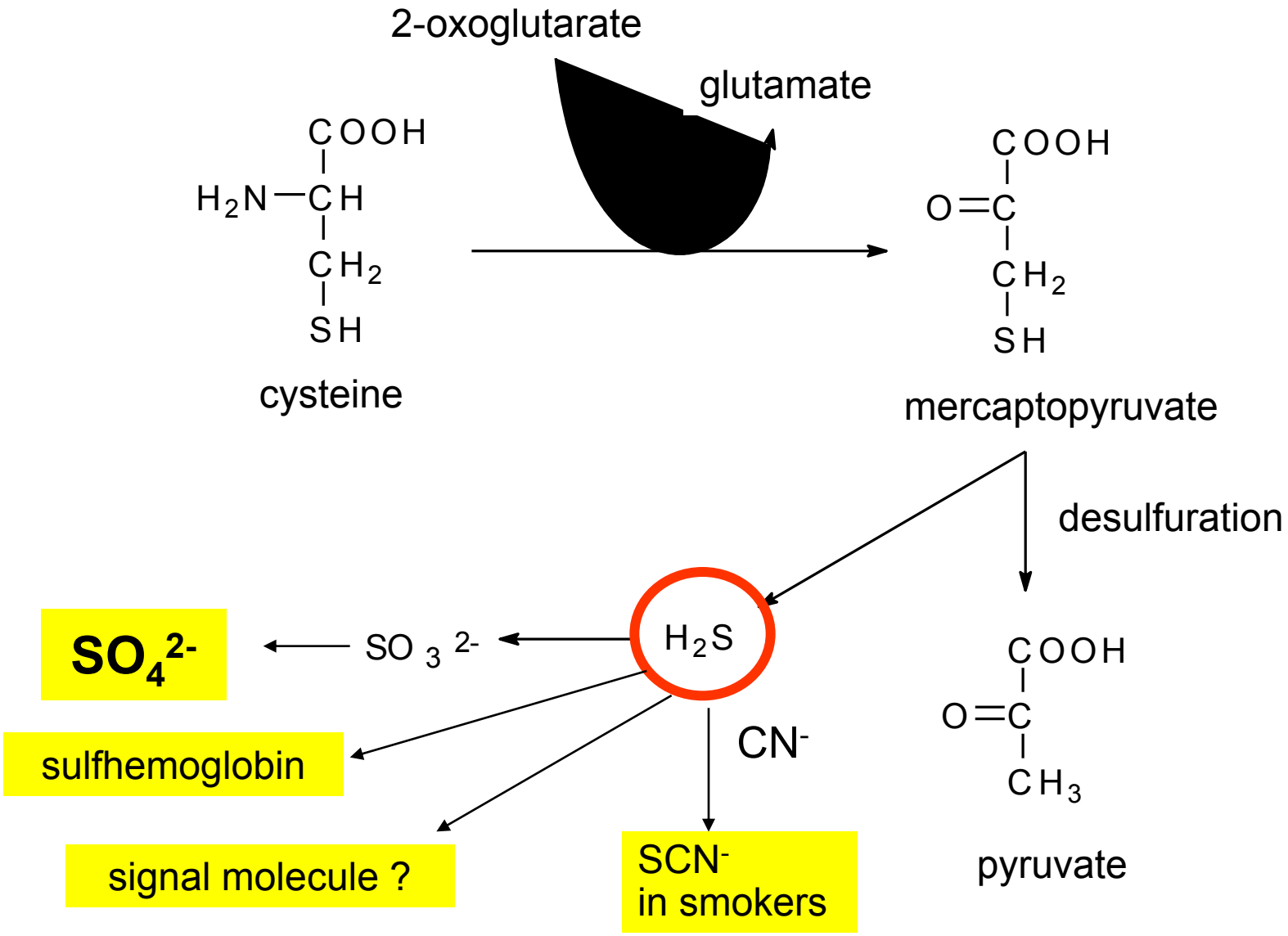
acidify
body fluids

reduce
molybdopterine

Distinguish

Sulfite	anion SO_3^{2-}
Sulfide inorganic	anion S^{2-} (e.g. ZnS zinc sulfide)
Sulfide organic	R-S-R dialkylsulfide
Sulfate	anion SO_4^{2-}

Transamination of cysteine and sulfane production



Cysteine - summary

- both pathways go to pyruvate (glucogenic)
- main catabolism: sulfur oxygenation → sulfite → sulfate
- high protein diet leads to physiologic acidosis
- cystein provids taurine – conjugation agent (e.g. bile acids)
- taurine is semiessential AA in metabolic stress
- taurine is a component of „energy drinks“
- cysteine – part of glutathione (GSH) - antioxidant
- decarboxylation of Cys – cysteamine, in CoA-SH
- in proteins – disulfide bonds (tertiary structure)
- cysteine proteases: active site contains –SH group

Six amino acids provide pyruvate

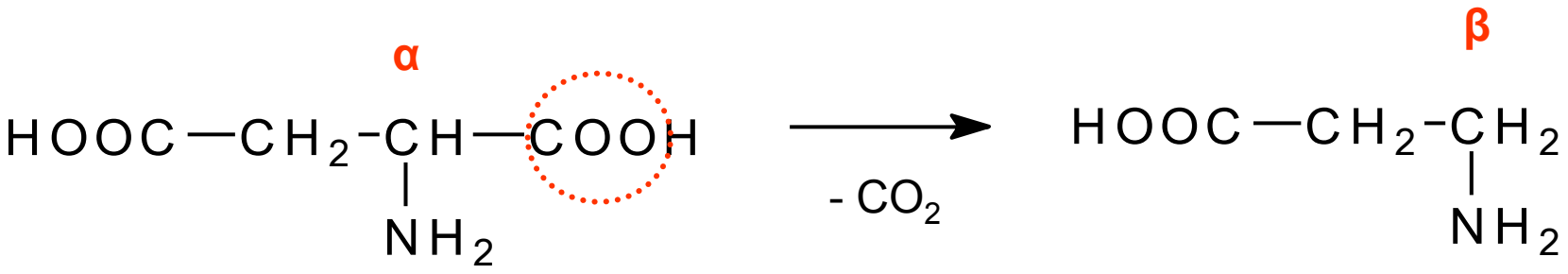
1. Serine – dehydratation + deamination
2. Glycine – *via* serine
3. Threonine – *via* glycine
4. Alanine – transamination (ALT)
5. Cysteine – both catabolic pathways
6. Tryptophan – *via* alanine (see later)

Aspartate

- Transamination of Asp → oxaloacetate (CAC)
- AST (aspartate aminotransferase) – clinically important enzyme
- in urea cycle, Asp donates one nitrogen into urea and releases fumarate
- decarboxylation of Asp → β-alanine (part of coenzyme A)
- donor of nitrogen in purine synthesis (fumarate released)
- whole structure given for pyrimidine bases synthesis
- aspartam (sweetener)
- condensation with ammonia → asparagine

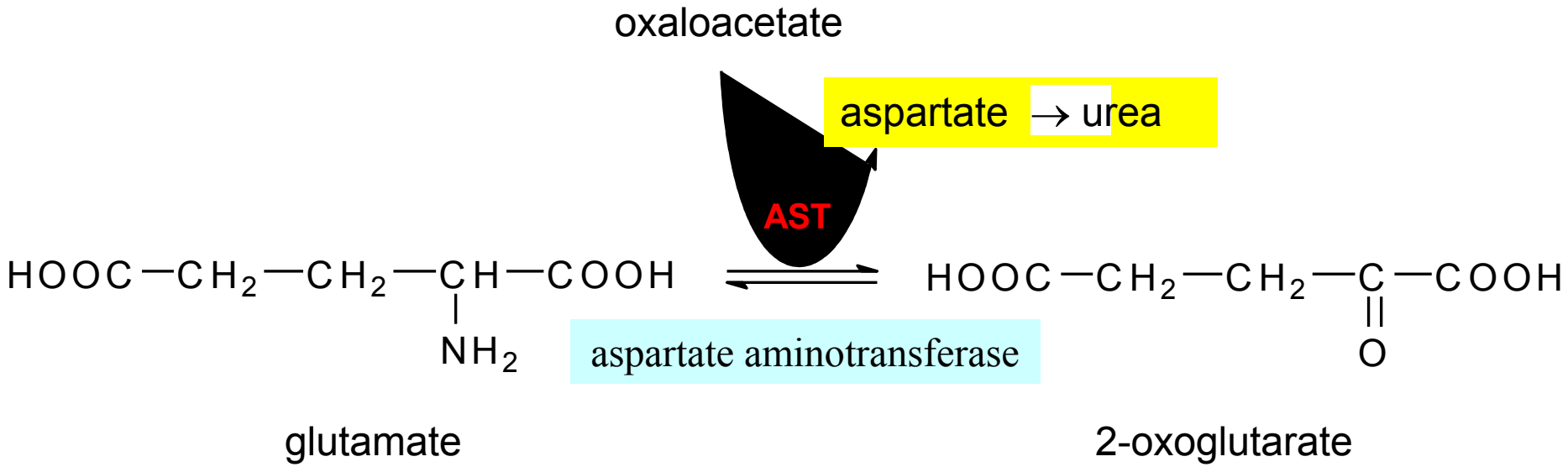
  (for cell utilization, not as detoxication of ammonia)

β-Alanine is made by the decarboxylation of aspartate



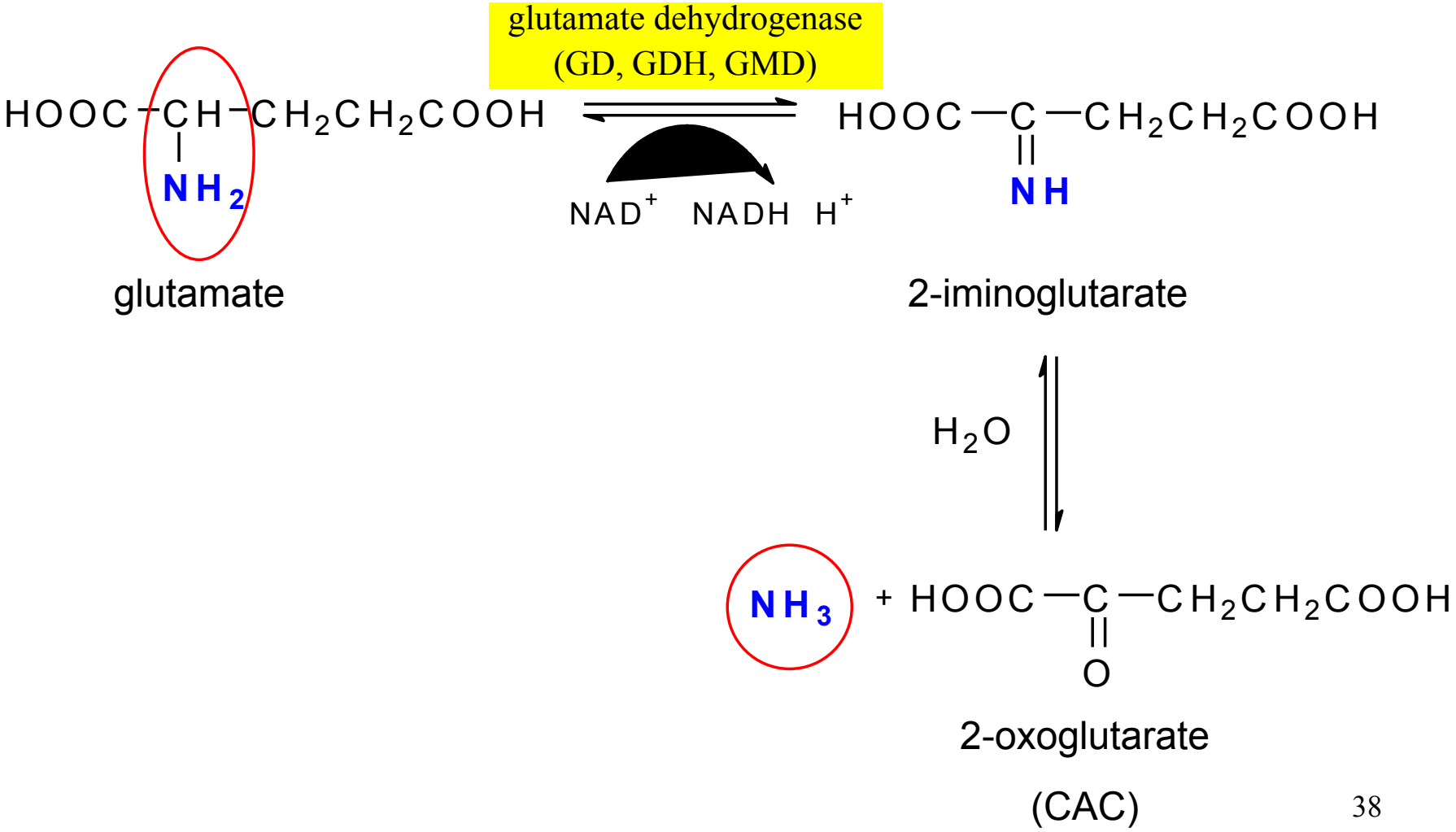
in the structure of CoA-SH

Glutamate with oxaloacetate afford aspartate (transamination)

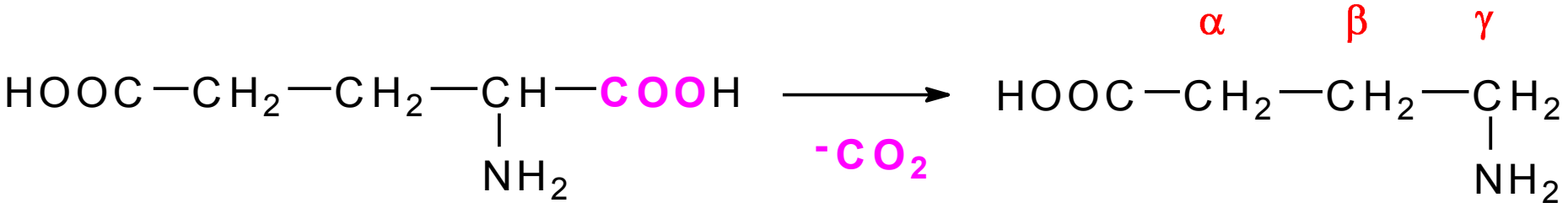


AST reaction produces aspartate for urea synthesis

Dehydrogenative deamination of glutamate is the main producer of ammonia in tissues



Decarboxylation of glutamate



glutamate

GABA

gama-aminobutyric acid

Glutamate - summary

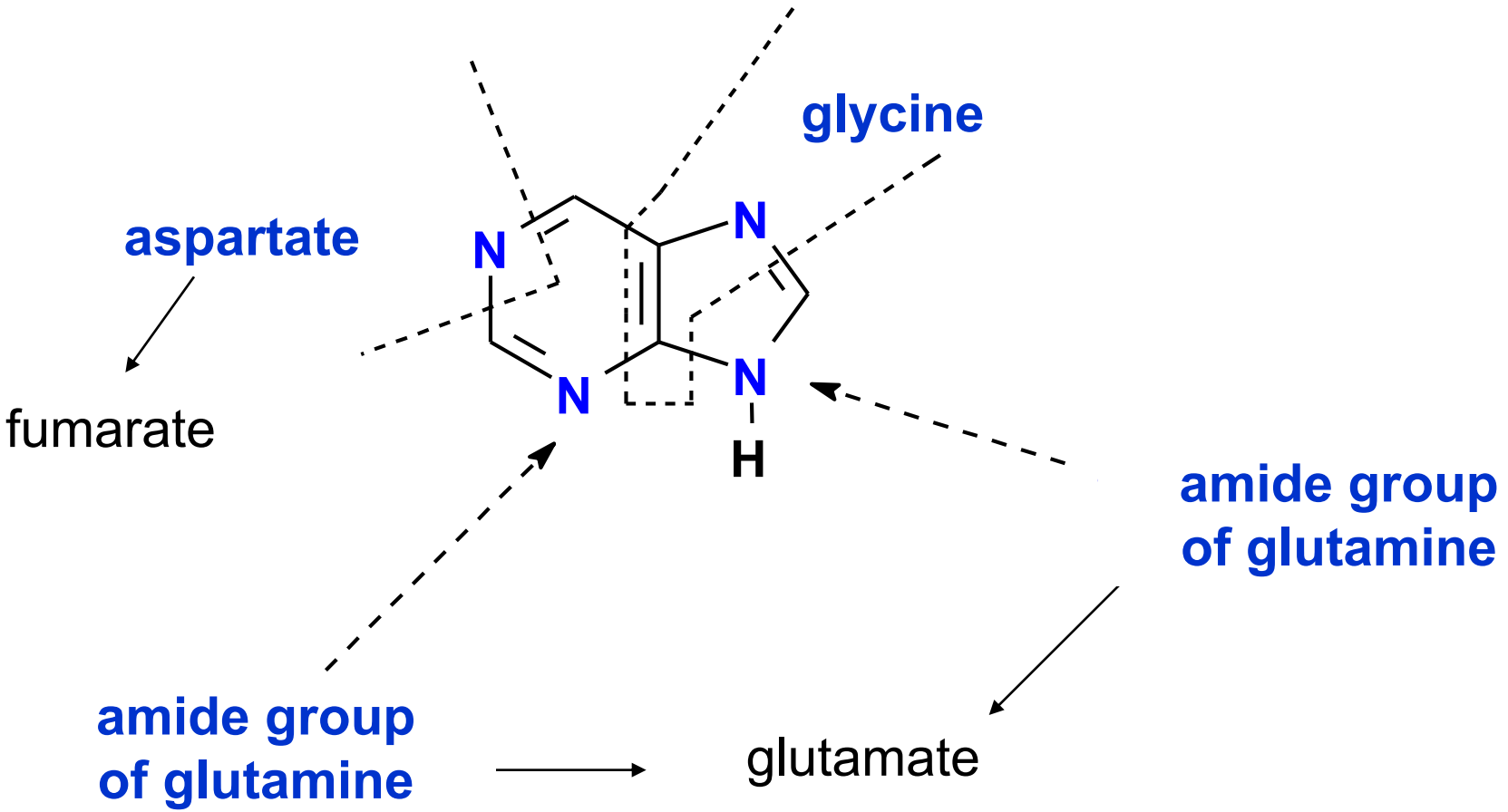
- produced in the transaminations of most AA
- glutamate dehydrogenase reaction produces most ammonia in body
- **transaminations are reversible**, so glutamate can be converted to 2-oxoglutarate (glucogenic)
- Glu + NH_3 ⇆ Gln (ammonia detoxification)
- glutamate is readily made from glutamine, histidine, proline, ornithine
- pure monosodium glutamate (MSG, E621), flavour enhancer, can cause health problems (chinese restaurant syndrome)

Glutamine

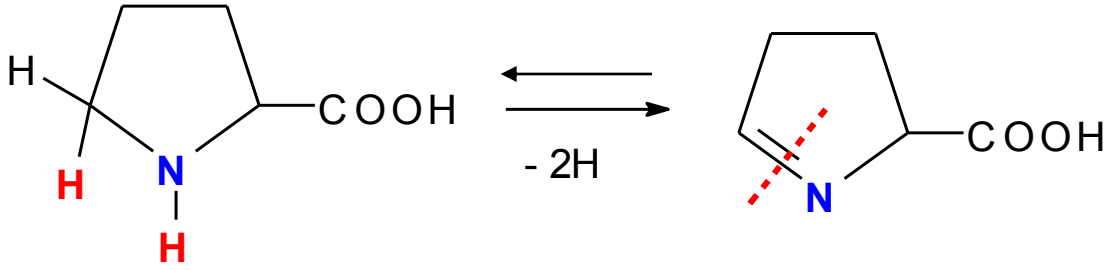
See also the previous lecture (AA-1)

- glutamine synthesis is the way of ammonia detoxification in tissues including liver
- in kidneys, glutamine releases ammonia (deamidation)
- metabolic fuel for some tissues (enterocytes, fibroblasts, lymphocytes, macrophages)
- donor of nitrogen for syntheses (glucosamine, purines)

Three amino acids donate four N atoms in purine bases synthesis



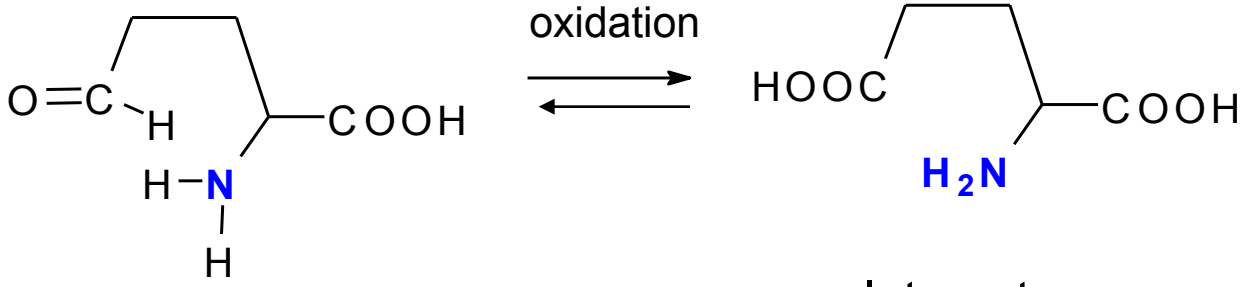
Proline is converted to glutamate (and *vice versa*)



proline

pyrroline-5-carboxylate

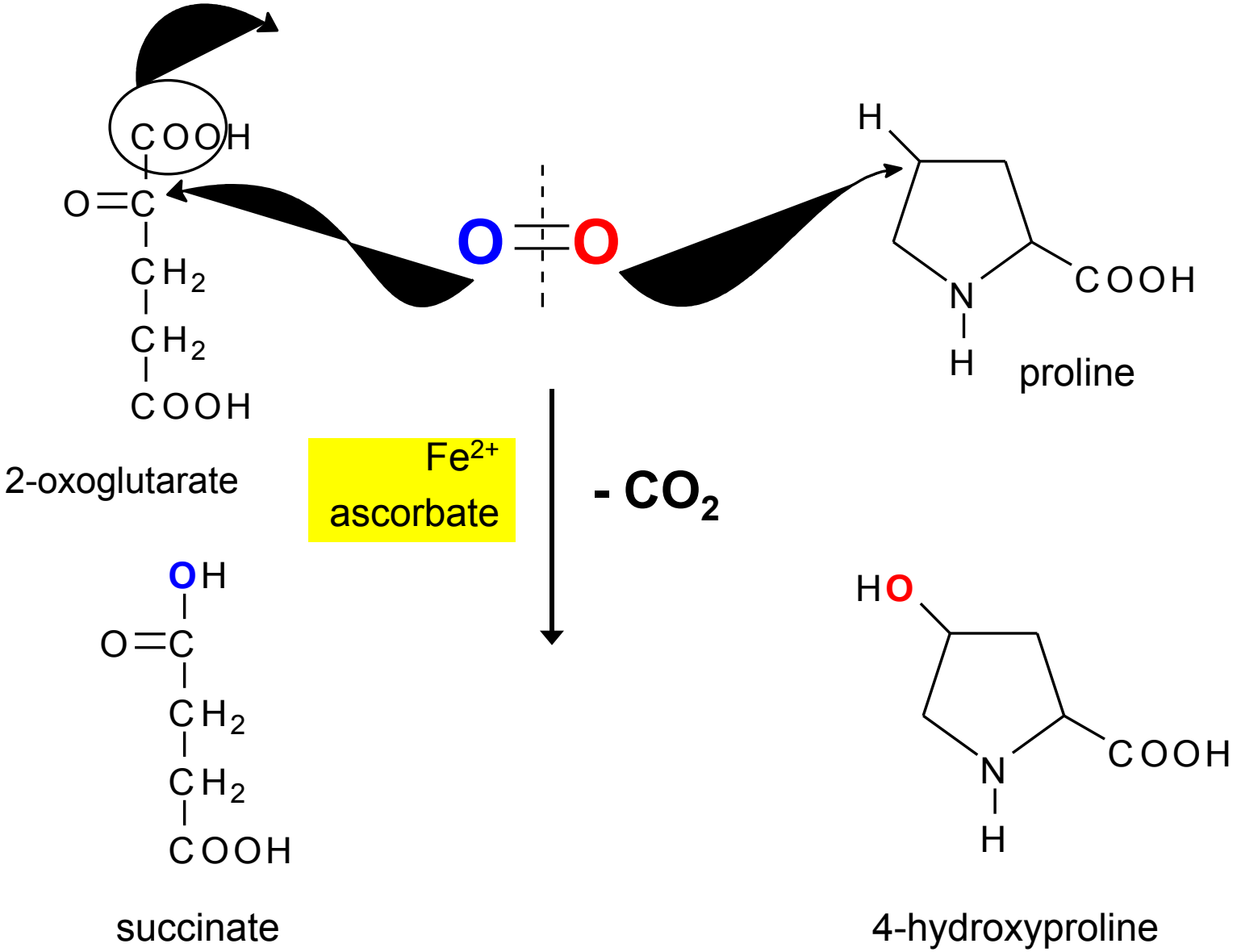
addition of H_2O
ring opening



glutamate 5-semialdehyde

glutamate

Hydroxylation of proline with 2-oxoglutarate as reductant



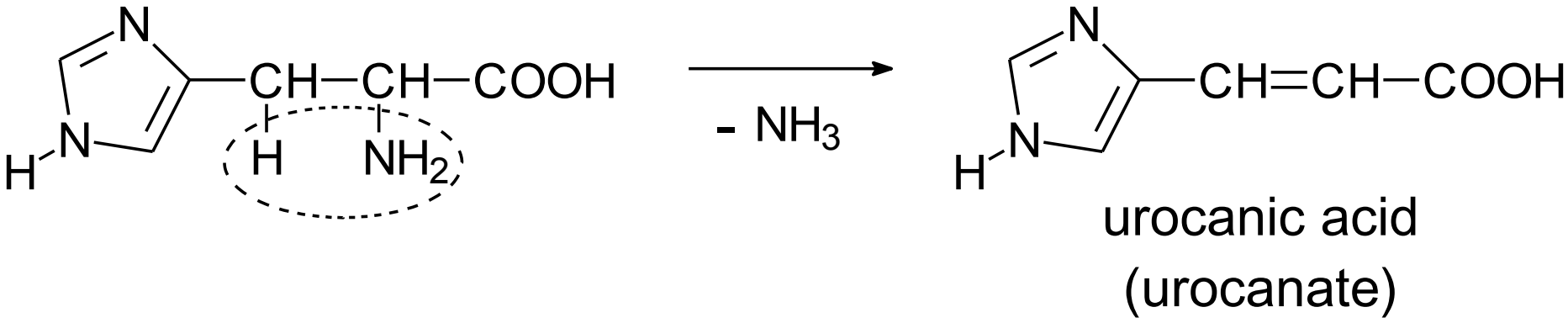
Proline - summary

- non-essential AA, can be formed from glutamate
- converted to glutamate (glucogenic)
- hydroxylation of proline in collagen is post-translation modification, requires ascorbate (vitamin C), Fe^{2+}, and 2-oxoglutarate (unusual co-reductant)
- 4-hydroxyproline is catabolized to pyruvate (see Harper)

Histidine

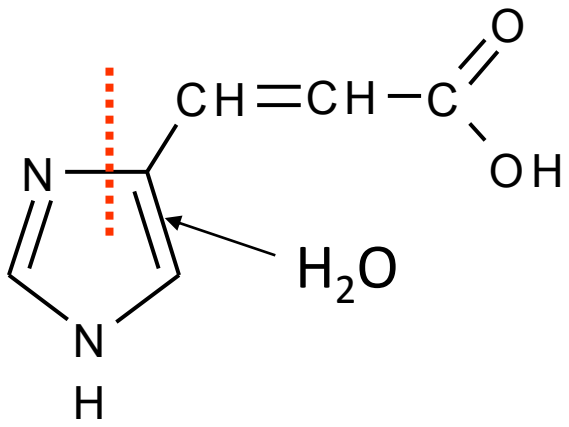
no transamination

Catabolism of histidine starts with desaturation and deamination



urocanic acid
(urocanate)

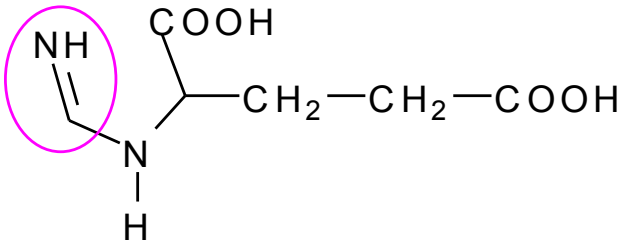
Urocanate cleavage affords C_1 fragment



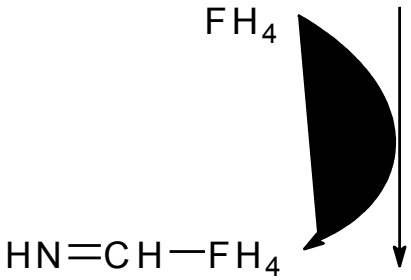
urocanate

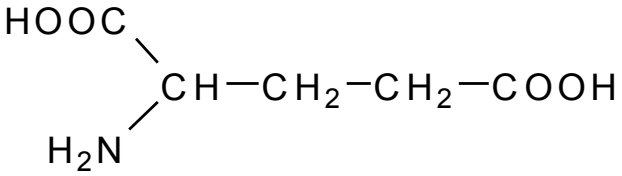
addition of water

oxidative ring splitting



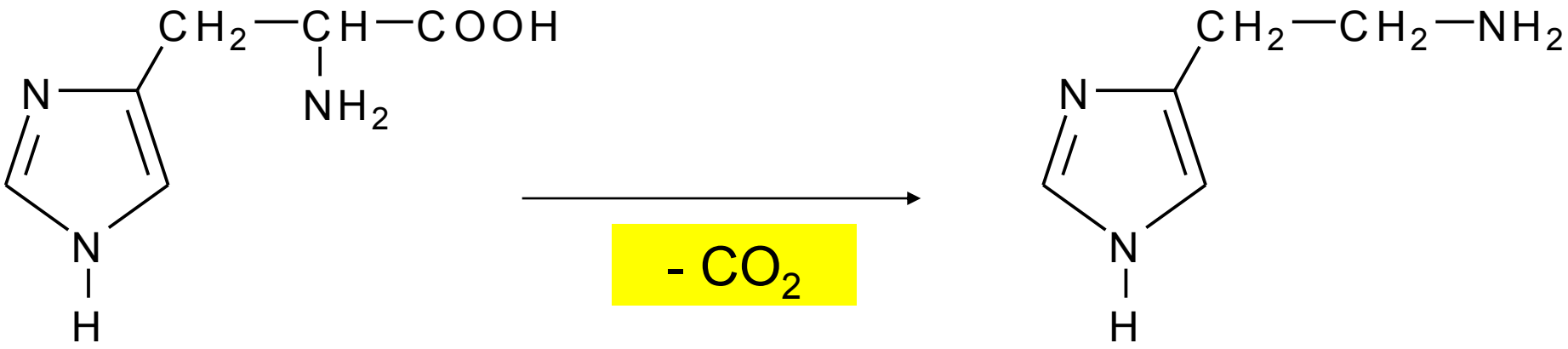
N-formiminoglutamate (Figlu)





glutamate

Decarboxylation of histidine → histamine

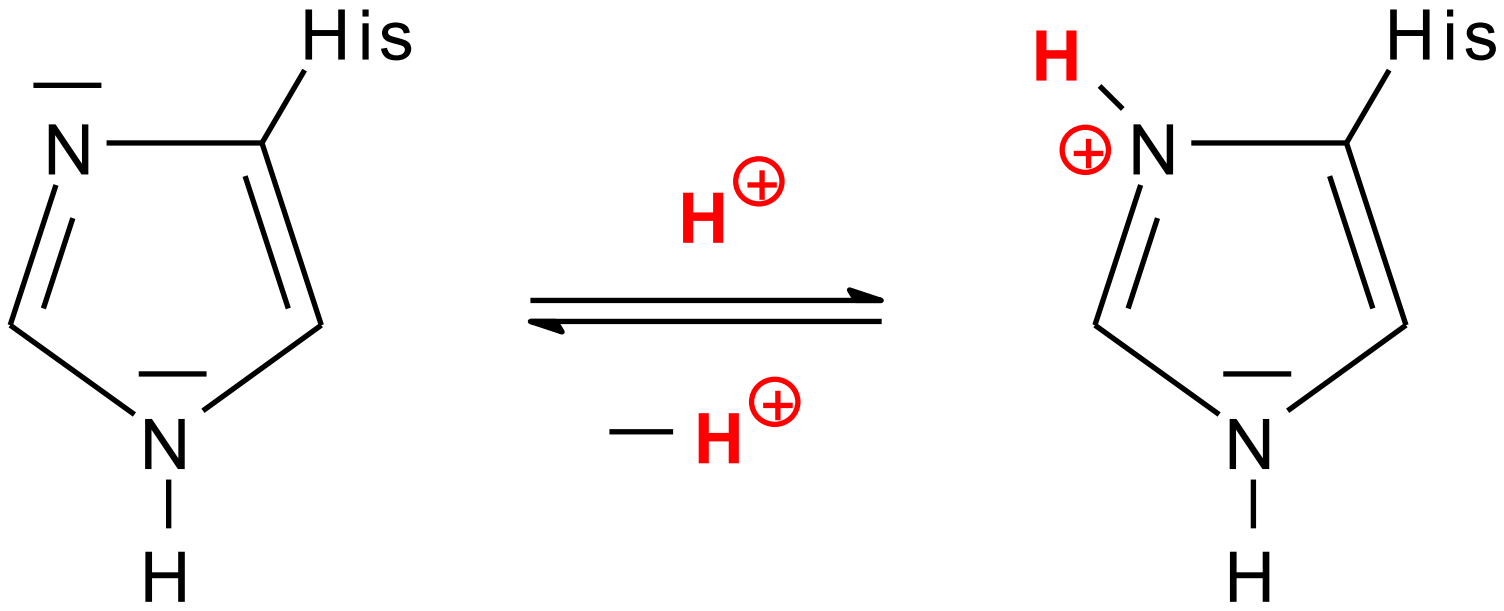


histidine

histamine

- histidine decarboxylase occurs in mast cells and basophils
- histamine stimulates HCl production in stomach
- is released in allergic reactions
- triggers inflammatory response
- antihistaminics are drugs blocking the action of histamine

Histidine is responsible for buffering actions of proteins



$pK_B = 8$

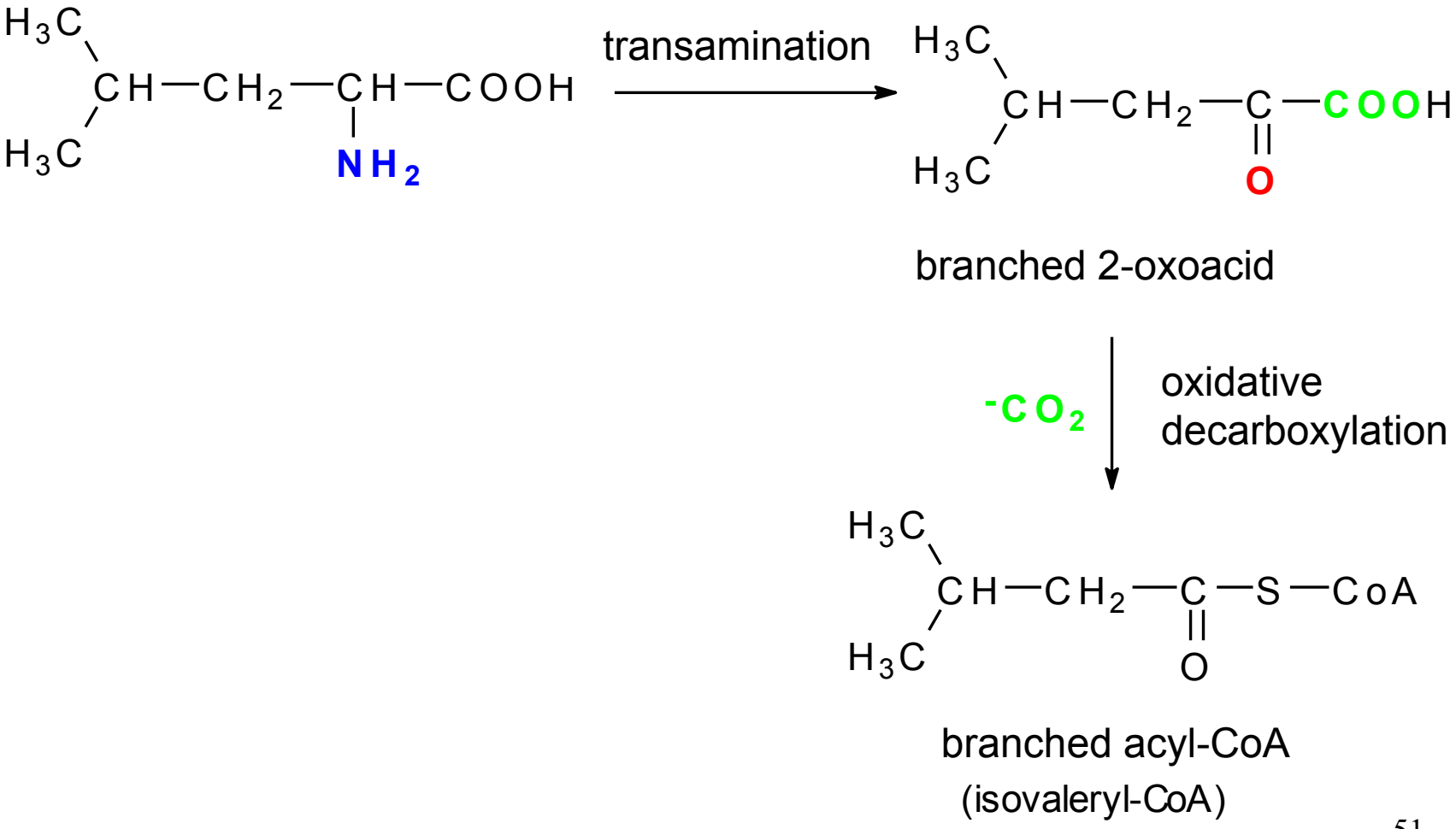
pK_A (His) = 6

pK_A (His in proteins) = 6-8

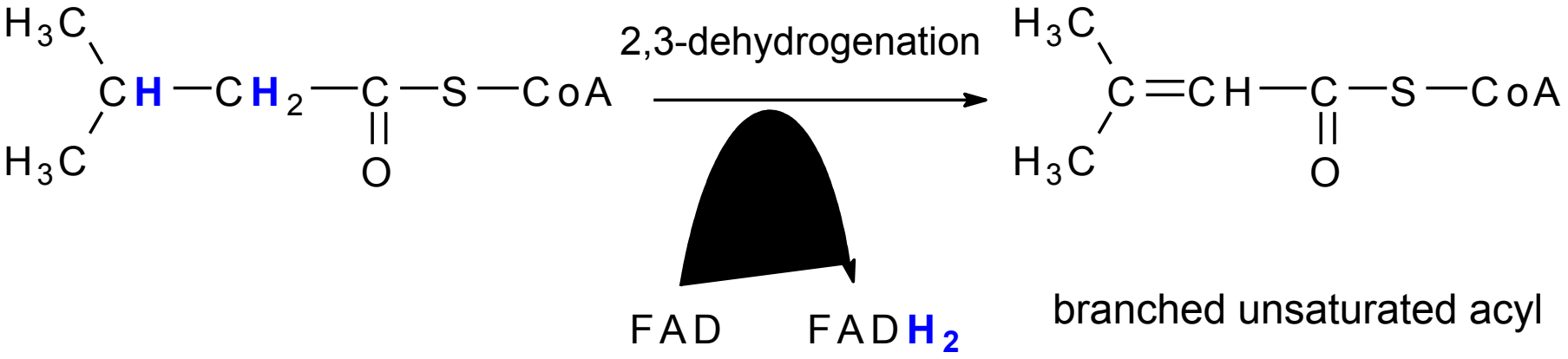
Histidine - summary

- semiessential AA
- no transamination, catabolism begins with desaturation and deamination
- the source of 1C groups (formimino)
- converted to glutamate (glucogenic)
- histidine is abundant in hemoglobin – buffer system
- post-translation modification: methylation of His in actine/myosine → 3-methylhistidine – its urine excretion is the indicator of muscle proteolysis and nutrition status

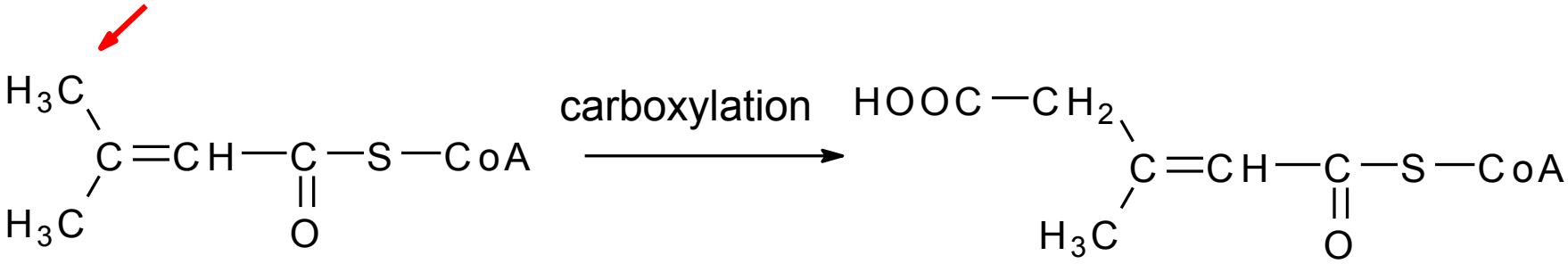
Leucine (1) - transamination + decarboxylation



Leucine (2) - dehydrogenation



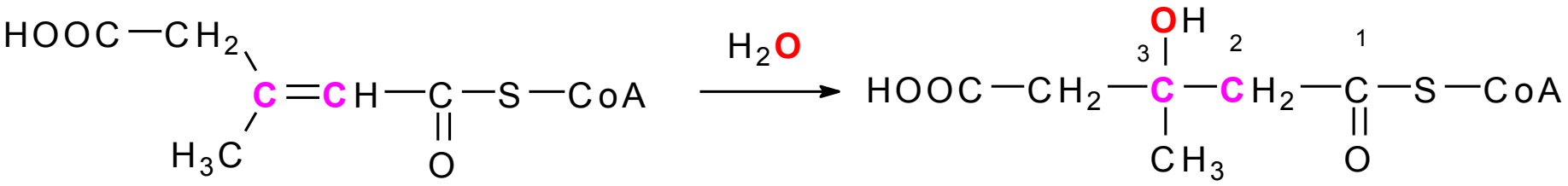
Leucine (3) – carboxylation at C4



acyl of dicarboxylic

branched unsaturated acid

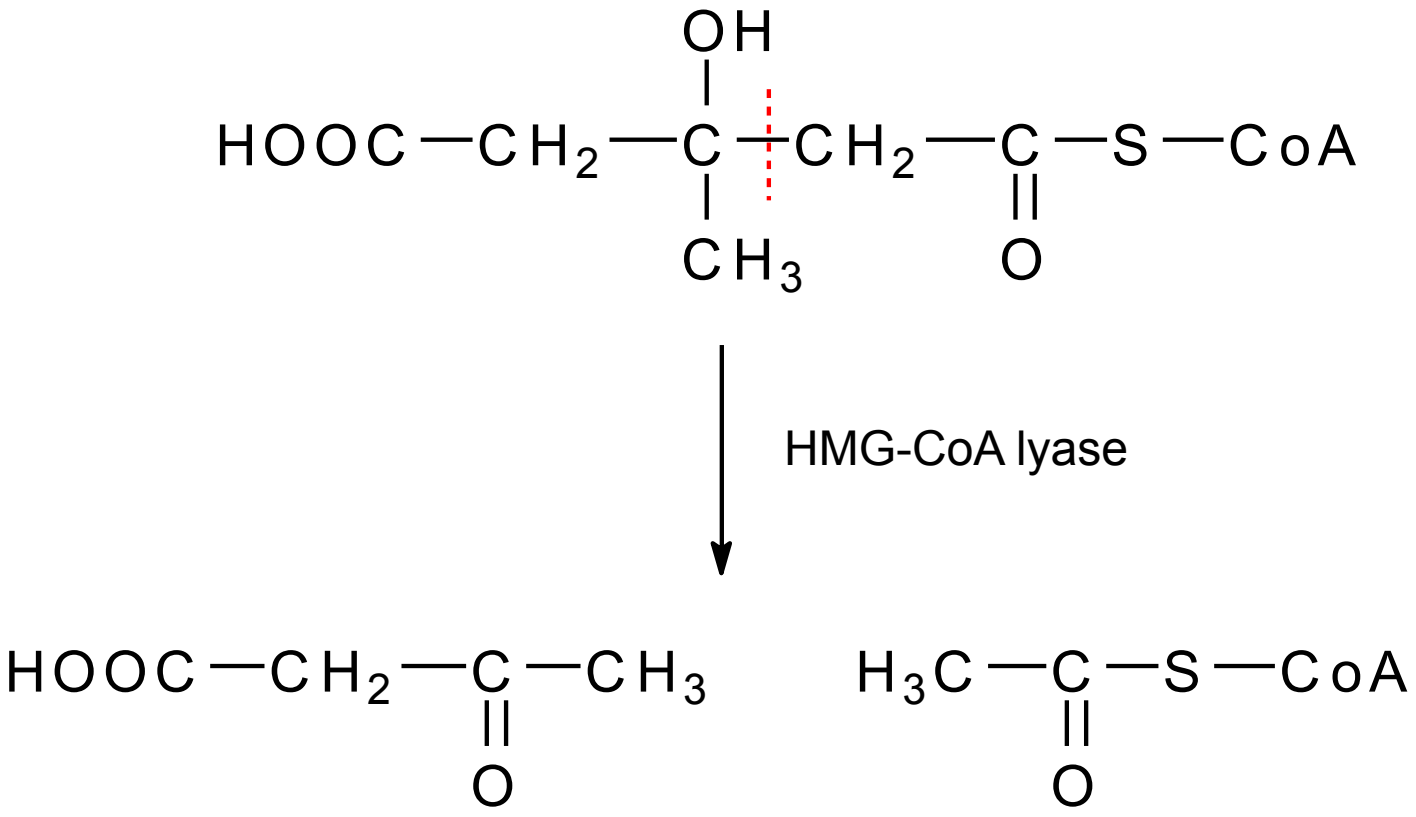
Leucine (4) – hydratation of double bond



3-hydroxy-3-methylglutaryl-CoA

(HMG-CoA)

Leucine (5) – splitting the C-C bond in HMG-CoA



acetoacetate **acetyl-CoA**

Compare the final products of BCAA

Leucine	acetyl-CoA + acetoacetate	ketogenic
B_{12} **Isoleucine**	acetyl-CoA + succinyl-CoA	ketogenic glucogenic
B_{12} **Valine**	succinyl-CoA	glucogenic

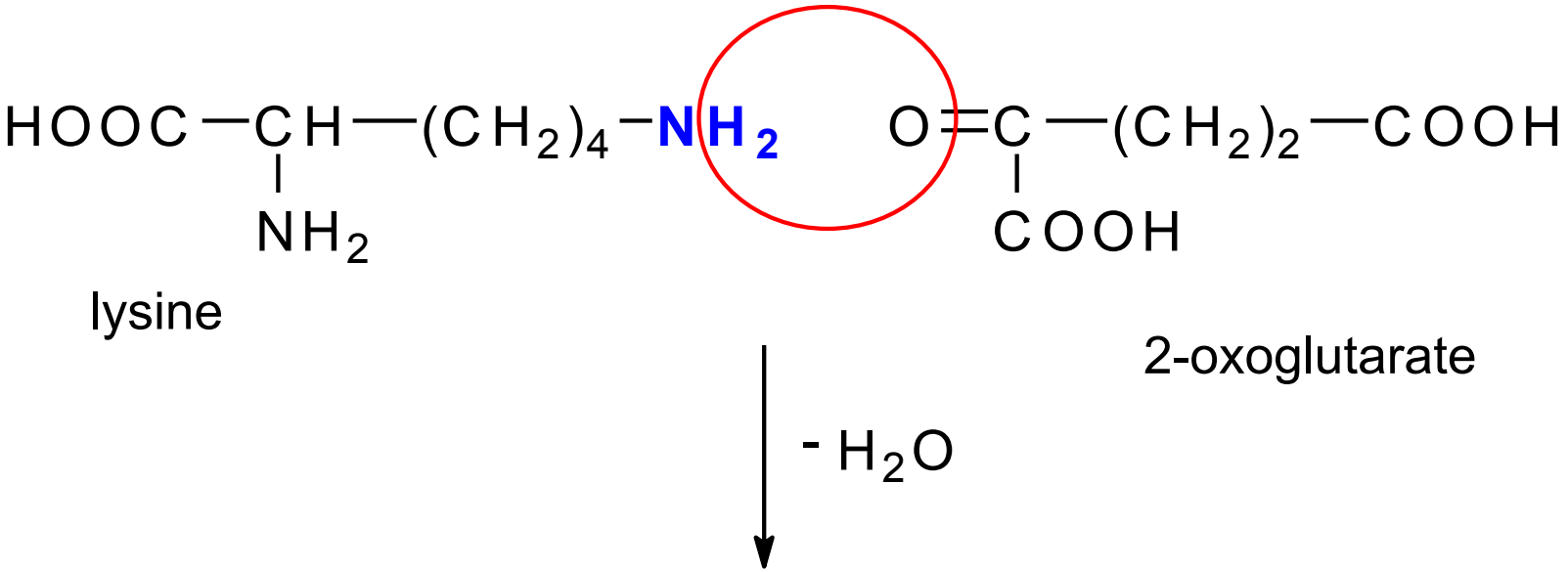
BCAA - summery

- all BCAA are essential
- the first three reactions are the same (transamination, oxid. decarboxylation, dehydrogenation), final products are different
- leucine – ketogenic, valine – glucogenic, isoleucine – mixed
- after meal, BCAA make about 70 % of AA in blood, because the liver does not utilize them (lack of aminotransferases)
- **BCAA are most utilized in muscles and brain**
- BCAA infusion are applied in severe catabolic conditions

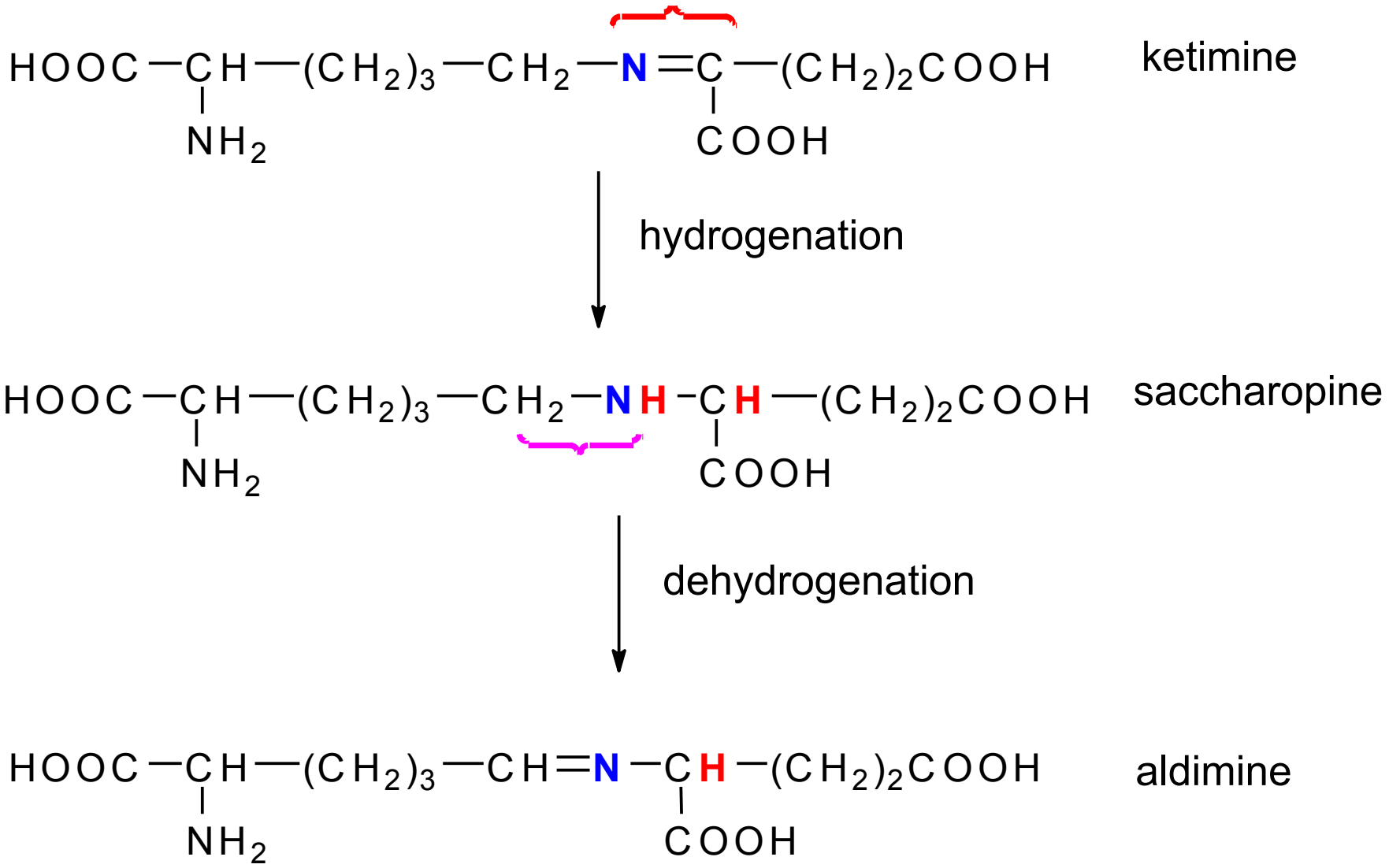
Lysine

no transamination

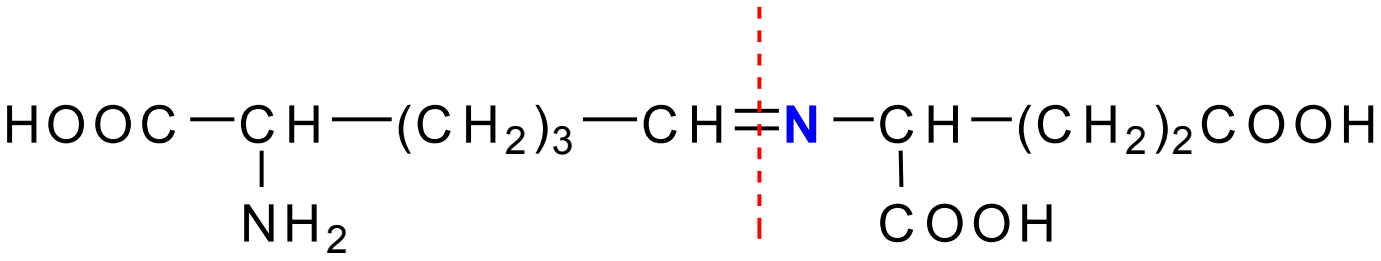
Lysine catabolism (1)



Lysine catabolism (2)

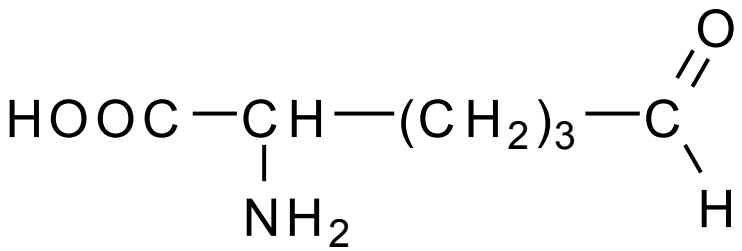


Lysine catabolism (3)

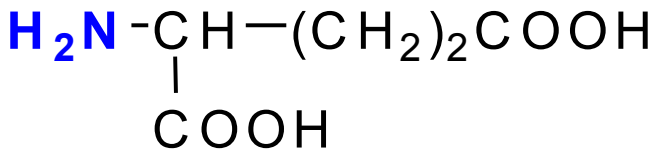


aldimine

hydrolysis

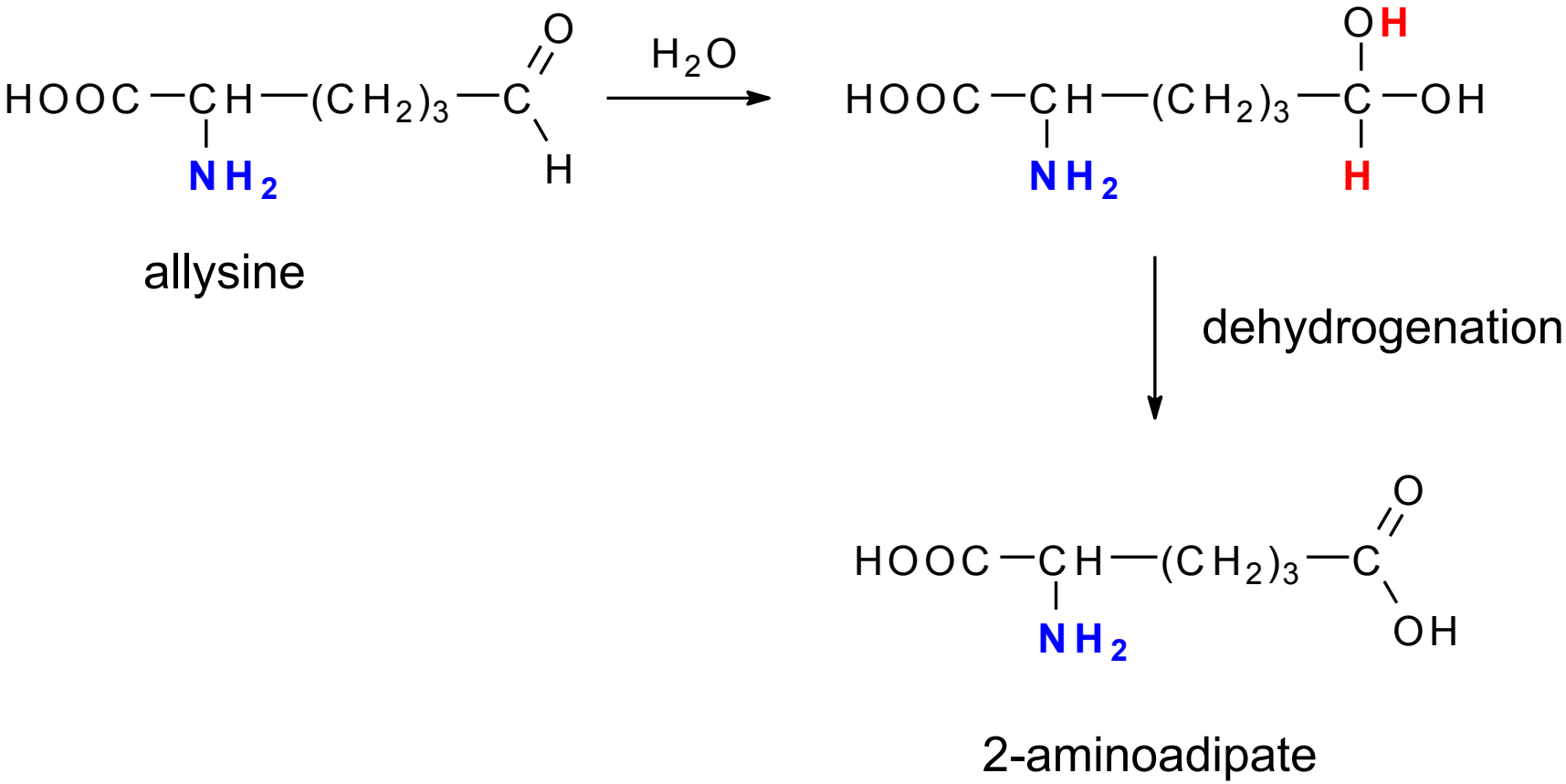


allysine



glutamate

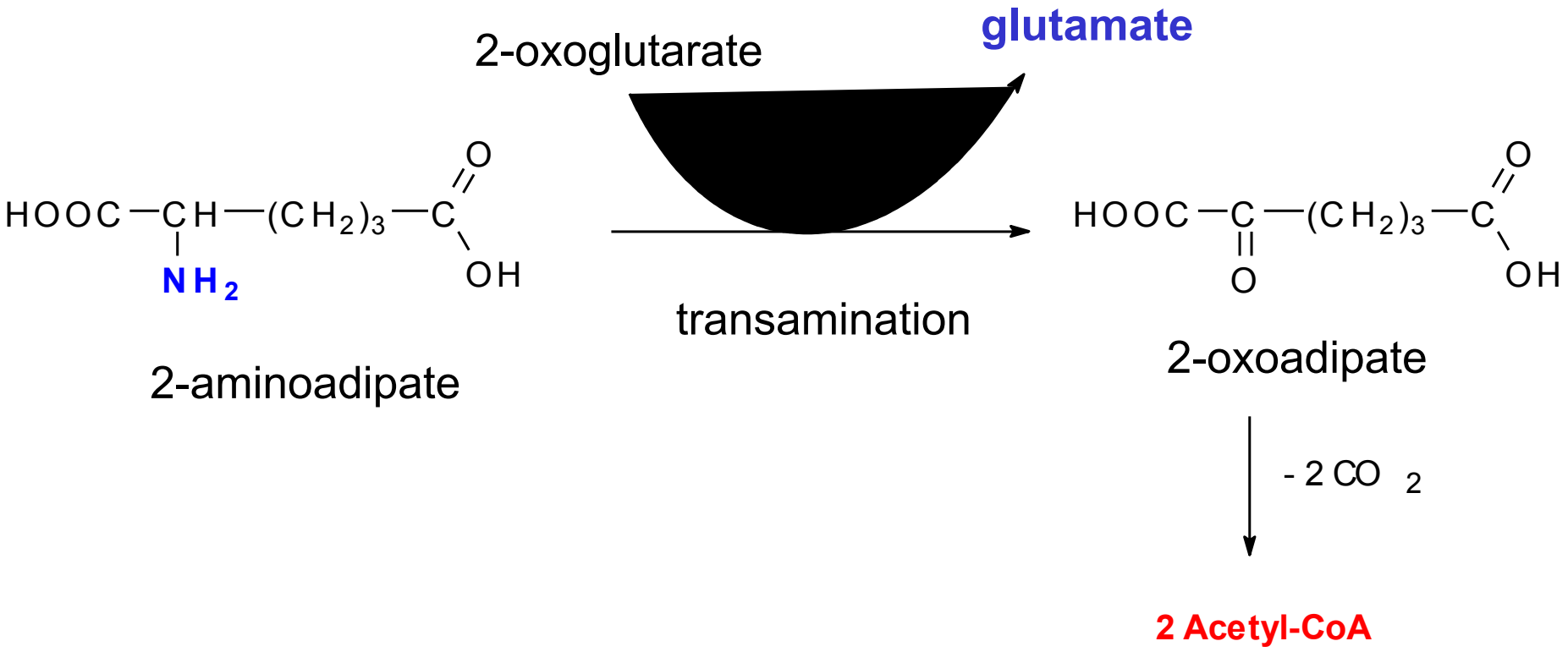
Lysine catabolism (4)



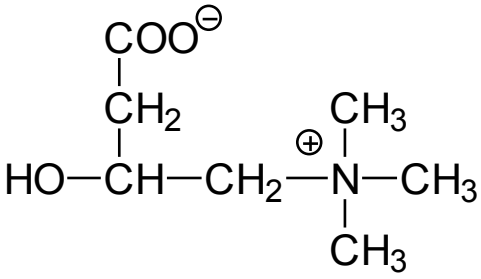
allysine

2-aminoadipate

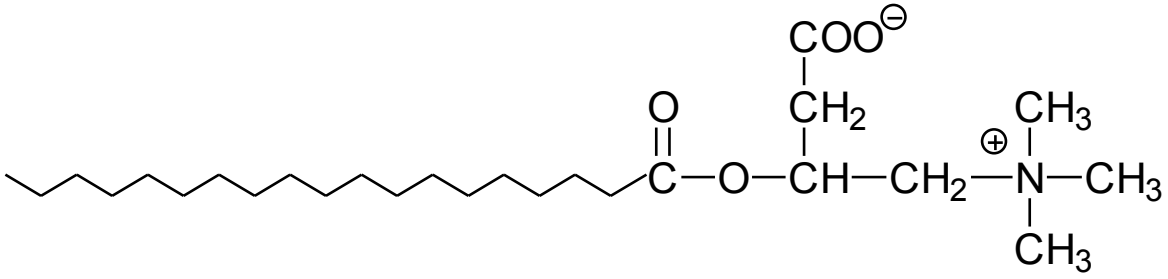
Lysine catabolism (5)



Lysine is the substrate for carnitine (the transfer of FA from cytosol to mitochondria)



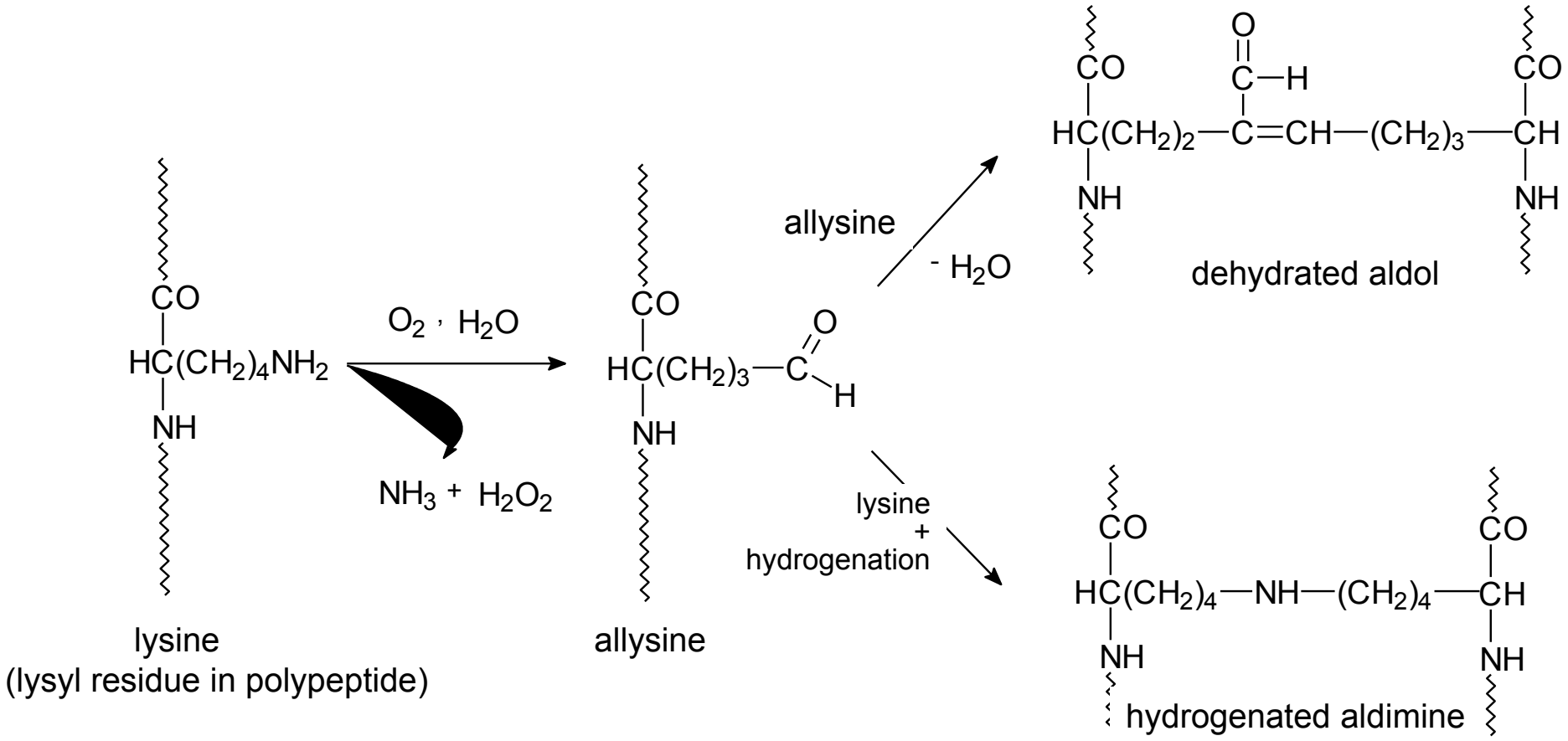
carnitine



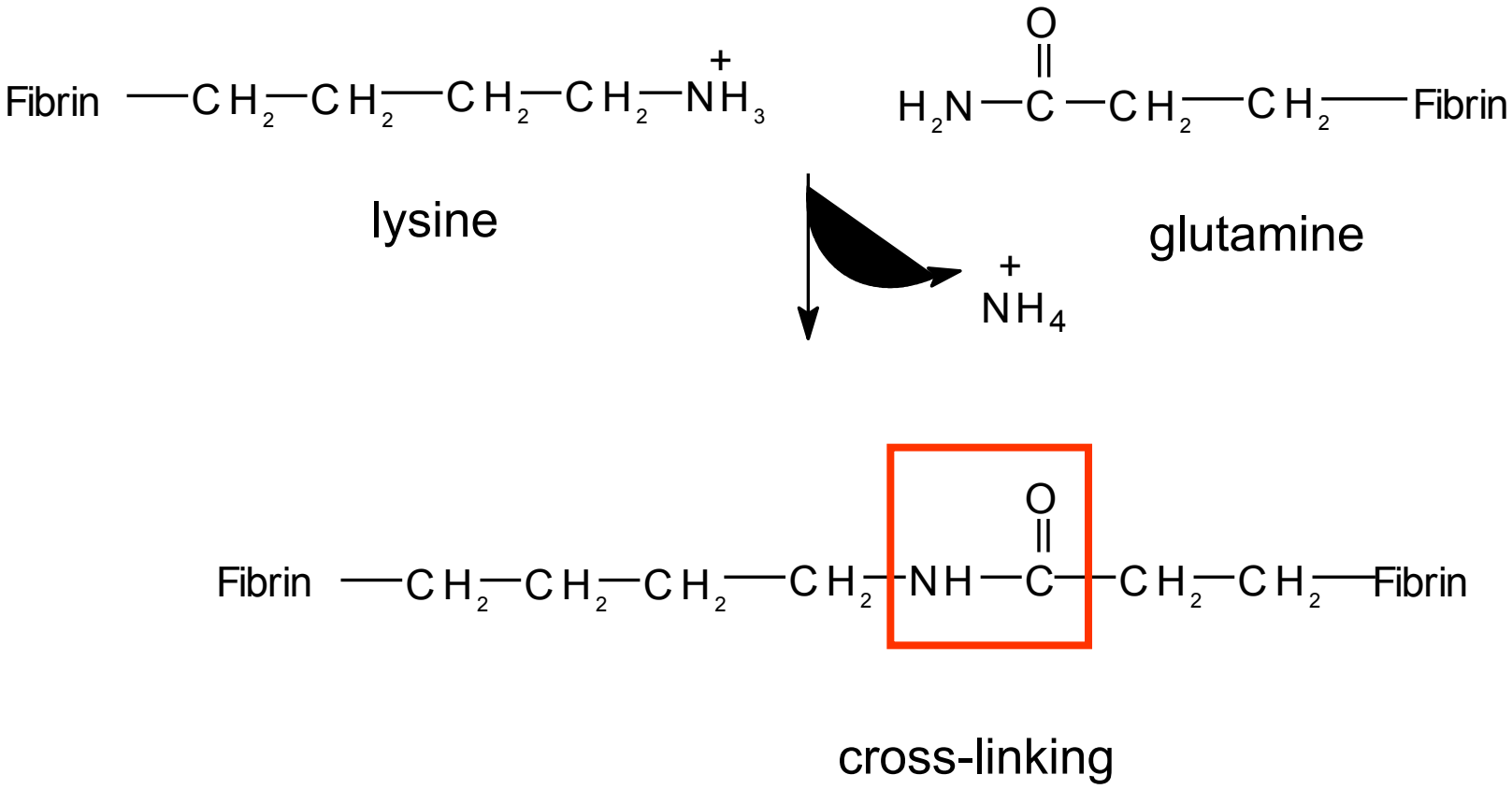
acylcarnitine

Cross-links in collagen

products of reaction between the amino groups in side chains of **lysine** with the modified lysine side chains comprising the aldehyde group (the result of oxidation of lysine to **allysine**) – aldol type or aldimine type of cross-links.



Formation of fibrin clot during blood coagulation (cross-linking of fibrin)



Lysine - summary

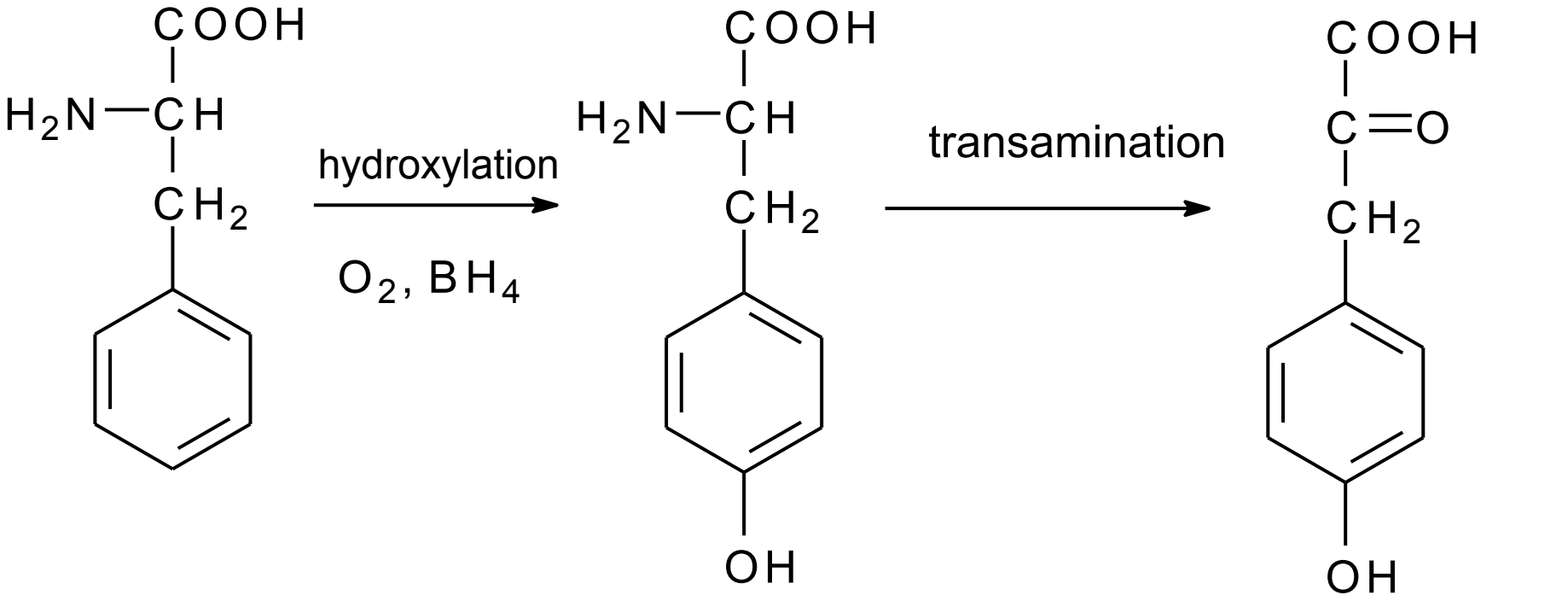
- essential AA, no transamination
- ε-amino group is removed as glutamate
- α-amino group is removed from aminoadipate by transamination
- final product acetyl-CoA (ketogenic)

Other conversions:

- lysine in many proteins binds ubiquitin (targeting for proteasome)
- carnitine (transport system for FA to mitochondria)
- decarboxylation → cadaverine
- in collagen: cross bridges, hydroxylation → hydroxylysine
- in fibrin: cross linking during blood coagulation

Phenylalanine, Tyrosine

Catabolism (1)

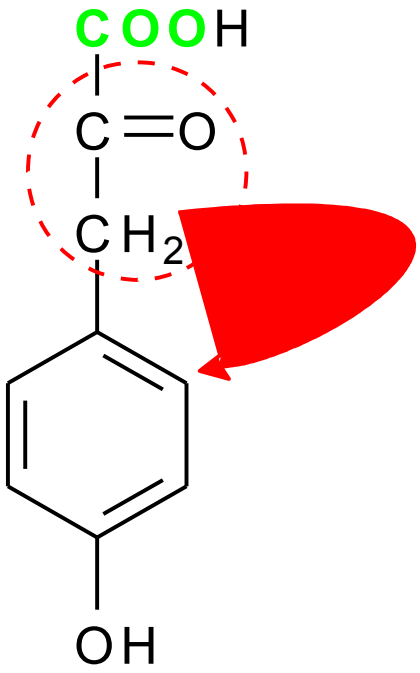


phenylalanine

tyrosine

p-hydroxyphenylpyruvate

Catabolism (2)



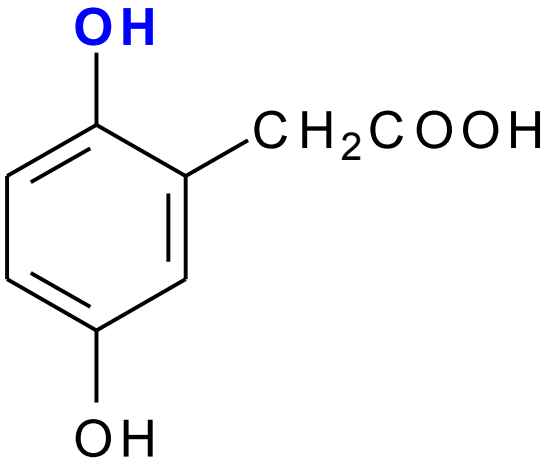
p-hydroxyphenylpyruvate

oxidative decarboxylation

rearrangement

hydroxylation

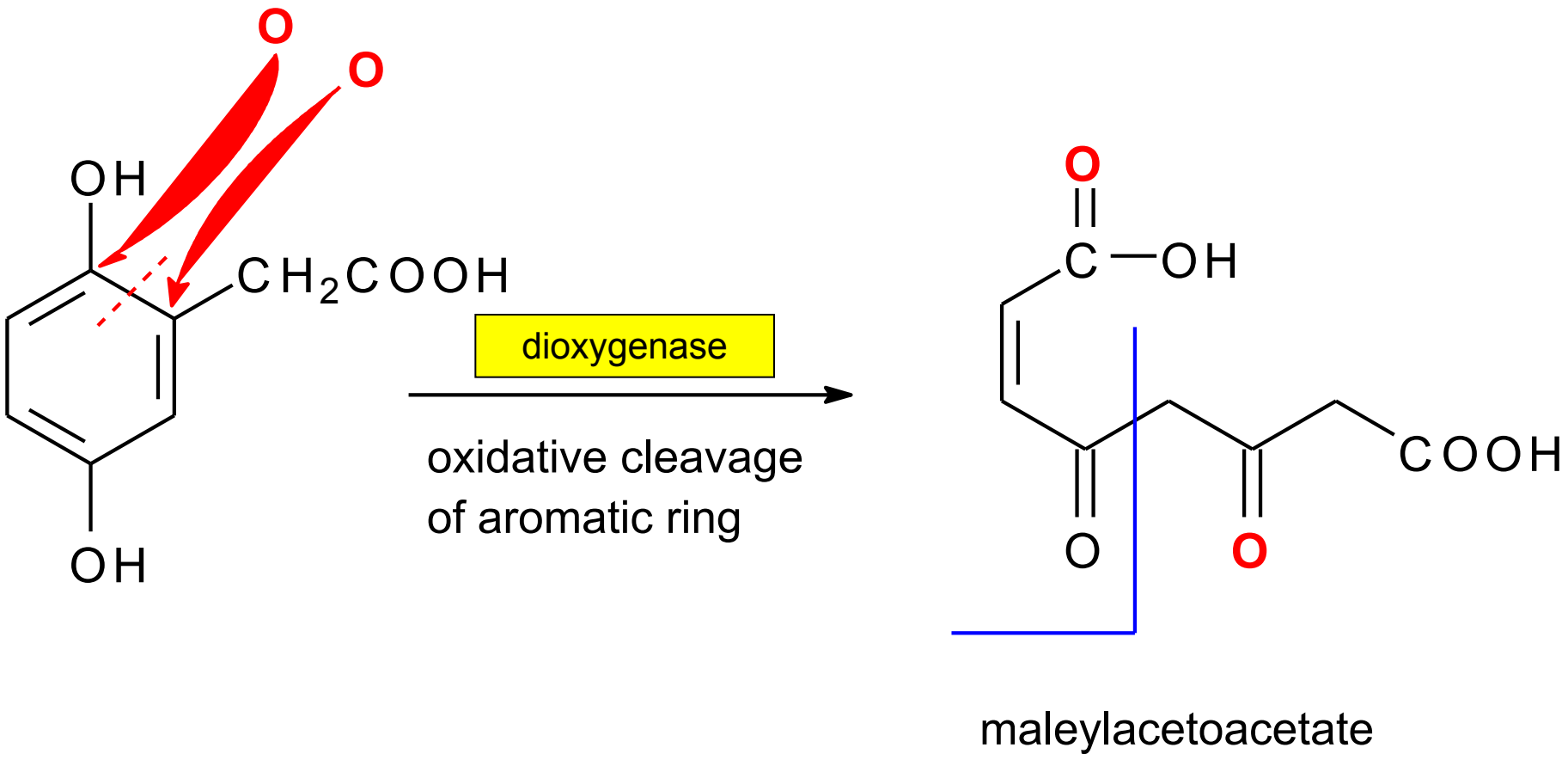
$-CO_2$



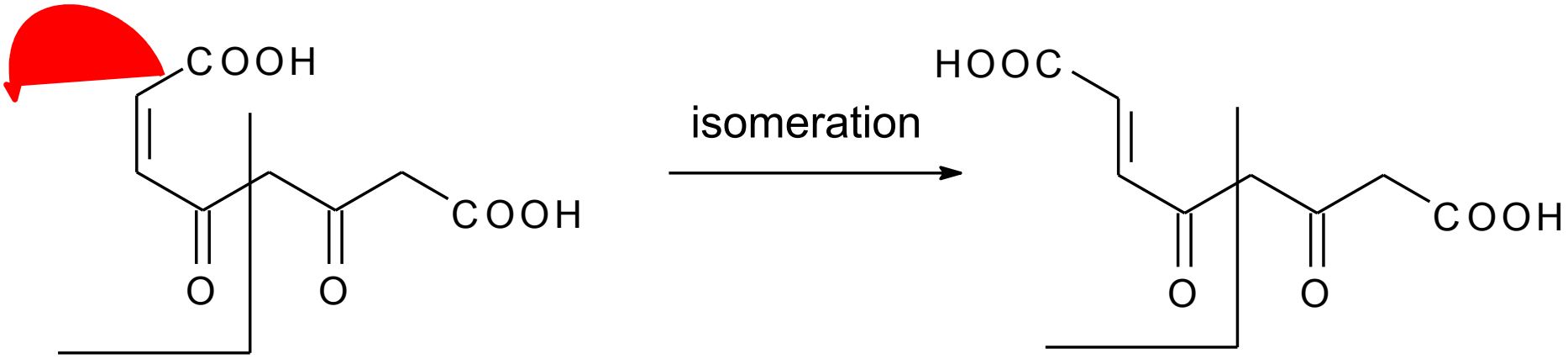
homogentisate

(2,5-dihydroxyphenylacetate)

Catabolism (3)



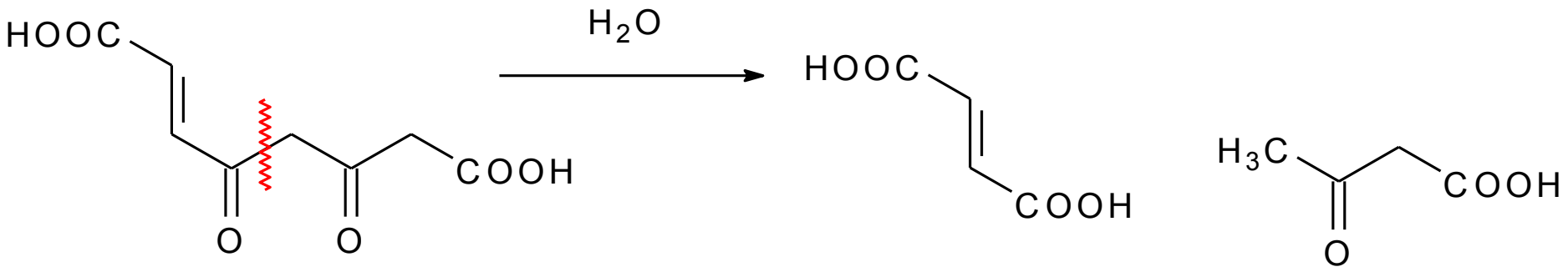
Catabolism (4)



maleylacetoacetate

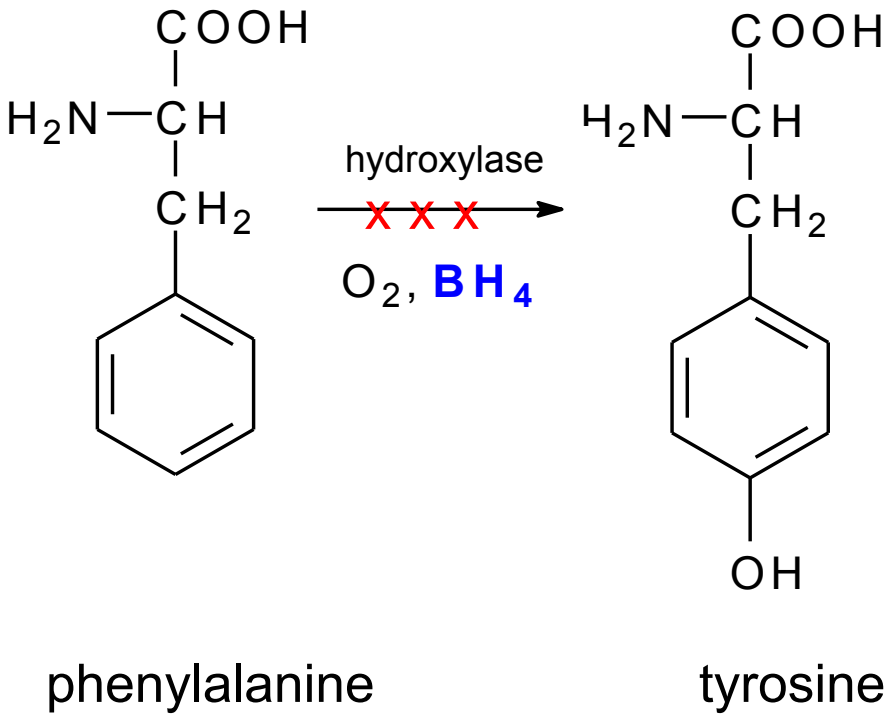
fumarylacetoacetate

Catabolism (5)



fumarylacetoacetate fumarate acetoacetate

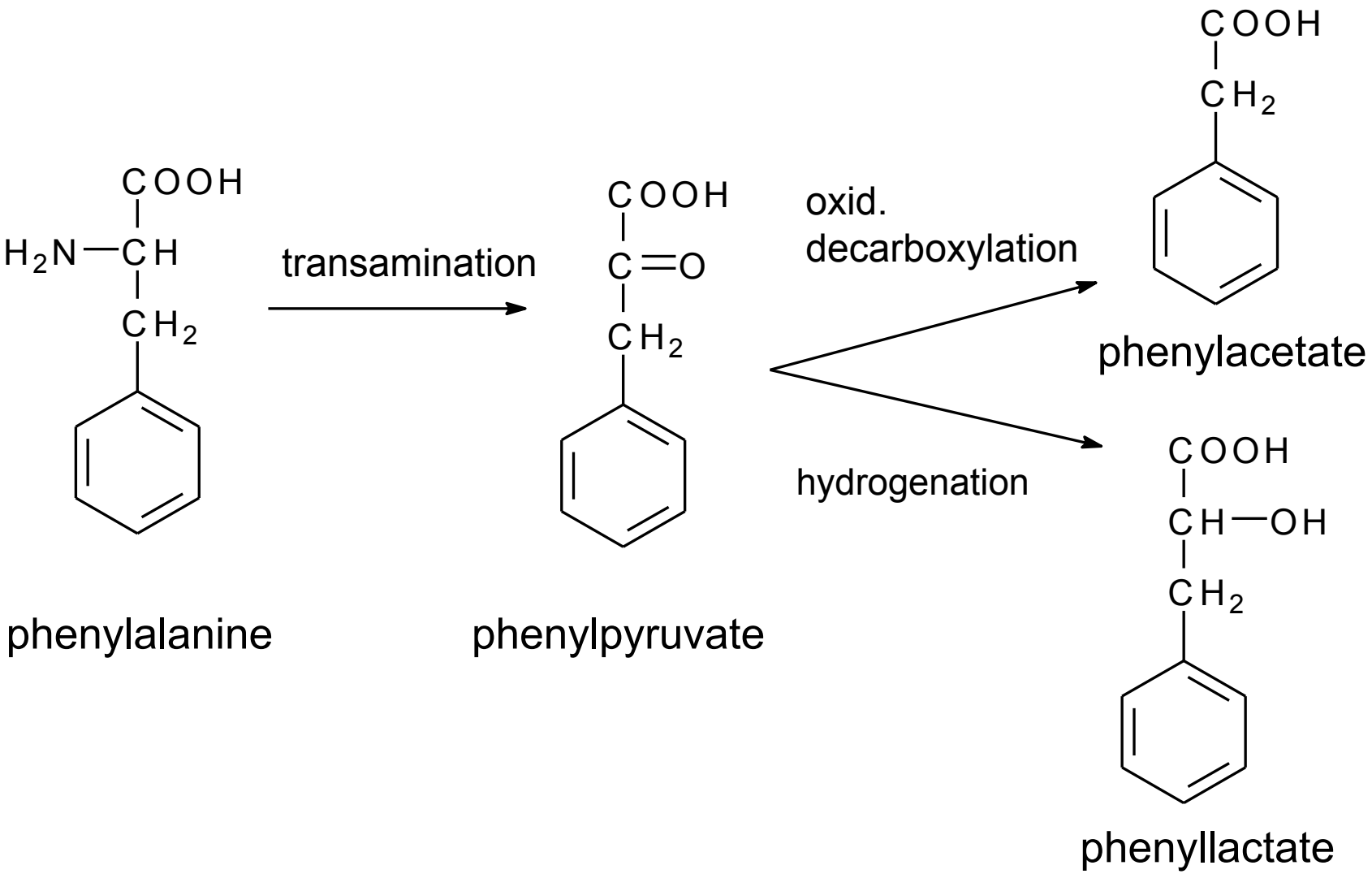
Hyperphenylalaninemia and Phenylketonuria



phenylalanine tyrosine

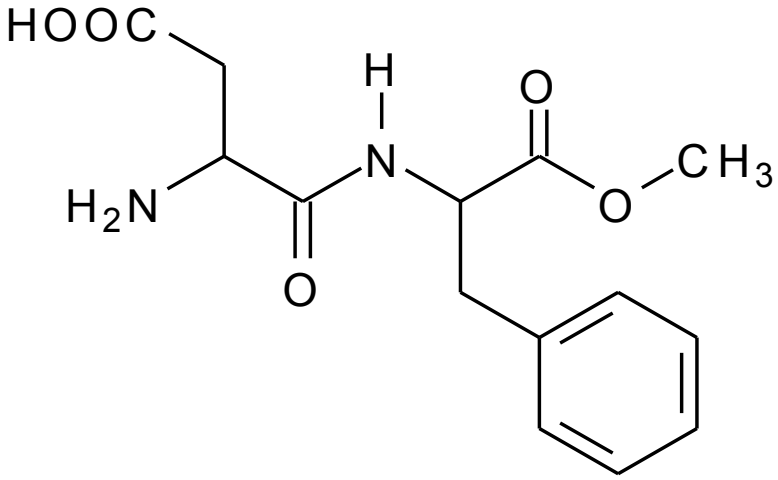
- deficit of hydroxylase or BH_4
- elevated blood Phe and its metabolites
- excretion of phenylpyruvate by urine

Metabolites of phenylalanine

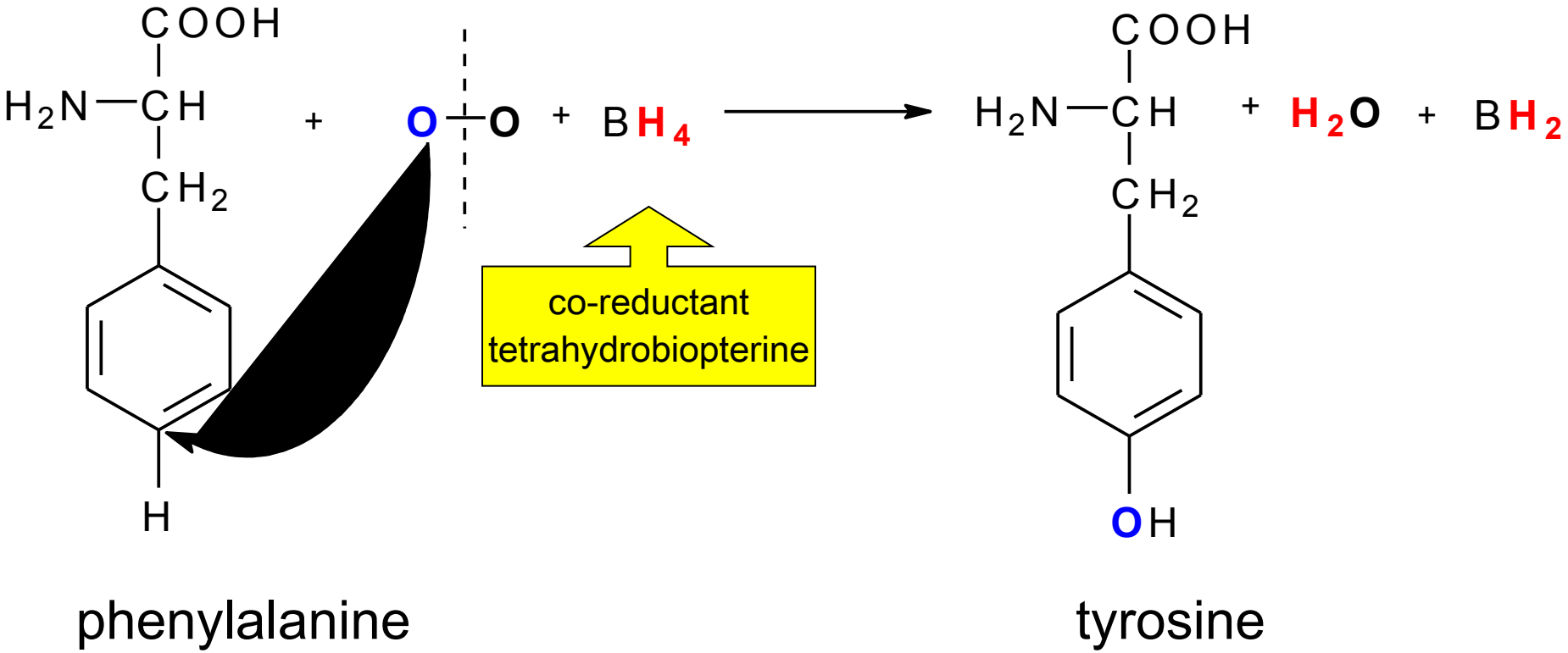


Hyperphenylalaninemia and Phenylketonuria

- if not treated properly – mental retardation and other problems
- treatment – low phenylalanine diet
- products containing sweetener **aspartam** must be avoided
- L-aspartyl-L-phenylalanine methyl ester - phenylalanine is released by hydrolysis:



Hydroxylation of phenylalanine gives tyrosine

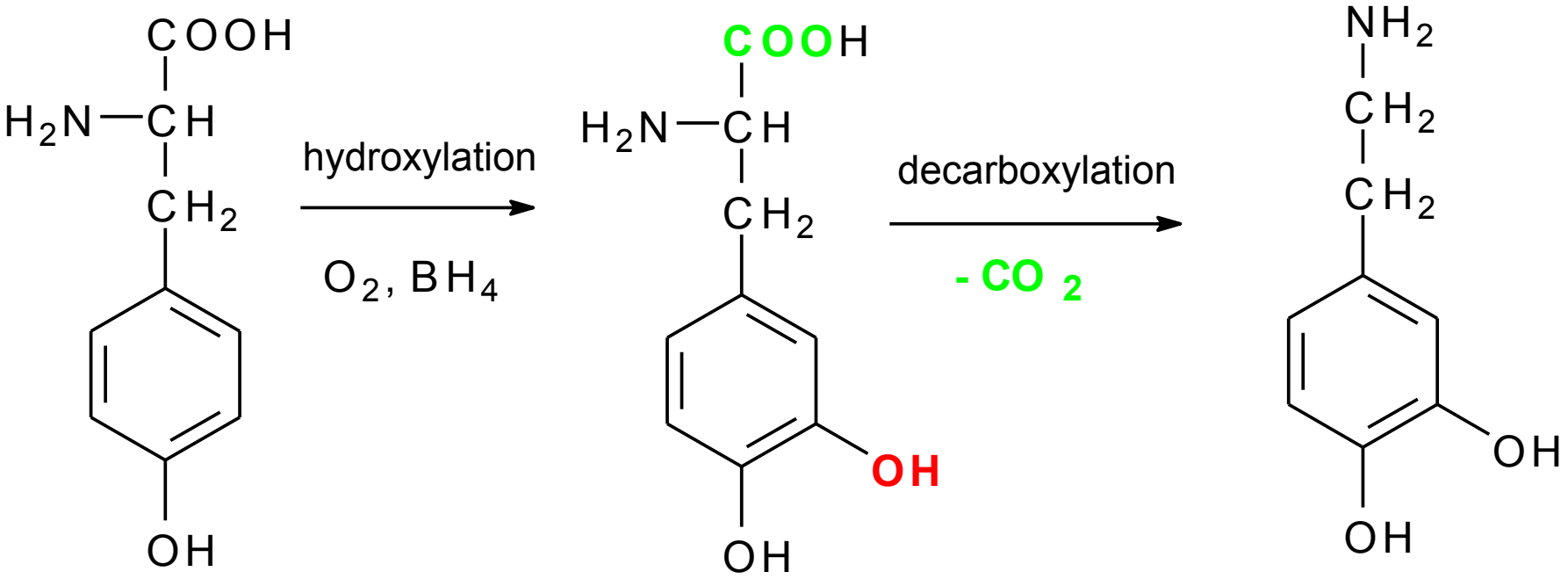


phenylalanine

tyrosine

Tyrosine

DOPA and dopamine from tyrosine



tyrosine

DOPA
(3,4-dihydroxyphenylalanine)

dopamine
(catecholamine)

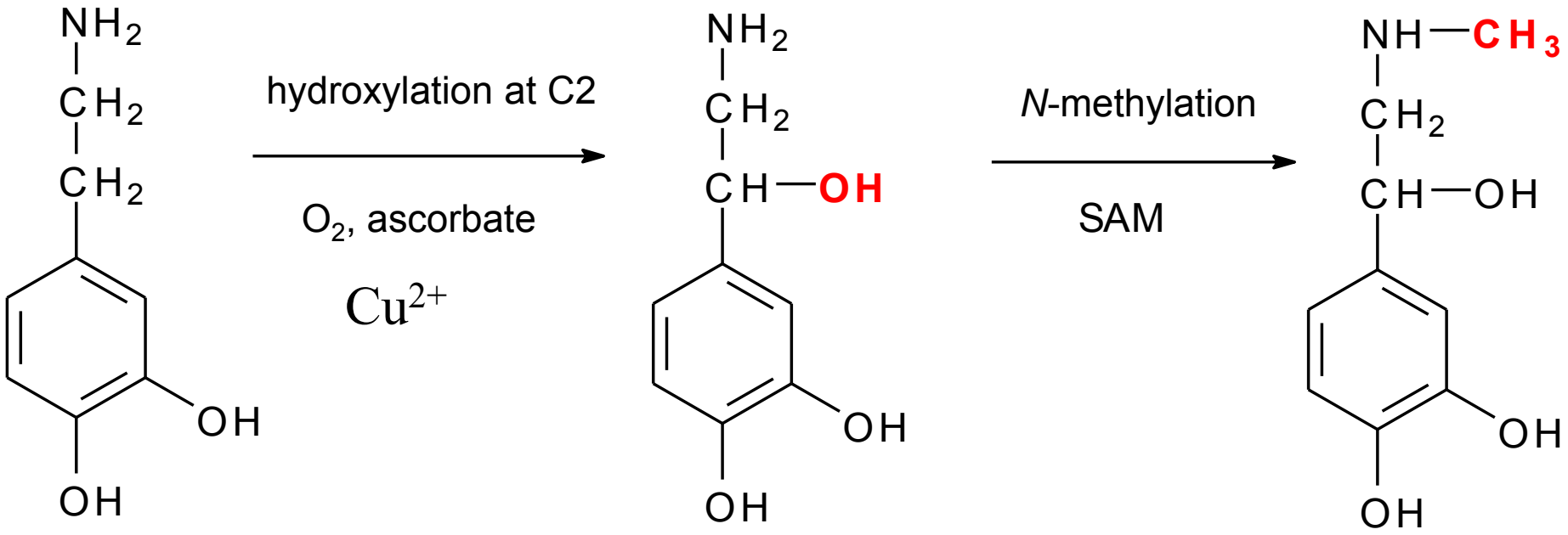
Linguistic note

- abbreviation **DOPA** comes from older English nomenclature
- oxo group and hydroxyl group were not distinguished properly:

  DOPA = **d**i**o**xo**p**heny**l**alanine

- correct chemical name is: 3-(3,4-dihydroxyphenyl)alanine

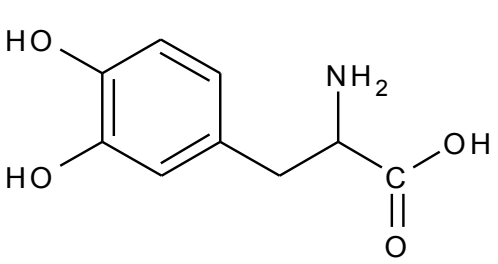
Two more catecholamines from dopamine



dopamine noradrenaline adrenaline

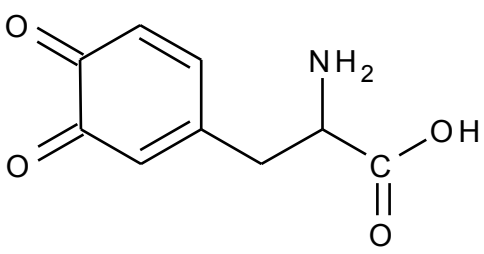
nor- = *N*-demethyl

Conversion of tyrosine to melanin, a dark pigment of skin, hair, fur



DOPA

- 2H

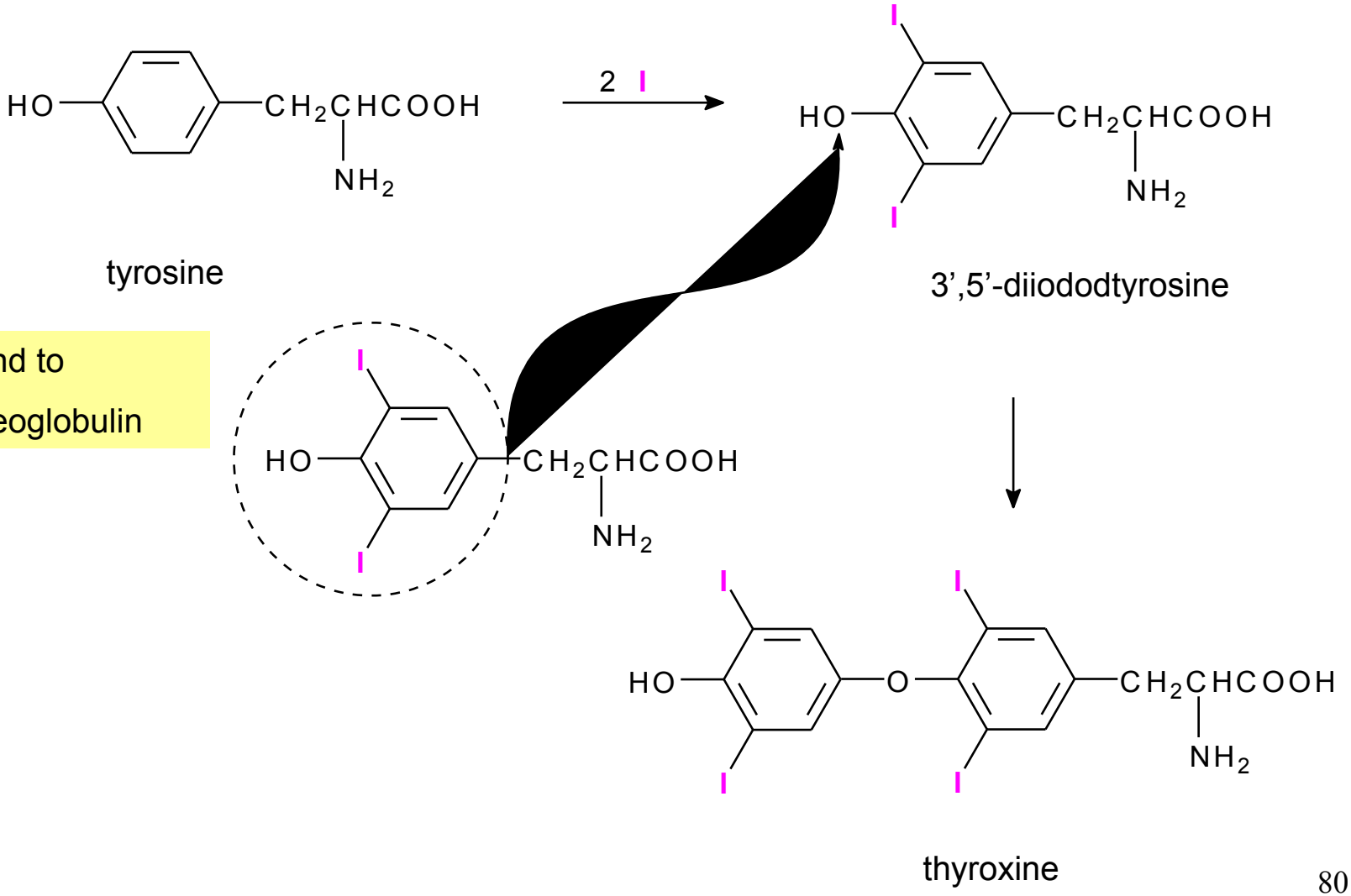


dopaquinone

condenzation

→ → → melanin

Conversion of tyrosine to thyroxine



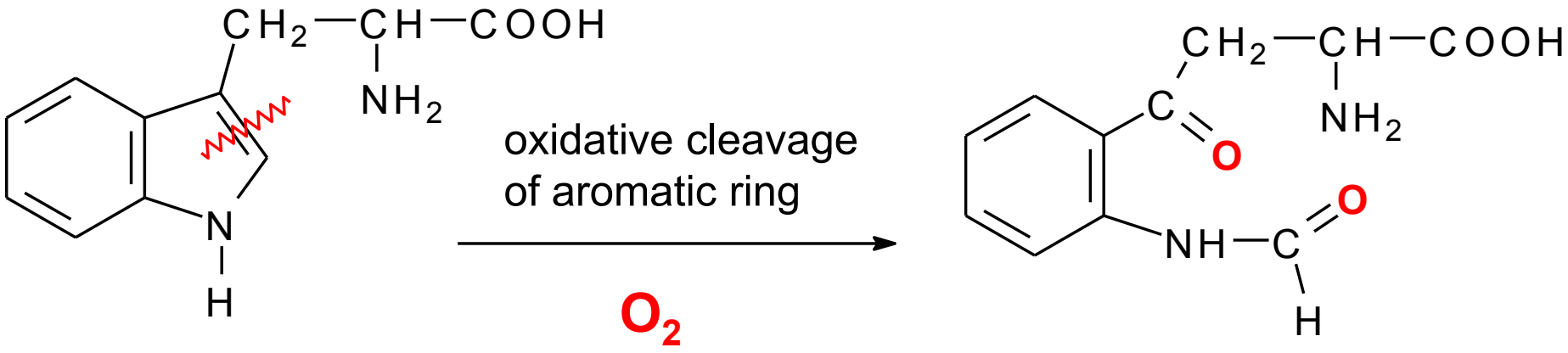
Phenylalanine, tyrosine - summary

- Phe is essential amino acid, Tyr not
- Tyr is made by Phe hydroxylation (tetrahydrobiopterine cofactor)
- catabolism is the same for both AA (mixed AA)
- provide fumarate for CAC (glucogenic)
- acetoacetate (ketone body)
- tyrosine is converted to hormones (catecholamines, thyronines) and dark skin pigment melanin

Tryptophan

no transamination

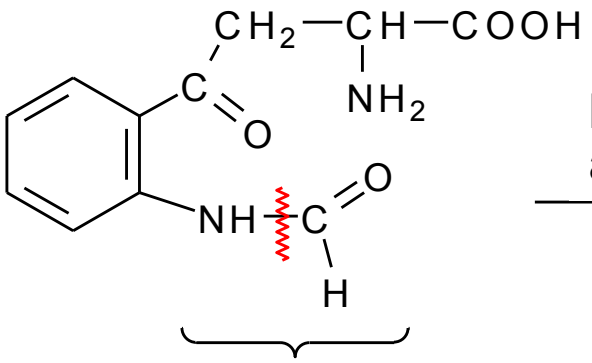
Catabolism (1)



tryptophan

N-formylkynurenine

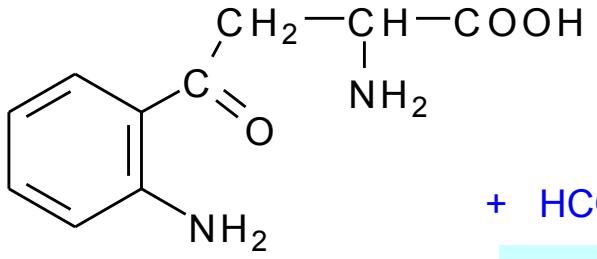
Catabolism (2)



formamide

hydrolysis of amide group

H_2O

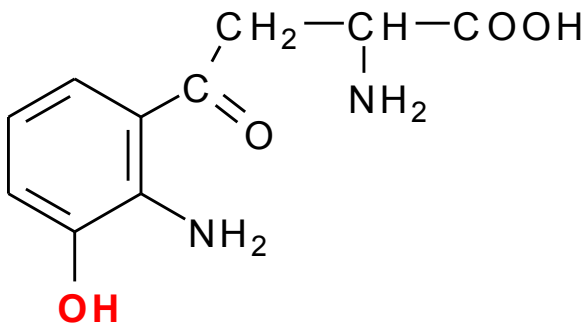


kynurenin

+ HCOOH

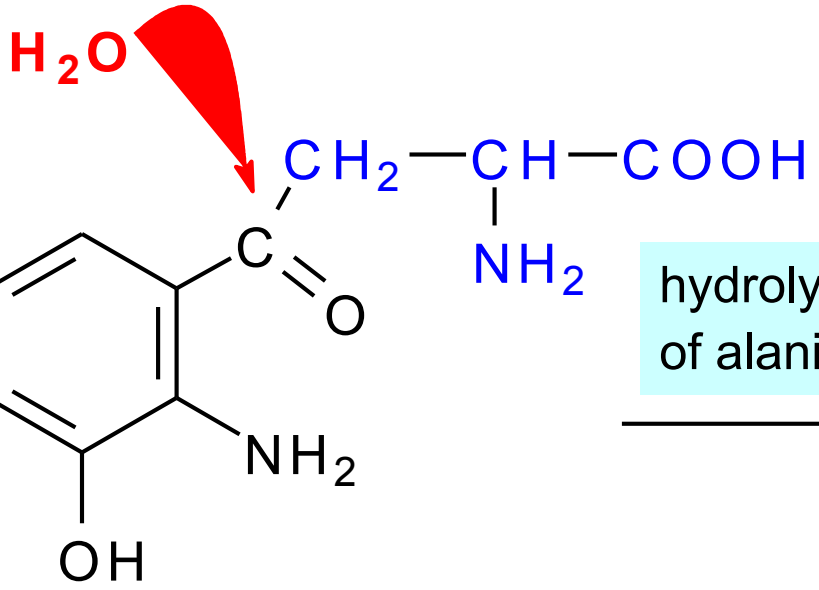
formate

hydroxylation



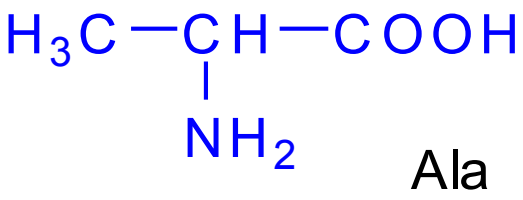
3-hydroxykynurenin

Catabolism (3)

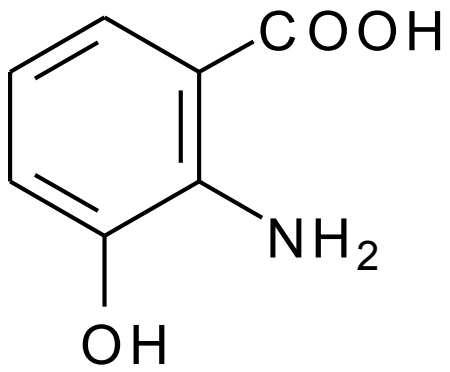


3-hydroxykynurenin

hydrolytic cleavage of alanine

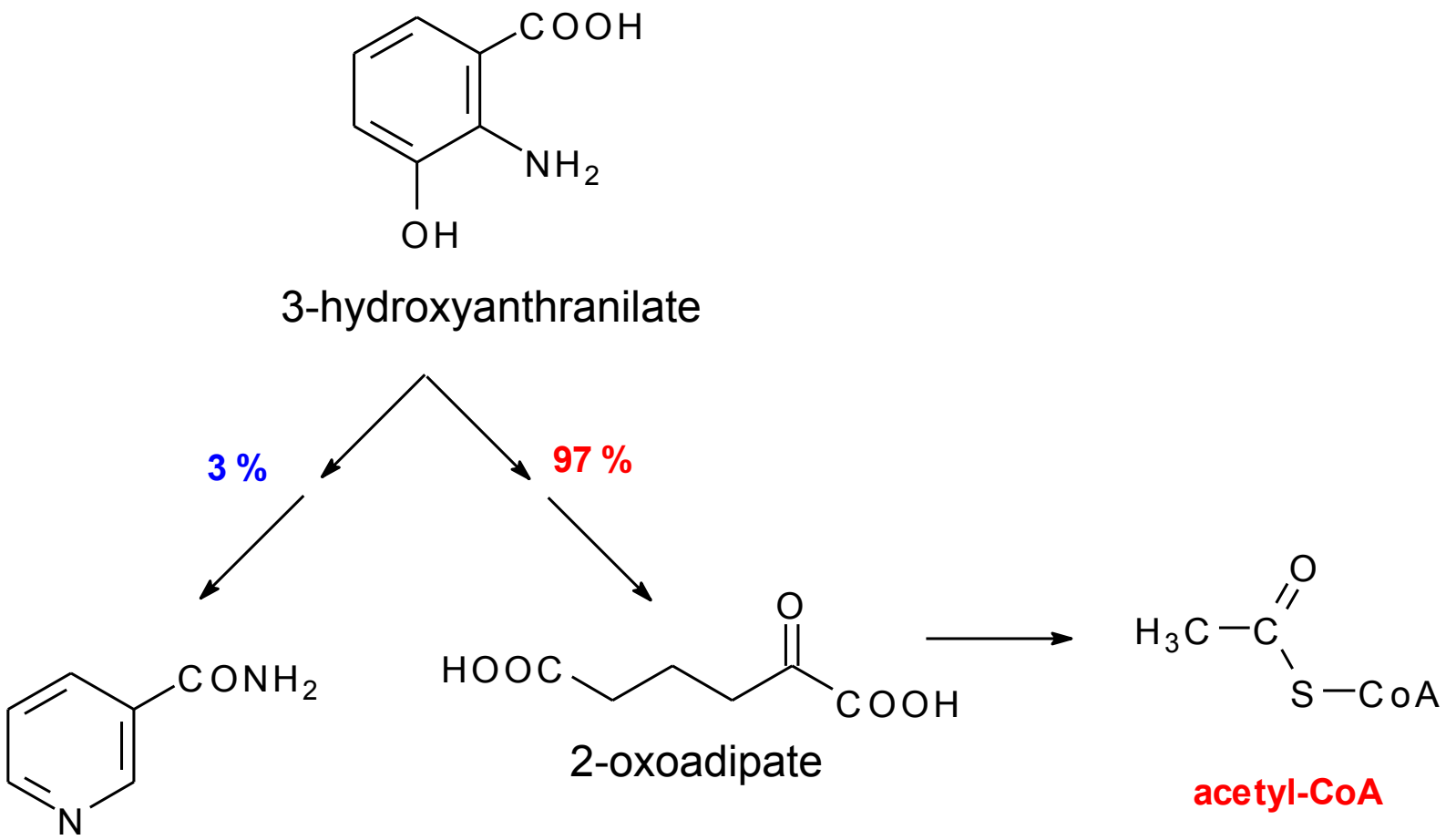


Ala



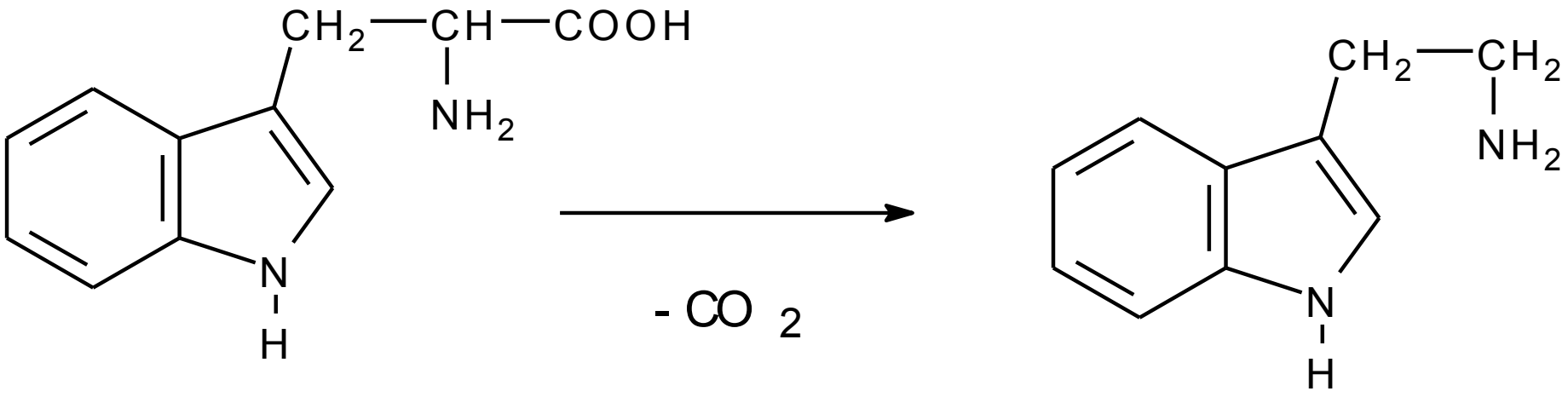
3-hydroxyanthranilate

Catabolism (4)



nicotinamide

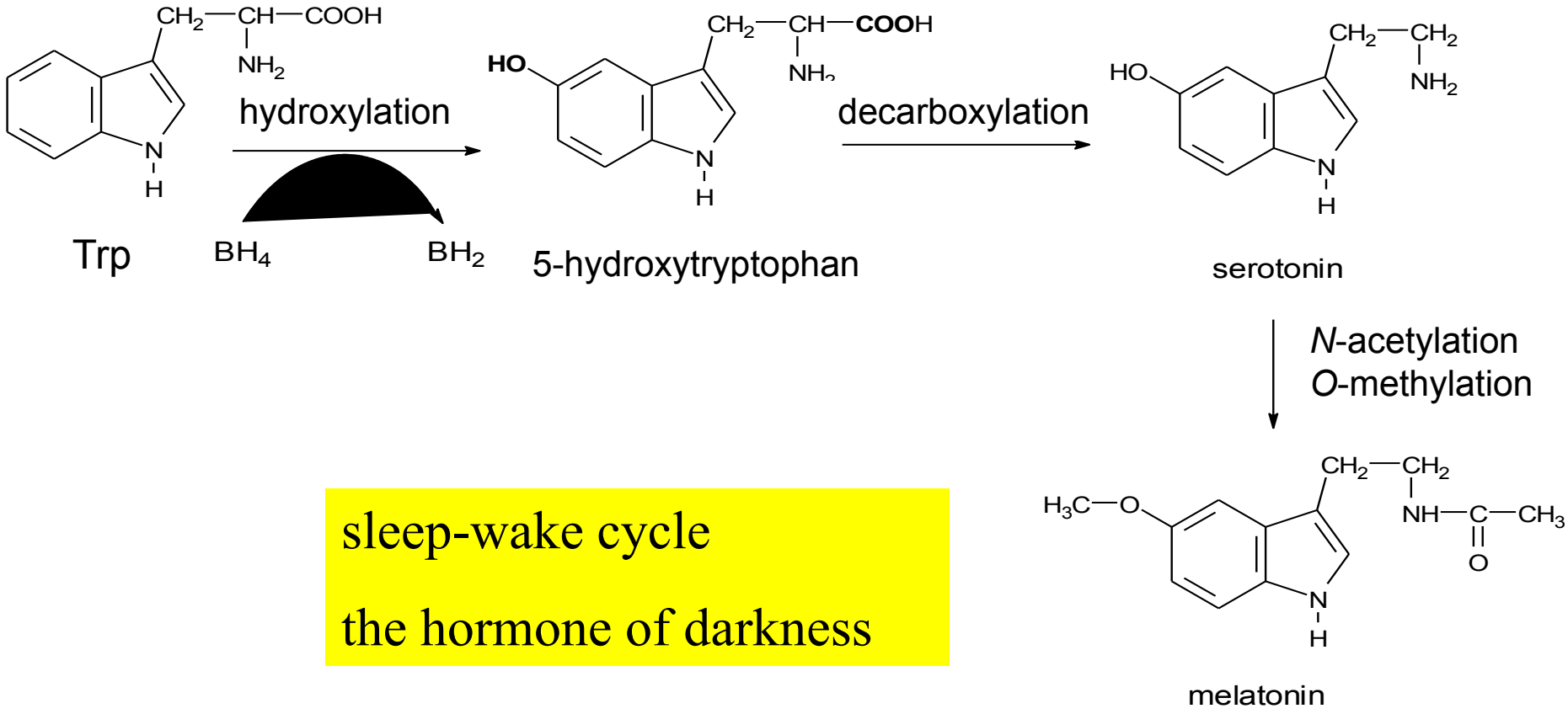
Decarboxylation of tryptophan



tryptophan

tryptamine

Conversion of tryptophan to melatonin



sleep-wake cycle

the hormone of darkness

Tryptophan - summary

- essential AA
- complicated catabolism
- donor of 1C fragment (formic acid - formate)
- no transamination, amino group leaves as alanine (glucogenic)
- final product acetyl-CoA (ketogenic)
- source of nicotinamide and NAD^+
- bacterial decomposition in large intestine $\rightarrow$ indole and skatole (3-methylindole) – exhibit strong fecal odor

Five vitamins are formed in the body, only four are utilized

Vitamin	Where and how produced
Niacin	in tissues, from tryptophan
Biotin	large intestine (bacteria)
Phylloquinone	large intestine (bacteria)
Calciol	skin, from cholesterol (UV radiation)
Cobalamine	large intestine (bacteria) – **not absorbed!**

Seven amino acids do not undergo transamination

Amino acid	α-NH_2 group is removed as
Arginine	ornithine
Lysine	2-aminoadipate
Methionine	homoserine
Threonine	glycine
Tryptophan	alanine
Proline	glutamate
Histidine	NH_3 (desaturation deamination)

AA	Biochemically relevant product
Ala	pyruvate → glucose
Arg	urea, NO, creatine
Ser	ethanolamine → choline → betaine; donor of 1C fragment, selenocysteine
Gly	heme, creatine, GSH, conjugation reagent (e.g. glycocholate)
Met	donor of methyl, creatine, homocysteine, cysteine
Cys	glutathione (GSH), taurine, SO_4^{2-}, PAPS, cysteamine (CoA)
Asp	donor of -NH_2 (urea, pyrimidines), oxaloacetate, fumarate, β-alanine (CoA)
Glu	NH_4^+, 2-oxoglutarate, GABA, ornithine
Gln	NH_4^+, donor of -NH_2 (synthesis of glucosamine, purines)
Pro	glutamate, hydroxyproline
His	glutamate, histamine, donor of 1C fragment
Lys	glutamate, allysine (collagen), carnitine, cadaverine
Tyr	fumarate, catecholamines, thyroxine, melanins
Trp	nicotinamide, serotonin, melatonin, donor of 1C fragment, indole, skatole

Overview: decarboxylation of amino acids

AA	Product	Comments
Ser	ethanolamine	part of phospholipids, precursor of choline
Cys	cysteamine	part of coenzyme A (CoA-SH)
Phe	phenethylamine	structural part of stimulants (amphetamine, ephedrine etc.)
Tyr	tyramine	occurs in some foods, may cause migraine
Asp	β-alanine	part of pantothenic acid, CoA-SH, carnosine
Glu	GABA	gama-aminobutyric acid, inhibition neurotransmiter
Lys	cadaverine	product of putrefaction (decay of proteins)
Arg	agmatine	signal molecule in CNS
His	histamine	triggers allergic reactions
Trp	tryptamine	precursor of serotonine and melatonine
DOPA	dopamine	catecholamine, precursor of noradrenaline/adrenaline
Ornithine	putrescine	putrefaction product; precursor of spermidine/spermine