

BCH3120: GENERAL INTERMEDIARY METABOLISM

LECTURE 15, MARCH 20

LUC POITRAS, LPOITRAS@UOTTAWA.CA

Lecture 15 : Amino acid biosynthesis

Amino acids biosynthesis

- Many amino acids are synthesized by metabolic pathways that are only present in plants and microorganisms (bacteria and archaea)
 - Since mammals (humans) need to obtain these amino acids through their diets, these amino acids are identified as **essential amino acids**.
 - Amino acids that can be synthesized by mammals are also known as **non-essential amino acids**.

Essential and non-essential amino acids

TABLE 18.1 Nutritional requirements for amino acids in mammals

Essential

Arginine,* histidine, isoleucine, leucine, lysine, methionine,* phenylalanine, threonine, tryptophan, valine

Nonessential

Alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine**

* Although mammals can synthesize arginine and methionine, the use of these amino acids for the production of urea and methyl groups, respectively, is greater than the capacity of their biosynthetic pathways.

** Tyrosine is considered nonessential because mammals can produce it during phenylalanine degradation via the phenylalanine hydroxylase reaction.

Essential amino acids

TABLE 18.1 Nutritional requirements for amino acids in mammals

Essential

Arginine,* histidine, isoleucine, leucine, lysine, methionine,* phenylalanine, threonine, tryptophan, valine

- Private Tim Hall mnemonic trick

PVT TIM HALL

P henylalanine	T ryptophane	H istidine
V aline	I soleucine	A rginine
T hreonine	M ethionine	L eucine
		L ysine



Essential amino acids

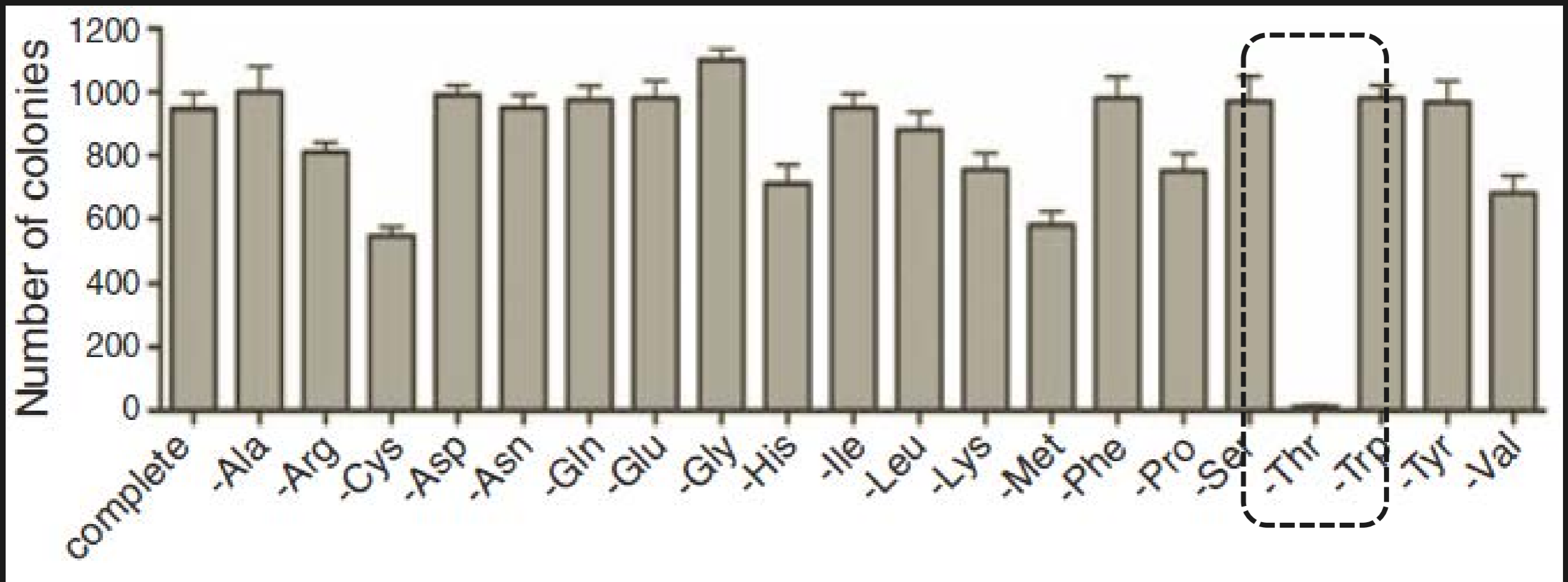
Dependence of Mouse Embryonic Stem Cells on Threonine Catabolism

Jian Wang,¹ Peter Alexander,¹ Leeju Wu,¹ Robert Hammer,¹
Ondine Cleaver,² Steven L. McKnight^{1*}

Measurements of the abundance of common metabolites in cultured embryonic stem (ES) cells revealed an unusual state with respect to one-carbon metabolism. These findings led to the discovery of copious expression of the gene encoding threonine dehydrogenase (TDH) in ES cells. TDH-mediated catabolism of threonine takes place in mitochondria to generate glycine and acetyl-coenzyme A (CoA), with glycine facilitating one-carbon metabolism via the glycine cleavage system and acetyl-CoA feeding the tricarboxylic acid cycle. Culture media individually deprived of each of the 20 amino acids were applied to ES cells, leading to the discovery that ES cells are critically dependent on one amino acid—threonine. These observations show that ES cells exist in a high-flux backbone metabolic state comparable to that of rapidly growing bacterial cells.

Dependence of mouse embryonic stem cells on threonine catabolism. *Science*. 2009 Jul 24;325(5939):435-9.

Essential amino acids

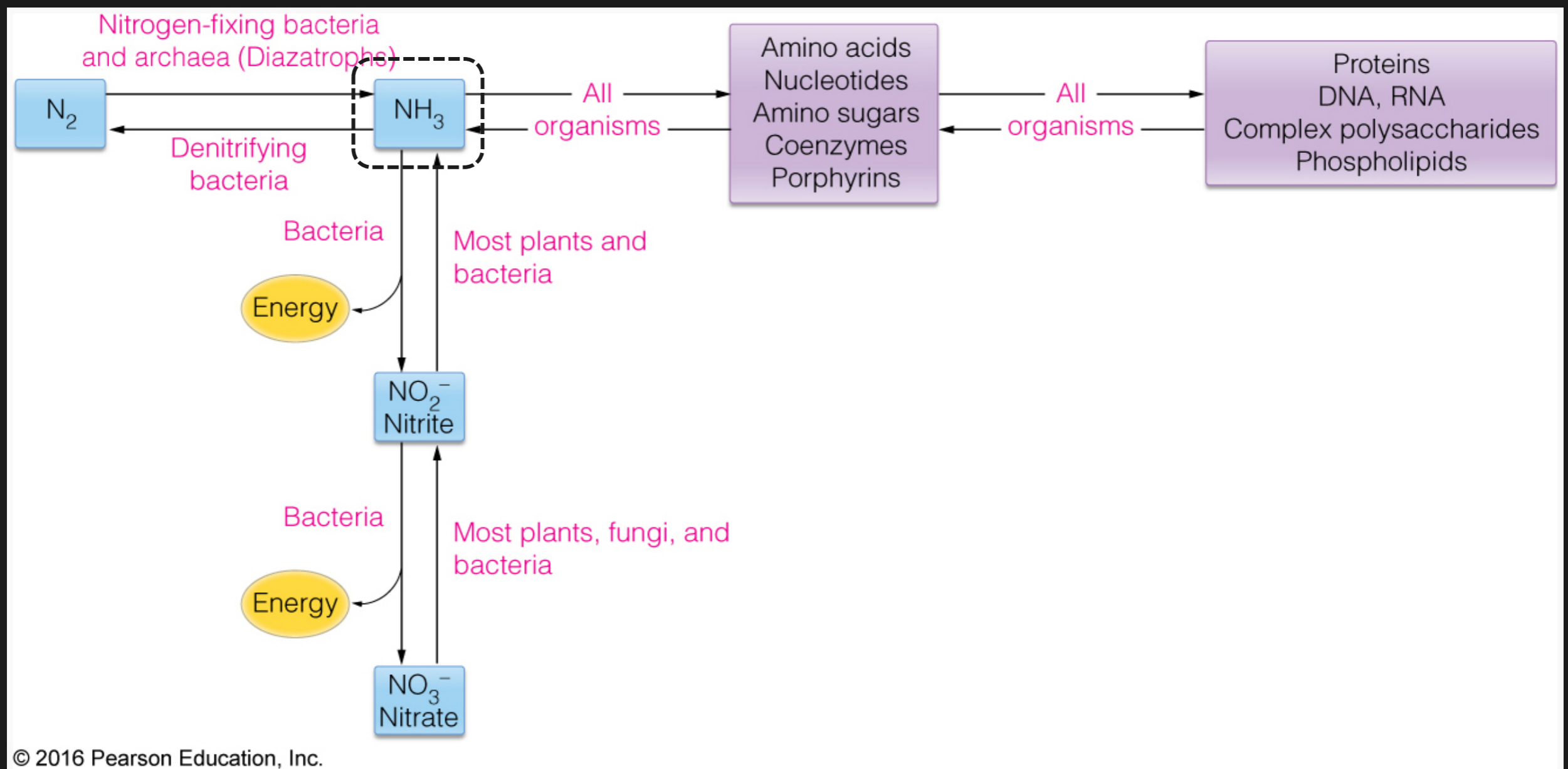


Dependence of mouse embryonic stem cells on threonine catabolism. *Science*. 2009 Jul 24;325(5939):435-9.

Biosynthesis of essential amino acids

Bacteria and plants

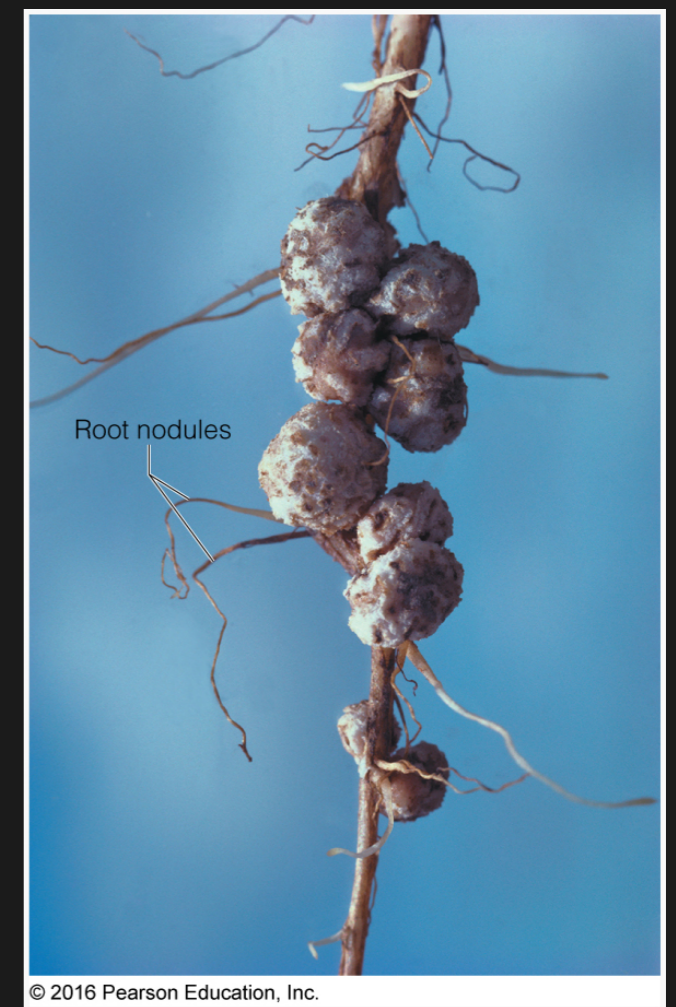
The nitrogen cycle: Inorganic and organic nitrogen metabolism



The nitrogen cycle: Nitrogen fixation

Some bacteria and archaea

- Inorganic nitrogen (N_2) is the most abundant component of earth's atmosphere.
- Only few microorganisms can reduce N_2 to NH_3 (NH_4^+), there are called diazotrophs.
- This reduction process is called Nitrogen fixation.
- This process is catalyzed by the nitrogenase complex.

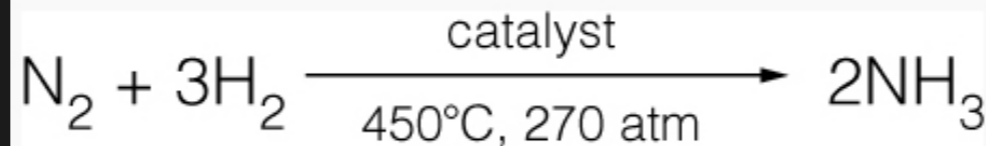


The site of nitrogen fixation is symbiotic root nodules

The nitrogen cycle: Nitrogen fixation

Some bacteria and archaea

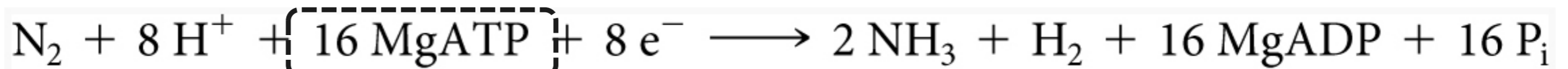
- The triple-bonded N_2 (bond energy of 940kJ/mol) is really difficult to reduce:



The Haber–Bosch process

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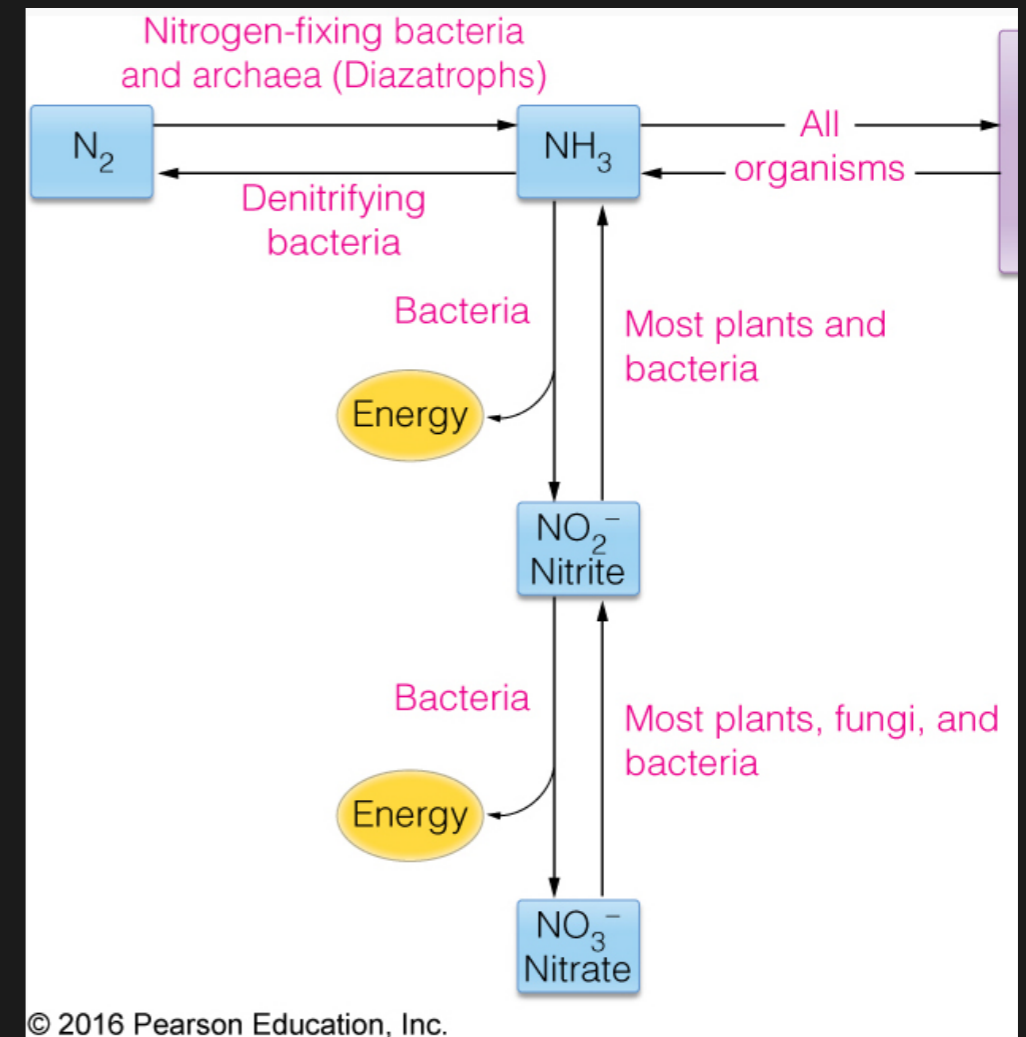
- It is not surprising that nitrogen fixation is a very expensive process:



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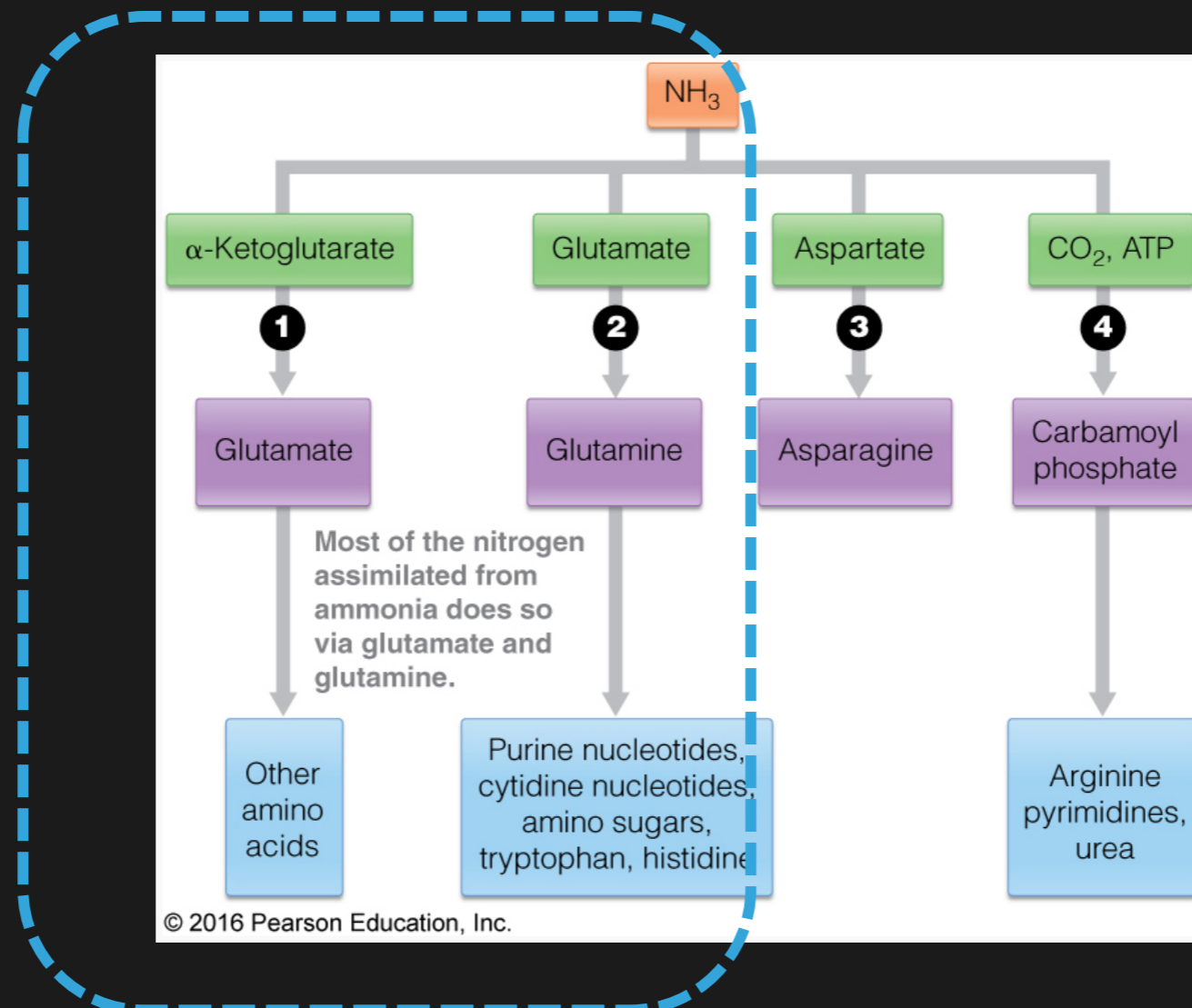
The nitrogen cycle: Nitrate conversion to ammonia

- Most plant, fungi and bacteria are able to use nitrate ions (NO_3^-) to generate ammonia (NH_3).
- NO_3^- is essential for the growth of most plants.



The nitrogen cycle: Nitrogen assimilation

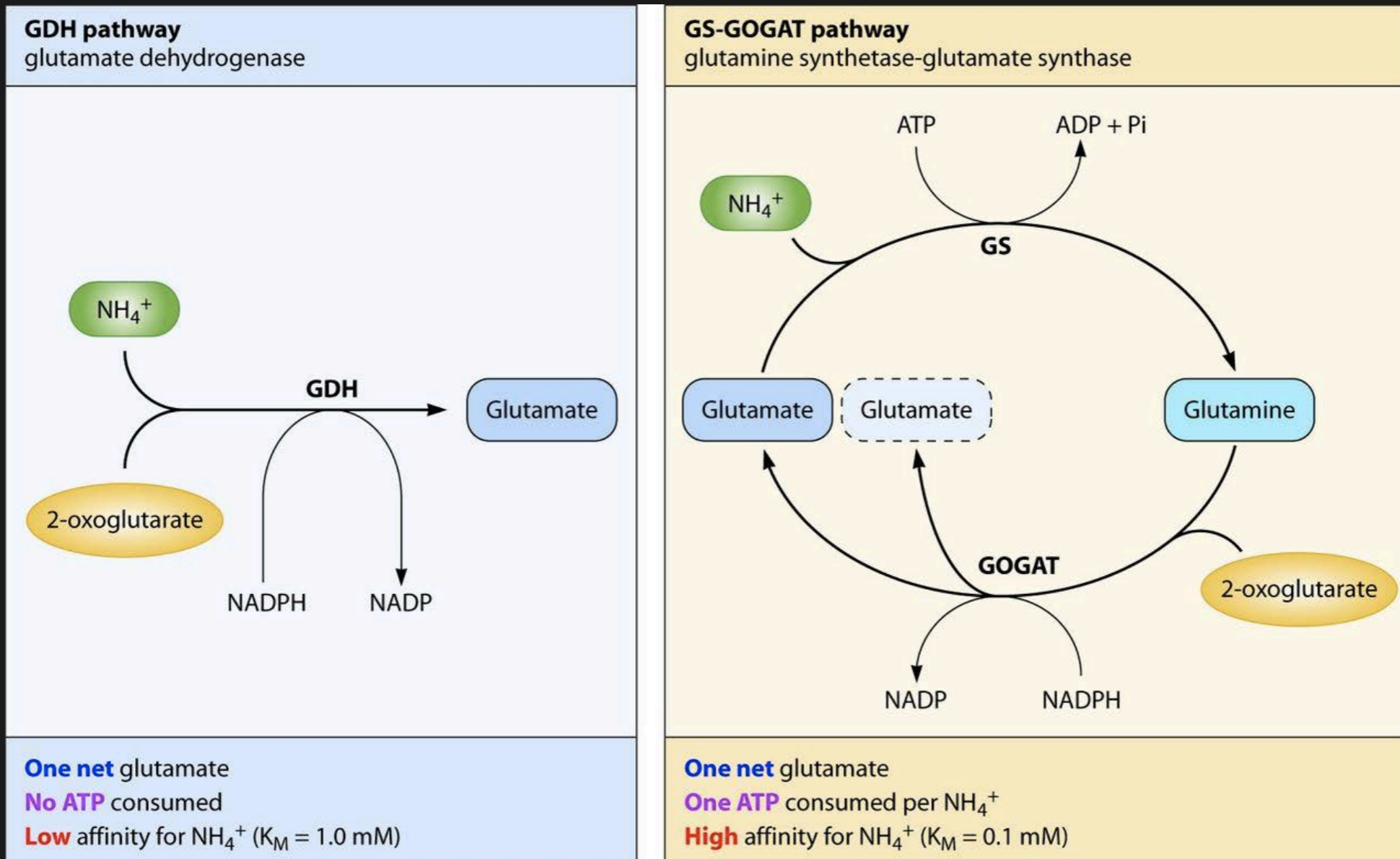
- In plants and bacteria, the process by which ammonia will be used to form organic nitrogen-containing molecule like amino acids is called nitrogen assimilation.



The nitrogen cycle: Nitrogen assimilation

- Most the nitrogen assimilation is carried out by two pathways:
 - Glutamate dehydrogenase (GDH)
 - Production of glutamate
 - Glutamine synthetase-glutamine:2-oxoglutarate amido transferase pathway (GS-GOGAT)
 - Production of glutamine

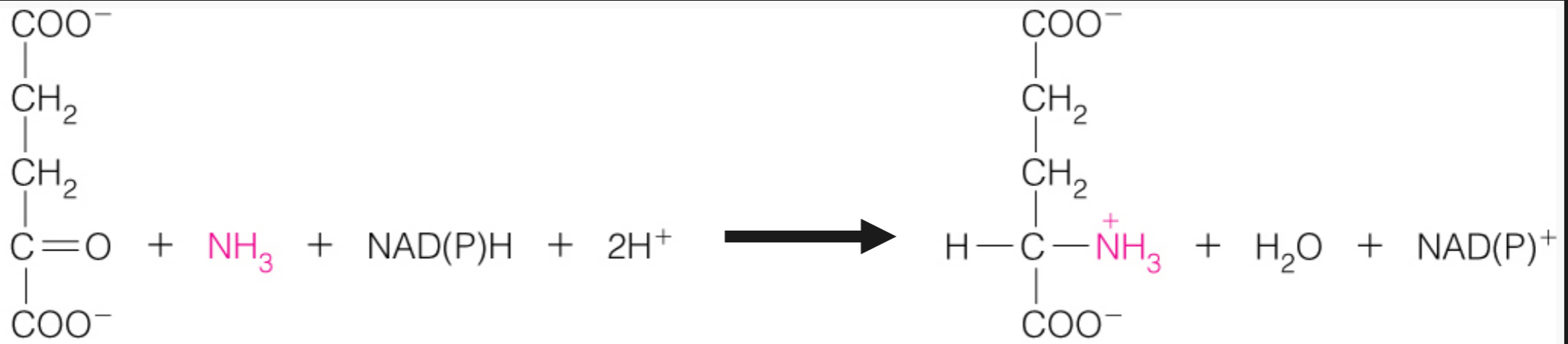
The nitrogen cycle: Nitrogen assimilation



The nitrogen cycle: Nitrogen assimilation

Glutamate dehydrogenase (GDH) pathway

- Conversion of α -ketoglutarate into glutamate
 - Pathway present in plants and bacteria.



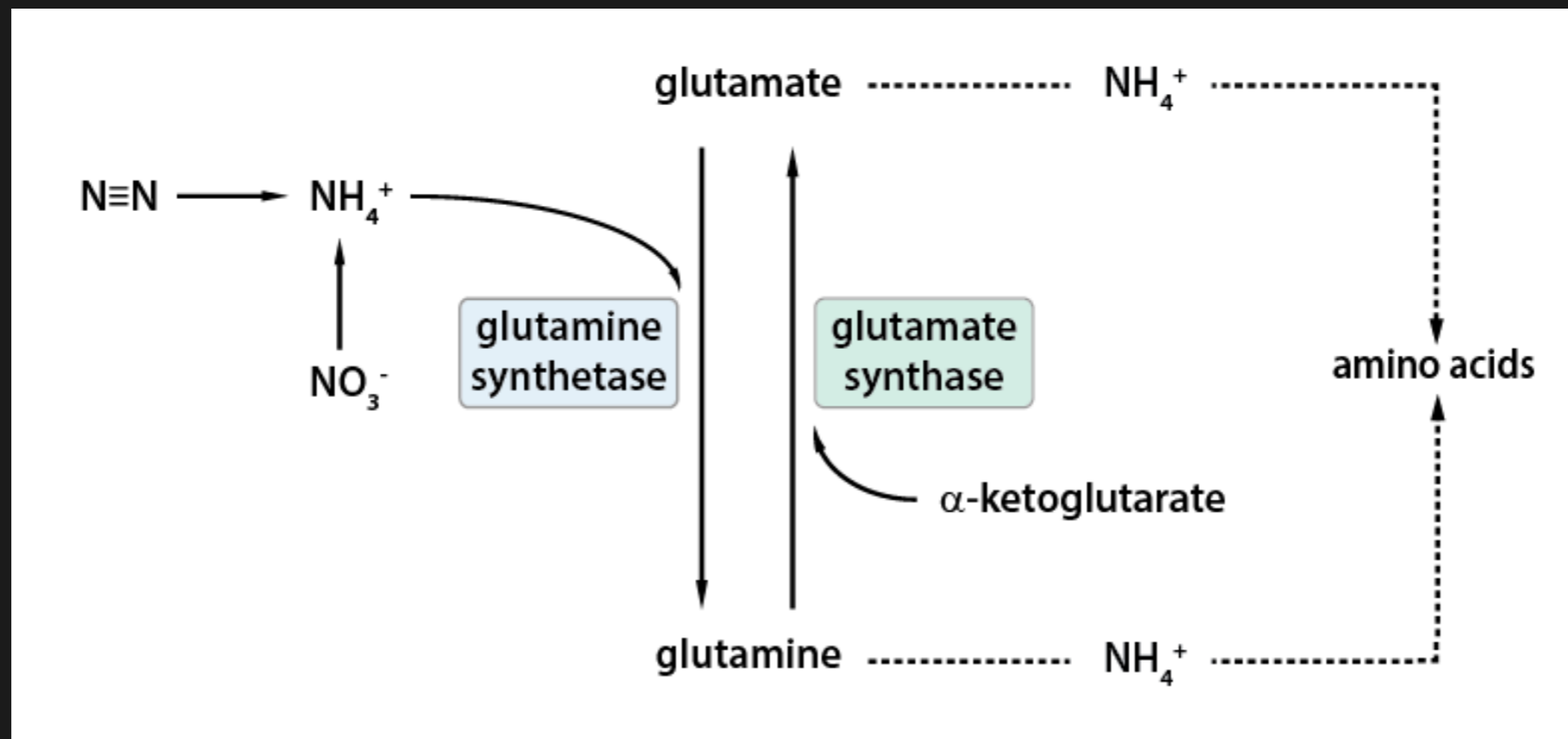
α -Ketoglutarate

Glutamate

The nitrogen cycle: Nitrogen assimilation

Glutamine synthetase-glutamine:2-oxoglutarate amido transferase pathway (GS-GOGAT)

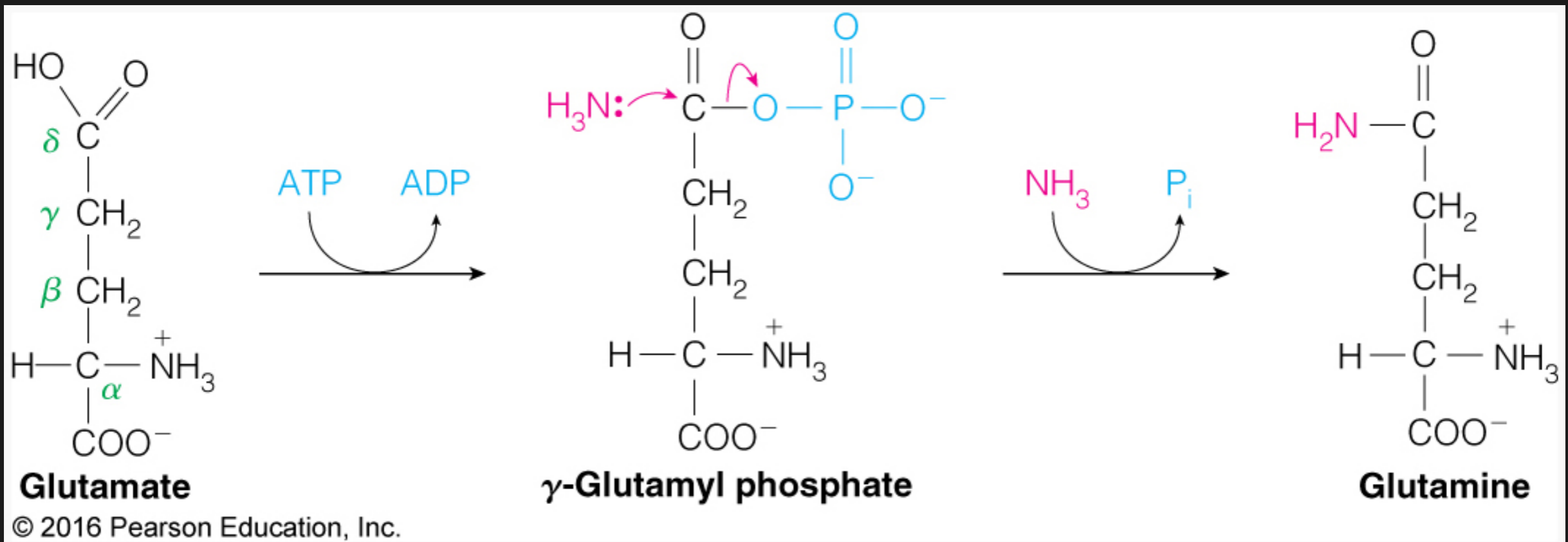
- Conversion of glutamate into glutamine and back to glutamate
 - Pathway present in plants and bacteria.



The nitrogen cycle: Nitrogen assimilation

GS-GOGAT: First step

- Conversion of glutamate to glutamine
 - Reaction catalyzed by Glutamine synthetase (GS)
 - Requires one ATP



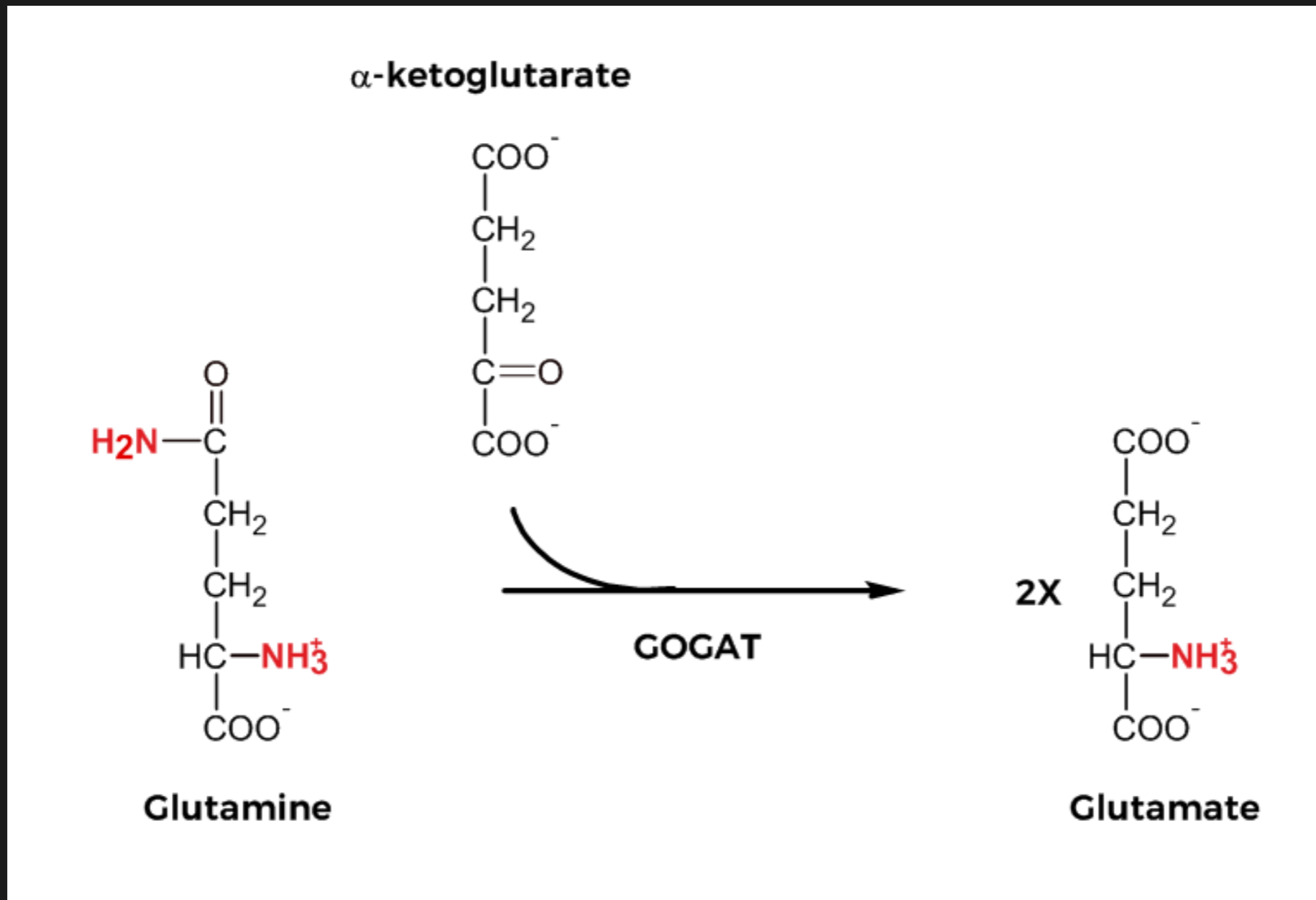
The nitrogen cycle: Nitrogen assimilation

GS-GOGAT: Second step

- One molecule of glutamine and α -ketoglutarate (2-oxoglutarate) are used to generate 2 molecules of glutamate.
- This transamination is catalyzed by glutamine:2-oxoglutarate amido transferase.

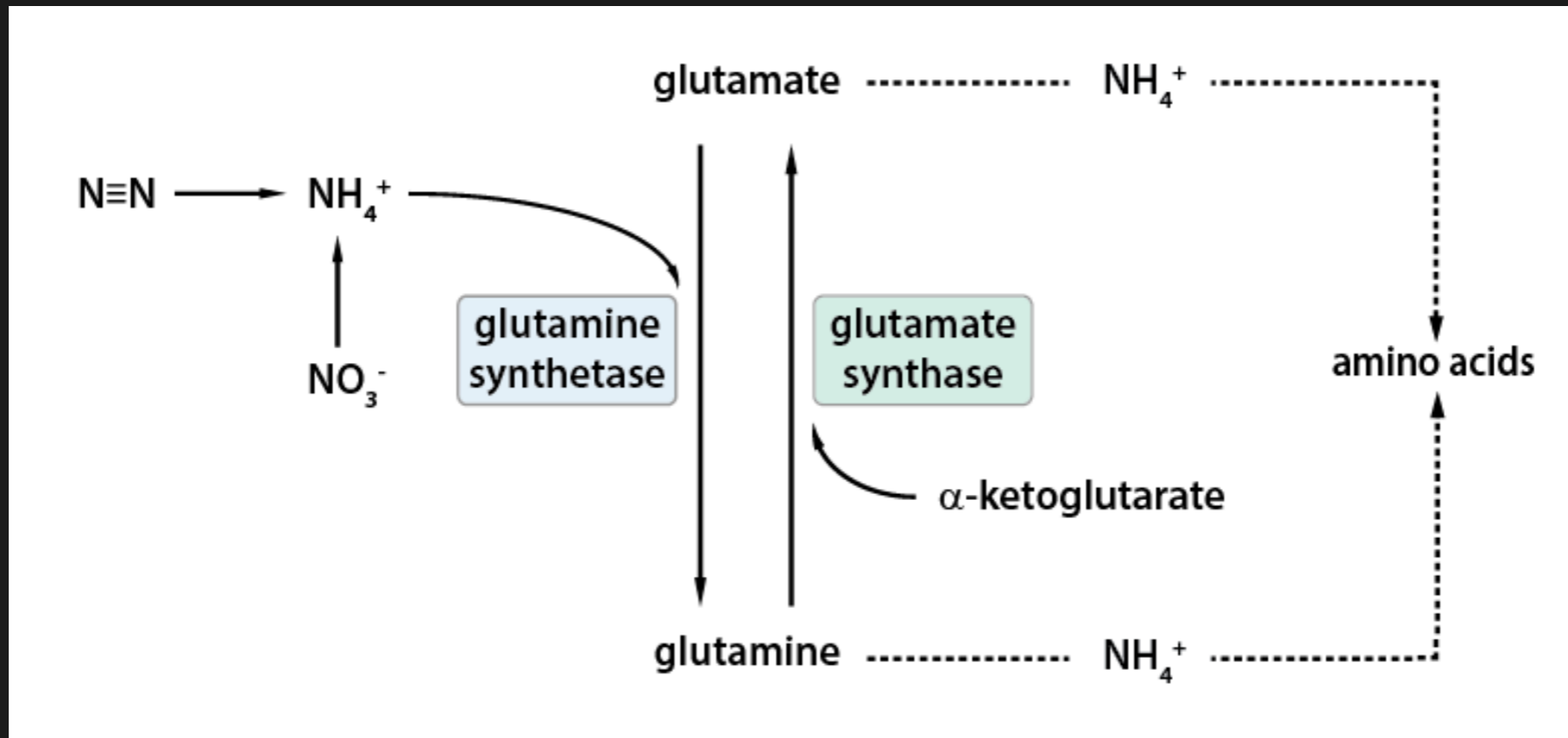
The nitrogen cycle: Nitrogen assimilation

GS-GOGAT: Second step

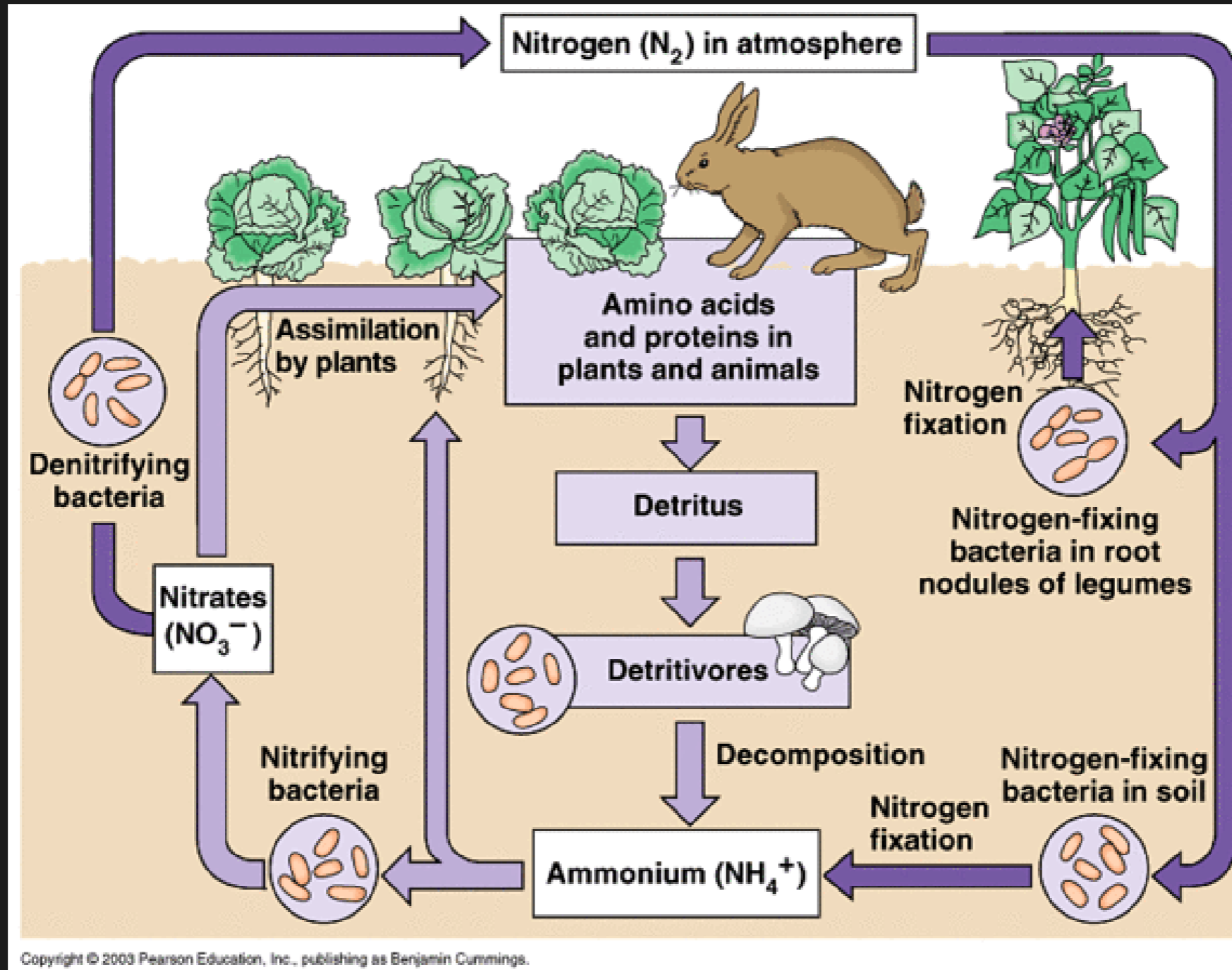


The nitrogen cycle: Nitrogen assimilation

GS-GOGAT



The nitrogen cycle



Essential vs non-essential AA

Milk and Meat proteins



- Contains amino acids in proportions required for human health

Bean proteins



- Rich in lysine
- Deficient in methionine

Wheat proteins



- Rich in methionine
- Deficient in lysine

Essential amino acids

TABLE 18.1 Nutritional requirements for amino acids in mammals

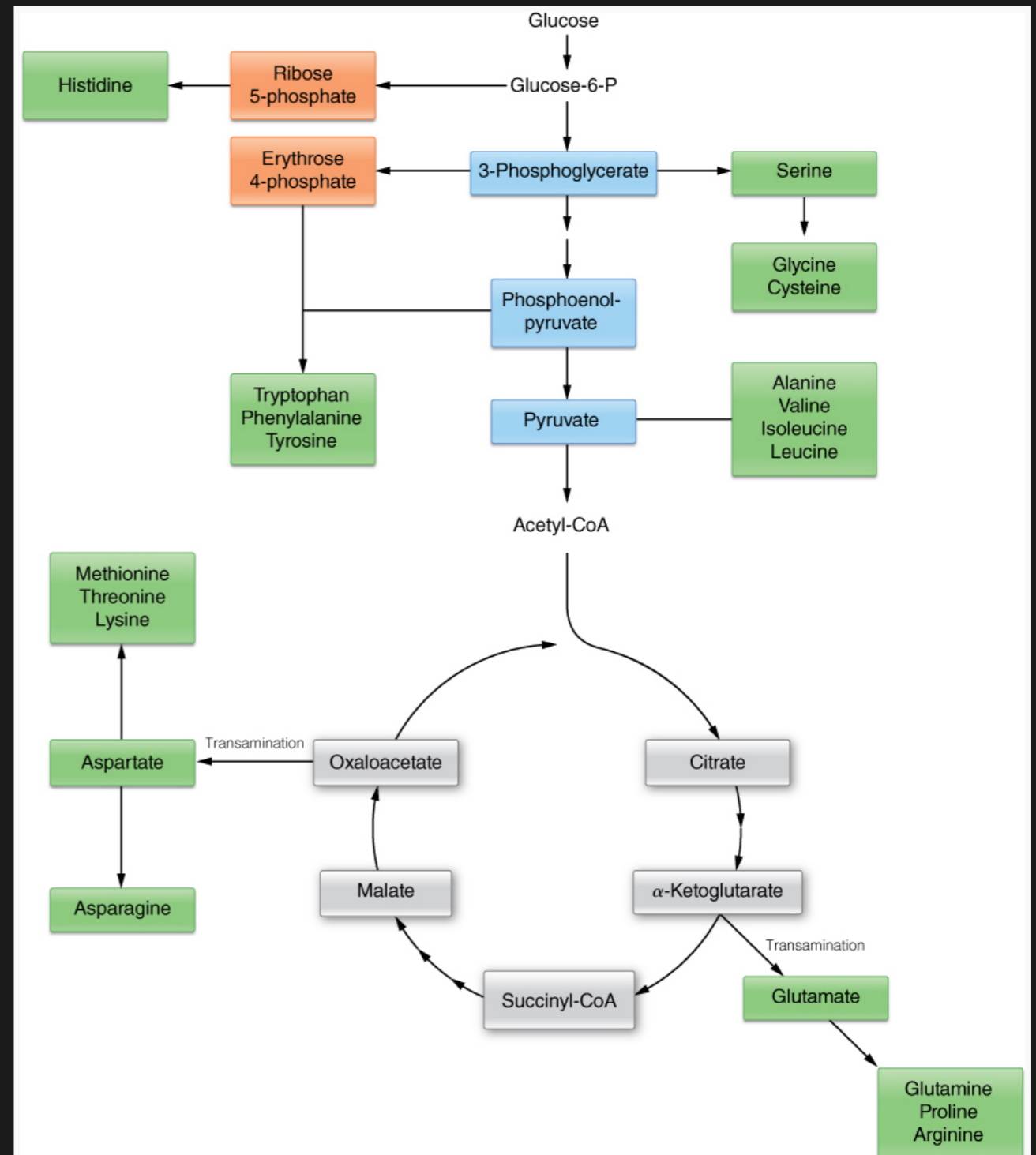
Essential

Arginine,* histidine, isoleucine, leucine, lysine, methionine,* phenylalanine, threonine, tryptophan, valine

Biosynthesis of non-essential amino acids

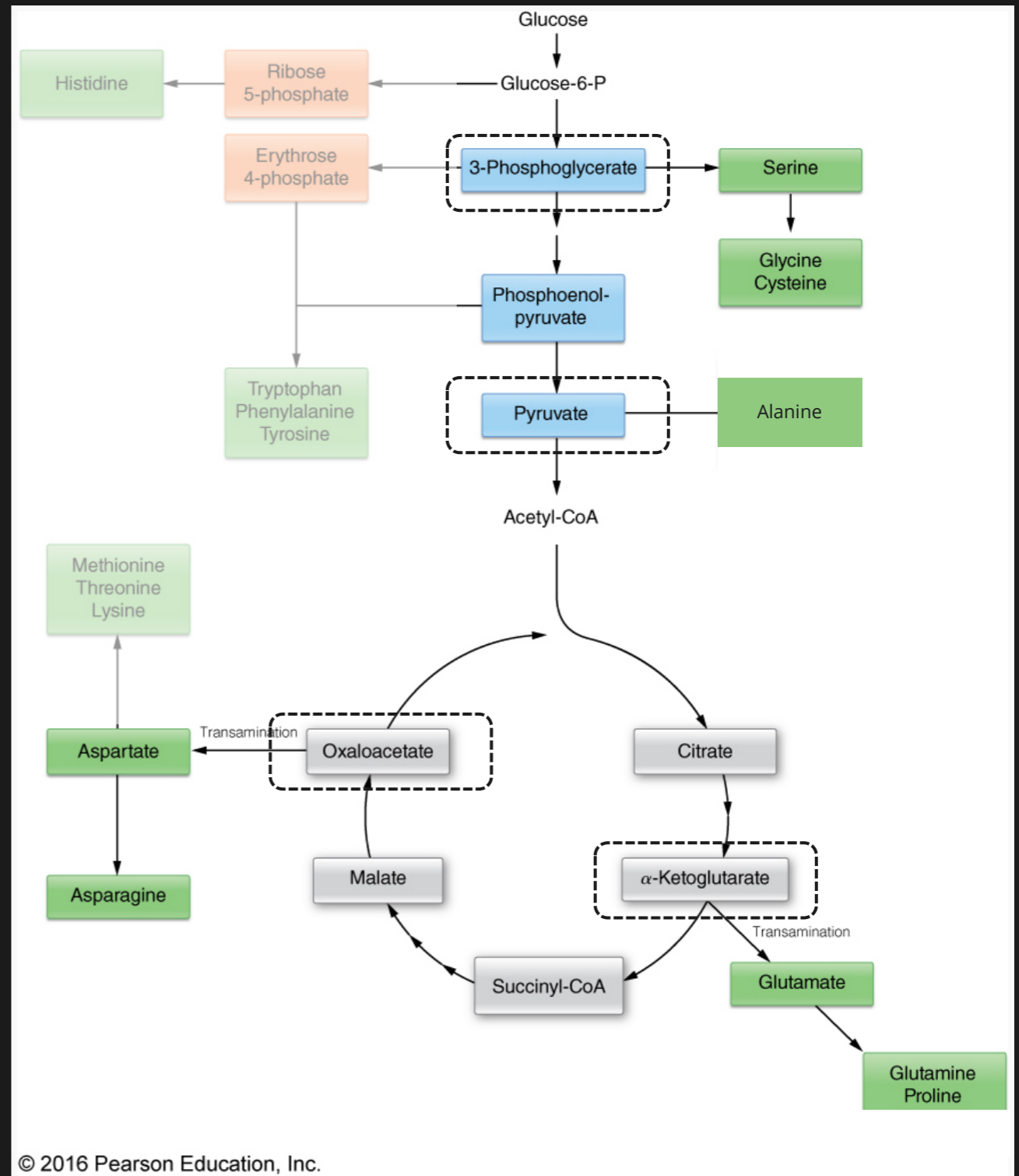
Non-essential amino acids biosynthesis

- All amino acids can be synthesized from intermediates in glycolysis, the pentose phosphate pathway or the citric acid cycle.
- This is true for most bacteria and plants



Non-essential amino acids biosynthesis

- Non-essential amino acids are synthesized from 4 common intermediates:
 - 3-phosphoglycerate (glycolysis)
 - Pyruvate (glycolysis)
 - α -ketoglutarate (TCA cycle)
 - Oxaloacetate (TCA cycle)



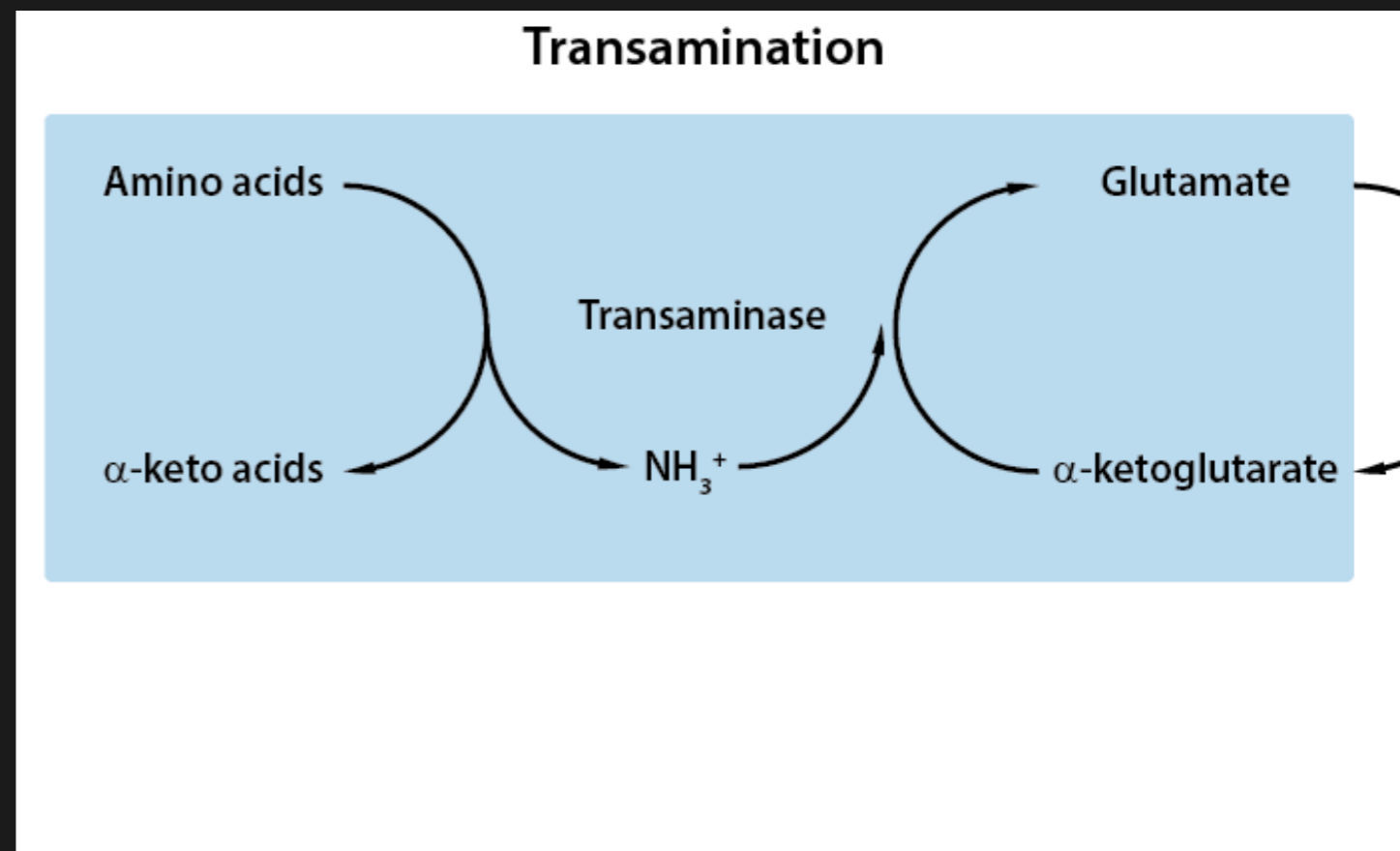
Non-essential amino acids biosynthesis

- Non-essential amino acids are synthesized from 4 common intermediates:

Intermediates	Non-essential amino acids
3-phosphoglycerate	Serine Glycine Cysteine
Pyruvate	Alanine
α -ketoglutarate	Glutamate Glutamine Proline Arginine*
Oxaloacetate	Aspartate Asparagine

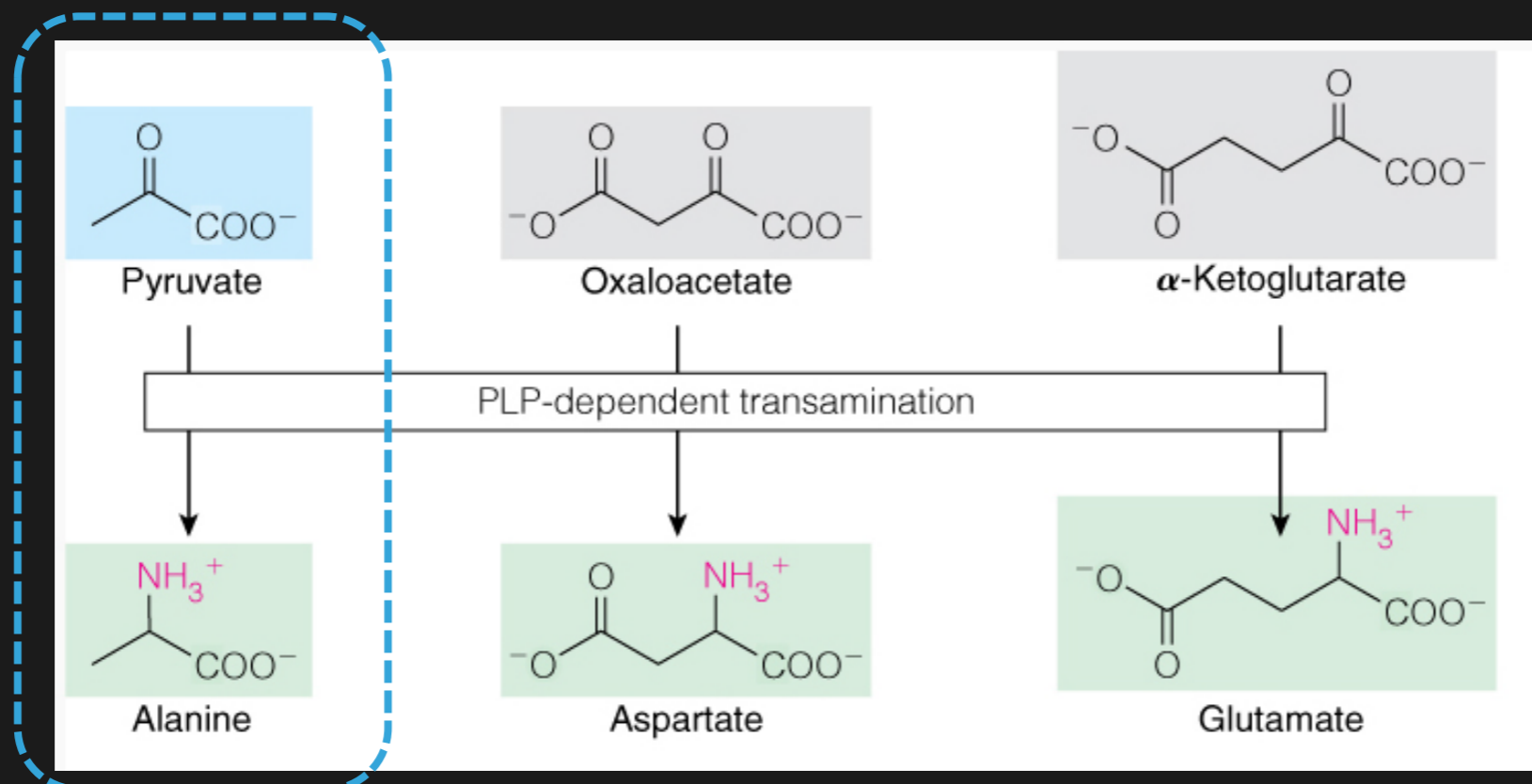
The 3 keto acids

- Three of these intermediates are keto acids that can be used in transamination reactions.
 - Pyruvate
 - α -ketoglutarate
 - Oxaloacetate
- Figure from lecture 14



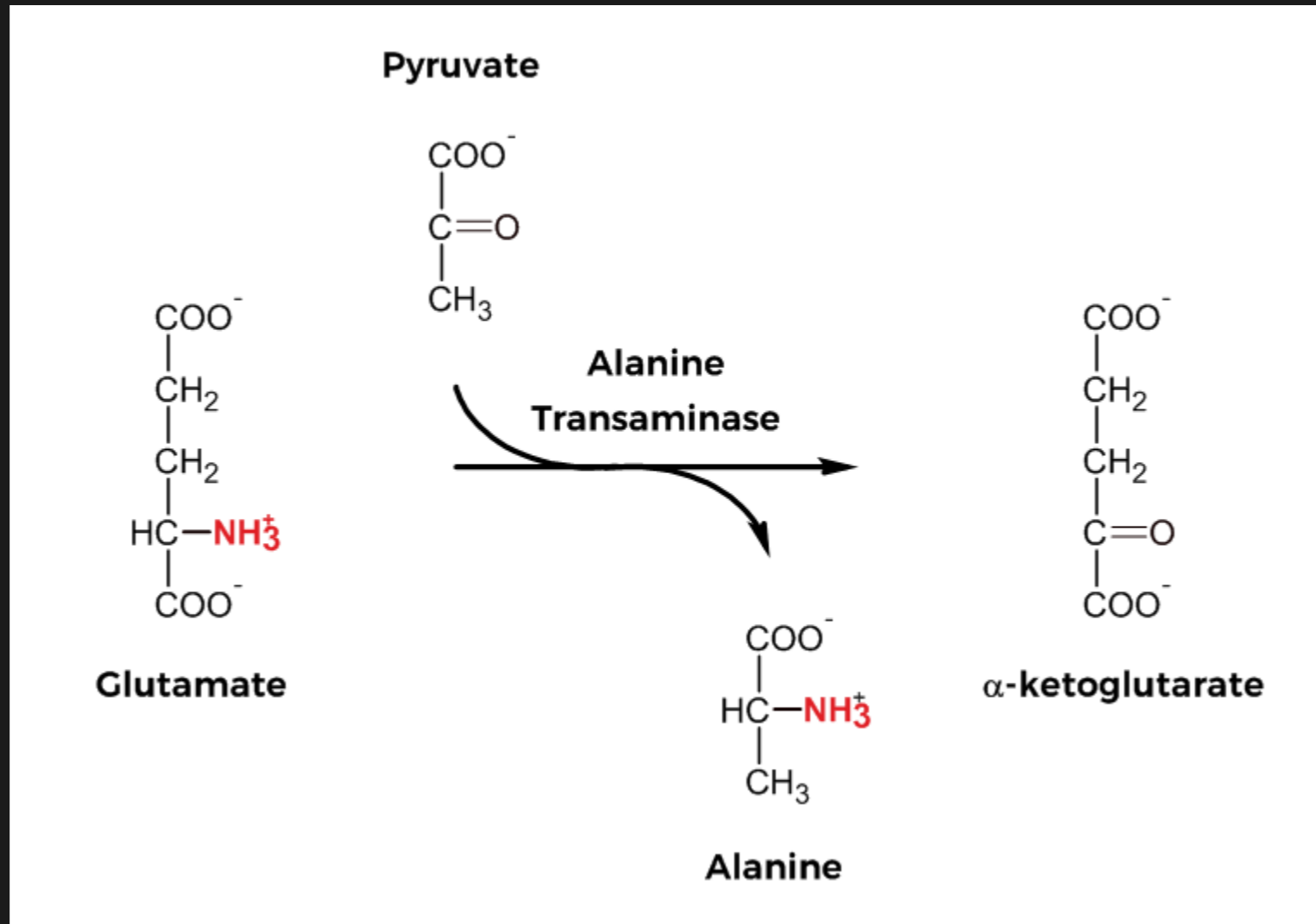
Transamination of the 3 keto acids intermediates

- A single transamination reaction can convert keto acids into amino acids.
 - Alanine transaminase (ALT)
 - Glucose alanine cycle
 - Aspartate transaminase (AST)



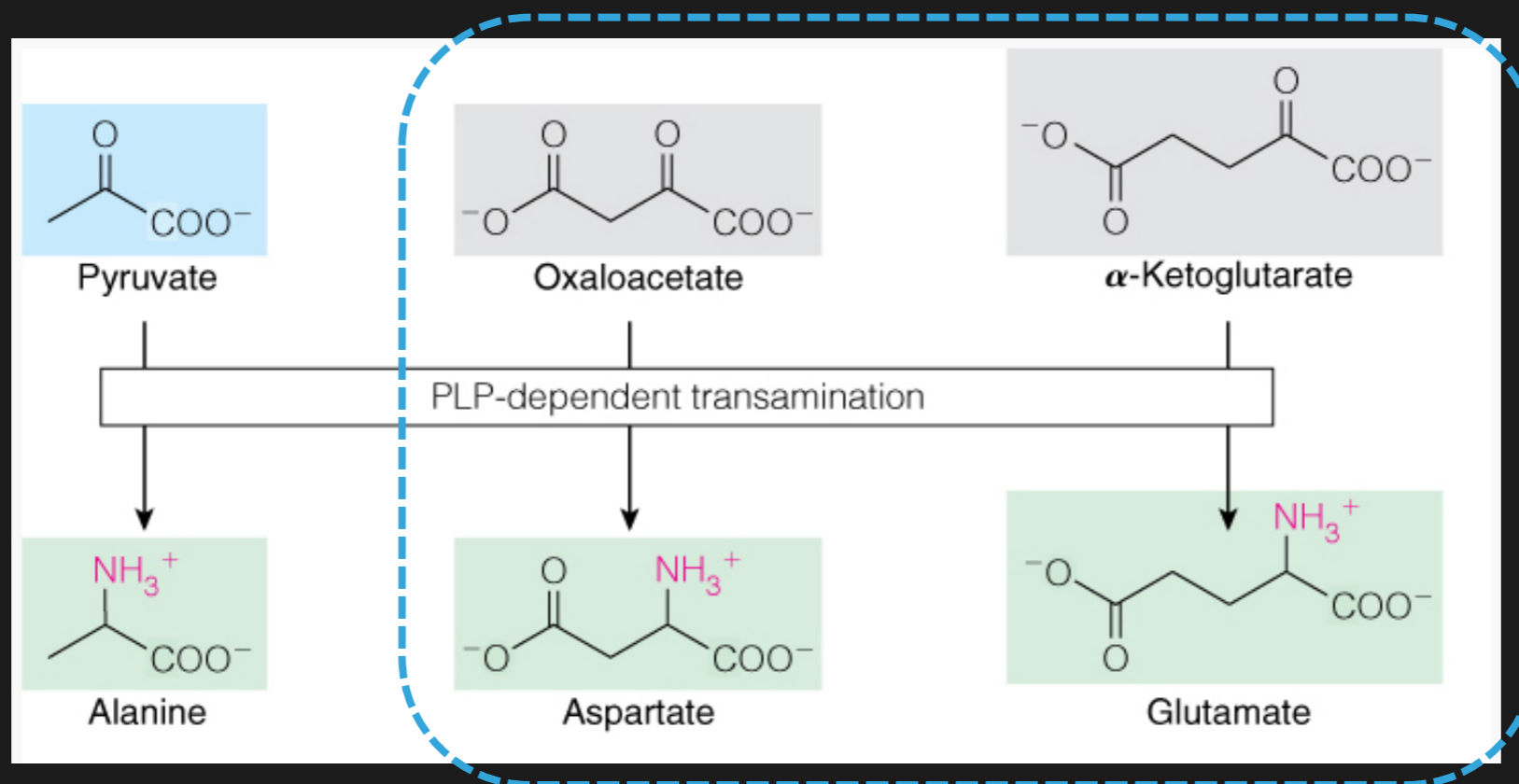
Transamination

Alanine



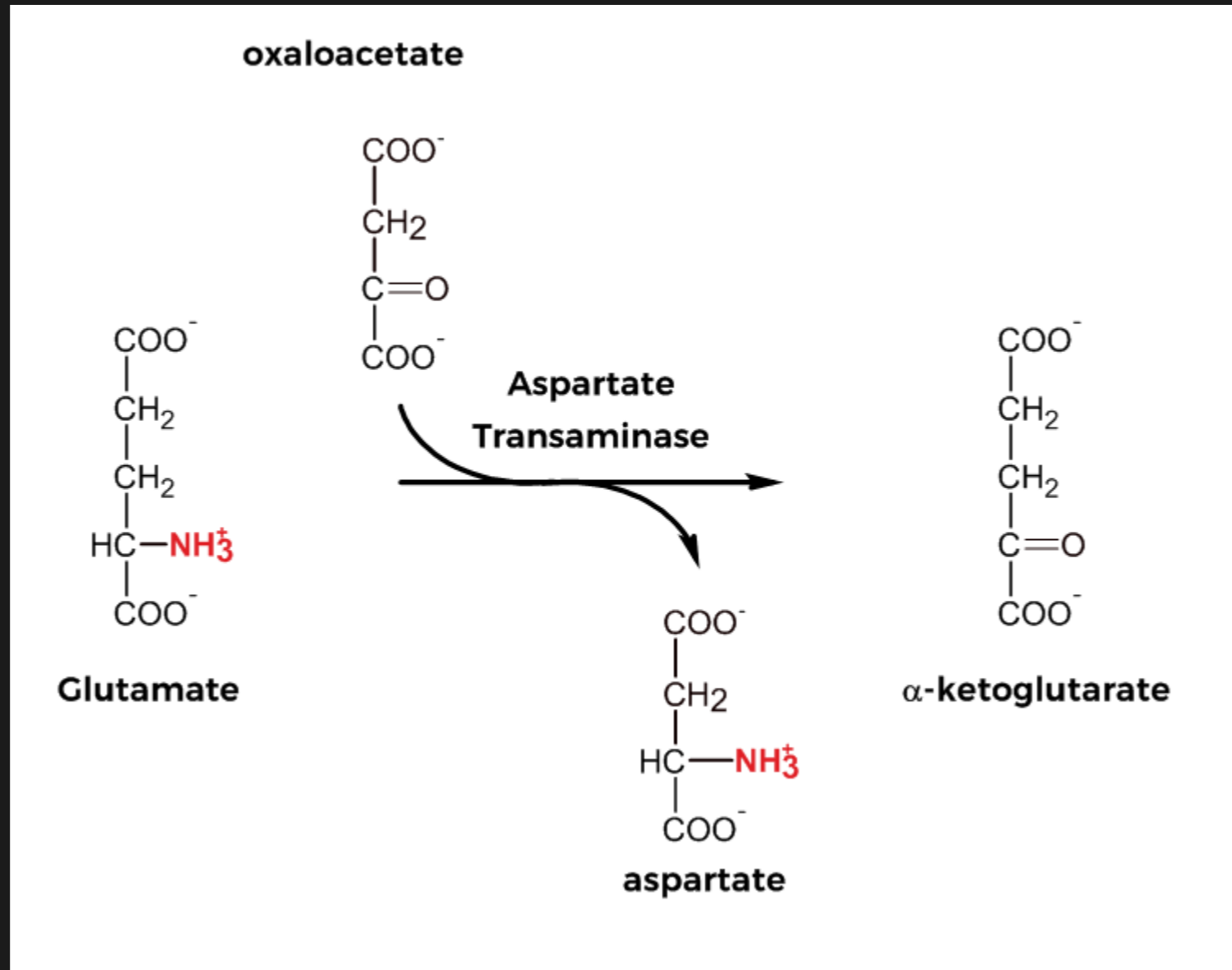
Transamination of the 3 keto acids intermediates

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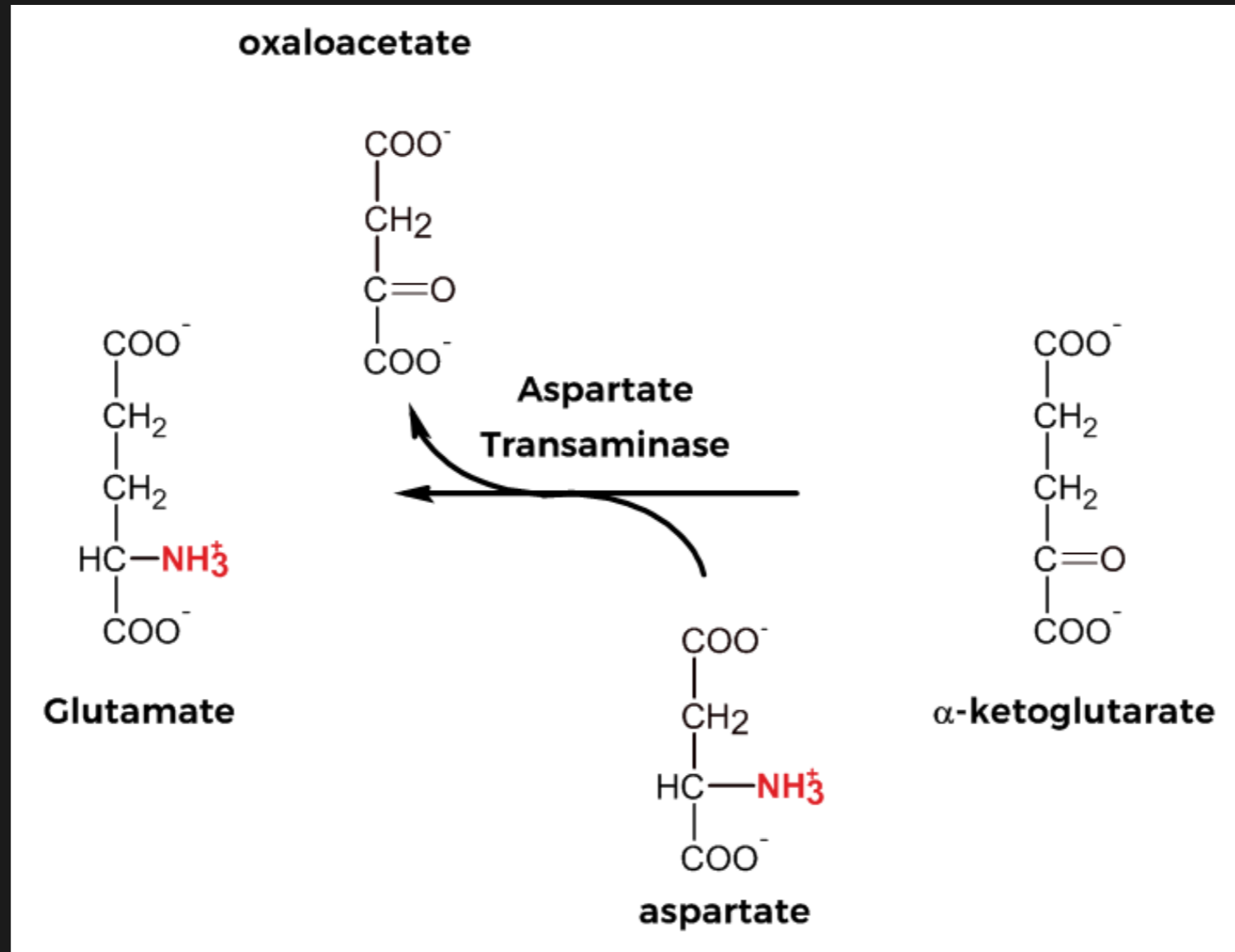
Transamination

Aspartate and glutamate

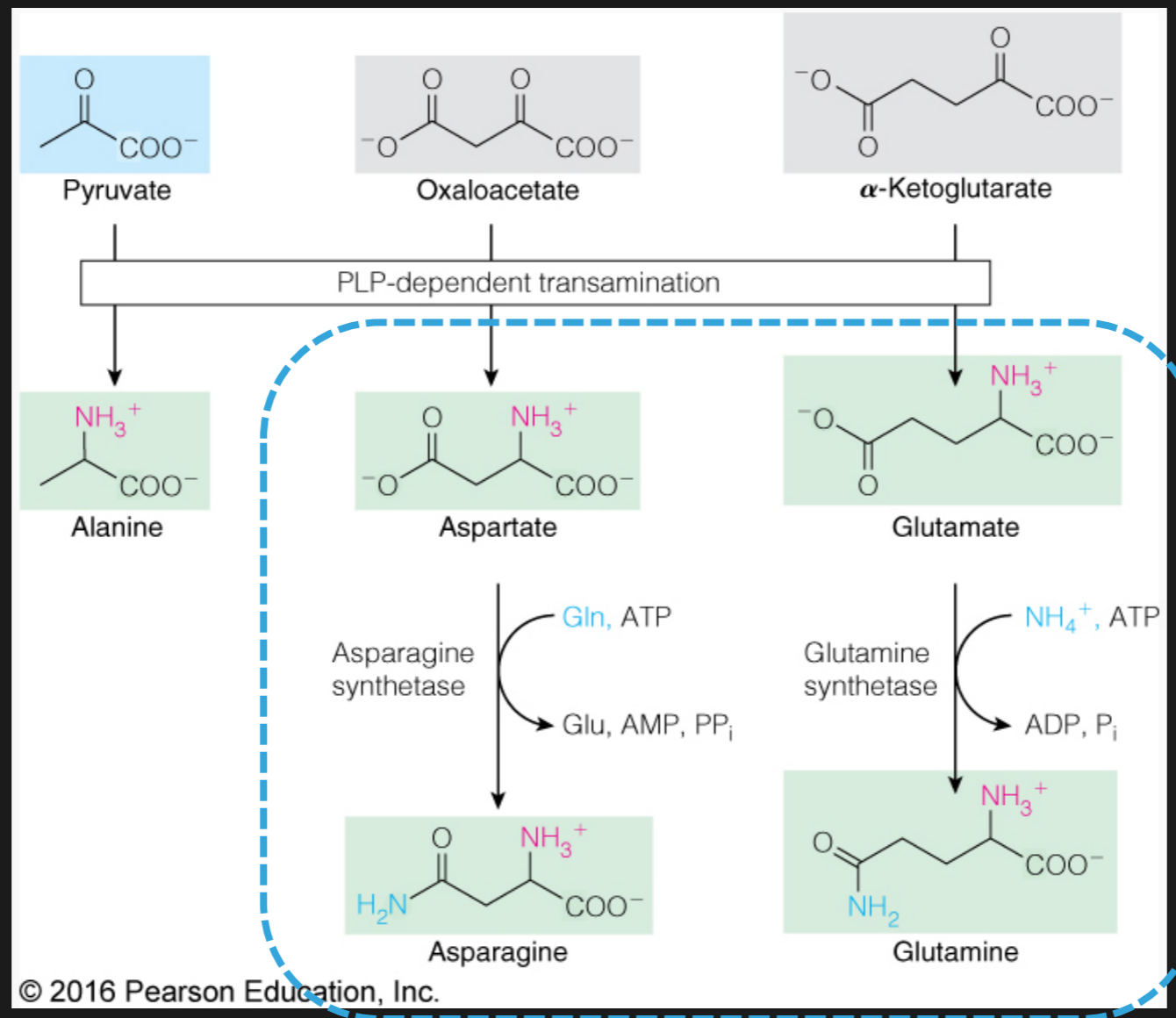


Transamination

Aspartate and glutamate

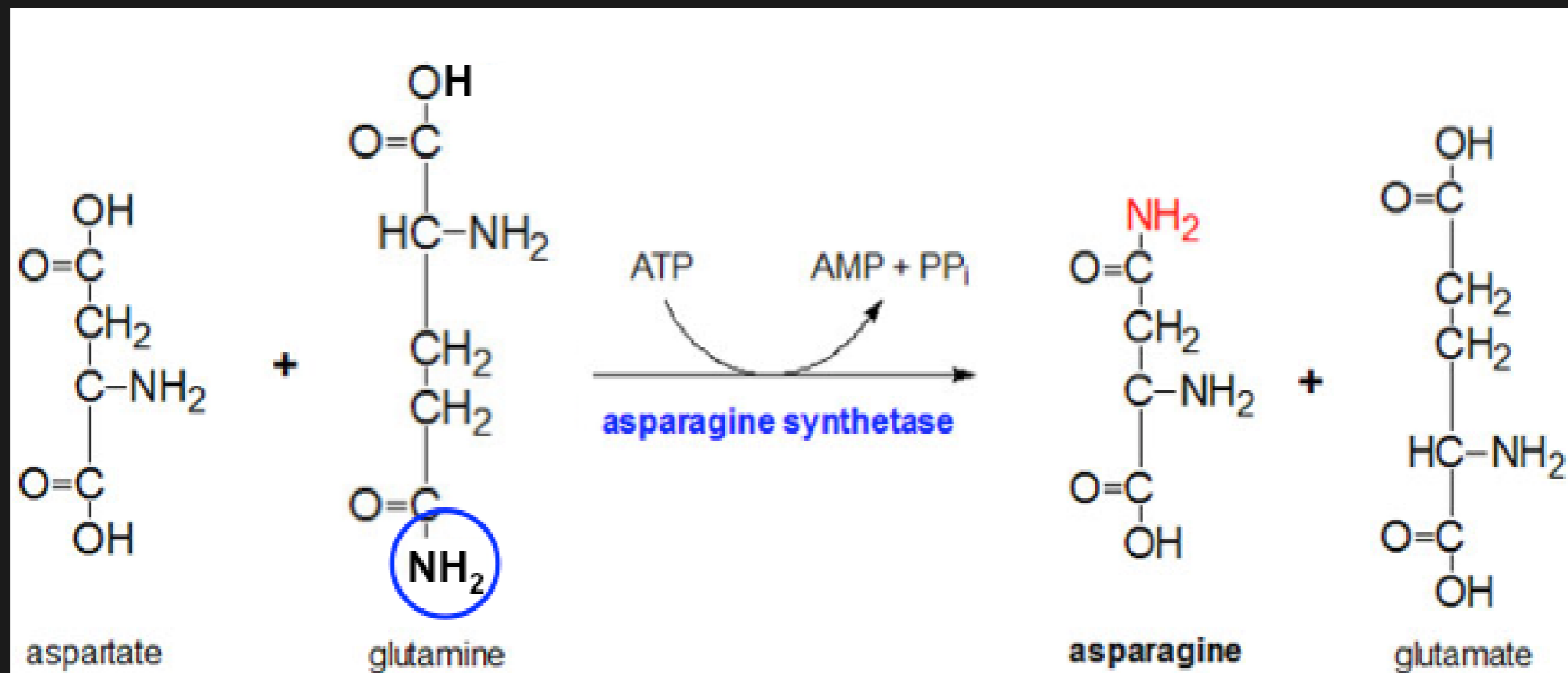


Amidation reactions using aspartate and glutamate as substrates



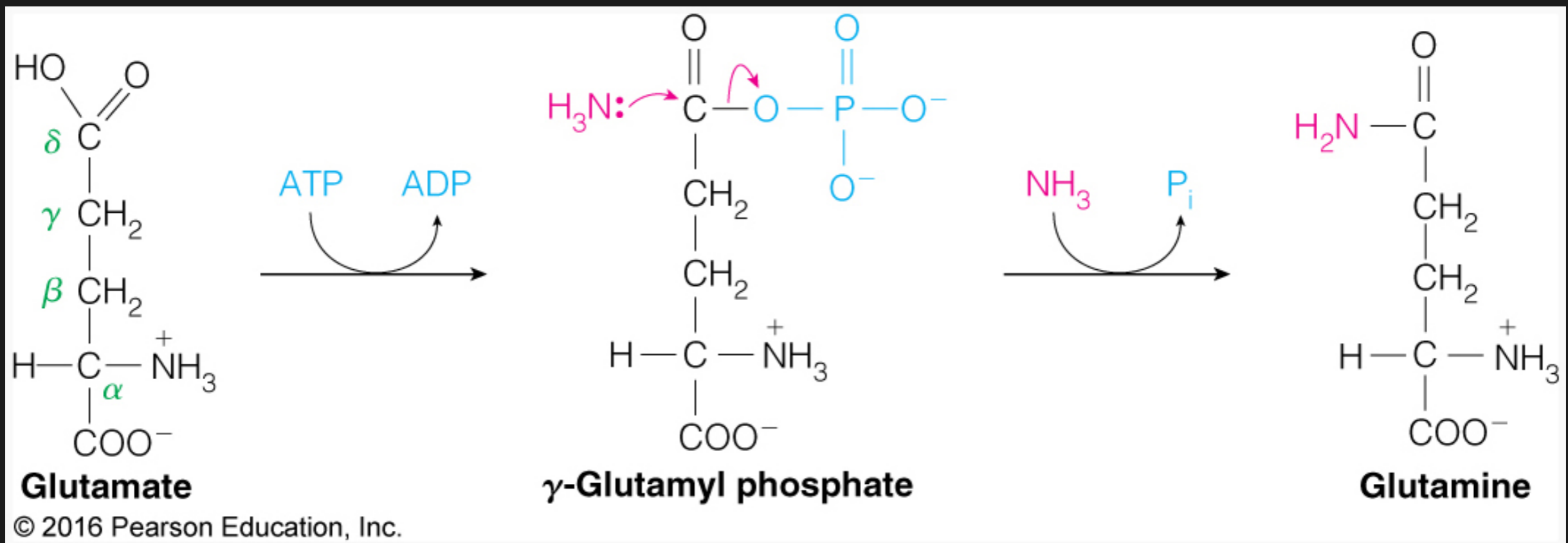
Asparagine synthesis

- Asparagine synthetase catalyzes amidation reaction of Aspartate to form Asparagine.



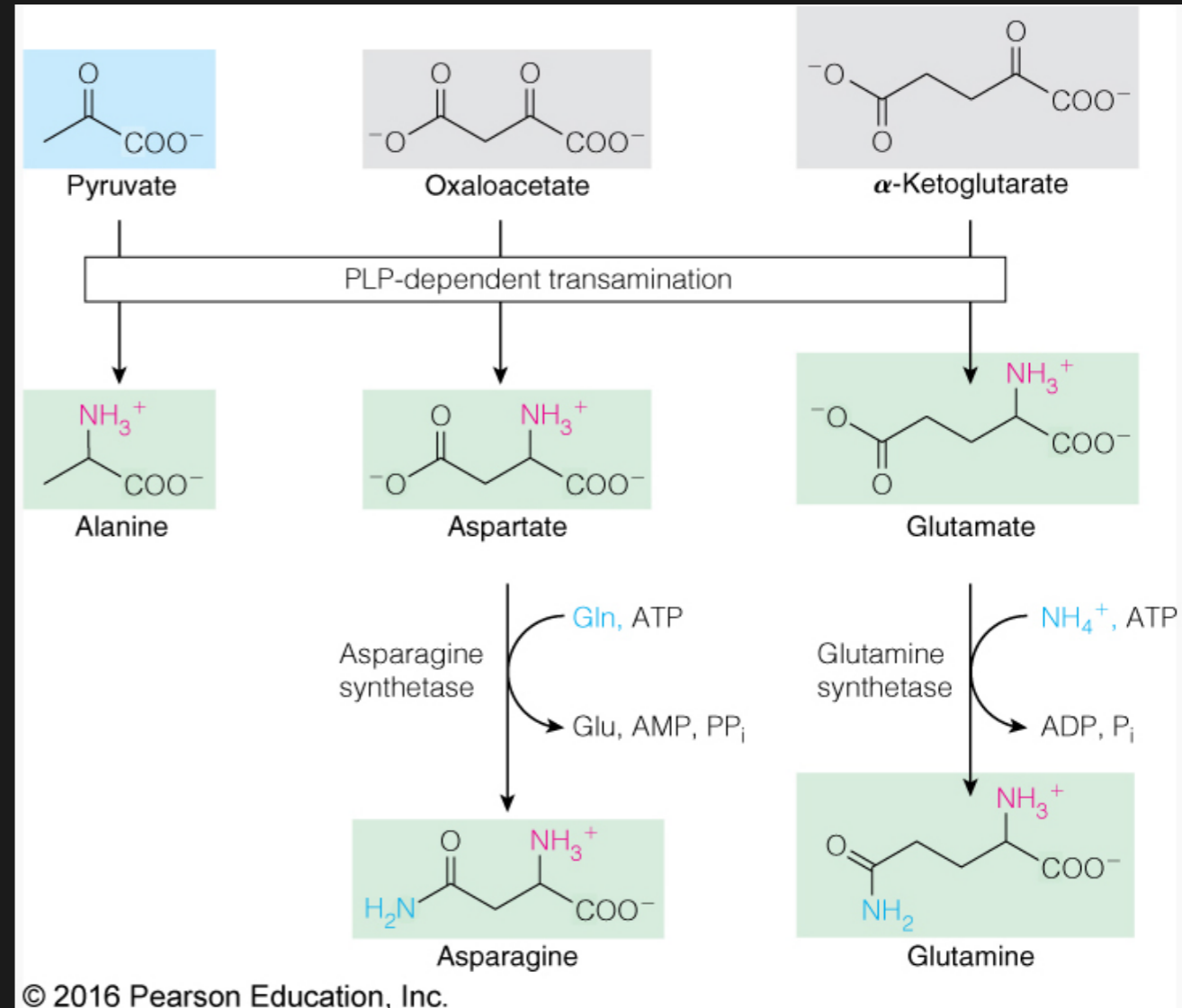
Glutamine synthesis

- Glutamine synthetase catalyzes amidation reaction of glutamate to form glutamine.



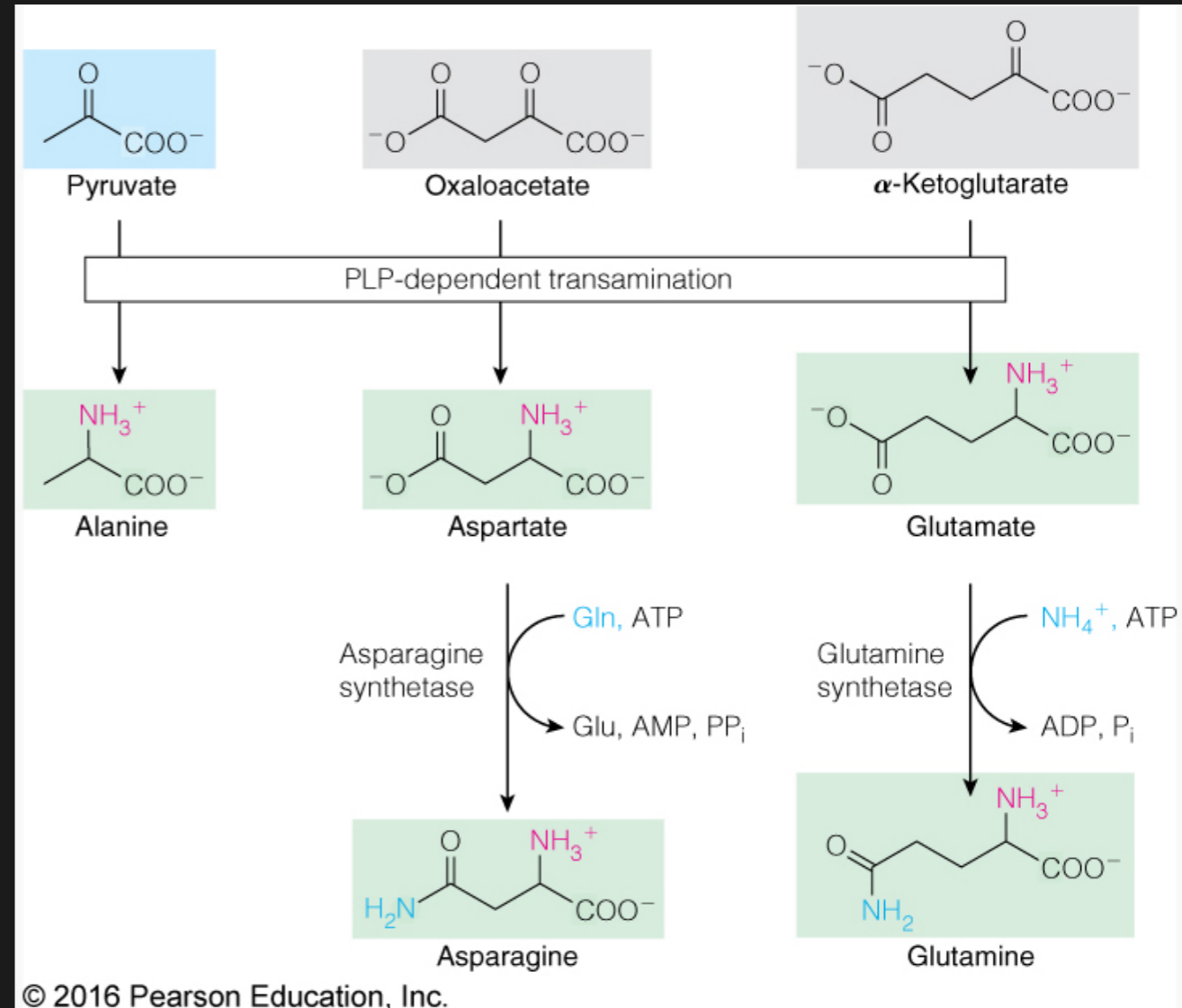
Summary: Keto acids intermediates

- Transamination reactions
 - Alanine, aspartate and glutamate synthesis



Summary: Keto acids intermediates

- Transamination reactions
 - Alanine, aspartate and glutamate synthesis
- Transamination and amidation reactions
 - Asparagine and glutamine synthesis



Non-essential amino acids biosynthesis

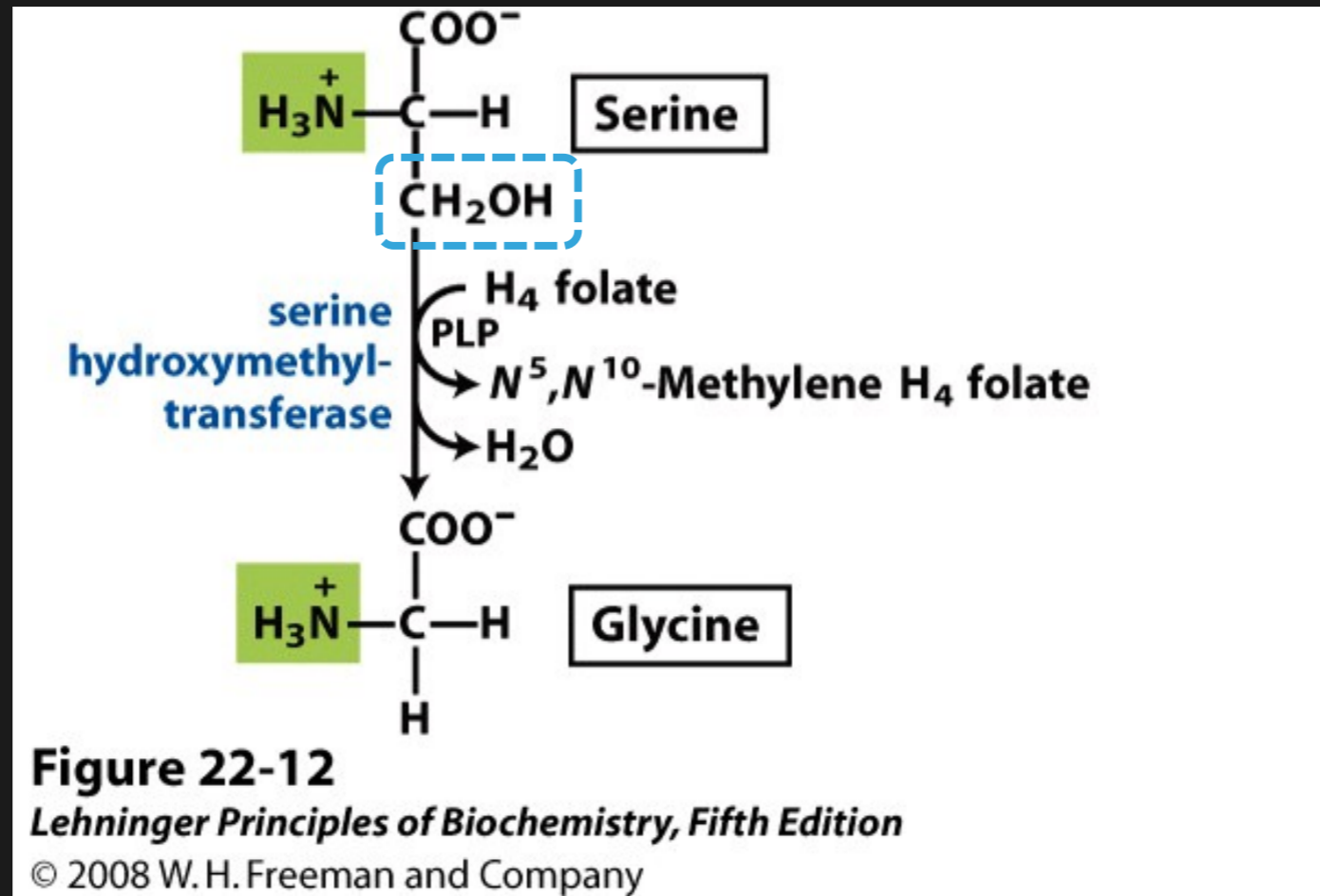
- Non-essential amino acids are synthesized from 4 common intermediates:

Intermediates	Non-essential amino acids
3-phosphoglycerate	Serine Glycine Cysteine
Pyruvate	Alanine
α -ketoglutarate	Glutamate Glutamine Proline Arginine*
Oxaloacetate	Aspartate Asparagine

AA biosynthesis using 3-phosphoglycerate

Glycine

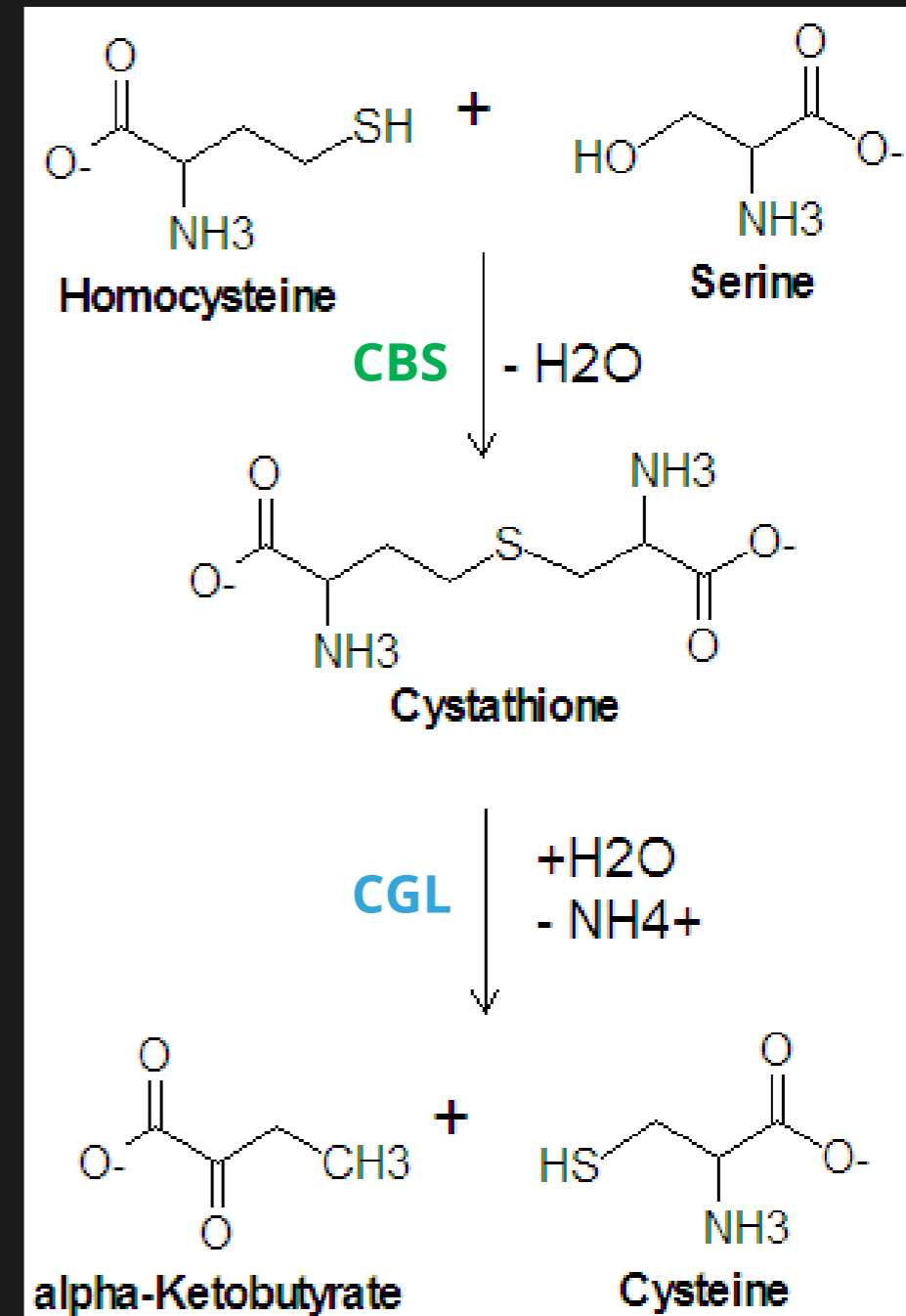
- Glycine is produced from serine.
 - An hydroxymethyl is removed from serine and transferred to H₄ folate (tetrahydrofolate, THF).



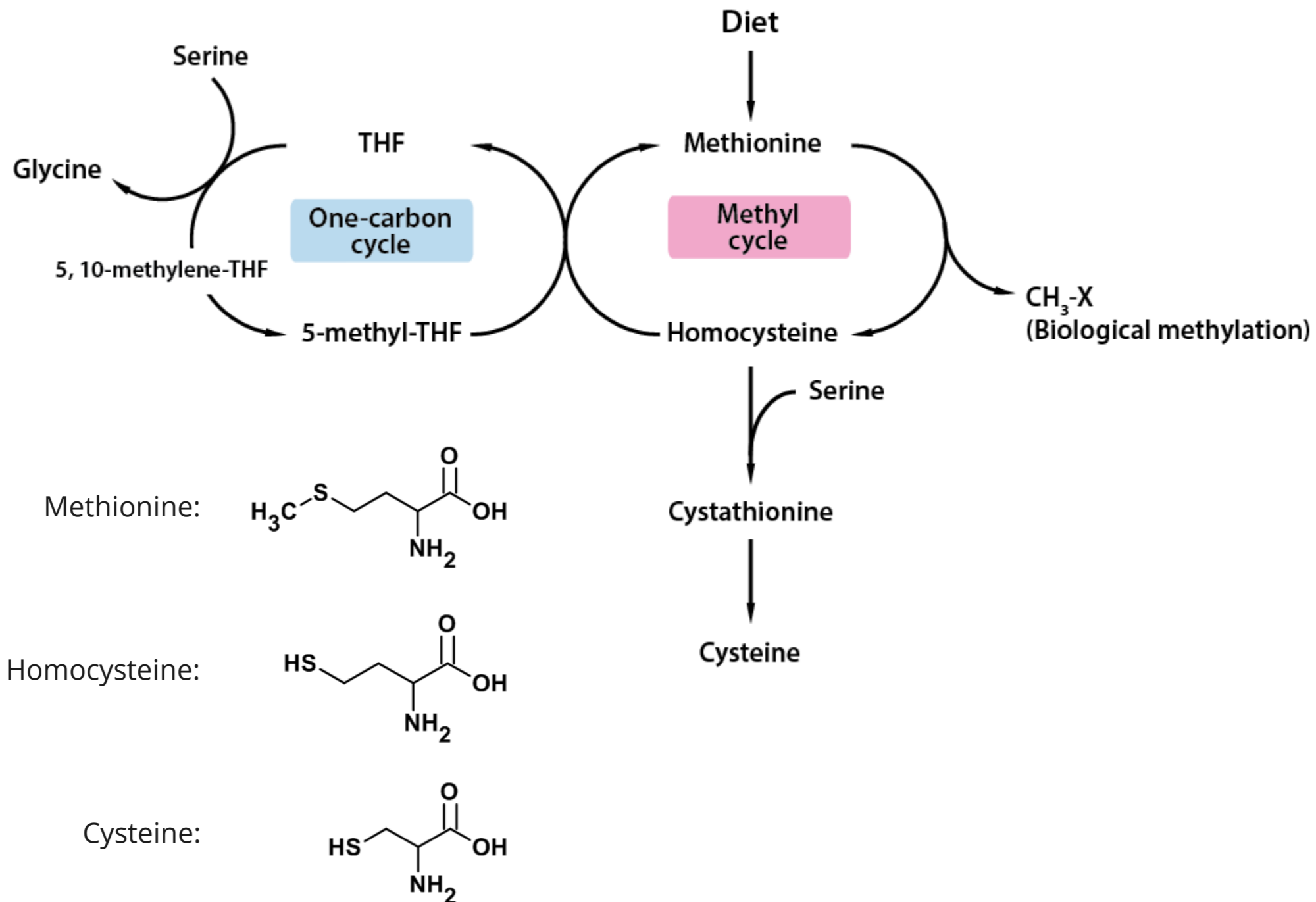
AA biosynthesis using 3-phosphoglycerate

Cysteine

- Cysteine synthesis from homocysteine and serine via cystathione intermediate
 - Cystathione β -synthase (CBS)
 - Cystathione γ -lyase (CGL)



Cysteine: A semi-essential AA (animals)?



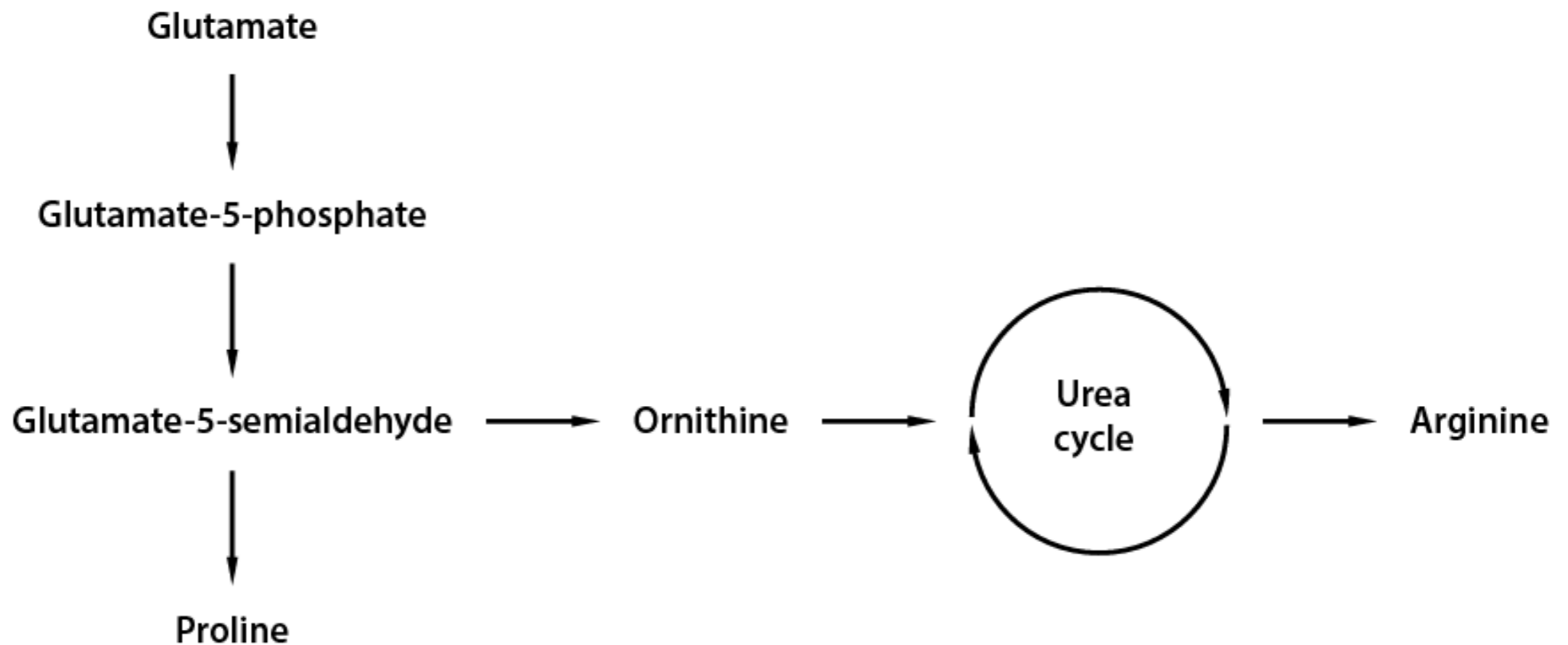
Non-essential amino acids biosynthesis

- Non-essential amino acids are synthesized from 4 common intermediates:

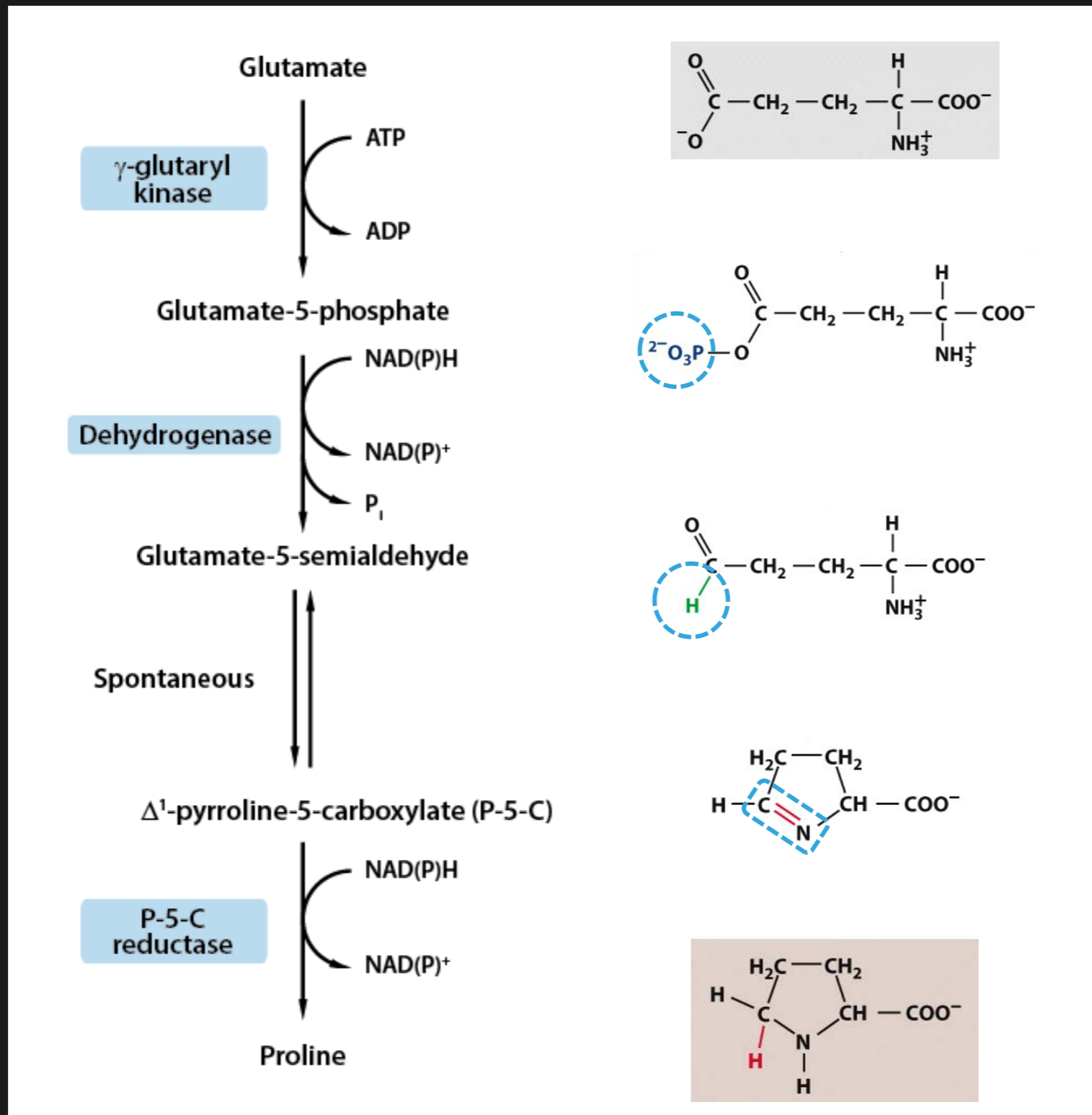
Intermediates	Non-essential amino acids
3-phosphoglycerate	Serine Glycine Cysteine
Pyruvate	Alanine
α -ketoglutarate	Glutamate Glutamine Proline Arginine*
Oxaloacetate	Aspartate Asparagine

Proline and arginine biosynthesis

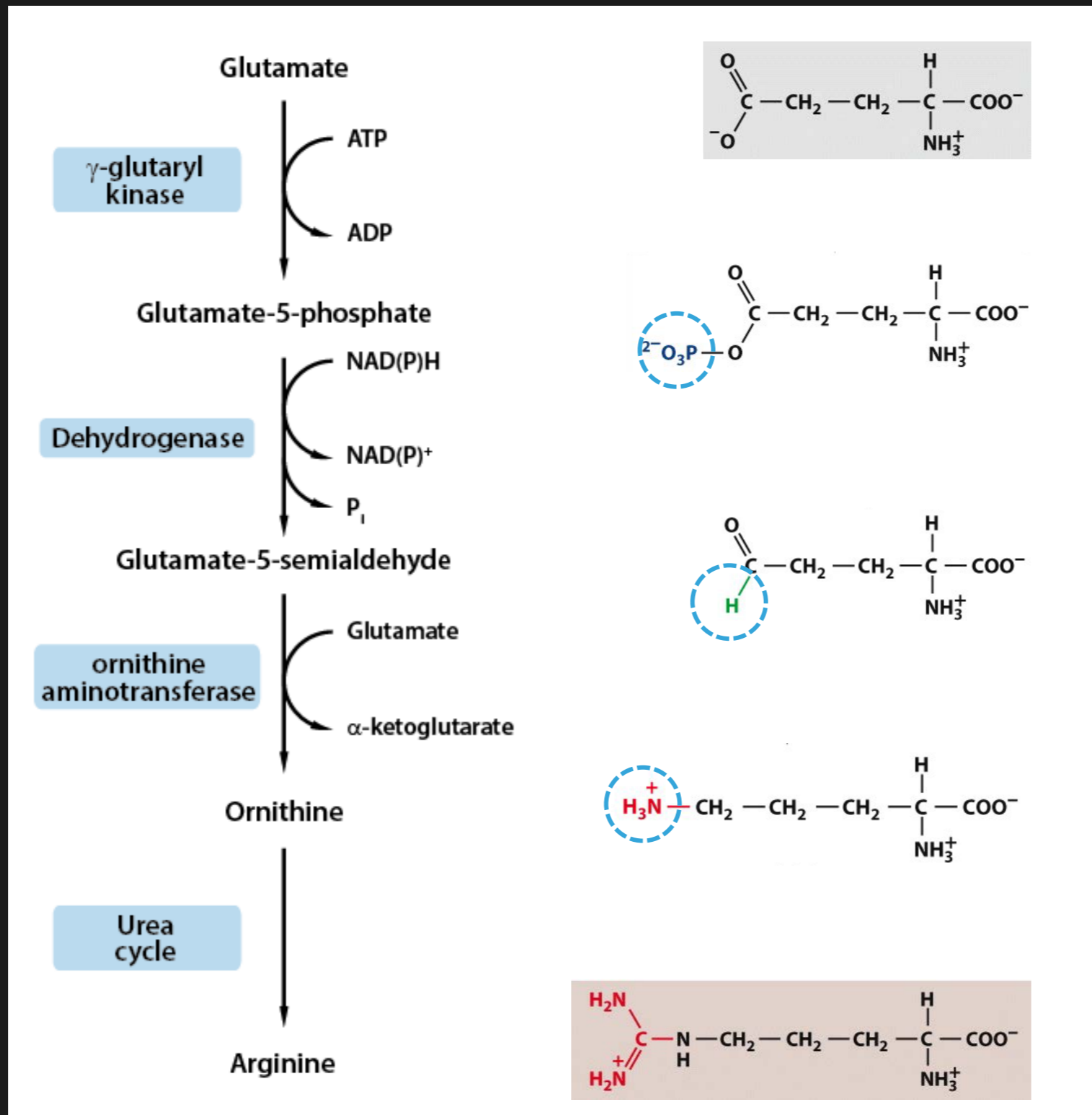
- Synthesized from glutamate



Proline biosynthesis



Arginine biosynthesis



Summary: Amino acid synthesis

- Transamination and amidation are the major biochemical reactions involved in amino acid synthesis
- Precursors for nonessential amino acids are all derived from glycolysis and TCA cycles
- Importance of glutamate in amino acid metabolism

Reading materials

- Biochemistry: Concepts and connections, Dean R. Appling, Spencer J. Anthony-Cahill and Christopher K. Mathews, Pearson Education, 2014
 - Chapter 18
 - Section 18.1, 18.2 and 18.7