

BCH 384

AMINO ACIDS AND PROTEIN METABOLISM

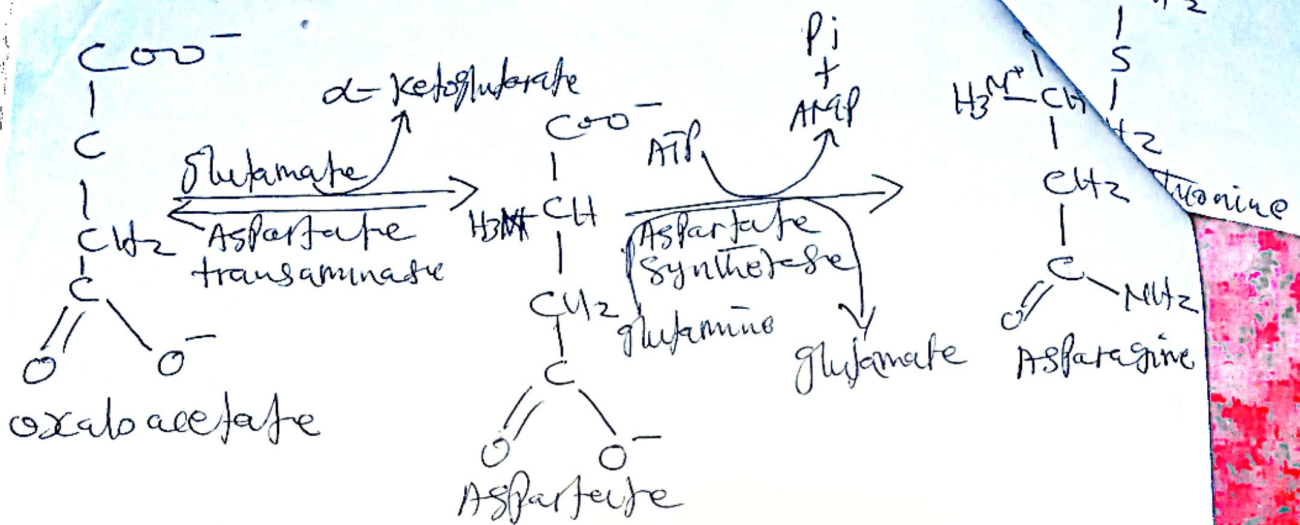
Biosynthesis of Amino Acids.

amino acid biosynthesis is a process by which organisms create amino acids from compounds in their diet or growth media. The process involves biochemical pathways that use intermediates from different pathways such as glycolysis, the citric acid cycle, or the pentose phosphate pathway.

There are 20 essential amino acids. The biosynthetic pathways leading to the 20 common amino acids are related to other metabolic pathways.

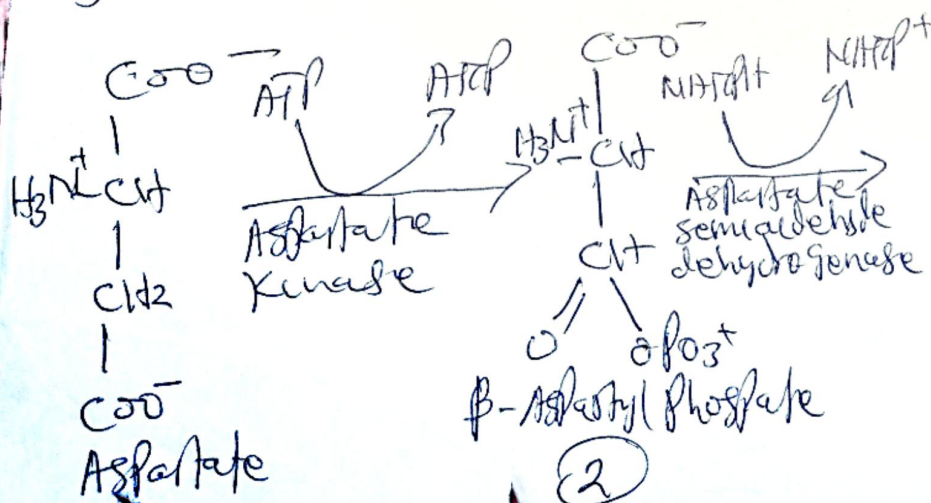
Note that 11 of the 20 essential amino acids are synthesized from intermediates in the citric acid cycle, the others ~~are~~ require simple precursors.

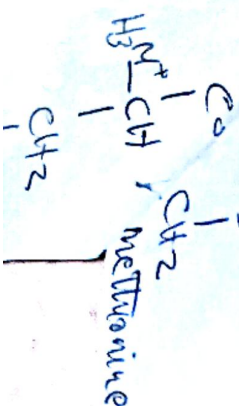
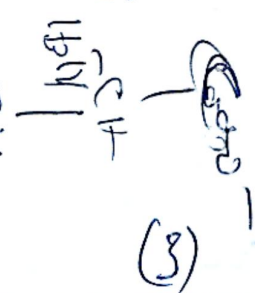
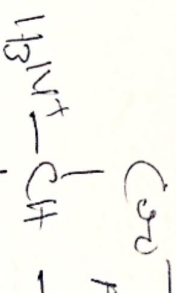
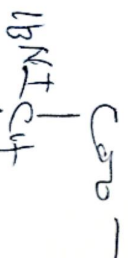
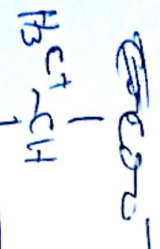
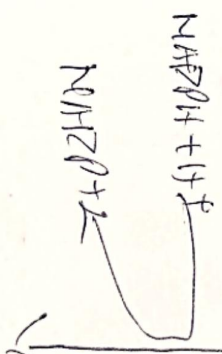
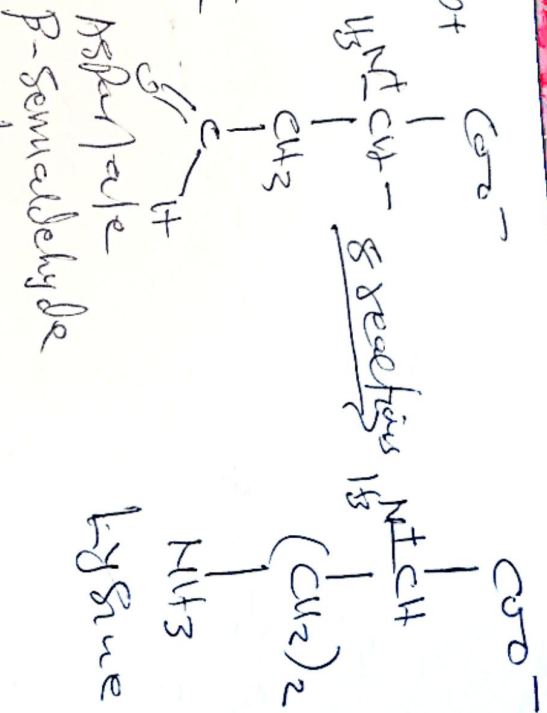
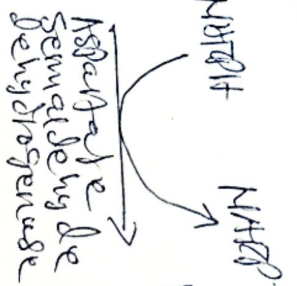
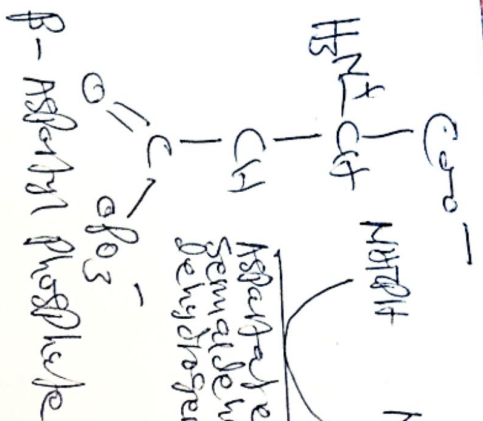
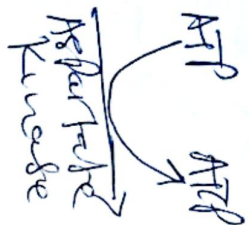
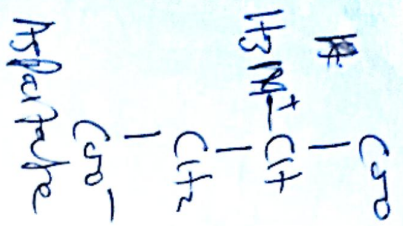
Aspartate and Asparagine



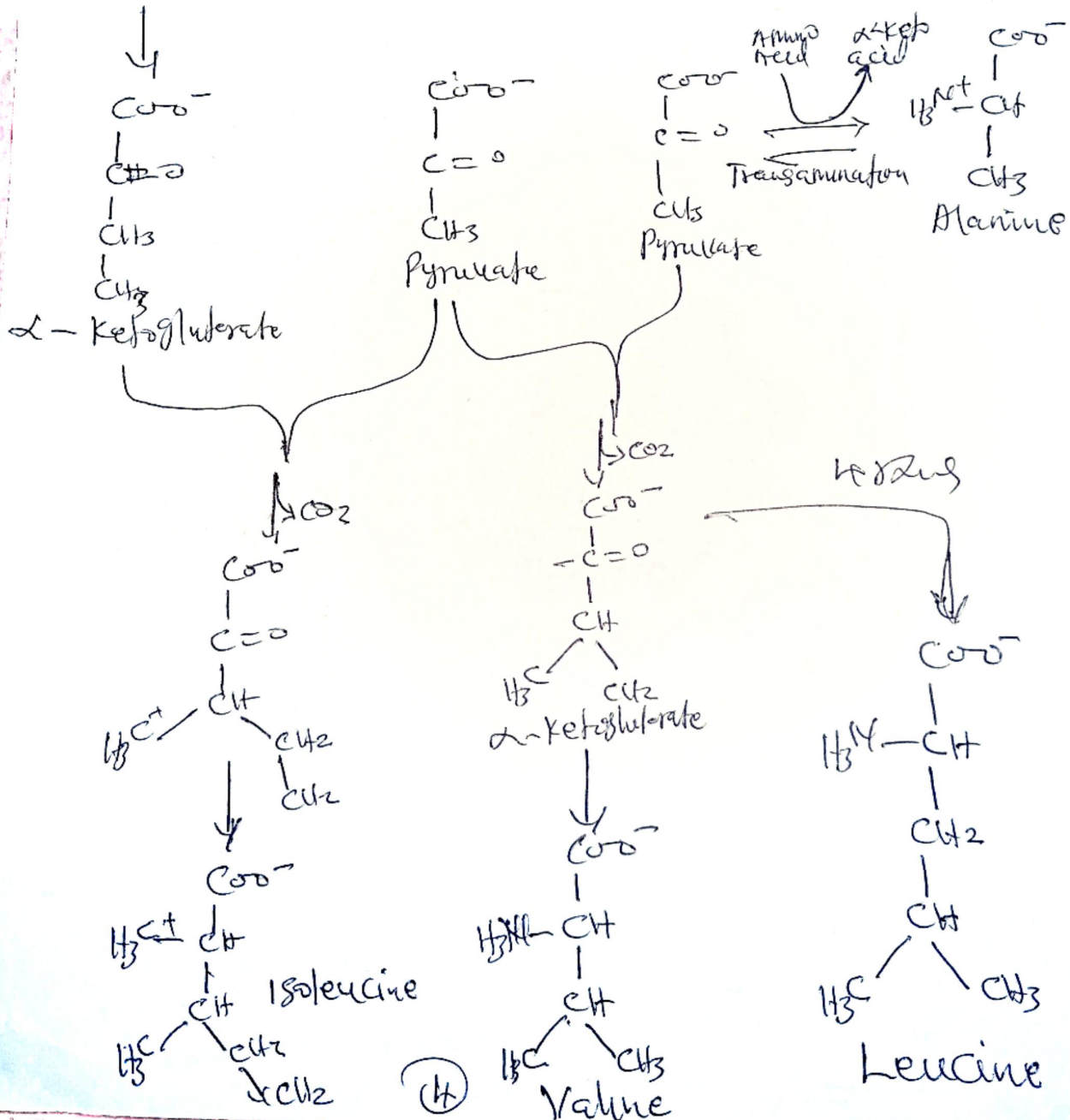
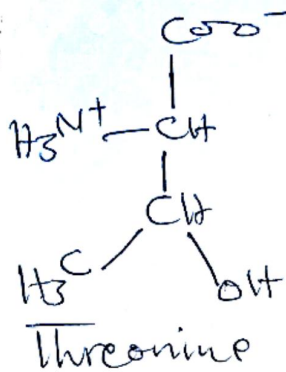
Lysine, Methionine and Threonine

Aspartate is the precursor of lysine, methionine and threonine. The first step in the pathway is the phosphorylation of aspartate in a reaction catalyzed by aspartate kinase. In the second step aspartyl phosphate is converted to aspartate β -semialdehyde. This step is catalyzed by aspartate semialdehyde dehydrogenase.



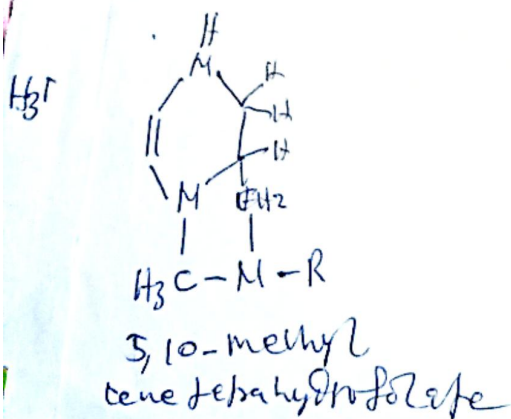
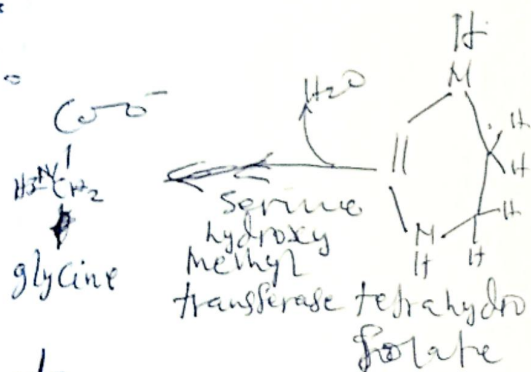
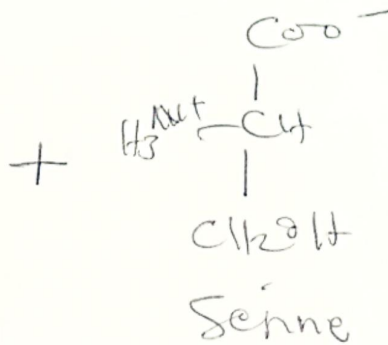
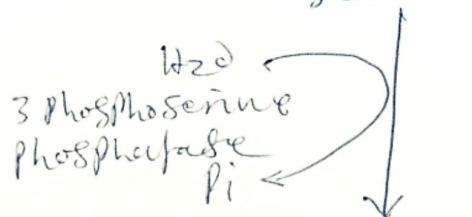
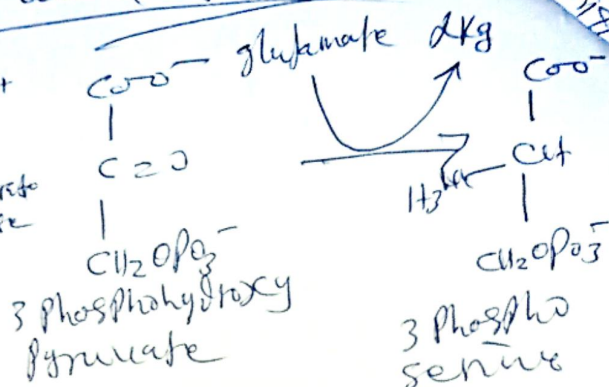
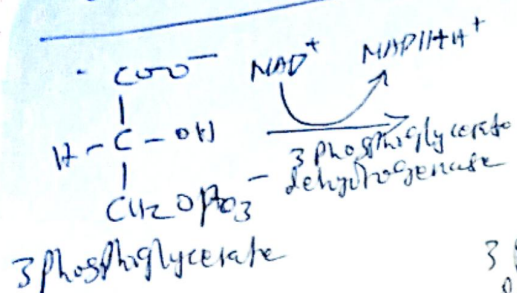


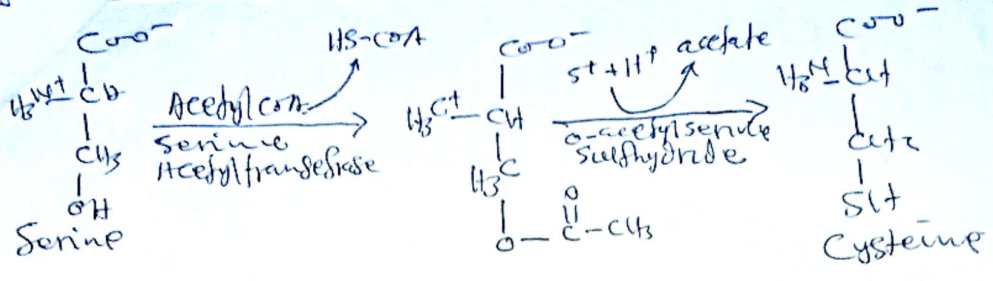
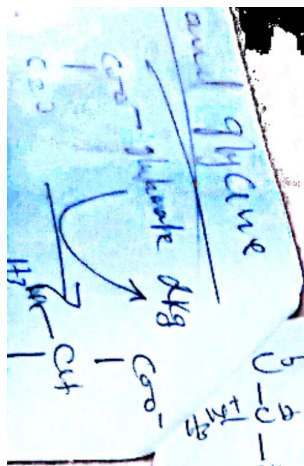
Chetana / Proline



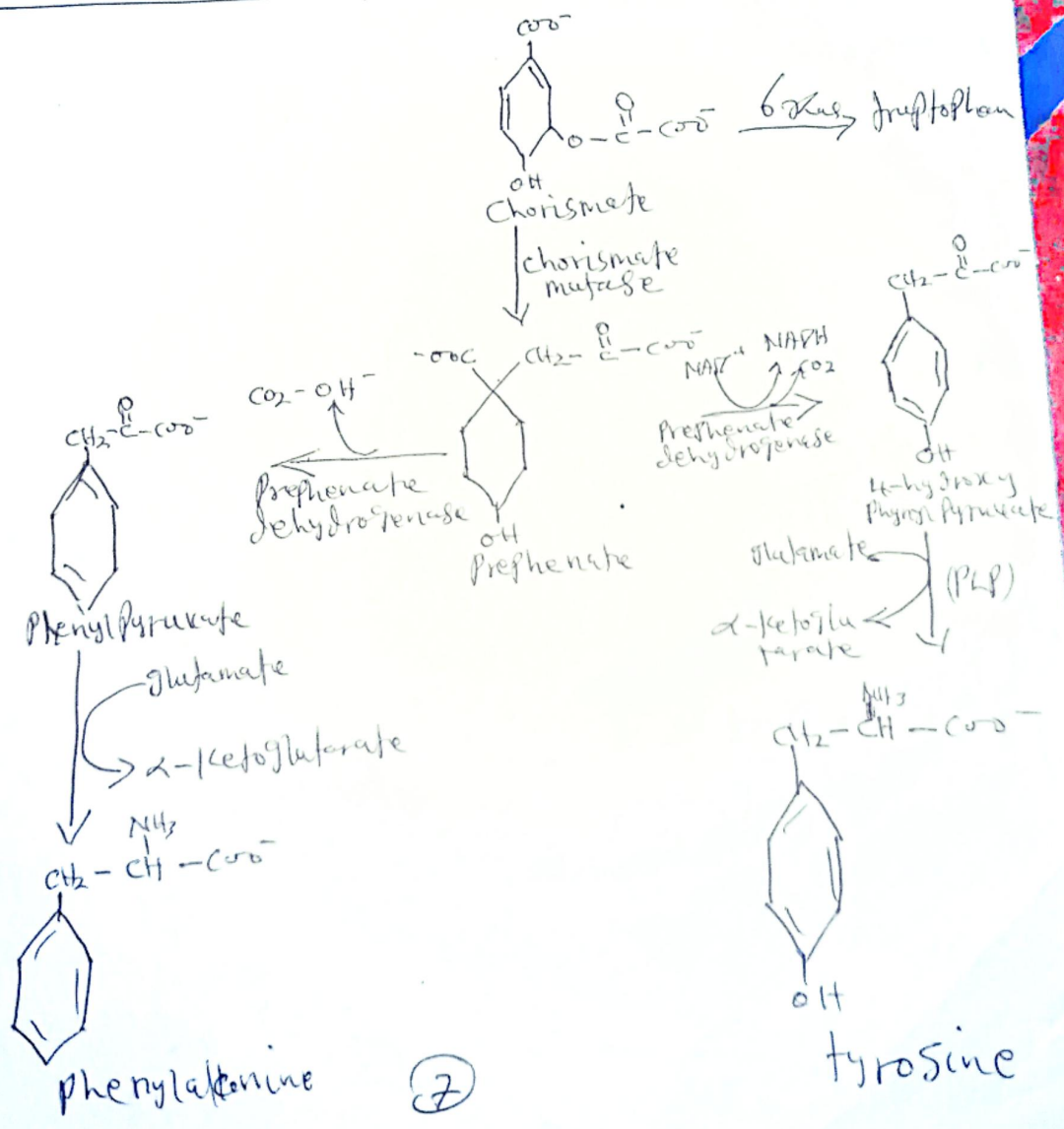
1806



$$\frac{\text{Acetyl}}{\text{serine}} \quad \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{OH}$$




Phenylalanine, Tyrosine and Tryptophan



PROTEIN TURNOVER

Proteins are continually synthesized and degraded in all cells in a process called turnover. Individual proteins turnover at different rates. Their half lives can vary from few minutes to several weeks but half life of a given protein in different organs and species are generally similar.

Rapid protein turnover ensures that certain regulatory proteins are degraded so that cells can respond to constantly changing conditions. Such proteins have evolved to be relatively unstable.

The rate of hydrolysis of protein can be inversely related to the stability of its tertiary structure. As a result misfolded and unfolded proteins are quickly degraded.

Apoptosis — Programmed cell death

Apoptosis is a series of morphological changes in a cell that leads to its death. The changes include a decrease in cell volume, damage to the plasma membrane, swelling of mitochondria and fragmentation of chromatin.

the hormone
action
during the
antibody pro
disease or
some

and
turnover.

Some harmful cells die or are removed by the action of proteases. Some cells die normally during development or in the control of antibody production, others die as a result of disease or faulty Apoptosis (as in case of some neurodegenerative disease).

All eukaryotic cells have a similar set of endogenous enzymes responsible for cell death. called Caspases. These are cysteine containing hydrolases that act on the carboxyl side of aspartate residue.

Degradation of Amino Acids & Proteins

The degradation of amino acids converts them to citric acid cycle intermediates or their precursors so that they can be metabolised to CO_2 & H_2O or used in gluconeogenesis.

Oxidative breakdown of amino acids accounts for 10 to 15% of the metabolic energy generated.

Amino acids can be glucogenic or ketogenic or both. This description of amino acids is based on their catabolic pathways.

- Glucogenic amino acids are those whose carbon skeletons are degraded to pyruvate, α -ketoglutarate, succinyl CoA, fumarate or oxaloacetate. All these intermediates can be used to form glucose.

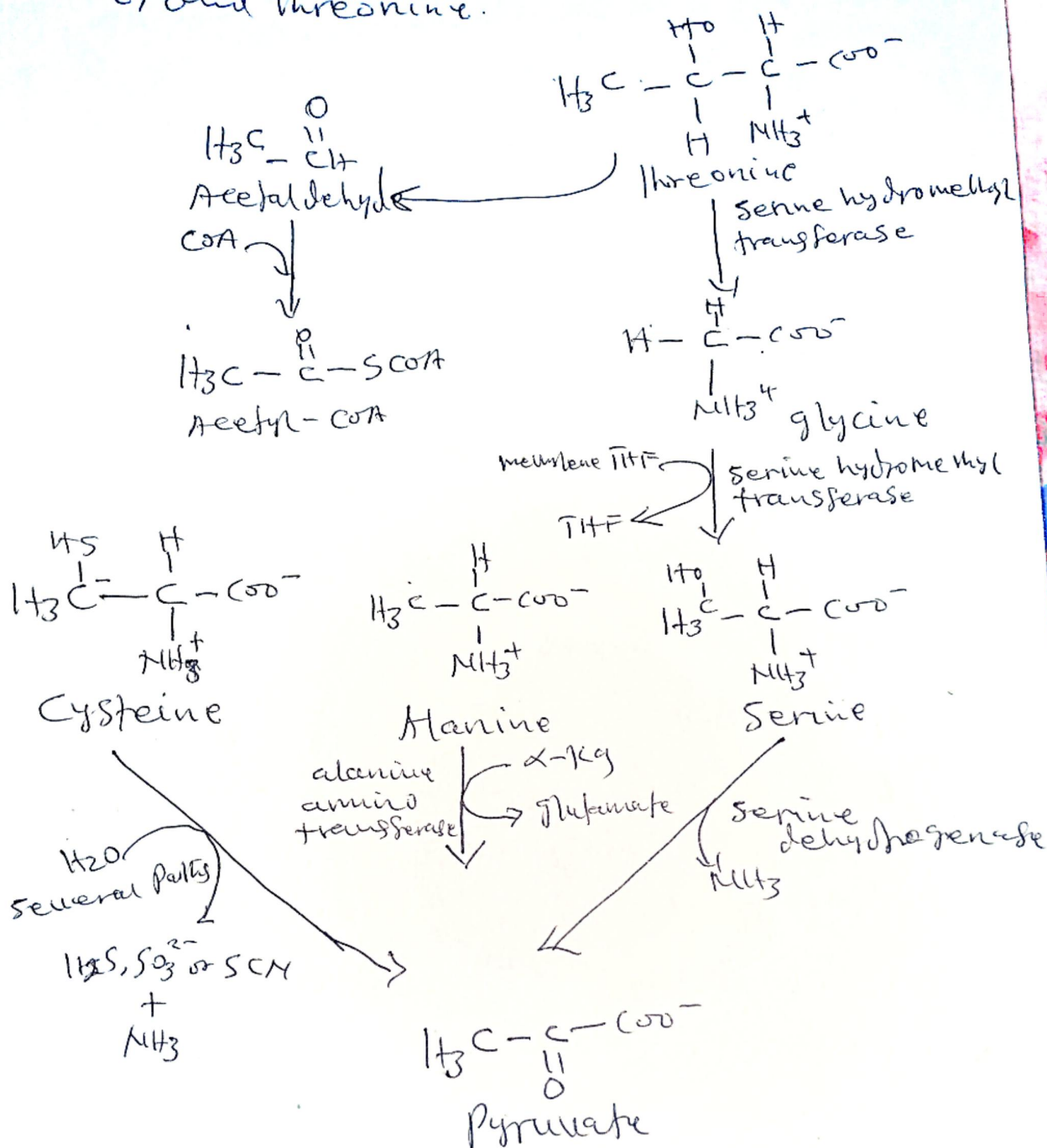
Eg, alanine is a glucogenic amino acid because its transamination product pyruvate can be converted to glucose via gluconeogenesis.

- Ketogenic Amino Acids are those whose carbon skeletons are broken down to acetyl CoA or acetoacetate and thus can be converted to ketone bodies or fatty acids. (Eg) leucine, its carbon skeleton is converted to Acetyl-CoA or acetoacetate.

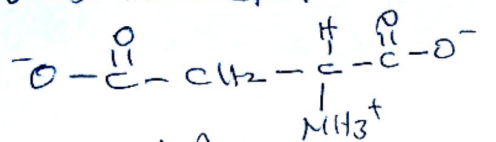
- Since animals lack any metabolic pathway for the conversion of acetoacetate to glucogenic precursors, leucine cannot synthesize glucose.

Other Ketogenic Amino Acids 15 leucine, phenylalanine, tyrosine, Threonine and tryptophan are both glucogenic & ketogenic. For example 15 leucine is broken down to Acetyl CoA & succinyl CoA and hence is a precursor of both carbohydrates and ketone bodies. (10)

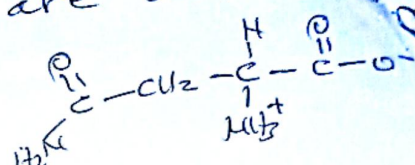
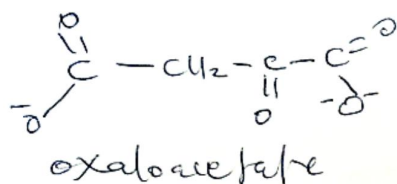
Metabolism of Alanine, cysteine, glycine, serine, and threonine.



Asparagine and Aspartate are degraded to oxaloacetate.

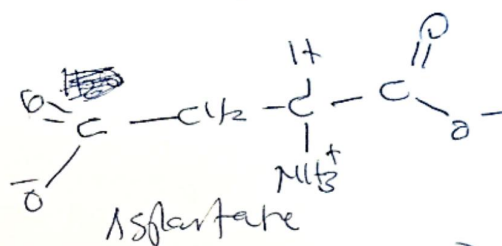


Aspartate
 $\xrightarrow[\text{Glutamate}]{\alpha\text{-KG}}$ aminotransferase



Asparagine.

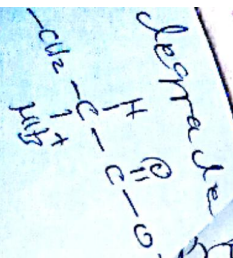
$\xrightarrow[\text{NH}_4^+]{\text{H}_2\text{O}}$ Asparaginase



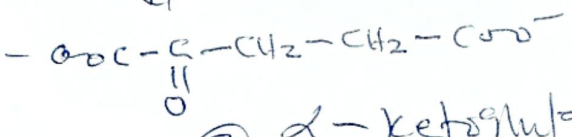
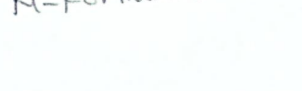
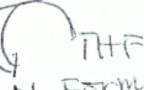
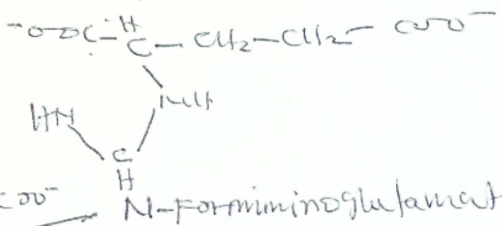
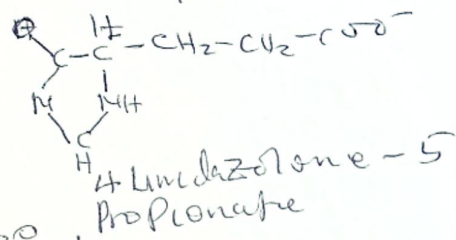
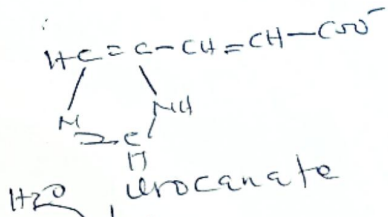
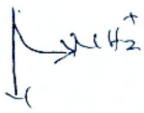
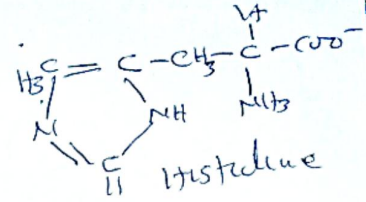
Like aspartate, Asparagine is also converted to oxaloacetate in this manner after its hydrolysis to aspartate by asparaginase.

Asparaginase is an effective chemotherapeutic agent in the treatment of cancers that must obtain asparagine from the blood.
 ex) Acute lymphoblastic leukemia.

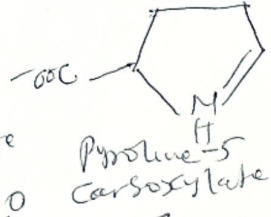
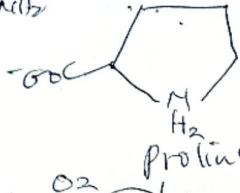
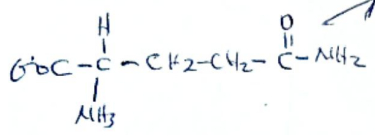
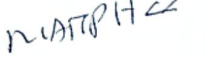
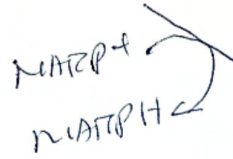
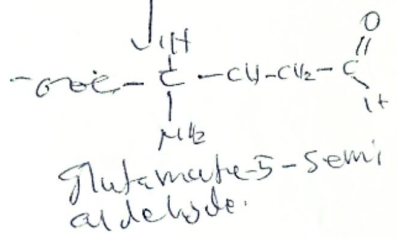
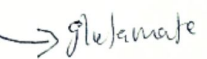
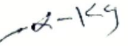
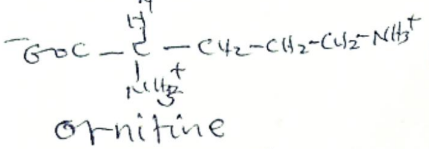
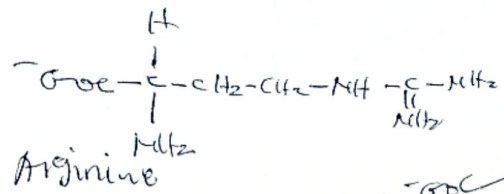
The cancerous cells express low levels of the enzyme asparagine synthetase and hence die without an external source of asparagine.



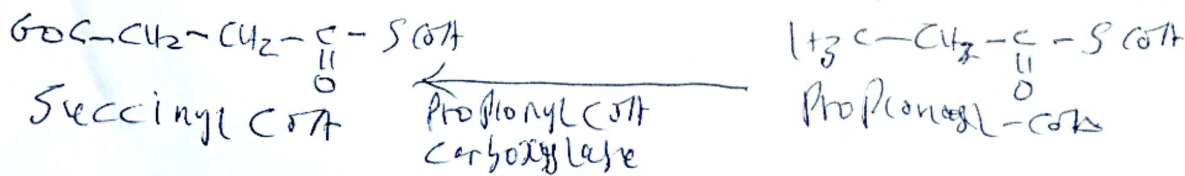
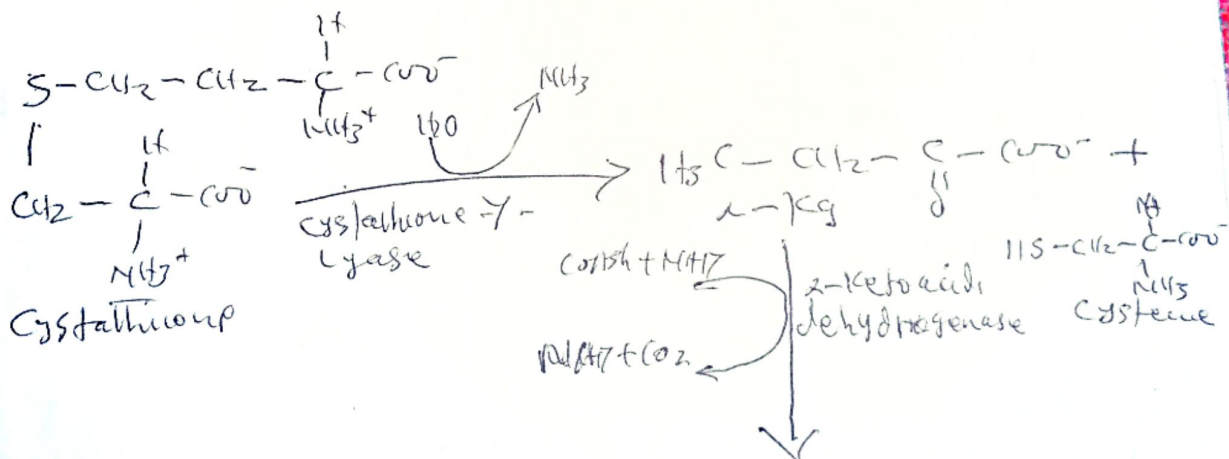
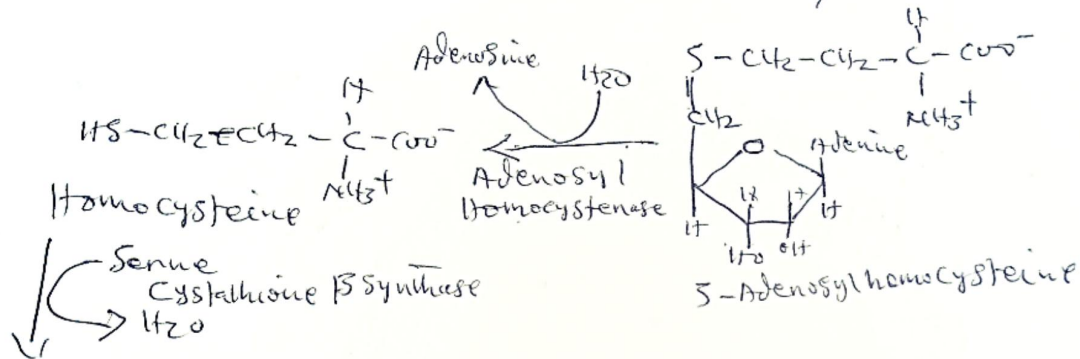
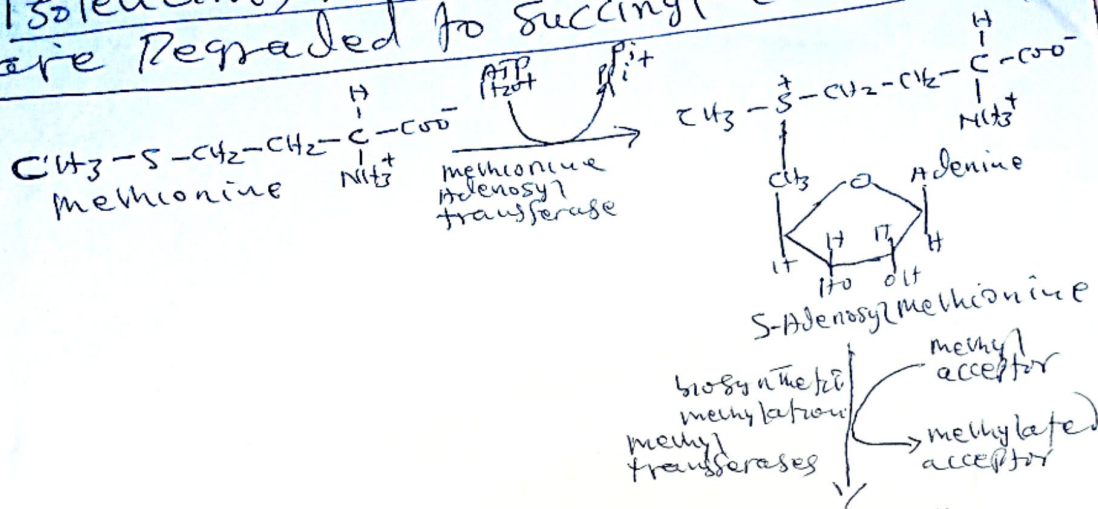
Arginine, Glutamate, glutamine, histidine and proline are degraded to α -ketoglutarate.



(B) α -ketoglutarate



Isoleucine, Methionine and Valine are Regarded to Succinyl-CoA



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Nitrogen cycle & nitrogen fixation

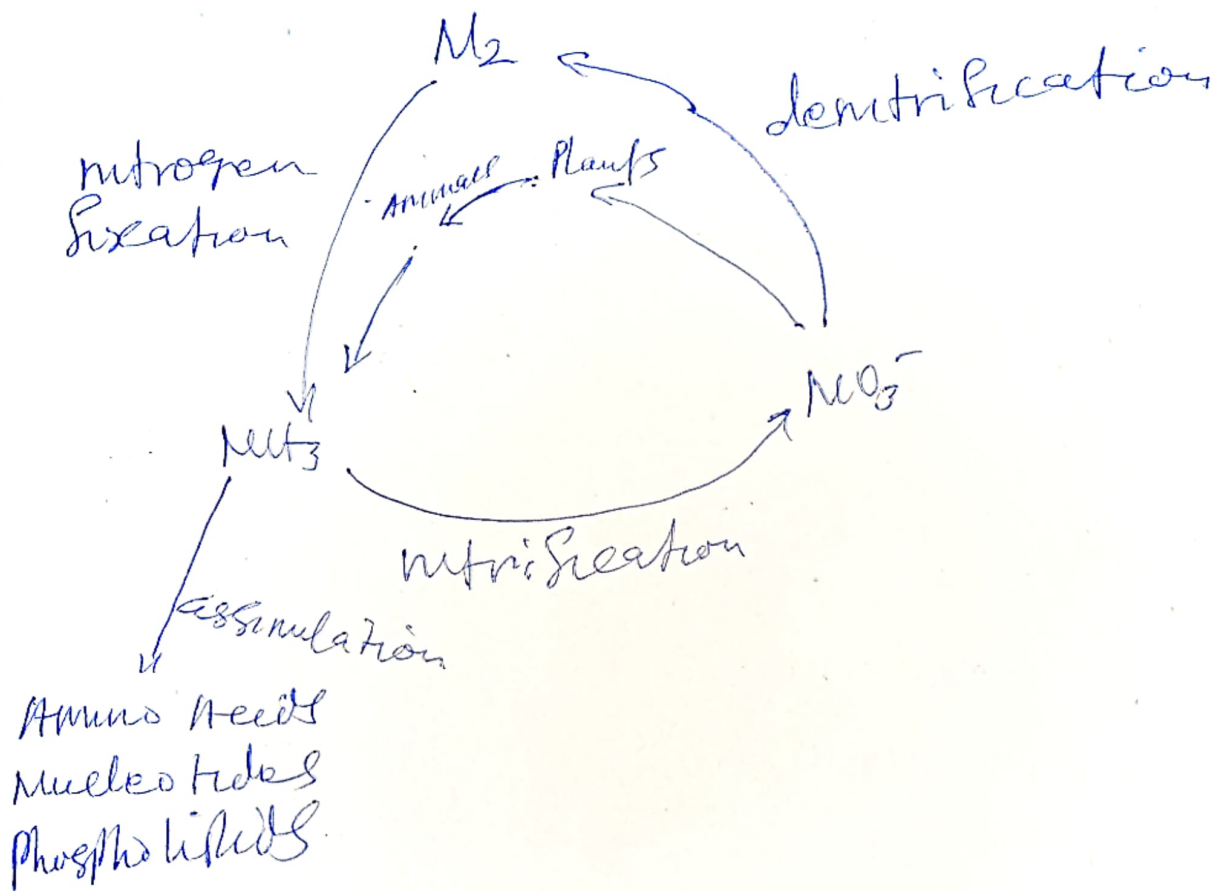
The nitrogen needed for Amino Acids and heterocyclic bases of nucleotides come from two major sources. Nitrogen gas N_2 in the atmosphere and Nitrate NO_3^- in the soil. Atmospheric Nitrogen which constitutes about 80% of the atmosphere is the ultimate source of biological nitrogen. This molecule can only be metabolized by only a few species of bacteria. N_2 and NO_3^- must be reduced, in other to be used in metabolism.

The ammonia produced is incorporated into amino acids via glutamate, glutamine & carbamyl phosphate.

N_2 is chemically unreactive because of the great strength of $M \equiv N$ bond. Some bacteria have a specific enzyme Nitrogenase that can catalyze the reduction of N_2 to NH_3 in a process called nitrogen fixation.

The flow of nitrogen from N_2 to nitrogen oxides, ammonia and nitrogenous biomolecules and then back to nitrogen is called nitrogen cycle.

Nitrogen cycle is crucial for all life on earth. because nitrogen is needed to make some of the most important biomolecules which includes DNA, RNA and proteins that are needed by all living things. without nitrogen there will be no life at all.



The Interrelationship Between Amino Acid Metabolism and Carbohydrate & Lipid Metabolism

Metabolism is the sum of all chemical reactions in the body that help sustain life. The three major biomolecules carbohydrates, lipids, and proteins are metabolized through interconnected pathways. Amino acid metabolism, which involves the breakdown and utilization of amino acids, is closely linked to both carbohydrate and lipid metabolism. This interrelationship is crucial for maintaining energy balance and ensuring that the body efficiently uses available nutrients.

1. Overview of Amino Acid Metabolism

Amino acids, obtained from dietary proteins, are primarily used for protein synthesis. However, excess amino acids cannot be stored in the body and must be metabolized. This metabolism involves:

- **Deamination:** Removal of the amino group ($-NH_2$) to form ammonia, which is excreted as urea.
- **Transamination:** Transfer of the amino group to another molecule, forming new amino acids.
- **Carbon Skeleton Utilization:** The remaining carbon skeletons enter metabolic pathways that connect with carbohydrate and lipid metabolism.

2. Link Between Amino Acid and Carbohydrate Metabolism

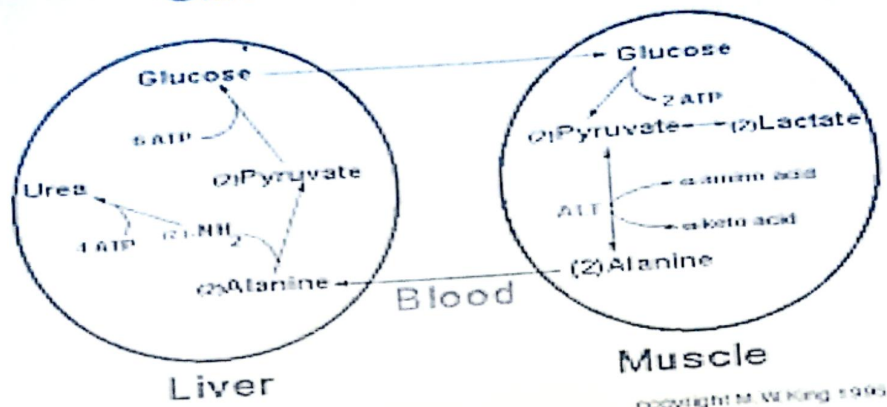
The carbon skeletons of amino acids can be converted into intermediates of the citric acid (Krebs) cycle, which is a key pathway in carbohydrate metabolism. This occurs in several ways:

- **Gluconeogenesis:** Certain amino acids (glucogenic amino acids) can be converted into glucose through gluconeogenesis in the liver. Examples include alanine and glutamine.
- **Entry into the Krebs Cycle:** Some amino acids are broken down into intermediates like pyruvate, oxaloacetate, or α -ketoglutarate, which can then be used to generate ATP.
- **Energy Production:** When carbohydrates are scarce, amino acids provide an alternative energy source by feeding into glycolysis and the Krebs cycle.

Simple Pathway Representation

1. Protein $\rightarrow$ Amino Acids $\rightarrow$ Deamination $\rightarrow$ Carbon Skeletons
2. Carbon Skeletons $\rightarrow$ Pyruvate $\rightarrow$ Glucose (via gluconeogenesis) $\rightarrow$ Energy (ATP)
3. Carbon Skeletons $\rightarrow$ Krebs Cycle Intermediates $\rightarrow$ Energy Production

Glucose/Alanine Cycle



3. Link Between Amino Acid and Lipid Metabolism

Amino acid metabolism also intersects with lipid metabolism in several ways:

- **Ketogenic Amino Acids:** Some amino acids, like leucine and lysine, are broken down into acetyl-CoA, which can be used to synthesize fatty acids or ketone bodies.
- **Fatty Acid Synthesis:** Excess carbon skeletons from amino acids can contribute to the formation of acetyl-CoA, which is a building block for fatty acid and cholesterol synthesis.
- **Energy Storage:** When energy intake is high, excess amino acids can be converted into triglycerides (fat) for storage in adipose tissue.

Simple Pathway Representation

1. Protein → Amino Acids → Deamination → Carbon Skeletons
2. Carbon Skeletons → Acetyl-CoA → Fatty Acids → Triglycerides (Fat Storage)
3. Acetyl-CoA → Ketone Bodies (in case of carbohydrate scarcity)

4. Summary of Interrelationship

- Amino acids can be used to produce glucose via gluconeogenesis (link to carbohydrate metabolism).
- Amino acids can be broken down into acetyl-CoA, which is a key precursor for lipid synthesis and ketone body production (link to lipid metabolism).

- The Krebs cycle serves as a central hub where carbon skeletons from amino acids integrate with pathways of carbohydrate and lipid metabolism.
- During fasting or starvation, amino acids contribute to both glucose production and energy generation through ketone bodies.

Conclusion

The metabolism of amino acids is intricately linked to carbohydrate and lipid metabolism, ensuring a balance between energy production, glucose availability, and fat storage. This interconnection allows the body to adapt to varying energy demands and dietary conditions, maintaining homeostasis.

This fundamental understanding of metabolism is crucial for further studies in biochemistry, physiology, and medical sciences.

Metabolism of One-Carbon Units

Introduction

The metabolism of one-carbon (C1) units is essential for various biochemical processes, including amino acid metabolism, nucleotide synthesis, and methylation reactions. One-carbon metabolism primarily involves the transfer of single carbon groups, such as methyl (-CH₃), methylene (-CH₂-), and formyl (-CHO) groups, between molecules. The key carriers of these one-carbon units are folate and S-adenosylmethionine (SAM).

Folate and One-Carbon Metabolism

Folate, or vitamin B₉, plays a crucial role in one-carbon metabolism. It exists in several forms, with tetrahydrofolate (THF) being the active form. THF serves as a carrier of one-carbon units in different oxidation states and is involved in important cellular processes.

Conversion of Folate into Active Forms

1. **Folate Reduction:** Dietary folate is converted to dihydrofolate (DHF) and then to tetrahydrofolate (THF) via the enzyme **dihydrofolate reductase (DHFR)**.
2. **Addition of One-Carbon Units:** THF can receive one-carbon units from sources such as amino acids (serine, glycine, histidine) and convert them into different derivatives:
 - **Formyl-THF (-CHO):** Used in purine nucleotide synthesis.
 - **Methylene-THF (-CH₂-):** Important for thymidylate (DNA synthesis).
 - **Methyl-THF (-CH₃):** Involved in methylation reactions via homocysteine to methionine conversion.

The Methionine Cycle and SAM

The **methionine cycle** links folate metabolism with methylation reactions.

1. **Methionine Activation:** Methionine is converted into **S-adenosylmethionine (SAM)** by the enzyme **methionine adenosyltransferase**.
2. **Methyl Group Donation:** SAM donates its methyl group to DNA, proteins, neurotransmitters, and lipids. This reaction is catalyzed by methyltransferases.
3. **Recycling of Homocysteine:** After donating the methyl group, SAM is converted to **S-adenosylhomocysteine (SAH)**, which is then hydrolyzed to homocysteine. Homocysteine can either:
 - Be remethylated back to methionine using **methyl-THF** and **methionine synthase**.
 - Enter the transsulfuration pathway to form cysteine and glutathione.

Importance of One-Carbon Metabolism

One-carbon metabolism is critical for several physiological functions:

1. **DNA and RNA Synthesis:** Essential for the production of purines and thymidine, which are needed for DNA replication and cell division.
2. **Amino Acid Metabolism:** Serine, glycine, and histidine contribute to one-carbon metabolism and are interconverted through THF-dependent reactions.
3. **Methylation Reactions:** SAM-mediated methylation regulates gene expression, neurotransmitter synthesis, and lipid metabolism.
4. **Detoxification:** The methionine cycle and glutathione synthesis play a role in oxidative stress protection and detoxification.

Clinical Relevance

Disruptions in one-carbon metabolism can lead to various health issues:

- **Folate Deficiency:** Causes megaloblastic anemia and neural tube defects in developing embryos.
- **Hyperhomocysteinemia:** Elevated homocysteine levels are linked to cardiovascular diseases and neurodegenerative disorders.
- **Cancer Risk:** Abnormal DNA methylation patterns due to defective one-carbon metabolism are associated with cancer development.

Conclusion

One-carbon metabolism is a fundamental biochemical pathway that supports DNA synthesis, amino acid metabolism, and methylation reactions. The interplay between folate, SAM, and homocysteine ensures proper cellular function, making it vital for health and disease prevention. Understanding these pathways can help in diagnosing and treating metabolic disorders linked to one-carbon metabolism.

One-carbon (C1) metabolism refers to biochemical reactions that transfer and utilize single-carbon groups. These reactions are crucial for the synthesis of amino acids, nucleotides, and other important biomolecules. The key player in one-carbon metabolism is **tetrahydrofolate (THF)**, a coenzyme derived from folic acid that carries and transfers single-carbon units in different oxidation states. Other molecules like **S-adenosylmethionine (SAM)** and **cobalamin (Vitamin B12)** also play important roles in these pathways.

Sources of One-Carbon Units

One-carbon units can be derived from several sources:

1. **Serine and Glycine** – The primary donors of one-carbon units via their conversion to 5,10-methylene-THF.
2. **Formate** – A one-carbon donor converted to 10-formyl-THF.
3. **Histidine** – Provides one-carbon units in the form of 5-formimino-THF.
4. **Choline and Methionine** – Important in the methionine cycle, contributing to methylation reactions.

One-Carbon Pool and Tetrahydrofolate (THF)

THF carries one-carbon groups in different oxidation states:

- **Formyl (-CHO)**: Used in purine synthesis.
- **Methylene (-CH₂-)**: Involved in thymidylate synthesis.
- **Methyl (-CH₃)**: Used in methylation reactions, particularly in methionine synthesis.

These one-carbon units interconvert through enzymatic reactions, forming the **one-carbon pool**, which serves as a central hub for distributing these units for biosynthesis.

One-Carbon Metabolism Pathway

The metabolism of one-carbon units primarily occurs in the **folate cycle**, **methionine cycle**, and **transsulfuration pathway**.

1. Folate Cycle:

- **Serine hydroxymethyltransferase (SHMT)** converts serine into glycine while transferring a one-carbon unit to THF, forming **5,10-methylene-THF**.
- 5,10-methylene-THF can be converted into **5-methyl-THF**, the most reduced form, which is crucial for methionine synthesis.
- It can also be converted into **10-formyl-THF**, required for purine nucleotide biosynthesis.

2. Methionine Cycle:

- 5-Methyl-THF donates its methyl group to homocysteine, converting it into **methionine** via the enzyme **methionine synthase (MS)**, which requires Vitamin B12 as a cofactor.
- Methionine is then converted to **S-adenosylmethionine (SAM)**, an important methyl donor in numerous methylation reactions, including DNA and protein methylation.
- After donating its methyl group, SAM is converted back into homocysteine, completing the cycle.

3. Transsulfuration Pathway:

- If homocysteine is not remethylated to methionine, it is directed towards the transsulfuration pathway to form **cysteine**, which is important for synthesizing glutathione (an antioxidant).

Biological Significance of One-Carbon Metabolism

- **Nucleotide Synthesis:** The formyl groups of THF are essential for purine biosynthesis, while methylene-THF is necessary for thymidylate (dTMP) formation, which is crucial for DNA replication.
- **Methylation Reactions:** SAM donates methyl groups for DNA methylation, histone modification, and neurotransmitter synthesis.
- **Amino Acid Metabolism:** One-carbon units contribute to methionine, serine, and glycine metabolism, linking these amino acids to essential cellular functions.

- **Redox Balance:** The transsulfuration pathway helps maintain glutathione levels, protecting cells from oxidative stress.

Conclusion

One-carbon metabolism is essential for numerous biochemical processes, including DNA synthesis, methylation, and amino acid metabolism. THF, SAM, and Vitamin B12 are key molecules facilitating the transfer of one-carbon units across various metabolic pathways. Any disruption in this cycle can lead to serious health problems such as neural tube defects, cardiovascular diseases, and cancer. Ensuring adequate intake of folate, vitamin B12, and methionine-rich foods supports proper functioning of one-carbon metabolism.

