David L. Nelson and Michael M. Cox

LEHNINGER
PRINCIPLES OF BIOCHEMISTRY

Sixth Edition

CHAPTER 22
Biosynthesis of Amino Acids, Nucleotides, and Related Molecules
(아미노산, 누클레오티드 및 관련 물질의 생합성)

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CHAPTER 22
Nitrogen Assimilation, Biosynthetic Use, and Excretion

Key topics:

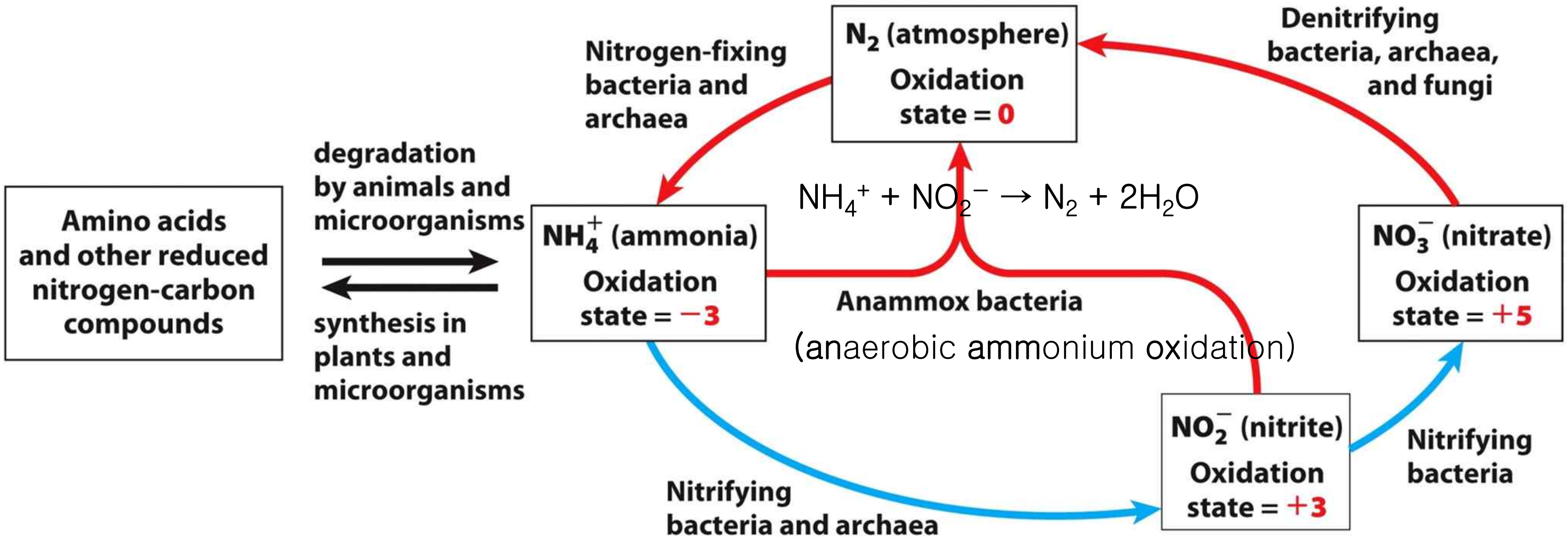
- Nitrogen fixation
- Incorporation of ammonia into biomolecules
- Biosynthesis of amino acids
- Biosynthesis of heme
- Biosynthesis of nucleotides
- Catabolism of purines

22.1 Overview of Nitrogen Metabolism

- 질소화합물: 아미노산(단백질의 구성단위), purine nucleotide, pyrimidine nucleotide (핵산의 구성단위)
- 식물, 미생물: 질산이온 또는 암모니아에서 질소화합물 합성
- 동물: 필수아미노산은 섭취, 비필수아미노산은 생체 내 합성. 주된 공급원은 단백질 섭취(아미노산 형태)

The Nitrogen Cycle

연간 10^{11}kg의 공기중의 질소가 암모니아로 고정



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단독 유리질소고정세균:
- 호기성세균: Azotobacter
- 혐기성세균: Klebsiella, Clostridium

공생 유리질소고정세균: 뿌리혹박테리아 (Rhizobium)

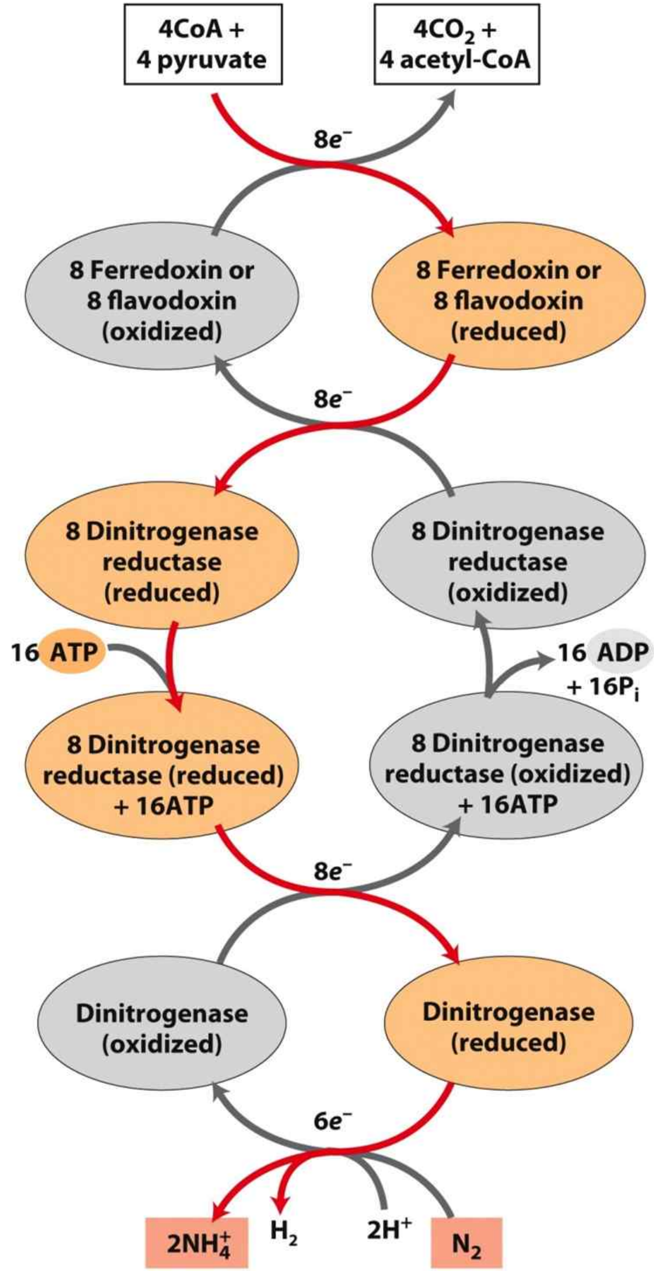
Nitrogen Fixation by the Nitrogenase Complex (질소화복합체)

- $N_2 + 3H_2 \rightarrow 2NH_3$ $\Delta G° = -33.5$ kJ/mol (N_2 삼중결합 때문에 활성화 에너지가 대단히 높음(ATP이용을 통해 극복)

- 질소화효소 복합체(dinitrogenase reductase와 dinitogenase의 복합체)에 의해 고정:

- $N_2 + 10H^+ + 8e^- + 16ATP \rightarrow 2NH_4^+ + 16ADP + 16Pi + H_2$

- 질소화효소복합체는 산소에 의해 불활성화(뿌리혹박테리아는 leghemoglobin이 보호, 시아노박테리아는 산소가 세포내로 들어올 수 없는 heterocysts에서 질소고정



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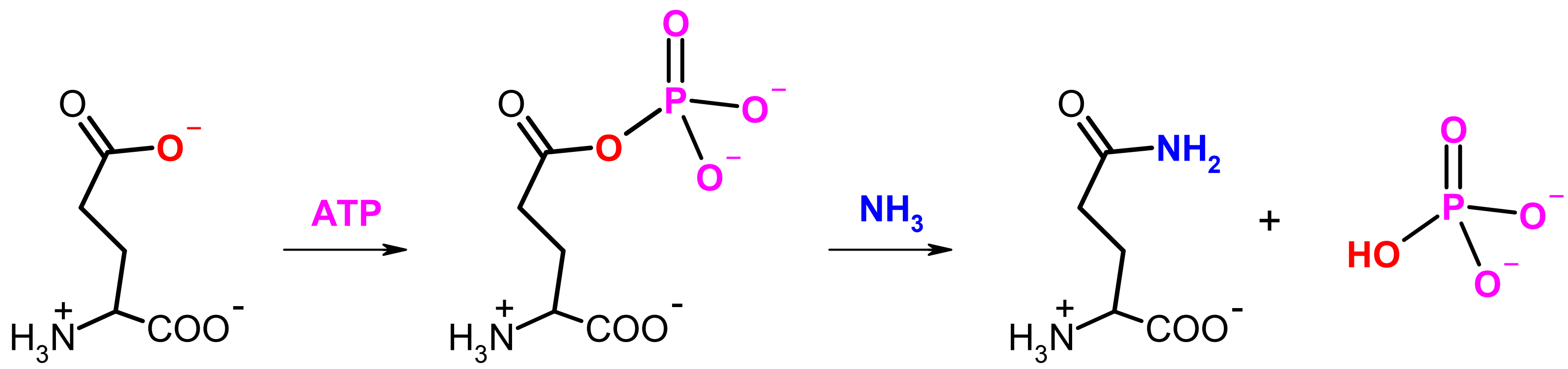
아미노산의 대사경로

- 탄수화물과 지방이 충분히 공급되면 단백질과 아미노산이 에너지 생산을 위해 분해되는 일은 없음 → 펩타이드나 단백질 합성, transamination에 의한 다른 아미노산 합성, 질소를 함유하거나 함유하지 않은 화합물 합성 등에 이용됨
- 위의 3가지 작용에 쓰이고 남은 필요 이상의 아미노산은 deamination 반응에 의하여 분해되거나 탄소골격으로 대사됨.
- 과량의 NH_3는 어떤 형태로 배설(예: 요소)되며, 필요에 의해 새로운 질소화합물의 합성에 이용
- NH_3 동화의 중요한 경로는 동식물, 세균에 존재하는 glutamine synthetase에 의한 glutamine의 합성임.
- Glutamic acid는 질소대사에서 중요하며, 다른 아미노산 합성의 전구체로 작용

Ammonia is incorporated into biomolecules through Glu and Gln

- Glutamine is made from Glu by glutamine synthetase in a two-step process:



Glu + ATP → γ-glutamyl phosphate + NH_4^+ → Gln + P_i

- <u>Phosphorylation of Glu</u> creates a good leaving group that can be easily displaced by ammonia

암모니아에서 글루타민과 글루탐산의 합성

- 모든 생물: 글루타민 합성은 글루타민 합성효소 (glutamine synthetase)에 의해 촉매

  Glutamate + NH_4^+ + ATP → glutamine + ADP + Pi + H^+ – (A)

- 세균과 식물: 글루탐산 합성은 글루탐산 생성효소 (glutamate synthase)에 의해 촉매

  α–ketoglutarate + glutamine + NADPH + H^+ → 2 glutamate + $NADP^+$ – (B)

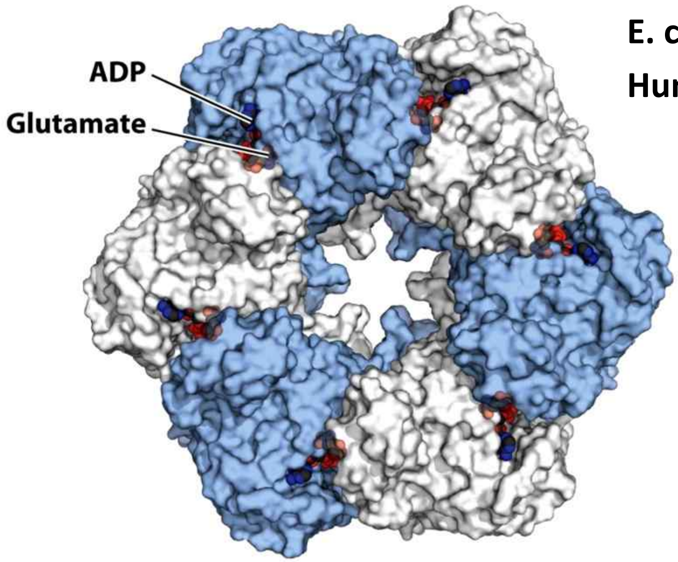
- (A)와 (B)의 전체 반응식:

  α–ketoglutarate + NH_4^+ + NADPH + ATP → L–glutamate + $NADP^+$ + ADP + Pi

- 동물에는 글루탐산 생성효소 없음. 아미노기 전달반응에 의해 α–ketoglutarate에서 글루탐산 합성 (Fig 18–4)
- L–글루탐산 탈수소효소(L–glutamate dehydrogenase)에 의해 글루탐산이 만들어지기도 함(모든 생물)

  α–ketoglutarate + NH_4^+ + NADPH → L–glutamate + $NADP^+$ + H_2O

Regulation of Gln Synthetase —by Six Endpoints of Gln Metabolism



E. coli: 12 subunits

Human: 8 subunits

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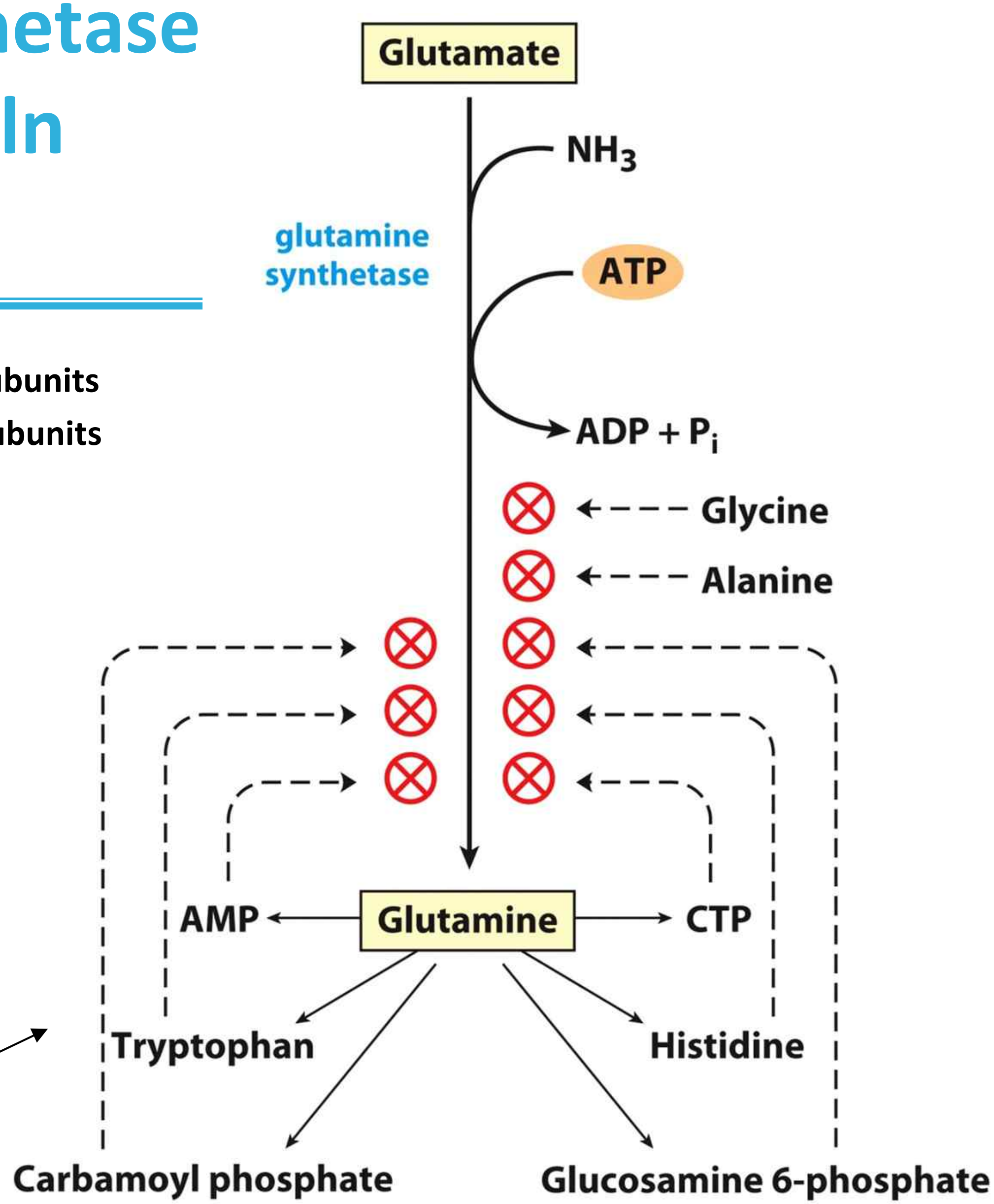
6가지 생성물에 의한 조절



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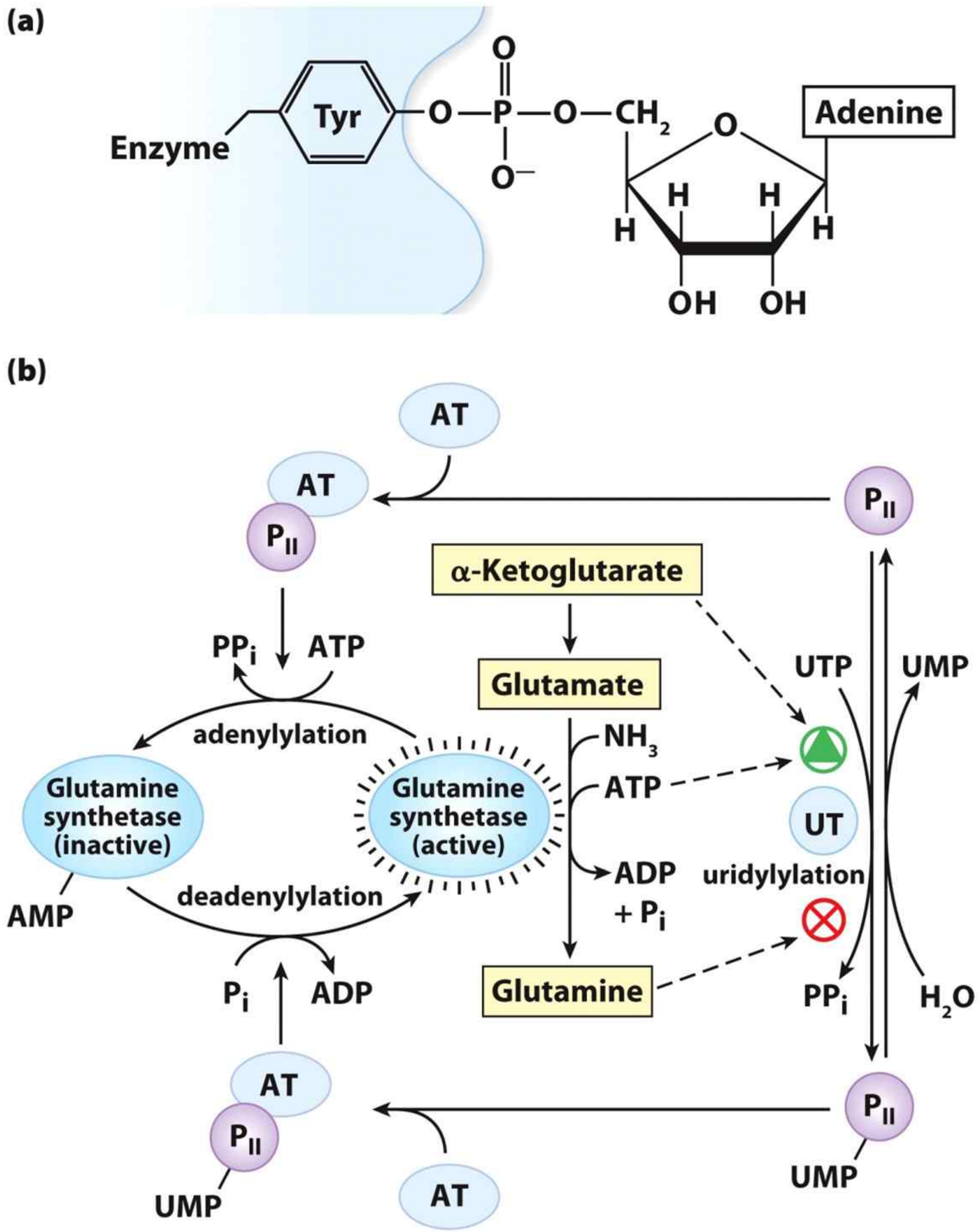
Covalent Modification of Gln Synthetase

: 제2레벨에서의 조절



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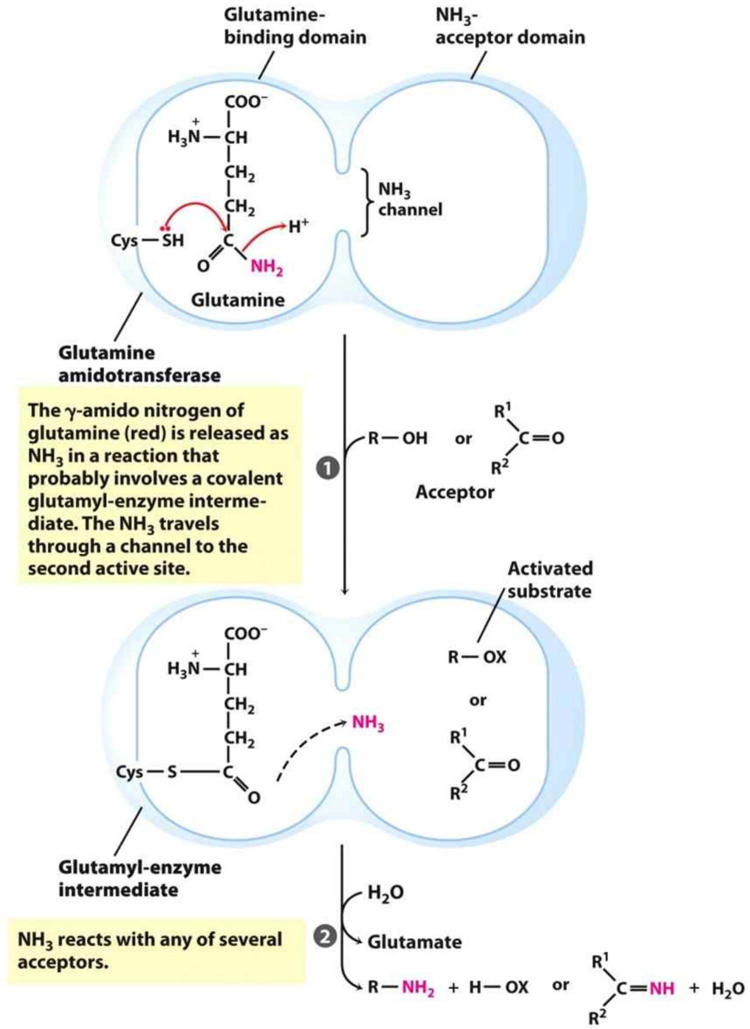
AT: adenylyltransferase
P_{II}: AT 조절단백질

Proposed Mechanism for Glutamine Amidotransferases (글루타민 아미노기 전달효소)

- 글루타민은 아미노기의 주요한 생리학적 원료로 작용

- 글루타민 아미드기 전달 효소(glutamine amidotransferases)에 의해 아미노기를 다른 화합물에 전달



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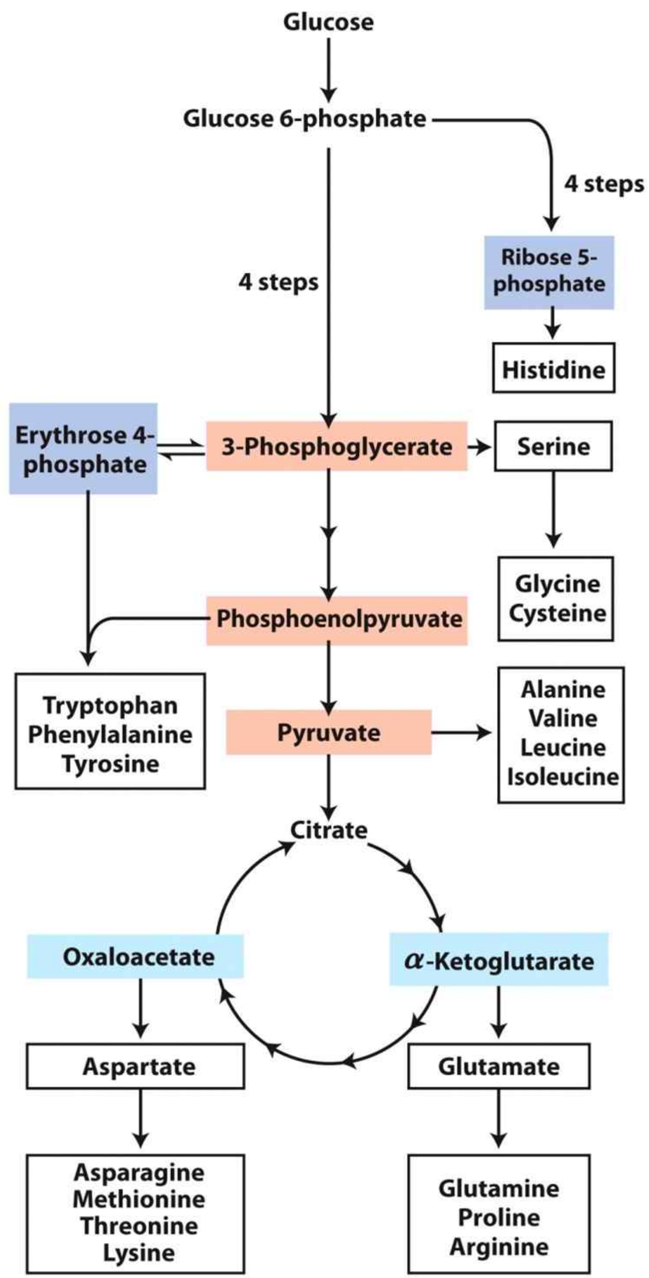
22.2 Biosynthesis of Amino Acids

- 모든 아미노산은 해당경로, 시트르산 경로, 펜토오스 인산경로에서 유래. 질소는 글루타민과 글루탐산 형태로 이 경로에 참여.
- 세균과 식물은 대개 20가지 아미노산 합성
- 포유류는 절반 정도 합성 가능. 필수 아미노산은 음식물로 섭취
- 아미노산 생합성 경로는 대사 전구체(탄소골격 제공)에 따라 분류



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대사전구체에 따른 아미노산 생합성 분류

TABLE 22-1 Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

α-Ketoglutarate	**Pyruvate**
Glutamate	Alanine
Glutamine	Valine*
Proline	Leucine*
Arginine	Isoleucine*
3-Phosphoglycerate	**Phosphoenolpyruvate and erythrose 4-phosphate**
Serine	Tryptophan*
Glycine	Phenylalanine*
Cysteine	Tyrosine†
Oxaloacetate	**Ribose 5-phosphate**
Aspartate	Histidine*
Asparagine	
Methionine*	
Threonine*	
Lysine*	

*Essential amino acids in mammals.

†Derived from phenylalanine in mammals.

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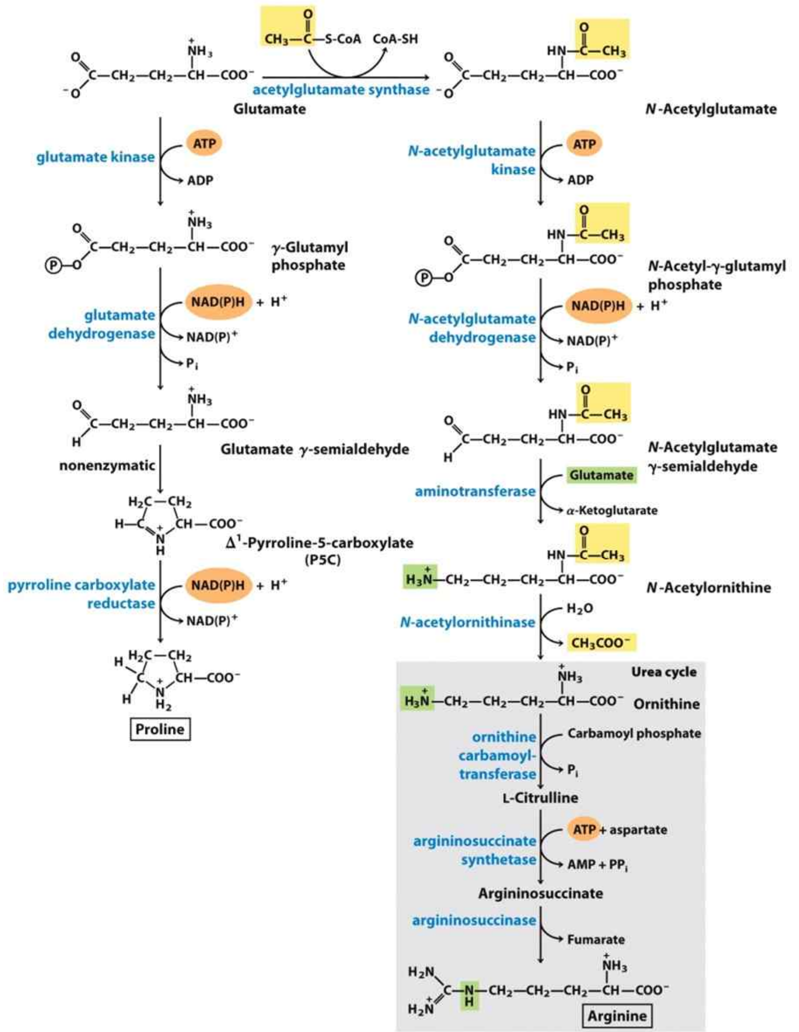
Nucleotide 합성 중간체인

5-phosphoribosyl-1-pyrophosphate(PRPP): ribose-5-phosphate로부터 합성

Biosynthesis of Pro and Arg from Glu in Bacteria



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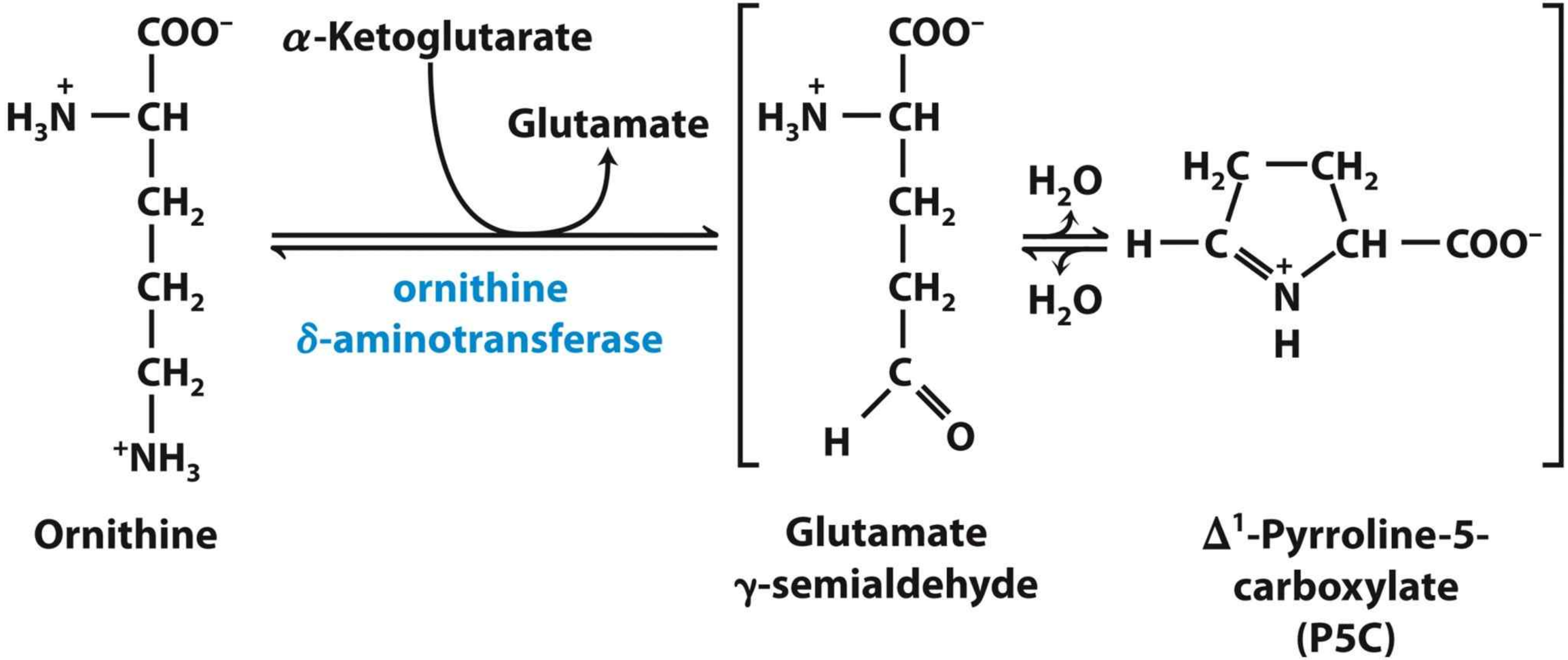
In animals, proline can ALSO be synthesized from arginine

- Arginase converts Arg to ornithine
- Ornithine δ-aminotransferase converts ornithine to glutamate γ-semialdehyde that cyclizes and converts to Pro
- See Fig 22-13

Mammalian Conversion of Ornithine (from Arg) to Cyclized Precursor to Pro



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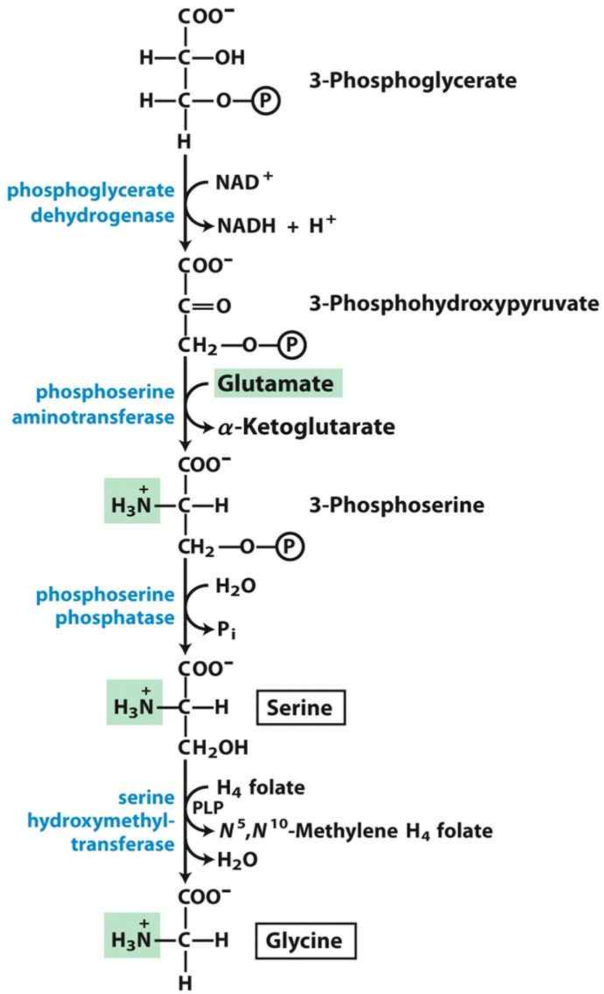
Biosynthesis of Ser and Gly from 3-Phosphoglycerate in all organisms



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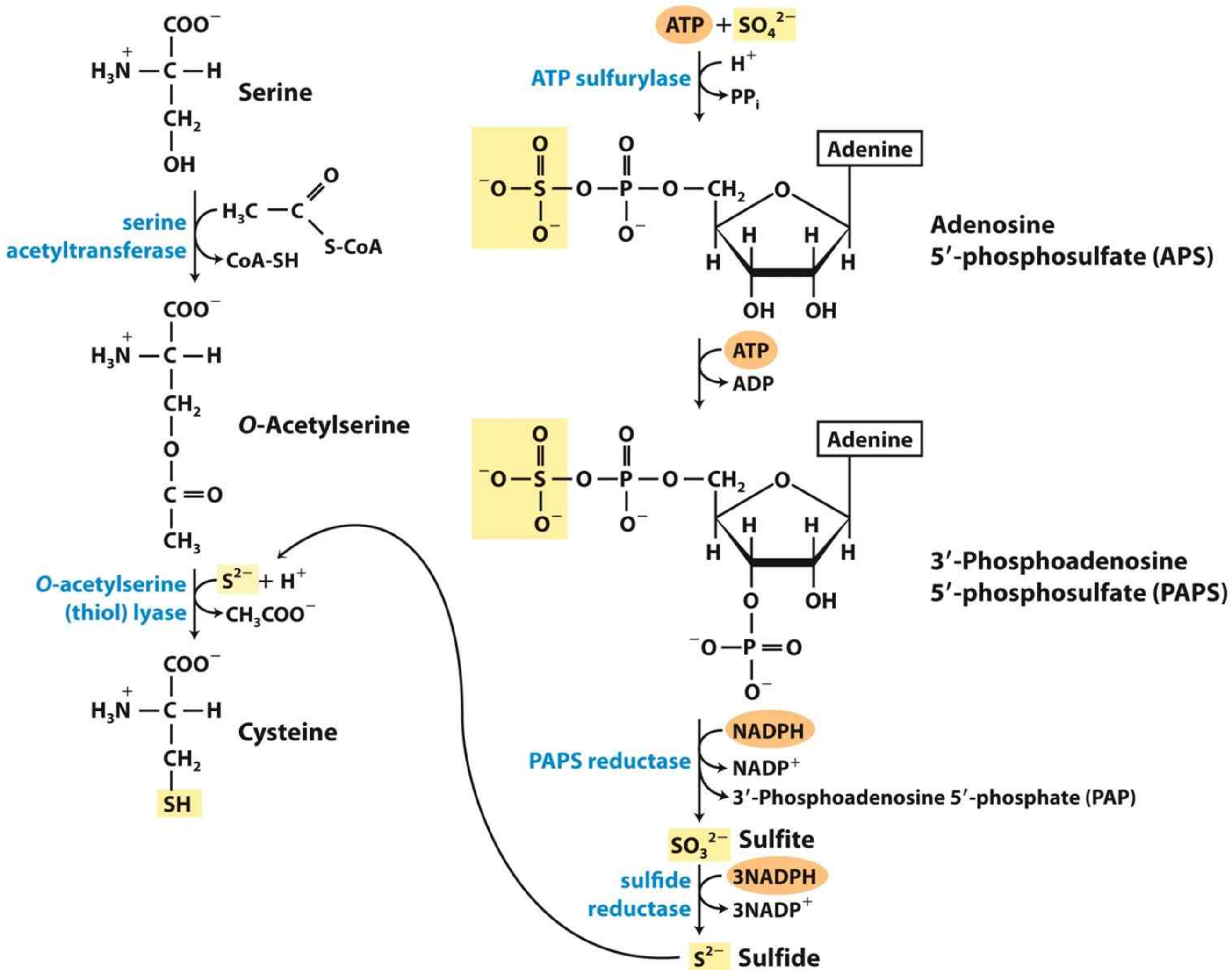
Biosynthesis of Cys from Ser in Plants and Bacteria



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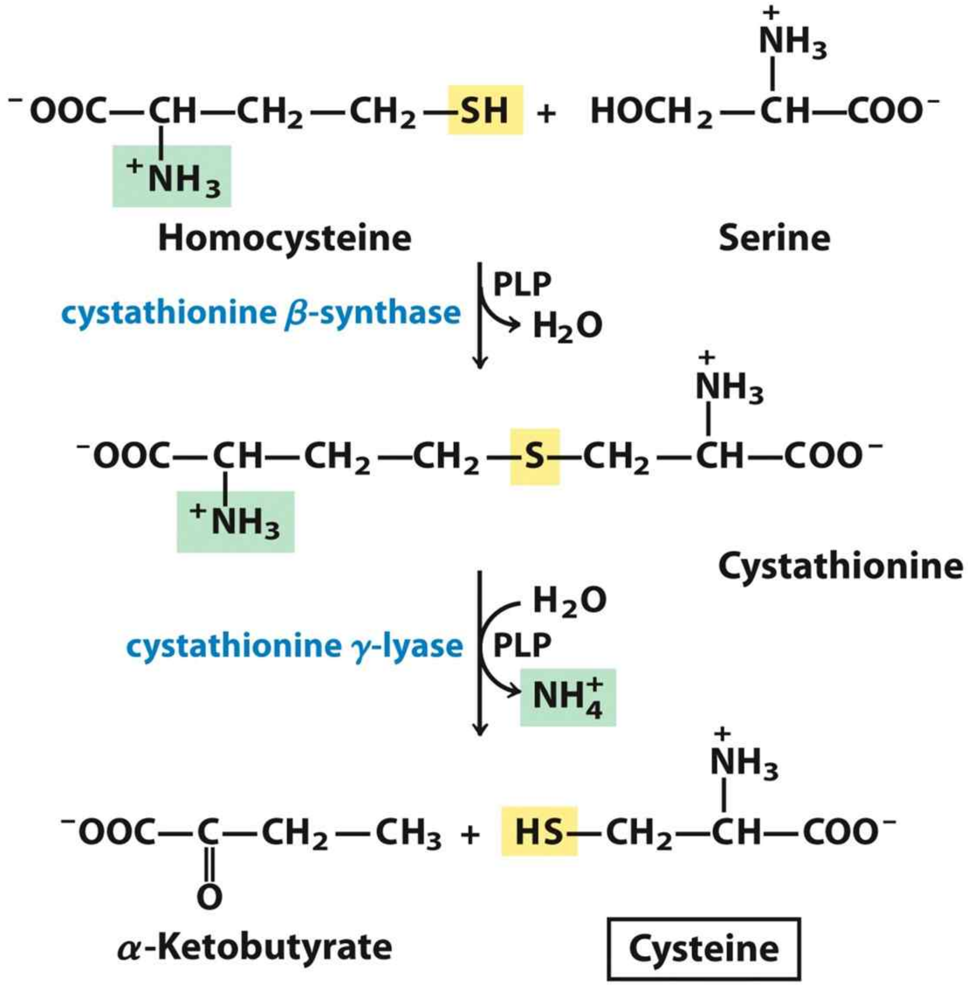
Biosynthesis of Cys from Homocysteine and Ser in Mammals



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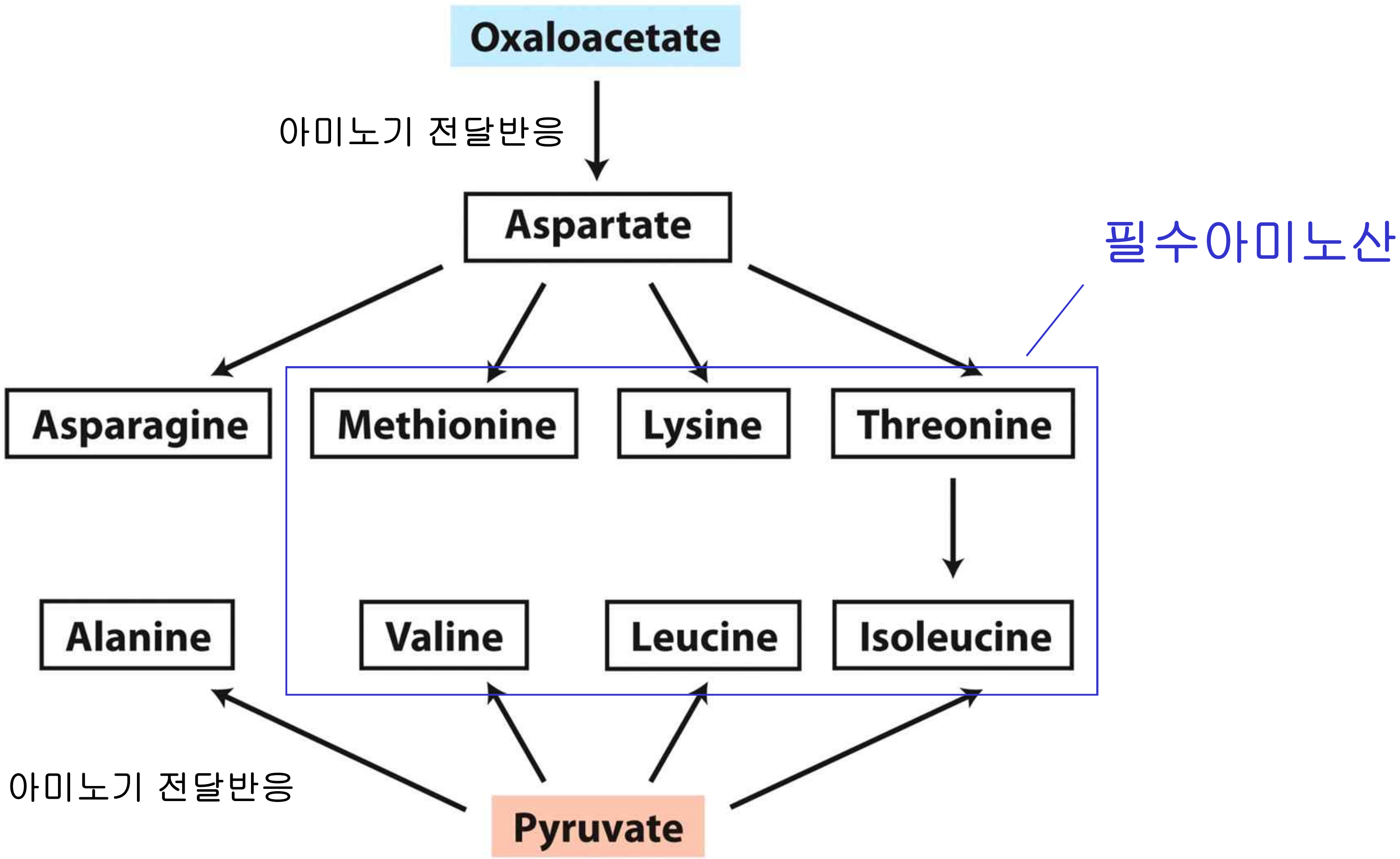
옥살로아세트산과 피루브산으로부터 3종의 비필수 아미노산과 6종의 필수 아미노산의 합성

(Fig 22-17 참조)



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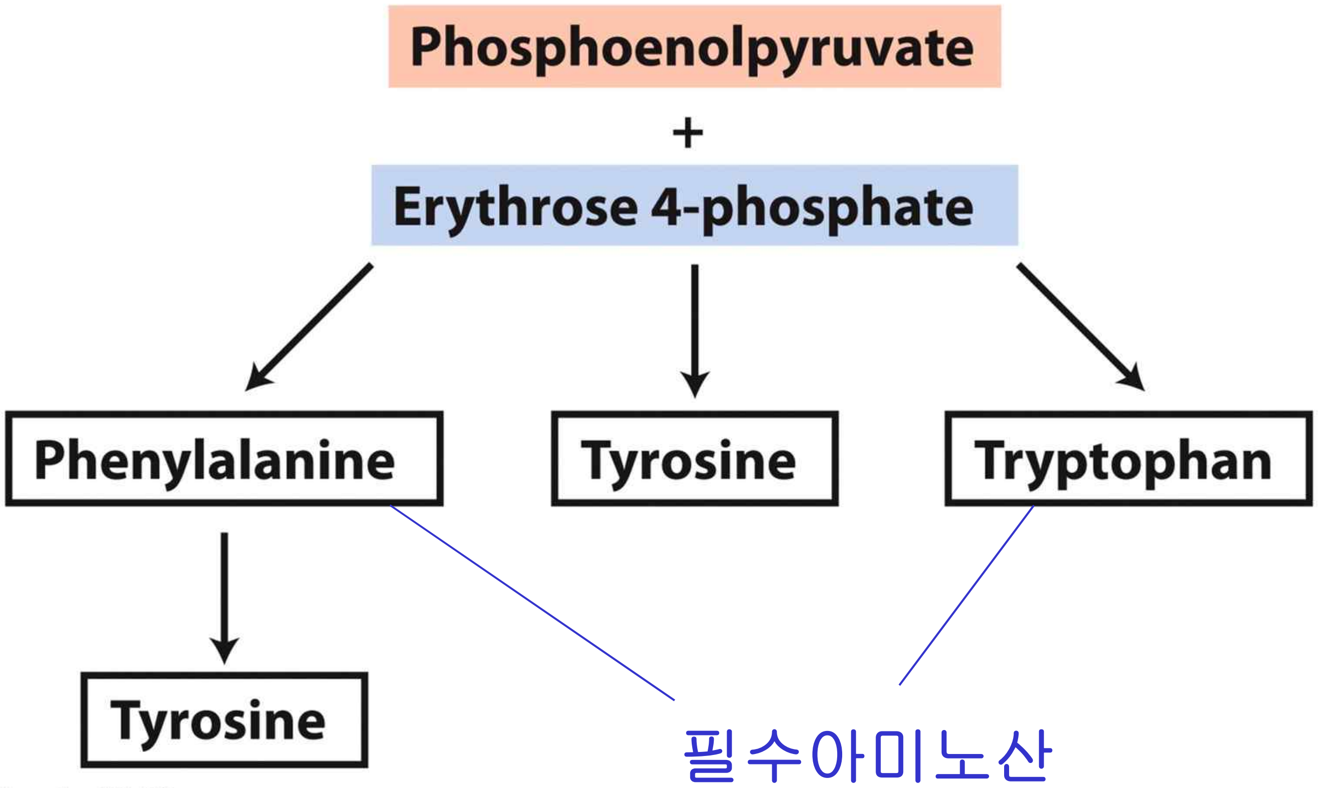
세균과 식물에서 방향족 아미노산의 생합성



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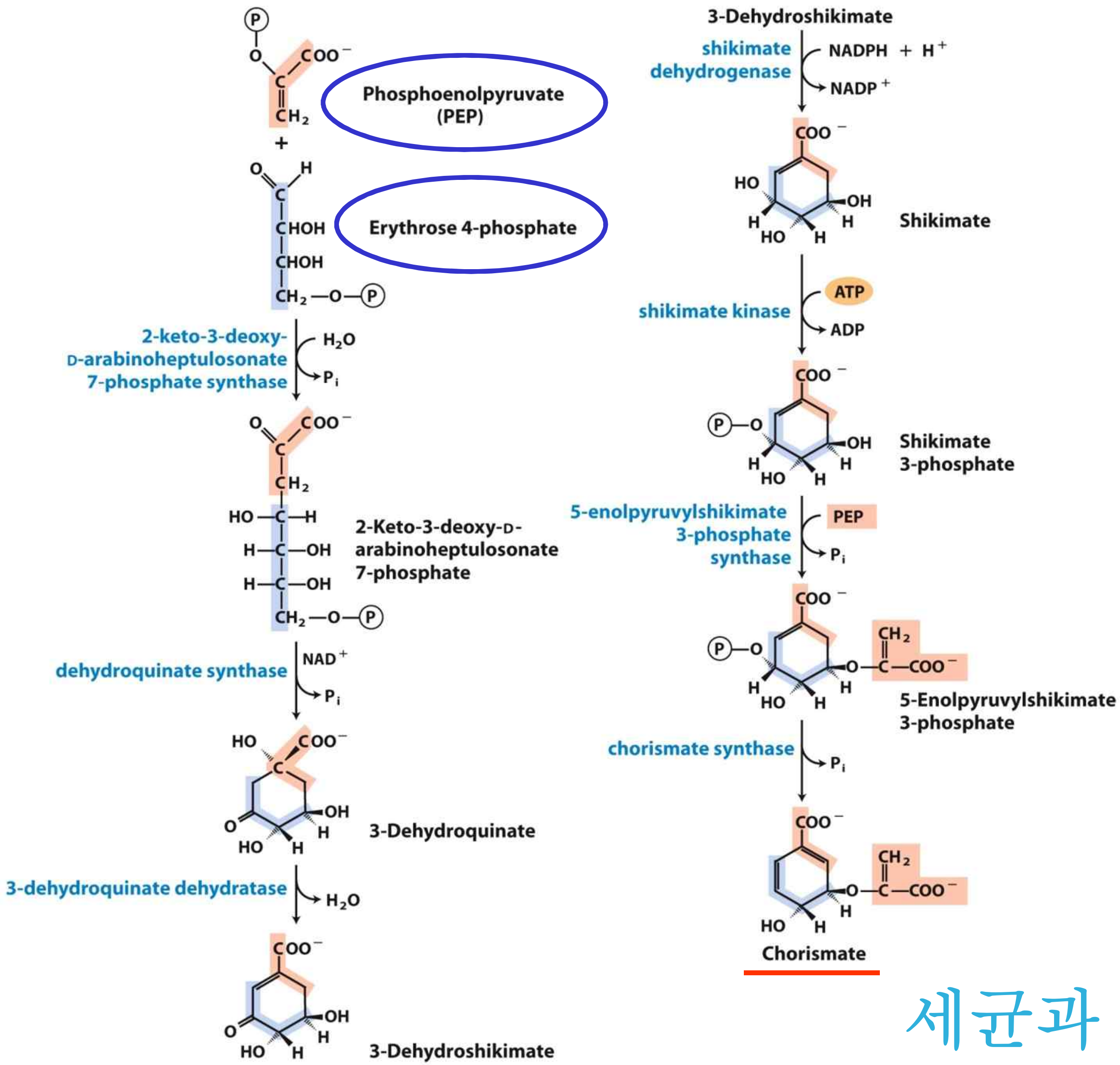

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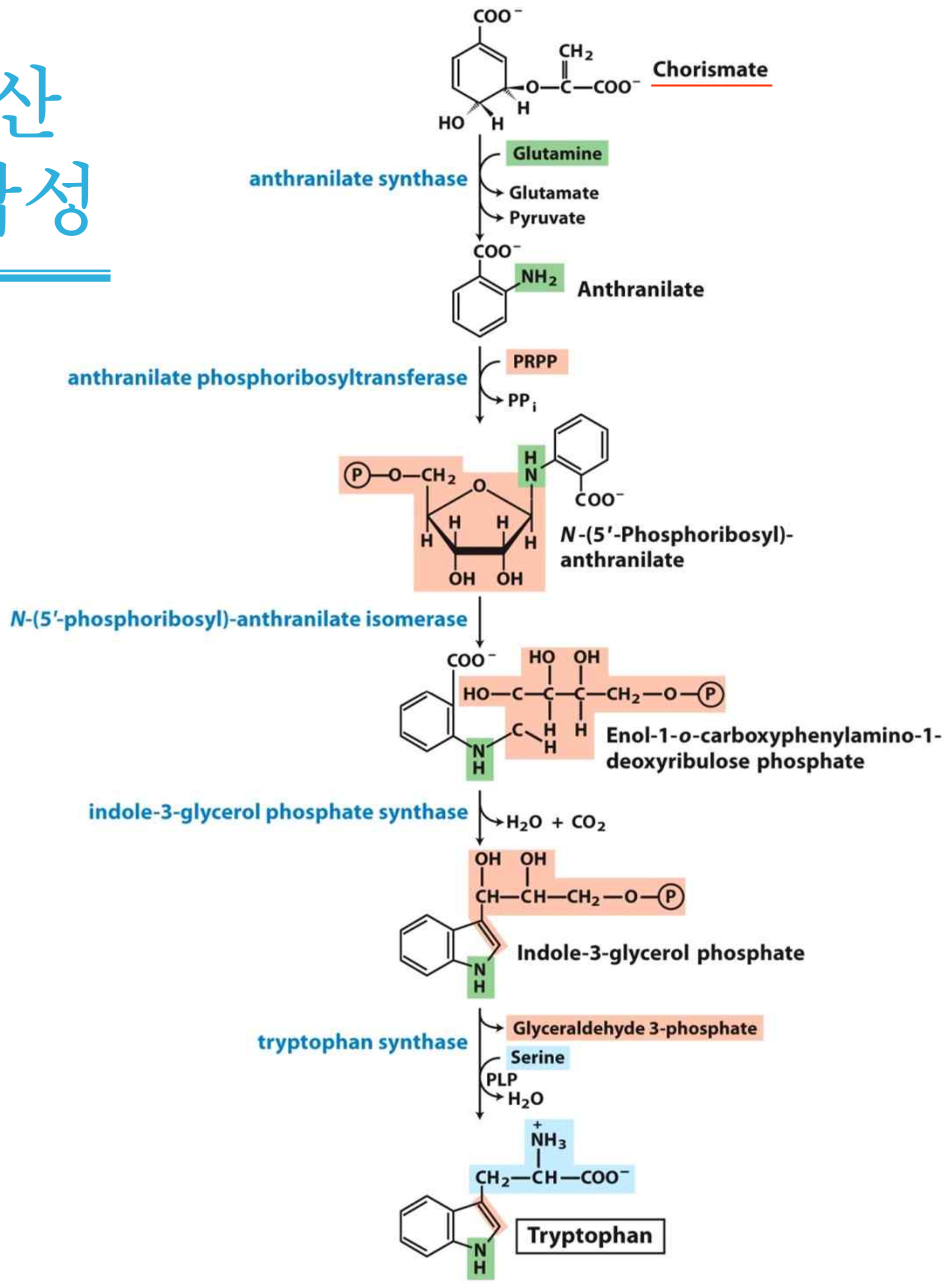
세균과 식물에서 방향족 아미노산의 중간체가 되는 코리슴산의 합성

세균과 식물에서 코리슴산으로부터 트립토판의 생합성

- Tryptophan synthase($\alpha_2\beta_2$ 구조)가 촉매
- α 소단위체: Indole-3-glycerol phosphate → indole + glyceraldehyde-3-phosphate
- β_2 소단위체: indole + serine → tryptophan + H_2O



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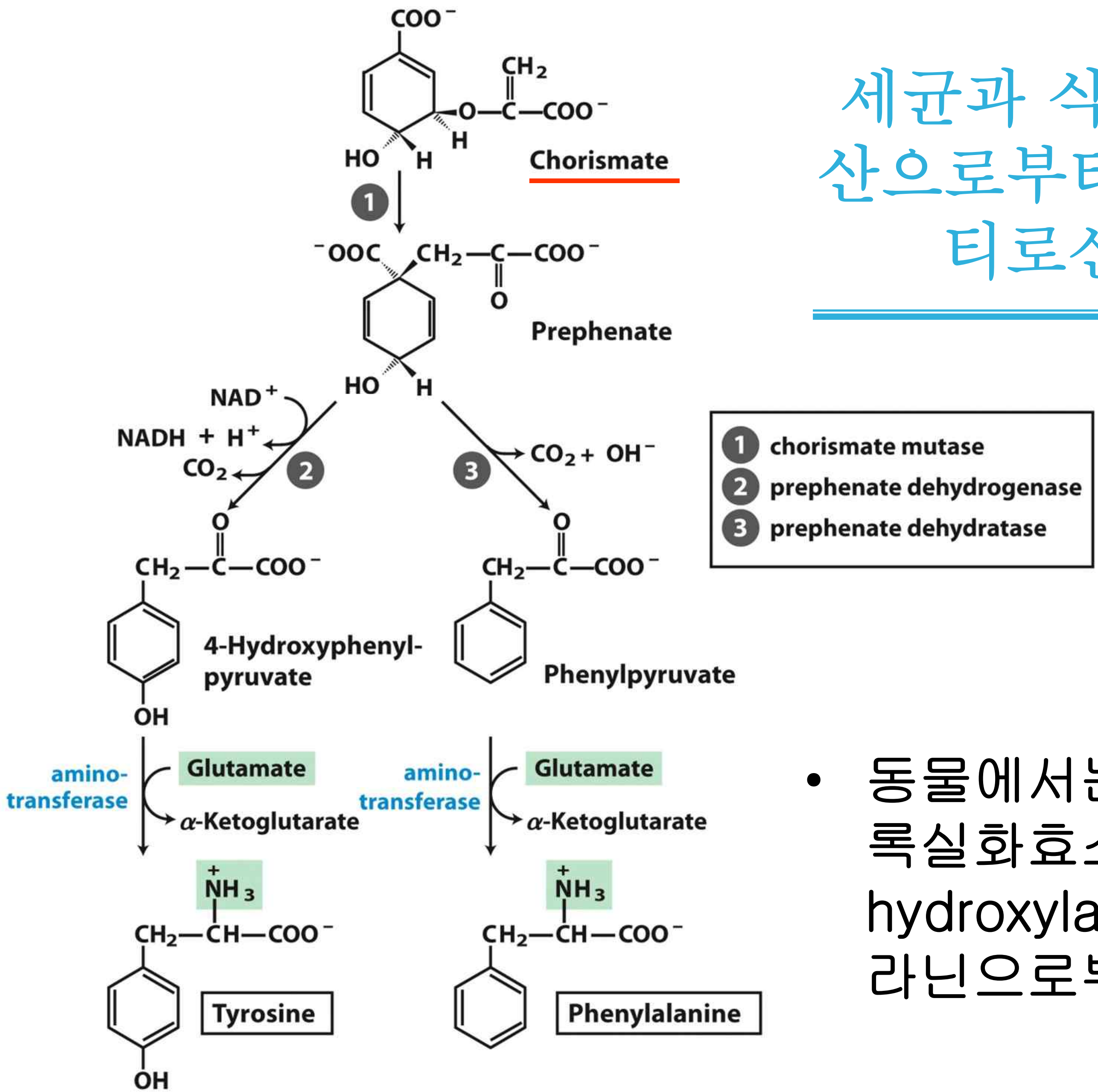
세균과 식물에서 코리슴산으로부터 페닐알라닌과 티로신의 생합성



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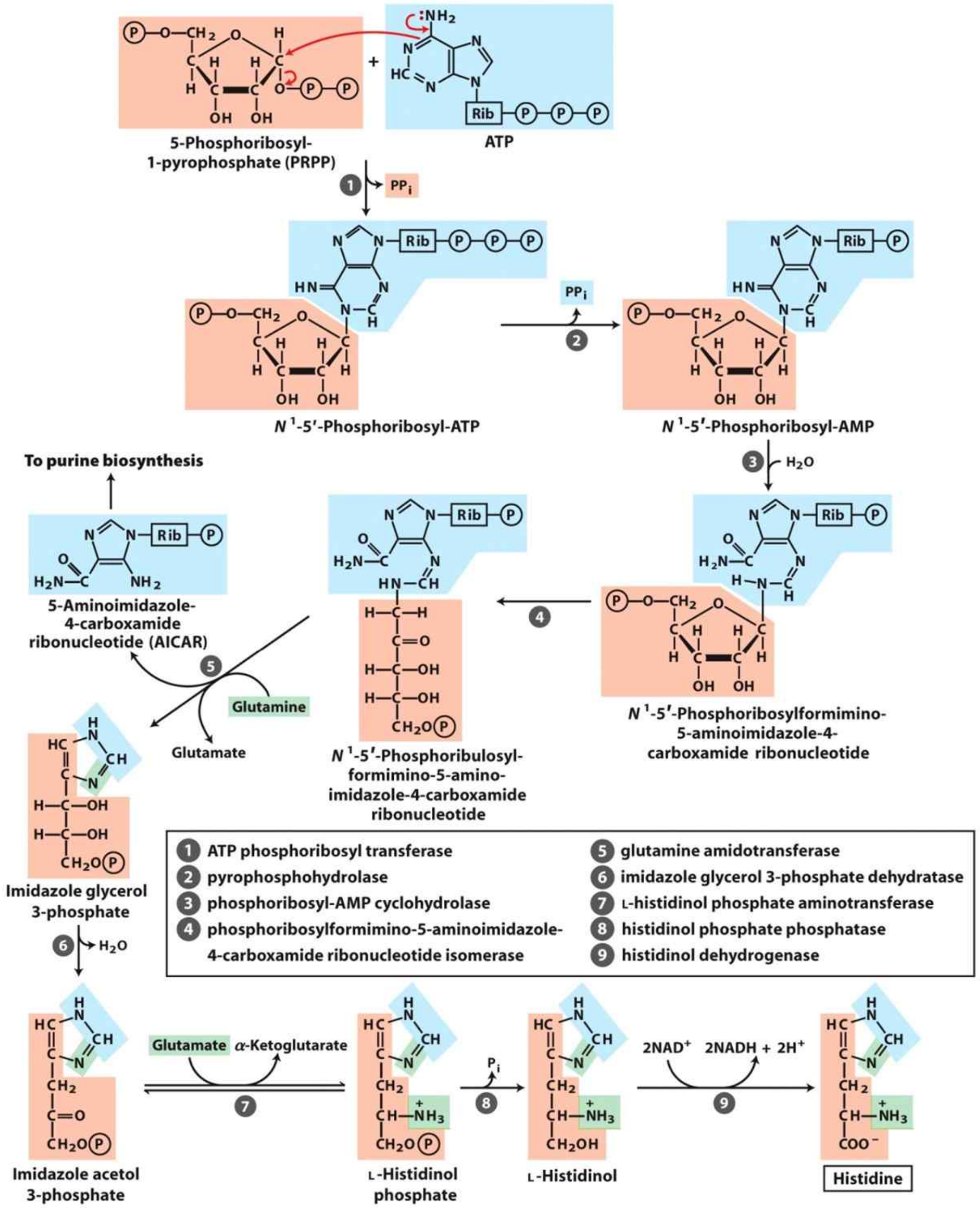
- 동물에서는 페닐알라닌 히드록실화효소(phenylalanine hydroxylase)에 의해 페닐알라닌으로부터 티로신 합성

세균과 식물에서 히스티딘의 생합성

- 푸린 생합성 전구체 이용
- 히스티딘은 3가지 종류의 전구체로부터 유도: PRPP에서 5개의 탄소(적색), ATP의 푸린고리에서 1개의 질소와 1개의 탄소(청색), 글루타민과 글루탐산에서 2개의 질소(녹색).



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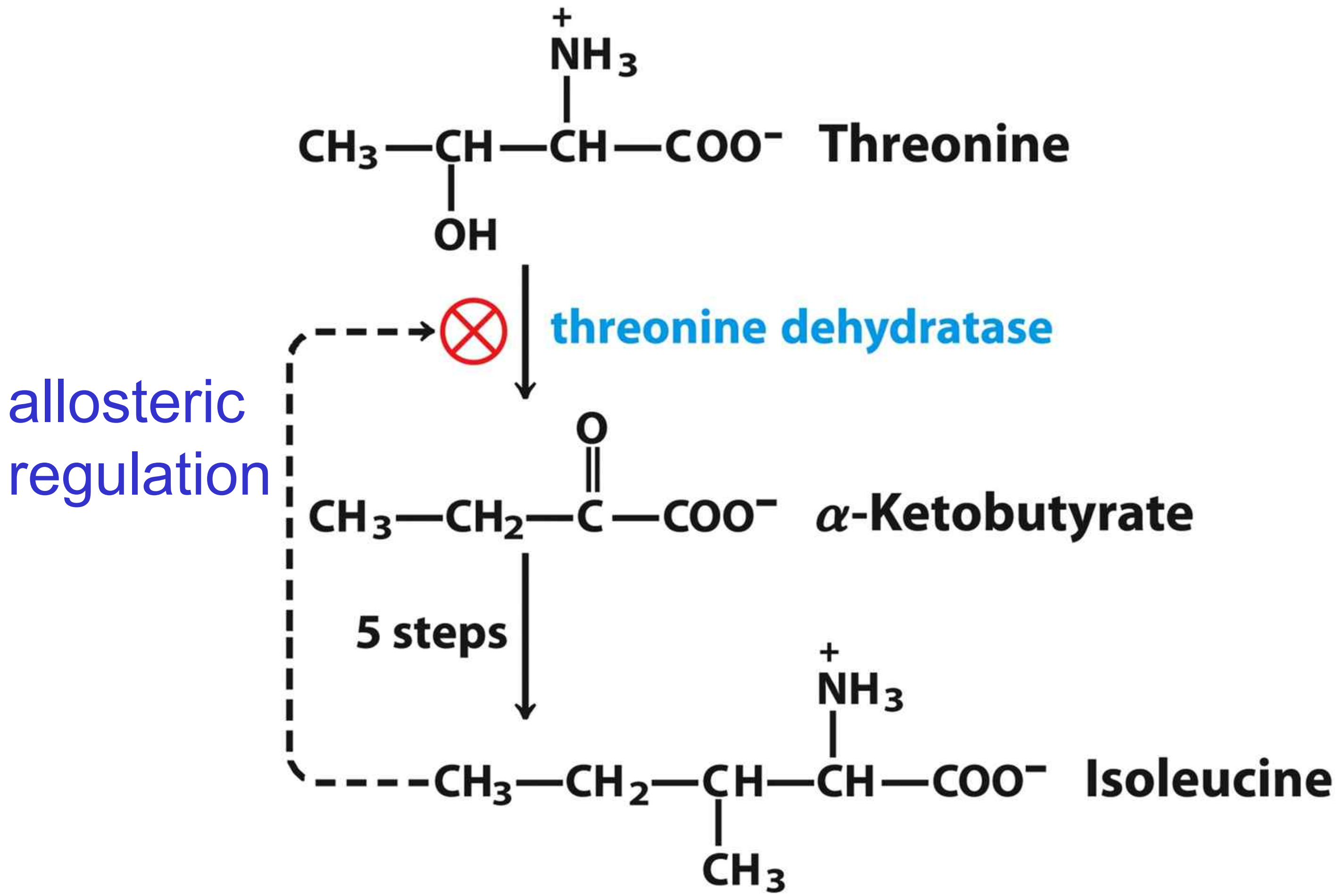
Feedback Inhibition in Ile Synthesis from Thr



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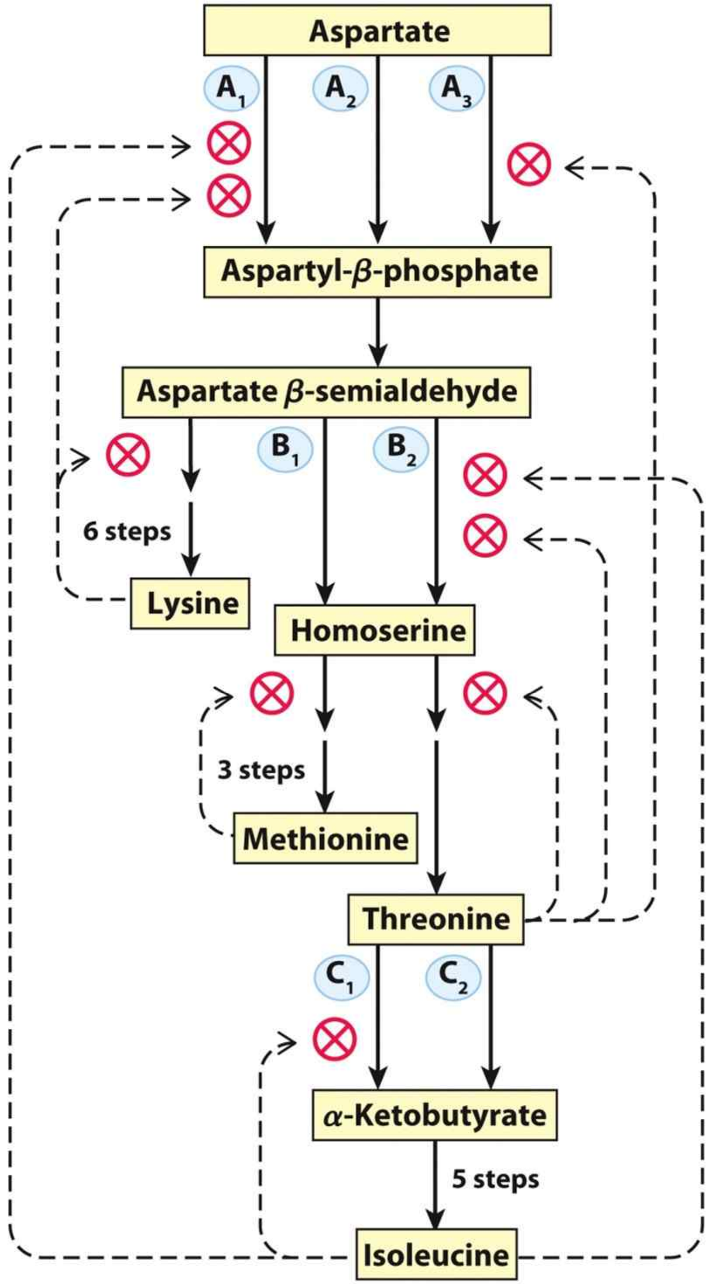
Regulation of Aspartate-Derived Pathways

- 대장균에서 아스파르트산으로부터 유도되는 여러가지 아미노산 생합성 조절기전이 서로 맞물려서 일어남



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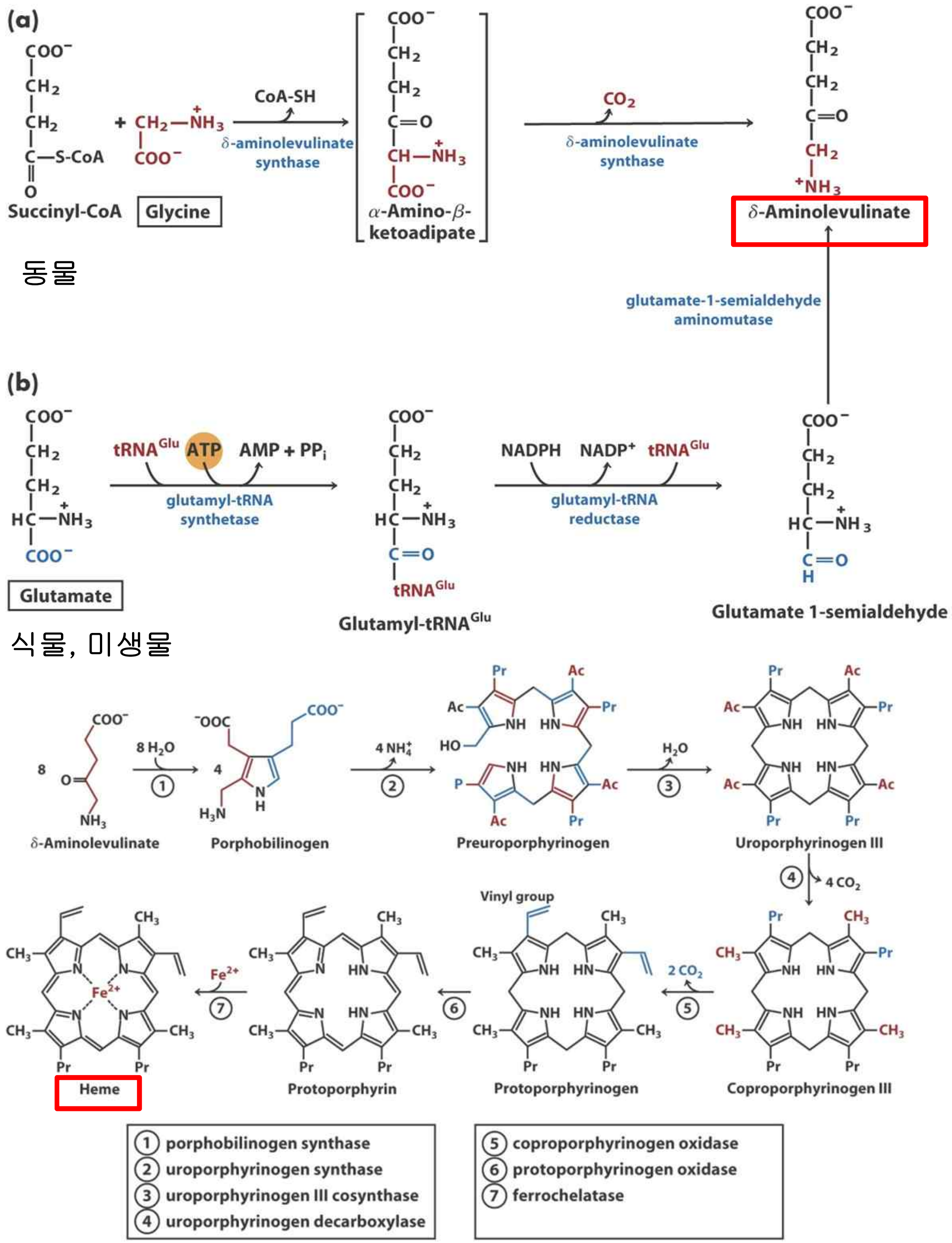
22.3 Molecules Derived from Amino Acids

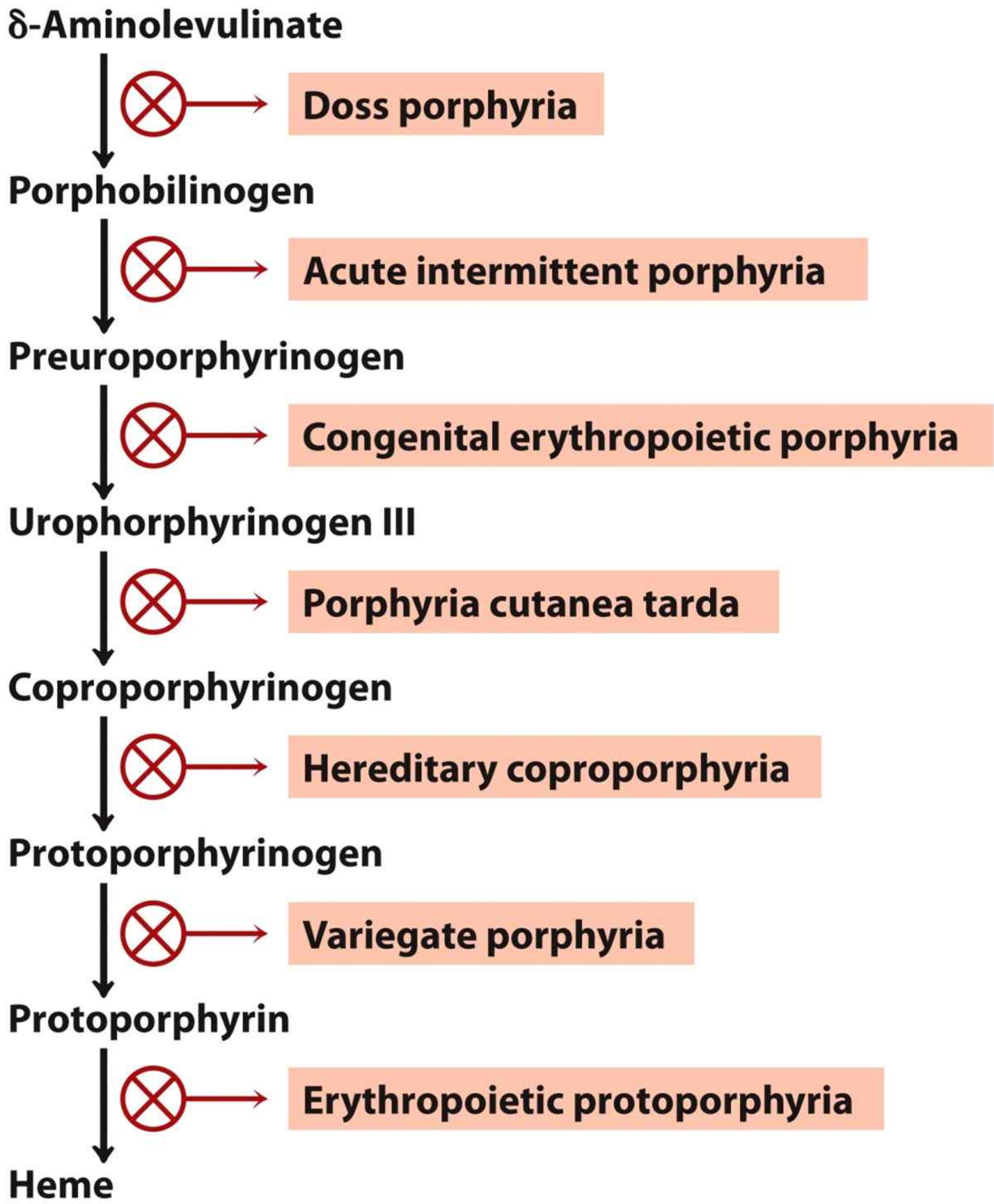
- Porphyrin: Gly에서 유도
- Phosphocreatine: 골격근의 중요한 에너지 저장물질. Gly, Arg, Met 등에서 유도
- D-아미노산: 세균에서 발견. Amino acid racemase에 의해 L-이성질체에서 만들어짐
- Lignin: 식물의 단단함 유지. Phe과 Tyr에서 유도
- Tannin, morphine, cinnamon oil, vanilla, 정향(clove), 육두구(nutmeg) 등도 Phe과 Tyr에서 유도
- 식물성장호르몬인 auxin은 Trp에서 유도
- Spermine과 spermidine: DNA packaging에 이용. Met과 ornithine에서 유도
- neurotransmitters:
  - dopamine, norepinephrine, epinephrine: Tyr에서 유도
  - γ-aminobutyrate(GABA)는 Glu, Histamine은 His, Serotonin은 Trp에서 유도

Heme (iron-porphyrin)의 생합성

- glycine이 hemoglobin과 cytochrome의 porphyrin의 전구체로 작용
- 포르피린 생합성의 유전적 결함은 포르피린증(porphyria) 유발
- 수명이 다된 적혈구는 비장(spleen)에서 파괴되어 bilirubin 생성. bilirubin은 간에서 담즙 색소인 bilirubin diglucuronide로 변환



Enzymes Inhibited in Heme Synthesis Defects



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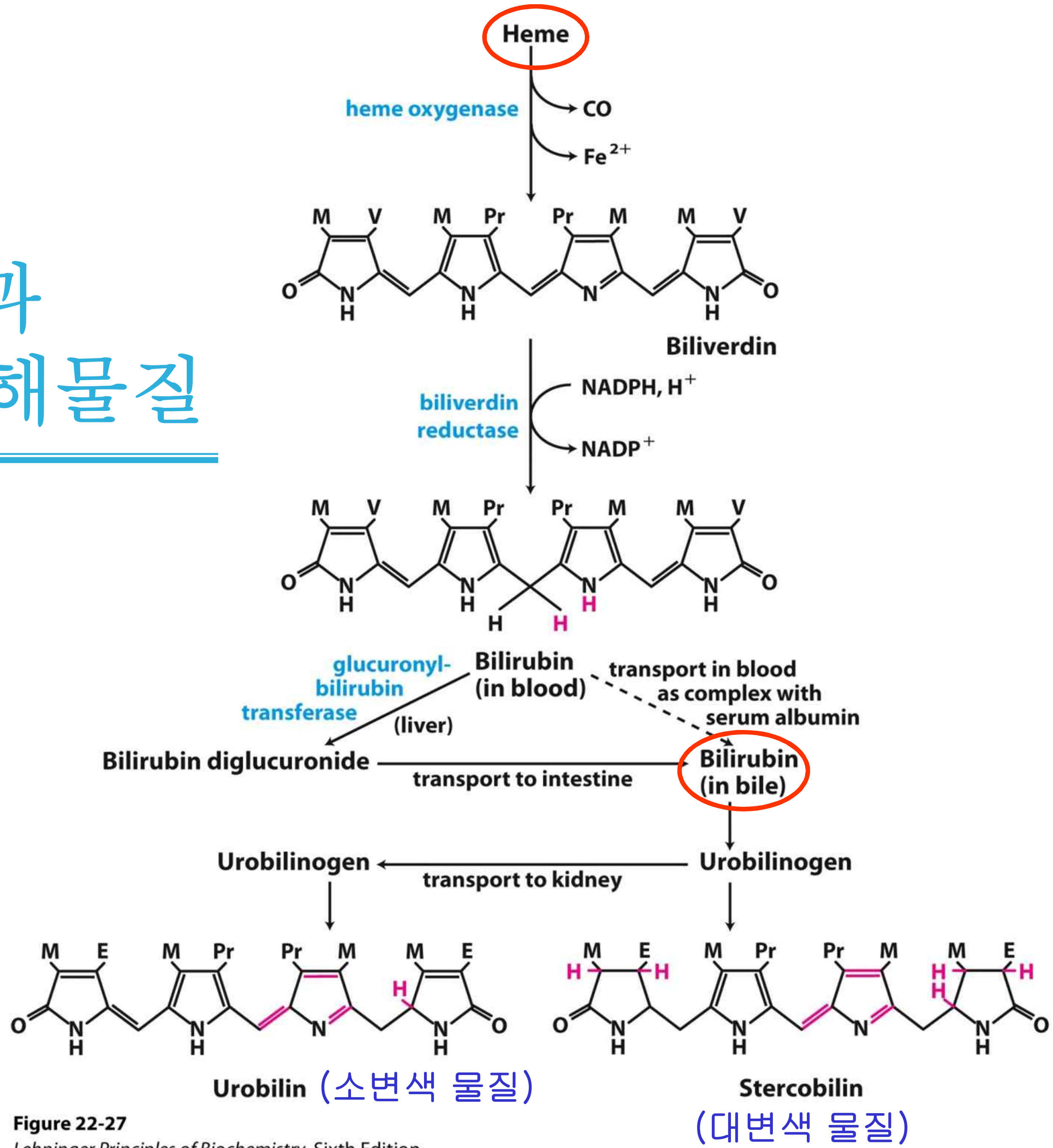
빌리루빈과
빌리루빈의 분해물질



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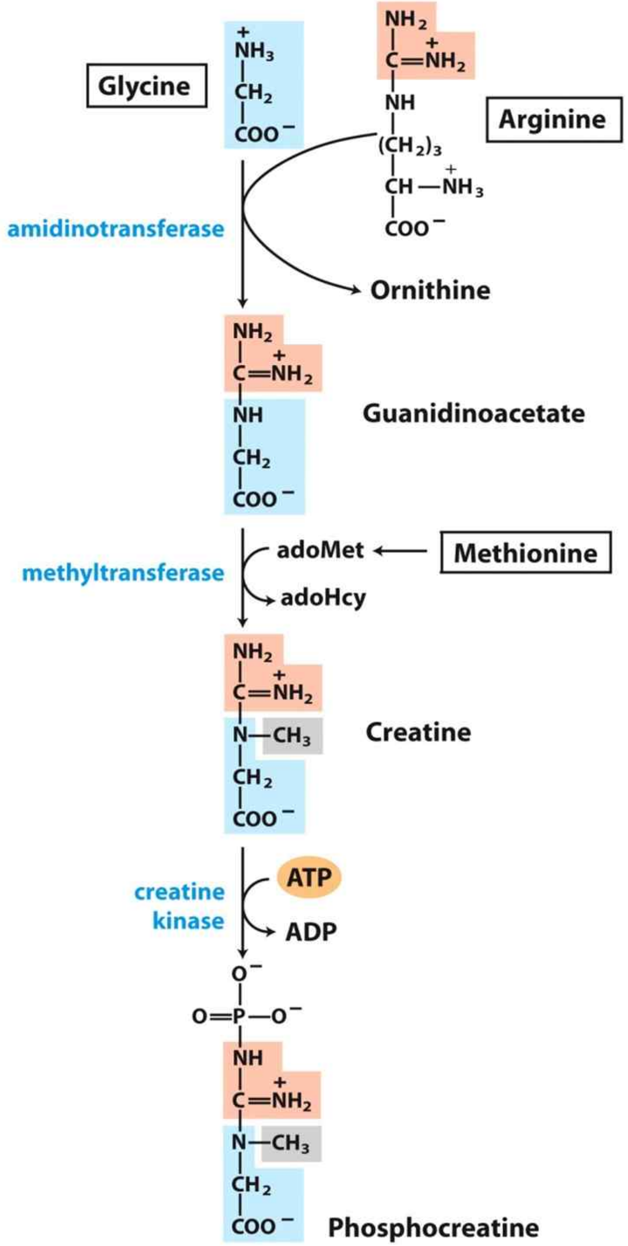
크레아틴과 포스포 크레아틴의 생합성



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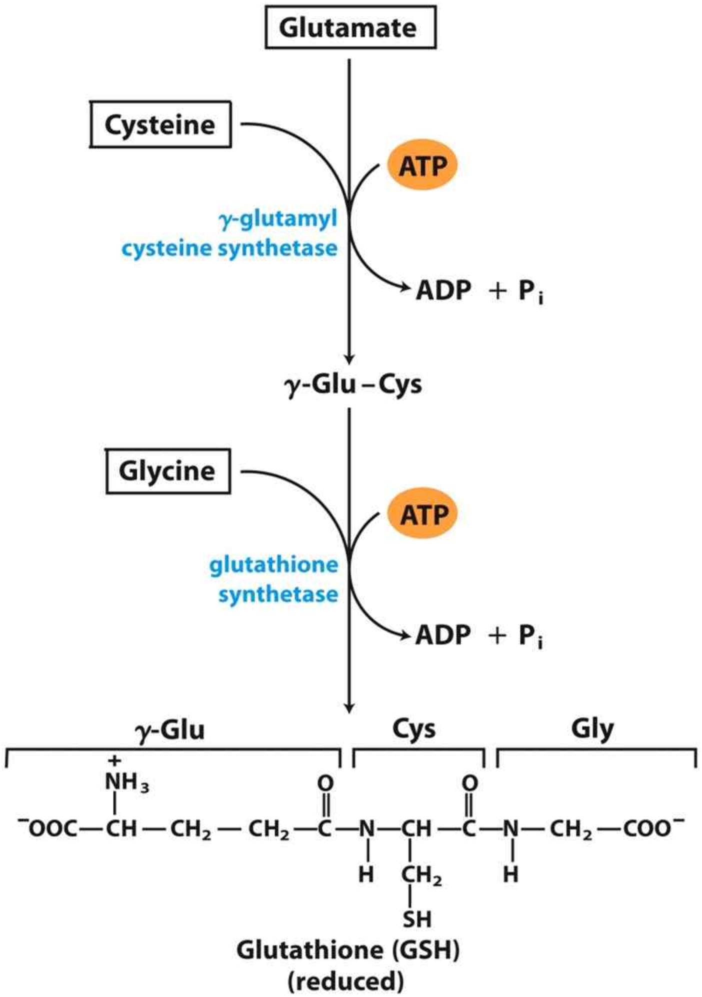
Biosynthesis and Oxidation of Glutathione



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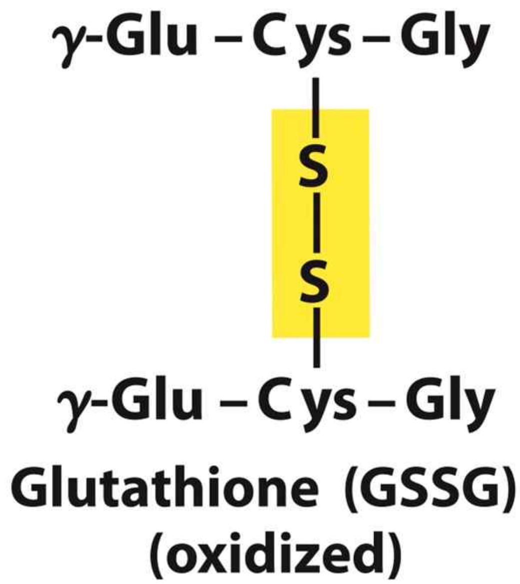

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- Glutathione(GSH)의 역할:
  - Cytosol의 환원상태 유지
  - Heme의 Fe^{2+} 유지
  - Peroxide 제거

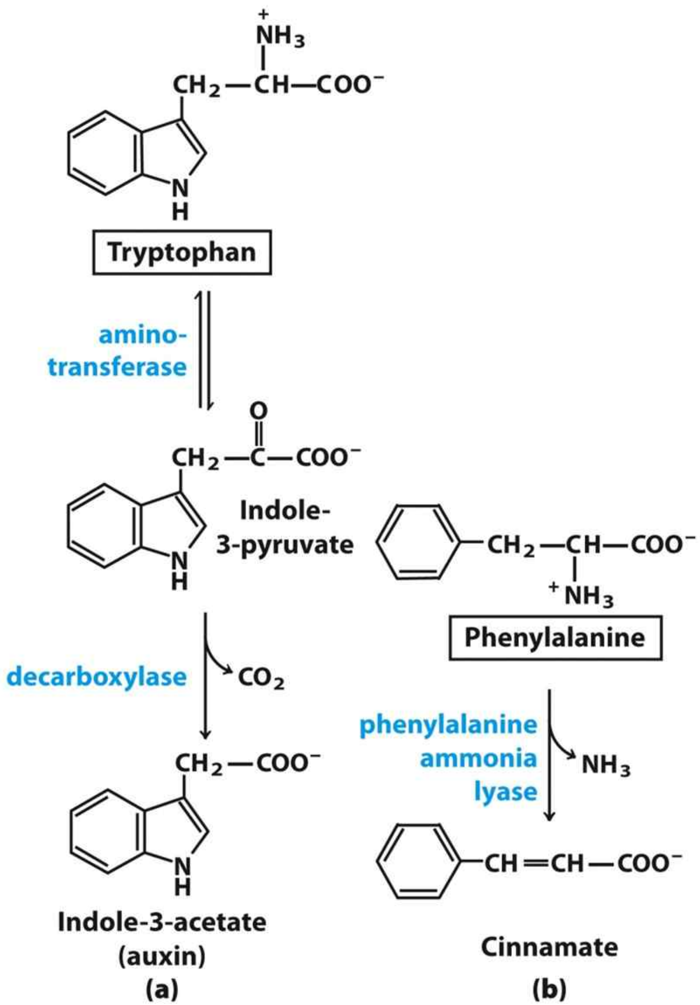
D-amino acids in bacteria arise from racemases

- Bacterial peptidoglycans contain D-Ala and D-Glu
- Racemases act on D-amino acids, use PLP as cofactor
- Racemase inhibitors are used/studied as antibiotic targets

Aromatic amino acids are precursors to plant lignins, hormones, and natural products

- **Lignin** (rigid polymer in plants) from Phe and Tyr
- **Auxin** (growth hormone indole-3-acetate) from Trp
- Other extracts: spices (nutmeg, vanilla), alkaloids (morphine), etc.

Biosynthesis of Auxin from Trp and Cinnamate from Phe in plants



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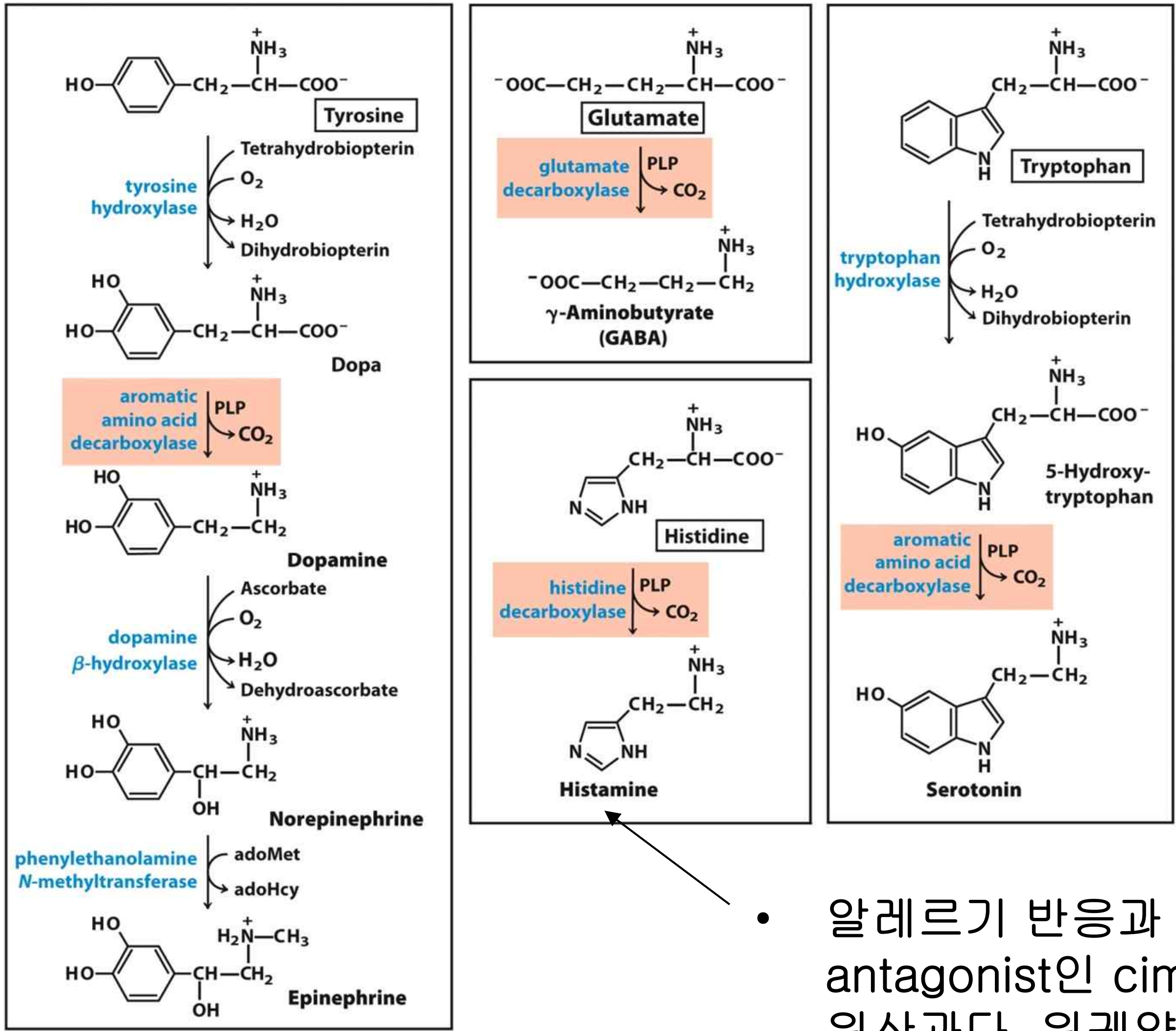
Amino acid decarboxylation yields neurotransmitters, inhibitors

- Decarboxylations often require PLP
- Tyr yields catecholamines such as **dopamine, norepinephrine,** and **epinephrine**
- Glu yields neurotransmitter γ-aminobutyrate **(GABA)** and Trp yields **serotonin**
- His yields the vasodilator and stomach acid secretion stimulant **Histamine**

Biosynthesis of Some Neurotransmitters



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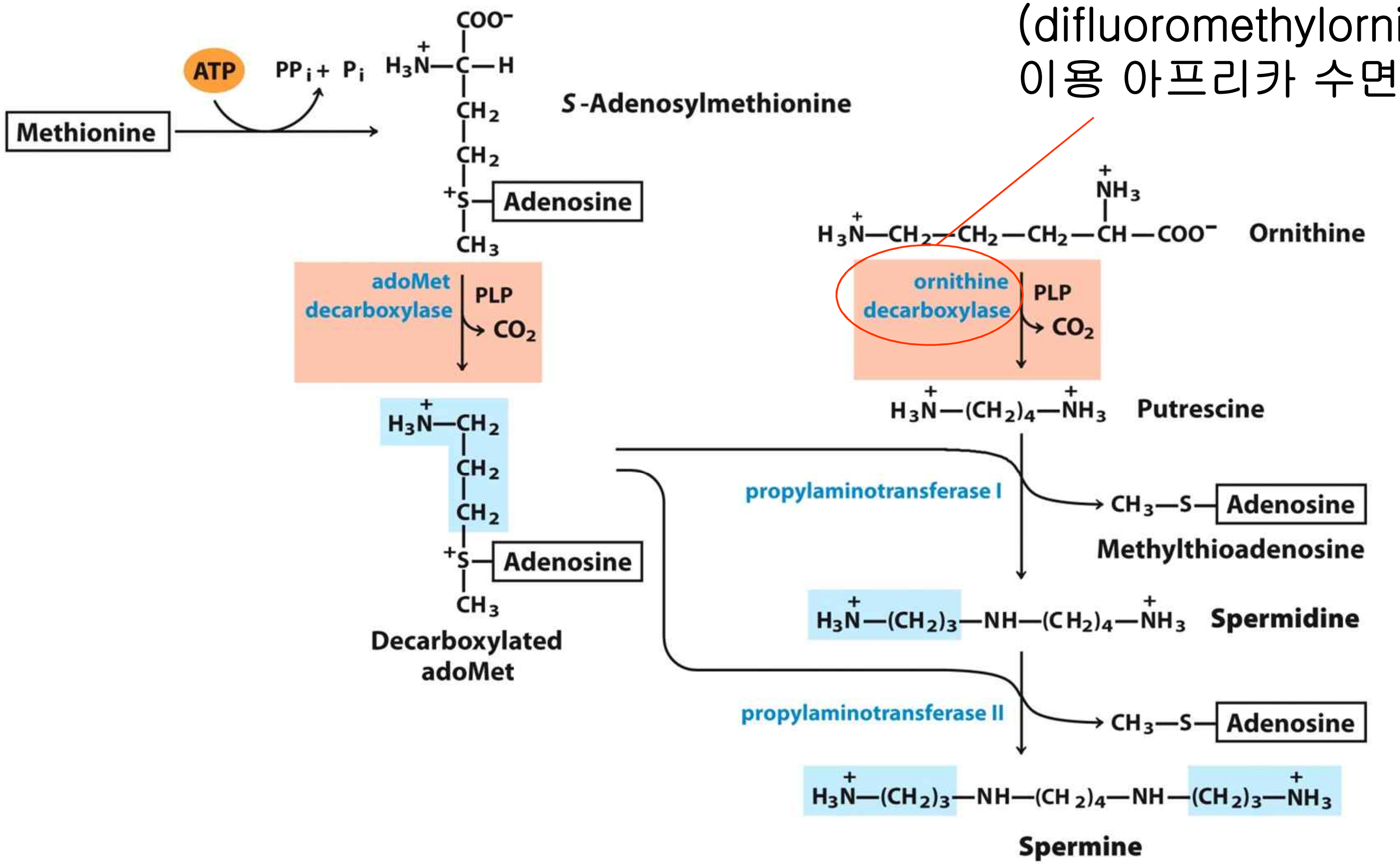
- 알레르기 반응과 위산 분비촉진: antagonist인 cimetidine(Tagamet)은 위산과다, 위궤양 치료제로 쓰임

DNA pakaging에 관여하는 Spermidine과 spermine의 생합성

- 저해제인 DFMO (difluoromethylornithine)를 이용 아프리카 수면병 치료



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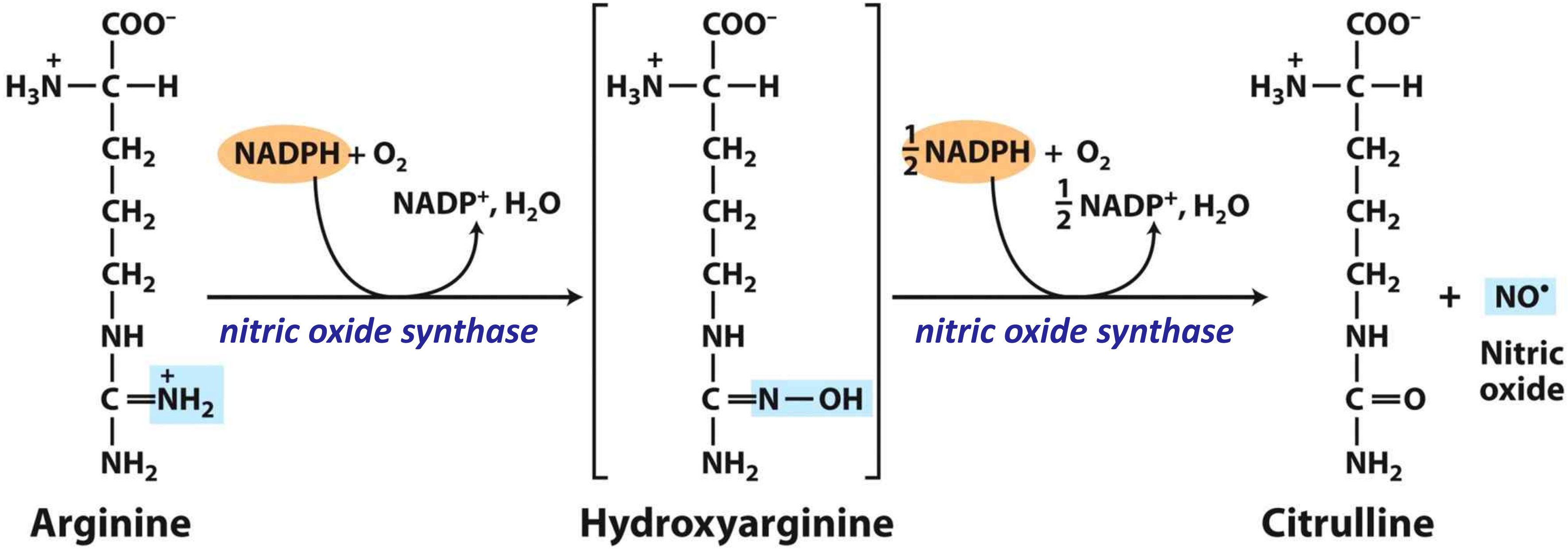
Biosynthesis of Nitric Oxide (일산화질소)



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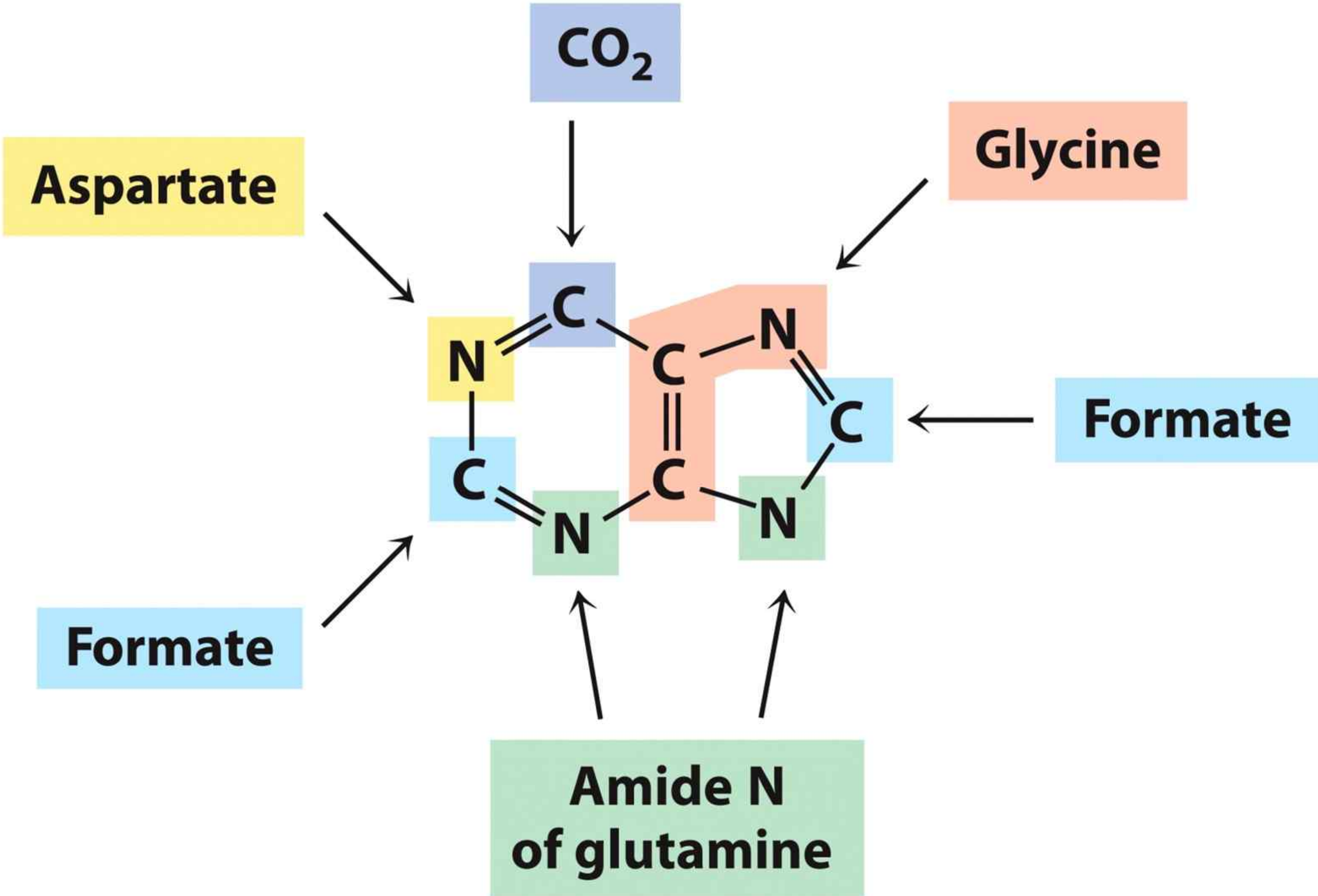
- NO는 신경전달물질, 혈액응고, 혈압조절에 관여

22.4 Biosynthesis and Degradation of Nucleotides

- Nucleotide의 생합성:
  - Purine nucleotide: PRPP, Gly, N-formyltetrahydrofolate, Asp로부터 생합성
  - Pyrimidine nucleotide: Asp, PRPP, carbamoyl phosphate로부터 생합성
- Nucleotide의 분해:
  - Purine nucleotide: 염기는 요산으로 변환
  - Pyrimidine nucleotide: 염기는 요소로 변환
- Deoxyribonucleotide는 ribonucleotide에서 생성

Origin of Ring Atoms in Purines



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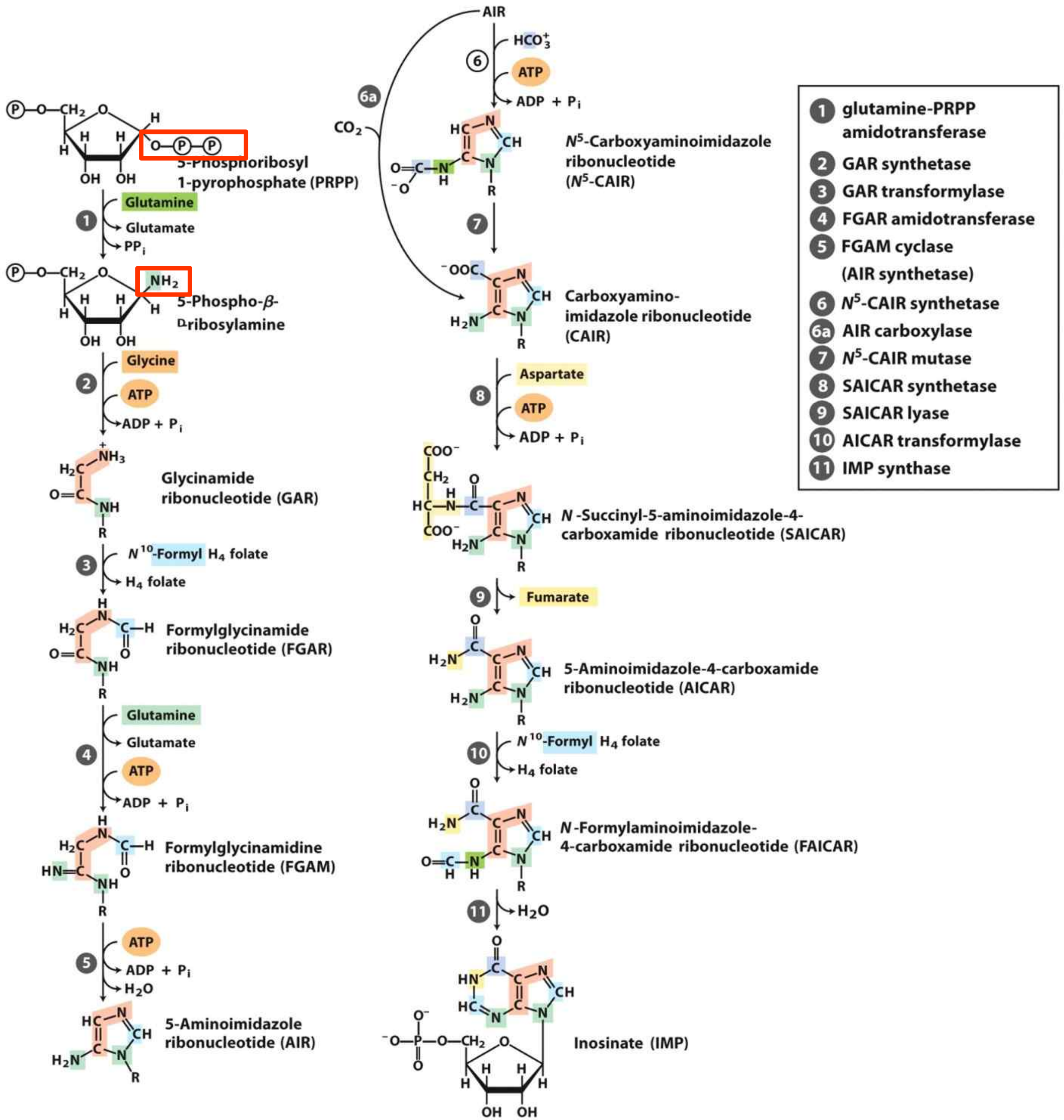
Purine nucleotide의 신생합성

- 5-phosphoribosyl-1-pyrophosphate(PRPP)에서 이노신산(inosinate, IMP) 생성



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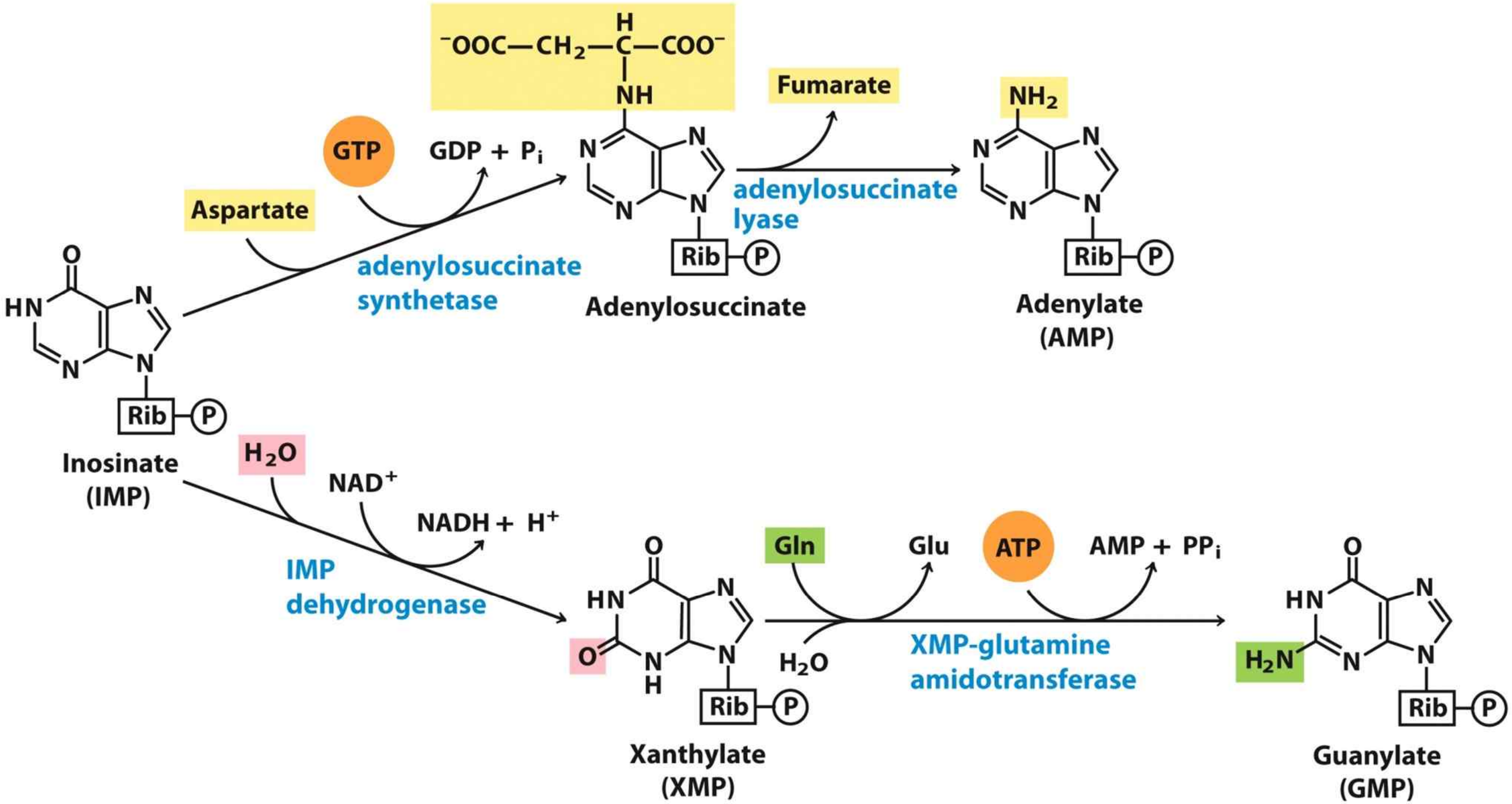
Synthesis of AMP and GMP from IMP



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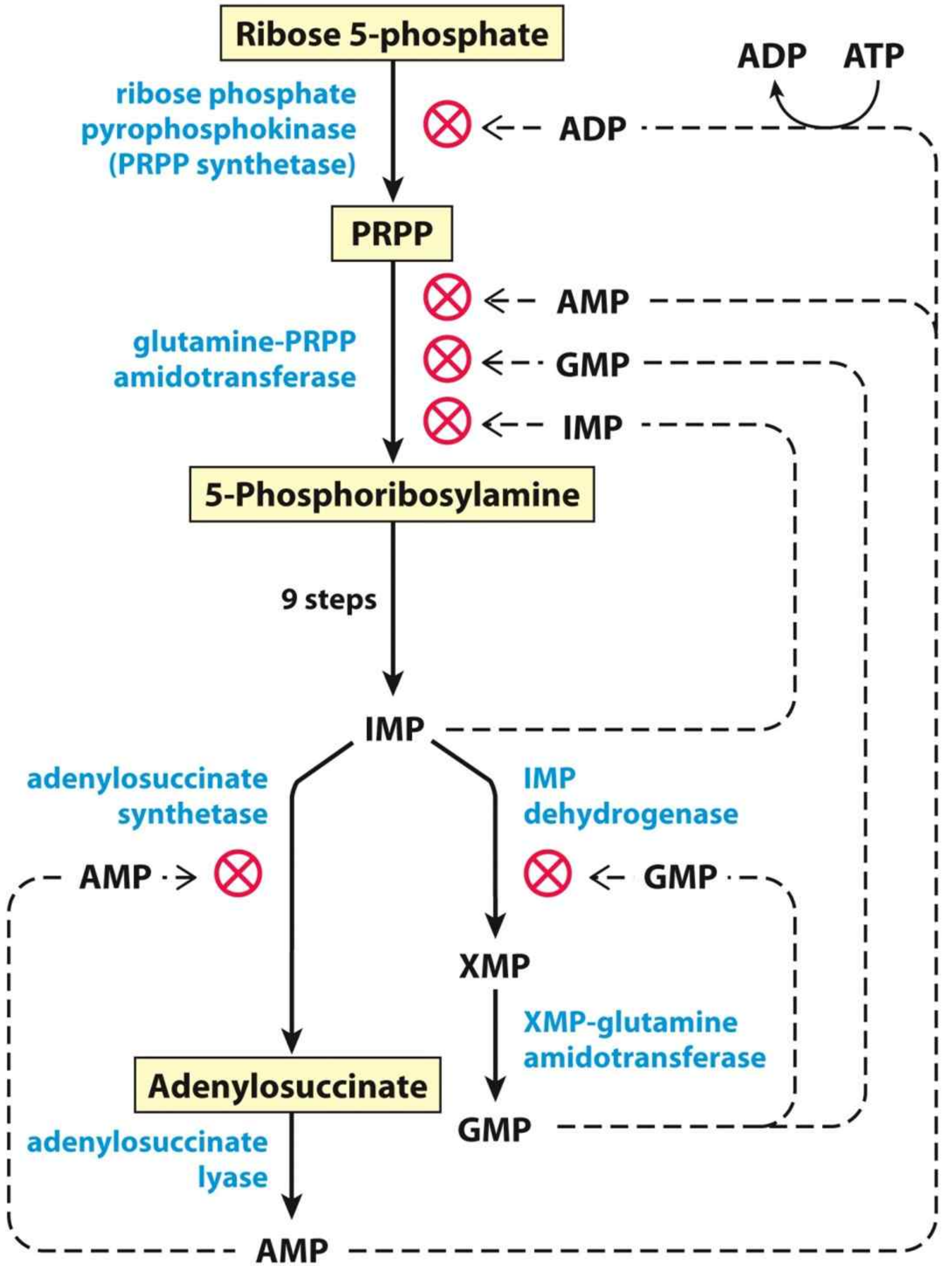
Regulation of Adenine and Guanine Biosynthesis in *E. coli*



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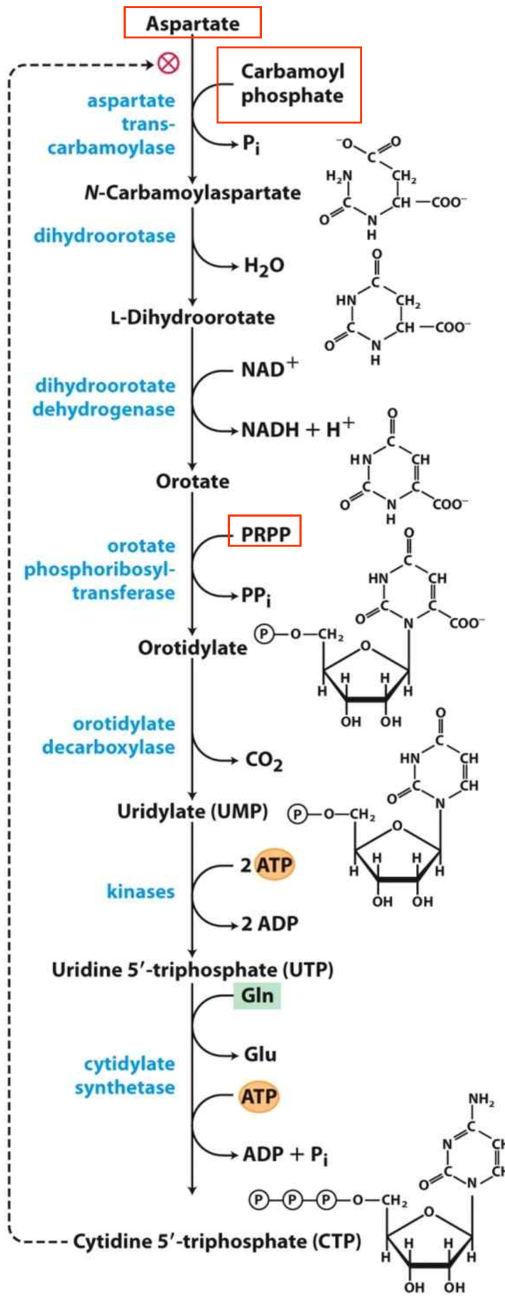
Pyrimidines are made from Asp, PRPP, and carbamoyl phosphate

- Unlike purine synthesis, pyrimidine synthesis proceeds *by first making the pyrimidine ring* and *then* attaching it to ribose 5-phosphate

- First committed step is rx between Asp and N-carbamoylphosphate, catalyzed by *aspartate transcarbamoylase* (ATCase)

Pyrimidine nucleotide의 신생합성



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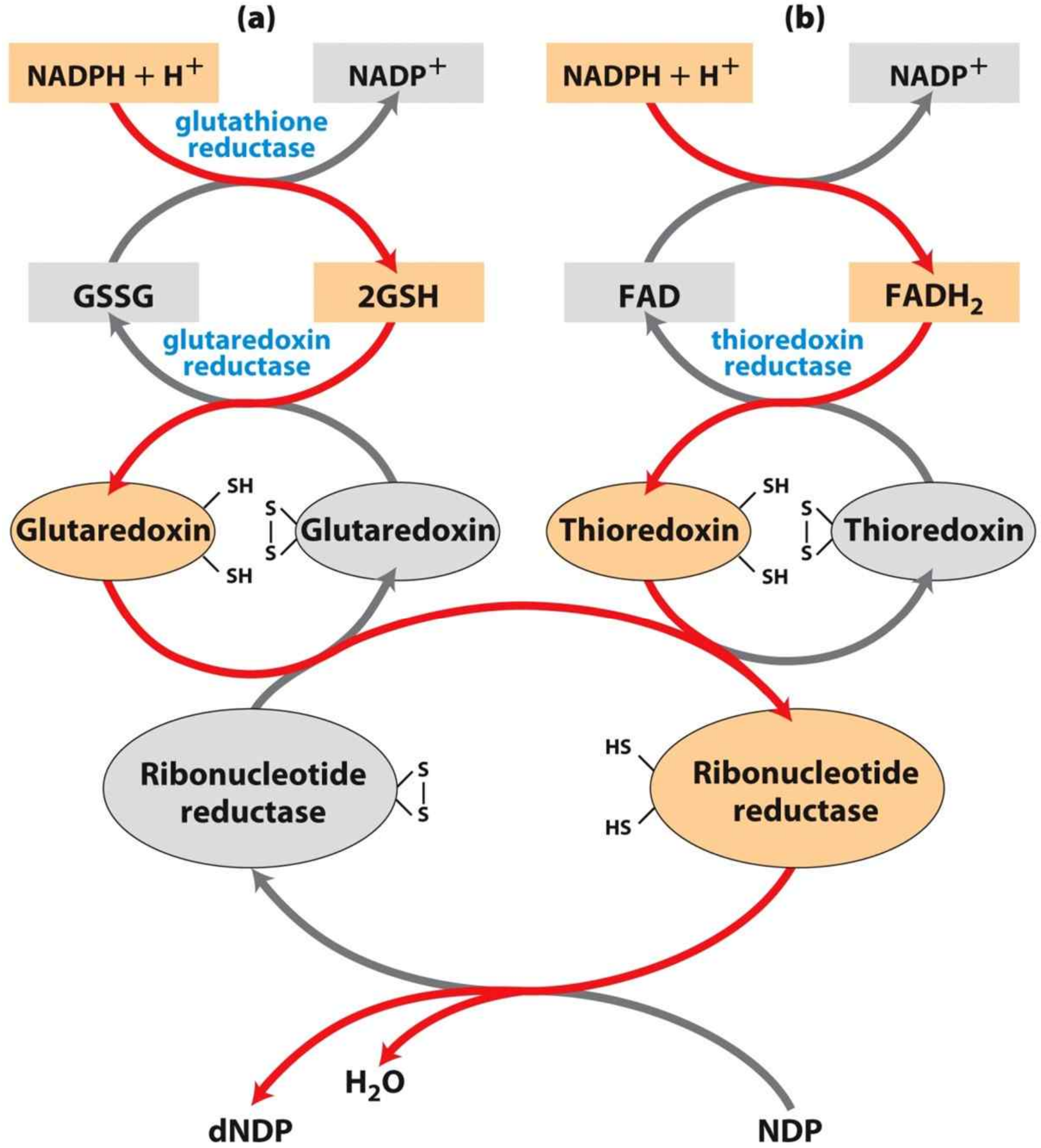
Ribonucleotides are precursors to deoxyribonucleotides

- 2'C-OH bond is directly reduced to 2'-H bond…without activating the carbon!
  - Catalyzed by *ribonucleotide reductase*
- Mechanism: Two H atoms are donated by NADPH and carried by proteins thioredoxin or glutaredoxin

Reduction of Ribonucleotides to Deoxyribonucleotides by Ribonucleotide Reductase



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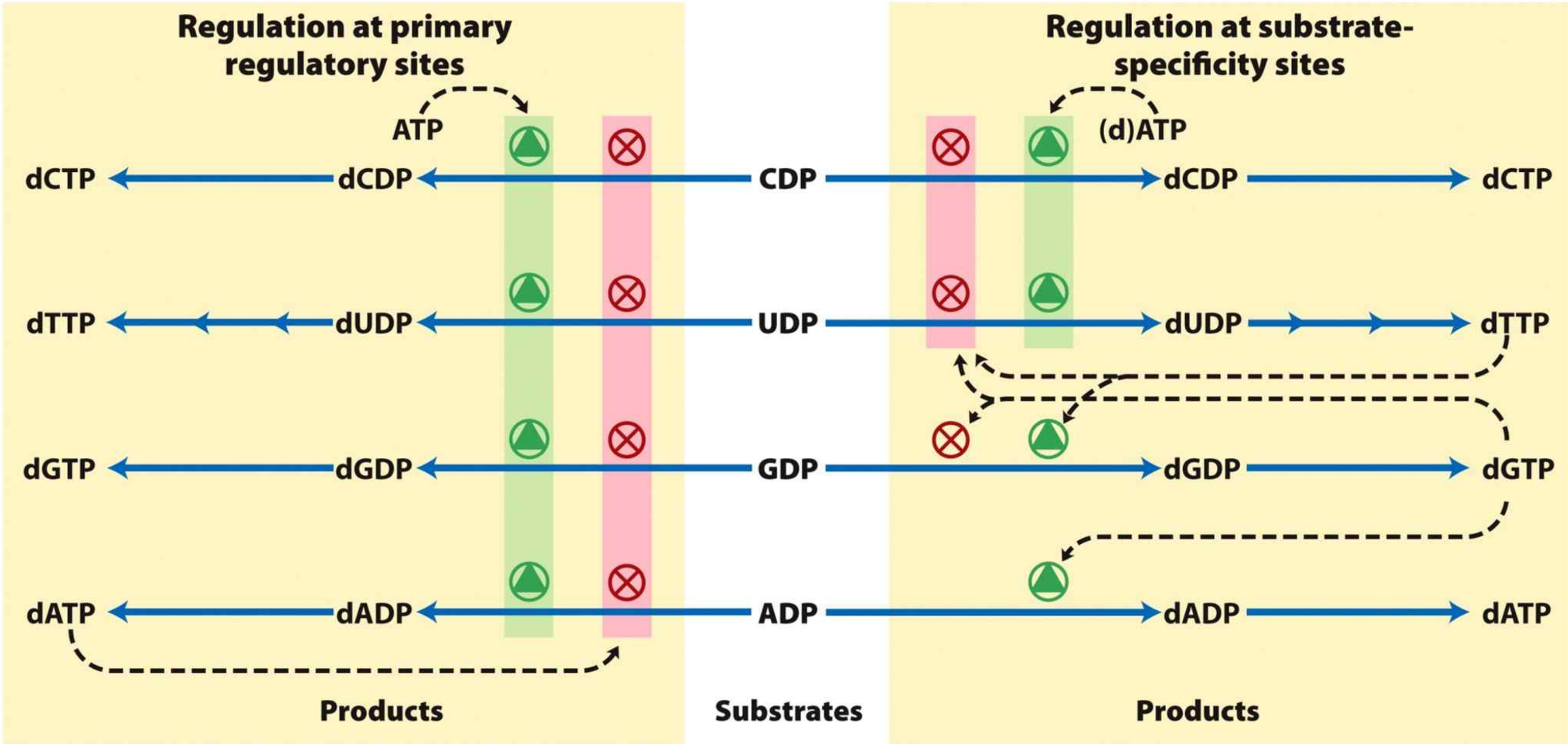
Regulation of Ribonucleotide Reductase by dNTPs



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dTMP is made from dUTP

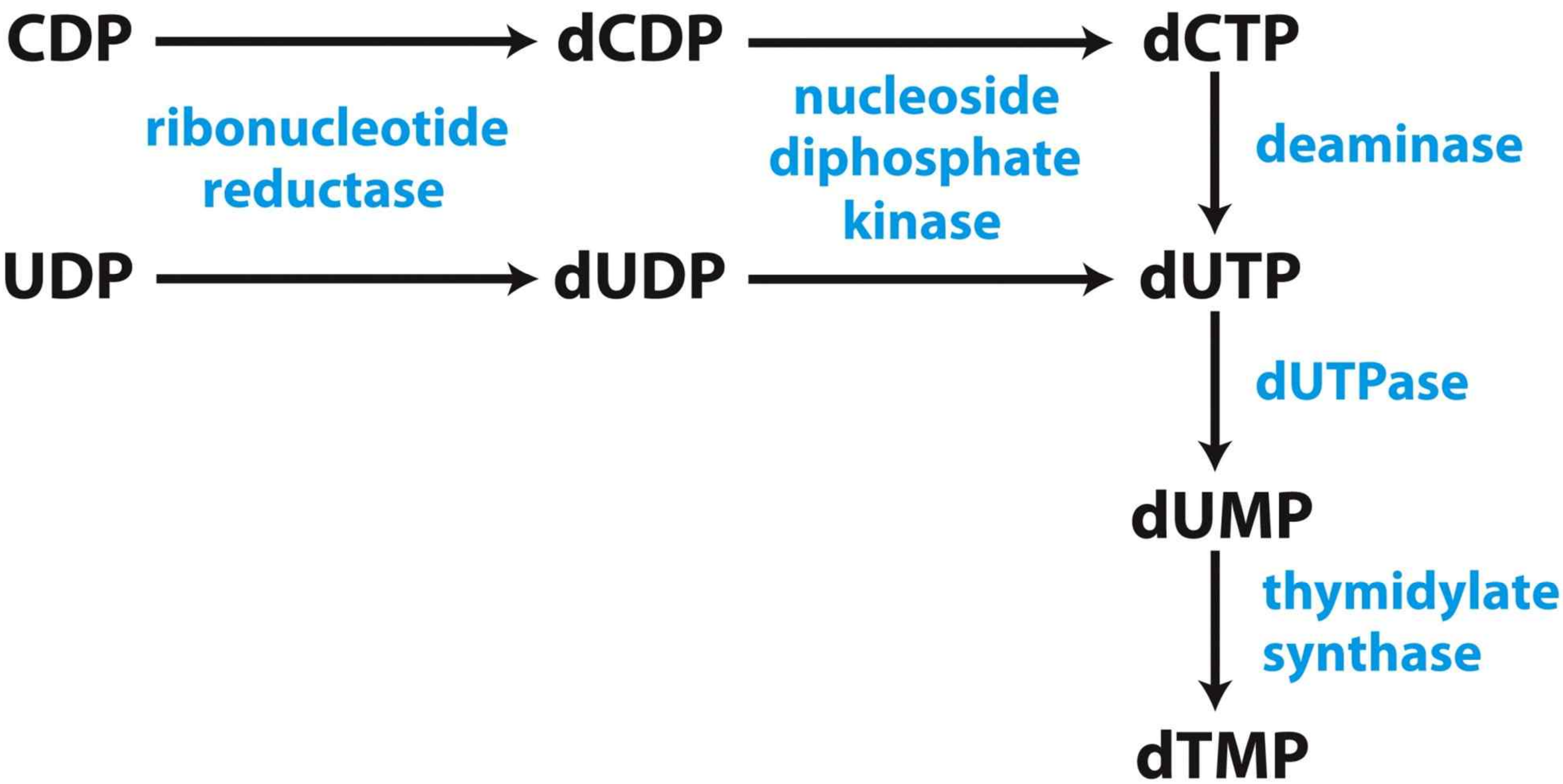
- Roundabout pathway…

1. dUTP is made (via deamination of dCTP or by phosphorylaton of dUDP)
2. dUTP → to dUMP by dUTPase
3. dUMP → dTMP by *thymidylate synthase*

   - adds a methyl group from *tetrahydrofolate*

Thymidylate synthase is a target for some anticancer drugs.

Thymidylate(dTMP)의 생합성



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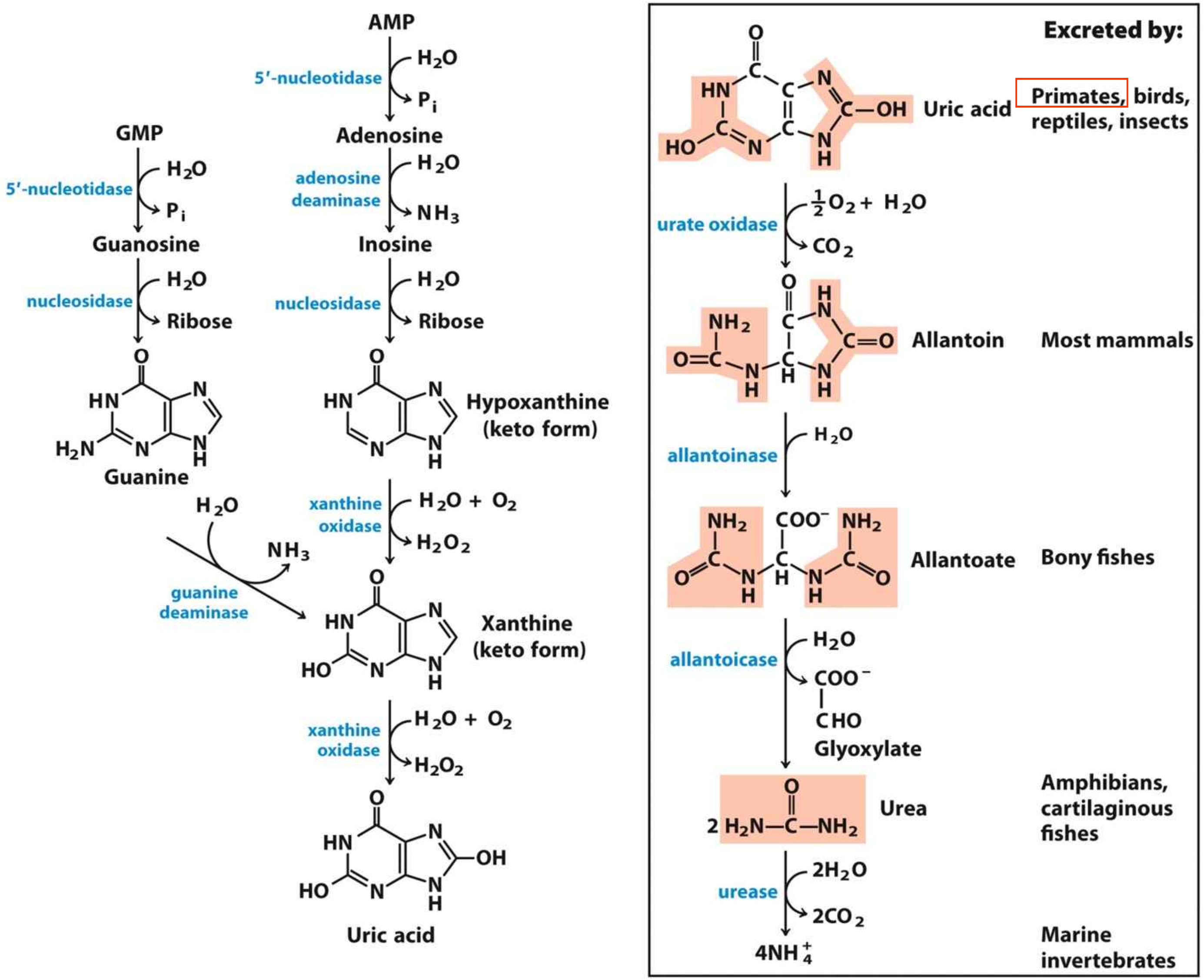
Folic acid deficiency leads to reduced thymidylate synthesis

- Folic acid deficiency is widespread, especially in nutritionally poor populations
- Reduced thymidylate synthesis causes uracil to be incorporated into DNA
- Repair mechanisms remove the uracil by creating strand breaks that affect the structure and function of DNA
  - Associated with cancer, heart disease, neurological impairment

Catabolism of Purines: Formation of Uric Acid

- Degradation of purines proceeds through dephosphorylation (via *5'-nucleotidase*)
- Adenosine is deaminated to inosine and then hydrolyzed to hypoxanthine and ribose
- Guanosine yields xanthine via these hydrolysis and deamination reactions
- Hypoxanthine and xanthine are then oxidized into uric acid by ***xanthine oxidase***
- Spiders and other arachnids lack xanthine oxidase

Purine nucleotide의 이화과정



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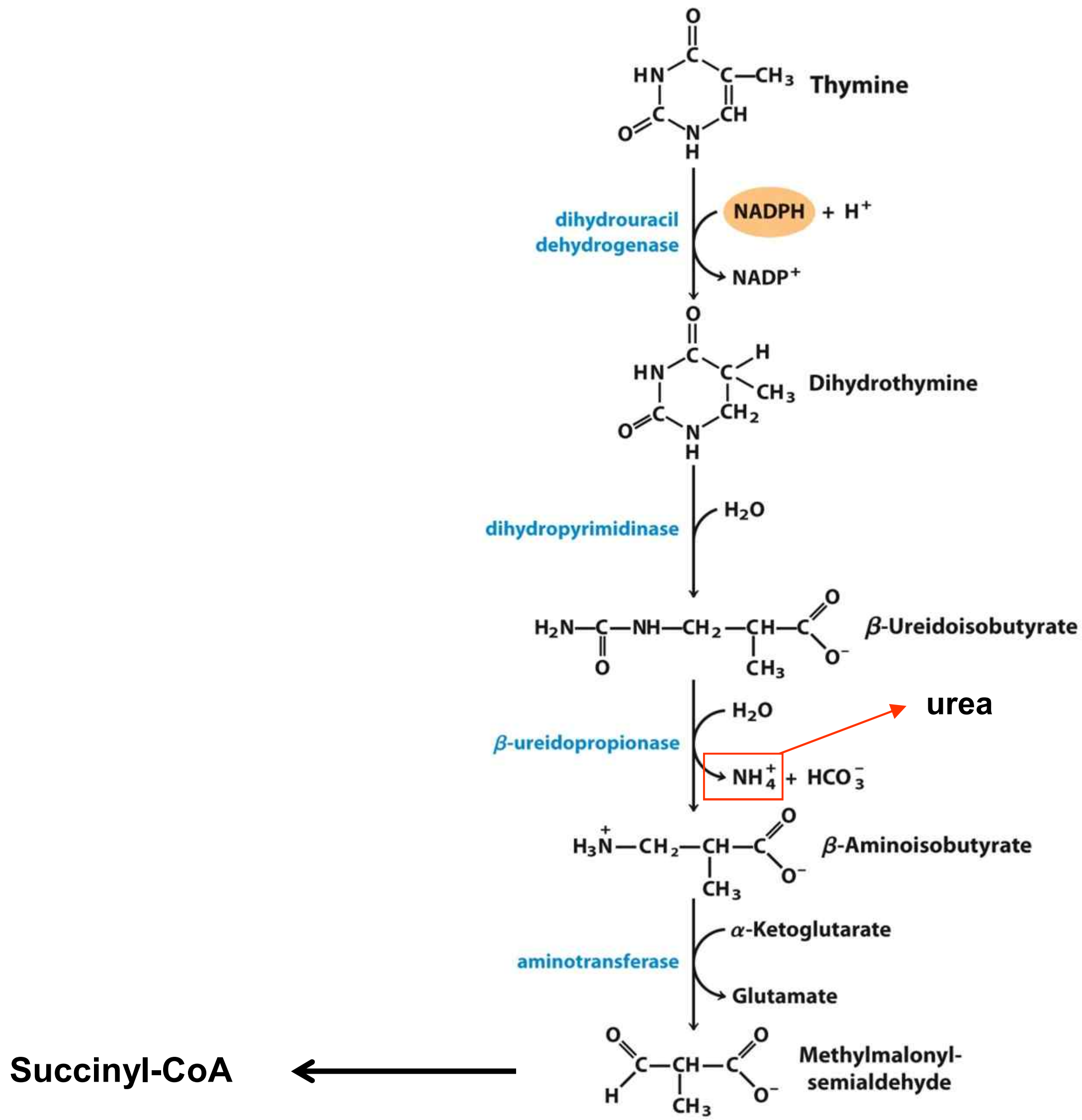
Catabolism of Pyrimidines

- Leads to NH_4^+ then urea
- Can produce intermediates of citric acid cycle
  - Example: Thymine is degraded to succinyl-CoA

Catabolism of Thymine, a Pyrimidine



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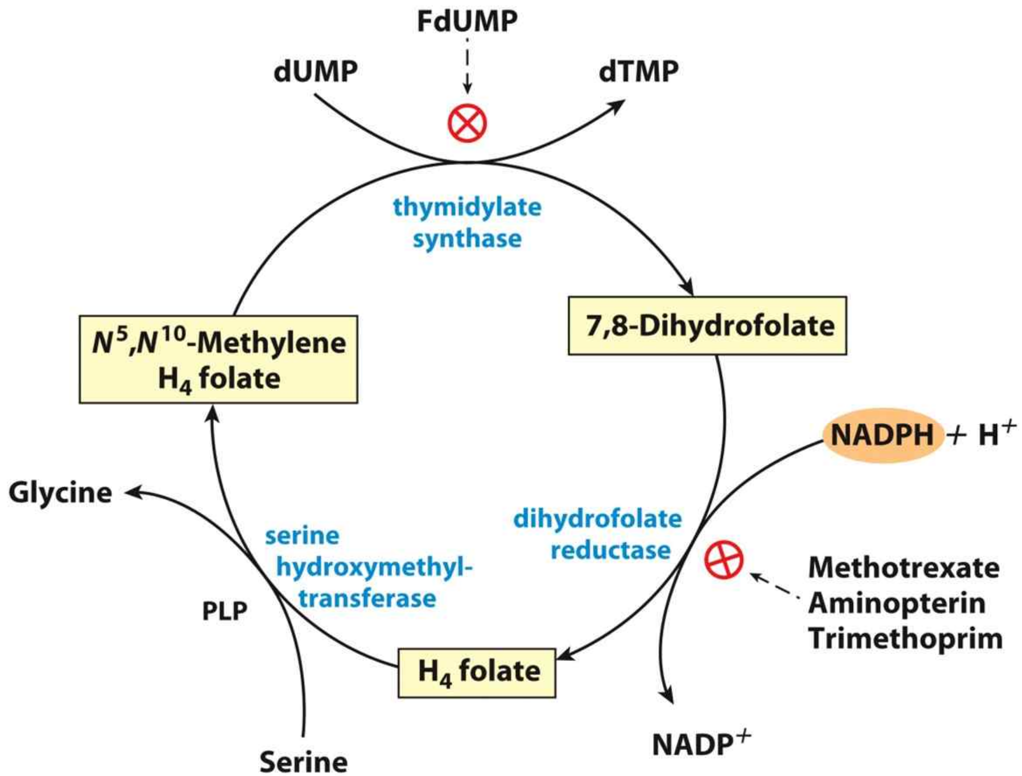
nucleotide 생합성 효소를 표적으로 하는 항암제의 종류

- Azaserine, acivicin: 글루타민 유사체. Glutamine amidotransferase 활성 저해를 통해 nucleotide 생합성 억제
- Fluorouracil(5-FU): thymidylate synthase의 활성 저해를 통해 thymine 합성 억제
- Methotrexate, aminopterin: dihydrofolate reductase 활성 억제

Chemotherapy Targets—Thymidylate Synthesis and Folate Metabolism



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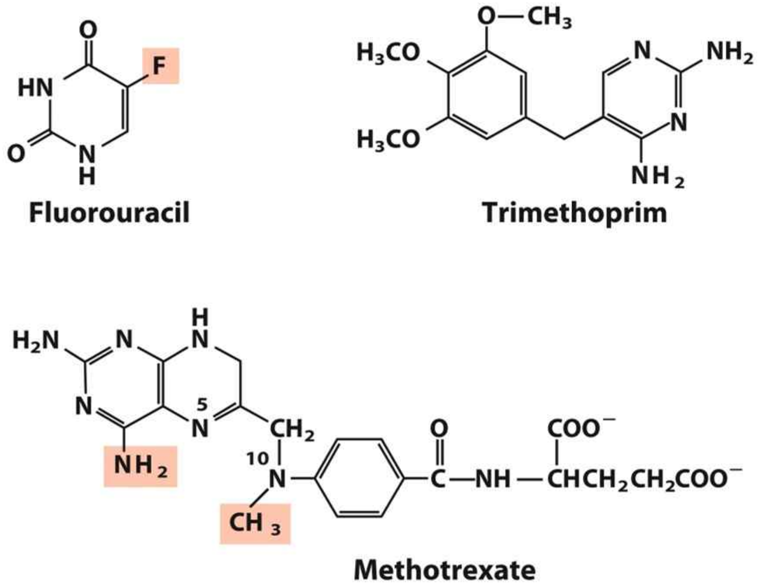

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Chapter Summary

In this chapter, we learned:

- Some prokaryotes are able to reduce molecular nitrogen into ammonia; understanding details of the nitrogen fixation is one of the holy grails in biochemistry
- The 20 common amino acids are synthesized via difficult-to-remember pathways from α-ketoglutarate, 3-phosphoglycerate, oxaloacetate, pyruvate, phosphoenolpyruvate, erythrose 4-phosphate, and ribose-5-phosphate
- Nucleotides can be synthesized either de novo from simple precursors, or reassembled from scavenged nucleobases
- Purine degradation pathway in most organisms leads to uric acid, but the fate of uric acid is species-specific