AL-FARABI KAZAKH NATIONAL UNIVERSITY
FACULTY OF BIOLOGY AND BIOTECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY

Lecture 8

Catabolism of the Carbon Skeletons of Amino Acids

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Lecture Plan

1.Introduction: AminoAcid Catabolism Overview
2.The Fate of the Amino Group:Transamination and Oxidative Deamination
3.The Urea Cycle (Brief Overview)
4.The Fate of the Carbon Skeleton
5.Glucogenic vs. Ketogenic Amino Acids
6.Entry Points into the Citric Acid Cycle
7.Pyruvate-Generating Amino Acids
8.Acetyl-CoA and Acetoacetyl-CoA Generating Amino Acids 9.Alpha-Ketoglutarate and Succinyl-CoA Generating Amino Acids 10.Fumarate and Oxaloacetate Generating Amino Acids 11.Metabolic Disorders of Amino Acid Catabolism

CONTENTS

Learning objectives

By the end of this lecture,students should beable to:

1. Describe the generaltwo-step process of amino acid catabolism (removal of the amino group and breakdown of the carbon skeleton).
2. Explain the processes of transamination and oxidative deamination.
3. Define glucogenic and ketogenic amino acids and give examples of each.
4. Identify the seven major metabolic intermediates that amino acid carbon skeletons enter the Citric Acid Cycle as.
5. Describe the enzymatic reactions that convert specific amino acids into pyruvate, acetyl-CoA, alpha-ketoglutarate, succinyl-CoA, fumarate, and oxaloacetate.
6. Explain why some amino acids are strictly ketogenic while others are both glucogenic and ketogenic.
7. Relate defects in amino acid catabolism to specific metabolic disorders (e.g., Phenylketonuria, Maple Syrup Urine Disease).

What is Amino Acid Catabolism?

Amino acid catabolism is theprocessbywhichcellsbreakdown amino acids to generate energy or synthesize other molecules.Why do cells catabolize amino acids?

· Dietary excess: When protein intake exceeds the body's need for protein synthesis.

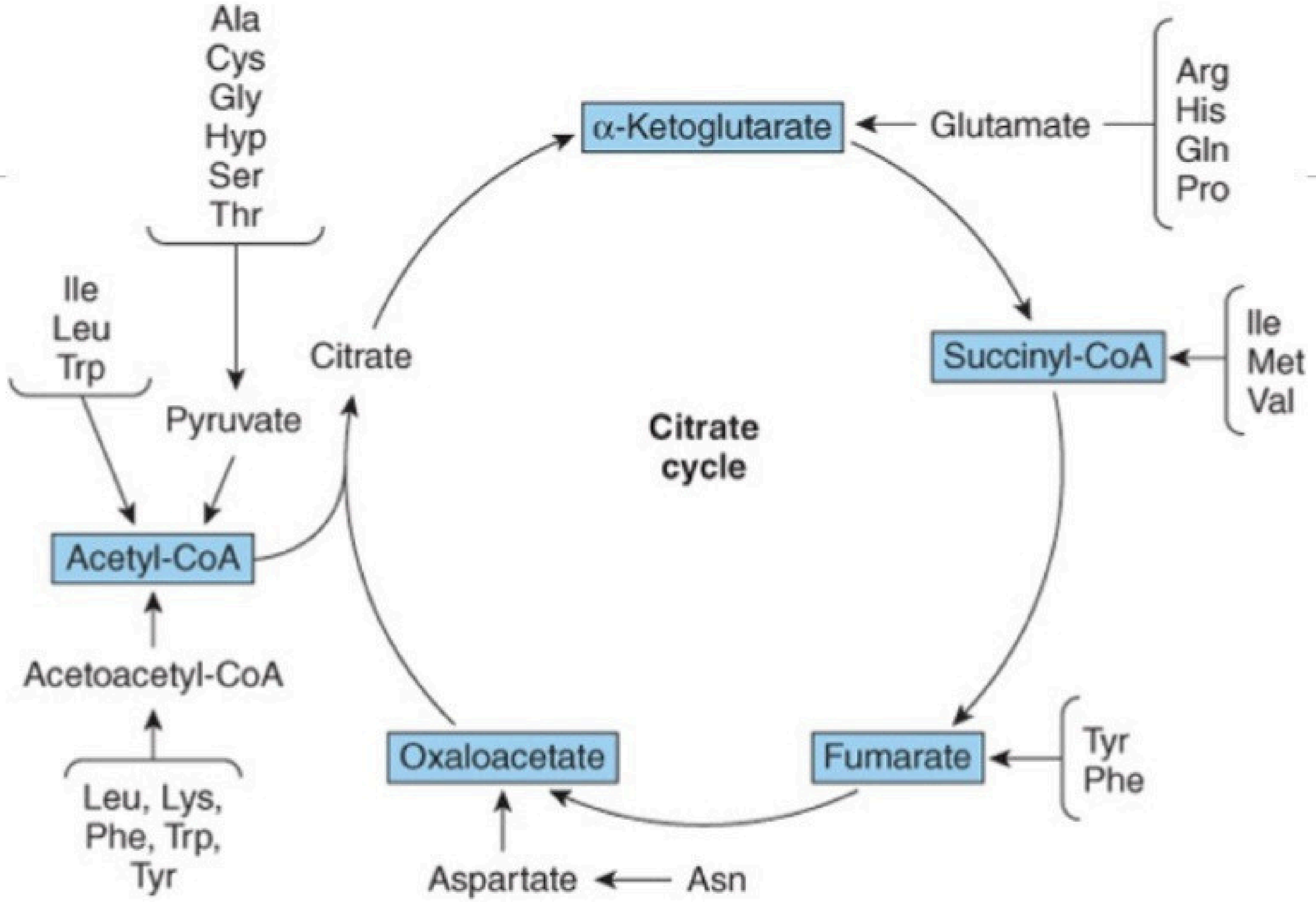
· Starvation/Starvation response: During fasting, muscle protein is broken down to provide energy.

· Cellular turnover: Normal degradation of damaged or unneeded cellular proteins.

The central problem: Unlike carbohydrates and fats, which contain only carbon, hydrogen, and oxygen, amino acids also contain nitrogen. Therefore, the catabolism of amino acids requires two distinct phases:
1. Removal of the amino group ($-NH_2$): The nitrogen must be safely removed and eventually excreted.
2. Breakdown of the carbon skeleton: The remaining carbon backbone is oxidized to produce ATP.

Major Areas of Amino Acid Catabolism

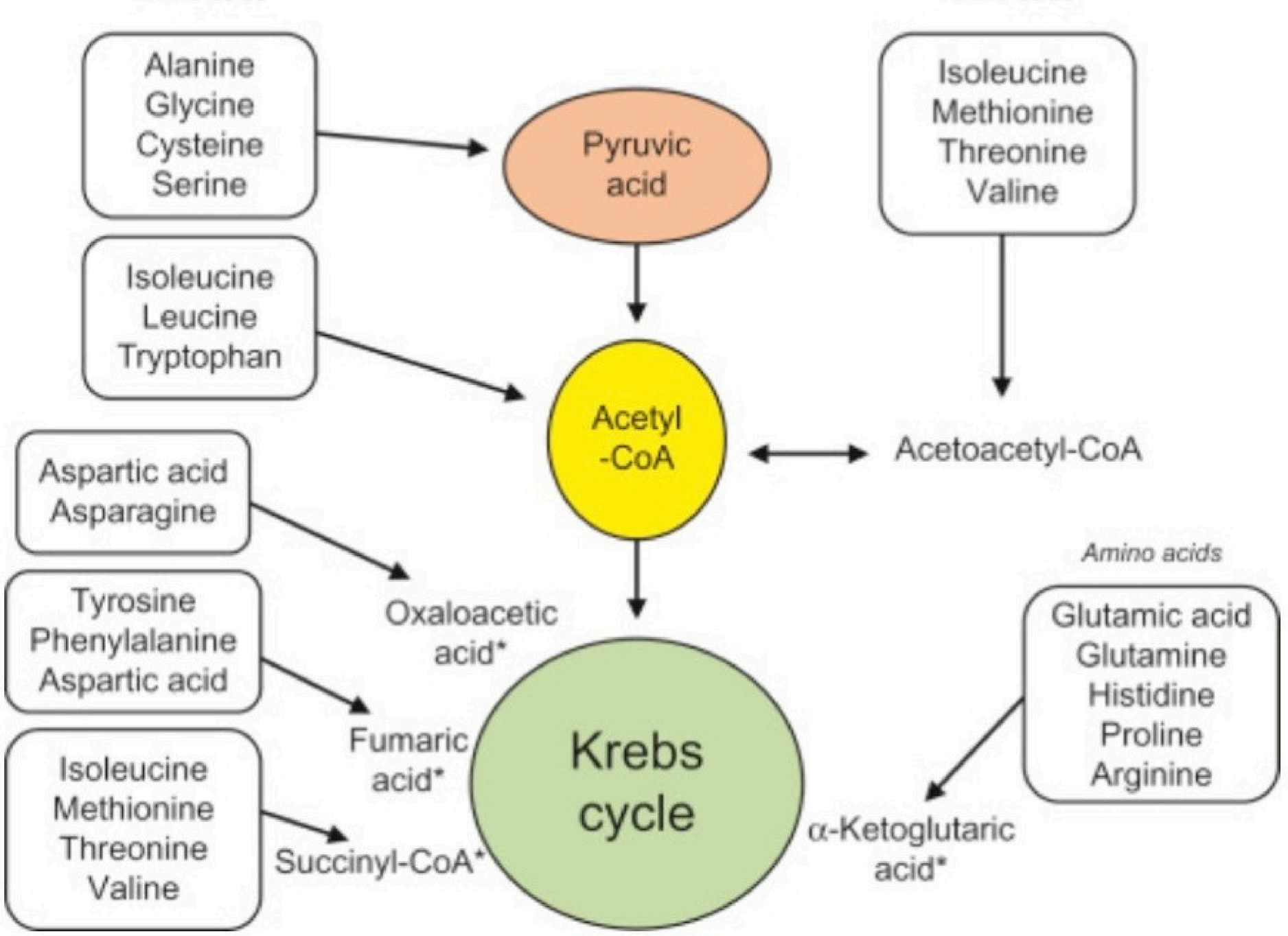
Deamination	**The removal of the amino group from amino acids to form ammonia and a corresponding alpha-keto acid.**
Urea Cycle	The conversion of toxic ammonia into non-toxic urea in the liver for excretion.
Carbon Skeleton Oxidation	The conversion of the remaining carbon backbone into intermediates of the Citric Acid Cycle.
Energy Utilization	ATP production via oxidative phosphorylation when carbon skeletons enter the mitochondria.


Ala
Cys
Gly
Hyp
Ser
Thr
Ile
Leu
Trp
Pyruvate
Citrate
α-Ketoglutarate
Glutamate
Arg
His
Gln
Pro
Succinyl-CoA
Ile
Met
Val
Citrate cycle
Acetyl-CoA
Acetoacetyl-CoA
Leu, Lys,
Phe, Trp,
Tyr
Oxaloacetate
Aspartate
Asn
Fumarate
Tyr
Phe

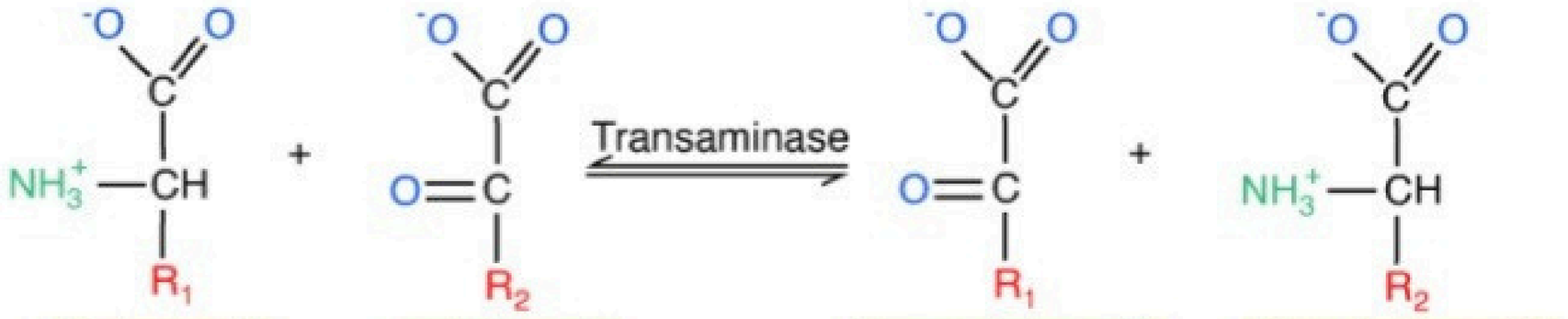
The Fate of the Amino Group

1. Transamination:· The amino group is transferred from an amino acid to an alpha-keto acid (usually alpha-ketoglutarate).· Catalyzed by aminotransferases (transaminases).· Requires Pyridoxal Phosphate (PLP) derived from Vitamin B6.· Result: The original amino acid becomes an alpha-keto acid, and alpha-ketoglutarate becomes glutamate.

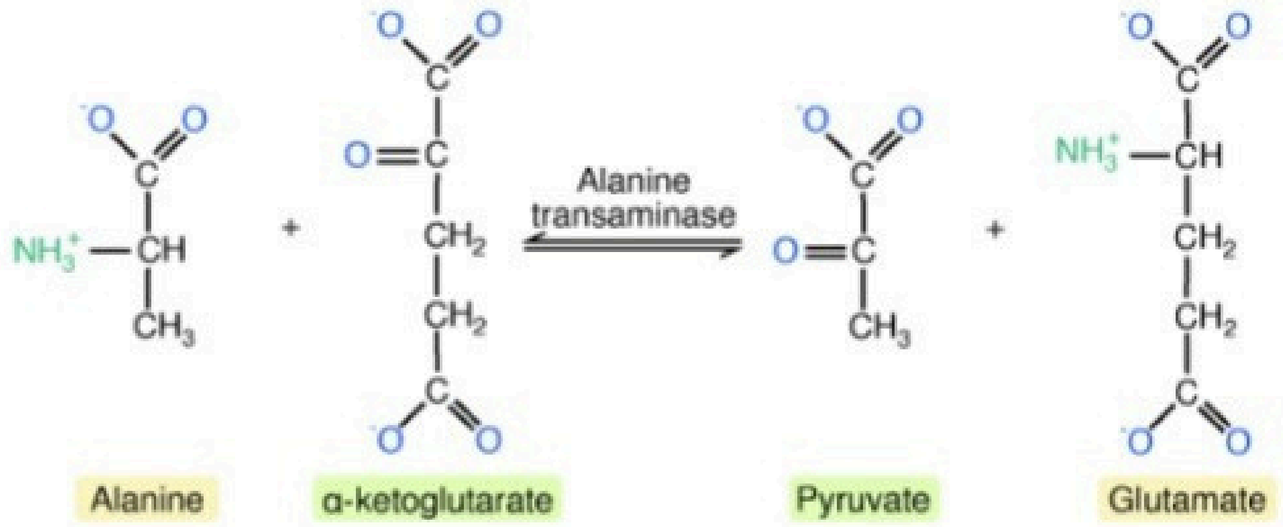
2. Oxidative Deamination:· Glutamate is transported into the mitochondria and undergoes oxidative deamination.· Catalyzed by glutamate dehydrogenase.· Result: Glutamate is converted back to alpha-ketoglutarate, and free ammonia (NH_4^+) is released.


Alanine
Glycine
Cysteine
Serine
Pyruvic acid
Isoleucine
Methionine
Threonine
Valine
Isoleucine
Leucine
Tryptophan
Acetyl -CoA
Acetoacetyl-CoA
Aspartic acid
Asparagine
Oxaloacetic acid*
Amino acids
Tyrosine
Phenylalanine
Aspartic acid
Fumaric acid*
Glutamic acid
Glutamine
Histidine
Proline
Arginine
Krebs cycle
Isoleucine
Methionine
Threonine
Valine
Succinyl-CoA*
α-Ketoglutaric acid*

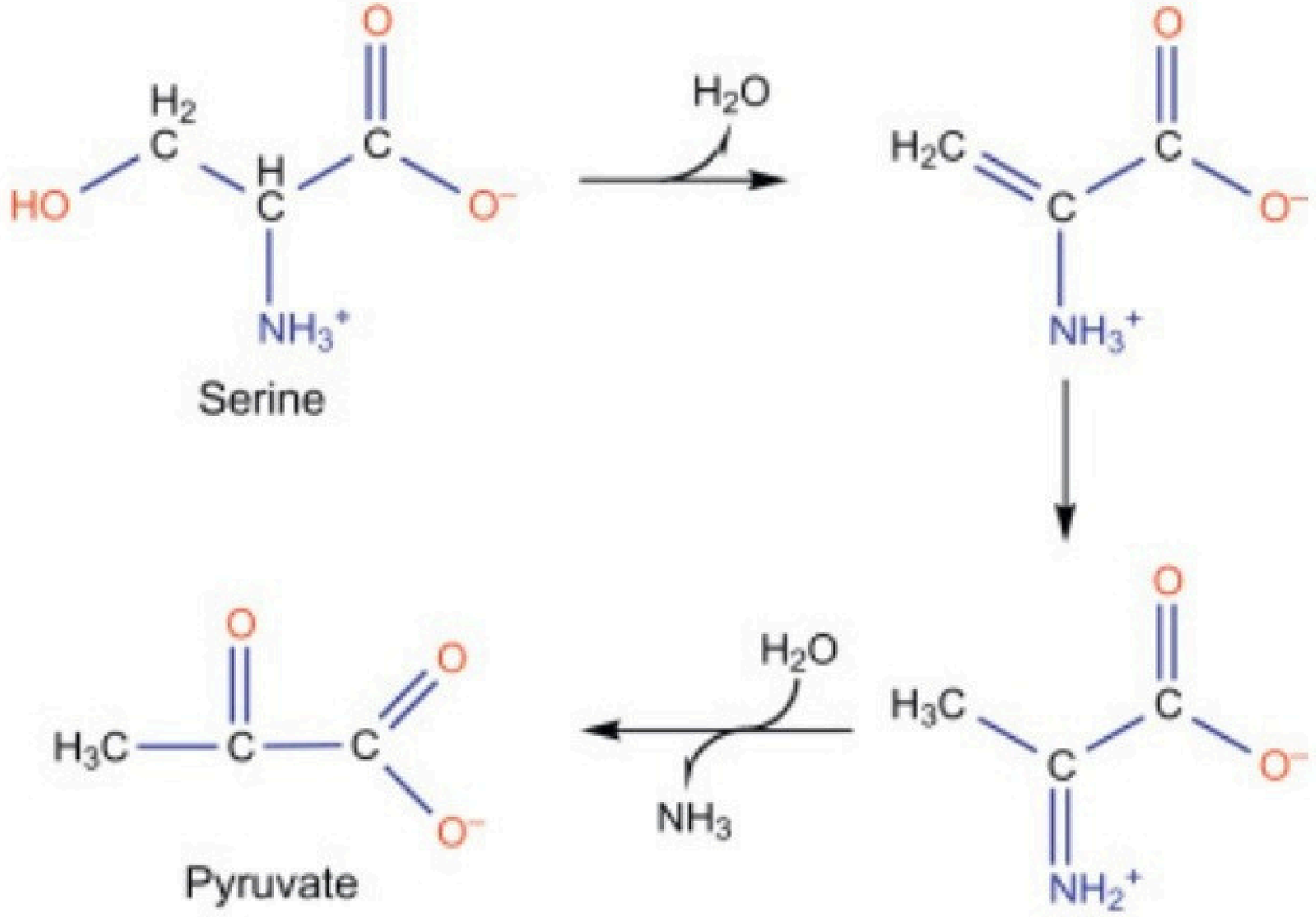
Transamination Reaction



Example



OXIDATIVE DEAMINATION	NON-OXIDATIVE DEAMINATION
Process occurs via oxidation (of amino group amino acids).	Process occurs via other reactions which are not oxidation reactions (mainly hydrolysis, reduction or intramolecular reactions).
Main enzymes that are involved are glutamate dehydrogenase and monoamine oxidase.	Main enzymes that are involved include dehydratases, lyases, and amide hydrolases.
Only occurs in the liver and kidney.	Occurs in the other types of organisms.


Serine
Pyruvate
H_2O
NH_3
H_2O

The Fate of the Carbon Skeleton

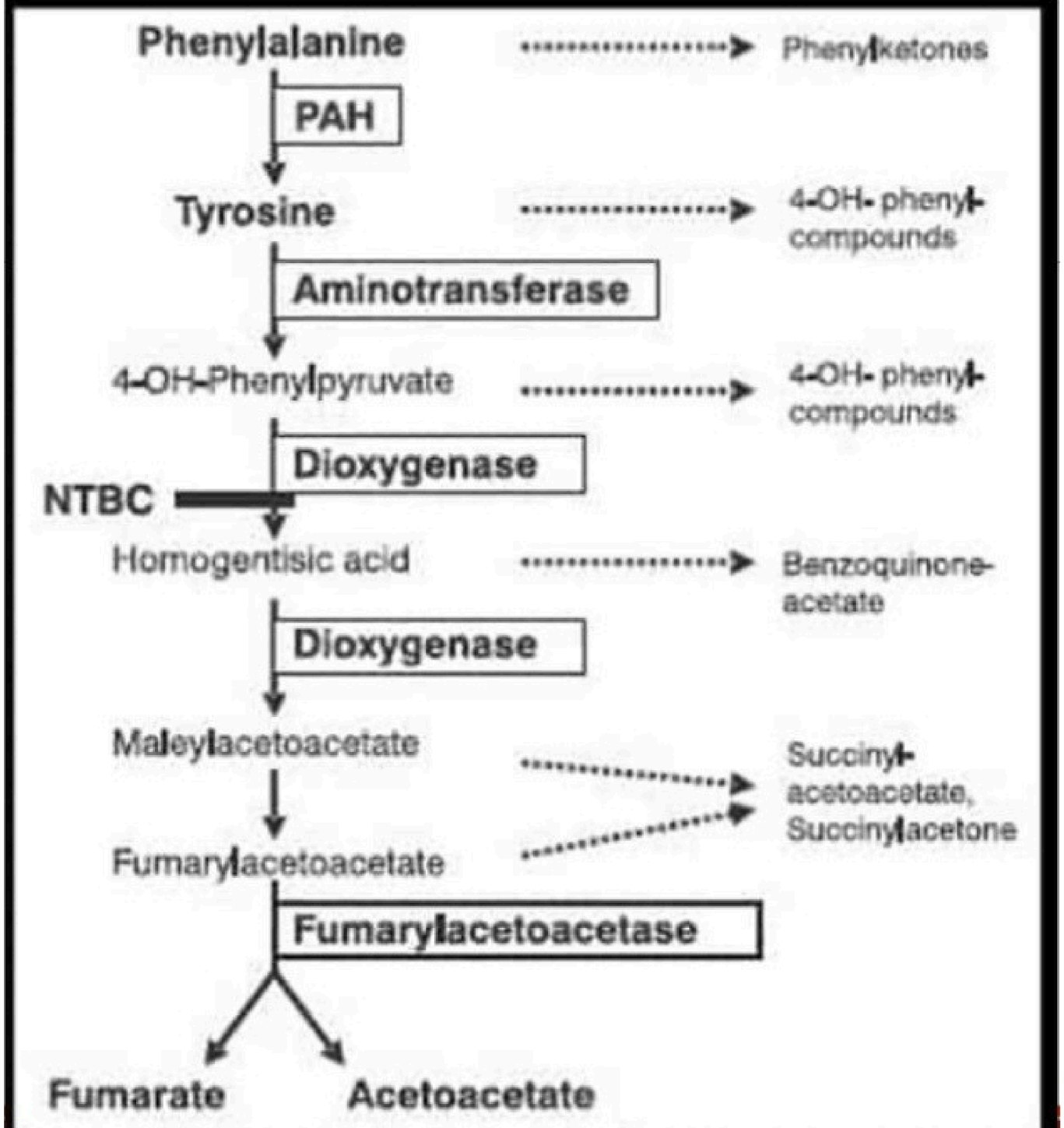
Once the amino group is removed, the remaining molecule is an alpha-keto acid (carbon skeleton). These carbon skeletons can be recycled to synthesize new amino acids if needed, but if they are in excess, they are catabolized for energy.

The Fate of the Carbon Skeleton

Where do they go?The carbon skeletons are converted into one of seven intermediate molecules that can enter the Citric Acid Cycle (Krebs Cycle):

1. Pyruvate
2. Acetyl-CoA
3. Acetoacetyl-CoA
4. Alpha-Ketoglutarate
5. Succinyl-CoA
6. Fumarate
7. Oxaloacetate

When these intermediates enter the Citric Acid Cycle, they are oxidized, producing NADH, $FADH_2$, and ATP.


Phenylalanine
Phenylketones
PAH
Tyrosine
4-OH- phenyl- compounds
Aminotransferase
4-OH-Phenylpyruvate
4-OH- phenyl- compounds
Dioxygenase
NTBC
Homogentisic acid
Benzoquinone-acetate
Dioxygenase
Maleylacetoacetate
Succinyl- acetoacetate, Succinylacetone
Fumarylacetoacetate
Fumarylacetoacetase
Fumarate
Acetoacetate

Glucogenic vs. Ketogenic Amino Acids

GLUCOGENIC AMINO ACIDS:

· Their carbon skeletons can be converted into glucose via gluconeogenesis.

· They degrade to Pyruvate, Alpha-ketoglutarate, Succinyl-CoA, Fumarate, or Oxaloacetate (all of which can lead to glucose production).

· Examples: Alanine, Glutamate, Aspartate, Serine, Glycine.

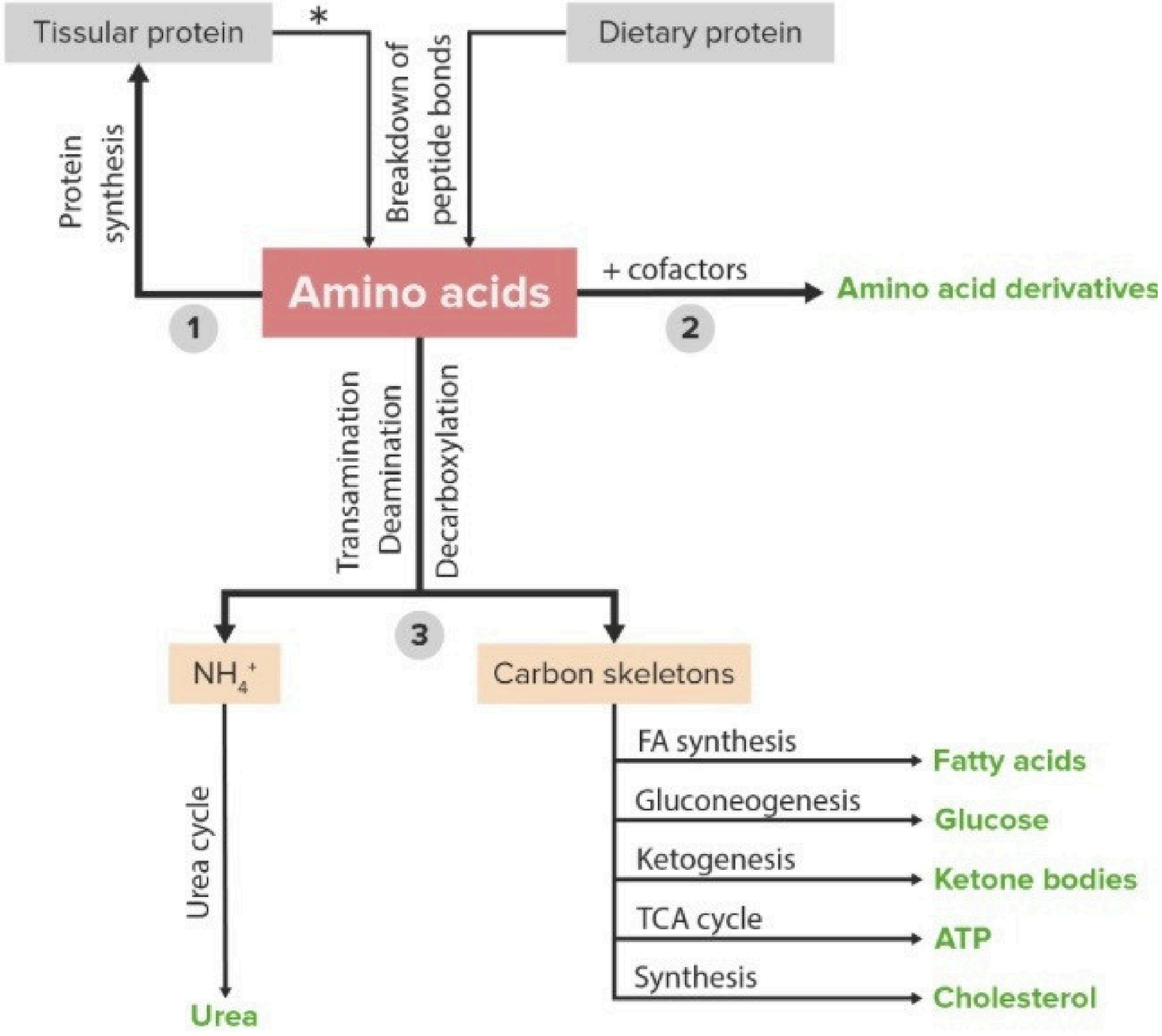
KETOGENIC AMINO ACIDS:

· Their carbon skeletons cannot be converted into glucose.

· They degrade to Acetyl-CoA or Acetoacetyl-CoA, which are used to synthesize ketone bodies or fatty acids.

· Examples: Leucine, Lysine.

Some amino acids are both glucogenic and ketogenic, e.g., Isoleucine, Phenylalanine, Tyrosine, Tryptophan



* Tissular protein breakdown is increased during periods of fasting/starvation

Entry Point 1: Pyruvate-Generating Amino Acids

Several aminoacids are converted directlyinto pyruvate.Examplesof reactions:

· Alanine: Transaminated to pyruvate (catalyzed by Alanine Aminotransferase).

· Serine: Converted to pyruvate by Serine Dehydratase (removes water and ammonia).

· Glycine: Converted to serine, then to pyruvate.

· Cysteine: Converted to pyruvate.

· Threonine: Converted to pyruvate.Significance: Pyruvate is a central hub. It can be converted to Acetyl-CoA (for the Citric Acid Cycle) or used in gluconeogenesis. This makes these amino acids strongly glucogenic

Entry Point 2 & 3: Acetyl-CoA and Acetoacetyl-CoA-Generating Amino Acids

These are the strictly ketogenic amino acids (and some dual ones).

Examples:· Leucine: Degraded into Acetyl-CoA and Acetoacetate (strictly ketogenic).· Lysine: Degraded into Acetyl-CoA and Acetoacetyl-CoA (strictly ketogenic).· Isoleucine: Degraded into both Acetyl-CoA (ketogenic) and Propionyl-CoA (glucogenic).· Phenylalanine & Tyrosine: Degraded into Fumarate (glucogenic) and Acetoacetate (ketogenic).· Tryptophan: Degraded into Alanine (glucogenic) and Acetyl-CoA (ketogenic).

Significance: Because animals cannot convert Acetyl-CoA or Acetoacetyl- CoA into glucose, these amino acids cannot maintain blood glucose levels during fasting. They are instead used for ketone body production or lipid synthesis.

Entry Point 4 & 5: Alpha-Ketoglutarate and Succinyl-CoA-Generating AminoAcids

These are important glucogenic amino acids.

Alpha-Ketoglutarate:

· Glutamate: Converted directly to alpha-ketoglutarate via oxidative deamination.

· Arginine, Proline, Histidine, Glutamine: Converted to glutamate, then to alpha-ketoglutarate.

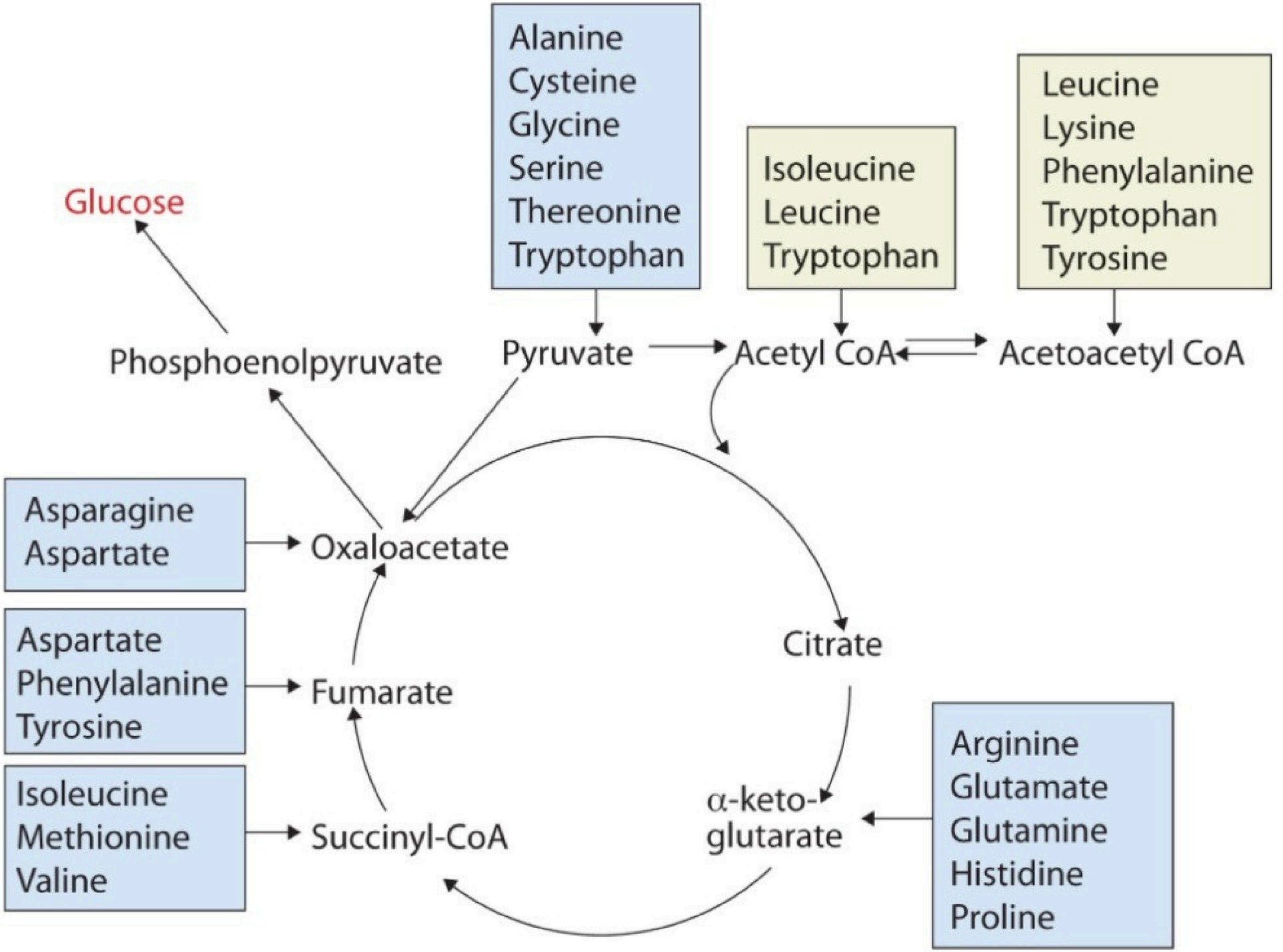
Succinyl-CoA:

· Methionine, Isoleucine, Threonine, Valine: These amino acids are converted into Propionyl-CoA.

· Propionyl-CoA is then carboxylated to form D-methylmalonyl-CoA, which is isomerized to Succinyl-CoA.Significance: Succinyl-CoA enters the Citric Acid Cycle directly, generating GTP and reducing equivalents (NADH, $FADH_2$).

Entry Point 6 & 7: Fumarate and Oxaloacetate- Generating Amino Acids

These are the final glucogenic entry points.
Fumarate:· Phenylalanine & Tyrosine: Degraded to Fumarate and Acetoacetate.
· Aspartate: Converted to fumarate via the purine nucleotide cycle.
Oxaloacetate:· Aspartate: Transaminated to oxaloacetate (via Aspartate Aminotransferase).
· Asparagine: Hydrolyzed to aspartate, then transaminated to oxaloacetate.
Significance: Oxaloacetate is a critical intermediate in the Citric Acid Cycle. It is also a substrate for gluconeogenesis. Aspartate is a key nitrogen donor for the urea cycle.


Alanine
Cysteine
Glycine
Serine
Thereonine
Tryptophan
Isoleucine
Leucine
Tryptophan
Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Glucose
Phosphoenolpyruvate
Pyruvate
Acetyl CoA
Acetoacetyl CoA
Asparagine
Aspartate
Oxaloacetate
Aspartate
Phenylalanine
Tyrosine
Fumarate
Citrate
Isoleucine
Methionine
Valine
Succinyl-CoA
α-keto-
glutarate
Arginine
Glutamate
Glutamine
Histidine
Proline

Summary: The Complete Picture

The catabolism of carbonskeletons is a highly integratedprocess.

·Amino acids are deaminated to remove nitrogen.

·The liver converts ammonia to urea (Urea Cycle).

·The remaining carbon skeletons are funneled into the Citric Acid Cycle at one of seven points.

·The breakdown of these carbon skeletons generates NADH, $FADH_2$, and ATP.

·Intermediates like Oxaloacetate and Pyruvate can be used to synthesize glucose (gluconeogenesis) during fasting.

Overall pathway:Amino Acids → Deamination → Carbon Skeleton → Citric Acid Cycle → Electron Transport Chain → ATP

Clinical Relevance: Metabolic Disorders

Defects in the enzymes of amino acid catabolism lead to severe metabolic disorders.

1. Phenylketonuria (PKU): Deficiency of phenylalanine hydroxylase. Phenylalanine cannot be converted to tyrosine. Phenylalanine accumulates and is converted to phenylpyruvate, causing severe intellectual disability if untreated. Treatment: Low-phenylalanine diet.

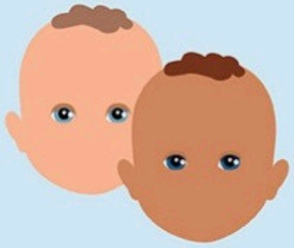
2. Maple Syrup Urine Disease (MSUD):Deficiency of branched-chain alpha-keto acid dehydrogenase. Affects the degradation of Leucine, Isoleucine, and Valine. These amino acids and their keto acids accumulate in the blood, causing neurological damage and a sweet, maple syrup-like odor in urine.

3. Alkaptonuria: Deficiency of homogentisate oxidase in the phenylalanine/tyrosine pathway.· Homogentisic acid accumulates and is excreted in urine, turning it black upon exposure to air.

Symptoms of phenylketonuria in children



Musty odor (breath, sweat, urine)



Changes in skin, hair and eyes



Nausea and vomiting



Growth delay

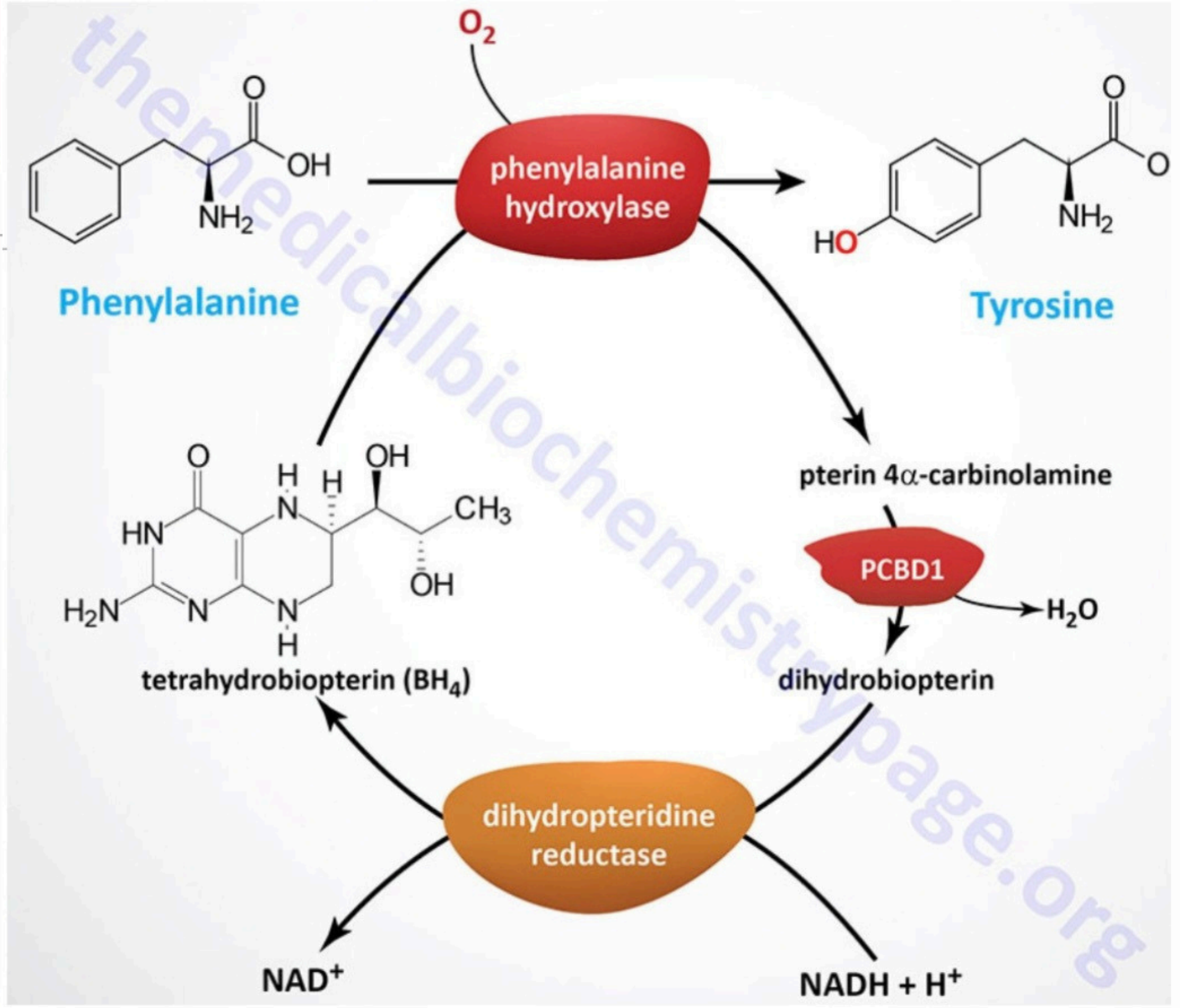


Eczema



Tremors

Cleveland Clinic



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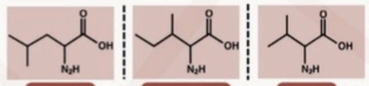
MAPLE SYRUP URINE DISEASE

PMF IAS

- Gene therapy offers new treatment options for **Maple Syrup Urine Disease (MSUD).**

MSUD

1. A rare **Genetic disorder** caused by **BCKDH** deficiency, **preventing** the **metabolism** of **BCAAs** like leucine, isoleucine, and valine.



2. **Inheritance Pattern:**
Autosomal recessive; requires mutated genes from both parents.



Types of MSUD

Classic MSUD
Most severe and common; symptoms emerge within days of birth.

Intermittent MSUD
Triggered by illness or stress; higher BCAA tolerance than classic MSUD.



Intermediate MSUD
Milder than classic; symptoms appear between 5 months and 7 years.

Thiamine-Responsive MSUD
Improves with high-dose B1 and dietary restrictions.

Traditional Treatment Approaches

Dietary Management
Lifelong **low-protein diet** to restrict BCAA intake.



Liver Transplant
BCKDH enzyme therapy offers a cure but involves surgical risks.



Symptoms of MSUD



Distinct Odor
Sweet, maple syrup-like odor in urine, sweat, or earwax.



Neurological Symptoms
Lethargy, irritability, and poor feeding in infants.



Severe Complications
If untreated, can cause seizures, coma, or death

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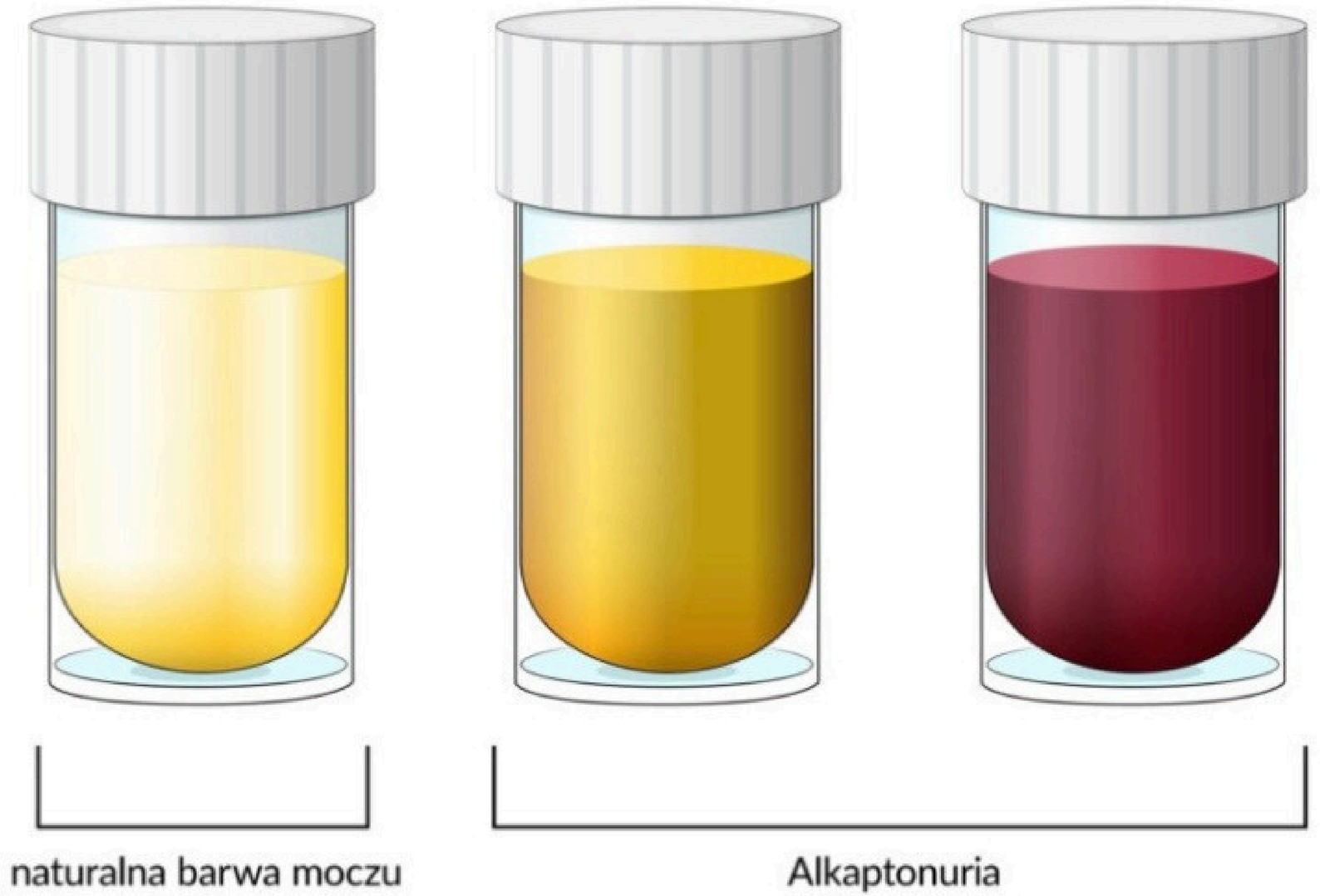
Advancements in Gene Therapy

Recent Developments
Adeno-associated viral (AAV) vector based gene therapy delivers functional BCKDHA and BCKDHB genes.

Adeno-Associated Viral (AAV) Vector:
AAVs are favored in gene therapy for low pathogenicity and efficient gene delivery.



ALKAPTONURIA



Student task

Task 1 - Check your understanding:

1. Why must the aminogroup be removed before the carbon skeleton can be used for energy?
2. What are the two main processes by which the amino group is removed from an amino acid?
3. Define glucogenic and ketogenic amino acids.
4. Which two amino acids are strictly ketogenic?
5. Into what seven intermediates do amino acid carbon skeletons enter the Citric Acid Cycle?
6. What is the significance of Propionyl-CoA in amino acid catabolism?
7. Explain why patients with MSUD have a "maple syrup" odor in their urine.

Task 2 - Complete the pathway:

Complete the degradation of Methionine:

Methionine → … → Propionyl-CoA → (Enzyme 1) → D-Methylmalonyl-CoA → (Enzyme 2) → Succinyl-CoA

Then explain: 1. Where does Succinyl-CoA enter the Citric Acid Cycle? 2. Why is Methionine considered a glucogenic amino acid?

Conclusion

Aminoacid catabolism is essential for energy production when carbohydrates and fats are scarce.

· The amino group is removed via transamination and oxidative deamination, with the nitrogen eventually excreted as urea.

· The carbon skeletons are degraded into seven key intermediates that feed into the Citric Acid Cycle.

· Amino acids are classified as glucogenic or ketogenic based on their degradation products.

· Understanding these pathways is crucial for diagnosing and treating metabolic disorders like PKU and MSUD.

· The carbon skeletons ultimately yield ATP, connecting protein metabolism directly to cellular bioenergetics.

References

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