

Biochemistry

Metabolism

22.11.2018 - 11.12.2017

Bioamines
C1-Metabolism

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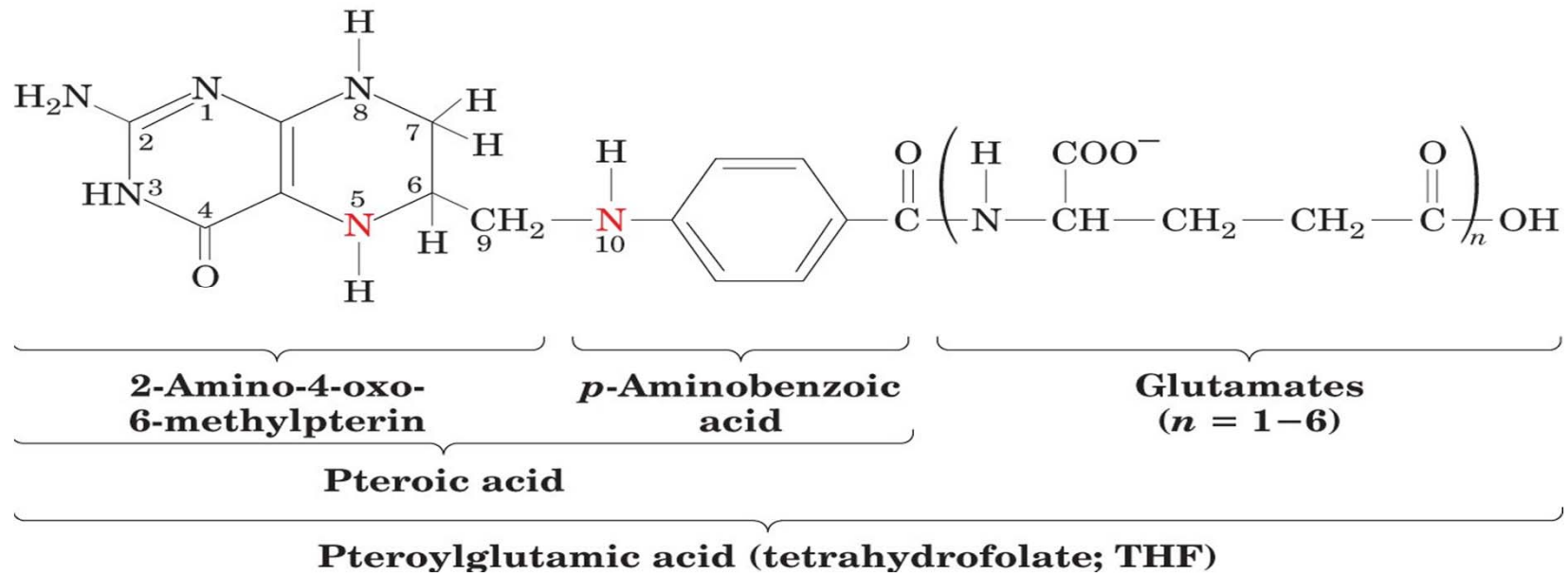
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TABLE 24.2 One-carbon groups carried by tetrahydrofolate

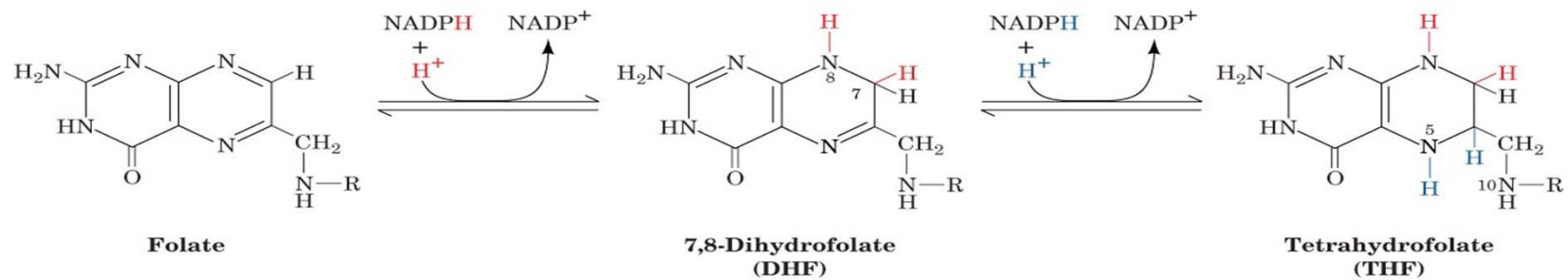
Oxidation state		Group
Most reduced (= methanol)	$-\text{CH}_3$	Methyl
Intermediate (= formaldehyde)	$-\text{CH}_2-$	Methylene
Most oxidized (= formic acid)	$-\text{CHO}$	Formyl
	$-\text{CHNH}$	Formimino
	$-\text{CH}=\text{}$	Methenyl

Tetrahydrofolate (THF)



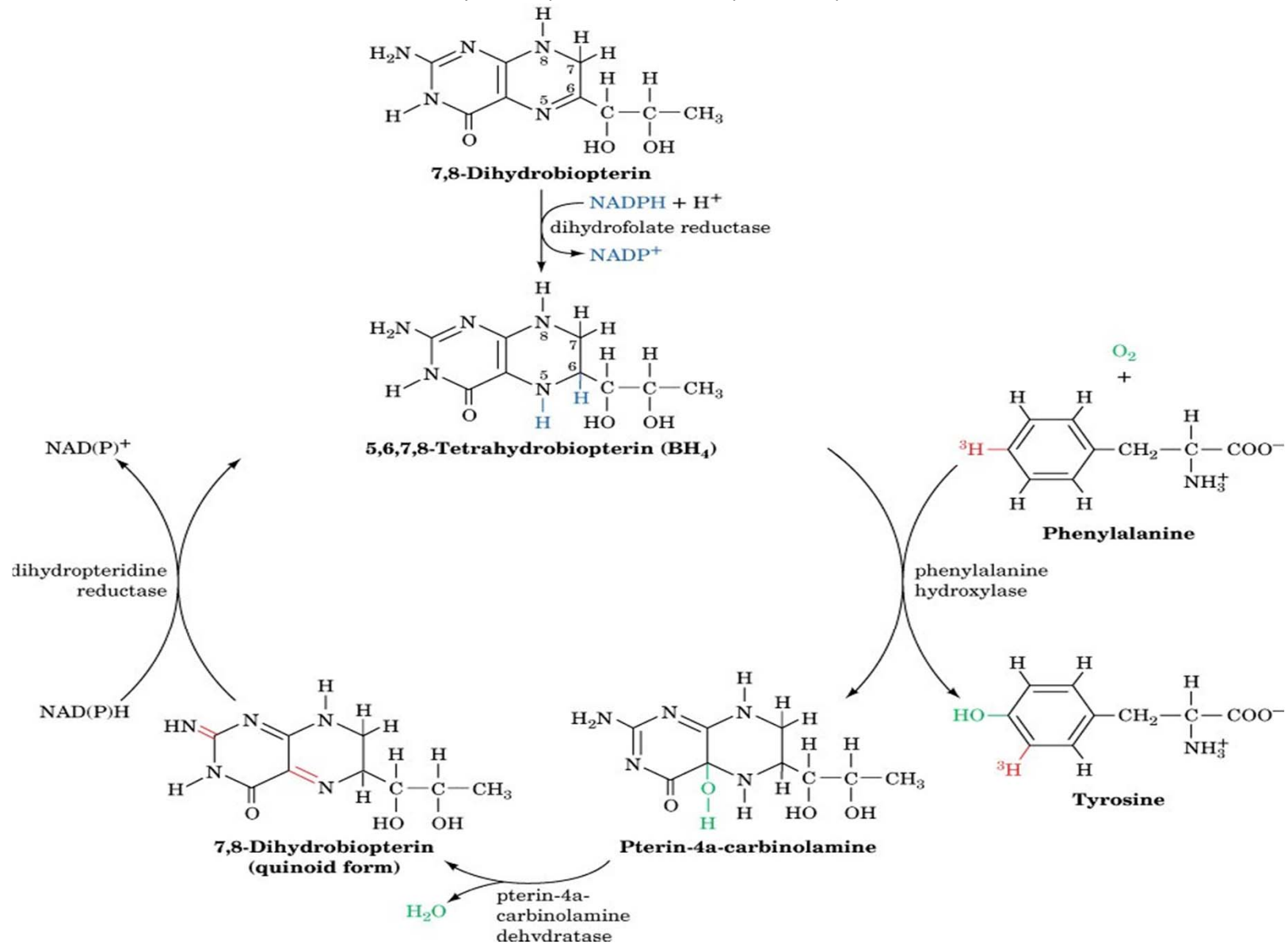
Note: THB (BH_4 , Tetrahydrobiopterin)

The two-stage reduction of folate to THF

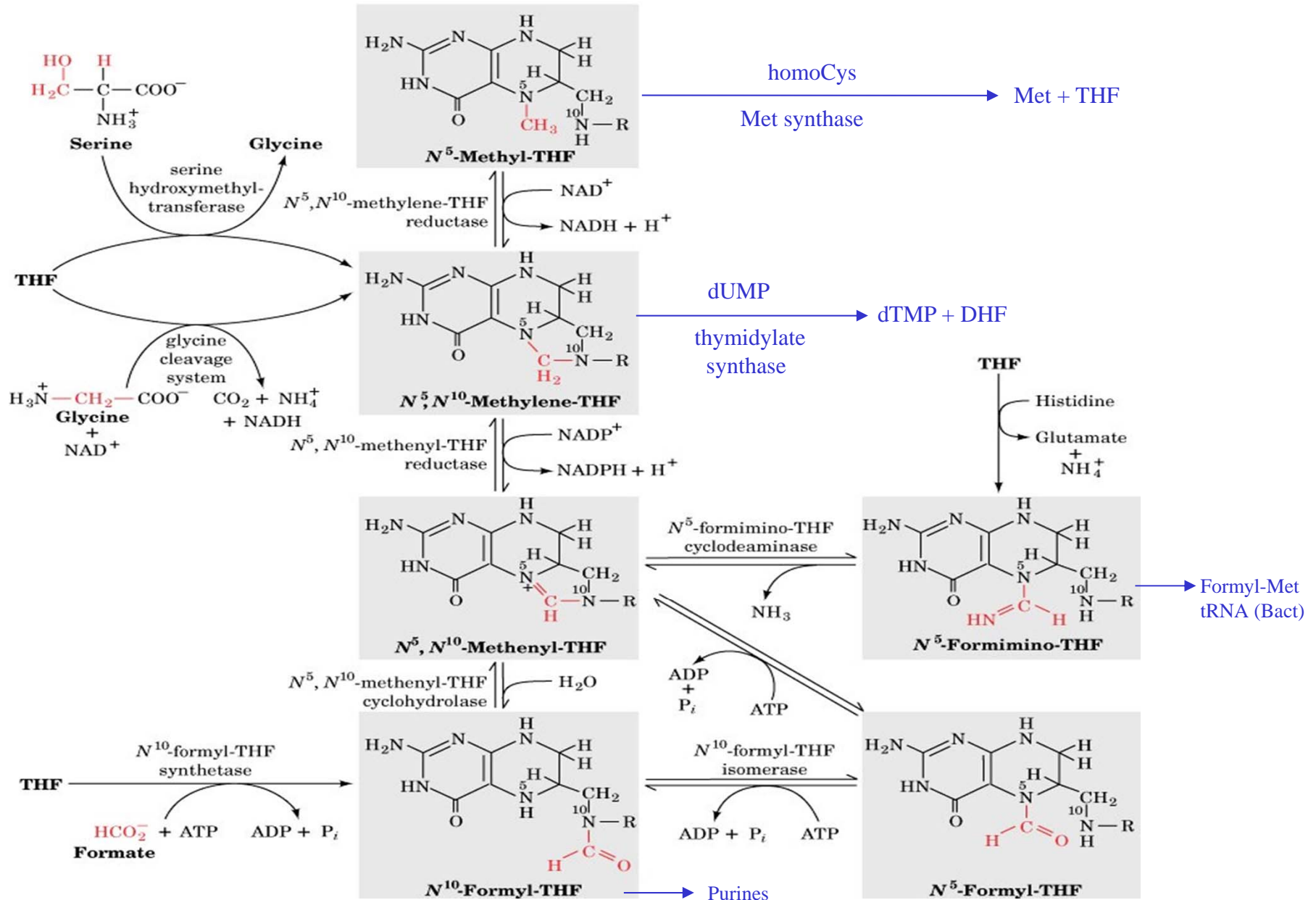


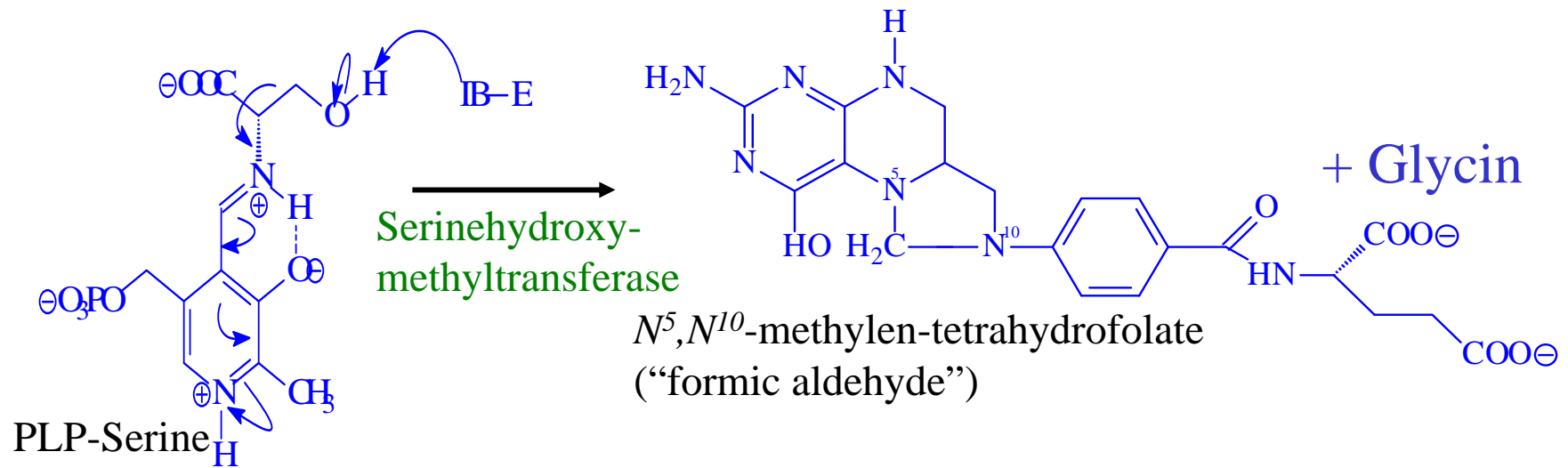
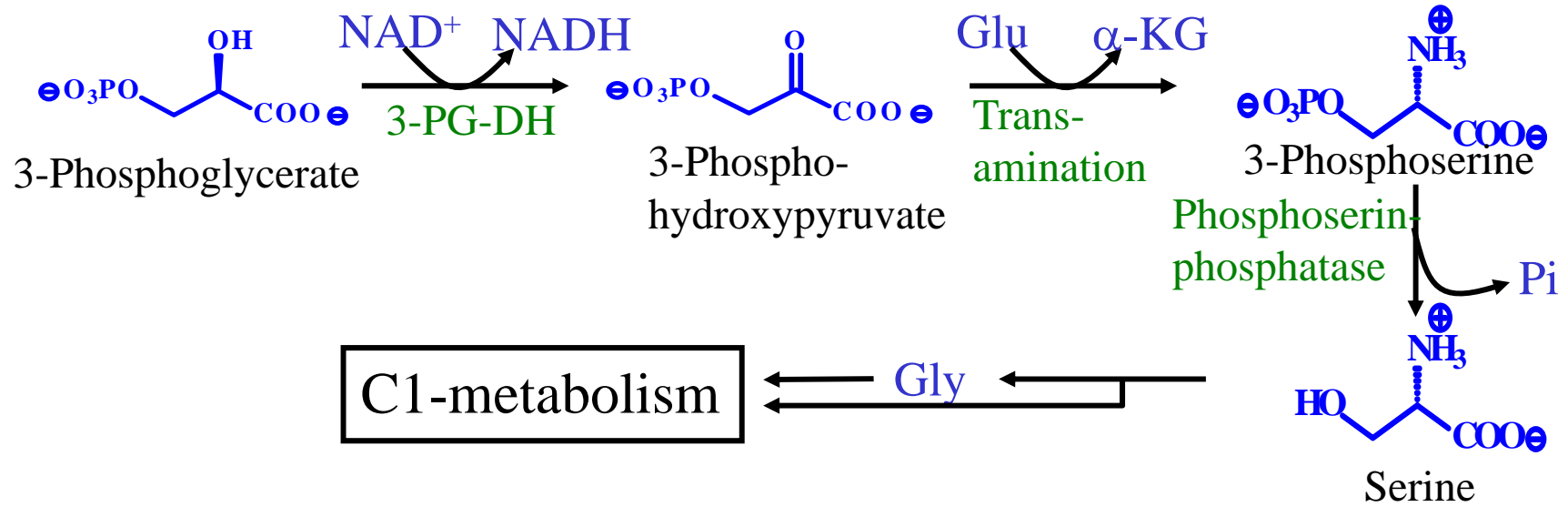
Both reactions are catalyzed by **dihydrofolate reductase**

The formation, utilization, and regeneration of 5,6,7,8-tetrahydrobiopterin (BH₄) in the phenylalanine hydroxylase reaction

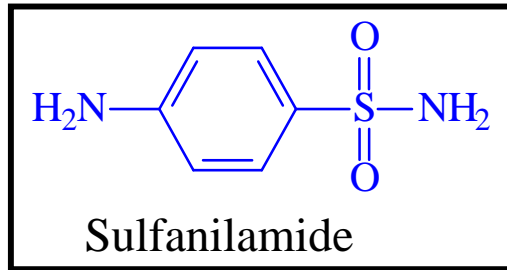


Interconversion of the C₁ units carried by THF.

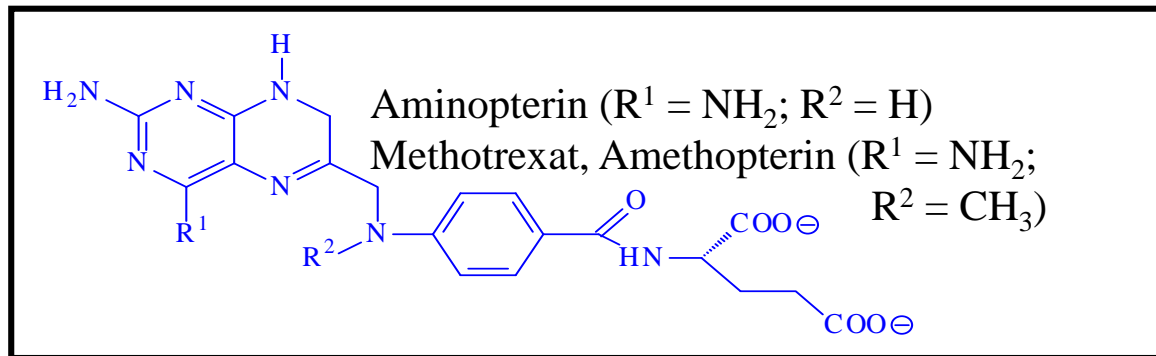




THF in medicine

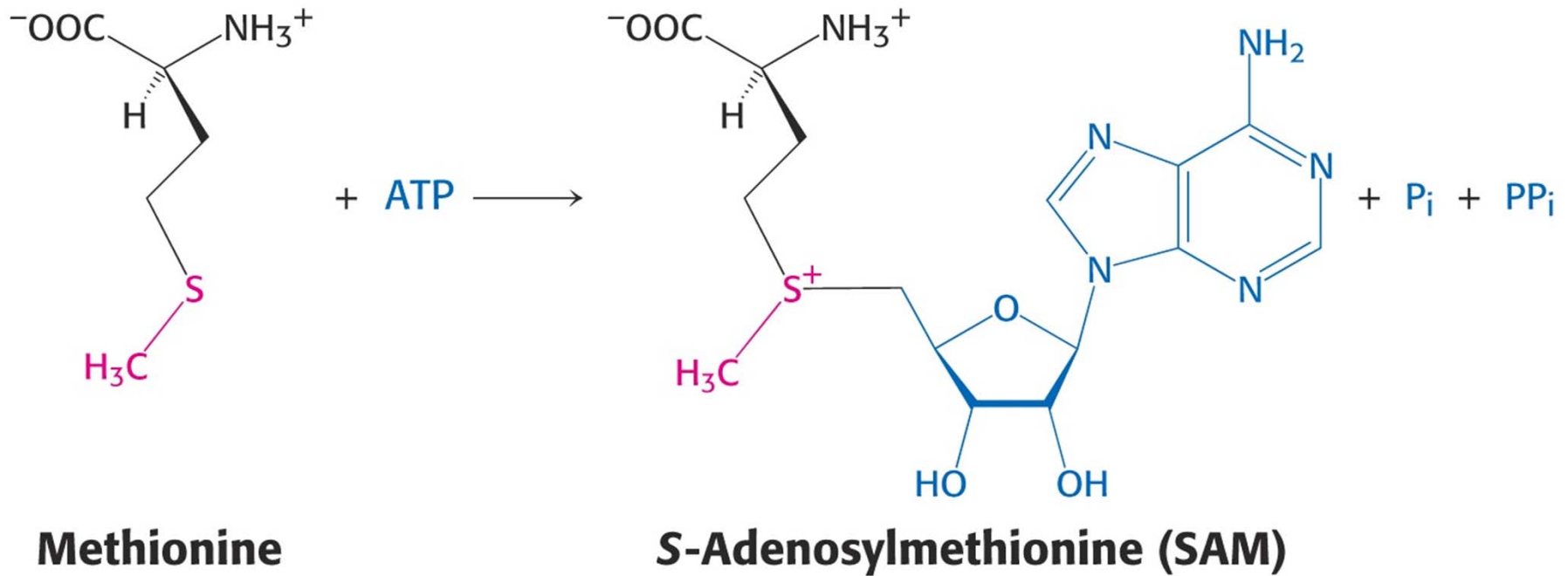


Antibiotics: Structural analogs of p-aminobenzoic acid

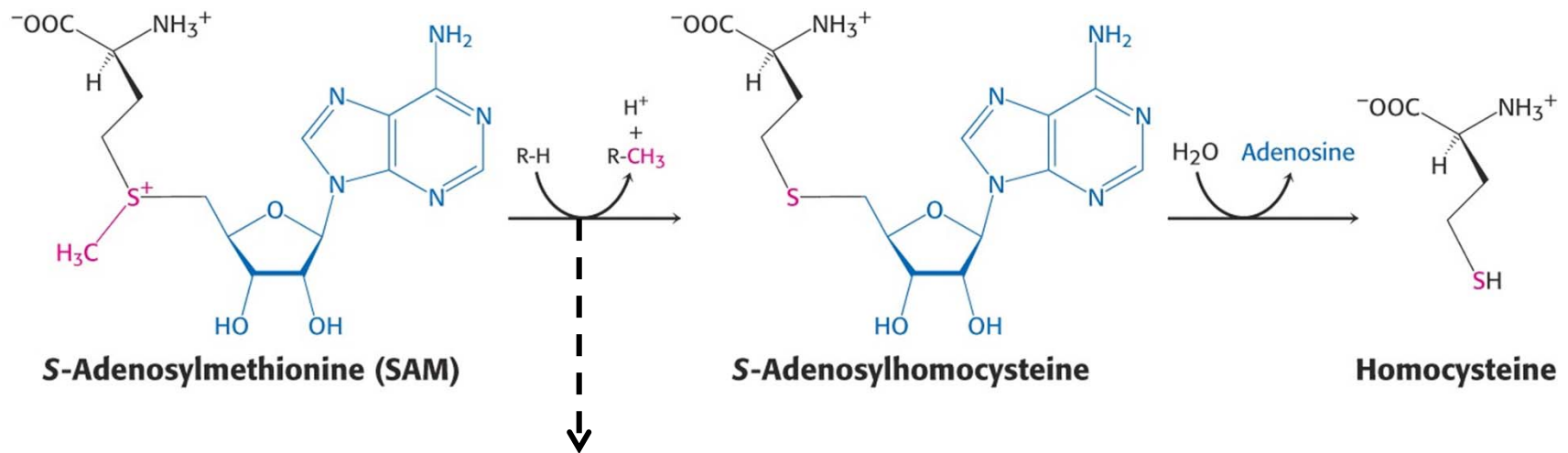


Cytostatica: Structural analogs of folic acid

S-Adenosylmethionine is the major donor of methyl groups

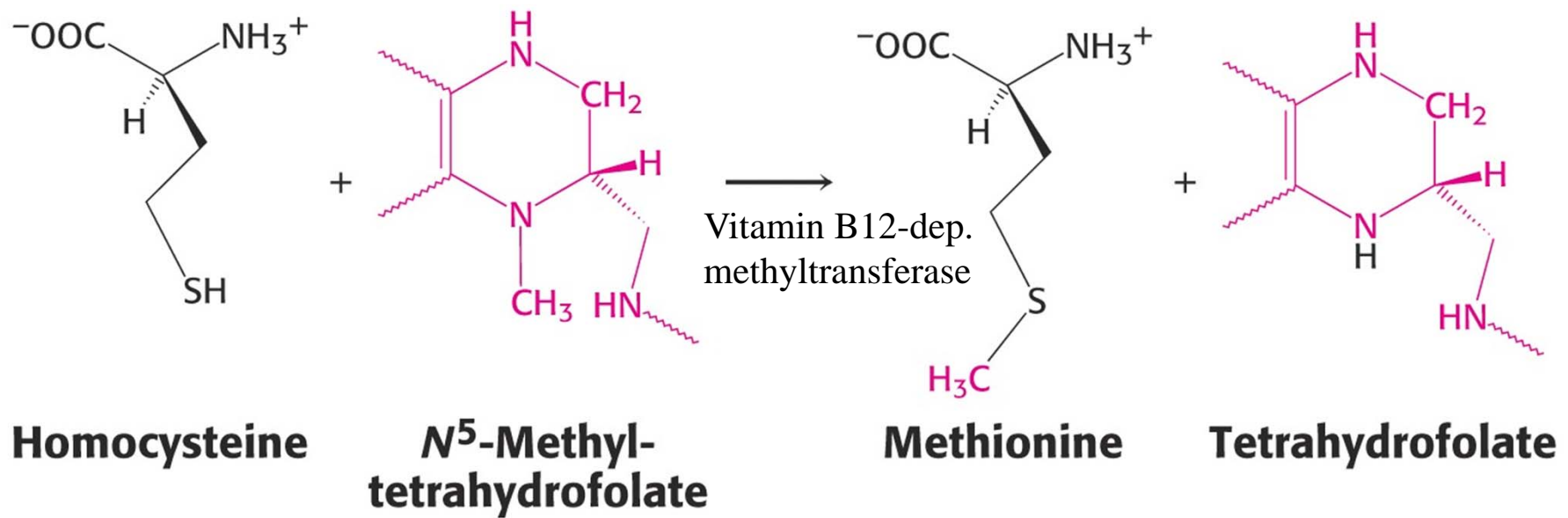


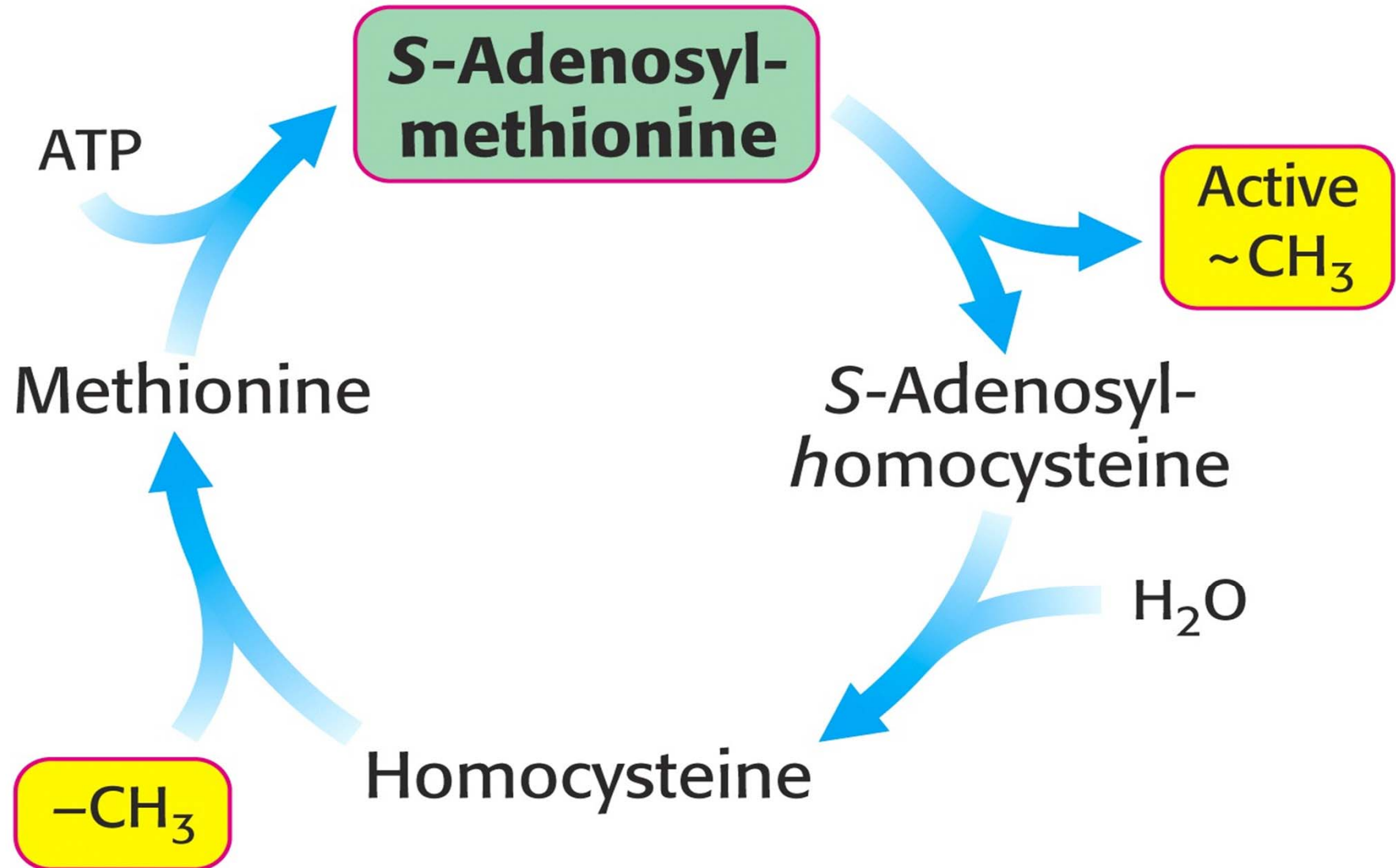
Methylation is Accompanied by Generation of Homocysteine



- Methylation of ethanolamine to choline
- Methylation of noradrenaline to adrenaline
- Methylation of mRNA (methyl-caps on aminogroup of terminal G)
- Methylation of DNA and of histones (epigenetic memory)

Recovery of Methionine by Methylation of Homocysteine





Activated methyl cycle. The methyl group of methionine is activated by the formation of S-adenosylmethionine

Hyperhomocysteinemia (Hhcys)

Reasons for Hhcys are poorly understood.

Hhcys is closely associated with **cardiovascular disease**, **cognitive impairment**, and **neural tube defects** (the cause of a variety of severe birth defects including **spina bifida** - defects in the spinal column leading to paralysis, and **anencephaly** - invariably fatal failure of the brain to develop leading to infant death).

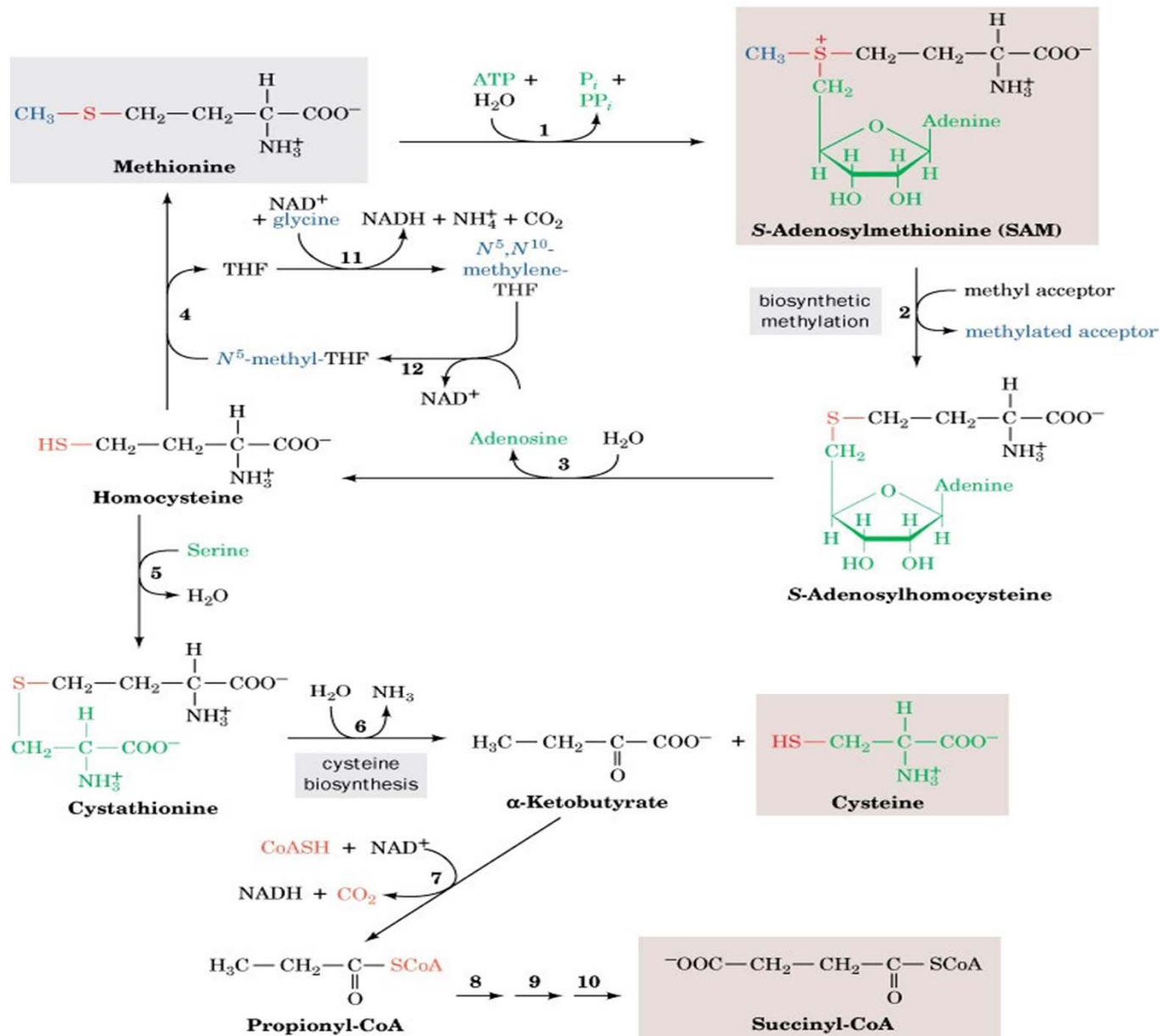
Hhcys is readily controlled by ingesting vitamins of the B complex including niacin, riboflavin, pyridoxine, cobalamine, and **folate**. The latter especially appears to alleviate Hhcys since its administration to pregnant women dramatically reduces the incidence of neural tube defects in newborns.

This had led to the discovery that 10 % of the population is homozygous for the A222V mutation in N⁵,N¹⁰-methyleneTHF reductase, the enzyme that generates N⁵-methylTHF for the Met synthase reaction. The mutation causes loss of the essential flavin cofactor. Folate derivatives bind to the enzyme thus reducing flavin loss and enabling an increase of the mutant enzyme's activity to reduce homoCys concentration.

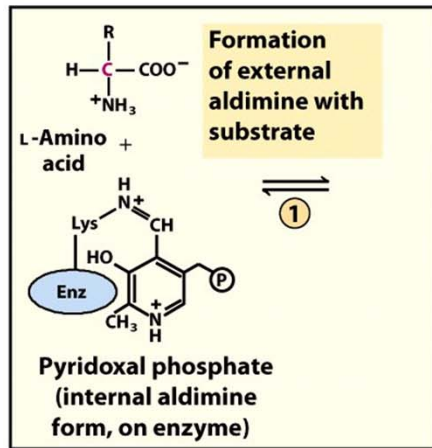
Alternative Metabolization of Homocysteine to Cysteine



The pathway of methionine degradation, yielding cysteine and succinyl-CoA as products



Pyridoxal phosphate facilitated decarboxylation



Glutamate \longrightarrow GABA

Histidine \longrightarrow Histamine

Tryptophan \longrightarrow Serotonin
(5-hydroxytryptamine)
DMT (dimethyltryptamine,
psychedelic drug)

Tyrosine \longrightarrow Dopamine
Noradrenaline
Adrenaline

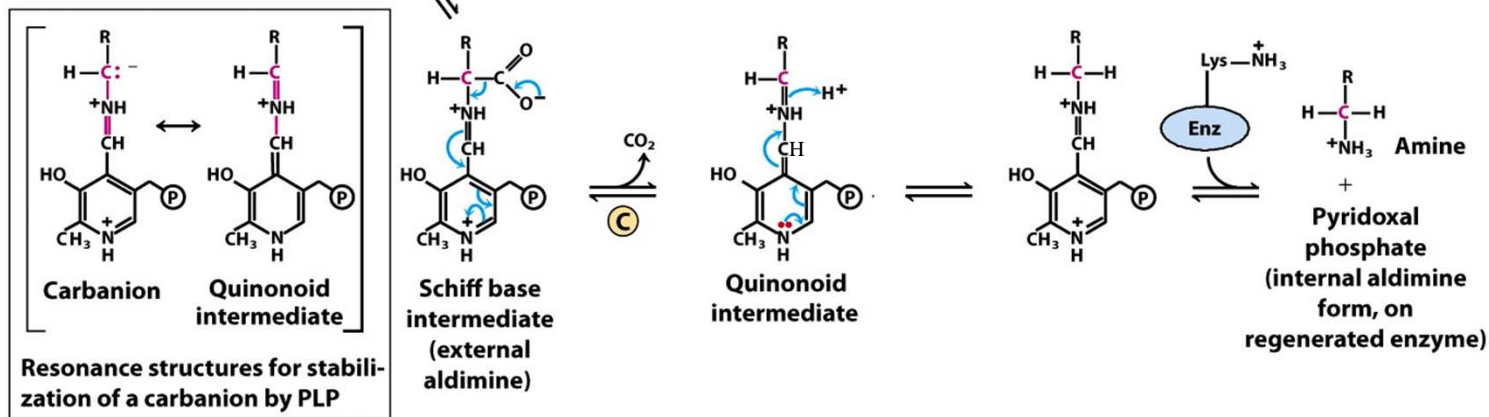


Figure 18-6 part 3

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The Cori cycle

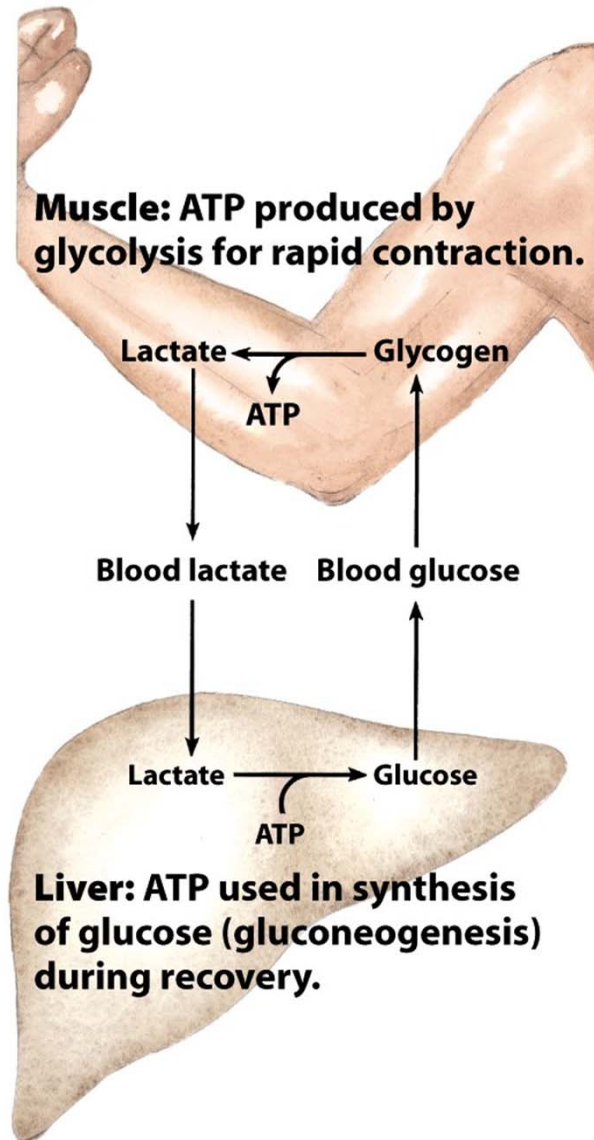


Figure 23-20
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Glucose-alanine cycle

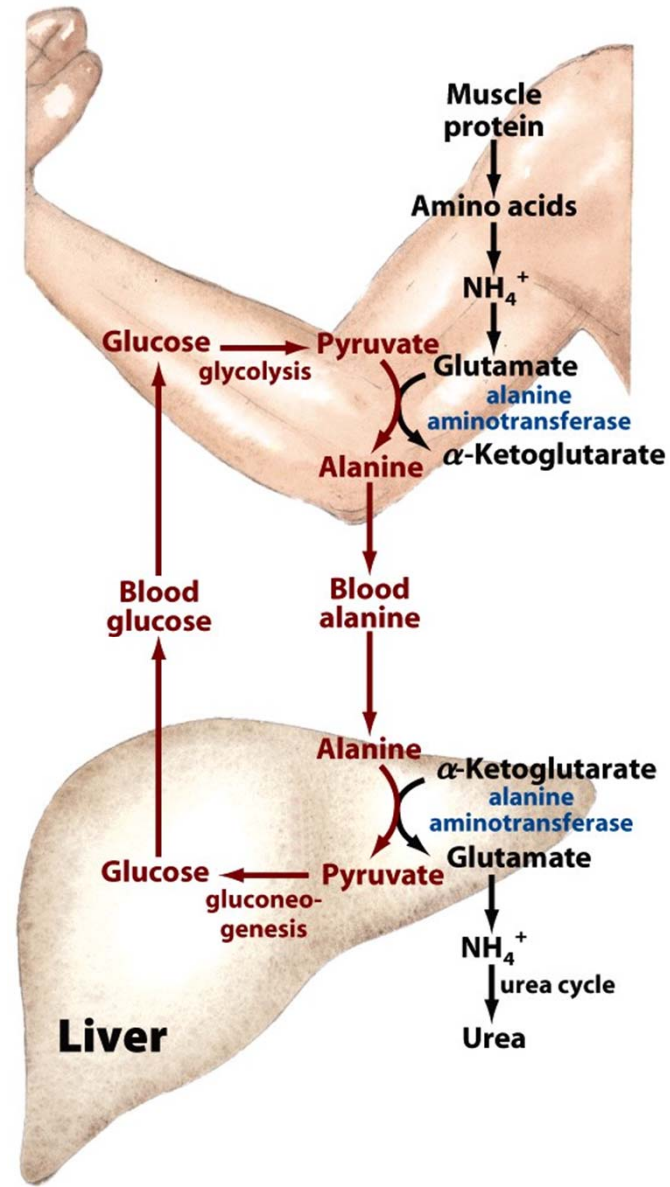


Figure 18-9
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