THE METABOLIC DISPOSITION OF BIOACTIVE AGENTS

Abstract

The metabolic disposition of bioactive agents refers to the processes by which these agents are metabolized and eliminated from the body. This typically involves enzymatic reactions that transform the bioactive agent into various metabolites, which are then further processed and excreted. Enzymes play a crucial role in the metabolism of bioactive agents. They catalyze specific chemical reactions that facilitate the breakdown, transformation, or conjugation of these agents. Here are some examples of enzymes commonly involved in the metabolic disposition of bioactive agents:

Cytochrome P450 (CYP) enzymes: This super family of enzymes is involved in the oxidation of a wide range of bioactive agents. They play a significant role in drug metabolism by introducing functional groups (e.g., hydroxyl, carboxyl) onto the bioactive agent, making it more water-soluble and facilitating elimination.

UDP-glucuronosyltransferases (UGTs): UGTs are responsible for glucuronidation, a conjugation reaction that adds a glucuronic acid moiety to the bioactive agent. Glucuronidation enhances the water solubility of the agent and promotes its excretion in bile or urine.

Sulfotransferases (SULTs): SULTs catalyze sulfation reactions, where a sulfate group is attached to the bioactive agent. Sulfation is another conjugation reaction that increases the water solubility of the agent and promotes its elimination.

Glutathione S-transferases (GSTs): GSTs facilitate the conjugation of glutathione to bioactive agents, forming glutathione conjugates. This process, known as glutathione conjugation, plays a role in detoxification by rendering the agent more easily excretable.

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N-acetyltransferases (NATs): NATs catalyze the acetylation of bioactive agents by transferring an acetyl group from acetyl-CoA. Acetylation reactions can modify the activity and pharmacokinetics of certain drugs.

Keywords: Cytochrome, Sulfotransferases, N-acetyltransferases, Glutathione S-transferases.

I. INTRODUCTION

The main focus of discussions of the physiological detoxification routes has been the phase I and phase II enzyme systems. In particular, UDP glucuronosyl transferases, glutathione S-transferases, amino acid transferases, N-acetyl transferases, and methyltrans ferases played a major role in disposal of bioactive contents especially phase I and phase II cytochrome P450 enzymes. These are just a few examples of the many enzymes involved in the metabolic disposition of bioactive agents. The specific enzymes and metabolic pathways engaged depend on the structure and properties of the agent in question. Understanding these processes is essential in drug development and optimizing therapeutic efficacy while minimizing adverse effects. This chapter is discussed about the biological disposition of natural origins and its detoxification-related processes.

II. CYTOCHROME P450 (CYP) ENZYME MEDIATED BIOACTIVE COMPOUNDS METABOLIC DISPOSAL

Cytochrome P450 (CYP) enzymes are a superfamily of enzymes found in various organisms, including humans. They play a crucial role in the metabolism and disposal of a wide range of bioactive compounds, including drugs, toxins, hormones, and endogenous substrates. These enzymes are primarily located in the liver, although they can also be found in other tissues, and are involved in the oxidative metabolism of compounds through various reactions, such as hydroxylation, dealkylation, and deamination. Here's how the process generally works:

1. **Metabolism of Bioactive Compounds:** When bioactive compounds such as drugs or other foreign substances enter the body, they are often chemically modified to make them more water-soluble and easier to excrete. This is a crucial step for eliminating these compounds from the body and preventing their accumulation.

2. **Oxidative Reactions:** Cytochrome P450 enzymes catalyze oxidative reactions, which involve adding an oxygen atom to the compound. The oxygen atom comes from molecular oxygen (O2), and the reactions are often referred to as "Phase I metabolism." The addition of an oxygen atom can introduce a functional group (such as a hydroxyl group) into the compound, altering its structure and properties.

3. **Substrate Specificity:** Different CYP enzymes are responsible for metabolizing specific classes of compounds. This specificity is due to the three-dimensional structure of the active site of the enzyme, which allows it to bind to specific substrates. There are multiple CYP enzymes, each with its own substrate preferences.

4. **Drug Interactions:** The activity of CYP enzymes can affect drug interactions. If one drug is metabolized by a specific CYP enzyme and another drug inhibits or induces that enzyme, it can lead to changes in the concentration and effectiveness of the first drug.

5. **Genetic Variability:** Genetic factors can influence the activity of CYP enzymes. Polymorphisms in the genes encoding these enzymes can lead to variations in their activity levels, which can impact how individuals metabolize certain drugs or compounds. This can have implications for drug efficacy and potential adverse reactions.

6. **Metabolite Formation:** The products of CYP-mediated metabolism are often more polar and water-soluble than the original compounds. This transformation facilitates their excretion through urine or bile. In some cases, the metabolites themselves may be biologically active or toxic.

Cytochrome P450 (CYP) enzymes are not only involved in the metabolism of drugs and synthetic compounds but also play a crucial role in the metabolism of a wide range of natural molecules that are endogenous to the body or obtained from dietary sources. These natural molecules include hormones, fatty acids, vitamins, plant-derived compounds, and more. Here are some examples of how CYP enzymes are involved in the metabolism of natural molecules:

1. **Steroid Hormones Metabolism:** CYP enzymes are involved in the metabolism of steroid hormones, which are critical for various physiological processes. For instance, CYP19A1 (aromatase) converts androgens to estrogens, contributing to the regulation of the female reproductive system. CYP11A1 is involved in the synthesis of steroid hormones in the adrenal glands.

2. **Vitamin D Metabolism:** CYP enzymes are essential for the synthesis and activation of vitamin D. Vitamin D undergoes hydroxylation by CYP enzymes, mainly CYP27B1, in the liver and kidney to become its active form, calcitriol, which regulates calcium and phosphate homeostasis.

3. **Fatty Acid Metabolism:** CYP enzymes are involved in the metabolism of fatty acids and eicosanoids, which are signaling molecules derived from fatty acids. CYP enzymes can metabolize arachidonic acid to produce various eicosanoids, such as prostaglandins, thromboxanes, and leukotrienes, which play roles in inflammation and other physiological processes.

4. **Plant-Derived Compounds Metabolism:** CYP enzymes in the gut and liver are involved in the metabolism of various phytochemicals from plants, such as flavonoids, polyphenols, and alkaloids. These compounds are often ingested through the diet and can have effects on health and disease prevention.

5. **Bilirubin Metabolism:** CYP enzymes contribute to the metabolism of bilirubin, a waste product of heme catabolism. CYP enzymes convert bilirubin into more water-soluble forms, allowing for its elimination from the body through bile and urine.

6. **Vitamin A Metabolism:** CYP enzymes are involved in the metabolism of retinol (vitamin A) into its active form, retinoic acid, which plays a role in cell differentiation and gene expression.

7. **Neurotransmitter Metabolism:** CYP enzymes in the brain are involved in the metabolism of neurotransmitters, such as serotonin and dopamine, which are critical for mood regulation and brain function.

8. **Heme Biosynthesis:** CYP enzymes are part of the heme biosynthesis pathway, contributing to the production of heme, a component of hemoglobin and other essential proteins

9. **Cholesterol Metabolism:** CYP enzymes are involved in cholesterol metabolism, playing a role in the synthesis and breakdown of cholesterol.

The purpose of CYP450 enzymes is to add a reactive group by oxidation, reduction, and/or hydrolysis processes, such as a hydroxyl, carboxyl, or an amino group. Due to the creation of reactive electrophilic species, these first events have the potential to produce oxidative damage within cell systems. It is acknowledged that any variation in the amount of CYP450 enzymes may have advantages or disadvantages for how a person reacts to a toxin's effects. Pharmacology has focused on the clinical application of this knowledge of these phases I CYP450 enzymes in order to comprehend the nature of medication interactions, adverse effects, and interindividual variability in drug metabolism.90% of currently used medications can be metabolized by people, but how well they can do so will mainly rely on how these enzymes express themselves genetically. It is known that several of these CYP450 genes are susceptible to genetic variations, which affect how each enzyme expresses and functions.

The metabolism of hormones, prescription medications, and procarcinogens is regulated by the CYP1A family. Cruciferous vegetables (indole-3-carbinol), resveratrol, and other natural substances CYP1A breaks down itadori tea, green and black teas, peanuts, wine, grapes, and soy. Ellagic acid is metabolized by CYP1A1. Blackcurrants, berries, pomegranates, grapes, walnuts, turmeric, curry powder, soybean oil, garlic and its oil, fish oil, and rosemary extract all contain curcumin.

Both CYP1A1 and CYP1A2 are involved in the metabolism of astaxanthin-containing algae, yeast, salmon, trout, krill, shrimp, and crayfish. Curcumin found in turmeric, curry powder, and cruciferous vegetables is also detoxified by CYP1B1.Chicory root's CYP2A and CYP2A6 metabolisms are both impacted by quercetin. Apple, apricot, blueberries, yellow onion, kale, broccoli, green beans, and alfalfa sprouts, in addition to black tea and quercetin from chili powder. CYP2E1 metabolizing and CYP2B2 for Rosemary fatty fish Chinese radish The elagic acid Blackcurrants, grapes, walnuts, pomegranates, and berries Sulforaphane from cruciferous vegetables and CYP2B1 turmeric CYP2C metabolizing green tea stout tea The elagic acid CYP2C9 metabolizing berries, pomegranate, grapes, walnuts, and blackcurrants Resveratrol Peanuts, soy, wine, grapes, and itadori Myricetin Red wine, berries, onions, and grapes CYP2C19 and myricetin metabolism Kale Resveratrol is metabolized by CYP2E1 and found in grapes, wine, peanuts, soy, and itadori tea. The elagic acid Blackcurrants, grapes, walnuts, pomegranates, and berries Dandelion Chrysin Honeycomb with honey MCTs, or medium-chain triglycerides N-acetyl cysteine and kale are both metabolized by coconut oil and CYP2D6.

It's important to note that while CYP enzymes are crucial for the metabolism of many compounds, they are not the only enzymes involved in these processes. Other enzymes, such as UDP-glucuronosyl transferases (UGTs) and sulfotransferases, also play essential roles in the conjugation and elimination of bioactive compounds.

In summary, cytochrome P450 enzymes are a diverse group of enzymes that are central to the metabolism and disposal of various bioactive compounds in the body. Their activity has a significant impact on drug effectiveness, interactions, and overall physiological responses to foreign substances. Overall, CYP enzymes are versatile and play a critical role in the metabolism of a wide range of natural molecules that are vital for normal physiological functioning. Their involvement in these processes highlights their significance in maintaining overall health and homeostasis in the body.

III. UDP-GLUCURONOSYLTRANSFERASES (UGTS) ENZYME MEDIATED BIOACTIVE COMPOUNDS METABOLIC DISPOSAL

UGTs are a family of enzymes that play a crucial role in the metabolism and disposal of bioactive compounds in the body. These enzymes are responsible for a process called glucuronidation, which involves adding a glucuronic acid molecule to a substrate, typically making the compound more water-soluble and facilitating its excretion from the body. Glucuronidation is a Phase II metabolic reaction, often following Phase I reactions like those catalyzed by cytochrome P450 enzymes. Here's an overview of how UGTs and glucuronidation work in the metabolic disposal of bioactive compounds:

1. **Glucuronidation Reaction:** UGT enzymes catalyze the transfer of a glucuronic acid moiety from UDP-glucuronic acid (a co-substrate) to a substrate molecule. This covalent attachment of glucuronic acid to the substrate is known as glucuronidation. The result is the formation of a glucuronide conjugate.

2. **Substrate Specificity:** UGTs have a high degree of substrate specificity, with different UGT isoforms being responsible for metabolizing specific classes of compounds. These compounds include drugs, xenobiotics, endogenous substances like bilirubin and steroid hormones, and their metabolites.

3. **Increased Water Solubility:** Glucuronidation increases the water solubility of the substrate, which makes the conjugate more suitable for excretion via urine or bile. The increased water solubility prevents the reabsorption of the compound in the kidneys' tubular system and enhances its elimination from the body.

4. **Active Metabolites:** In some cases, glucuronidation can lead to the formation of active metabolites. While glucuronidation is often considered a detoxification process, certain glucuronide conjugates have physiological activities of their own.

5. **Genetic Variability:** Genetic polymorphisms in UGT genes can lead to variations in the activity of UGT enzymes. This can result in differences in how individuals metabolize specific compounds, which may impact drug efficacy and potential side effects.

6. **Drug Interactions:** Similar to CYP enzymes, UGTs can also be influenced by drug interactions. Some drugs can induce or inhibit UGT activity, affecting the metabolism of other drugs and potentially leading to altered therapeutic outcomes.

7. **Bilirubin Metabolism:** One of the most well-known roles of UGTs is the conjugation of bilirubin, a waste product of heme catabolism. Conjugation with glucuronic acid converts bilirubin into a water-soluble form that can be excreted in bile.

UDP-glucuronosyltransferases (UGTs) enzymes play a crucial role in the metabolism of various natural molecules in the body. They are responsible for a process called glucuronidation, which involves the transfer of a glucuronic acid molecule from UDP-glucuronic acid to a substrate molecule. This modification enhances the water solubility of the substrate, making it easier to eliminate from the body through urine or bile. Here are some examples of how UGTs are involved in the metabolism of natural products : Cruciferous vegetables, Resveratrol-containing foods like grapes, wine, peanuts, soy, tea, citrus fruits, dandelion and Rooibos tea, rosemary and soy extract, as well as curcumin and astaxanthin, are all detoxifying UGTs.

1. **Bilirubin Metabolism:** One of the most well-known roles of UGTs is the metabolism of bilirubin, a waste product of heme breakdown. UGTs conjugate bilirubin with glucuronic acid, forming bilirubin glucuronide, which is then excreted in bile. This process makes bilirubin water-soluble and prevents its accumulation, which can lead to jaundice.

2. **Steroid Hormones Metabolism:** UGTs are involved in the metabolism of steroid hormones, such as androgens and estrogens. These hormones are conjugated with glucuronic acid, facilitating their excretion and preventing their accumulation.

3. **Phenolic Compounds:** UGTs metabolize various phenolic compounds, including plant-derived compounds like flavonoids and polyphenols found in foods. Conjugation with glucuronic acid can enhance their solubility and aid in their elimination from the body.

4. **Bile Acids:** UGTs contribute to the metabolism of bile acids. Conjugation of bile acids with glucuronic acid increases their water solubility, allowing for their elimination through bile.

5. **Thyroid Hormones Metabolism:** UGTs play a role in the metabolism of thyroid hormones, which are important regulators of metabolism and development. Conjugation with glucuronic acid can contribute to their inactivation and elimination.

6. **Fatty Acids and Lipid Metabolites:** UGTs can metabolize certain lipid-soluble compounds, enhancing their solubility and facilitating their excretion.

7. **Drugs and Xenobiotics:** While UGTs are primarily involved in the metabolism of endogenous molecules, they also participate in the metabolism of drugs and environmental toxins, making these compounds more water-soluble and easier to eliminate.

8. **Biliverdin Metabolism:** UGTs are involved in the conversion of biliverdin, a product of heme degradation, into bilirubin. This is an important step in heme metabolism.

9. **Neurotransmitter Metabolism:** UGTs are also involved in the metabolism of neurotransmitters, aiding in their elimination from the body.

In summary, UDP-glucuronosyltransferases (UGTs) are essential enzymes involved in the glucuronidation of various bioactive compounds, making them more water-soluble and facilitating their elimination from the body. This process is a crucial part of Phase II metabolism and works in conjunction with Phase I reactions, such as those catalyzed by cytochrome P450 enzymes, to ensure the efficient disposal of foreign and endogenous substances. In summary, UDP-glucuronosyltransferases (UGTs) enzymes are integral to the metabolism of a wide range of natural molecules in the body. Their glucuronidation reactions increase the water solubility of substrates, which is critical for efficient excretion and preventing the accumulation of potentially harmful or unnecessary substances. UGTs' involvement in the metabolism of both endogenous and exogenous molecules highlights their significance in maintaining overall health and homeostasis.

IV. SULFOTRANSFERASES (SULTS) ENZYME MEDIATED BIOACTIVE COMPOUNDS METABOLIC DISPOSAL

SULTs are enzymes that play a vital role in the metabolism and disposal of bioactive compounds in the body. They catalyze a process called sulfation, which involves the transfer of a sulfate group (SO4) from the co-substrate 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to a substrate molecule. Sulfation is a Phase II metabolic reaction, similar to glucuronidation, and it enhances the water solubility and excretion of compounds. SULT detoxifies Coffee, cocoa, black tea, green tea, and retinoic acid (a bioactive form of vitamin A) all contains caffeine. Retinol is found in meat (particularly liver), fish, eggs, and dairy products; provitamin a carotenes are found in apple, apricot, artichokes, arugula, asparagus, and other plant foods. Here's an overview of how SULTs and sulfation work in the metabolic disposal of bioactive compounds:

1. **Sulfation Reaction:** SULT enzymes facilitate the transfer of a sulfate group from PAPS to specific functional groups on a substrate. This covalent attachment of a sulfate group to the substrate is known as sulfation.

2. **Substrate Specificity:** Different SULT isoforms are responsible for metabolizing specific classes of compounds. SULTs have varying substrate specificities and can metabolize a wide range of molecules, including drugs, hormones, neurotransmitters, and xenobiotics.

3. **Increased Water Solubility:** Similar to glucuronidation, sulfation increases the water solubility of the substrate. This modification enhances the compound's ability to be eliminated through urine or bile, preventing its reabsorption in the kidneys and aiding in its efficient removal from the body.

4. **Detoxification:** Sulfation is generally considered a detoxification process, as it often leads to the formation of less active or more readily excreted metabolites.

5. **Pharmacological Activity:** In some cases, the sulfate conjugates formed by SULTs can have biological activity. These conjugates may serve as prodrugs that are activated upon being metabolized or may directly influence receptor interactions.

6. **Drug Interactions:** As with other metabolic enzymes, drug interactions can impact SULT activity. Some drugs can induce or inhibit SULT enzymes, leading to altered metabolism of other compounds and potential changes in therapeutic outcomes.

7. **Tyrosine Sulfation:** While most SULTs catalyze the sulfation of small molecules, there are also specialized SULTs responsible for post-translational modification of proteins. For instance, certain proteins contain tyrosine residues that can be sulfated, which can affect protein-protein interactions and signaling pathways.

8. **Genetic Variability:** Genetic variations in SULT genes can lead to differences in enzyme activity and substrate preferences, influencing how individuals metabolize various compounds.

Sulfotransferases (SULTs) are enzymes that play a significant role in the metabolism of various biomolecules and natural compounds in the body. They catalyze a process called sulfation, where they transfer a sulfate group (SO4) from the co-substrate 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to a substrate molecule. Sulfation is a form of Phase II metabolism, enhancing the water solubility and aiding in the elimination of compounds. Here are some examples of how SULTs are involved in the metabolism of biomolecules and natural compounds:

1. **Hormones:** SULTs are involved in the metabolism of hormones such as thyroid hormones and steroid hormones. Sulfation can influence the activity and solubility of these hormones, affecting their transport and elimination from the body.

2. **Neurotransmitters:** SULTs play a role in the metabolism of neurotransmitters like dopamine and serotonin. Sulfation can modulate their biological activity and help regulate neurotransmitter levels.

3. **Phenolic Compounds:** SULTs metabolize various phenolic compounds found in foods, plants, and the environment. Sulfation can enhance the water solubility of these compounds, facilitating their excretion.

4. **Conjugation with Xenobiotics:** SULTs contribute to the detoxification of xenobiotics and environmental toxins by adding a sulfate group, making them more water-soluble and easier to eliminate.

5. **Bile Acids:** SULTs are involved in bile acid metabolism. Sulfation of bile acids can affect their solubility, aiding in their transport and elimination.

6. **Carbohydrates and Glycosaminoglycans:** SULTs play a role in the sulfation of carbohydrates and glycosaminoglycans (GAGs), which are components of connective tissues, cartilage, and the extracellular matrix. Sulfation of GAGs affects their structure and function.

7. **Tyrosine Sulfation:** Some SULTs are responsible for post-translational modification of proteins by adding sulfate groups to tyrosine residues. This modification can influence protein-protein interactions and cellular signaling.

8. **Flavonoids and Polyphenols:** SULTs metabolize certain dietary polyphenols and flavonoids, contributing to their detoxification and elimination.

9. **Xenobiotic Metabolism:** SULTs can metabolize a variety of xenobiotics, including drugs and environmental pollutants. Sulfation enhances their solubility and elimination.

10. Catecholamines: SULTs are involved in the metabolism of catecholamines like adrenaline and noradrenaline, which are important for the "fight or flight" response.

11. **Heparin and Heparan Sulfate:** SULTs are involved in the biosynthesis of heparin and heparan sulfate, which are glycosaminoglycans with critical roles in various biological processes, including blood clotting and cell signaling.

In summary, sulfotransferases (SULTs) are important enzymes involved in the sulfation of bioactive compounds, enhancing their water solubility and facilitating their elimination from the body. This process is a crucial part of Phase II metabolism, working alongside other metabolic pathways like glucuronidation and reactions catalyzed by cytochrome P450 enzymes, to ensure effective metabolic disposal of foreign and endogenous substances. In summary, sulfotransferases (SULTs) play a diverse and critical role in the metabolism of biomolecules and natural compounds in the body. Their sulfation reactions enhance the water solubility and excretion of substrates, contributing to the regulation of physiological processes, detoxification of xenobiotics, and maintenance of overall health and homeostasis.

V. GLUTATHIONE S-TRANSFERASES (GSTS) ENZYME MEDIATED BIOACTIVE COMPOUNDS METABOLIC DISPOSAL

Glutathione S-transferases (GSTs) are a family of enzymes that play a significant role in the metabolism and disposal of bioactive compounds, particularly by facilitating the conjugation of these compounds with glutathione. This process is a detoxification mechanism that helps make the compounds more water-soluble and readily excretable. GSTs are involved in Phase II metabolism, working in tandem with Phase I enzymes like cytochrome P450 to neutralize and eliminate potentially harmful substances.

Carnosic acid (conjugated linoleic acid), Genistein in soy products, Quercetin anthocyanin, Ellagic acid and Genistein which are present in berries like pomegranate, grapes, and blackcurrants, and Selenium in Brazil nuts, and pork, fish oil, and amino acids like Cystine Glycine Glutamine and Taurine and ornithine arginine and Alpha-lipoic acid, folic acid. are all metabolized by GST.Here's an overview of how GSTs and glutathione conjugation work in the metabolic disposal of bioactive compounds:

1. **Glutathione Conjugation Reaction:** GST enzymes catalyze the transfer of the tripeptide glutathione (composed of glutamic acid, cysteine, and glycine) to reactive functional groups on a substrate. This reaction is referred to as glutathione conjugation or GST-catalyzed glutathione S-transferase reaction.

2. **Substrate Specificity:** Different GST isoforms are responsible for metabolizing specific classes of compounds. GSTs have varying substrate preferences and can metabolize a

wide range of molecules, including drugs, toxins, carcinogens, and environmental pollutants.

3. **Neutralization and Detoxification:** The glutathione conjugation reaction neutralizes the electrophilic and reactive properties of the substrate, making it less harmful and more easily excreted from the body. This process is a detoxification step that helps protect cells and tissues from damage.

4. **Water Solubility Enhancement:** The addition of a glutathione molecule to the substrate increases its water solubility, which aids in its elimination through urine or bile. This prevents reabsorption in the kidneys and enhances overall excretion.

5. **Formation of Mercapturic Acid Conjugates:** The glutathione-conjugated compounds can undergo further metabolism, leading to the formation of mercapturic acid conjugates. These are highly water-soluble metabolites that are typically excreted in urine.

6. **Protection against Oxidative Stress:** Glutathione is a critical antioxidant molecule in cells, and GSTs help maintain cellular redox balance by participating in reactions that counteract oxidative stress.

7. **Drug Resistance:** In some cases, overexpression of certain GST isoforms has been associated with drug resistance in cancer cells, as they can help these cells eliminate chemotherapeutic drugs.

8. **Genetic Variability:** Genetic polymorphisms in GST genes can lead to variations in enzyme activity and substrate preferences, influencing how individuals metabolize various compounds.

9. **Environmental Exposure:** GSTs are also involved in the detoxification of environmental toxins and pollutants, making them important in adapting to varying environmental conditions.

Glutathione S-transferases (GSTs) are enzymes that are involved in the metabolism of various biomolecules and natural compounds in the body. They catalyze reactions that transfer the tripeptide glutathione (GSH) to electrophilic compounds, forming glutathione conjugates. This process enhances the water solubility of the compounds, making them more suitable for excretion. Here are some examples of how GSTs are involved in the metabolism of biomolecules and natural compounds:

1. **Endogenous Molecules and Oxidative Stress:** GSTs play a critical role in protecting cells from oxidative stress by catalyzing the conjugation of glutathione with reactive oxygen species (ROS) and other electrophiles. This detoxification process helps prevent damage to biomolecules like proteins, lipids, and DNA.

2. **Metabolism of Xenobiotics:** GSTs contribute to the detoxification of xenobiotics, which are foreign compounds like drugs, environmental pollutants, and carcinogens. By conjugating xenobiotics with glutathione, GSTs make them more water-soluble and easier to eliminate from the body.

3. **Phase II Metabolism:** GSTs are a key component of Phase II metabolism, which involves the conjugation of compounds to make them more suitable for elimination. They often work in conjunction with other Phase II enzymes, such as UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs).

4. **Detoxification of Metabolites:** GSTs can detoxify toxic metabolites produced during the metabolism of endogenous compounds. For example, they can neutralize the reactive intermediates formed during the breakdown of bilirubin.

5. **Fatty Acid Metabolites:** GSTs are involved in the metabolism of lipid peroxidation products, which are formed when lipids are oxidized. These peroxidation products can be damaging to cells, and GSTs help neutralize them.

6. **Conjugation of Epoxides:** GSTs are known for their ability to conjugate epoxides, which are highly reactive intermediates formed during the metabolism of certain chemicals. Conjugation with glutathione prevents the formation of DNA adducts and other harmful consequences of epoxide exposure.

7. **Protection against Electrophiles:** GSTs play a role in protecting cells against electrophilic compounds that can damage cellular components.

8. **Inflammation and Immune Response:** Some GSTs are involved in modulating inflammation and the immune response. They can influence the production of inflammatory mediators and regulate cellular responses to inflammation.

9. **Protein Conjugation:** GSTs can also catalyze the conjugation of glutathione to proteins, which can impact their function and activity.

In summary, glutathione S-transferases (GSTs) are crucial enzymes that facilitate the conjugation of glutathione to bioactive compounds, making them less toxic and more water-soluble for efficient excretion. This detoxification process is a key component of Phase II metabolism and works alongside other metabolic pathways like Phase I reactions (e.g., catalyzed by cytochrome P450 enzymes) to ensure the safe disposal of foreign and endogenous substances from the body. In summary, glutathione S-transferases (GSTs) are versatile enzymes that are critical for the metabolism of a wide range of biomolecules and natural compounds. Their activities contribute to detoxification, protection against oxidative stress, modulation of inflammation, and maintenance of cellular homeostasis. By facilitating the conjugation of glutathione with various electrophiles, GSTs play an important role in overall health and defense mechanisms against harmful substances.

VI. V.N-ACETYLTRANSFERASES (NATS) ENZYME MEDIATED BIOACTIVE COMPOUNDS METABOLIC DISPOSAL

NATs are enzymes that play a role in the metabolism and disposal of various bioactive compounds in the body. They catalyze the transfer of an acetyl group from acetyl coenzyme A (acetyl-CoA) to the amino or hydroxyl groups of substrates. This process is a form of acetylation and is involved in modifying the chemical structure of compounds to

enhance their water solubility and facilitate their elimination from the body. NATs are part of Phase II metabolism, working alongside other enzymes like cytochrome P450 and UGTs.
Here's an overview of how N-acetyltransferases and acetylation work in the metabolic disposal of bioactive compounds:

1. **Acetylation Reaction:** NAT enzymes catalyze the transfer of an acetyl group (-COCH3) from acetyl-CoA to specific functional groups on a substrate. This covalent attachment of an acetyl group to the substrate is known as acetylation.

2. **Substrate Specificity:** Different NAT isoforms are responsible for metabolizing specific classes of compounds. NATs have varying substrate preferences and can acetylate a range of molecules, including drugs, carcinogens, and endogenous compounds.

3. **Enhanced Water Solubility:** Acetylation increases the water solubility of the substrate, which aids in its excretion through urine or bile. This modification prevents reabsorption in the kidneys and enhances overall elimination.

4. **Detoxification:** Acetylation can lead to the formation of metabolites that are less reactive and toxic than the original compounds, contributing to detoxification.

5. **Pharmacological Activity:** In some cases, acetylation can lead to the formation of active metabolites. These metabolites may have distinct pharmacological activities or contribute to the overall therapeutic effects of a drug.

6. **Genetic Variability:** Genetic polymorphisms in NAT genes can result in variations in enzyme activity and substrate preferences. This genetic variability can influence an individual's susceptibility to certain compounds and their metabolism.

7. **Slow and Fast Acetylators:** One well-known example of NAT-related genetic polymorphism is the distinction between slow acetylators and fast acetylators. Slow acetylators have reduced NAT activity and may have prolonged exposure to certain compounds, potentially affecting drug efficacy and adverse effects.

8. **Isoniazid Metabolism:** NATs are involved in the metabolism of isoniazid, a drug commonly used to treat tuberculosis. Slow acetylators are at a higher risk of experiencing adverse reactions due to the slower metabolism of isoniazid.

N-acetyltransferases (NATs) are enzymes that play a role in the metabolism of various biomolecules and natural compounds in the body. They catalyze the transfer of an acetyl group (-COCH3) from acetyl coenzyme A (acetyl-CoA) to substrates, leading to the formation of N-acetyl derivatives. This process, known as acetylation, can modify the chemical and functional properties of molecules, influencing their solubility, stability, and biological activity. Here are some examples of how NATs are involved in the metabolism of biomolecules and natural compounds:

1. **Amino Acid Metabolism:** NATs are involved in the acetylation of amino acids. For instance, NATs play a role in the acetylation of the amino acid tryptamine, which is a precursor to serotonin, a neurotransmitter involved in mood regulation.

2. **Histone Acetylation:** NATs participate in histone acetylation, a critical process in epigenetic regulation. Acetylation of histones affects chromatin structure and gene expression, influencing various cellular processes.

3. **Drug Metabolism:** NATs contribute to the metabolism of certain drugs and xenobiotics. Acetylation can lead to the inactivation or activation of drugs, influencing their pharmacological effects and elimination.

4. **Neurotransmitter Metabolism:** NATs are involved in the metabolism of neurotransmitters like dopamine, norepinephrine, and serotonin. Acetylation can modulate the activity of these neurotransmitters and influence neuronal signaling.

5. **Detoxification of Xenobiotics:** NATs participate in the detoxification of xenobiotics, including aromatic amines and hydrazines found in tobacco smoke and certain foods. Acetylation can make these compounds more water-soluble, facilitating their excretion.

6. **Biotransformation of Dietary Compounds:** NATs can acetylate dietary compounds like dietary amines and polyamines. This metabolic process may influence the bioavailability and biological effects of these compounds.

7. **Metabolism of Sulfa Drugs:** NATs are involved in the metabolism of certain drugs containing sulfonamide groups, such as sulfa antibiotics. Acetylation of these drugs can affect their pharmacokinetics and efficacy.

8. **Detoxification of Endogenous Metabolites:** NATs can help detoxify endogenous metabolites, such as p-aminobenzoic acid, a breakdown product of folic acid.

9. **Activation of Prodrugs:** In some cases, acetylation by NATs can activate prodrugs, converting them into their active forms. This is observed with certain anticancer agents.

10. **Plant Compounds:** NATs can acetylate phytochemicals and secondary metabolites present in plants, which may impact their bioavailability and potential health effects.

In summary, N-acetyltransferases (NATs) are essential enzymes that facilitate the acetylation of bioactive compounds, enhancing their water solubility and aiding in their elimination from the body. This detoxification process is a significant component of Phase II metabolism and works alongside other metabolic pathways, contributing to the efficient disposal of foreign and endogenous substances. In summary, N-acetyltransferases (NATs) are enzymes that play a diverse role in the metabolism of biomolecules and natural compounds. Through acetylation reactions, they modify the properties of molecules, influencing their biological activity, detoxification, and elimination from the body. NATs' involvement in the metabolism of a wide range of substrates highlights their significance in maintaining cellular homeostasis and overall health.

REFERENCES

[1] Romilly E. Hodges, Deanna M. Minich, 2015. Journal of Nutrition and Metabolism, Review Article Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application, 1-23. http://dx.doi.org/10.1155/2015/760689.
[2] Wanwimolruk, Virapong Prachayasittikul 2014.Review article: Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (part 1) Sompon EXCLI Journal 13:347-391.
[3] Mohamed Ouzzine, Sandrine Gulberti,Nick Ramalanjaona, Jacques Magdalou,Sylvie Fournel-Gigleux 2014. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxicationrontiers in Cellular Neuroscience 8 (349):1-12. doi: 10.3389/fncel.2014.00349
[4] Zhongqiu Liu, Ming Hu 2007. Natural Polyphenol Disposition via Coupled Metabolic Pathways. Expert Opin Drug Metab Toxicol. 3(3): 389–406. doi:10.1517/17425255.3.3.389.
[5] David P. Dixona, Robert Edwards, 2010. Glutathione Transferases, The Arabidopsis Book pp.1-15.

