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BHIMAVARAM

DEPARTMENT OF PG MICROBIOLOGY

STUDY MATERIAL

SEMESTER-II

MBY-201: MICROBIOL PHYSIOLOGY AND METABOLISM

MBY-201: MICROBIOL PHYSIOLOGY AND METABOLISM

NUTRITIONAL TYPES

Bacteria are prokaryotic organisms that require nutrients and energy for their growth and development like other living organisms. They require carbon, hydrogen, oxygen, nitrogen, metals and water for their biochemical processes. On the basis of their energy source and the carbon, bacteria are divided into two major classes: autotrophs and heterotrophs.

The classification of bacteria based on nutrition is as follows:

Autotrophs

Organisms that obtain carbon from carbon dioxide and use light energy or inorganic chemical compounds to produce complex organic compounds are known as autotrophs. These are bacteria that can synthesise their own food from inorganic compounds.

Autotrophic bacteria are further classified into two:

Photoautotroph

Photoautotrophic bacteria use CO_2 as their carbon source to convert it into carbohydrates in the presence of sunlight. These bacteria have bacteriochlorophyll and bacterioviridin pigments in their photosystems. Example: cyanobacteria, purple sulphur bacteria and green sulphur bacteria.

Chemoautotroph

Chemoautotrophs are organisms that use inorganic sources to synthesise organic compounds in the absence of light. These bacteria lack any pigments and carry out only the dark phase of photosynthesis. Example: sulphur bacteria that oxidise elemental sulphur to gain energy, *Hydromonas* (hydrogen bacteria) that convert hydrogen into water, iron bacteria that obtain energy by oxidising dissolved ferrous oxides, methanogens and nitrifying bacteria.

Heterotrophs

Heterotrophs are organisms that cannot make their own food but instead obtain nutrition from other organic sources that may be living or dead. Heterotrophs can be divided into two:

Photoheterotrophs

Photoheterotrophic bacteria are those that use light as their source of energy but cannot use carbon dioxide as the carbon source. Instead they obtain nutrition from organic compounds

found in the environment such as alcohols, carbohydrates and fatty acids. Examples: purple non-sulphur bacteria, heliobacteria and green non-sulphur bacteria.

Chemoheterotrophs

Chemoheterotrophs are organisms that derive their energy as well as their carbon source from organic compounds such as carbohydrates and lipids. Example: saprophytic bacteria.

On the basis of **electron source** organisms are designated as:

Lithotrophs:

- Some organisms can use reduced organic compounds as electron donors and are termed as Lithotrophs.
- They can be Chemolithotrophs and Photolithotrophs

Organotrophs:

- Some organisms can use organic compounds as electron donors and are termed as organotrophs.
- Some can be Chemoorganotrophs and Photoorganotrophs.

Thus, bacteria may be either:

Photo-lithotrops:

- These bacteria gain energy from light and use reduced inorganic compounds such as H_2S as a source of electrons. eg: *Chromatium okeinii*.

Photo-organotrophs:

- These bacteria gain energy from light an d use organic compounds such as Succinate as a source of electrons.eg; *Rhodospirillum*.

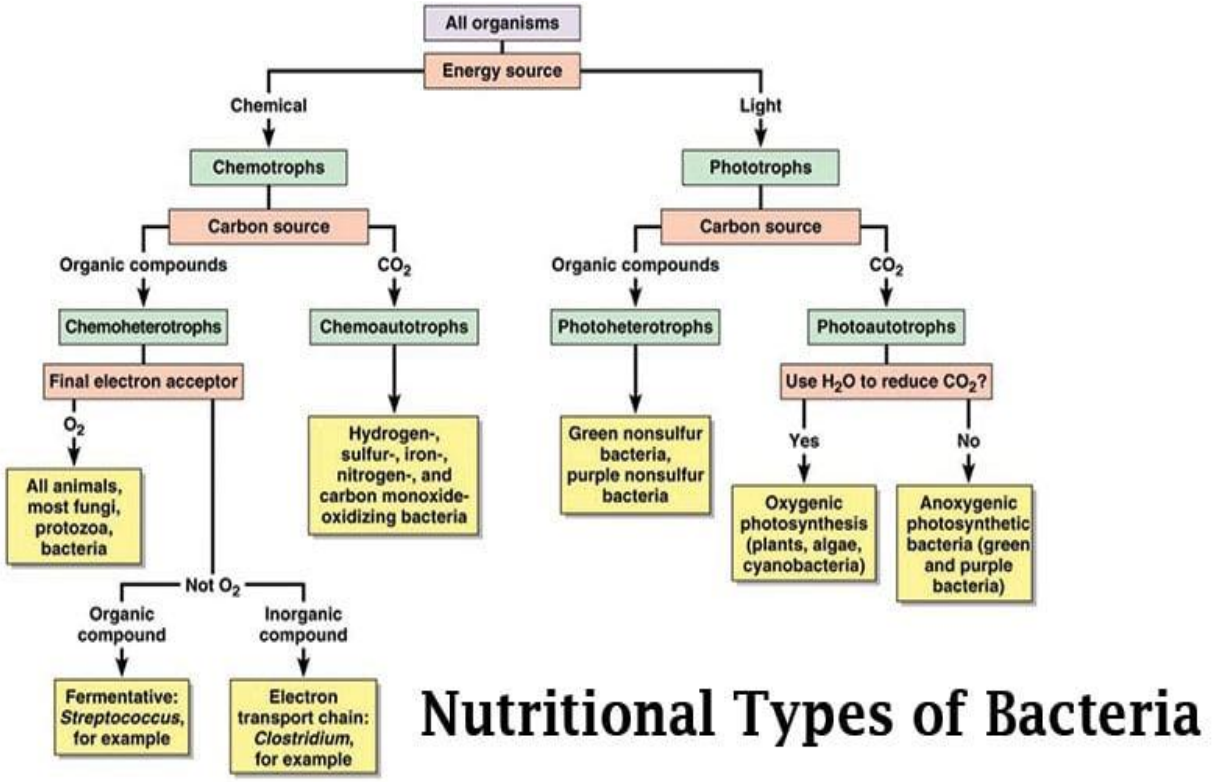
Chemo-lithotrophs:

- These bacteria gain energy from reduced inorganic compounds such as NH3 as a source of electron eg; *Nitrosomonas*.

Chemo-organotrophs:

- These bacteria gain energy from organic compounds such as glucose and ammino acids as a source of electrons.eg; *Pseudomonas pseudoflora*.
- Some bacteria can live ether chemo-lithotrophs or chemoorganotrophs like *Pseudomonas pseudoflora* as they can use either glucose or H2S as electron source.

MBY-201: MICROBIOL PHYSIOLOGY AND METABOLISM



MICROBIAL GROWTH:

Microbial growth refers to the proliferation of microorganisms such as bacteria, fungi, protozoa, and viruses under suitable environmental conditions. These conditions typically include factors like nutrients, temperature, pH, moisture, oxygen availability, and other environmental factors.

Factors Influencing Microbial Growth:

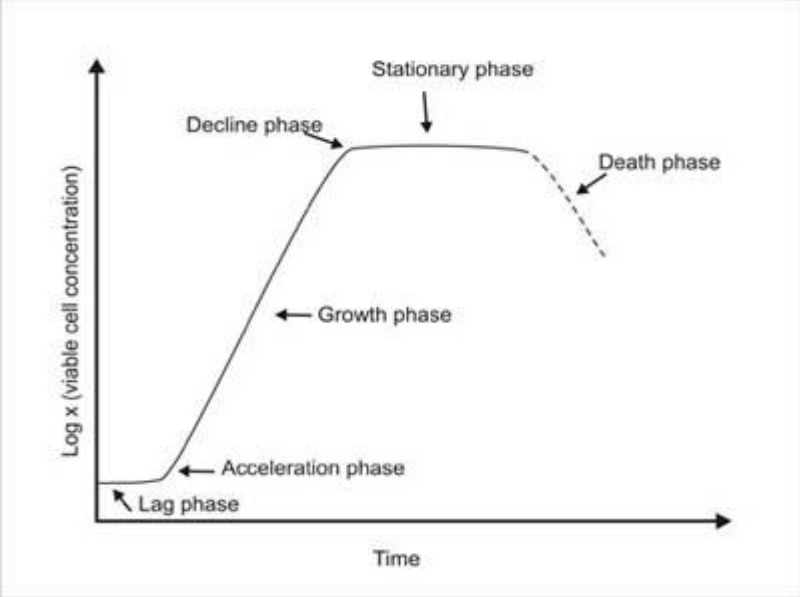
1. **Nutrients**: Microorganisms require various nutrients such as carbon, nitrogen, sulfur, phosphorus, and trace elements to grow and reproduce. These nutrients can be found in organic matter or inorganic compounds.
2. **Temperature**: Each microorganism has an optimal temperature range for growth. Psychrophiles grow best at cold temperatures (0-20°C), mesophiles at moderate temperatures (20-45°C), and thermophiles at high temperatures (45-80°C or higher).
3. **pH**: Microorganisms have specific pH ranges where they thrive. Acidophiles prefer acidic environments (pH < 5), neutrophiles grow best at neutral pH (pH 5.5-8.5), and alkaliphiles prefer alkaline conditions (pH > 8.5).
4. **Moisture**: Most microorganisms require moisture for growth, though the amount needed varies. Water activity (aw) is a measure of water availability in a substance, with lower water activity inhibiting microbial growth.

5. **Oxygen**: Oxygen availability affects the growth of microorganisms. Aerobes require oxygen for growth, anaerobes grow in the absence of oxygen, while facultative anaerobes can grow in both oxygen-rich and oxygen-poor environments.
6. **Light**: Some microorganisms, particularly phototrophs like algae and certain bacteria, require light for growth through photosynthesis.
7. **Environmental Factors**: Factors such as pressure, radiation, and salinity can also influence microbial growth, especially in extremophiles that thrive in extreme environments.

Phases of Microbial Growth:

Microbial growth typically occurs in distinct phases:

1. **Lag Phase**: Initially, microorganisms adjust to the new environment, synthesizing enzymes and preparing for growth. There is no significant increase in population during this phase.
2. **Log Phase (Exponential Phase)**: Microorganisms grow and divide rapidly, doubling in number at a constant rate. This phase continues as long as conditions are favorable and nutrients are abundant
3. **Stationary Phase**: Growth rate slows as nutrients become limited, waste products accumulate, and environmental conditions become less favorable. The number of cells dividing equals the number dying, resulting in a plateau in population growth.
4. **Death Phase**: If unfavorable conditions persist, cells start to die at a faster rate than new cells are formed, leading to a decline in a pollution.



MBY-201: MICROBIOL PHYSIOLOGY AND METABOLISM

CARBOHYDRATE METABOLISM IN MICROBES:

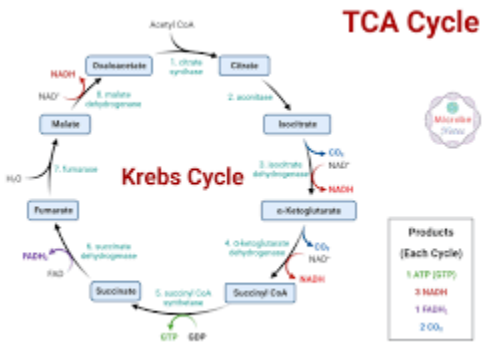
1. Carbohydrate metabolism in microbes involves the biochemical processes by which microorganisms acquire, convert, and utilize carbohydrates (sugars) as sources of energy and building blocks for cellular processes.
2. **Sources of Carbohydrates:**
    - Microbes can metabolize a variety of carbohydrates, including monosaccharides (glucose, fructose), disaccharides (sucrose, lactose), and polysaccharides (starch, cellulose, glycogen).
3. **Pathways Involved:**
    - **Glycolysis:**
        - **Definition:** The conversion of glucose (or other sugars) into pyruvate.
        - **Steps:** Glucose is phosphorylated and cleaved into two molecules of glyceraldehyde-3-phosphate (G3P), which are then oxidized to pyruvate, producing ATP and reducing equivalents (NADH).
    - **Fermentation:**
        - **Definition:** Anaerobic breakdown of sugars into simpler organic compounds (e.g., lactic acid, ethanol, or other acids) to regenerate NAD+ for glycolysis.
        - **Importance:** Allows microbes to generate ATP in the absence of oxygen, essential for anaerobic environments.
    - **Citric Acid Cycle (TCA cycle or Krebs cycle):**
        - **Definition:** Aerobic pathway that completes the oxidation of glucose-derived pyruvate to CO2 and H2O, generating ATP and reducing equivalents (NADH, FADH2).
        - **Steps:** Pyruvate is converted to acetyl-CoA, which enters the TCA cycle to produce ATP, NADH, and FADH2.
    - **Pentose Phosphate Pathway (PPP):**
        - **Function:** Generates NADPH and ribose-5-phosphate (for nucleotide synthesis) from glucose-6-phosphate.
        - **Importance:** Provides reducing equivalents (NADPH) for biosynthetic processes and helps maintain cellular redox balance.
4. **Regulation of Carbohydrate Metabolism:**
    - **Enzyme Regulation:** Key enzymes in glycolysis, TCA cycle, and PPP are regulated by feedback inhibition and allosteric modulation to control metabolic flux.
    - **Regulatory Proteins:** Transcriptional regulators (e.g., catabolite activator protein, CAP) control the expression of genes involved in carbohydrate utilization in response to environmental signals (e.g., glucose availability).
5. **Diverse Metabolic Strategies:**
    - **Heterotrophic Metabolism:** Most microbes are heterotrophic, utilizing organic carbon sources (like sugars) as their primary energy and carbon source.
    - **Autotrophic Metabolism:** Some microbes (e.g., certain bacteria and archaea) can fix CO2 and utilize inorganic carbon sources through pathways such as the Calvin cycle or the reductive TCA cycle.
6. **Applications and Importance:**

- **Biotechnology:** Engineering microbes for the production of biofuels (e.g., ethanol), industrial enzymes, and biopolymers.
- **Environmental Bioremediation:** Microbes metabolize carbohydrates to degrade organic pollutants in soil, water, and wastewater treatment.
- **Pathogenesis:** Understanding microbial carbohydrate metabolism helps in studying virulence mechanisms and developing antimicrobial strategies.

Understanding carbohydrate metabolism in microbes is crucial for various fields, including biotechnology, medicine, and environmental science, providing insights into microbial physiology, ecology, and industrial applications

KREB'S CYCLE:

1. **Definition:**
   - The Krebs Cycle is a central metabolic pathway found in aerobic organisms that oxidizes acetyl-CoA derived from carbohydrates, fats, and proteins to produce ATP and metabolic intermediates.
2. **Location:**
   - It takes place in the mitochondrial matrix of eukaryotic cells and the cytoplasm of prokaryotic cells.



3. **Steps of the Krebs Cycle:**
   - **Step 1: Formation of Citrate**
     - Acetyl-CoA (2-carbon molecule) combines with oxaloacetate (4-carbon molecule) to form citrate (6-carbon molecule), catalyzed by citrate synthase.
     - Coenzyme A (CoA) is released.
   - **Step 2: Isomerization**
     - Citrate undergoes isomerization to form isocitrate, catalyzed by aconitase.
   - **Step 3: Oxidative Decarboxylation**
     - Isocitrate is oxidized to α-ketoglutarate, releasing CO2 and producing NADH. This reaction is catalyzed by isocitrate dehydrogenase.
   - **Step 4: Formation of Succinyl-CoA**

        - α-ketoglutarate is oxidized to form succinyl-CoA, releasing CO2 and producing NADH. This reaction is catalyzed by α-ketoglutarate dehydrogenase complex.
    - **Step 5: Substrate-level Phosphorylation**
        - Succinyl-CoA undergoes substrate-level phosphorylation to form succinate, releasing CoA and producing GTP (which can be converted to ATP). This reaction is catalyzed by succinyl-CoA synthetase.
    - **Step 6: Oxidation of Succinate**
        - Succinate is oxidized to fumarate, producing FADH2. This reaction is catalyzed by succinate dehydrogenase (which is also part of the electron transport chain).
    - **Step 7: Hydration of Fumarate**
        - Fumarate is hydrated to form malate, catalyzed by fumarase.
    - **Step 8: Oxidation of Malate**
        - Malate is oxidized to oxaloacetate, producing NADH. This reaction is catalyzed by malate dehydrogenase.
4. **Role of Coenzymes:**
    - The Krebs Cycle generates reduced coenzymes NADH and FADH2, which carry high-energy electrons to the electron transport chain for ATP production through oxidative phosphorylation.
5. **Regulation:**
    - Enzymes involved in the Krebs Cycle are regulated allosterically and by substrate availability, energy needs of the cell (ATP/ADP ratio), and hormonal signals (e.g., insulin, glucagon).
6. **Function:**
    - **ATP Production:** The Krebs Cycle produces ATP directly through substrate-level phosphorylation (GTP) and indirectly through the electron carriers NADH and FADH2, which donate electrons to the electron transport chain.
    - **Intermediary Metabolites:** Provides precursor molecules (e.g., oxaloacetate, α-ketoglutarate) for biosynthesis of amino acids, nucleotides, and other cellular components.
7. **Importance:**
    - The Krebs Cycle is a central hub of metabolism, integrating carbohydrate, lipid, and protein metabolism to provide energy and building blocks for cellular processes.
    - It plays a crucial role in maintaining cellular redox balance and responding to metabolic demands under varying conditions.
8. **Clinical Relevance:**
    - Dysregulation of the Krebs Cycle enzymes or intermediates is implicated in metabolic disorders (e.g., mitochondrial diseases, diabetes mellitus) and certain cancers where altered metabolism supports tumor growth.

Understanding the Krebs Cycle is fundamental in biochemistry and provides insights into how organisms generate energy, maintain cellular functions, and synthesize essential biomolecules for growth and survival.

MBY-201: MICROBIOL PHYSIOLOGY AND METABOLISM

METABOLISM OF AMINO ACIDS:

Metabolism of amino acids involves intricate biochemical pathways that play crucial roles in energy production, biosynthesis of biomolecules, and maintaining cellular homeostasis. Here's an overview of the key aspects of amino acid metabolism:

1. Amino Acid Catabolism:

- **Transamination:** Amino acids undergo transamination where the amino group (-NH2) is transferred to α-ketoglutarate to form glutamate, catalyzed by aminotransferases (transaminases). This process yields α-keto acids, which can enter metabolic pathways or be converted to intermediates for energy production.
- **Deamination:** Glutamate undergoes oxidative deamination by glutamate dehydrogenase, releasing ammonia (NH3) and forming α-ketoglutarate. Ammonia is toxic and is usually converted to urea in the liver (urea cycle) for excretion.
- **Urea Cycle:** Ammonia produced from amino acid catabolism, primarily in the liver, combines with carbon dioxide to form urea, a less toxic compound excreted in urine. The urea cycle involves several enzymatic steps and occurs in the mitochondria and cytoplasm of liver cells.

2. Carbon Skeleton Utilization:

- **Glucogenic vs. Ketogenic:** Amino acids can be classified based on the fate of their carbon skeletons after deamination:
    - **Glucogenic:** Carbon skeletons can be converted to intermediates of glycolysis or the TCA cycle to produce glucose (gluconeogenesis).
    - **Ketogenic:** Carbon skeletons can be converted to acetyl-CoA or acetoacetyl-CoA, which can enter ketogenesis to produce ketone bodies (acetone, acetoacetate, and β-hydroxybutyrate).

3. Biosynthesis of Non-Essential Amino Acids:

- **Transamination and De Novo Synthesis:** Non-essential amino acids can be synthesized from intermediates of glycolysis, the TCA cycle, or pentose phosphate pathway. Transamination reactions transfer amino groups from glutamate or glutamine to form specific amino acids as needed by the cell.

4. Essential Amino Acids:

- **Dietary Sources:** Essential amino acids cannot be synthesized by the body and must be obtained from the diet. They are critical for protein synthesis and various metabolic functions.

5. Regulation and Integration:

- **Regulation:** Enzymes involved in amino acid metabolism are regulated allosterically, by feedback inhibition, and through hormonal signals to maintain metabolic balance and respond to nutritional status.
- **Integration:** Amino acid metabolism is interconnected with carbohydrate and lipid metabolism. Intermediates from amino acid breakdown feed into glycolysis, the TCA cycle, or gluconeogenesis to provide energy or building blocks for cellular processes.

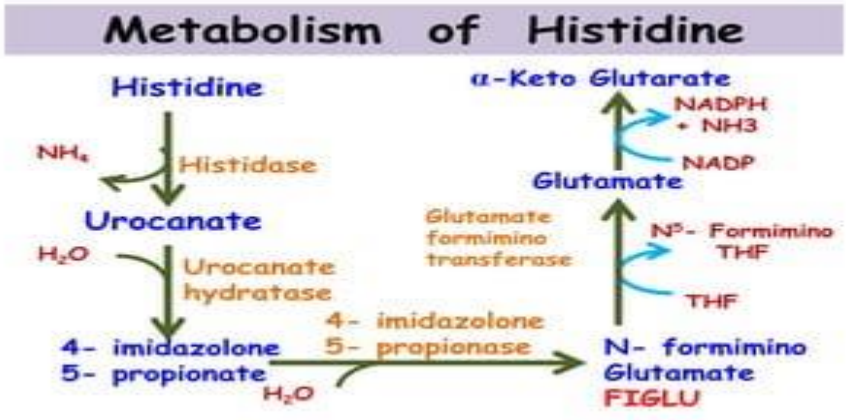
6. Clinical Implications:

- **Inborn Errors of Metabolism:** Genetic defects in enzymes of amino acid metabolism lead to inborn errors of metabolism (e.g., phenylketonuria, maple syrup urine disease) characterized by abnormal accumulation of amino acids or their toxic intermediates.
- **Nutritional Disorders:** Malnutrition or deficiencies in essential amino acids can impair protein synthesis, growth, and overall health.

Understanding amino acid metabolism is essential for comprehending cellular physiology, nutrition, and the biochemical basis of metabolic diseases. It underscores the dynamic interplay between diet, metabolism, and cellular function in maintaining health and responding to metabolic challenges

<u>METABOLISM OF HISTIDINE:</u>

1. **Introduction:**
   - Histidine is an essential amino acid required for protein synthesis and serves as a precursor for the synthesis of histamine, carnosine, and other bioactive compounds.
2. **Dietary Sources:**
   - Histidine is obtained from dietary sources such as meat, poultry, fish, dairy products, and some plant sources.
3. **Synthesis and Metabolism Pathways:**



   - **Histidine Biosynthesis:**

- In bacteria and plants, histidine biosynthesis involves a series of enzymatic steps starting from phosphoribosyl pyrophosphate (PRPP) and leads to the formation of histidine via several intermediates.
  - **Histidine Catabolism:**
- Histidine catabolism primarily occurs in the liver and involves several enzymatic reactions:

1. **Step 1: Histidine to Urocanate**
   - Histidine is first converted to urocanate by the enzyme histidine ammonia-lyase (or histidase), releasing ammonia as a byproduct.
2. **Step 2: Urocanate to 4-Imidazolone-5-Propanoate**
   - Urocanate is converted to 4-imidazolone-5-propanoate by urocanase.
3. **Step 3: 4-Imidazolone-5-Propanoate to Formiminoglutamate**
   - 4-Imidazolone-5-propanoate is converted to formiminoglutamate by the enzyme imidazolonepropionase.
4. **Step 4: Formiminoglutamate to Glutamate**
   - Formiminoglutamate undergoes hydrolysis to form glutamate by formiminoglutamase.
5. **Step 5: Glutamate to α-Ketoglutarate**
   - Glutamate is converted to α-ketoglutarate through oxidative deamination, producing ammonia and generating NADH or NADPH.
6. **Step 6: α-Ketoglutarate to Citric Acid Cycle**
   - α-Ketoglutarate enters the citric acid cycle (Krebs cycle) to be oxidized further for energy production or used in biosynthetic pathways.

4. **Functions and Roles in the Body:**
   - **Protein Synthesis:** Histidine is incorporated into proteins during translation, contributing to the structure and function of proteins.
   - **Histamine Production:** Histidine serves as a precursor for histamine synthesis, which plays roles in allergic responses, neurotransmission, and gastric acid secretion.
   - **Carnosine Synthesis:** Histidine, along with β-alanine, forms the dipeptide carnosine, which acts as a pH buffer and antioxidant in muscle tissues.
5. **Clinical Significance:**
   - **Histidinemia:** A rare genetic disorder characterized by elevated levels of histidine in blood and urine due to deficiency of histidase enzyme. It can lead to neurological symptoms if untreated.
   - **Nutritional Considerations:** Histidine is essential for growth and development, and deficiency can impact protein synthesis and overall health.
6. **Regulation and Pathophysiology:**
   - Enzymes involved in histidine metabolism are regulated at transcriptional and post-translational levels to maintain metabolic balance and respond to dietary and physiological changes.
7. **Research and Future Directions:**

- Continued research focuses on understanding the roles of histidine in health and disease, exploring therapeutic potentials in conditions involving histamine dysregulation and metabolic disorders.

Understanding the metabolism of histidine provides insights into its roles in protein synthesis, histamine production, and overall metabolic health. It underscores the complex interplay between dietary intake, biochemical pathways, and physiological functions in maintaining cellular homeostasis.

CATABOLISM OF AMINO ACIDS:

- **Introduction:**
  - Amino acids are essential building blocks of proteins and play vital roles in various biochemical processes. Their catabolism involves breaking down amino acids to generate energy, produce metabolic intermediates, and eliminate nitrogen in the form of urea or ammonia.
- **General Pathways:**
  - **Transamination:**
    - Amino acids undergo transamination where the amino group (-NH2) is transferred to α-ketoglutarate (derived from the TCA cycle) to form glutamate.
    - Transaminases (aminotransferases) catalyze this reversible reaction, transferring the amino group from the amino acid to α-ketoglutarate, yielding glutamate and the corresponding α-keto acid (e.g., pyruvate from alanine, oxaloacetate from aspartate).
  - **Deamination:**
    - Glutamate undergoes oxidative deamination by glutamate dehydrogenase, releasing ammonia (NH3) and forming α-ketoglutarate.
    - Ammonia can be toxic and is processed further to urea or excreted directly as ammonia in some organisms.
  - **Urea Cycle:**
    - In mammals and some other organisms, excess ammonia generated from amino acid breakdown is converted to urea in the liver through a series of enzymatic reactions known as the urea cycle.
    - The urea cycle occurs in the mitochondria and cytosol of liver cells and involves the incorporation of ammonia into urea, which is less toxic and excreted in the urine.

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LIPID METABOLISM :

1. **Introduction:**
   - Lipids are a diverse group of molecules that include fats, oils, phospholipids, and steroids. Lipid metabolism refers to the processes by which lipids are synthesized, stored, and utilized for energy and cellular functions.
2. **Types of Lipids:**
   - **Fatty Acids:** Building blocks of many lipids, consisting of long hydrocarbon chains with a carboxyl group.
   - **Triglycerides:** Storage form of lipids, composed of glycerol linked to three fatty acids.
   - **Phospholipids:** Essential components of cell membranes, consisting of glycerol linked to two fatty acids and a phosphate group.
   - **Steroids:** Lipids with a characteristic four-ring structure, including cholesterol and steroid hormones.
3. **Lipid Digestion and Absorption:**
   - **Digestion:** Dietary fats (triglycerides) are broken down by lipases into glycerol and fatty acids in the intestine.
   - **Absorption:** Glycerol and fatty acids are absorbed into intestinal cells (enterocytes), re-esterified into triglycerides, and packaged into chylomicrons for transport via lymphatic and blood circulation.
4. **Lipid Storage and Mobilization:**
   - **Storage:** Excess dietary lipids or synthesized lipids (lipogenesis) are stored as triglycerides in adipose tissue and liver cells (as lipid droplets).
   - **Mobilization:** During fasting or energy demand, stored triglycerides are hydrolyzed into glycerol and fatty acids (lipolysis) and released into the bloodstream for energy production.
5. **Fatty Acid Oxidation (Beta-Oxidation):**
   - **Process:** Fatty acids are oxidized in the mitochondria through beta-oxidation, which involves sequential removal of two-carbon units (acetyl-CoA) from the fatty acid chain.
   - **Products:** Acetyl-CoA enters the TCA cycle for ATP production via oxidative phosphorylation.
6. **Ketogenesis:**
   - **Definition:** During prolonged fasting or low carbohydrate intake, excess acetyl-CoA from fatty acid oxidation leads to the production of ketone bodies (acetoacetate, β-hydroxybutyrate, acetone) in the liver.
   - **Utilization:** Ketone bodies are transported to extrahepatic tissues (e.g., brain, muscle) and oxidized for energy in mitochondria.
7. **Lipogenesis:**
   - **Definition:** Synthesis of fatty acids and triglycerides from acetyl-CoA, predominantly occurring in the liver and adipose tissue in response to excess dietary carbohydrates or calorie intake.
   - **Regulation:** Enzymes involved in lipogenesis (e.g., acetyl-CoA carboxylase, fatty acid synthase) are regulated by hormonal signals (e.g., insulin), nutritional status, and substrate availability.

8. **Cholesterol Metabolism:**
    - **Synthesis:** Cholesterol is synthesized primarily in the liver from acetyl-CoA through a series of enzymatic steps (e.g., HMG-CoA reductase).
    - **Transport:** Cholesterol is transported in the bloodstream as lipoproteins (e.g., LDL, HDL) and plays roles in cell membrane structure, bile acid synthesis, and steroid hormone production.
9. **Regulation of Lipid Metabolism:**
    - **Hormonal Regulation:** Insulin promotes lipid storage (lipogenesis) and inhibits lipolysis. Glucagon and epinephrine stimulate lipolysis and fatty acid oxidation during fasting or stress.
    - **Transcriptional Regulation:** Nuclear receptors (e.g., PPARs, LXR) and transcription factors (e.g., SREBP, ChREBP) regulate genes involved in lipid metabolism in response to metabolic signals.
10. **Clinical Relevance:**

- **Dyslipidemia:** Imbalances in lipid metabolism contribute to disorders such as hyperlipidemia (elevated blood lipids), atherosclerosis, and metabolic syndrome.
- **Therapeutic Interventions:** Pharmacological agents (e.g., statins, fibrates) and lifestyle modifications (diet, exercise) are used to manage lipid disorders and reduce cardiovascular risk.

11. **Research and Future Directions:**

- Ongoing research focuses on understanding the molecular mechanisms of lipid metabolism in health and disease, exploring new therapeutic targets for lipid-related disorders.
- Advances in lipidomics and metabolic profiling contribute to personalized medicine approaches in managing lipid disorders and metabolic diseases.

Understanding lipid metabolism is crucial for understanding energy homeostasis, cellular function, and metabolic health. It underscores the complex interplay between dietary intake, biochemical pathways, hormonal regulation, and physiological responses in maintaining lipid balance and overall metabolic function.

MBY-201: MICROBIOL PHYSIOLOGY AND METABOLISM

BIOSYNTHESIS OF PURINS AND PYRAMIDINS NUCLEOTIDS:

1. **Introduction:**
    - Purine nucleotides (adenine and guanine) are essential components of nucleic acids (DNA and RNA) and play critical roles in cellular energy metabolism (ATP, GTP) and signaling pathways (cAMP).
2. **Key Intermediates and Pathway:**
    - **PRPP Synthesis:** The synthesis of purine nucleotides starts with the formation of 5-Phosphoribosyl-1-pyrophosphate (PRPP) from ribose-5-phosphate and ATP, catalyzed by PRPP synthetase.
    - **Purine Ring Formation:**
        - **Step 1: Formation of Inosine Monophosphate (IMP):**
            - PRPP reacts with glutamine to form 5-phosphoribosylamine (PRA).
            - PRA undergoes multiple enzymatic steps to form IMP, which is the first nucleotide in the purine biosynthetic pathway.
        - **Step 2: Conversion to AMP and GMP:**
            - IMP can be converted to AMP (adenosine monophosphate) or GMP (guanosine monophosphate) through separate branches of the pathway.
            - AMP is derived from IMP by the addition of aspartate and GTP.
            - GMP is derived from IMP by the addition of glutamine and ATP.
3. **Regulation:**
    - **Feedback Inhibition:** The pathway is tightly regulated by feedback inhibition, where the end products (AMP and GMP) inhibit enzymes earlier in the pathway to prevent overproduction.
    - **PRPP Regulation:** PRPP availability regulates the rate of purine nucleotide synthesis. PRPP synthetase activity is allosterically activated by PRPP and inhibited by purine nucleotides.
4. **Clinical Relevance:**
    - **Purine Metabolism Disorders:** Defects in enzymes of purine biosynthesis can lead to metabolic disorders such as Lesch-Nyhan syndrome (deficiency of HGPRT enzyme) or gout (due to excessive production or impaired excretion of uric acid).
5. **Antimetabolites:**
    - **Chemotherapy:** Drugs like methotrexate and 6-mercaptopurine are antimetabolites that inhibit purine nucleotide synthesis, used in cancer chemotherapy to inhibit cell proliferation.

Biosynthesis of Pyrimidine Nucleotides:

1. **Introduction:**

- Pyrimidine nucleotides (cytosine, thymine, and uracil) are essential components of nucleic acids (DNA and RNA) and play roles in energy metabolism (CTP, UTP) and biosynthetic pathways.

2. **Pathway:**
   - **Synthesis of Uridine Monophosphate (UMP):**
     - **Step 1: Formation of Carbamoyl Phosphate:**
       - Carbamoyl phosphate is synthesized from glutamine, bicarbonate, and ATP.
     - **Step 2: Formation of Orotate:**
       - Carbamoyl phosphate reacts with aspartate to form orotate, catalyzed by aspartate transcarbamoylase.
     - **Step 3: Formation of UMP:**
       - Orotate is converted to UMP through a series of enzymatic reactions, involving decarboxylation and phosphorylation steps.
   - **Conversion to Other Pyrimidine Nucleotides:**
     - UMP serves as a precursor for other pyrimidine nucleotides:
       - UTP (Uridine Triphosphate)
       - CTP (Cytidine Triphosphate)
       - dTTP (Deoxythymidine Triphosphate) in DNA synthesis.
3. **Regulation:**
   - **Feedback Inhibition:** The pathway is regulated by feedback inhibition, where the end products (CTP, UTP) inhibit enzymes earlier in the pathway to control nucleotide synthesis.
   - **PRPP Regulation:** Similar to purine biosynthesis, PRPP availability regulates pyrimidine nucleotide synthesis.
4. **Clinical Relevance:**
   - **Pyrimidine Metabolism Disorders:** Defects in enzymes of pyrimidine biosynthesis can lead to metabolic disorders such as orotic aciduria (deficiency in UMP synthase) or hereditary orotic aciduria.
5. **Antimetabolites:**
   - **Chemotherapy:** Drugs like 5-fluorouracil and cytarabine are antimetabolites that inhibit pyrimidine nucleotide synthesis, used in cancer chemotherapy to inhibit cell proliferation.

Understanding the biosynthesis of purine and pyrimidine nucleotides is crucial for understanding cellular metabolism, DNA/RNA synthesis, and the development of therapeutic strategies for metabolic disorders and cancer treatment. These pathways illustrate the intricate regulation and integration of biochemical processes essential for cellular function and survival