章節：**CH21　Metabolism of Nitrogenous Compounds II: Amino Acids, Porphyrins, and Neurotransmitters**	
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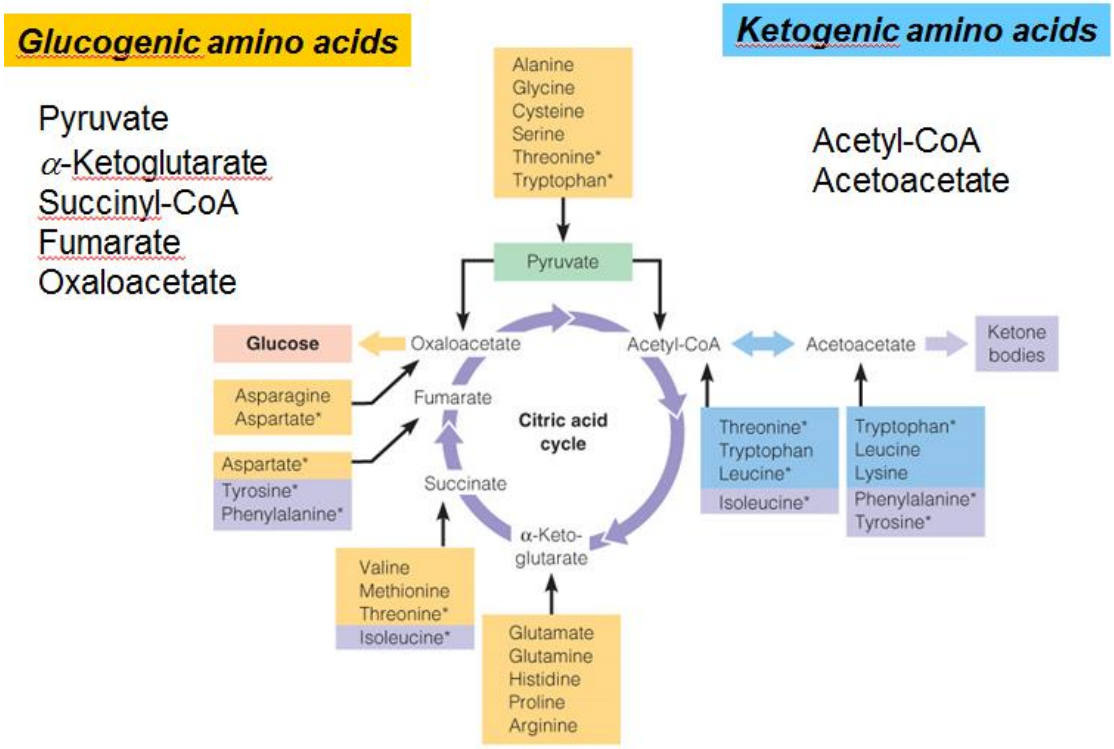
Outline:

- Pathways of Amino Acid Degradation
- Amino Acids as Biosynthetic Precursors
- Porphyrin and Heme Metabolism
- Amino Acids and Their Metabolites as Neurotransmitters and Biological Regulators
- Amino Acid Biosynthesis

Pathways of Amino Acid Degradation

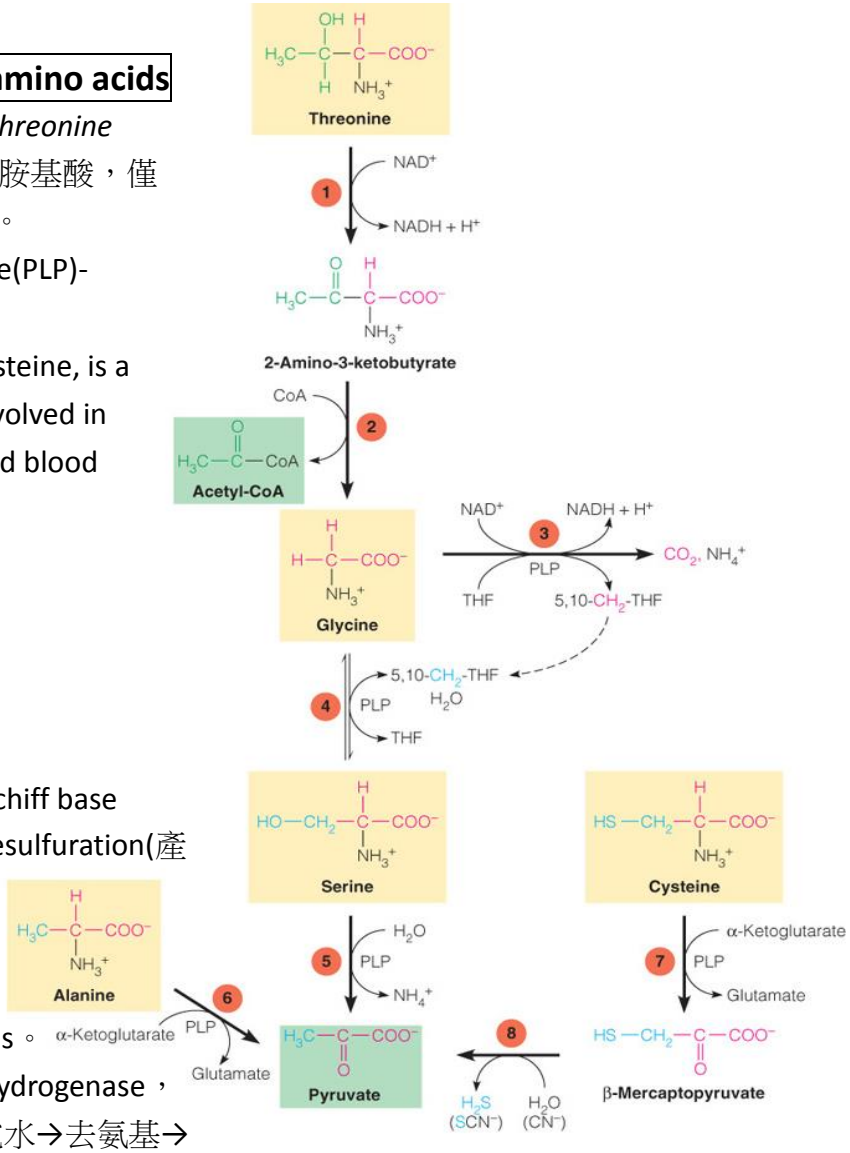
1. 動物大部分能量來自於醣類與脂質的氧化，而另外 10%~15%則來自 degradation of amino acid。
2. 20 種胺基酸有不同的 degradation pathway，但 20 條路徑會匯集到 7 種中間產物，其中 5 種(Pyruvate, α-Ketoglutarate, Succinyl-CoA, Fumarate, Oxaloacetate)稱為 **Glucogenic amino acids**，這些是糖類合成的前驅物；另外 2 種(Acetyl-CoA, Acetoacetate)稱為 **Ketogenic amino acids**，此二者會被轉化為 ketone bodies。當然有些胺基酸同時屬於上述二類。
3. 以下將針對 7 種中間產物，詳述其路徑與反應。



Pyruvate family of glucogenic amino acids

→ *alanine, serine, cysteine, glycine, threonine*

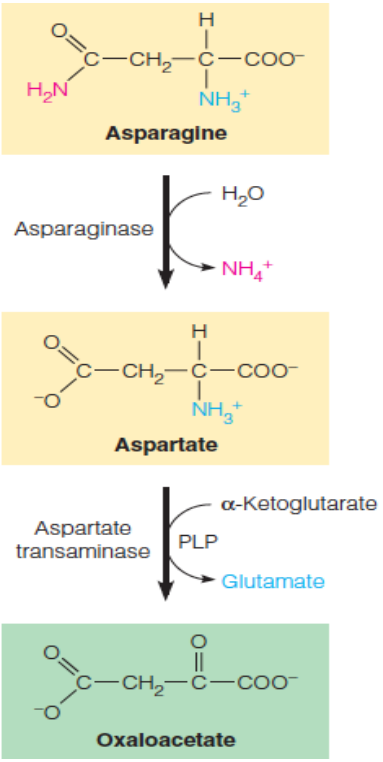
1. Alanine, serine, cysteine 為 3 碳骨架的胺基酸，僅經過 1~2 步驟即成為 3 碳的 pyruvate。
2. 步驟 3,4,5,6,7 皆有 pyridoxal phosphate(PLP)-Dependent enzymes 參與。
3. Hydrogen sulfide (H_2S), derived from cysteine, is a powerful gaseous signaling molecule involved in the regulation of vascular blood flow and blood pressure.
4. 重要酵素:
   ①. Threonine dehydrogenase
   ②. 2-amino-3-ketobutyrate ligase
   ③. Glycine cleavage enzyme
   ④. Serine hydroxymethyltransferase
   ⑤. Serine-threonine dehydratase : planar Schiff base
   ⑥. Mercaptopyruvate sulfurtransferase : Desulfuration(產生 H_2S)、Detoxification of cyanide
5. 步驟 3 的 glycine cleavage system 若缺陷，則會造成 Nonketotic hyperglycinemia- neurological symptoms。
6. 人體缺乏步驟 1 所需之 threonine dehydrogenase，故此步驟於人體中會以「threonine 脫水→去氨基→產生 Succinyl-CoA」的方式進行。



Oxaloacetate family of glucogenic amino acids

→ *asparagine, aspartate (都是 four-carbon skeleton)*

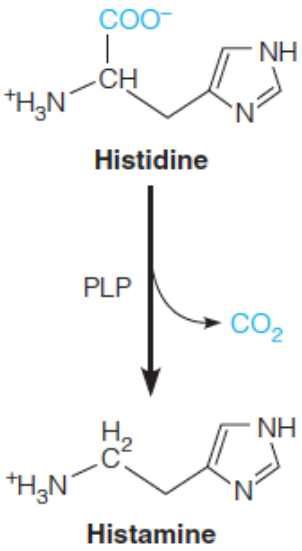
1. Asparaginase 催化 asparagine amide 進行 hydrolytic cleavage 產生 aspartate 和 ammonium(NH_4^+)。
2. 接著 aspartate transaminase (或稱 glutamate-oxaloacetate aminotransferase, GOT)催化 Aspartate 進行 transamination 產生 oxaloacetate。
3. Enzyme-based chemotherapy 的例子: Bacterial asparaginase (E.coli)用以治療 lymphoblastic leukemia。



α-Ketoglutarate family of glucogenic amino acids

→ *arginine, glutamate, glutamine, histidine, proline* (主碳鏈都 5 個 C)

1. **注意:步驟 5 會考。**Histidine 行 decarboxylation 產生 histamine。
2. Histamine is a substance with multiple biological actions:
   (1) 胃會分泌 histamine 以促進 HCl 和 pepsin(胃蛋白酶)的分泌，幫助消化。
   (2) 可做為 vasodilator(血管擴張劑)，釋放於受傷、發炎、過敏反應的部位。
3. Benadryl、Clarinex 等抗組織胺藥物(Antihistamines) 可防止 histamine 與其受體結合，治療過敏與發炎反應。



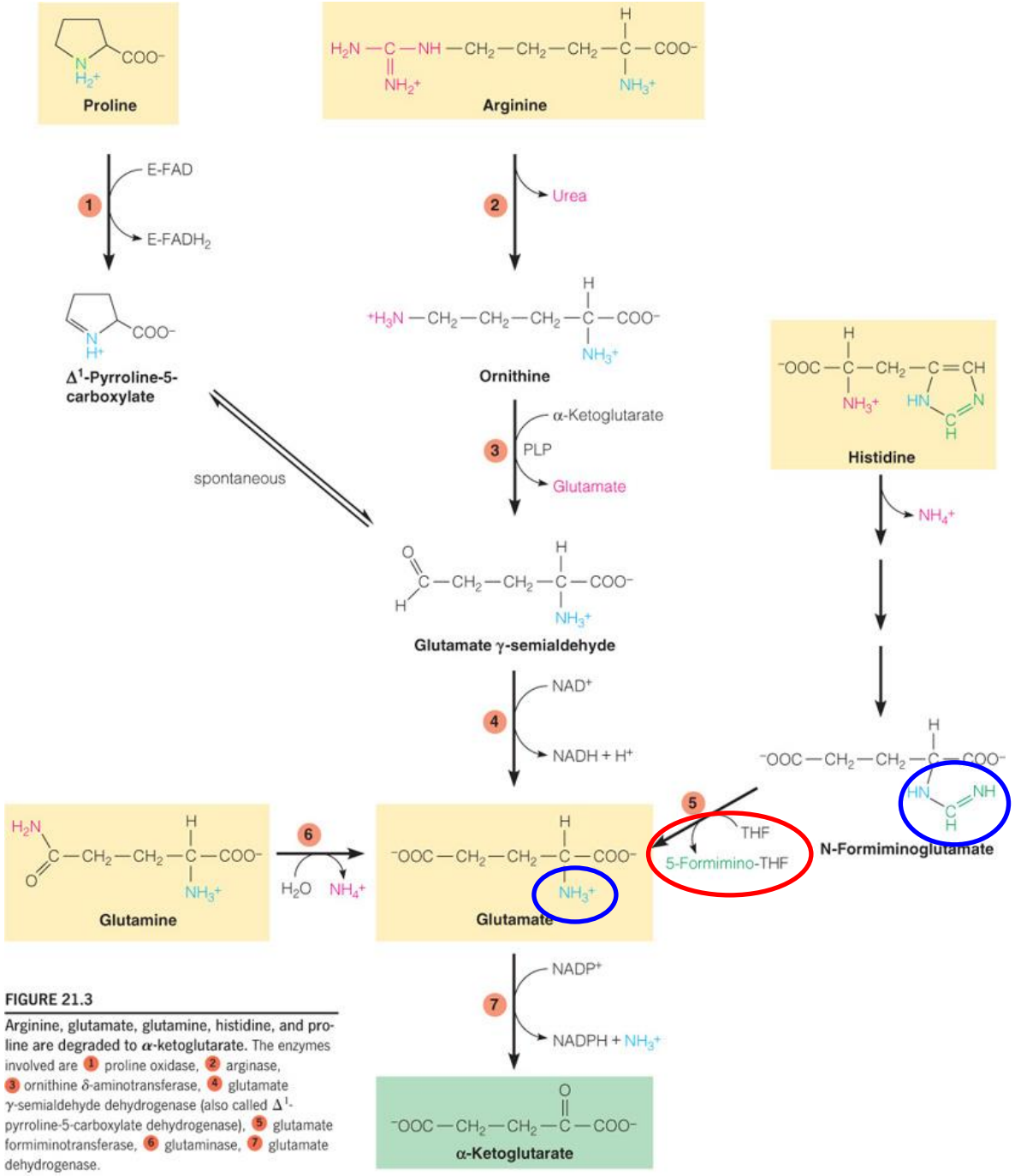
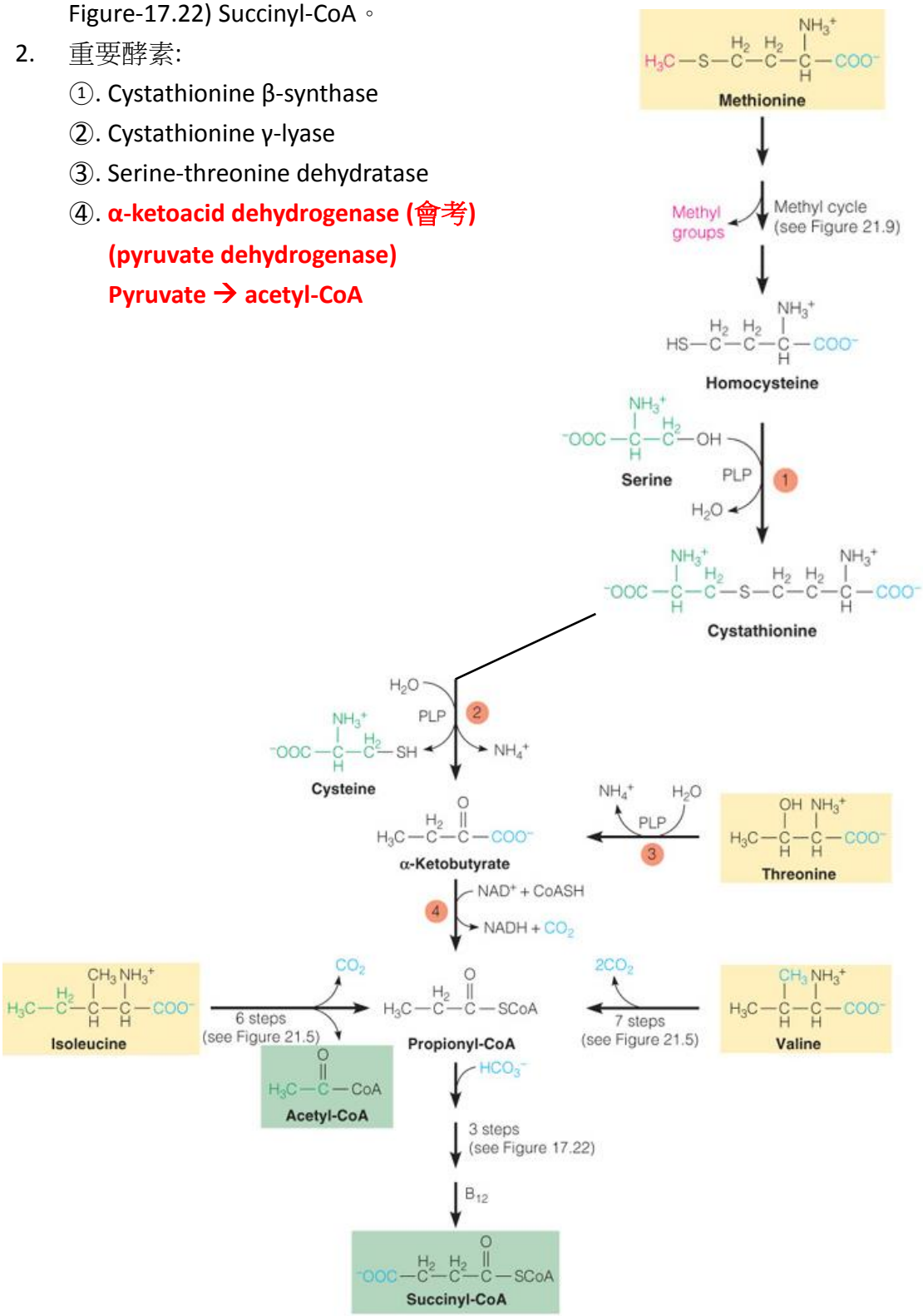


FIGURE 21.3
Arginine, glutamate, glutamine, histidine, and proline are degraded to α-ketoglutarate. The enzymes involved are 1 proline oxidase, 2 arginase, 3 ornithine δ-aminotransferase, 4 glutamate γ-semialdehyde dehydrogenase (also called Δ¹-pyrroline-5-carboxylate dehydrogenase), 5 glutamate formiminotransferase, 6 glutaminase, 7 glutamate dehydrogenase.

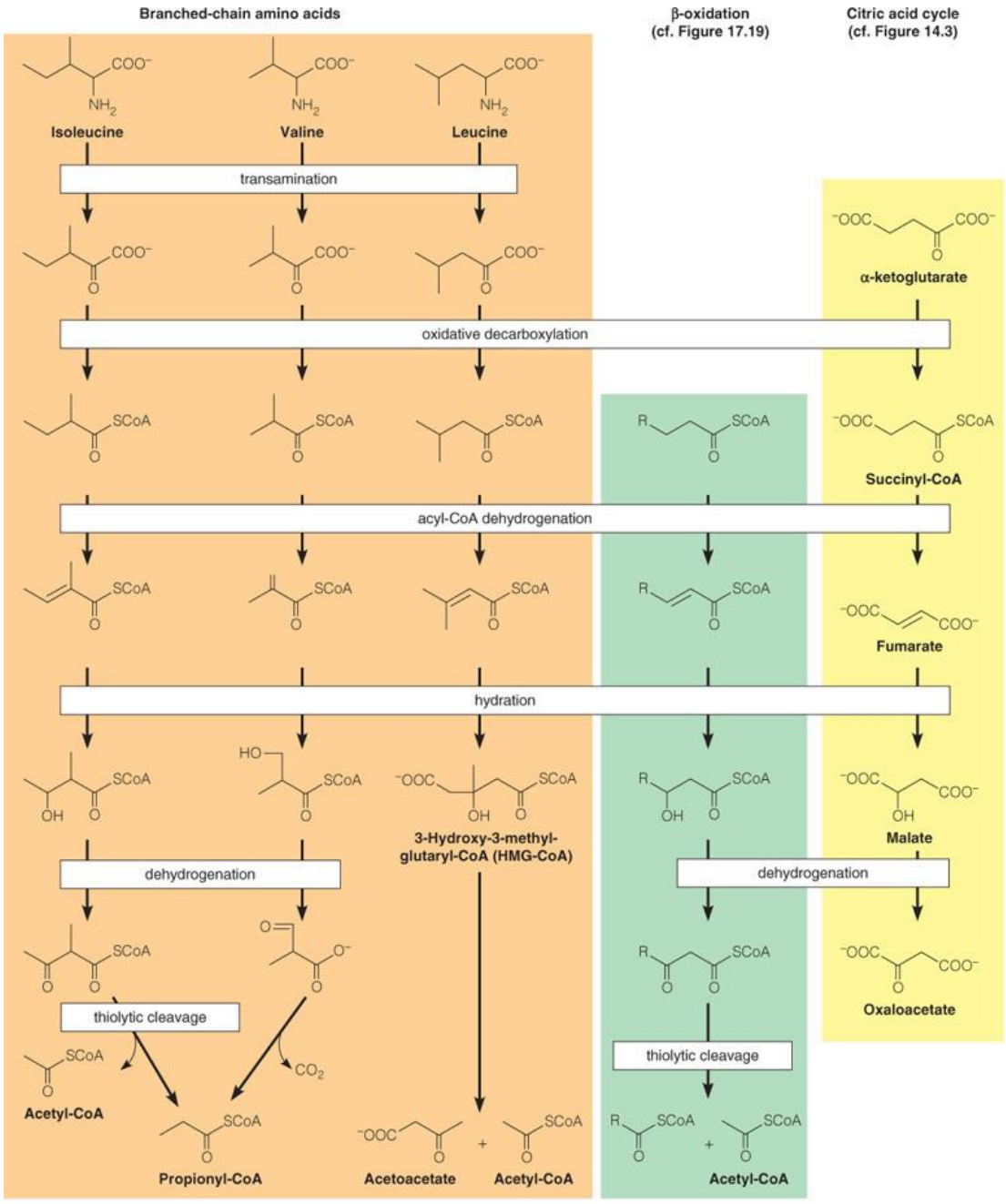
Succinyl-CoA family of glucogenic amino acids

→ *Isoleucine, valine, threonine, methionine*

1. 此 4 種氨基酸都會先反應成 propionyl-CoA，再合成(步驟詳見課本 p732 Figure-17.22) Succinyl-CoA。
2. 重要酵素:
   ①. Cystathionine β-synthase
   ②. Cystathionine γ-lyase
   ③. Serine-threonine dehydratase
   ④. **α-ketoacid dehydrogenase (會考)**
   (pyruvate dehydrogenase)
   Pyruvate → acetyl-CoA



3. Branched-chain amino acid oxidation, fatty acid b-oxidation, and the citric acid cycle share a common chemical strategy(如下圖)。
4. Branched-chain a-keto acid dehydrogenase complex 在人體中可代謝 valine, leucine, isoleucine，若缺乏將造成 maple syrup urine disease，嚴重影響心智發展。
5. Branched-chain amino acid aminotransferase 在肝中較少，故此反應在肝中部發生；而 Extrahepatic tissues(肝外組織)如肌肉、脂肪、腎、腦，此反應則是飢餓時的主要能量來源。



Acetoacetate/Acetyl-CoA family of glucogenic amino acids

→ *lysine, tryptophan, phenylalanine, tyrosine*

Lysine Degradation：

1. Lysine 能藉由很多種方式被分解，然而哺乳動物體內最主要的路徑是 saccharopine pathway，此法策略與前面的 Branched-chain amino acid 類似，移除 e-amino group。
2. Saccharopine 是此二步驟反應(如下圖-a)的中間產物，a-aminoadipic semialdehyde synthase 是 bifunctional enzyme，催化此二步驟。
3. 此反應與 urea cycle 中的 argininosuccnate synthetase-argininosuccnase 反應(如下圖-b)很類似。

Formation of α-aminoadipic semialdehyde

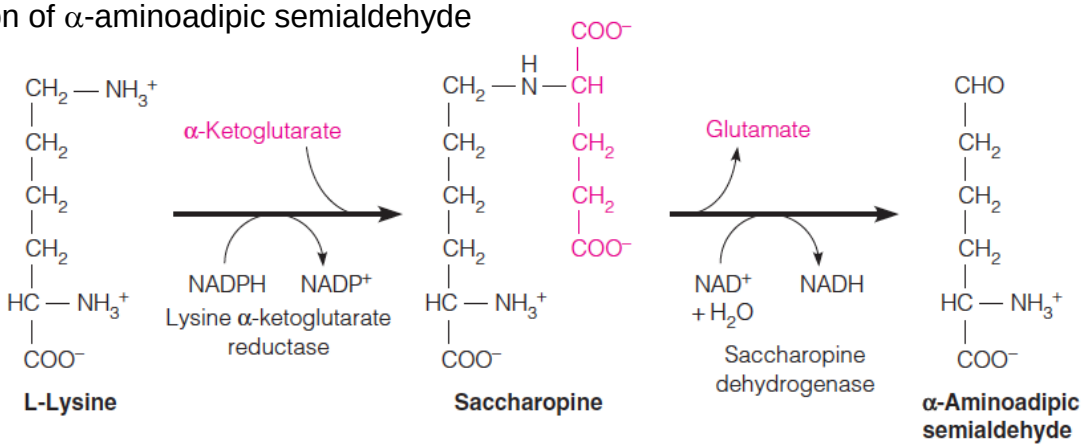


圖 a

Formation of fumarate

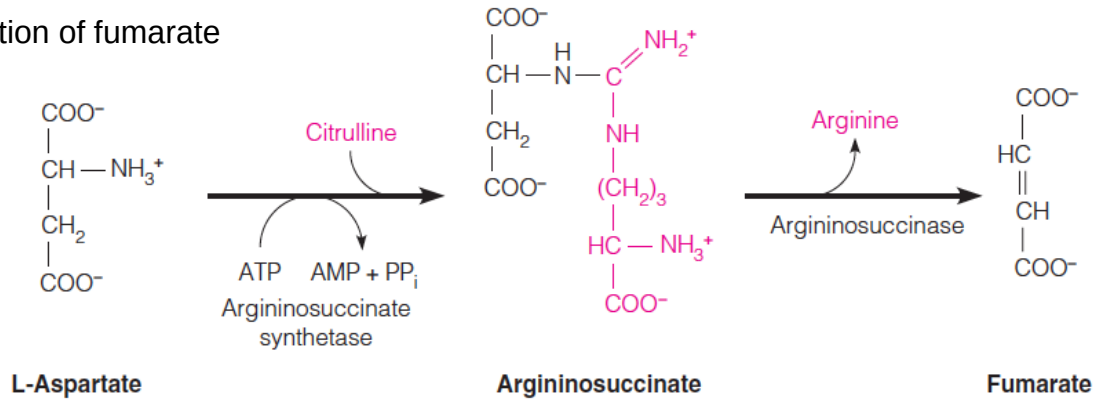
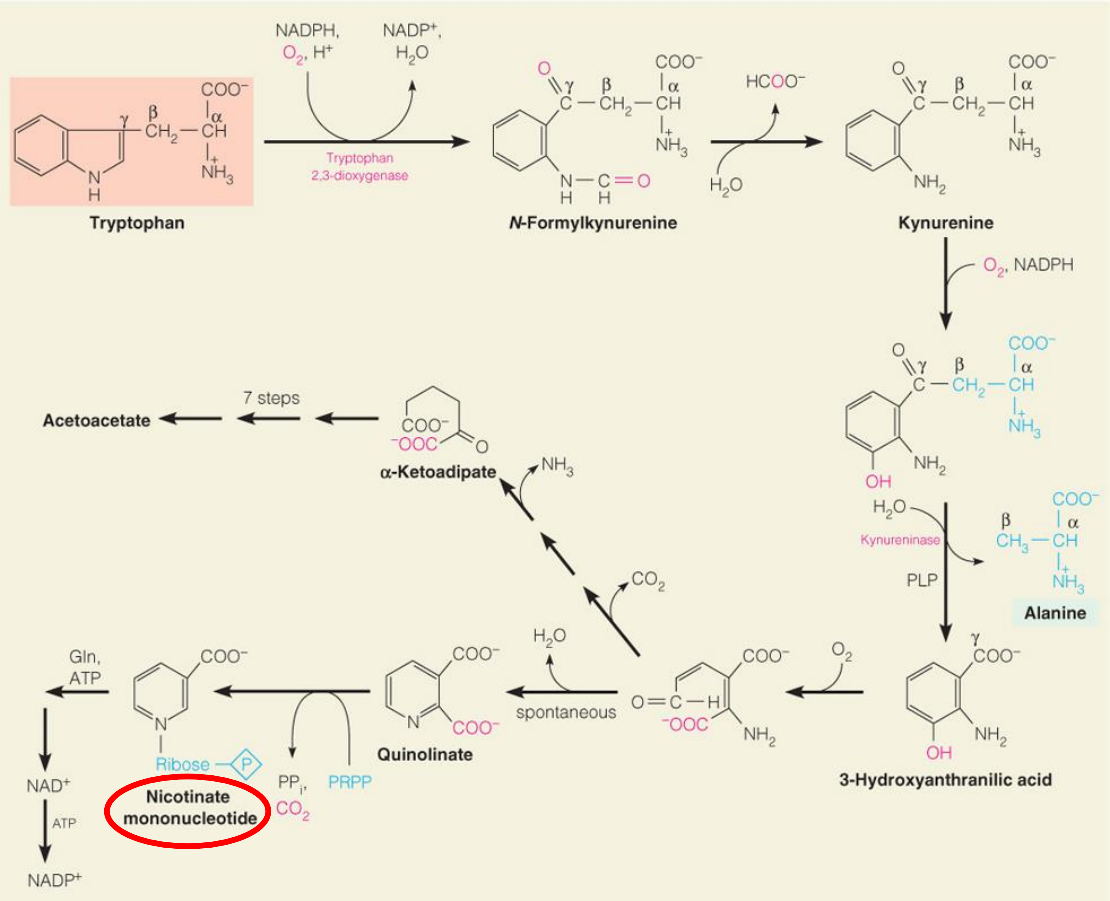


圖 b

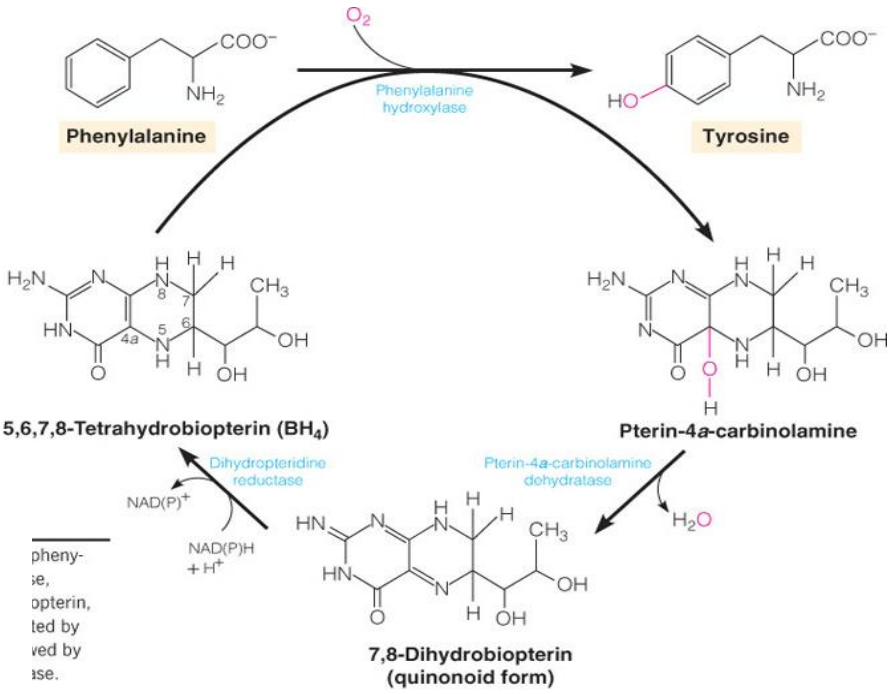
Tryptophan Degradation：

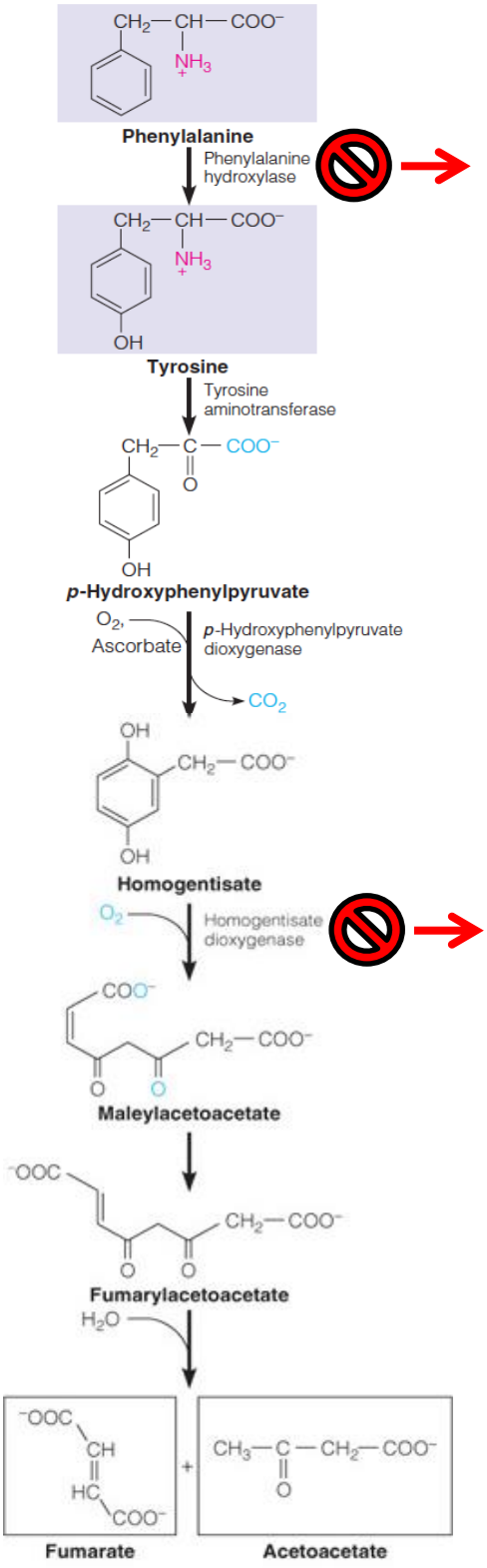
1. 代謝反應中 tryptophan 大多會被分解為 acetoacetate and alanine。
2. 同時會有 nicotinate mononucleotide 產生。
3. Tryptophan 是合成 nicotinamide nucleotides (NAD+)的重要前驅物，占 50%。



Phenylalanine and Tyrosine Degradation：

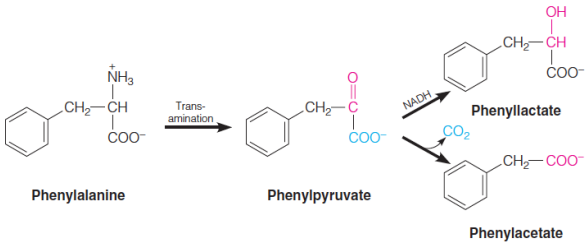
1. Phenylalanine 和 tyrosine 的分解是經由同一條路徑。
2. 酵素 phenylalanine hydroxylase 催化使 phenylalanine 發生 hydroxlation，轉變為 tyrosine。





Phenylketonuria (PKU) (苯丙酮尿症)

遺傳性缺乏酵素 phenylalanine hydroxylase，轉為 tyrosine 的路徑受阻使 phenylalanine 累積高濃度於體內(hyperphenylalaninemia)，這些過多的 phenylalanine 會透過其他較少用到的路徑代謝為 phenylpyruvate(屬於 phenylketone)，接著會再進一步代謝為 phenyllactate and phenylacetate (如下圖)。



Alkaptonuria (黑尿症)

遺傳性缺乏酵素 Homogentisate dioxygenase，使化合物 Homogntisate(深色)累積於體內並藉由尿液大量排出。

Amino Acids as Biosynthetic Precursors

一、Transmethylation：

(1) AdoMet → AdoHcy，受質可以是 polymeric protein or nucleic acids。Creatine & Phosphatidtlcholine 的合成需要經過 transmethylation，與 DNA & RNA 的 methylation 有關(Chapter 29 將提到)。

TABLE 21.1 Some AdoMet-dependent transmethylations

Methyl Group Acceptor	Methylated Product
Norepinephrine	Epinephrine (Figure 21.24)
Guanidinoacetic acid	Creatine (Figure 21.16)
Phosphatidylethanolamine	Phosphatidylcholine (page 784)
DNA-adenine or -cytosine	DNA-*N*-methyladenine or 5-methylcytosine
tRNA bases	Methylated tRNA bases
Nicotinamide	N^1-Methylnicotinamide
Protein amino acid residues	Methylated amino acid residues

(2) Lysine, Arginine 皆是 methylatable (可被甲基化的) → 在 Histone 的 Post-translational modifications 扮演重要角色，進而影響轉錄與轉譯 → Epigenome (外遺傳：環境影響的基因調控)。

(3) ε-N-trimethyllysine 是由 methylated protein 水解而得，是 Carnitine 的 Precursor(與 fatty acyl group 的穿膜有關)。

(4) In bacteria, methylation plays an important role in chemotaxis(化學趨向性，當細菌感受到一化學物質，牠移向或遠離它的過程)。Chemotaxis 與 MCPs 蛋白有關。

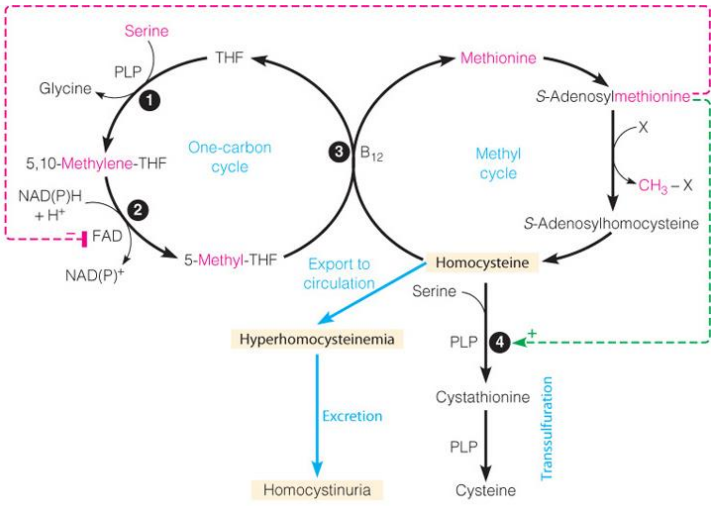
(5) Methylation 可以保護 proteins

(I) By blocking sites of ubiquitination, methylation evidently helps protect proteins from turnover.

(II) 老化過程中自然發生的傷害，methylation 可以啟動期修復機制。

(6) The only known methyl group transfer that does not involve AdoMet is the synthesis of methionine itself.

二、Methyl Cycle：



(1) Methyl cycle 和 one-carbon cycle 緊密結合。所有來自 AdoMet 的 methyl group 的最終來源是 tetrahydrofolate one-carbon pool. Serine 經由 PLP-dependent serine hydroxymethyltransferase 成為 one-carbon unit 的主要提供者。

(2) Methionine synthase 是在 eukaryotes 中唯一一個使用 5-methyl-THF 的 protein。

(3) 若 methionine synthase 被阻擋(如 B12 缺乏)造成 5-methyl-THF 累積，是導致 methyl trap(見 chapter 20)的基礎。

(4) MTHFR reaction catalyze the step of methyl group biogenesis。
MTHFR 的調控在所有有機體都非常重要，MTHFR 受 AdoMet 負回饋調控；AdoMet 防止 CH_2-THF 被用盡。

(5) MTHFR： N 端：catalytic site； C 端：regulatory site(AdoMet allosteric binding site)

(6) 植物和細菌的 MTHFR 調控不是由 AdoMet，且 enzyme 使用 NADH 非 NADPH。因為當 NAD^+/NADH 比值上升時，反應將逆向；因此不須 AdoMet 調控。

(7) AdoMet 在 transsulfuration 的第一步是 positive allosteric effector.
在 methionine & methyl group 都適量的情況下，AdoMet 會使過量的 Homocysteine 不進入 transsulfuration。

三、Deficiency (methylenetetrahydrofolate reductase，MTHFR)

(1) Cystathionine β-synthase deficiency → homocystinuria → mental retardation, 血管受損, 水晶體易位。可用 B6 治療。

(2) Methioninie synthase deficiency：megaloblastic anemia(葉酸缺少性貧血) & homocystinuria，但在人類很少見。

(3) MTHFR deficiency 較常見，嚴重案例少；North America 常見。

是一個在人類 MTHFR gene exon 4 上的 C→T 突變使得 Ala→Val(Alanine 丙胺酸→Valine 纈胺酸) in catalytic domain.

這是一個 single nucleotide polymorphism(Polymorphism 是指一個特定突變發生

率特高。)

生化研究指出人類在此處 Val 較 Ala 不穩定許多，較 thermolabile(熱敏性)。

(4)bacterial MTHFR 並無 regulatory domain，牠們以 flavin cofactor(FAD)調控。

研究指出 E. coliy 在此處 Val & Ala 並不影響 K_M or K_{cat}，但 Val 會使其容易丟失 FAD cofactor，這使其對熱不穩定。Folate substrate 會協助其抵抗 flavin loss。

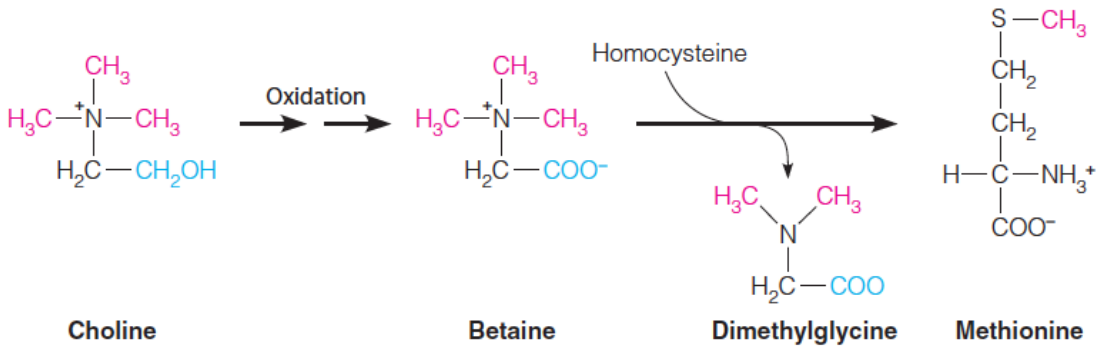
若 folate level 適當，MTHFR 所受影響不大；folate level 過低，MTHFR 變得 thermolabile，5-methyl-THF 合成出問題。

(5 必考)葉酸(folic acid)、B6、B12 攝取不足與 cystathionine β-synthase、methionine synthase 和 MTHFR 的缺乏皆會導致 homocystinuria。

四、Betain(甜菜鹼)(老師提較少)

(1) Liver & kidney 有另一條 methionine synthesis 的路徑，需用 betain 當作 methyl donor.

(2) Betain 又稱作 trimethylglycine 在 choline 的 mitochondrial oxidation 中形成。



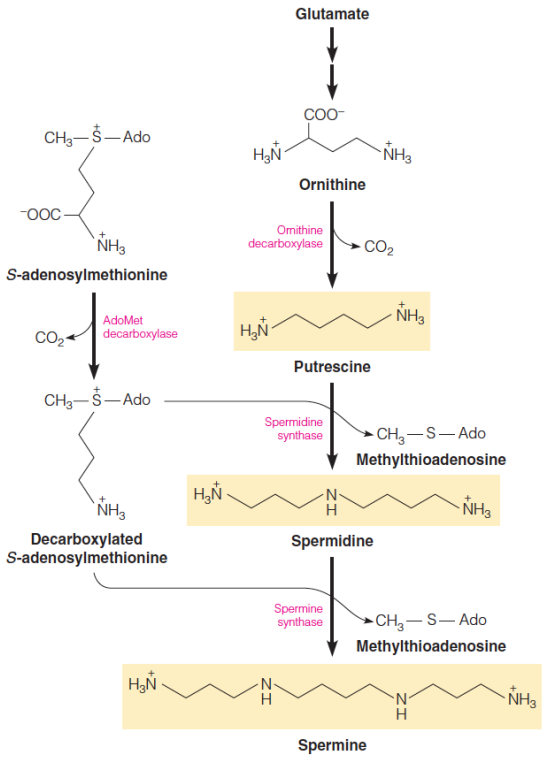
(3) Positive charge，四級胺結構(quaternary amine derivative of an amino acid)，像 AdoMet 一樣有 high transfer potential。

(4) 在植物中當作重要的 osmoprotectants，協助植物抵抗高鹽環境。
Betain 的合成需要 methyl group，高鹽環境下植物的 methyl group 幾乎全拿來形成 betain，因此長不高。

五、Polyamine (重點：Polyamine 原料是 Glutamate)

(1) Spermine & spermidine 都是帶負電的(cationic cell components)，在分裂快速細胞中較充裕。

(2) Ornithine decarboxylate 成 putrescine(又稱 1,4-diaminobutane)



(3) Putrescine & cadaverine 皆是 diamine；

↑ decarboxylation ↑

Ornithine　　Lysine

(必考)Ornithine 是由 Glutamate 合成

Ornithine decarboxylase 受許多 hormone 影響，短半生期，活性與蛋白質降解(protein degration)有關。

(4) Polyamine 帶負電與 DNA&RNA 雙股的穩定有關。

在細菌中有穩定膜和滲透壓的功能。

Polyamine 的合成和 nucleic acid 的合成有關。

抗寄生蟲藥物 DFMO(difluoromethylornithine)有阻止細胞分裂的功能，因為它限制了 Ornithine decarboxylase。

(5) Snyder-Robinson Syndrome：

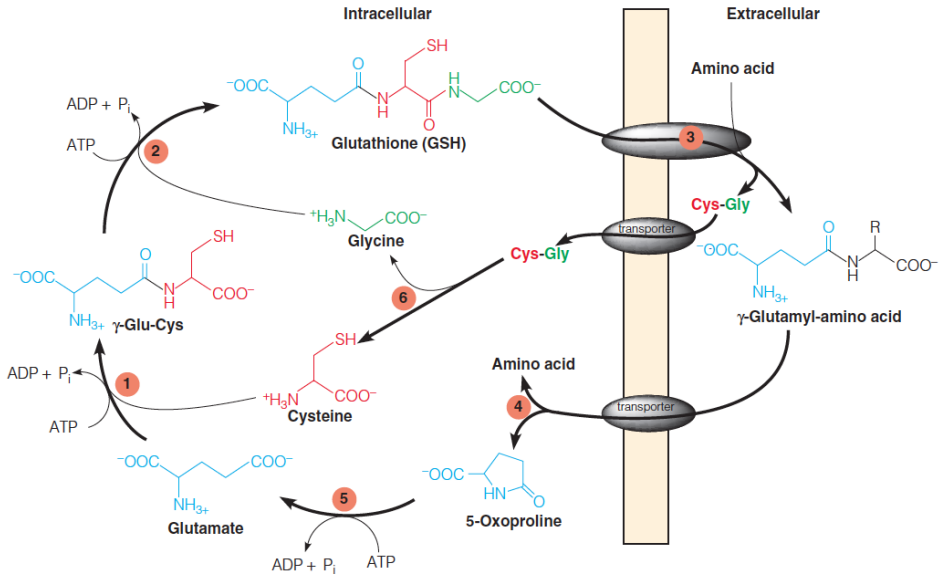
X 染色體上負責 spermine synthase 的部分 mutation→mental retardation、skeletal defects(骨骼缺陷)、osteoporosis(骨質疏鬆)和 facial asymmetry(臉部兩側不均勻)。

六、Other Precursor Function of Glutamate

(1) Glutamate 可以 decarboxylate 得 γ -aminobutyric acid, GABA；兩者皆是 neurotransmitter。

(2) Glutathione(GSH), or γ - glutamylcysteinylglycine 是 glutamate 由 γ -carboxyl linkage 形成(非 α -carboxyl linkage)。

(3) γ -glutamyl cycle 能運輸 amino acid 進入細胞。



(4) γ -glutamyl transpeptidase 是一個膜蛋白，active site 朝向 extracellular space。γ -glutamyl group 的穿膜向外運輸不需消耗 ATP，因為反映中含有一個肽鍵轉移。

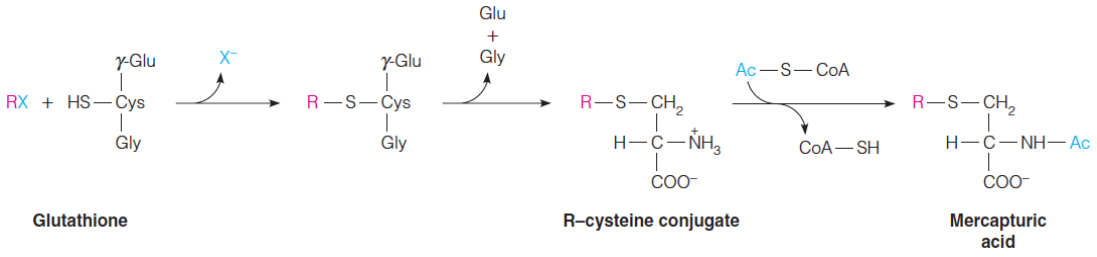
(5) γ -glutamyl group 在膜外形成 γ -Glutamyl-amino acid conjugate，向膜內運輸後會分解為 free amino acid 和 5-oxoproline。5-oxoproline 會再消耗 ATP 形成 Glutamate。

(6) γ -glutamyl cycle 在細胞很重要，尤其是有分泌功能的細胞，如：腎、胰、小腸。

七、Glutathione

(1) 它可還原過氧化物和自由基(radical)。如此以維持胞內適當環境。

(2) Glutathione S-transferase 分布極廣，glutathione 參與許多 detoxification(排毒)。Glutathione 可與 radiation-damaged DNA 的產物和 lipid oxidation 的產物反應，最終形成 mercaputuric acid，由尿液排出。

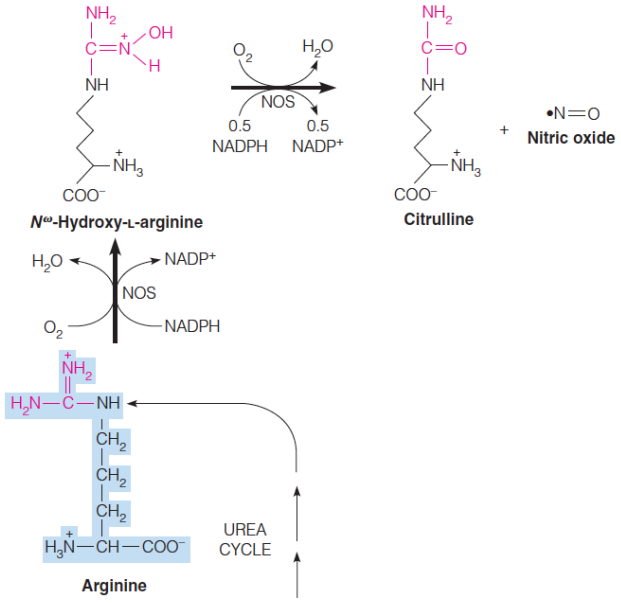


(3) Glutathione 可還原為 Ovothiols，ovothiols 在禽類剛受精的蛋有抗氧化功能。

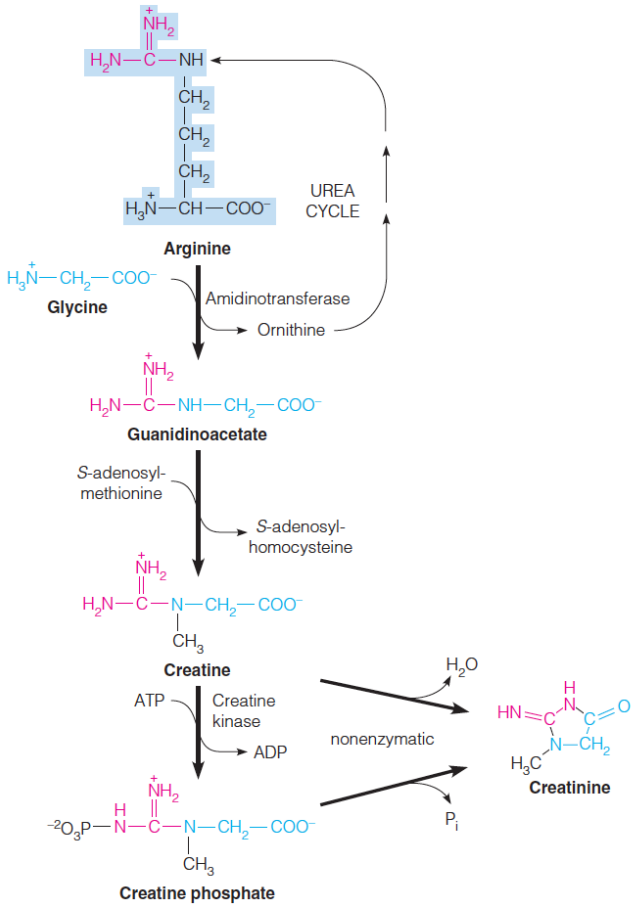
(4) Glutamate is involved in the synthesis, via an ATP-dependent conjugating system, of the polyglutamate tails of folic acid and its coenzymes. As in glutathione synthesis, the glutamate residues in the polyglutamate tails are linked through their γ -carboxyl group.

八、NO & Creatine Phosphate

(1) Arginie 會消耗 NADPH & O_2 經 NO synthase(NOS)產生 NO & Citruline。



(2) Arginie 也形成儲存能量的 Creatine phosphate，過程需使用 glycine。



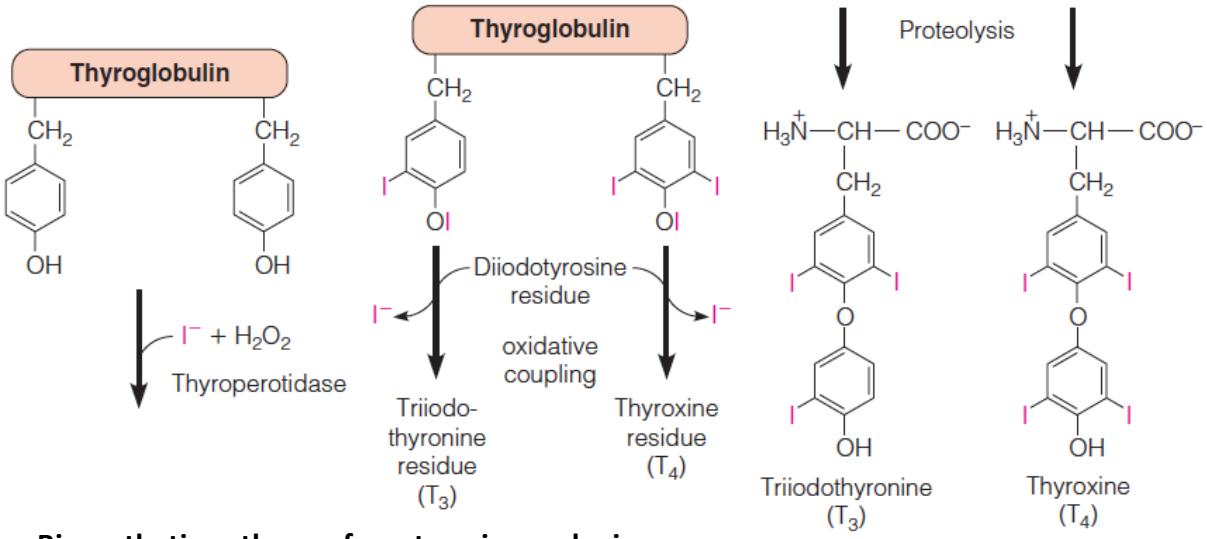
(3) The amidinotransferase reaction 是 creatine 合成的速率決定步驟，受 creatine 負回饋調控。

(4) Creatine 的合成在哺乳類中由腎臟和 Guanidinoacetate 並送至肝臟進行 methylation 以得 creatine。而後 creatine 分泌至血流中，高耗能組織(如肌肉和腦)會再將其磷酸化為 creatine phosphate 加以使用。

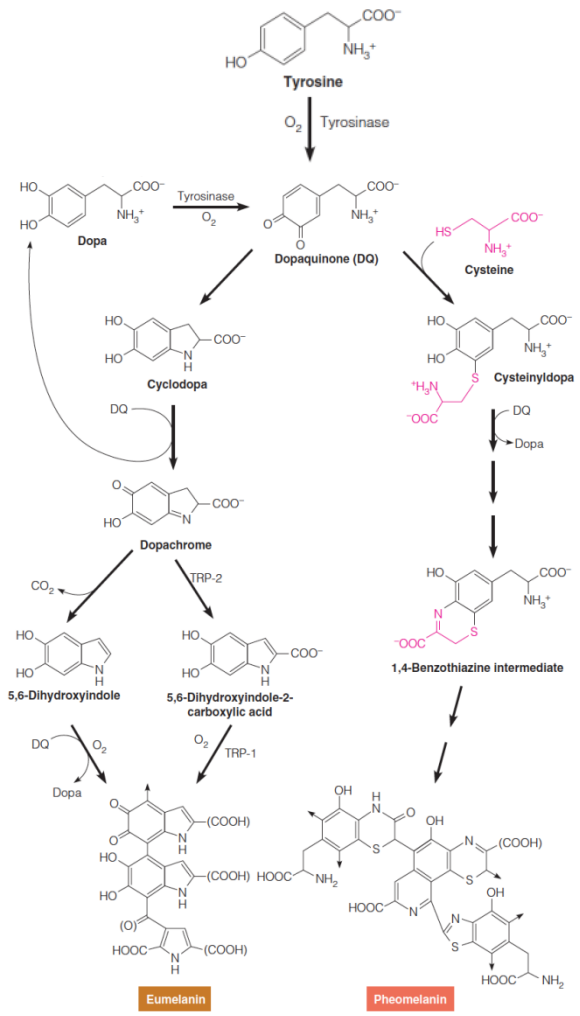
(5) Creatine & creatine phosphate 皆能代謝為 creatinine，由尿液排出。

Biosynthesis of thyroid hormones as residues in the protein thyroglobulin:

- Tyrosine 當作 Thyroglobulin 的側鍊時，可以做為甲狀腺素 T3(triiodothyronine)、T4(thyroxine)合成的前驅物，與碘鍵結
  的 tyrosine 可以利用酵素切出 T3、T4。
- 缺碘時，會造成甲狀腺腫大(goiter)。



Biosynthetic pathways from tyrosine melanins

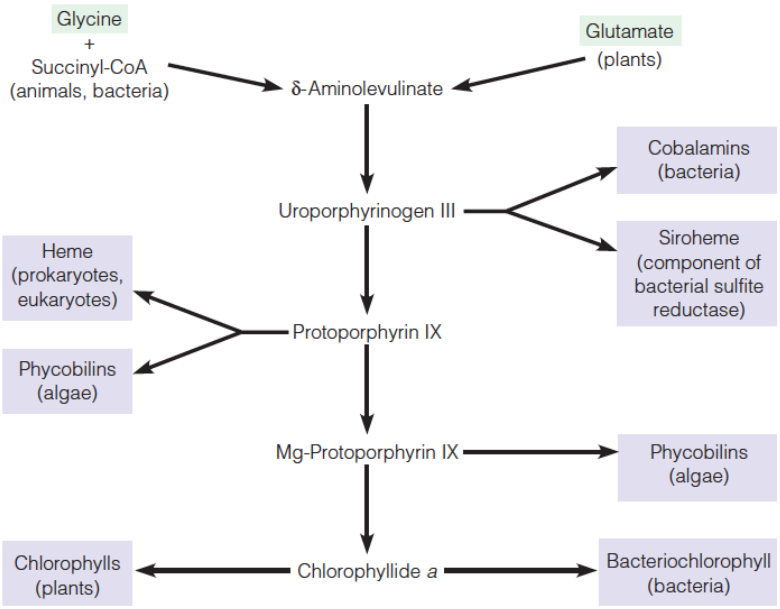


本反應多為自發性反應，僅少數步驟需要酵素催化。一些步驟需要 dopaquinone(DQ)行氧化還原，Dopa 與 DQ 可藉由 Tyrosinase 轉換。圖中 Pheomelanin 上的箭頭可以接其他物質，形成別的 melanin。

- 速率決定步驟為：Tyrosine→DQ
- TRP：Tyrosinase related protein
- Dopa：3,4-dihydroxyphenlalanine
- Tyrosinase 是含有銅的氧化型催化劑
- 白子缺乏 Tyrosinase

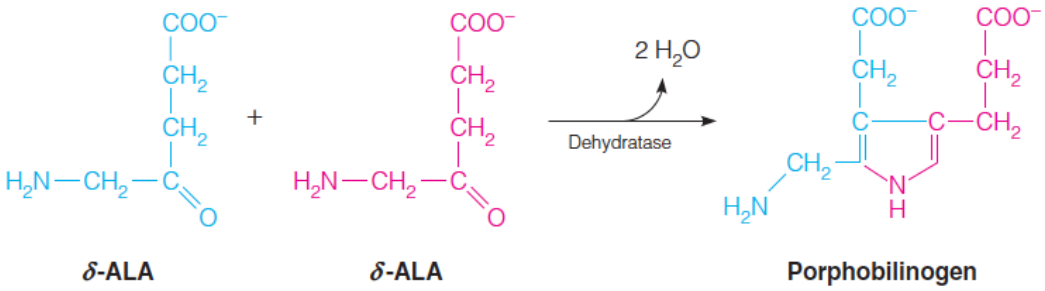
Porphyrin and Heme Metabolism

- Glycine 與 Tetrapyrroles 的合成有關，Tetrapyrroles 包含 Heme(含 iron)、Chlorophylls(存在於植物與光合細菌)、Phycobilins(藻類的光合色素)、Cobalamins(維他命 B12 及其衍生物)。
- 所有的 Tetrapyrrole 皆以 δ-aminolevulinic acid(ALA，也稱為 5-aminolevulinic acid)為前驅物。
- Heme 的氮原子是由 Glycine 而來的，而碳原子是由 Glycine 與 Succinate 而來。



Porphyrin 的合成包含三個步驟:

1. 用 ALA 合成 Porphobiblinogen
2. 四個 Porphobiblinogen 形成 porphyrinogen。
3. 修飾 sidechain(脫氫….)，形成 Heme。



δ-ALA **δ-ALA** **Porphobilinogen**

兩個δ-aminolevulinic acid 經過 Dehydratase 脫兩分子水形成 Porphobiblinogen。

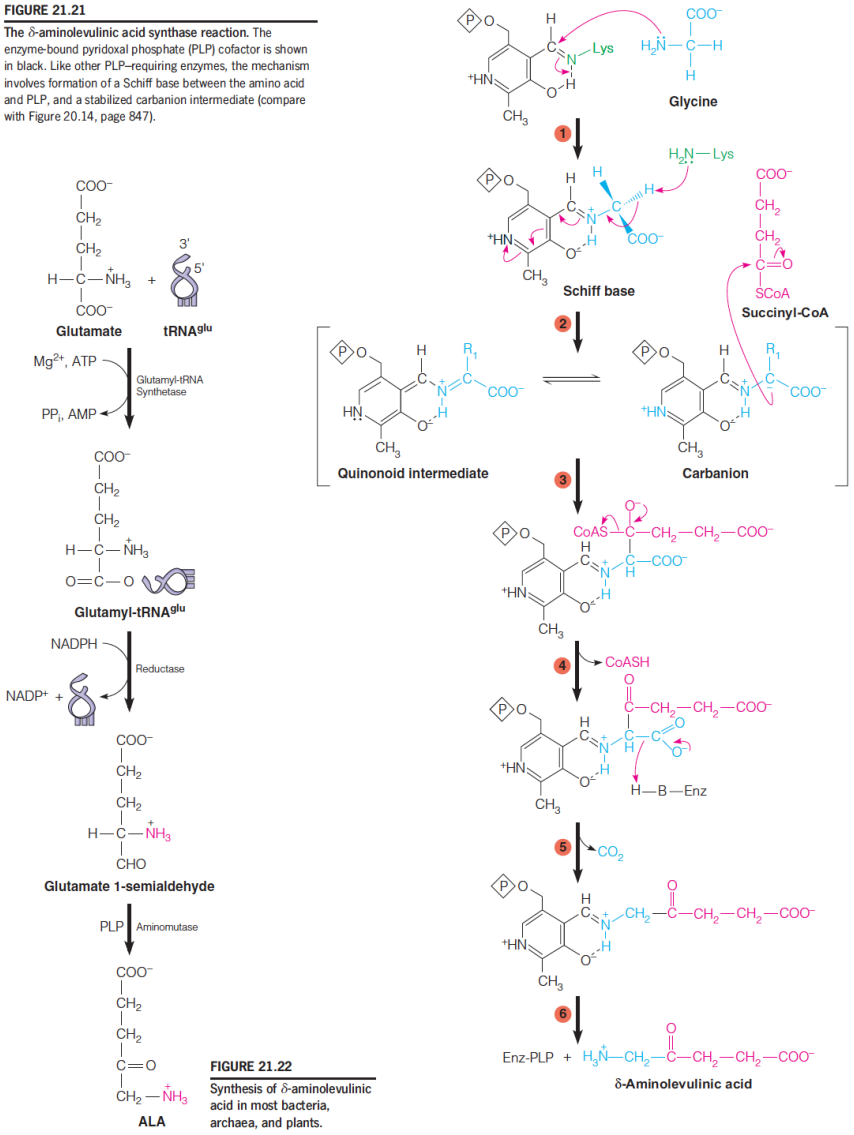


FIGURE 21.21
The δ-aminolevulinic acid synthase reaction. The enzyme-bound pyridoxal phosphate (PLP) cofactor is shown in black. Like other PLP–requiring enzymes, the mechanism involves formation of a Schiff base between the amino acid and PLP, and a stabilized carbanion intermediate (compare with Figure 20.14, page 847).

FIGURE 21.22
Synthesis of δ-aminolevulinic acid in most bacteria, archaea, and plants.

1. 在細菌、植物、古細菌中，ALA 的合成(Glutamate 路徑)：
   Glutamate 的羧基端與 tRNA 結合，利用 NADPH 還原成 Glutamate 1-semialdehye。在經過 PLP 重組形成 ALA。
2. ALA 經由 Glycine 路徑合成(Succinate-Glycine pathway)：
   Glycine 與 PLP 結合，活化 Glycine 上的 α 碳使 succinyl-CoA 上的 thioester carbon 與之結合。脫去 CoASH 與脫羧形成 ALA。

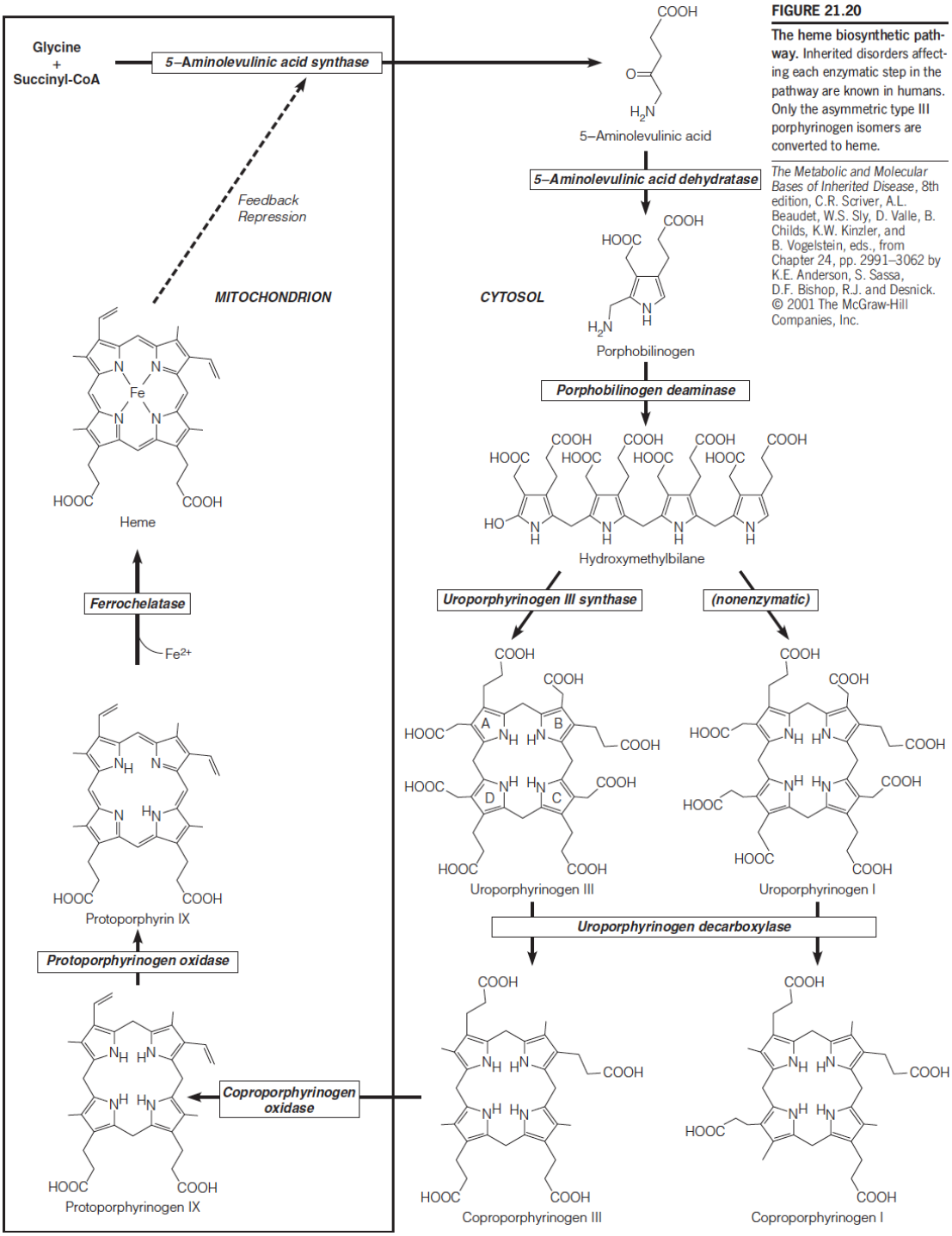


FIGURE 21.20

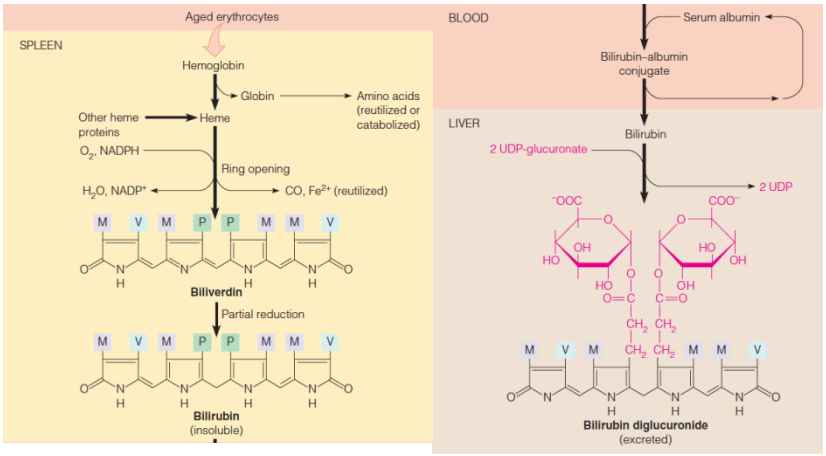
The heme biosynthetic pathway. Inherited disorders affecting each enzymatic step in the pathway are known in humans. Only the asymmetric type III porphyrinogen isomers are converted to heme.

The Metabolic and Molecular Bases of Inherited Disease, 8th edition, C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, B. Childs, K.W. Kinzler, and B. Vogelstein, eds., from Chapter 24, pp. 2991–3062 by K.E. Anderson, S. Sassa, D.F. Bishop, R.J. and Desnick. © 2001 The McGraw-Hill Companies, Inc.

Heme 的合成存在兩個地方，Glycine 與 Succinyl-CoA 在粒線體經由 5-Aminolevulinic acid synthase 形成 ALA，再將 ALA 送至細胞質。ALA 經由 5-Aminolevulinic acid dehydratase 合成 Porphobilinogen，再經過 Porphobilinogen deaminase 合成 Hydromethylbilane，可經由酵素與非酵素路徑分別形成 Coproporphyrinogen III 與 Coproporphyrinogen I，這兩個化合物再送回粒線體加上亞鐵離子形成 Heme。

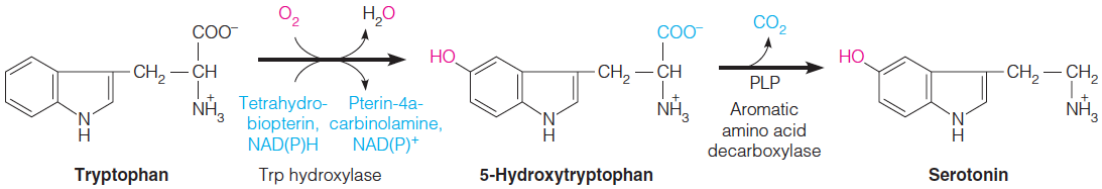
Porphyrin and Heme Metabolism

1. 大多數的 Heme 來自老化的紅血球細胞，在脾臟分解，產生 bilirubin 和 heme。另有一些來自於色素細胞及其他含 heme 的細胞。
2. 由於 bilirubin 無法直接代謝分解成 CO_2，所以會在肝臟接上醣類分子使其可溶於水，代謝排出體外。



Amino Acids and Their Metabolites as Neurotransmitters and Biological Regulators

1. 主概念：Glutamate, tyrosine, glycine, and tryptophan 可以經一連串生化合成產生 neurotransmitters 或其前驅物。
2. Tryptophan 利用 Trp hydroxylase 羥基化形成 5-Hydroxytryptophan，再利用 Aromatic amino acid decarboxylase(PLP 為輔酶)產生 serotonin。



補充：serotonin 的功能：代謝產生 melatonin，掌管睡眠週期。

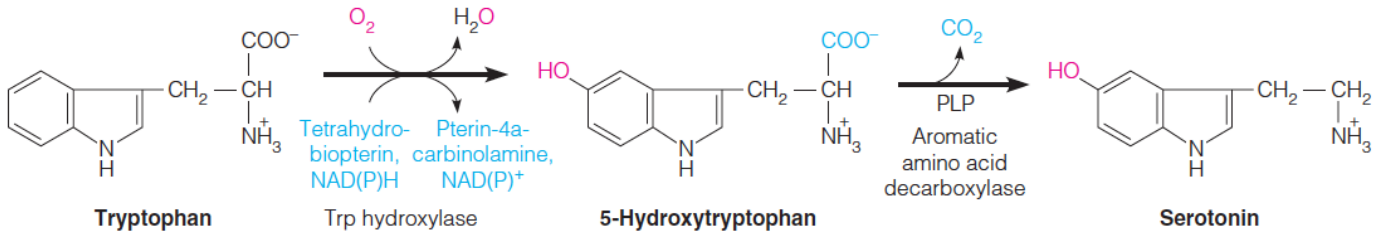
Amino Acids and Their Metabolites as Neurotransmitters and Biological Regulators

Many amino acids and their metabolites participate in signal transduction processes. Among canonical amino acids that serve directly as neurotransmitters are glycine and glutamate. GABA (the decarboxylation product of glutamate) is also a neurotransmitter. Several aromatic amino acid metabolites also function in neurotransmitter. They include histamine, derived from histidine; **serotonin** (5-hydroxytryptamine), derived from tryptophan; and the **catecholamines** --- **epinephrine**, **dopamine**, and **norepinephrine** --- derived from tyrosine.

Biosynthesis of Serotonin and Catecholamines

1. Serotonin

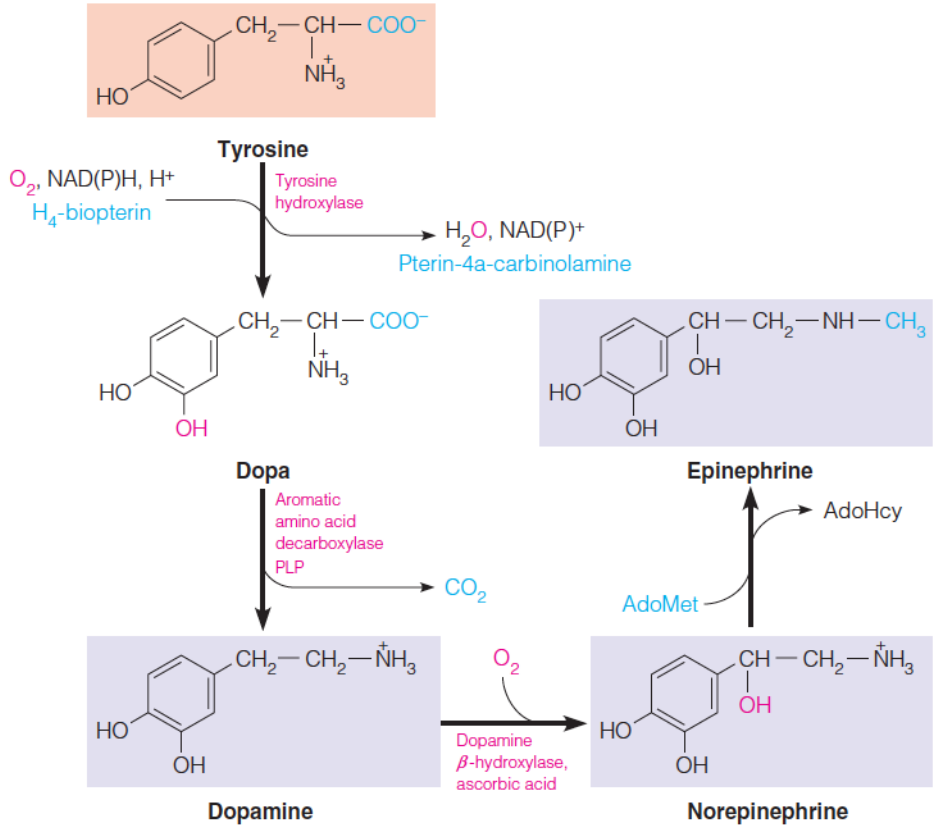
The pathway to serotonin begins with hydroxylation of tryptophan by a tetrahydrobiopterin-dependent aromatic amino acid hydroxylase, similar to phenylalanine hydroxylase. This reaction is followed by a PLP-dependent decarboxylation to yield ***serotonin***.



Serotonine: a vasoconstrictor precursor of melatonin, in pineal gland, light-dark cycles

2. Catecholamines (dopamine, norepinephrine, and epinephrine)

Tyrosine hydroxylase catalyzes the rate-limiting step of catecholamine synthesis, and it is feedback inhibited by the end products of the pathway—dopamine, norepinephrine, and epinephrine.



3. Serotonin & Catecholamines 合成之比較

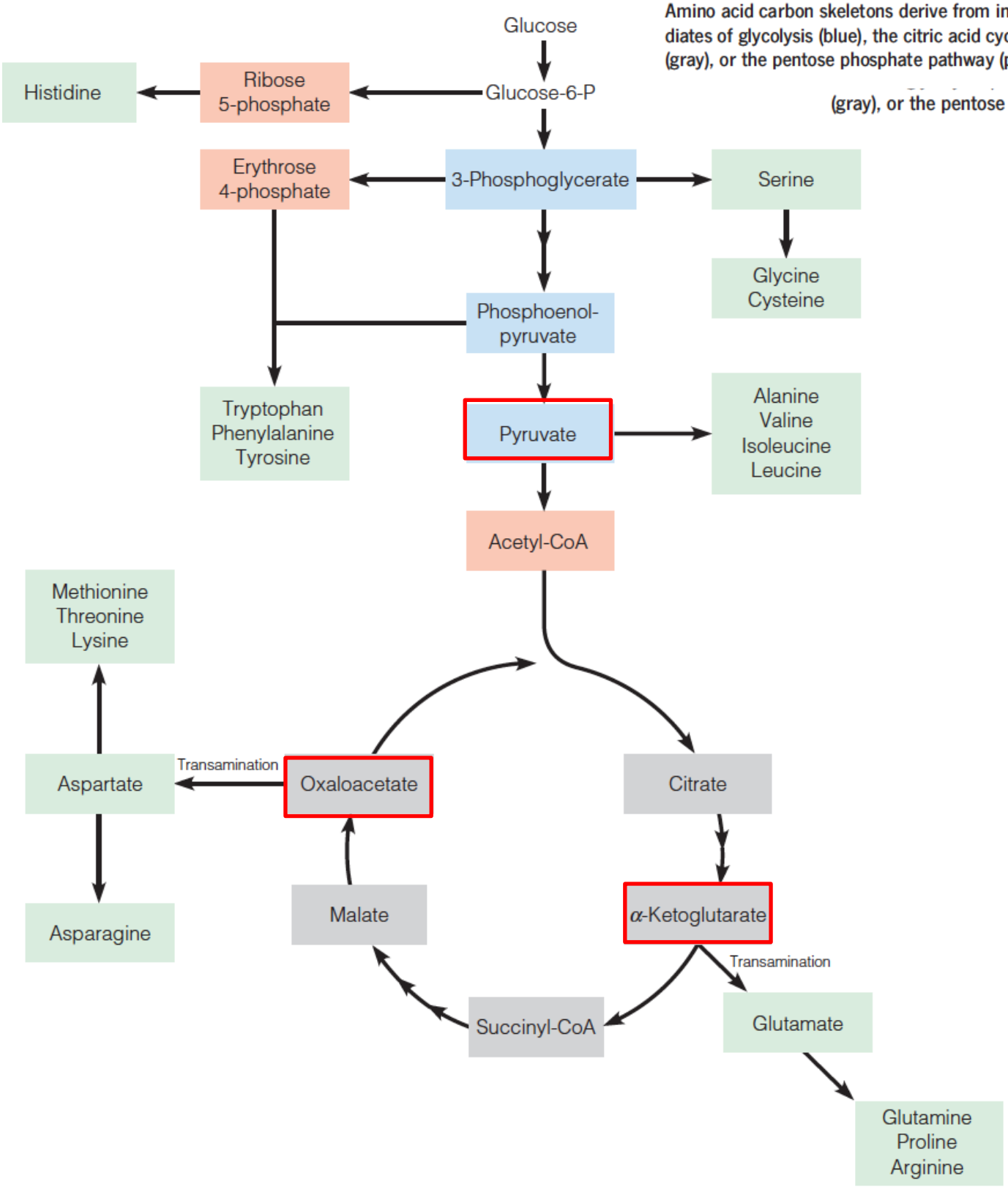
Tryptophan hydroxylase and **tyrosine hydroxylase** are both tetrahydrobiopterin-dependent monooxygenases and are mechanistically and structurally related to phenylalanine hydroxylase.

Amino Acid Biosynthesis

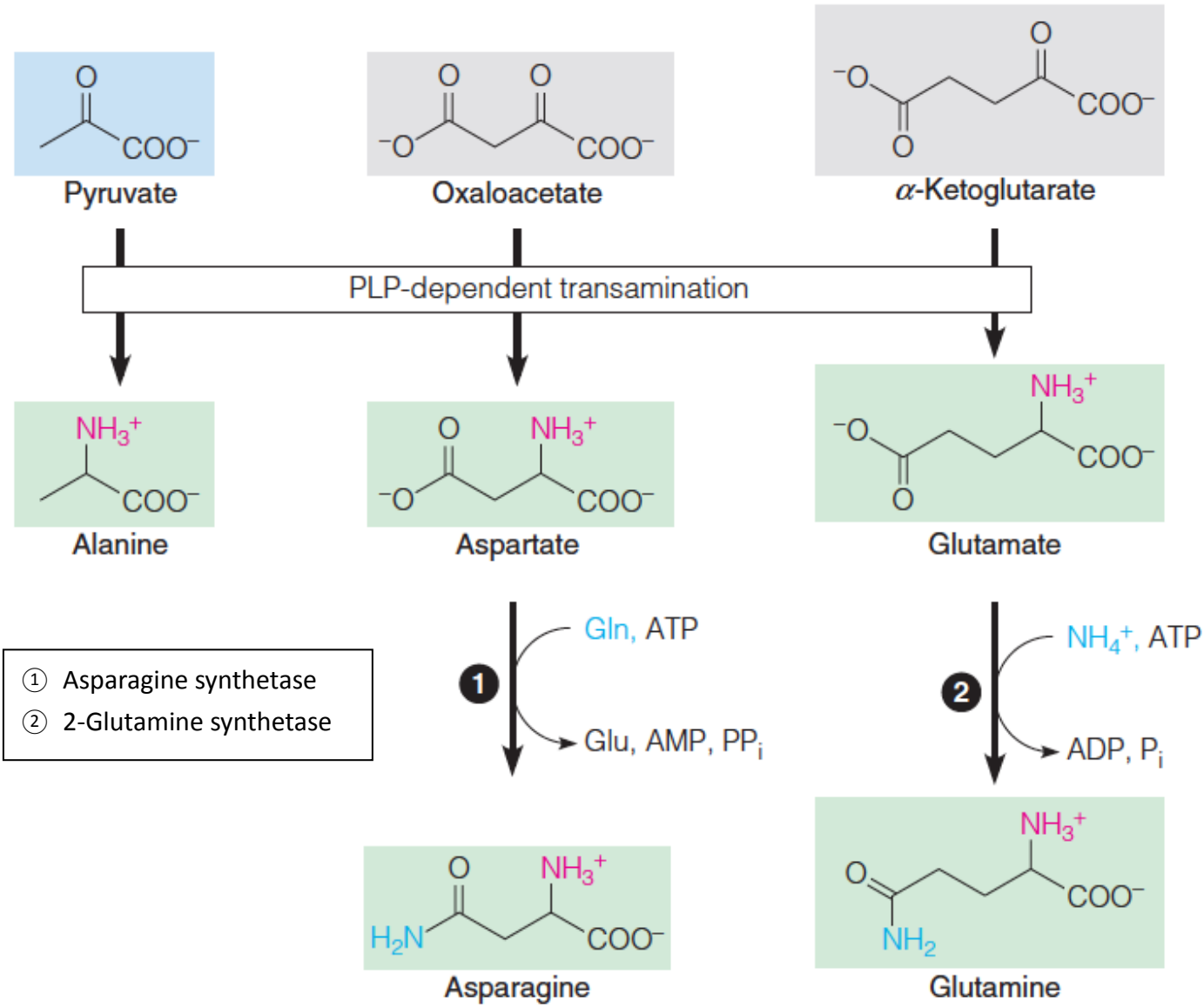
All amino acids can be synthesized from intermediates in glycolysis, the pentose phosphate pathway, or TCA cycle. About half are synthesized from intermediates in TCA cycle or from pyruvate. We include in this family alanine, aspartate, and glutamate, which can be formed by transamination from pyruvate, oxaloacetate, and α-ketoglutarate, respectively.

FIGURE 21.25

Amino acid carbon skeletons derive from intermediates of glycolysis (blue), the citric acid cycle (gray), or the pentose phosphate pathway (pink).

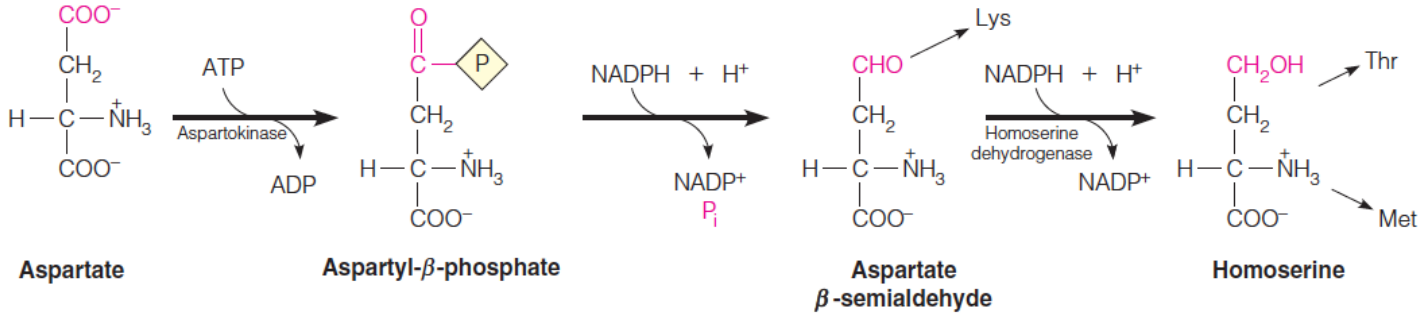


Synthesis of Alanine, Aspartate, Glutamate, Asparagine, and Glutamine

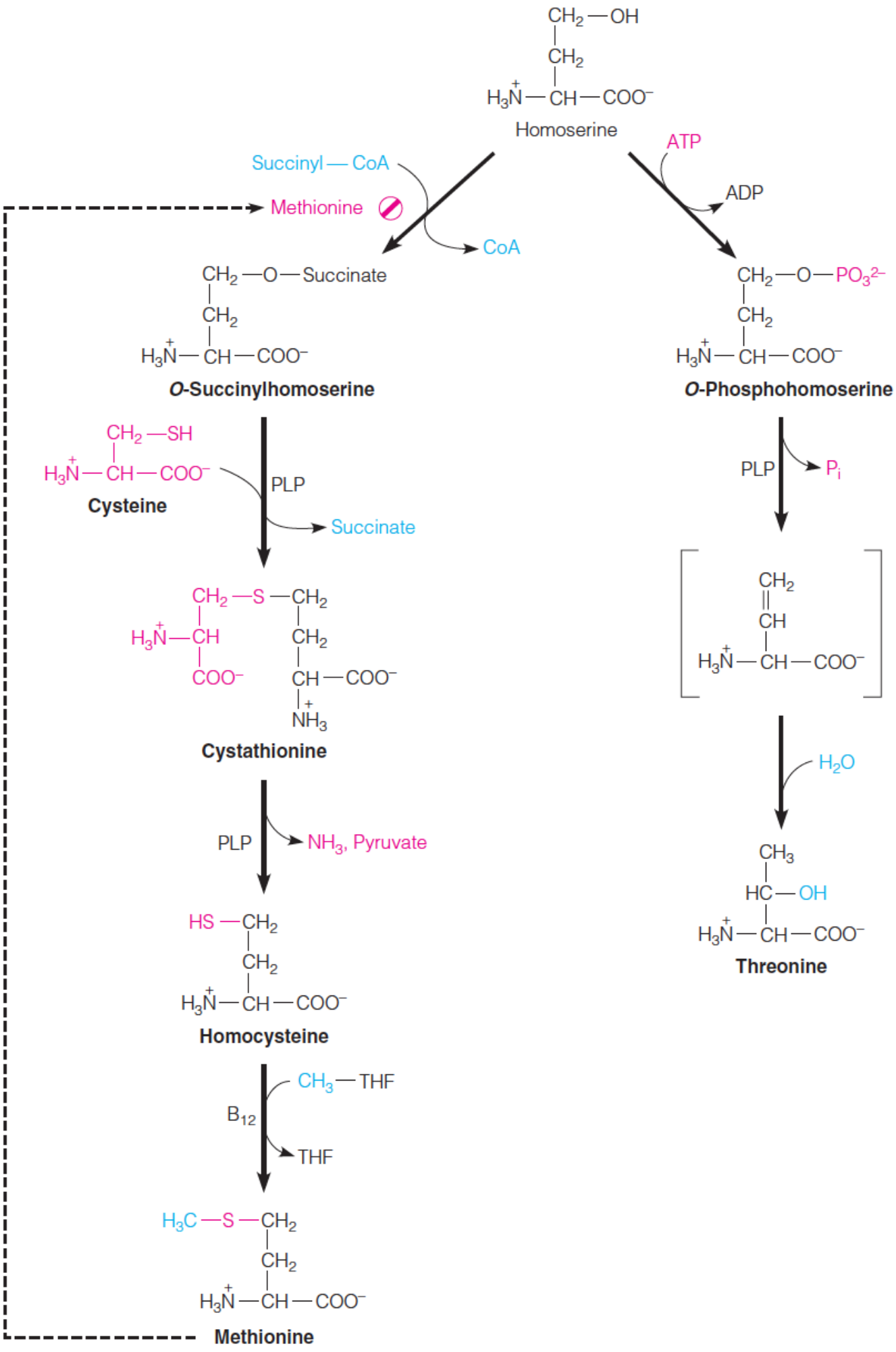


Synthesis of Threonine, Lysine, and Methionine from Aspartate

In plants and bacteria, aspartate is a precursor to three other amino acids via its conversion to **aspartate β-semialdehyde** and **homoserine**. Separate pathways then lead from aspartate β-semialdehyde to lysine and from homoserine to methionine and threonine.



In plants and bacteria, homoserine provides the carbon skeleton for methionine synthesis, with the sulfur coming from cysteine.

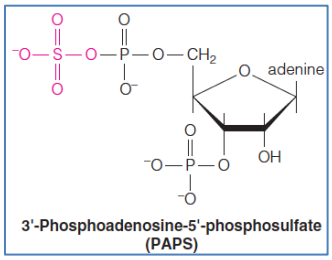

Homoserine
Succinyl — CoA
CoA
Methionine
ATP
ADP
O-Succinylhomoserine
O-Phosphohomoserine
Cysteine
PLP
Succinate
Cystathionine
PLP
Pi
PLP
NH3, Pyruvate
H2O
Homocysteine
Threonine
B12
CH3 — THF
THF
Methionine

Metabolism of Sulfur-Containing Amino Acids

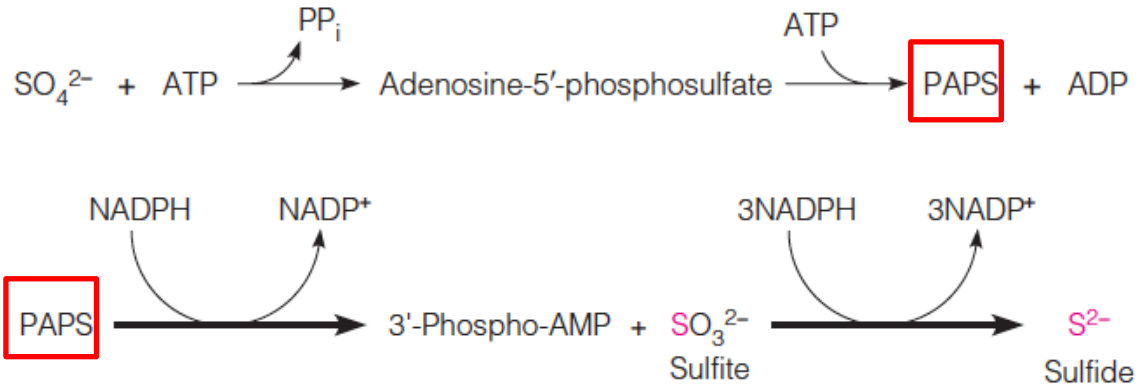
1. Reduction of inorganic sulfur

Like carbon and nitrogen, sulfur is made available to organism largely in the form of inorganic compounds --- principally sulfate (SO_4^{2-}). The utilization of sulfate requires metabolic activation to a form that can undergo reduction. The process for sulfate is largely confined to plants and bacteria. The end product is sulfide (S^{2-}), and is used for cysteine and methionine synthesis.

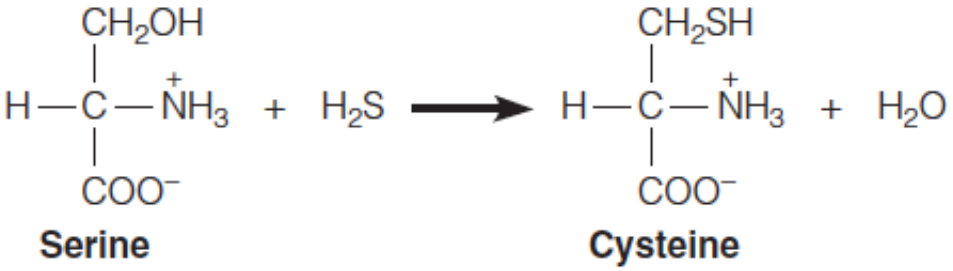
Phosphoadenosine phosphosulfate (**PAPS**) is an activated form of sulfate used both for sulfation reactions and as a substrate for sulfate reduction.



3'-Phosphoadenosine-5'-phosphosulfate (PAPS)

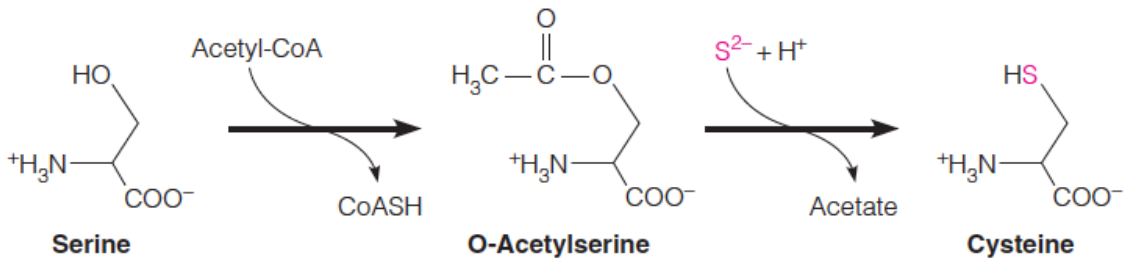


2. Synthesis of cysteine in plants and bacteria



Some bacteria can condense with serine directly, via a pyridoxal phosphate–dependent enzyme.

Plants and most microorganisms use O-acetylserine as the substrate reacting with H_2S.

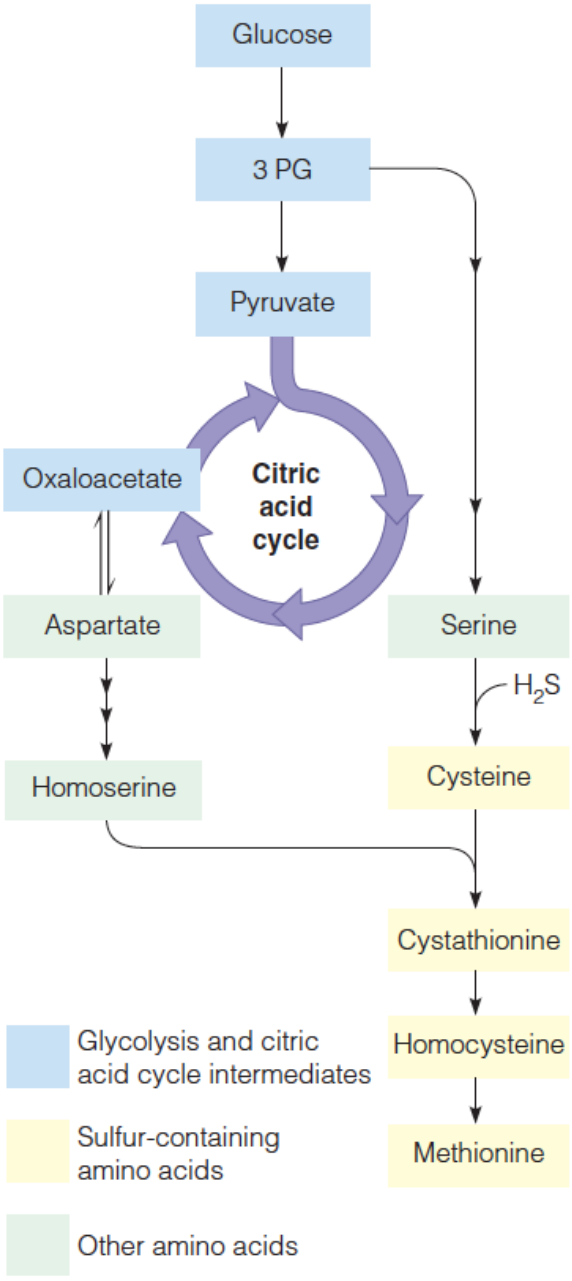


Outline of pathways for cysteine and methionine synthesis in plants and bacteria.

☆ **考點:**

1. Plants and bacteria synthesize cysteine from inorganic sulfur and synthesize methionine from cysteine.

2. Animals synthesize cysteine from dietary methionine. (過程中加入 Serine)

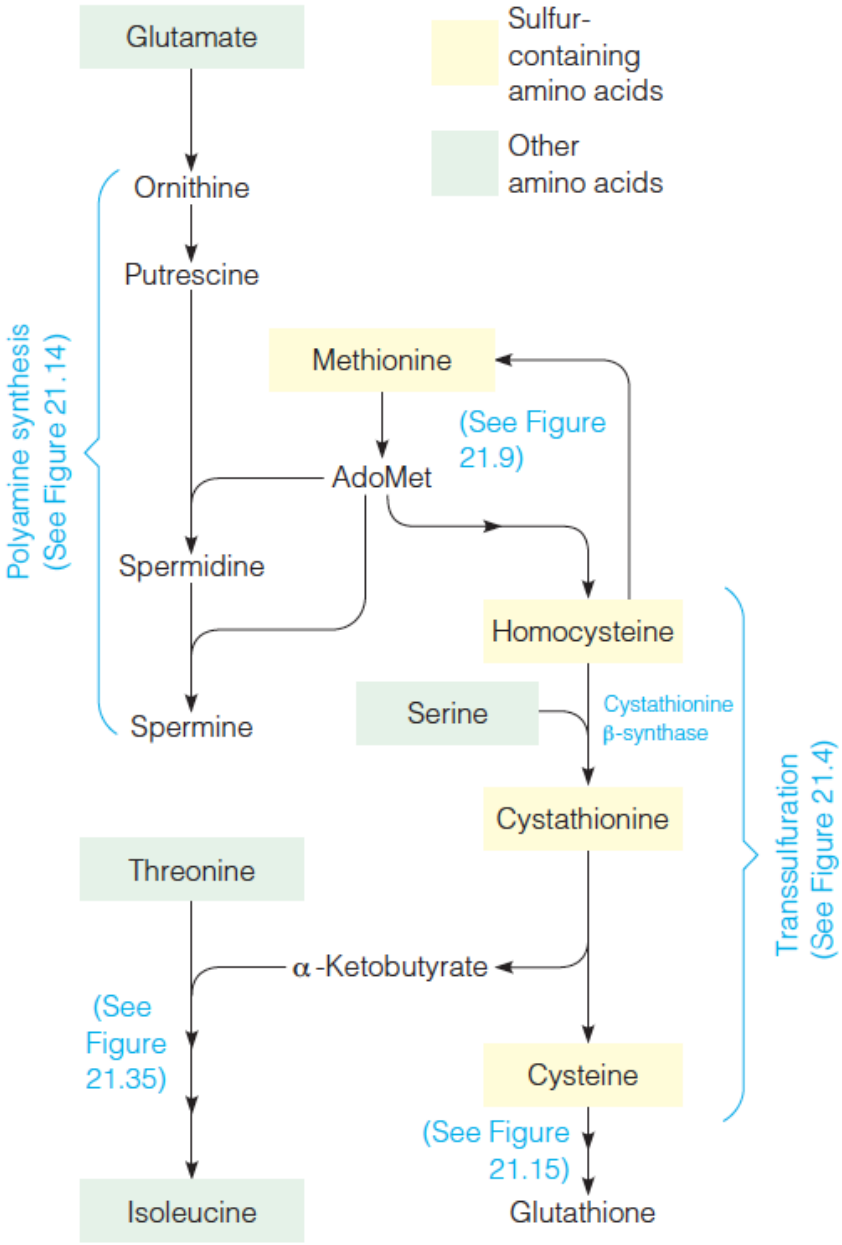


3. Methionine as source of cysteine sulfur in animals

Methionine is classified as an essential amino acid for mammals, and cysteine is not. The synthesis of cysteine in animals resembles the reverse of the methionine biosynthetic pathway in plants and bacteria that we just discussed.

Outline of methionine metabolism:

Except for the synthesis of isoleucine from threonine, which is limited to plants and bacteria, these pathways occur in virtually all organisms.



Cysteine is also the precursor for a nonprotein amino acid, taurine.

Taurine biosynthesis:

The most abundant free amino acid in animal tissue– 25 mM

Biological roles:

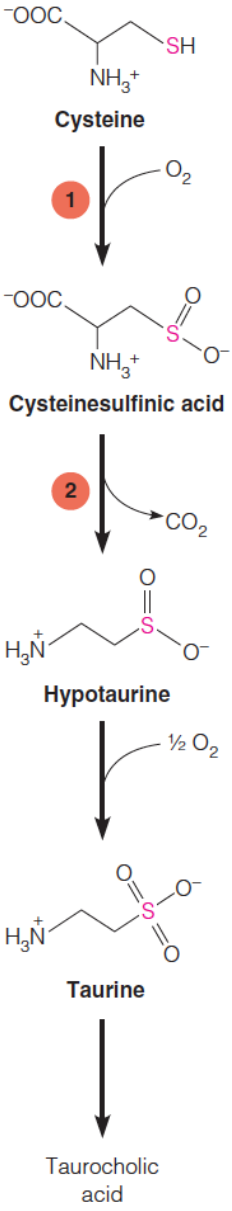
Synthesis of bile acid taurocholate

Regulation of blood pressure

Osmolyte

Antioxidant

Anti-inflammation agent

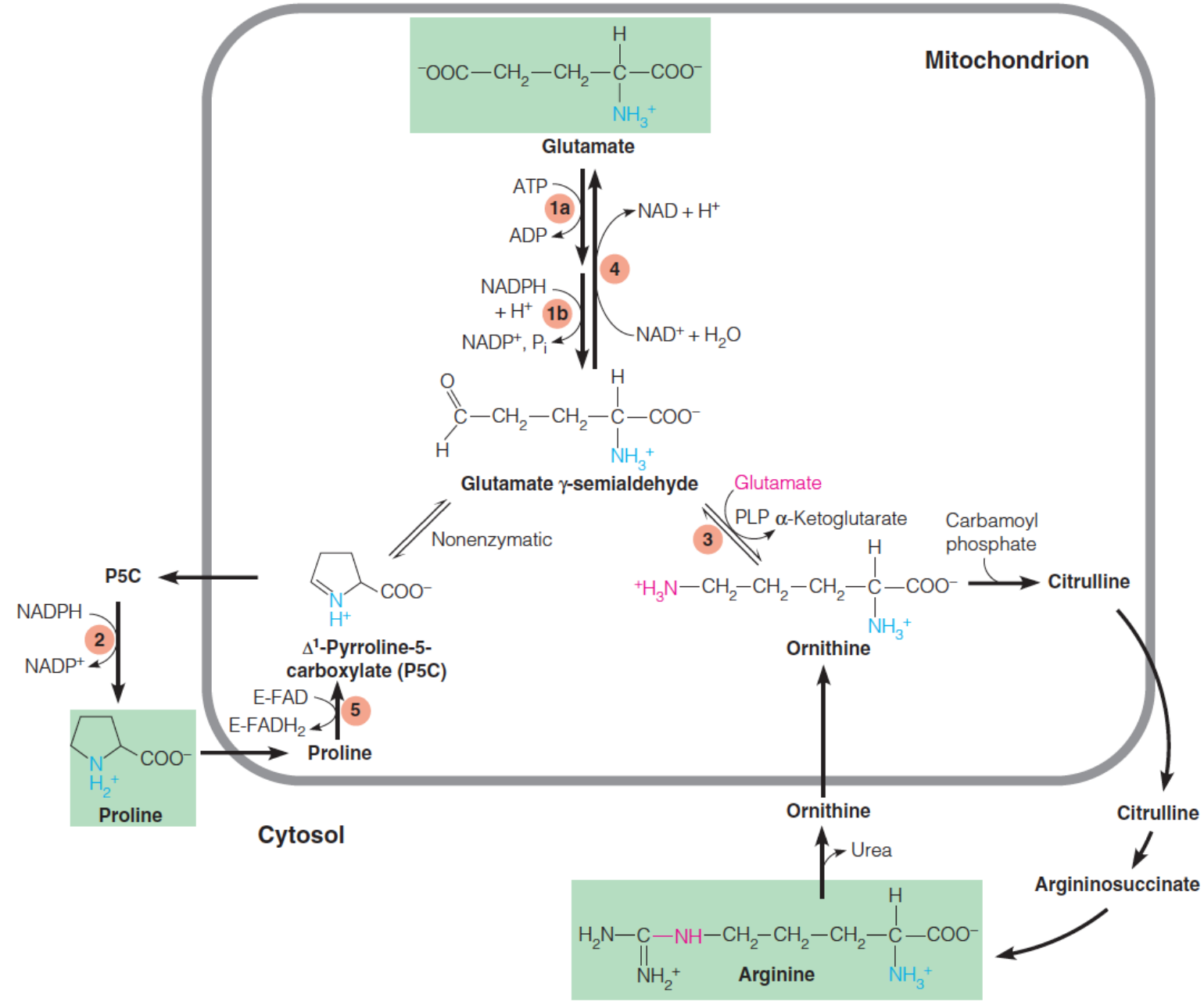


Synthesis of Proline, Ornithine, and Arginine from Glutamate

Glutamate, one of the most metabolically active amino acids, is a precursor to:

- Glutamine
- Arginine
- Creatine phosphate
- Proline
- Hydroxyproline
- Polyamines
- Glutathione
- *g*-Aminobutyric acid

Proline and arginine are synthesized and degraded by opposing pathways that utilize different enzymes and different cofactors, and occur in multiple compartments.



1. Proline and arginine are derived from glutamate

The enzymes involved are:

① D^1-Pyrroline-5-carboxylate (P5C) synthase, a bifunctional enzyme comprising

a) Glutamate kinase

b) Glutamyl phosphate reductase

② D^1-Pyrroline-5-carboxylate reductase

③ Ornithine *d*-aminotransferase

④ Glutamate *g*-semialdehyde dehydrogenase

⑤ Proline oxidase

2. Biosynthesis of ornithine from glutamate in bacteria

The reduction of N-acetylglutamate (step 2) begins with phosphorylation of the carboxyl group by ATP, followed by NADPH-dependent reduction of the activated carboxyl group.