Chapter 12

Endogenous Antioxidants-I

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ABSTRACT

Endogenous antioxidants are critical components of the body's defense system against oxidative stress caused by free radicals. These antioxidants, both enzymatic and nonenzymatic, work together to neutralize reactive oxygen species (ROS) and prevent cellular damage. The enzymatic antioxidant defense includes key enzymes such as superoxide dismutase (SOD) and catalase, which play pivotal roles in detoxifying harmful free radicals. Superoxide dismutase (SOD) is one of the primary enzymatic antioxidants, responsible for catalyzing the dismutation of the superoxide radical into oxygen and hydrogen peroxide. This process is crucial as it converts the highly reactive superoxide radical into less harmful molecules. Following this, catalase, another essential antioxidant enzyme, converts hydrogen peroxide into water and oxygen, effectively reducing the potential for oxidative damage. These enzymatic defenses are complemented by nonenzymatic antioxidants, such as vitamins C and E, glutathione, and flavonoids, which scavenge free radicals and protect cells from oxidative damage. Together, these antioxidant systems form a comprehensive network that safeguards the body against oxidative stress, maintaining cellular integrity and reducing the risk of chronic diseases associated with free radical damage. The efficiency of these endogenous antioxidants is vital for health, making them a key focus in the study of aging and disease prevention.

INTRODUCTION

Antioxidants are compounds that protect cells from damage caused by oxidative stress. Oxidative stress results from an imbalance between free radicals (reactive oxygen species, ROS) and the body's ability to neutralize them with antioxidants. Here's a detailed introduction:

1. **What Are Antioxidants?**

   Antioxidants are molecules that neutralize free radicals by donating electrons, thus preventing or reducing damage to cellular components like DNA, proteins, and lipids. This helps mitigate the risk of various diseases and slows down the aging process.

2. **Types of Antioxidants:** Antioxidants can be classified into two main categories

   a. **Endogenous Antioxidants:** These are produced within the body. Key examples include:

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- **Enzymatic Antioxidants:** Such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. These enzymes neutralize specific types of ROS.
- **Non-Enzymatic Antioxidants:** Such as glutathione, which is crucial for detoxifying free radicals.

b. **Exogenous Antioxidants:** These are obtained from the diet and include:

- **Vitamins:** Vitamin C (ascorbic acid), Vitamin E (tocopherol), and Vitamin A (beta-carotene) are potent antioxidants that protect against oxidative damage.
- **Minerals:** Selenium and zinc play crucial roles in the antioxidant defense system by acting as cofactors for antioxidant enzymes.
- **Phytochemicals:** Plant-derived compounds such as flavonoids, polyphenols, and carotenoids have strong antioxidant properties and are found in fruits, vegetables, tea, and other plant-based foods.

3. **Mechanism of Action:** Antioxidants combat oxidative stress through several mechanisms:

   a. **Scavenging Free Radicals:** Directly neutralizing free radicals by donating electrons.

   b. **Chelating Metal Ions:** Binding to metal ions that catalyze the formation of free radicals (e.g., iron and copper).

   c. **Regenerating Other Antioxidants:** Some antioxidants can regenerate other antioxidants, such as Vitamin C regenerating Vitamin E.

   d. **Modulating Enzyme Activity:** Influencing the activity of enzymes involved in oxidative stress responses.

4. **Health Benefits**

   a. **Disease Prevention:** Antioxidants help reduce the risk of chronic diseases such as cardiovascular disease, cancer, and neurodegenerative disorders by minimizing oxidative damage.

   b. **Aging:** They play a role in slowing down the aging process by protecting cells from oxidative damage.

   c. **Immune Function:** Enhancing the immune system's ability to combat infections and inflammation.

5. **Sources of Antioxidants**

   a. **Fruits:** Berries, citrus fruits, and pomegranates are rich in antioxidants.

   b. **Vegetables:** Leafy greens, bell peppers, and tomatoes provide various antioxidant compounds.

   c. **Nuts and Seeds:** Almonds, walnuts, and flaxseeds contain important antioxidants.

   d. **Herbs and Spices:** Turmeric, cinnamon, and green tea are high in antioxidants.

6. **Considerations and Potential Issues**

   a. **Balance:** While antioxidants are beneficial, an excessive intake from supplements may disrupt the body's natural oxidative balance and have adverse effects.

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b. **Interactions:** Antioxidants can interact with medications or other nutrients, so balance and moderation are essential.

ENDOGENOUS ANTIOXIDANTS

Enzymatic and Nonenzymatic Antioxidant Defense

1. **Enzymatic Antioxidants:** Enzymatic antioxidants are proteins that catalyze reactions to neutralize reactive oxygen species (ROS) and protect cells from oxidative damage. They work by facilitating the conversion of ROS into less harmful molecules. Major enzymatic antioxidants include:

   a. **Superoxide Dismutase (SOD)**

   - **Function:** Catalyzes the conversion of superoxide radicals (O_2^-) into hydrogen peroxide (H_2O_2) and oxygen (O_2).
   - **Types**
     - **Copper-Zinc SOD (Cu/Zn-SOD):** Found in the cytoplasm.
     - **Manganese SOD (Mn-SOD):** Located in the mitochondria.
     - **Extracellular SOD (Ec-SOD):** Found in the extracellular matrix.
   - **Importance:** Helps reduce the damaging effects of superoxide radicals, which are highly reactive and can damage cellular components.

   b. **Catalase**

   - **Function:** Converts hydrogen peroxide (H_2O_2) into water (H_2O) and oxygen (O_2).
   - **Location:** Predominantly found in peroxisomes.
   - **Importance:** Helps detoxify hydrogen peroxide, which can be harmful in high concentrations.

   c. **Glutathione Peroxidase (GPx)**

   - **Function:** Catalyzes the reduction of hydrogen peroxide (H_2O_2) and organic peroxides using glutathione (GSH) as a reducing agent, converting them into water and alcohol.
   - **Types:** Various isoforms exist in different cellular compartments, including cytosolic, mitochondrial, and extracellular forms.
   - **Importance:** Plays a critical role in detoxifying peroxides and maintaining cellular redox balance.

   d. **Glutathione Reductase**

   - **Function:** Regenerates reduced glutathione (GSH) from its oxidized form (GSSG) using NADPH as a reducing agent.
   - **Importance:** Maintains high levels of reduced glutathione, crucial for effective antioxidant defense.

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2. **Nonenzymatic Antioxidants:** Nonenzymatic antioxidants are small molecules that neutralize ROS and other free radicals directly. They are typically obtained through diet and include:

   a. **Glutathione**

   - **Function:** Acts as a major intracellular antioxidant, directly neutralizing ROS and participating in various redox reactions.
   - **Importance:** Helps maintain the redox state of cells and supports various enzymatic antioxidant systems.

   b. **Vitamin C (Ascorbic Acid)**

   - **Function:** Scavenges free radicals, including superoxide radicals and hydroxyl radicals, and regenerates other antioxidants like Vitamin E.
   - **Importance:** Contributes to collagen synthesis, immune function, and acts as a potent water-soluble antioxidant.

   c. **Vitamin E (Tocopherol)**

   - **Function:** Protects cell membranes by scavenging lipid peroxyl radicals and preventing lipid peroxidation.
   - **Importance:** Acts as a fat-soluble antioxidant, maintaining the integrity of cellular membranes.

   d. **Vitamin A (Beta-Carotene)**

   - **Function:** Acts as a precursor to Vitamin A and possesses antioxidant properties by neutralizing free radicals.
   - **Importance:** Supports vision, immune function, and skin health.

   e. **Polyphenols**

   - **Function:** Includes flavonoids, phenolic acids, and other compounds with antioxidant properties. They neutralize free radicals and modulate oxidative stress-related pathways.
   - **Importance:** Found in fruits, vegetables, tea, and red wine, contributing to overall antioxidant defense.

   f. **Coenzyme Q10 (Ubiquinone)**

   - **Function:** Participates in the electron transport chain in mitochondria and has antioxidant properties, protecting cellular components from oxidative damage.
   - **Importance:** Supports cellular energy production and protects against oxidative stress.

Superoxide Dismutase

1. **Overview:** Superoxide dismutase (SOD) is a key enzymatic antioxidant that protects cells from oxidative damage by catalyzing the dismutation of superoxide radicals (O_2^-) into less harmful molecules. Superoxide radicals are highly reactive and can cause significant damage to cellular components, such as lipids, proteins, and DNA.

2. **Function**

   a. **Catalytic Reaction:** SOD catalyzes the reaction:

   $$2O_2^- + 2H^+ \rightarrow O_2 + H_2O_2$$

   This reaction converts two superoxide radicals (O_2^-) into one molecule of oxygen (O_2) and one molecule of hydrogen peroxide (H_2O_2). Hydrogen peroxide is then further broken down by other antioxidant enzymes, such as catalase or glutathione peroxidase.

3. **Types of Superoxide Dismutase:** SOD exists in several forms, each with specific cellular locations and metal cofactors:

   a. **Copper-Zinc SOD (Cu/Zn-SOD)**
      - **Location:** Primarily found in the cytoplasm and in extracellular spaces.
      - **Cofactor:** Contains copper (Cu) and zinc (Zn) at its active site.
      - **Importance:** Most abundant form in humans, playing a crucial role in neutralizing superoxide radicals in the cytoplasm.

   b. **Manganese SOD (Mn-SOD)**
      - **Location:** Located in the mitochondria.
      - **Cofactor:** Contains manganese (Mn) at its active site.
      - **Importance:** Essential for protecting mitochondrial components from oxidative damage, as mitochondria are major sources of superoxide radicals.

   c. **Extracellular SOD (Ec-SOD)**
      - **Location:** Found in the extracellular matrix and fluids.
      - **Cofactor:** Contains copper (Cu) and zinc (Zn).
      - **Importance:** Protects extracellular tissues from oxidative damage and regulates inflammation.

4. **Mechanism of Action**

   a. **Superoxide Radicals:** SOD helps in reducing the harmful effects of superoxide radicals, which are produced as by-products of various metabolic processes and can damage cells if not neutralized.

   b. **Conversion of Superoxide:** By converting superoxide radicals into hydrogen peroxide and oxygen, SOD reduces the concentration of superoxide radicals and prevents their interaction with other molecules that could lead to oxidative damage.

5. **Clinical Relevance**

   a. **Oxidative Stress:** Dysregulation or deficiency of SOD is associated with increased oxidative stress and has been implicated in various diseases, including neurodegenerative disorders (e.g., amyotrophic lateral sclerosis), cardiovascular diseases, and cancer.

b. **Therapeutic Potential:** SOD mimetics and gene therapies aimed at enhancing SOD activity are being investigated for their potential therapeutic benefits in treating conditions related to oxidative stress.

Catalase

1. **Overview:** Catalase is an essential enzyme in the endogenous antioxidant defense system. It plays a critical role in protecting cells from oxidative damage by decomposing hydrogen peroxide (H_2O_2), a potentially harmful byproduct of metabolic processes, into water (H_2O) and oxygen (O_2).

2. **Function**

   a. **Catalytic Reaction:** Catalase catalyzes the following reaction:

   $$2H_2O_2 \rightarrow 2H_2O + O_2$$

   This reaction breaks down hydrogen peroxide into water and oxygen, thereby preventing the accumulation of hydrogen peroxide, which can be damaging at high concentrations.

3. **Structure**

   a. **Composition:** Catalase is a tetrameric enzyme, meaning it is composed of four identical subunits. Each subunit contains a heme group, which is essential for its catalytic activity.

   b. **Active Site:** The heme group contains an iron atom that facilitates the breakdown of hydrogen peroxide.

4. **Mechanism of Action**

   a. **Decomposition of Hydrogen Peroxide:** Catalase rapidly decomposes hydrogen peroxide into water and oxygen, mitigating its potential to generate harmful hydroxyl radicals (•OH) through the Fenton reaction or other oxidative processes.

   b. **Efficiency:** Catalase is highly efficient and can process millions of hydrogen peroxide molecules per second, making it one of the fastest enzymes in terms of turnover rate.

5. **Distribution and Localization**

   a. **Cellular Locations:** Catalase is predominantly found in peroxisomes, organelles that are involved in fatty acid oxidation and the breakdown of hydrogen peroxide. It can also be found in the cytoplasm of some cells.

   b. **Concentration:** The concentration of catalase varies between different tissues and organs, reflecting its role in managing oxidative stress based on metabolic activity and exposure to ROS.

6. **Clinical Relevance**

   a. **Oxidative Stress:** Reduced activity or deficiency of catalase can lead to an accumulation of hydrogen peroxide, contributing to oxidative stress and associated damage to cellular structures. This can be linked to various health conditions, including neurodegenerative diseases (e.g., Alzheimer's disease) and certain cancers.

b. **Genetic Disorders:** Mutations in the catalase gene can lead to genetic disorders such as acatalasemia, where individuals lack functional catalase, resulting in increased sensitivity to oxidative damage.

c. **Therapeutic Research:** Catalase supplementation or gene therapy aimed at enhancing catalase activity is being explored for its potential benefits in treating diseases related to oxidative stress.

Glutathione Peroxidase

1. **Overview:** Glutathione peroxidase (GPx) is a crucial enzyme in the endogenous antioxidant defense system. It protects cells from oxidative damage by reducing hydrogen peroxide (H_2O_2) and organic peroxides using glutathione (GSH) as a reducing agent.

2. **Function**

   a. **Catalytic Reaction:** GPx catalyzes the following reactions:

   $$2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$$
   $$R - OOH + 2GSH \rightarrow R - OH + GSSG + H_2O$$

   Here, GSH (reduced glutathione) is oxidized to GSSG (oxidized glutathione) as it reduces hydrogen peroxide (H_2O_2) or organic peroxides to water or alcohols.

   b. **Role in Detoxification:** By converting hydrogen peroxide and organic peroxides into less harmful substances, GPx helps prevent the accumulation of reactive oxygen species (ROS) and protects cellular components from oxidative damage.

3. **Structure and Isoforms**

   a. **Structure:** GPx is a tetrameric enzyme composed of four identical subunits. Each subunit contains a selenocysteine residue at its active site, which is crucial for its enzymatic activity.

   b. **Isoforms:** There are several isoforms of GPx, each with specific cellular locations and functions:

   - **GPx1:** Found in the cytoplasm and mitochondria.
   - **GPx2:** Present in the gastrointestinal tract.
   - **GPx3:** Located in the extracellular fluid.
   - **GPx4:** Associated with cellular membranes and the nucleus.

4. **Mechanism of Action**

   a. **Reduction of Peroxides:** GPx uses glutathione (GSH) to reduce hydrogen peroxide (H_2O_2) and organic peroxides to water or alcohols, respectively. This reaction is essential for controlling oxidative stress within the cell.

   b. **Regeneration of GSH:** The oxidized glutathione (GSSG) formed in the reaction is subsequently regenerated to GSH by glutathione reductase, using NADPH as a reducing agent.

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5. **Distribution and Localization**
   a. **Cellular Locations:** GPx isoforms are distributed in various cellular compartments:
      - **GPx1:** Predominantly in the cytoplasm and mitochondria.
      - **GPx2:** In the gastrointestinal mucosa.
      - **GPx3:** In the plasma and extracellular fluids.
      - **GPx4:** In cellular membranes and the nucleus.

   b. **Concentration:** The concentration of GPx varies depending on tissue type and metabolic activity, reflecting its role in managing oxidative stress.

6. **Clinical Relevance**
   a. **Oxidative Stress:** Reduced GPx activity can lead to increased oxidative stress and cellular damage, contributing to various health conditions, including cardiovascular diseases, neurodegenerative disorders, and cancer.

   b. **Selenium Deficiency:** GPx activity is dependent on selenium, and selenium deficiency can impair GPx function, leading to increased oxidative damage and related health issues.

   c. **Therapeutic Potential:** Enhancing GPx activity through supplementation or gene therapy is being explored for its potential benefits in managing diseases associated with oxidative stress.